The Influence of Environmental Factors on Gastric Cancer in the Northwest of Iran

Farhad Pourfarzi

2006

Submitted for
The Degree of Doctor of Philosophy
School of Public Health and Community Medicine
Faculty of Medicine
University of New South Wales

Abstract

Background: Despite a declining trend in the incidence of gastric cancer (GC), it is still a major global public health concern of the 21st century. It afflicts one million people and kills 750,000 annually. It is believed that both genetic and environmental factors contribute to the gastric carcinogenesis. However geographic variation and immigrant studies highlight the role of environmental factors.

Objective: To evaluate the association of GC with the environmental factors of diet, helicobacter pylori (*H. pylori*) infection, lifestyle and occupation as well as family history in Iran.

Methodology: A population based case-control study was conducted in the Northwest of Iran where one of the highest incidence rates of the world has been reported. Two hundred and seventeen cases of GC and 394 age and gender matched controls were recruited. Participants were interviewed using a structured questionnaire which elicited information on demographic characteristics, socioeconomic status, family and medical history, lifestyle (smoking, alcohol drinking and substance abuse) and occupation. Ten milliliters of each subject's blood was collected for blood grouping and to investigate presence of IgG antibodies against *H. pylori* using an ELISA kit which had been locally validated for this study.

Results: Diet and *H. pylori* infection were found to be the most important determinants of GC in this study. High intake of allium vegetables and fruit, especially citrus fruit, appears to play a protective role. In addition to the consumption of fruit and vegetables, consumption of fresh fish was also inversely associated with GC. On the other, hand consumption of red meat and dairy products were positively associated with the risk of GC. Other dietary practices were also found to be important factors in the etiology of GC. People who had a preference for higher salt intake and drinking strong and hot tea were at higher risk. Finally, H. pylori infection was found to increase the risk of GC.

Conclusion: This study has provided important and original information about the etiology of gastric cancer particularly in the Iranian context. These findings could be used in planning preventive strategies for this malignancy, which is a major health problem in Iran.

In memory of my father to whom I owe my motivation for doing this research and to whom I dedicated my everyday dream from childhood that I could have saved him from gastric cancer. He never lived long enough to see the fruits of his inspiration. He passed away from gastric cancer when he was 39 years old.

Acknowledgment

I would like to thank the following people who made this thesis possible and an enjoyable experience for me through their support, contribution, encouragement and assistance.

First of all I wish to express my sincere gratitude to Dr Anna Whelan, Professor John Kaldor and Professor Reza Malekzadeh, for their generous supervision, support and encouragement over the last 45 months. They guided me through this project and helped whenever I was in need. Without their help, this work would not be possible.

I gratefully acknowledge the Ardabil University of Medical Science and Ministry of Health and Medical Education for providing the opportunity for me to do this research by granting me a scholarship. I am also indebted to my fellow colleagues and research assistants (too numerous to name) in Ardabil University of Medical Science for their tireless efforts. I also acknowledge Aras clinic and DDRC laboratories for blood collection and analysis.

Many appreciation is extended to people who participated in the study and gave their valuable time to us.

I am grateful to Professor Antony Zwi, Head of School and all staff of the School of Public Health and Community Medicine, University of New South Wales for their help and support given when it was needed. I am also indebted to Dr Deb Black who provided statistical advice. I would like to express my appreciation to Associate Professor Mary-Louise McLaws for her advice, Dr. Hazel Mitchell from School of school of Biotechnology and Biomolecular Science for her advice and assistance especially in the validation of an ELISA test for H. pylori and emeritus Professor John Hirshman for his support.

A special thanks also goes to my friend Keith Masnick who patiently proofread this entire thesis.

Finally, but importantly, I would like to extend my special gratitude to my wife Faranak for her constant support, encouragement and tolerance which has been crucial to the

completion of this study and to my daughter and son Sanaz and Amir Hossein for their love and understanding as I knew that, there was a kind family awaiting me at the end of a long day's study. I would also like to express my gratefulness to my mother for her love and patience not only during this study, but throughout my life. I am also greatly indebted to my brother. I would also like to thank my wonderful family for constantly being there and supporting me. Without this support, this thesis would not have been possible.

ABBREVIATIONS

AICR	American Institute for Cancer Research
ASR	Age standardized rate
BMI	Body mass index
Cag A	Cytotoxin associated gene A
CDC	Center for Disease Control
CFT	Complement fixation test
CI	Confidence interval
EBV	Epstein-Barr virus
ELISA	Enzyme Linked Immuno-sorbent Assay
FFQ	Food frequency questionnaire
GC	Gastric cancer
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
H. pylori	Helicobacter pylori
HERC	Human Ethics Research Committee
HRR	Hazard rate ratio
IARC	International Agency for Research on Cancer
ICD-O	International classification of diseases for oncology
ISCO – 88	International Standard Classification of Occupations
ISIC	Industrial classification of All Economic Activities
MOHME	Ministry of Health and Medical Education
NSAID	Non-steroid anti inflammatory drug
OR	Odds ratio
PCR	Polymerase chain reaction
PYLL	Person years life lost
RR	Relative risk
RUT	Rapid urease test
SES	Socioeconomic status
UBT	Urea breath test
UNSW	University of New South Wales
Vac A	Vaculating cytotoxine A gene
WCRF	World Cancer Research Fund
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

APPENDICES

CHAPTER ONE: INTRODUCTION

1.1 Background

Gastric cancer (GC) is still a major global public health concern of the 21st century. Despite a declining trend in incidence and mortality of GC which has been reported in most parts of the world, GC is among the most common cancers worldwide and the second major cause of cancer-related mortality in the world. It was ranked as the second most common cancer in the world till year 2000 but now it is third behind lung and breast cancer (Parkin, Bray et al. 2001). Some of the highest age standardized incidence rates (ASR) have been reported from Korea, Japan, Chile and China with 69.7, 62.0, 46.0 and 41.4 cases per 100,000 males and 26.8, 26.1, 17.7 and 19.2 cases per 100,000 females respectively. GC affects about 1,000,000 people and kills about 750,000 around the world annually. GC accounts for almost 10% of all cancer diagnoses. It is also predicted that the incidence and mortality will rise to 2.5 and 1.9 million people respectively in the year 2050 (Parkin, Bray et al. 2001; Ferlay, Bray et al. 2004).

Iran is located in Southcentral Asia, in the region with an intermediate risk of GC. According to a report by the Iranian Ministry of Health and Medical Education (MOHME), cancer is the third most common known cause of death in Iran, after cardiovascular diseases and accidents (Naghavi 2000). Among cancers, GC is the most common fatal cancer with an incidence (ASR) of 26.1 and 11.1 per 100,000 for men and women respectively (Figure 1.1). There is a wide intra-country variation in relation to the incidence and mortality rates. The highest incidence rate has been reported from Ardabil province in the Northwest of Iran (Sadjadi, Malekzadeh et al. 2003). This active

cancer surveillance in Ardabil province during a period of four years (1996-1999) showed that GC was the first among the five most common cancers in Ardabil with an incidence (ASR) of 49.1 and 25.4 per 100,000 for men and women respectively. These rates are approximately twice the rate of the entire country. The rate in Ardabil is also one of the highest rates reported in the world. According to a recent report GC constituted approximately one-third of all cancer related deaths each year in Ardabil (Ardabil University of Medical Science 2000), while this rate was about 20% for the entire country (Naghavi 2003).

Despite the declining trend of incidence which has been reported in most parts of the world, such a decline has not been seen in Iran and Ardabil. There are a few studies of GC in Iran. The first available report dates back to the 1960s when Habibi (1965) reported that GC constituted about 2.6% of all cancers in Iran during a period of twelve years (1948 – 1960). In that study GC was ranked as the ninth most common cancer. In another report in 1973 it was demonstrated that GC accounted for about 8% of all reported cancers in Ardabil (Mahboubi, Kmet et al. 1973) which is far below recent report of 31% (Sadjadi, Malekzadeh et al. 2003). This remarkable difference could be partly explained because of better survey methods. Although in a study of Mahboubi, Kmet et al. (1973) it was not clearly reported what proportion of GC was diagnosed histopathlogically, however it was stated that a high proportion of cases were diagnosed by radiological investigation. In a recent survey, 60.3% of cases were diagnosed using histopathologic reports (Sadjadi, Malekzadeh et al. 2003). In addition to the difference in the survey methods, improvement of diagnostic method especially the availability of endoscopy is also another possible reason for what appears to be an increasing trend. Endoscopic instruments allow doctors to distinguish cardia cancer from lower

esophagus cancer more precisely. However, the above mentioned factors may not explain all of this remarkable change, as similar increases was not observed for cancer in other parts of the digestive system. Although GC is a major public health problem in most parts of the world, it is more problematic in Iran particularly in the Northwest, as the declining trend which was observed in most parts of the world have not been seen in Iran and Ardabil.

There is a wide variation in the incidence (ASR) among different geographic regions of the world with approximately 100-fold difference between the highest and lowest rates. The highest incidence has been reported from some eastern Asian countries such as Korea, Japan and China, while the rate is very low in some African countries (Cameroon, Mozambique) with an ASR incidence of less than one per 100,000 people. Almost two-thirds of GC occur in less developed countries (Ferlay, Bray et al. 2004) (Figure 1.2) with the exception of the low incidence of GC in African countries. However, it is believed that relatively low life expectancies of Africans with extremely limited access to health care may be the reason for lower incidence of GC in Africa (Agha and Graham 2005). The distribution of incidence (ASR) around the world is shown in Appendices A and B for men and women respectively.

Migrant studies have shown that people who emigrate from high to low risk areas face a decreasing risk. A study by Haenszel and Kurihara (1968) showed that the incidence of GC decreased among Japanese who had immigrated to western countries, compared to their counterparts in Japan. In addition, second generations of immigrants had a lower risk of developing GC compared to the first generation. Therefore cancer trends for the first generation approximate more closely the pattern of the home country (Hanley, Choi et al. 1995).

1.2 Etiology

The real causes of gastric cancer are not fully understood, however, worldwide variation and immigrant studies provide evidence to support the impact of environmental factors on this malignancy. Several demographic and environmental factors have been implicated with GC. The main environmental factors that have been reported as being linked to GC are dietary habits, *Helicobacter pylori* infection (*H. pylori*), lifestyle and occupation. An association between GC and a positive family history of GC has also been frequently reported. However, this association between GC and family history may support the role of both genetics and environment in development to GC as family members may have similar exposure.

Demographic characteristics have been shown to be an important determinant in the development of GC. Gastric cancer occurs more frequently in men, with a male-female ratio of 1.5 – 2.5 (Nomura 1996; Parkin, Bray et al. 2001). Although risk of development of GC in males is approximately twice that of females, the mortality rate is approximately equal for both genders (Ferlay, Bray et al. 2004). The incidence of GC increases with age and it doubles through each decade: 55 to 65 and 65 to 75 and above (Bruckner, Morris et al. 2003). Most of the cases occur between the ages of 65 and 74 years in the USA with a median age of 70 for males and 74 for females. Moreover, risk varies among different ethnic groups. Gastric cancer occurs 1.5 times more frequently in black than white Americans (Ferlay, Bray et al. 2004). In addition, marked ethnic and geographic variations have been reported between Eastern and Western countries (Schottenfeld 1996). GC was reported to be the most common malignant neoplasm in Asia, particularly in Korea, Japan and China. In contrast, incidence of GC in the United

States is low among Caucasians and moderate to low among blacks (Schottenfeld and Fraumeni 1996; Ferlay, Bray et al. 2004).

Dietary factors have long been explained to play an important role in etiology of GC. Food items could play either a protective or promoter role depending on their components. It was thought that fresh fruits and vegetables, white meat (particularly fish) and green tea may protect against GC. Some of studies have reported a higher protective role for citrus fruits (Buiatti, Palli et al. 1989; Boeing, Frentzel-Beyme et al. 1991; Jansen, Bueno-de-Mesquita et al. 1999; De Stefani, Correa et al. 2001; De Stefani, Correa et al. 2004) and allium vegetables such as garlic and onion (You, Blot et al. 1989; Gao, Takezaki et al. 1999; De Stefani, Correa et al. 2001; Munoz, Plummer et al. 2001). It has also been hypothesized that improved preservation methods and refrigeration may decrease the risk by the year-round availability of fresh fruits and vegetables as well as decreasing salting and smoking as preservation methods (Lee, Park et al. 1995; Ekstrom, Serafini et al. 2000; Munoz, Plummer et al. 2001; Cai, Zheng et al. 2003). On the other hand, excessive consumption of salt, meat, preserved foods and dairy products have been reported to possibly increase the risk of GC (Kono and Hirohata 1996; Ward, Sinha et al. 1997; De Stefani, Boffetta et al. 1998b; Munoz, Plummer et al. 2001). Furthermore a positive correlation was reported between consumption of cereals and GC in 15 European countries (Hakama and Saxen 1967).

H. pylori infection is another factor which has been reported to play an important role in etiology of GC. This bacteria was primarily demonstrated by Warren and Marshall (1983) to link to gastroduodenal diseases. Following this demonstration, the majority of studies on GC have considered *H. pylori* infection as one of the independent variables in their investigation. A large body of literature has supported a positive association

between these two factors (Forman, Sitas et al. 1990; Forman, Newell et al. 1991; Nomura, Stemmermann et al. 1991; Parsonnet, Friedman et al. 1991; Sitas 1993; Asaka, Kimura et al. 1994; Hu, Mitchell et al. 1994; Aromaa, Kosunen et al. 1996; Chang, Kim et al. 2001; Wang, Wang et al. 2002) together with six related meta-analyses (Forman, Webb et al. 1994; Huang, Sridhar et al. 1998; Danesh 1999; Eslick, Lim et al. 1999; Helicobacter and Cancer Collaborative 2001; Xue, Xu et al. 2001). In addition, infection rates were shown to vary between social class, which is consistent with patterns of GC (Sitas, Forman et al. 1991). One decade after demonstration of *H. pylori* by Warren and Marshall (1983),The International Agency for Research on Cancer (IARC) classified *H. pylori* infection as a group I carcinogenic factor to humans (IARC 1994). On the other hand, some studies did not find a significant relationship between *H. pylori* and GC. This was especially so in Asian countries such as Taiwan (Lin, Wang et al. 1993; Lin, Wang et al. 1995), India (Sivaprakash, Rao et al. 1996), China (Webb, Yu et al. 1996) Korea (Kim, Cho et al. 1997) and Japan (Blaser, Kobayashi et al. 1993; Kato, Onda et al. 1996). The lack of association observed between GC and *H.pylori* in some studies was thought to be due to false negatives. The precursors of GC such as intestinal metaplasia have been reported to cause false negative, however, a positive association which was shown between *H. pylori* infection and GC is counter to this statement (Asaka, Kato, et al. 1995). These studies show that gastric carcinogenesis is a multi-step and multi-factorial process, therefore the onset of GC could not be related to one single factor, but possibly to a series of different variables. However, the lack of significant association in some of these studies could be due to small sample sizes. Further questions arise from the lack of conclusive findings from randomized control trials as eradication of *H. pylori* has not always been protective against the development to GC (Wong, Lam et al. 2004). However, it is believed that timing of eradication is an

important factor in the result of trial. The older the group recruited, the less likely treatment prevents development to GC (Feldman, 2001).

Lifestyle related factors were also reported to play a role in the development of GC. Smoking and alcohol drinking have been examined in many studies. There is inconsistency in the findings of these studies, with a higher level of inconsistency reported for alcohol than smoking. IARC published a monograph in 1986 which was not conclusive about the causal effect of smoking (IARC 1986). This monograph was updated in 2002 after the evaluation of new studies in which the carcinogenic effect of smoking was accepted (W.H.O and IARC 2004). However, some studies which were published after this monograph failed to show a dose dependency (Sasazuki, Sasaki et al. 2002; Gonzalez, Pera et al. 2003) or reported a weak association only among men (Minami and Tateno 2003). The results of the association between GC and alcohol are less consistent, the majority reporting no association. A monograph by IARC was not conclusive about the gastric carcinogenic effect of alcohol (1988). In addition to smoking and alcohol drinking, opium use has been reported to play a role in the malignancy of the aerodigestive system especially esophageal cancer, but this association has not been examined for GC (Hewer, Rose et al. 1978; Kmet 1978; Ghavamzadeh, Moussavi et al. 2001).

Occupation has also been considered by many researchers in relation to GC. These researchers have shown an association between GC and some particular industries and occupations. According to some of these studies, industrial exposure in agriculture, mining and construction (Cocco, Ward et al. 1996; Aragones, Pollan et al. 2002; Raj, Mayberry et al. 2003; Bucchi, Nanni et al. 2004) and possibly transport and metal and paper product manufacturing may increase the risk of GC (Cocco, Ward et al. 1998;

Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). Meanwhile other studies have focused on the role of occupation. These studies have reported an increasing risk in assembler, pulp and paper workers, publishing and printing workers as well as motor vehicle drivers, miners and food-related occupations including, butchery, bakery and food workers (Burns and Swanson 1995; Swaen, Meijers et al. 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Boffetta, Gridley et al. 2000; Aragones, Pollan et al. 2002). These occupations generally represent the above mentioned industries.

While occupational diseases are more common in developing countries, only a few studies have examined these associations in developing countries. In addition, the majority of these studies have used death certificates for assessing occupational exposure which is less informative. A study using the more appropriate method of assessment such as self reported work history, could be more informative in developing countries such as Iran.

Genetics has also been suspected as playing a role in etiology of GC. This role has been investigated in several studies in which an approximately 10% attributable risk was reported for genetic factors. To examine the role of heredity, some observational studies focused on family aggregation and blood typing. It has been reported that people with a positive family history of GC may develop GC approximately 1.5 – 4.0 times more than those without (La Vecchia, Negri et al. 1992; Palli, Galli et al. 1994; Inoue, Tajima et al. 1998b; Lissowska, Groves et al. 1999; Munoz, Plummer et al. 2001; Yatsuya, Toyoshima et al. 2002; Nomura, Hankin et al. 2003). It was also reported that GC in those with positive family history tended to occur at a younger age (Koea, Karpeh, et al. 2000). However it is not clear whether this tendency is due to a higher awareness of being screened because of a positive background in first-degree relatives or similar

exposure to the shared environmental risk factors among family members. In addition, a higher risk of GC has been inconsistently reported in people with blood "group A" than other blood groups (Glober, Cantrell et al. 1971; Bjelke 1974; Neugut, Hayek et al. 1996; Nomura 1996). In contrast a protective role was suggested for blood group O (Aird, Bentall et al. 1953).

1.3 Anatomical sub-sites and histopathology of GC

GC can occur in different locations of the stomach with different histopathology. Sub-sites of cancer are usually classified as "cardia and non-cardia" or "cardia and distal". Different patterns have been suggested for these sub-sites. It is believed that environmental factors is more closely linked to non-cardia than cardia cancer (Wang, Antonioli et al. 1986; MacDonald and MacDonald 1987; Blot, Devesa et al. 1991). Accordingly, it is thought that *H. pylori* infection is not an important factor in cardia cancer (Helicobacter and Cancer Collaborative 2001). However, several studies did not find a difference between these sub-sites in relation to environmental factors (Kono and Hirohata 1996; Ye, Ekstrom et al. 1999; Ekstrom, Serafini et al. 2000; Kato, Asaka et al. 2004).

GC has been histopathologicaly classified in two sub-types of intestinal and diffuse (Lauren 1965). Risk factors were reported to vary between these two different histopathologic sub-types. It has been suggested that intestinal types are mostly related to the environmental factors when compared to the diffuse types (Lehtola 1978; Lehtola 1981; Parsonnet, Vandersteen et al. 1991). In contrast it is thought that genetics is more important in the diffuse than intestinal types (Lehtola 1978; Lehtola 1981; Zanghieri, Di Gregorio et al. 1990; Parsonnet, Vandersteen et al. 1991; Lauren and Nevalainen 1993). However many studies could not find a significant difference between these two

histopathologic sub-types (Ye, Ekstrom et al. 1999; Ekstrom, Serafini et al. 2000; Kato, Asaka et al. 2004).

1.4 Objective of study

The main objective of this study is to elucidate the epidemiology of GC in the Ardabil population. Specific hypotheses are outlined in chapter three, but in general the hypothesis is that there are modifiable factors of dietary habits, *H. pylori* infection and possibly lifestyle and occupation, which contribute to GC. The ultimate goal is to establish some strategies to improve primary prevention.

1.5 Significance of this research

A decline in the incidence and mortality of GC has been reported in many regions of the world. However, such a decline has not been observed in Iran and Ardabil province and GC occurrence has remained high in recent years. It has been shown that the occurrence of GC in Iran during the last 40 years has been increasing and is still the most common cancer with the highest mortality. The high incidence and mortality of GC has been a major health problem in Iran. A descriptive study showed that GC in 18 provinces of Iran leads to 42986 total person years life lost (PYLL) (Naghavi 2003). GC has a poor prognosis with very low 5-year survival rate of about 10% (Braunwald 2001). The majority of these deaths can possibly be prevented by modification of diet, lifestyle or possibly by *H. pylori* eradication at an appropriate time.

High incidence of GC in this area (despite a substantial reduction of GC in most parts of the world), the high mortality and lack of epidemiological studies indicated a need to investigate factors which relate to GC specifically in Ardabil. Ultimately I saw a need to find a means to prevent such cancers if possible, as treatment is not yet very effective.

Therefore Ardabil was selected as the study region because it is in a high incidence area. It is the first case-control study of GC there. This population-based case-control study recruited a sufficient number of subjects to examine the impact of environmental factors using a logistic regression approach. In addition, the Ardabil Cancer Registry provides an appropriate system to collect precise information about cases. Findings of this study provide an understanding of GC and related factors in the Iranian context. Results of this study may lead to an improvement in primary prevention especially by focusing on dietary habits and *H. pylori* eradication. This study also provides some baseline information for future studies.

1.6 Structure of thesis

This thesis is reported in five main chapters. Chapter one provides an overview statement of the problem, the objective and the significance of this research. Chapter two critically reviews the existing articles and information on GC and related factors. The main focus is on the potential environmental factors which are dietary habits, *H. pylori* infection, lifestyle and occupation. This chapter also covers topics on demographic factors, epidemiology and pathogenesis of the disease. Chapter three focuses on methodological issues and covers study design, subject recruitment, data collection and analytical methods. In addition, evaluation of the measurement tools are discussed in this chapter. In chapter four, collected data are analyzed by different methods. Cases and controls are compared using univariate and multivariate analysis by logistic regression approach to see if there are any differences in exposure to the risk factors between GC patients and those who are cancer free. In addition, subgroups analyses for anatomical sub-sites and histopathologic classification are reported in the last section of chapter four. Chapter five discusses strengths and limitations of the study

as well as the study findings. Recommendation for future studies and implementation of this study are also discussed in this chapter.

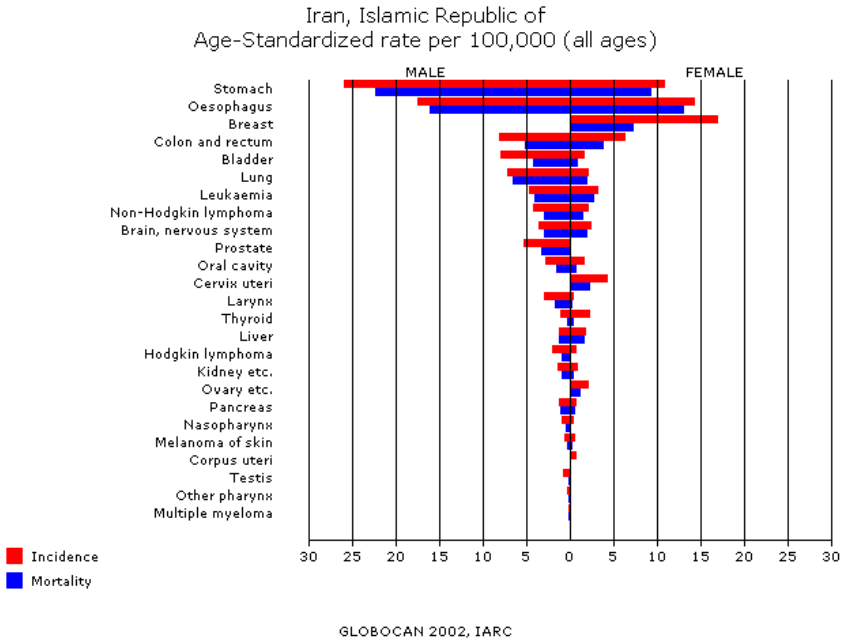


Figure 1. 1: Incidence and mortality rates of cancers in Iran (ASR per 100,000)
based on (Ferlay, Bray et al. 2004)

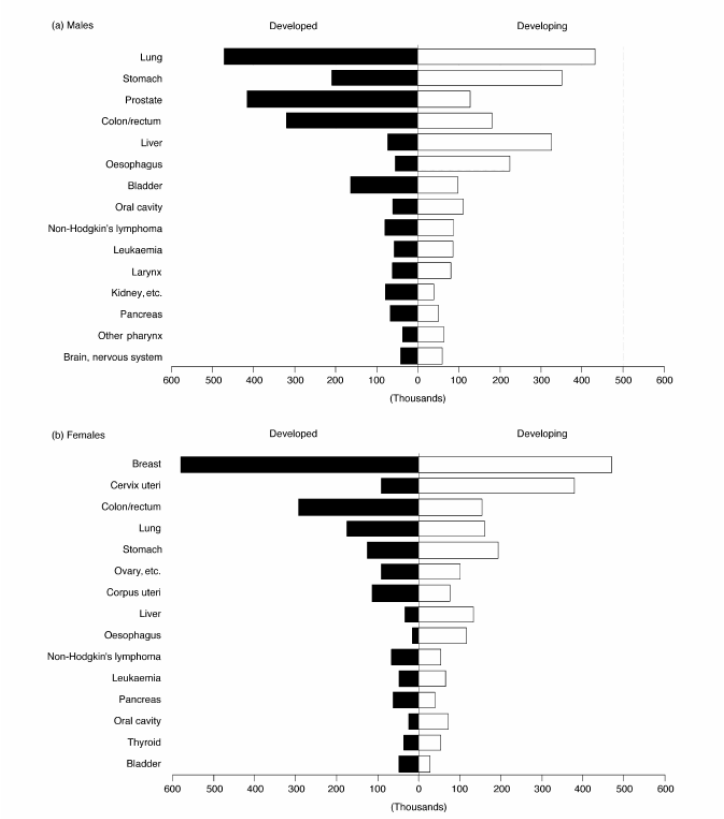


Figure 1. 2: Number of new cases of the 15 most common cancers in (a) males, 2000, (b) females, 2000.
from (Parkin, Bray et al. 2001)

CHAPTER TWO: LITERATURE REVIEW

Gastric cancer is a major health problem in the world although a decreasing trend in incidence and mortality has been observed during the last decades. The history of GC was clearly discussed by Alvarez (cited in Bruckner, Morris et al. 2003). Accordingly this malignancy was first described by Galen (131 – 202). Further information was provided by the eleventh-century Iranian physician Avicenna and then Vesalius (1514 – 1564) and Morgagni (1682 – 1771). Following this information about GC which were provided by ancient medical scientists, modern science sought to find factors relating to etiology of GC. To the best of my knowledge the first of these dates back to 1930s when the impact of alcohol on GC was reported (Wangensteen 1956). Since that time the etiology of GC has been the subject of many studies. Different epidemiological methods have been used to find related factors. While each study provides more clues to the mystery of the causes of cancer, none has collectively or singly proven any environmental component to be the exclusive cause of GC. To frame a theoretical background of the etiology of GC, a review of related articles was conducted and is outlined in this chapter.

2.1 Geographic and demographic distribution and time trend

IARC provides precise information about the descriptive epidemiology of cancers worldwide in a program named GLOBOCAN. This program is a unique source of the most up-to-date information on cancer incidence, mortality and prevalence in all the countries of the world (Ferlay, Bray et al. 2004). According to this data source, GC is one of the most common cancers worldwide and the second major cause of cancer-

related mortality in the world. GC has been a disease of interest for clinicians and researchers due to its burden on people's health. It was ranked in the 1980s as the second most common cancer in the world but now it is the third leading cancer behind lung and breast cancer and the second in the mortality (Parkin, Bray et al. 2001). GC afflicts about 1,000,000 people and kills about 750,000 around the world annually. It accounts for almost 10% of all cancer diagnosis. It is also predicted that the global number of cases and death will rise to 2.5 and 1.9 million people respectively in year 2050 (Parkin, Bray et al. 2001; Pisani, Bray et al. 2002; Ferlay, Bray et al. 2004). The predictive number of cases and deaths among different regions of the world is demonstrated in Table 2.1.

Table 2. 1: Predictive number of new cases and deaths (000) among different region of the world

Regions	2000		2010		2020		2050	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	880	650	1110	810	1440	1060	2440	1900
More developed regions	330	230	380	260	440	300	510	360
Less developed regions	540	420	730	550	990	760	1930	1540
Africa	30	20	40	30	50	40	30	110
Asia (Japan)	120	60	140	70	150	80	150	80
Asia (other)	450	340	670	460	900	640	1510	1200
Europe	190	160	240	180	260	200	300	220
South America	70	50	90	70	120	100	250	200
North America	30	20	30	20	40	30	50	30
Oceania	< 10	< 10	< 10	< 10	< 10	< 10	10	< 10

based on (Ferlay, Bray et al. 2004)

There is a worldwide variation in the incidence of GC. The highest rate was reported from Eastern Asia and Central and Eastern Europe while the risk is low in Northern America and Europe, Australia and most parts of Africa. Incidence and mortality

among different regions of the world are shown in Appendix C. The table there also presents information on the highest and lowest rates within each region showing about 100-fold difference in the incidence of GC between countries of the highest and the lowest rate. The highest incidence has been reported from Korea, Japan, Chile and China with ASR of 69.7, 62.0, 46.0, 41.4, among males and 26.8, 26.1, 17.7, 19.2 respectively among females, while this rate is very low in some African countries (Cameroon, Mozambique) with reported ASR incidence of less than one per 100,000 people (Parkin, Whelan et al. 2005). Age standardized incidence rates among males and females are shown in Figure 2.1 and 2.2 for the highest incidence countries.

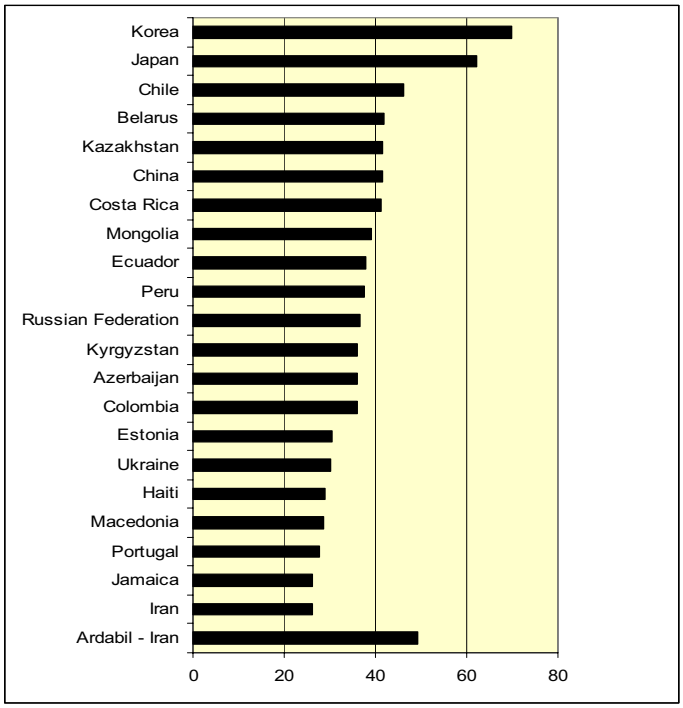


Figure 2. 1: Incidence of GC (ASR) among males in some of the highest risk countries and Ardabil based on (Sadjadi, Malekzadeh et al. 2003; Ferlay, Bray et al. 2004)

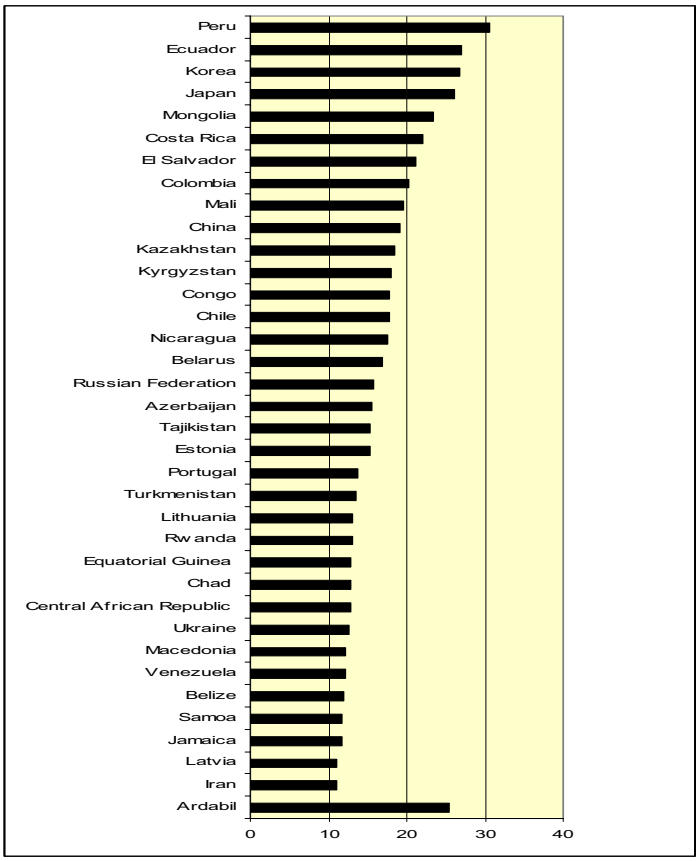


Figure 2. 2: Incidence of GC (ASR) among females in some of the highest risk countries and Ardabil

based on (Sadjadi, Malekzadeh et al. 2003; Ferlay, Bray et al. 2004)

GC has generally shown a declining trend in most parts of the world. A comparative worldwide incidence of GC was first provided in "The Cancer Incidence in Five Continents" in 1966 (Doll, Payne et al. 1966). This information has been updated every five years (Parkin, Whelan et al. 2005). Eight of these monographs have now been published and they present a declining trend of GC (Figure 2.3). Until the mid 1980s GC was reported to be the most common diagnosed malignancy in the world. After that GC became the second most common cancer after lung cancer (Sasako and Sugimura 1997). Currently, it has been ranked as the third common cancer behind breast cancer (Parkin, Bray et al. 2001). This decreasing trend was seen in different countries and ethnic groups (Hakama 1972; Sunny, Yeole et al. 2004; Parkin, Whelan et al. 2005).

A decline in the trend of GC has not been observed in Iran, while there is a report in the declining trend from most parts of the world which has been named as an unplanned triumph (Howson, Hiyama et al. 1986). Studies in GC in Iran are very few. The first information was provided in 1965 by Habibi who reported that GC constitutes less than 3% of all cancer in Iran (Habibi). The result of this study was based on 10,000 cancers which were diagnosed in three pathological laboratories in Tehran (capital city of Iran). In this study GC with 306 cases was the 9th most common cancer. The second article provided information about GC in north of Iran as well as Ardabil (Mahboubi, Kmet et al. 1973). According to this study, a cancer registry was started in Ardabil in 1970. This survey demonstrated that GC accounted about 8% of all reported cancers in Ardabil. Another survey which is based on the results of a population-based cancer registry provided the most reliable information on the situation of GC in Ardabil. In this study GC constituted 31% of all cancer diagnoses during a period of four years (1996-1999). This rate is very high in comparison to the 8% which was previously reported from Ardabil in the 1970s. It is also high compared to the 10% which is generally reported worldwide (Ferlay, Bray et al. 2004). These studies show an increasing trend although they are different in their data collection methods. In the first survey a high proportion of cases were diagnosed by radiographic method whereas microscopic verification was the most common method of GC diagnosis in the second survey (Sadjadi, Malekzadeh et al. 2003). In addition, the incidence of GC (ASR) in Ardabil is the highest in Iran with 49.1 and 25.4 per 100,000 cases in men and women respectively. These rates are approximately twice that of the entire country's rates which are 26.1 and 11.1 per 100,000 cases of men and women respectively. A report by Ardabil University of Medical Science (2000) showed that one-third of cancer related deaths in Ardabil was due to GC while this rate was about 20% for the entire country (Naghavi 2003).

It has been found that immigration from high risk to low risk areas may result in decreasing risk. For example, those Japanese who had emigrated to the Hawaii were at lower risk of GC compared to the Japanese living in their home country (Haenszel and Kurihara 1968). This decline was notably greater in second generation of immigrants (Hanley, Choi et al. 1995). This finding suggests that exposure in the early stage of life is very important.

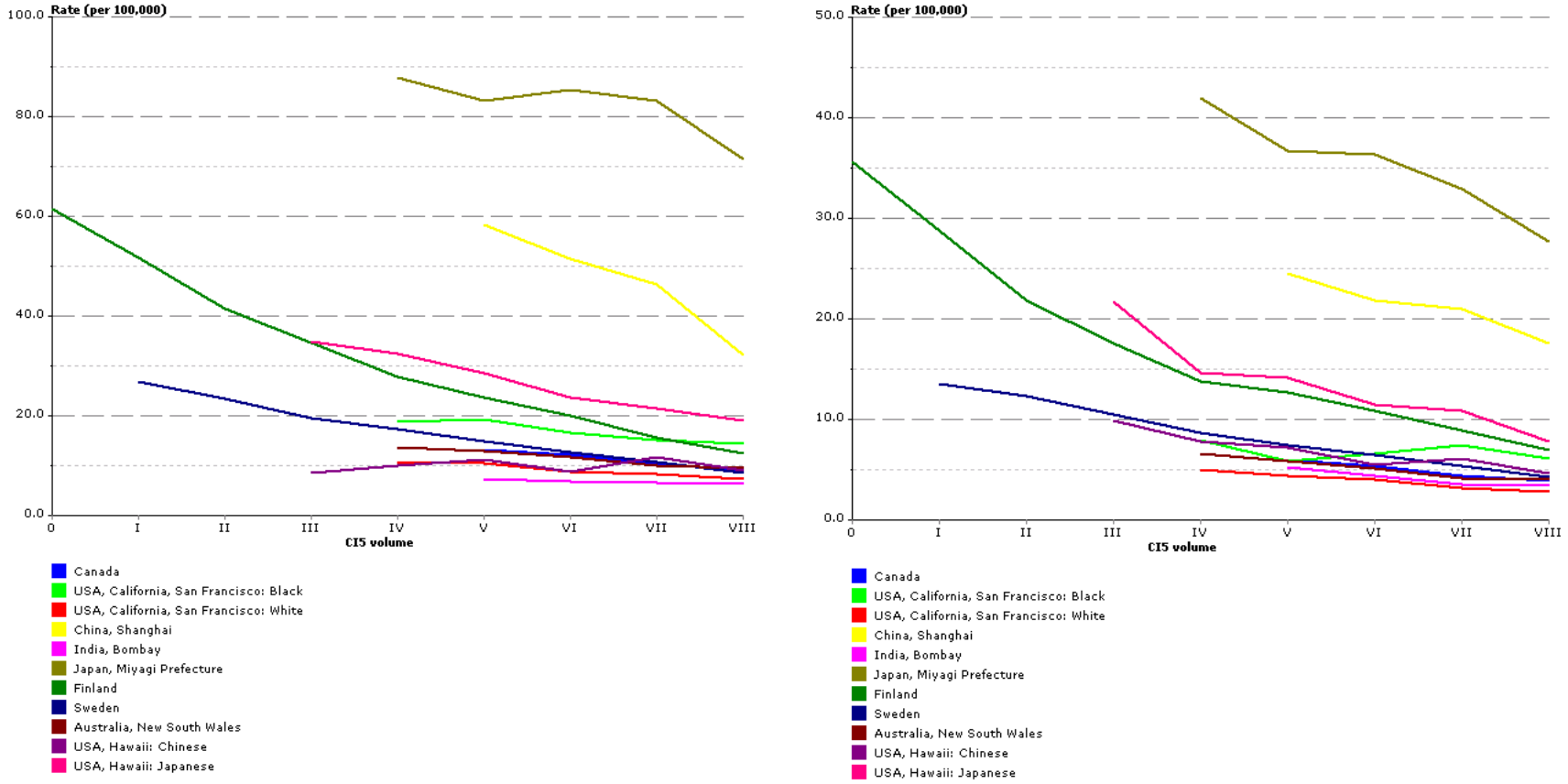


Figure 2. 3: Trends of incidence rates (ASR) per 100,000 males (left) and females (right) age [0-85+] in different countries and ethnic groups based on (Parkin, Whelan et al. 2005)

Demographic characteristics are an important determinant of GC. Gastric cancer is a cancer of the elderly with average age of 65 years at diagnosis. Except in Japan, it is rarely seen before the age of 50 (Nyren and Adami 2002). The risk increases by getting older and it is doubled in people aged 75 years and older compared to age 65 – 75 years (Bruckner, Morris et al. 2003). It occurs more frequently in males than females with a ratio of 1.5 – 2.5 to one throughout different countries (Nomura 1996; Parkin, Bray et al. 2001). However the mortality rate is approximately equal for both genders (Ferlay, Bray et al. 2004). Moreover, risk varies among different ethnic groups. Gastric cancer occurs approximately 1.5 times more frequently in blacks than whites. As seen in Figure 2.3 there was a declining trend between 1966 – 2002 for both white and black in USA, California, San Francisco, however the rate was higher for black males and females during that period (Parkin, Whelan et al. 2005).

2.2 Socioeconomic status

The risk of GC has been reported to vary among those of different socio-economic status (SES). It is thought that people in the lower level of SES are more vulnerable to GC than higher levels. Wide variations of rates between less and more developed regions also provide evidence to support this association as it has been shown that almost two-thirds of GC occurs in less developed countries (Parkin, Bray et al. 2001). In addition to the inter-country variation in relation to the risk of GC, intra-country variation was also observed among different levels of SES. For instance a negative gradient of GC incidence and mortality in urban residents of New South Wales (NSW) has been reported (Smith, Taylor et al. 1996). Different determinants of SES have been used for explanation of this association including education, income, expenses and domestic related variables as well as occupation. It has also been reported that GC

patients have lower levels of education (Hansson, Baron et al. 1994; La Vecchia, D'Avanzo et al. 1995b; van Loon, Goldbohm et al. 1998; Munoz, Plummer et al. 2001; Fujino, Tamakoshi et al. 2002; Nomura, Hankin et al. 2003), income (Gammon, Schoenberg et al. 1997; Nishimoto, Hamada et al. 2002) and access to general facilities such as piped water at home (Munoz, Plummer et al. 2001). Moreover, a higher risk was observed among those working in manual class occupation than non-manual classes (Brown, Harding et al. 1998). A higher survival rate was also shown in people of higher levels of SES (Fontana, Decensi et al. 1998).

While it is still unclear how SES contributes to GC, several explanations have been suggested for this association. Poor people may have a different lifestyle including smoking, nutritional and drinking habits and workplace exposures which could expose them to more carcinogens. *H. pylori* infection is another possible reason which may explain this association. *H. pylori* is an important risk factor for GC which is related to SES (Sitas, Forman et al. 1991). It has been hypothesized that acquisition of *H. pylori* is related to poor sanitary condition and overcrowding particularly in childhood. Accordingly low socioeconomic status and overcrowding has been reported to increase the risk of *H. pylori* infection (Mendall, Goggin, et al. 1992; Malaty, and Graham 1994; Kurosawa, Kikuchi et al. 2000; Moayyedi, Axon, et al. 2002). *H. pylori* afflicts a higher proportion of people in less developed compared to the more developed countries (Marshall 1994). This bacteria has infected about one-third of the adults in the more developed countries whereas this rate is about two-thirds in the less developed countries (Pounder and Ng 1995).

2.3 Sub-sites

Gastric cancer may occur in different anatomical sub-sites of the stomach. World Health Organization (WHO) has provided a different code for each sub-site including cardia, fundus, greater and lesser curvature and antrum in the International Classification of Diseases for Oncology (ICD-O, code 160-9) (Fritz 2000). However, in epidemiological studies it is often divided in two sub-sites of proximal and distal which are sometimes referred as cardia and non-cardia respectively. The proximal part includes the area of the cardia and gastro esophageal junction (GEJ) which, together, are commonly referred to as cardia. The remaining parts are grouped as distal or non-cardia GC (Neugut, Hayek et al. 1996).

An increasing risk of cardia cancer has been reported, while a decline has been demonstrated for overall GC (Blot, Devesa et al. 1991; Botterweck, Schouten et al. 2000). A decline which was observed in the incidence of GC is mostly due to reduction in antral GC rather than cardia GC (Rios-Castellanos, Sitas et al. 1992). For example an increase of 4% – 10% per year in cardia GC was reported from the United States during 1976 to 1987 (Blot, Devesa et al. 1991). The explanation for this increase has not been clearly stated, however it could be explained partly due to misclassification of cardia cancer or an improvement of sub-sites classification (Ekstrom, Signorello et al. 1999; Corley and Kubo 2004). For example if distal esophagus cancer is classified as cardia cancer, it will increase the rate of cardia cancer. However a concurrent increase of esophageal and cardia cancer which has been reported in some studies argues against this explanation (Thomas, Lade et al. 1996; Devesa, Blot et al. 1998).

By considering different demographic characteristics and trends for cardia versus non-cardia GC, some researchers have hypothesized that these two sub-sites of GC may

have different etiologies (Wang, Antonioli et al. 1986; MacDonald and MacDonald 1987; Blot, Devesa et al. 1991). A number of studies have examined the association of environmental and genetic factors with these sub-sites separately. An inconsistent risk difference was reported for cardia and non-cardia GC in relation to dietary habits, occupation and lifestyle. However, this inconsistency is low for *H. pylori* infection as most of the studies emphasized the carcinogenic effect of *H. pylori* on non-cardia cancer (Martin-de-Argila, Boixeda et al. 1997; Hansen, Melby et al. 1999). This difference was also shown in a combined analysis of 12 case-control studies nested within prospective cohorts, which suggested a relative risk of 5.9 for non-cardia cancer in those infected with *H. pylori*, while they did not find any association with cardia cancer (RR = 1.0; 95% CI: 0.7 – 1.4) (Helicobacter and Cancer Collaborative 2001). However a recent multi-centric case-control study in Japan with 2503 histologically confirmed GC and 6578 controls found an increasing risk of GC in both sub-sites, raising the level of the debate (Kato, Asaka et al. 2004).

2.4 Histopathology

Adenocarcinoma constitutes more than 90% of gastric cancers (Rotterdam 1989; Fuchs and Mayer 1995; Neugut, Hayek et al. 1996). Gastric adenocarcinoma has been histologically classified by different systems, however, the Lauren classification is the most widely used system (Lauren 1965). Accordingly, adenocarcinoma of the stomach is classified in two sub-types of intestinal and diffuse based on histopathological findings. Intestinal types constitute the majority of histology of GC. This proportion has been reported to be 50% – 75% (Boeing, Jedrychowski et al. 1991; Harrison, Zhang et al. 1997; Parsonnet, Friedman et al. 1997; Akre, Ekstrom et al. 2001; Uemura, Okamoto

et al. 2001; Nomura, Hankin et al. 2003). These two sub-types are thought to have different morphological patterns (Lauren 1991).

Intestinal type or well-differentiated carcinoma resembles adenocarcinoma of the colon in its growth pattern and cell types (Lauren 1991). It appears in a glandular pattern, in which nuclei are large and irregular and formed in columnar fashion. Intestinal types are frequently ulcerative, more commonly appearing in the antrum and lesser curvature of the stomach and often preceded by a prolonged precancerous process. It may occur more in older ages and in males (Nomura 1996). It has been shown that the intestinal type tends to predominate in the high-risk geographic regions than those regions with a declining trend (Munoz, Correa et al. 1968; Amorosi, Bianchi et al. 1988; Buiatti, Palli et al. 1991; Henson, Dittus et al. 2004). Correa, in his well known gastric carcinogenesis model (1988) referred to the intestinal type as "epidemic type". In contrast to the intestinal type, diffuse type or poorly differentiated carcinoma of GC has been characterized by small cells scattered either in solitary or in clusters. The glandular pattern is rarely seen in diffuse type (Nomura 1996). It occurs more often at younger ages and develops throughout the stomach including the cardia. While the incidence of intestinal type of carcinoma is declining in most of the world, the incidence of diffuse type remains similar in most populations.

It is thought that these two types may have different patterns with different epidemiology, however, this is not consistent across the body of research. For instance, several large case-control studies did not find any difference between these two types in terms of exposure to the dietary items (Boeing, Jedrychowski et al. 1991; Buiatti, Palli et al. 1991; Ekstrom, Serafini et al. 2000). In addition, a similar pattern was reported for these two factors in relation to lifestyle, SES and family history (Buiatti, Palli et al.

1991). This similarity was also observed in relation to the *H. pylori* infection in which both types had a high prevalence of infection (Hansson, Engstrand et al. 1995; Kikuchi, Crabtree et al. 1999). A large case-control study in Japan with 2503 cases and 6578 controls did not support different epidemiologic features for these two sub-types in relation to the *H. pylori* infection (Kato, Asaka et al. 2004).

2.5 Survival

The overall 5-year survival rate of GC is about 10%. However, 5-year survival in patients who undergo successful curative resection could be over 45%. The best prognosis has been reported from Japan with a 5-year survival rate of more than 60%, which could be due to the screening programs available in Japan (Kampschoer, Fujii et al. 1989; Kubota, Kotoh et al. 2000). However survival depends on several factors including tumor staging, anatomical sub-sites and histopathology of malignancy (Rustgi 2001). In relation to the histopathologic classification, a worse prognosis has been reported for diffuse compared to the intestinal type. In addition, the prognosis varies in relation to the anatomical sub-sites of GC; people with cardia tumors have shown a poorer prognosis compared to the non-cardia GC (Kasper and Harrison 2005).

2.6 Etiology

Gastric cancer has been a topic of epidemiological studies due to its impact on population health. One of the main questions in these studies was whether causal factors are attributed to inheritance or environmental factors. While there has been a debate about the etiology of GC, it is generally accepted that both genetics and environmental factors play a role in the pathogenesis of GC. Some evidence (i.e. polymorphism, blood group and familial aggregation) emphasizes the genetic dimension. On the other hand, the majority of studies have pointed to the etiological role of environmental factors by

focusing on dietary practices, *H. pylori* infection, lifestyle and occupation. The authors of those environmental studies used results of immigrant studies and geographical variation as supportive evidence for their hypotheses. This section will examine the debate on suspected etiological factors but the main focus will be on environmental factors.

2.6.1 Genetic

Genetic factors have been suspected as playing a role in etiology of GC. This role has been investigated in several studies reporting approximately 10% attributable risk to the genetic factors (Lissowska, Groves et al. 1999). However a study of 9.6 million Swedish families reported that a lesser risk of GC (approximately 1%) is attributed to the genetic factor (Czene, Lichtenstein et al. 2002). Several methods have been used to examine the role of genetics in GC including familial aggregation and twin studies and blood typing studies. These methods aim to determine whether heredity plays a role in GC or not.

2.6.1.1 Familial aggregation and twin studies

A familial aggregation has been observed in several studies. It has been found that the risk of GC may increase in first degree relatives approximately 1.5 – 4.0 times (Videbaek and Mosbech 1954; La Vecchia, Negri et al. 1992; Palli, Galli et al. 1994; La Vecchia, Ferraroni et al. 1995; Inoue, Tajima et al. 1998b; Lissowska, Groves et al. 1999; Munoz, Plummer et al. 2001; Yatsuya, Toyoshima et al. 2002; Nomura, Hankin et al. 2003). The level of association may vary based on the degree of proximity of relation, onset age, histopathological classification and anatomical sub-sites.

The proximity of generation is a factor which has been regarded in studies looking at familial aggregation. Approximately 5% – 10% of patients with GC have shown a history of GC in their relatives however, the risk is different between those with a positive history in sibling and parents. The subjects with a positive history in their siblings were shown to be more at the risk than those with history of GC in their parents (Zanghieri, Di Gregorio et al. 1990; Lissowska, Groves et al. 1999). Napoleon Bonaparte who died of GC has been used as an example as his father, grand father, four sisters and a brother also died of GC (Sokoloff 1938).

Histopathology and anatomical sub-sites of GC have shown different patterns in relation to the familial history. It has been reported that diffuse types of GC are more related to genetic factors whereas intestinal types are mostly thought to relate to the environmental factors (Lehtola 1978; Lehtola 1981; Parsonnet, Vandersteen et al. 1991). However, other studies did not find a remarkable difference between these two types of histopathologies in relation to the genetic factors (Zanghieri, Di Gregorio et al. 1990; Palli, Galli et al. 1994). An inconsistent association between anatomical sub-sites of GC and family history has also been noted (Palli, Bianchi et al. 1992; Inoue, Tajima et al. 1998b). These are in agreement with studies which suggested that cardia cancer may have different etiology from other sub-sites of GC (Wang, Antonioli et al. 1986; MacDonald and MacDonald 1987; Blot, Devesa et al. 1991).

Twin study is another method to show the relationship between GC and inheritance. Several studies have shown that the twin of a person with GC has an increased risk of development of the same cancer depending on zygosity: monozygote or dizygote. A study of 44788 twins in the Swedish, Danish and Finish twins' cohort showed an increased risk of GC in the monozygote twin of an afflicted person than dizygote. The

authors reported a higher relative risk of 9.9 and 19.7 for men and women respectively in monozygote compared to 6.6 and 6.2 in dizygote twin pairs. This study showed a concordance of 0.08 and 0.10 for GC in men and women respectively. It means 8% and 10% of an identical twin of a man and women respectively with GC has a probability of development to GC (Lichtenstein, Holm et al. 2000).

It is still unclear whether the association between family history and GC is due to the effect of genetic or environmental factors. Several studies have shown that GC occurs more commonly in first degree relatives and second pair of an affected twin, than in the general population. However, it is thought that this association may also be due to a shared environment (Czene, Lichtenstein et al. 2002). Family members have a shared environment with generally similar exposure to the environmental factors, such as diet, which may increase or decrease the risk of disease. Therefore a familial aggregation is not solely due to genetic exposure.

2.6.1.2 Blood group

Blood grouping has also been used as a determinant of heredity to examine the role of genetics in etiology of GC. A higher risk was reported among people with blood group "A" compared to the other blood groups (Glober, Cantrell et al. 1971; Bjelke 1974; Haenszel, Kurihara et al. 1976; Nomura 1996; Lissowska, Groves et al. 1999). Glober, Cantrell et al. (1971) reported that people with blood group A are 16% – 20% more at risk than the general population. An attributable risk of 7% was estimated for blood group "A" (Lissowska, Groves et al. 1999). This association has also been reported in the precancerous lesions of GC: intestinal metaplasia (OR = 1.28; 95% CI: 1.06 – 1.53) and dysplasia (OR = 1.39; 95% CI: 1.12 – 1.73) (You, Ma et al. 2000). These authors believed that blood group "A" is associated with transition from different precancerous

lesions and it precedes the onset of tumor. Meanwhile a protective role was suggested for blood group "O" (Aird, Bentall et al. 1953). However other studies did not find an association between GC and blood groups. For instance a large scale population-based case-control study of 2639 subjects in Italy reported no association between blood groups and GC (Palli, Galli et al. 1994).

2.6.2 Environmental factors

As discussed, environmental factors are thought to contribute to the risk of GC more than genetics. Several environmental factors have been hypothesized to play a role in etiology of GC. The most important factors isolated are dietary habits, *H. pylori* infection, lifestyle related habits and occupation. Diet is the most investigated factor in the development of chronic diseases as well as GC. *H. pylori* is the second most reported factor, following a report by Warren and Marshall (1983) in relation to its association to the gastroduodenal diseases. Lifestyle factors, particularly smoking and alcohol drinking are the next factors which could possibly play a role in the development to the GC. In relation to lifestyle factors, there are five articles suggesting an association between aerodigestive tract cancers and opium. However, this association has not been examined for GC. Occupation is also inconsistently reported to link to the GC. In addition to the diet, *H. pylori*, lifestyle and occupation, a number of other factors have been suggested to contribute to the GC: Epstein-Barr virus (EBV), body size, exposure to radiation, non-steroid anti-inflammatory drug and H_2 blockers. A model of gastric carcinogenesis was first proposed by Correa, Haenszel et al. (1975) which considered three major factors of nitroso compounds, high salt intake and low consumption of antioxidants such as ascorbic acid and carotenoid. This model was later modified as a new factor (*H. pylori*) was introduced (Correa 1988). According to this

model GC is a multi step and multi factorial disease. In most of cases, the initial stage is a chronic gastritis, followed by atrophy, intestinal metaplasia, dysplasia, and eventually carcinoma. Environmental factors may produce precancerous lesions or induce progression to the malignancy. This multi stage theory of carcinogenesis was also reported by Hakama (1971). He used epidemiologic evidence to show that there are several stages in the genesis of GC.

2.6.2.1 Dietary factors

Dietary factors have long been cited as playing an important role in GC. The idea that cancer occurrence is related to diet dates back to the 17th century when Wiseman explained that cancer might arise from an 'an errour in diet, a great acrimony in the meats and drinks meeting with a fault in the first Goncoction' (digestion) (Wiseman 1676 cited in WCRF and AICR 1997). Since that time many researchers have examined the relationship between different dietary factors and GC using different epidemiological methods. The majority of these studies examined the association of GC with food groups rather than dietary constituents. It is now generally agreed that any suggestion to reduce the risk of chronic diseases as well as cancer should be expressed in terms of food group and drinks. Dietary constituents could be addressed in the next step and policy developed that could allow for more practical recommendations (WCRF and AICR 1997).

A Medline based search was done using "stomach neoplasms" and combination of "diet" and "nutrition" as subject headings. By considering a systematic and comprehensive review and a global perspective which had been published in 1996 and 1997, special attention was paid to the studies published during the last ten years (Kono and Hirohata 1996; WCRF and AICR 1997). Following limitation to the English

language and careful reading of abstracts, 79 relevant articles to dietary factors were selected. Fifty six were case-control studies (Appendix D), of which 25 were population-based, and 23 cohort studies (Appendix E). The highest number of studies were conducted in Asia with 18 case-control and ten cohort studies (published in 11 articles) followed by America with 11 case-control (published in 20 articles) and four cohort studies. The lowest numbers of articles were published on European studies with ten case-control (published in 18 articles) and three cohort studies (published in eight articles). Most of the case-control studies measured relatively distant past rather than current dietary habits (5 -20 years prior to onset of symptom or signs). In this review, associations of GC with diet are examined in six food groups of vegetables and fruits, meat products, cereal and grain, dairy products, coffee and tea and nuts and seeds. Cooking methods and food preservation methods are also considered. In addition, the association of histopathological classification and anatomical sub-sites of GC were examined in relation to these food groups. Specific attention was paid to cohort and population-based case-control studies, although other articles were not omitted. Most of these studies measured frequency of food intake without considering the portion size of consumption.

2.6.2.1.1 Vegetables and fruits

The association of fresh fruits and vegetables with GC is the most investigated dietary factor. During the last ten years, 26 case-control and ten cohort studies have examined this association (Appendix F, G). It has been estimated that consumption of fresh vegetables and fruits may decrease the rate of GC by 50% (Norat and Riboli 2002). While the majority of these studies have shown an inverse association, there is a

controversy in findings about different types of vegetables (raw, green, yellow-orange and allium) and fruits (citrus and non-citrus).

Consumption of vegetables has been reported to play a protective role in development to GC (Kono and Hirohata 1996; WCRF and AICR 1997). As Figure 2.4 shows, the majority of the case-control studies have reported an OR of 0.2 – 0.6. Most of these findings were statistically significant, but not all (Cornee, Pobel et al. 1995; Harrison, Zhang et al. 1997; Zhang, Kurtz et al. 1997; Chen, Ward et al. 2002; Kim, Chang et al. 2002; Lissowska, Gail et al. 2004). This protective role has also been supported by several prospective cohort studies (McCullough, Robertson et al. 2001; Ngoan, Mizoue et al. 2002) but as seen in Figure 2.4 results in cohort studies are not as consistent as in case-control studies. While a protective role has been observed for consumption of raw vegetables, cooked and dried vegetables are not protective (Cornee, Pobel et al. 1995; De Stefani, Correa et al. 2001; Kim, Chang et al. 2002; De Stefani, Correa et al. 2004). It is believed that cooking may destroy the antioxidant components of vegetables which are thought to be protective against GC.

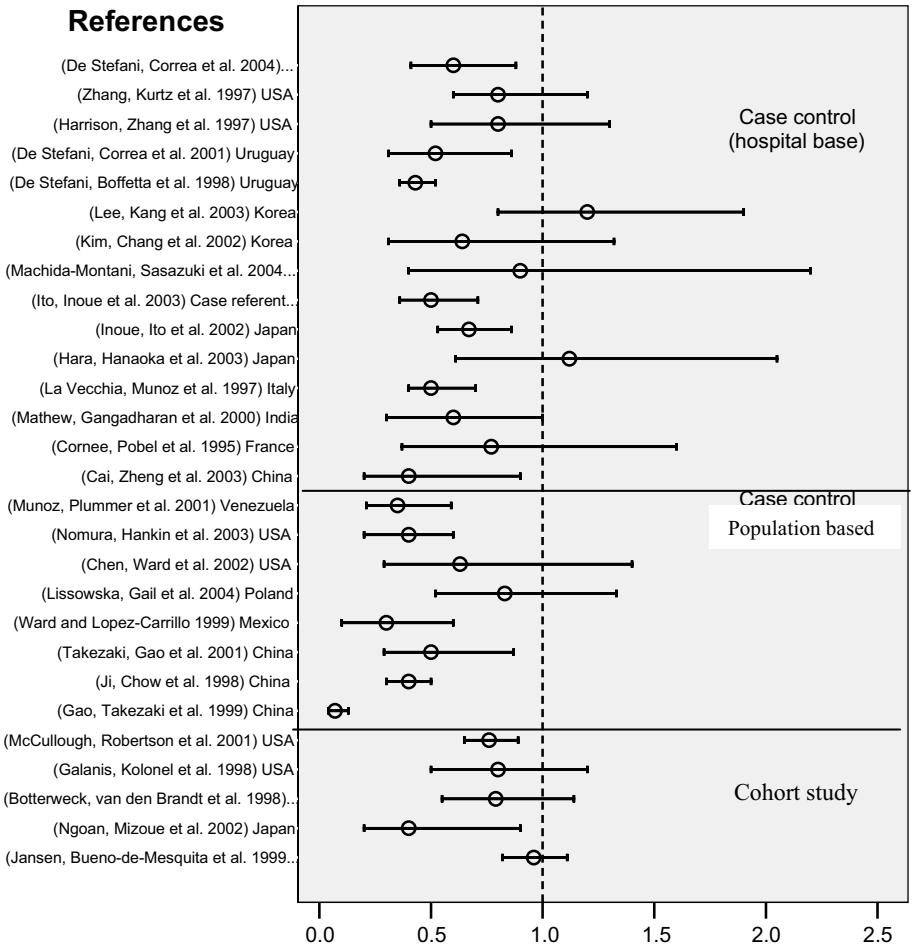


Figure 2. 4: OR (95% CI) of GC in relation to the highest vs. lowest consumption of vegetables in reviewed studies

Associations of GC have been examined for different types of vegetables. There was not much difference between green versus yellow-orange vegetables in case-control studies, however one cohort study showed that yellow vegetables are more protective than green vegetables (Kobayashi, Tsubono et al. 2002). In relation to the allium vegetables (garlic, onion, leeks), nine case-control studies have paid specific attention to allium vegetables, five of which reported an inverse association (Gao, Takezaki et al. 1999; De Stefani, Correa et al. 2001; Munoz, Plummer et al. 2001; Takezaki, Gao et al. 2001; Kim, Chang

et al. 2002). Among allium vegetables garlic has been more consistently reported to protect against development of GC but onion is still debatable. Although a few articles claimed that onions may increase the risk (Takezaki, Gao et al. 2001; Chen, Ward et al. 2002), others have supported a protective role (Gao, Takezaki et al. 1999; Ekstrom, Serafini et al. 2000; De Stefani, Correa et al. 2001; Munoz, Plummer et al. 2001). One study observed that consumption of onion may specifically prevent gastric cardia cancer (Ekstrom, Serafini et al. 2000). Prospective study on allium vegetables and GC is limited to a cohort study which reported an inverse association between onion and GC (Dorant, van den Brandt et al. 1996). It is thought that allium vegetables have an antibacterial effect particularly against *H. pylori* which is believed to be a risk factor.

In addition to vegetables, consumption of fresh fruits has also been considered as a protective factor for GC. An OR of 0.2 – 0.7 has been reported for consumption of fruits in several studies (Figure 2.5). Two prospective studies have also supported this negative association (Galanis, Kolonel et al. 1998; Jansen, Bueno-de-Mesquita et al. 1999). However this association is not consistent in all studies as two population-based case-control studies with sufficient sample size could not find a significant association between consumption of fruit and GC (Ward and Lopez-Carrillo 1999; Terry, Lagergren et al. 2001a). Another case-control study in Venezuela which reported an increasing risk of GC with consumption of fruit, challenged this association (Munoz, Plummer et al. 2001). This study which recruited about 300 cases and 500 controls reported approximately two times increase in the risk of GC with the highest versus lowest frequency of fruit intake (OR = 2.27; 95% CI: 1.40 – 3.70).

Several studies have paid specific attention to citrus fruits. Fruits are rich in vitamins and minerals and other bioactive compounds. Although these items could be different in

quantity and type among different fruits and vegetables, antioxidants such as vitamin C and E and carotenoid are believed to possibly be responsible for this protective role. It is also thought that vitamin C may play a bigger protective role in this association. Therefore several researchers have focused on a specific subgroup of fruits, namely citrus fruits. However there is an inconsistency in the findings as four case-control studies have reported a negative association but they were not statistically significant (Harrison, Zhang et al. 1997; Zhang, Kurtz et al. 1997; Chen, Ward et al. 2002; Kim, Chang et al. 2002). However three cohort studies have shown a protective role for consumption of citrus fruits (Botterweck, van den Brandt et al. 1998; Jansen, Bueno-de-Mesquita et al. 1999; McCullough, Robertson et al. 2001).

Interpretation of data on vegetables and fruits is difficult since they have been investigated in different ways. Some researchers examined it as an overall group of vegetables and fruits but in several studies it has been divided in subgroups of raw, green, yellow-orange and allium vegetables as well as citrus and non-citrus fruits. This inconsistency in the result could be explained by either difference in study design or difference in the micronutrients constituents of this food group. Therefore by considering the possibility of difference in the micronutrients, there is a need to examine the effect of dietary items on GC in different population based on their dietary practices.

Histopathologic classification and anatomical sub-sites were regarded in some of these studies. However a similar association was shown for intestinal and diffuse histopathological classification in most of these studies (Harrison, Zhang et al. 1997; Ward and Lopez-Carrillo 1999; Ekstrom, Serafini et al. 2000). Meanwhile no difference was observed for cardia and non-cardia cancer (Ekstrom, Serafini et al. 2000). This later statement is in agreement with a review by Kono and Hirohata (1996).

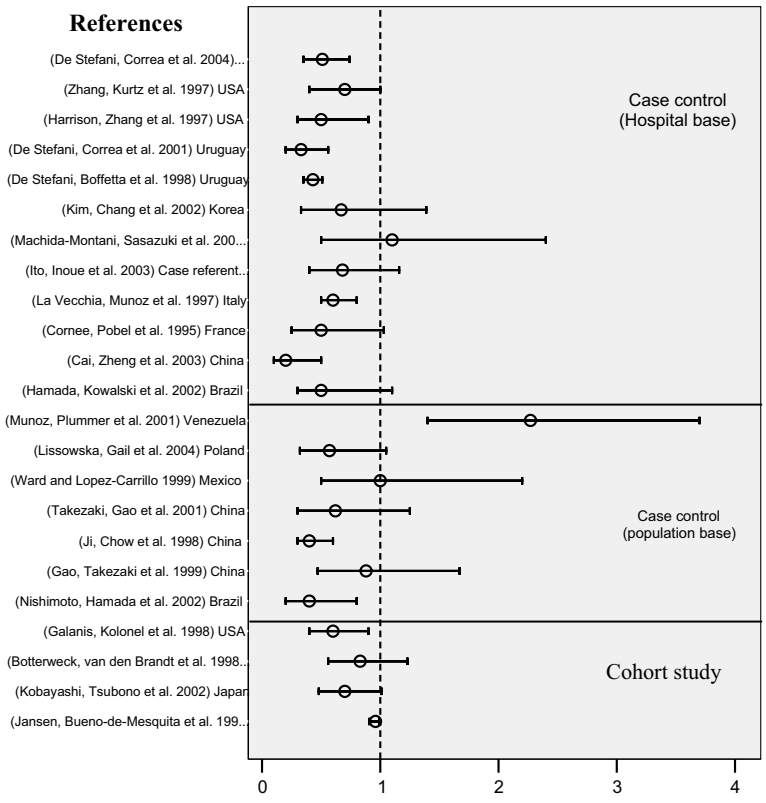


Figure 2. 5: OR (95% CI) of GC in relation to the highest Vs lowest consumption of fruits in reviewed studies

2.6.2.1.2 Meat, poultry, fish and eggs

Meat, poultry, fish and eggs are common sources of protein. They contain various micronutrients and have been examined in many studies for association with GC. Since 1995, 24 case-control and six cohort studies have investigated the role of meat products in GC (Appendices H and I). Ten case-control and two cohort studies have examined the role of meat as an overall food group. The majority of case-control studies reported an increasing risk but some of them were statistically non-significant. The highest risk was shown in a population-based case-control study which reported a three times increase in the risk of GC with consumption of meat (Ward and Lopez-Carrillo 1999). In addition a cohort study which examined the association of GC and meat as an overall

food group reported a non-significant positive association among males (Ngoan, Mizoue et al. 2002). This cohort study followed subjects for approximately ten years and identified 116 deaths from GC. Therefore, a comparatively small sample size in the study may be the reason for non-significance of the association. In addition, an inverse association which was reported from Venezuela, increased debate about the association of meat with GC (Munoz, Plummer et al. 2001). Several researchers have sought an association of GC with meat by classifying it as red and white meat. Red meat has been reported to increase the risk of GC moderately (Ward, Sinha et al. 1997; De Stefani, Ronco et al. 2001; Chen, Ward et al. 2002; Hamada, Kowalski et al. 2002; Kim, Chang et al. 2002; Rao, Ganesh et al. 2002) while an inverse association was reported for white meat, particularly fish (Munoz, Plummer et al. 2001; Ito, Inoue et al. 2003; De Stefani, Correa et al. 2004; Lissowska, Gail et al. 2004). However the findings were generally inconsistent.

Since results are inconclusive about the association of meat, a number of researchers have tried to examine this association for different anatomical sub-sites and histopathologic classifications of GC. A Mexican study observed greater risk among those consuming fresh and processed meat in the intestinal type compared to the diffuse type of GC (Ward and Lopez-Carrillo 1999). However this difference of risk was not observed in all studies (Harrison, Zhang et al. 1997). No difference was found between different histopathologic sub-types in relation to the consumption of fish. Prospective studies did not find any associations, either with red or white meats.

Eggs are another common source of protein. They have been examined as one of suspected foods for GC in nine case-control and one cohort studies. A significant positive association was observed in only two case-control studies (Gao, Takezaki et al.

1999; Nishimoto, Hamada et al. 2002). However, this positive association was not supported by a cohort study (Ngoan, Mizoue et al. 2002) and other case-control studies which examined this association (Cornee, Pobel et al. 1995; Ji, Chow et al. 1998; Mathew, Gangadharan et al. 2000; Munoz, Plummer et al. 2001; Takezaki, Gao et al. 2001; Ito, Inoue et al. 2003; De Stefani, Correa et al. 2004).

2.6.2.1.3 Cereal / grains

Nine case-control and three prospective studies examined association of cereals / grains with GC since 1995 (Harrison, Zhang et al. 1997; Zhang, Kurtz et al. 1997; De Stefani, Boffetta et al. 1999; Jansen, Bueno-de-Mesquita et al. 1999; Mathew, Gangadharan et al. 2000; McCullough, Robertson et al. 2001; Munoz, Plummer et al. 2001; Terry, Lagergren et al. 2001b; Chen, Ward et al. 2002; Kasum, Jacobs et al. 2002; Lissowska, Gail et al. 2004; Machida-Montani, Sasazuki et al. 2004). Two case-control studies reported a modest negative association particularly for consumption of whole grains (Zhang, Kurtz et al. 1997; Chen, Ward et al. 2002). The protective role of whole grains was also shown in two of four prospective studies (McCullough, Robertson et al. 2001; Kasum, Jacobs et al. 2002). Meanwhile, it was reported that refined grains / cereal may increase the risk of GC (De Stefani, Boffetta et al. 1999; Jansen, Bueno-de-Mesquita et al. 1999; Kasum, Jacobs et al. 2002). Cereals contain an average of 70% starch by weight. It also provides different amounts of non-starch polysaccharides/ dietary fibers, protein, vitamin B and E, iron and bioactive compounds (WCRF and AICR1997). Cereal foods may be eaten in whole grain form such as brown rice, whole meal bread and pasta or after refinement such as white bread and pasta made from white flour.

2.6.2.1.4 Dairy products

The association of dairy products and GC has been examined in ten case-control and two cohort studies. No association was shown in these articles with the exception of three case-control studies which reported 2.4 – 3.0 times increase in the risk with dairy product consumption (Ward and Lopez-Carrillo 1999; Mathew, Gangadharan et al. 2000; Munoz, Plummer et al. 2001). The remaining case-control and cohort studies could not find any significant association (Harrison, Zhang et al. 1997; Zhang, Kurtz et al. 1997; Galanis, Kolonel et al. 1998; Huang, Tajima et al. 2000; Chen, Ward et al. 2002; Kim, Chang et al. 2002; Ngoan, Mizoue et al. 2002; Ito, Inoue et al. 2003; De Stefani, Correa et al. 2004). This observed risk could be due to consequence of GC rather than a cause of the disease, because cases may drink more milk to control symptoms of the disease such as dyspepsia.

2.6.2.1.5 Coffee and tea

The association of GC with coffee has been examined in six case-control and two cohort studies (Galanis, Kolonel et al. 1998; Inoue, Tajima et al. 1998a; Chow, Swanson et al. 1999; Mathew, Gangadharan et al. 2000; Munoz, Plummer et al. 2001; Ngoan, Mizoue et al. 2002; Rao, Ganesh et al. 2002; De Stefani, Correa et al. 2004). One case-control study in India reported about a two fold increased risk of GC (Mathew, Gangadharan et al. 2000). However in this study drinking of coffee with milk was associated with GC. It is not clear whether this association was due to consumption of milk or coffee. In addition a cohort study showed an increasing risk of GC by drinking coffee only among males but this study did not find a dose dependency (Galanis, Kolonel et al. 1998). Two case-control studies have stirred the debate about the carcinogenic effects of coffee on

GC by reporting a negative association (Munoz, Plummer et al. 2001; De Stefani, Correa et al. 2004).

Tea has been inconsistently reported to reduce risk of GC in case-control studies (Chow, Swanson et al. 1999; Takezaki, Gao et al. 2001; Rao, Ganesh et al. 2002; De Stefani, Correa et al. 2004), even though some findings were not significant. This inverse association was not observed in cohort studies (Goldbohm, 1996). An argument was made against this negative association in a cohort study which showed an increasing risk of GC with drinking of tea, although this study did not adjust for SES (Kinlen, 1988). It is hypothesized that green tea may be more protective than black tea (Inoue, Tajima et al. 1998a; Chen, Chiou et al. 2000). Both forms are made from the same plants but are prepared in different ways. Black tea is produced by withering, fermentation and roasting of tea leaves but green tea is produced by a short time exposure of fresh tea leaves to a very high temperature, only long enough to deactivate enzyme fermentation. Black tea is consumed more commonly than green tea which is commonly used in Japan, China and Taiwan (WCRF and AICR1997). However, the majority of studies could not find a protective role for green tea in development to GC (Galanis, Kolonel et al. 1998; Nagano, Kono et al. 2001; Tsubono, Nishino et al. 2001; Hoshiyama, Kawaguchi et al. 2002; Koizumi, Tsubono et al. 2003). Only one study which examined drinking of herbal tea reported no association between the drinking herbal tea and GC (Chow, Swanson et al. 1999). The IARC monograph was not conclusive about the causal effect of coffee and tea on GC (WHO and IARC 1991)

Tea and coffee can be habitually consumed very hot and strong. A case-control study reported that drinking of hot tea may increase the risk of GC approximately three times (Dorzhgotov 1989).

2.6.2.1.6 Nuts and seeds

Different types of nuts and seeds are consumed in different countries in different amounts and constituents. They have a very high fat content and are therefore energy dense (WCRF and AICR1997). The association of nuts and seeds has been rarely investigated for GC. It has only been examined in one case-control study as a source of dietary fiber and no association was found between these two factors (Terry, Lagergren et al. 2001b).

2.6.2.1.7 Cooking methods

It is believed that the way in which meat products are cooked may be an important determinant in the development to the GC. Six case-control studies have investigated the association between GC and cooking methods. Three case-control studies reported that broiled, grilled and barbecued food could increase 1.6 – 6.3 times risk of GC (Ward, Sinha et al. 1997; Takezaki, Gao et al. 2001; Kim, Chang et al. 2002). Heterocyclic amines were found in the meats which had been cooked at a high temperature (Skog, Steineck et al. 1995). In contrast boiling and stewing have shown a tendency to decrease the risk. However, this association has not been reported consistently. A population-based case-control study in Sweden reported no association between these two factors (Terry, Lagergren et al. 2003). In addition, this association was not examined in prospective studies**.** Several cooking methods are used for preparation of food. Cooking methods may be different in terms of temperature, direct exposure to the flame and use of fat or oil. Steaming, boiling and stewing methods expose food to heat not exceeding 100° C. Baking, microwaving and roasting method expose food to temperatures up to 200° C but not to direct flame. Roasting usually involves basting the food with oils or fats. Grilling (broiling) and barbecuing use

temperatures up to 400° C and sometimes a direct flame. Pan frying normally uses high surface temperatures (WCRF and AICR 1997). It has been hypothesized that high temperature could produce chemicals such as polycyclic aromatic hydrocarbons and heterocyclic amines while meats are cooked (Adamson 1990; Layton, Bogen et al. 1995). These chemicals are suspected to be carcinogenic.

2.6.2.1.8 Food preservation

Several methods have been utilized for preservation of foods over time. Foods were usually preserved by smoking and salting before the introduction of the refrigerator. Salt is also added to food to improve its taste in addition to its preservative role.

Salt was demonstrated to play a carcinogenic role in the stomach in the Correa model. Since then it has been examined in several epidemiological studies. The majority of case-control studies have reported that excessive consumption of salt or salty foods increases the risk of GC 1.5 and 5.2 times. This association has already been reported in a review to be from 1.5 – 6.7 (Kono and Hirohata 1996). Of 14 case-control studies which have examined the impact of salt and salted food on GC, six reported a positive association (Lee, Park et al. 1995; Ji, Chow et al. 1998; Lopez-Carrillo, Lopez-Cervantes et al. 1999; Munoz, Plummer et al. 2001; Takezaki, Gao et al. 2001; Chen, Qiu et al. 2003). This association has not been found in prospective studies except one study which found a non-significant increase (Tsugane, Sasazuki et al. 2004). Based on the Correa model (1992), salt may cause irritation and mucosal damage in the stomach. Therefore the gastric mucosa will be prone to the other possible risk factors such as *H. pylori* infection. An interaction between salt intake and *H. pylori* infection was observed in a study which reported 14 times increase in the risk among those infected cases with *H. pylori* consuming high amounts of salt (Machida-Montani, Sasazuki et al. 2004).

This might indicate that bacterial infection is a co-factor with salt, which enhances carcinogenesis after the gastric epithelium is damaged (Joossens, Hill et al. 1996). Animal studies showed a synergistic effect of salt and *H. pylori* in gastric carcinogenesis. It was shown that excessive salt intake enhances *H. pylori* colonization in mice and induces gastric carcinogenesis (Fox, Dangler et al. 1999).

Smoking is another method of preservation. It has been noted that smoked foods may have carcinogenic poly cyclic aromatic hydrocarbons at their surface (WCRF and AICR1997). A few studies which have investigated this hypothesis have reported a weak or no association with GC (Ji, Chow et al. 1998; van den Brandt, Botterweck et al. 2003). One of the most important factors hypothesized in the preservation methods is that these methods may increase the formation of N-nitroso compounds. These substances are experimentally shown to be carcinogenic in animals (Sugimura and Fujimura 1967; Sugimura, Tanaka et al. 1971; Eisenbrand, Schmahl et al. 1976). N-nitroso compounds present in preserved meats or can be formed endogenously from nitrites and nitrates (Sen 1972; Wasserman, Fiddler et al. 1972). The carcinogenic role of N-nitroso compounds has been examined by several researchers who reported an inconsistent positive association (Zhang, Deng et al. 1991; La Vecchia, D'Avanzo et al. 1995a; Palli, Saieva et al. 2001). However, this hypothesis has not been supported in some articles. A study by Forman, Al-Dabbagh, et al (1985) observed an inverse association between GC and nitrite and nitrate levels in saliva. However some issues should be considered in the interpretation of this ecological study. Firstly, this study which reported a higher nitrite and nitrate levels in low risk area compared to high risk area of GC had recruited older people from low risk areas. Since an increasing level of salivary nitrate and nitrate was shown with increasing age, including older people in low

risk area (22% aged 55 – 74 years) compared to high risk area (10% aged 55 – 74) may explain this inverse association. Meanwhile, this ecological study discussed that several factors could contribute to the observed inverse relationship and help to mask a real carcinogenic effect from nitrates *in vivo.* These factors include smoking, multistage process of gastric carcinogenesis and level of exposure to anti-carcinogenic factors such as vitamin C. In addition, an increasing risk of GC was not observed in those with exposure to high concentration of nitrate in their workplace (Al-Dabbagh, Forman, et al. 1986). However despite this inconsistency, these compounds were considered as gastric carcinogenic in a comprehensive review (WCRF and AICR 1997).

Vegetables can also be preserved and consumed as pickled vegetables. This has been reported to increase the risk of GC with OR between 1.8 and 3.8 (Lee, Park et al. 1995; Gao, Takezaki et al. 1999; Takezaki, Gao et al. 2001; Cai, Zheng et al. 2003). A prospective study in Japan showed a positive association between pickled vegetables and GC in only men (Tsugane, Sasazuki et al. 2004).

Refrigeration began in early 1900s and gained widespread use in the 1950s in developed countries (Paik, Saborio et al. 2001) and coincided with the decline of GC incidence. It has been hypothesized that preservation of food in the refrigerator may decrease the risk of GC. Several studies have examined this hypothesis, with an OR of 0.2 – 0.7 reported. Almost all five case-control studies which tried to examine this hypothesis reported a protective role for using a refrigerator (Lee, Park et al. 1995; Ekstrom, Serafini et al. 2000; Munoz, Plummer et al. 2001; Kim, Chang et al. 2002; Cai, Zheng et al. 2003). This protective effect has been reported to be higher in those using refrigerator over a long term or during early stage of life particularly in their first and second decades (Lee, Park et al. 1995; Munoz, Plummer et al. 2001; Kim, Chang et al. 2002; Cai, Zheng et al.

2003). In addition, it was observed that those people who were using refrigerators for less than nine years are 4.7 times more at risk compared to those using for more than 20 years (Lee, Park et al. 1995). However, there is no evidence from prospective studies to support this hypothesis. A cohort study in Netherlands did not find an association between risk of GC and either duration of refrigerator use or percentage of freezer users (van den Brandt, Botterweck et al. 2003). The negative association between GC and refrigeration, if there is one, could be explained by (1) year-round availability of fresh fruits and vegetables, (2) shifting of preservation method from traditional methods such as smoking and salting to the refrigeration and (3) improvement of food hygiene and protection from bacterial overgrowth. However, the reasons for decline may vary for developed and developing countries. Since refrigerators have been introduced in developed countries earlier than the start of the declining trend the reason for this decline could be due to improvement of food storage rather than not using salting and smoking as preservation methods. However the temporal correlation between refrigeration and GC in countries like Japan where widespread use of refrigerators started in the 1960s, has not resulted in a GC decrease (Paik, Saborio et al. 2001)

In summary, according to this review, diet is an important determinant factor which should be taken into account in the epidemiology of GC. Fresh fruits and vegetables are believed to possibly protect people against development of GC. Among them a higher protective role was claimed for citrus fruits and allium and raw vegetables. In addition, improvement of preservation methods and refrigeration may decrease the risk by year-round availability of fresh fruits and vegetables as well as decrease in salting and smoking as preservation method. Furthermore a synergistic effect between *H. pylori* and diet, particularly salt, has been shown in some studies. On the other hand, consumption

of red meat and high salt intake have been reported to possibly increase the risk. It has also been reported that cooking of meat at high temperatures may increase the risk. Reports on dairy products, cereal, nuts and seeds and coffee are equivocal. Finally, a consistent difference was not reported either for different histopathologic sub-types (intestinal vs. diffuse) or anatomical sub-sites of GC (cardia vs. non-cardia).

2.6.2.2 Dietary assessment methods

To measure exposure to dietary factors, an accurate instrument is needed. While there is no perfect method to collect accurate dietary information, four main approaches have been utilized in epidemiological studies to assess dietary exposure. These methods are (1) 24-hour recall, (2) three to seven days of actual intake records, (3) diet history and (4) food frequency questionnaire (FFQ) (Block 1982; Willett 1998). Each method has its advantages and disadvantages and could be utilized in different situations. The first two methods collect information on recent dietary habits and are not useful for the measurement of long term exposure which is important in cancer epidemiology. Assessing the average long term diet is preferred to the short term diet as carcinogenesis occurs after long term exposure. It is possible to miss accurate intake measurement by looking to long term exposure due to recall bias. However it is preferable to replace precise intake measurement obtainable on recent days with more crude information relating to an extended period of time. Diet history which attempts to elicit long term exposure needs an extensive interview by a trained nutritionist. FFQ is the most often used tool in the dietary assessment and aims to collect information over the long term exposure (Block 1982; Willett 1998).

FFQ yields information on the frequency of intake with an optional section on the portion size. It includes a list of food items which are based on the study hypothesis. It

can include either a long list to collect information about all dietary habits or a short list in which specific attention is paid to the most informative items on the basis of prior information. A short questionnaire has advantages in terms of less cost and administration time which makes it less burdensome for participants to answer. Furthermore, data processing time is reduced in comparison to the long version of questionnaire. A comparable validity has been reported for short FFQ compared to the longer form (Ling, Horwath et al. 1998). It is believed that subjects are better able to describe frequency of use for more generalized categories than for specific foods.

2.6.3 Helicobacter pylori

H. pylori is a gram-negative spiral and flagellated bacterium which afflicts approximately half of the world's population. However, prevalence varies greatly among different geographic areas with higher occurrences in less-developed countries. *H. pylori* was primarily reported in the human gastric mucosa to cause gastric disease by Warren and Marshall (1983). Following this report, many researchers have hypothesized that *H. pylori* may be responsible for gastric malignancies. In this section, after a general overview on the history and epidemiology of *H. pylori*, its role in etiology of GC will be examined.

2.6.3.1 History of Helicobacter Pylori

The history of *H. pylori* is clearly discussed by Rathbone and Heatley (1992) and Marshall (2002) as going back to 1892 when Bizzozero showed colonization of spiral organisms in the stomach of a dog (Bizzozero 1892). His work was followed by Salmon (1896) who found similar organisms in the gastric mucosa of cats and rats but he could not find such an organism in the human stomach. Lucet's study (1910) confirmed the presence of bacteria in the stomach of a dog. In humans, gastric spirochetes were

demonstrated in necrotic materials on the surface of ulcerating carcinomas and in gastric secretions (Krienitz 1906; Luger 1917). A human gastric spiral organism was reported in a histological study by Doenges (1939) in which he reported that 43% of gastric autopsies were positive. This rate was 37.1% in another study (Freedberg and Barron 1940). This bacterium was also indirectly shown to exist in a human stomach by the presence of urease activity in the stomach (Fitzgerald and Murphy 1950) and was explained as being due to the presence of bacteria by Lieber and Lefevre (1957). This bacteria was later demonstrated to be in the epithelial cells of gastric ulcer patients (Steer and Colin-Jones 1975). Finally, Warren and Marshall (1983) reported that the majority of endoscopic specimens from patients with chronic gastritis and peptic ulcer were colonized with curved campylobacter like organisms. It was later identified by Goodwin, Armstrong et al. (1989) as *H. pylori* since the biochemical and ultra-structural characteristics of this bacteria were different from campylobacter.

2.6.3.2 Epidemiology

H. pylori infection occurs worldwide, but the prevalence varies between more and less developed regions. It infects about one-third of the adults in the more developed countries whereas this rate is about two-thirds in the less developed countries (Pounder and Ng 1995). In developed countries, such as the United States and the United Kingdom, the prevalence of infection with *H. pylori* ranges from 20% to 60%. Similar rates were reported in a multi-centric study from 11 developed countries (Megraud 1992). The prevalence of *H. pylori* infection in developed countries has declined which could be explained by improvement of the standard of living in early childhood (Duggan 2002). Infection rate is higher in developing countries such as Thailand, India, Bangladesh, Saudi Arabia and Iran with prevalence rates of 50% to 90% (Megraud,

Brassens-Rabbe et al. 1989; Al-Moagel, Evans et al. 1990; Perez-Perez, Taylor et al. 1990; Massarrat, Saberi-Firoozi et al. 1995) as well as Africa with a prevalence of 70% – 85% (Megraud, Brassens-Rabbe et al. 1989; Sullivan, Thomas et al. 1990; Holcombe, Omotara et al. 1992; Sitas, Sathar et al. 1997). While a higher risk of GC has been reported in areas with high infection rate, the risk is low in Africa where a high prevalence of infection was shown and named the "African enigma" (Holcombe 1992). However, this phenomenon has been challenged by reporting comparable rates of GC in Kenya to the Eastern European rates (McFarlane, Forman et al. 2001). A review explained this phenomenon as due to limited access to health care and a relatively short life expectancy (Agha and Graham 2005).

H. pylori infection is very common in most parts of Asia as well as Iran. Several studies indicated that Asian countries have a high prevalence of *H. pylori* infection as well as gastroduodenal diseases. For example a geographic association was reported between *H. pylori* and GC mortality among Chinese living in rural China by Forman, Sitas et al. (1990). In addition, a comparative seroepidemiologic study in two Iranian provinces of Ardabil and Yazd with high and low rate of GC, a higher prevalence of *H. pylori* infection (47.5%) was reported in Ardabil among people aged less than 20 years, whereas this rate was 30.6% in Yazd population at the same age (Mikaeli, Malekzadeh et al. 2000).

As shown in Figure 2.6 the pattern of infection with *H. pylori* seems to be different between developing and developed countries. In developing countries it starts from an early age (mostly acquired in the first ten years of life) and remains constant during adulthood. In contrast, developed countries have a low prevalence in childhood with a slight increase with age. The prevalence of infection in developing countries increases

to the maximum rate 75% – 90% during the first 10 – 20 years of age and continues for the rest of life. In developed countries infection starts at a lower age with a gradually increasing trend taking about 50 – 60 year to reach the maximum rate which is about 50% (Marshall 1994). The observed difference could be partly explained by cohort effect. It means prevalence of infection and its trend along the time is related to several factors such as environment and society changes. However it is difficult to measure the magnitude of each factor (Banatvala, Mayo, et al. 1993). Both genders can be afflicted at similar rates and once a subject is infected the bacterium persists for life unless treated (Pounder and Ng 1995).

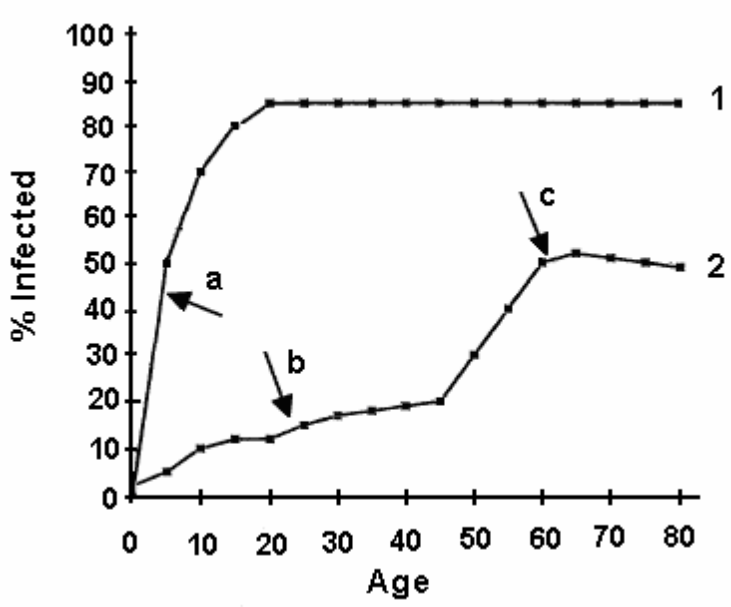


Figure 2. 6: Epidemiology of *H. pylori* infection in (1) underdeveloped and (2) western countries
(a) rapid acquisition in childhood , (b) low incidence of new infection in young people, (c) "carrier state" from childhood infection (before 1945) modified from (Marshall 1994)

2.6.3.3 Transmission

Humans are the major reservoir for *H. pylori*. While the main transmission route is not fully understood, person to person has been referred to as a dominant method of transmission. Person to person transmission may occur within the family (Miyaji,

Azuma et al. 2000; Wizla-Derambure, Michaud et al. 2001; Mosane, Malope et al. 2004) or extra familial in communities such as nursery school or kindergarten (Kurosawa, Kikuchi et al. 2000). These results shows that close person to person contacts, mainly in early age and within the family, or contact with other children, may play a role in transmission. In addition to the above mentioned routes, some other potential routes of transmission have been shown in different studies such as waterborne (Klein, Graham et al. 1991) and nosocomial transmission among those undergoing endoscopy (Langenberg, Rauws et al. 1990). Furthermore Mitchell, Lee et al. (1989) found that gastroenterologists are at higher risk of infection than age-matched blood donors and general practitioners. This could be due to close contact with patients with GI diseases.

2.6.3.4 H. pylori and GC

After infection, *H. pylori* colonizes in the stomach and leads to a range of clinical and sub-clinical symptoms and signs. These symptoms and signs vary from person to person depending on host factors and bacterial strains. *H. pylori* may cause inflammatory lesions in the gastric mucosa which may develop into GC a long time after infection. It is accepted that a large number of people with exposure to *H. pylori* may develop inflammatory changes such as chronic active gastritis and possibly intestinal metaplasia (Guarner, Mohar et al. 1993; Kuipers, Uyterlinde et al. 1995; Sakaki, Momma et al. 1995; Barreto-Zuniga, Maruyama et al. 1997; Watanabe, Kurata et al. 1997).

While the majority of infected people develop to precursor of GC, only a small proportion of them progress to GC. It is thought that *H. pylori* increases the risk of GC through pre-malignant lesions such as chronic active gastritis and intestinal metaplasia (Sakaki, Momma et al. 1995; Palli 1997; Watanabe, Kurata et al. 1997). It is also

hypothesized that *H. pylori* may be necessary for progression to gastritis and intestinal metaplasia but needs some other environmental factors such as diet and lifestyle to develop GC.

The association of GC with *H. pylori* has been investigated by many researchers using different epidemiological methods including ecological, retrospective and prospective studies. Ecological studies have provided equivocal results. A positive correlation was shown in several ecological studies (Correa, Fox et al. 1990; Kneller, Guo et al. 1992; The EUROGAST STUDY GROUP 1993). A large ecological study examined the geographic association between *H. pylori* infection and GC in 46 rural counties of China in which 40% correlation was reported between these two factors (Forman, Sitas et al. 1990). This association has also been reported in several case-control and prospective studies (Forman, Newell et al. 1991; Nomura, Stemmermann et al. 1991; Parsonnet, Friedman et al. 1991; Talley, Zinsmeister et al. 1991; Hansson, Engstrand et al. 1993; Asaka, Kimura et al. 1994; Hu, Mitchell et al. 1994; Fukuda, Saito et al. 1995; Yamaoka, Kodama et al. 1999; Chang, Kim et al. 2001; Wang, Wang et al. 2002). These studies have reported an increasing risk of 1.6 – 6.0 among *H. pylori* infected. Several meta-analyses have also provided evidence to support this association (Forman, Webb et al. 1994; Huang, Sridhar et al. 1998; Danesh 1999; Eslick, Lim et al. 1999; Helicobacter and Cancer Collaborative 2001; Xue, Xu et al. 2001). Meanwhile, The International Agency for Research on Cancer (IARC) as part of the World Health Organization (WHO) classified *H. pylori* as a group I carcinogen to humans (IARC 1994). This group of classifications is normally used when there is sufficient evidence of carcinogenicity in humans.

While several studies have found an increasing risk of GC with *H. pylori* infection, there are other studies which did not find an association between these two factors. An Italian study which compared two high-risk areas of GC with two low-risk areas showed little geographical variation in *H. pylori* (Palli, Decarli et al. 1993). Another study in France in which seven regions were compared reported no correlation between *H. pylori* and GC (Broutet, Sarasqueta et al. 1999). It is also believed that the association at the group level does not necessarily represent an existing association at the individual level. This is a major problem in ecological studies and has been termed as "Ecologic Fallacy" (Selvin 1958 cited in Morgenstern 1998). In addition to the inconsistency in the results of ecological studies, studies examining individual level have also not been conclusive. A wide magnitude of associations have been reported in different studies from negative or no association (Archimandritis, Bitsikas et al. 1993; Muszynski, Dzierzanowska et al. 1995; Kim, Cho et al. 1997; Fujioka, Fahey et al. 2001) to a highly significant association. A nested case-control study in China did not find an association between *H. pylori* and GC (Webb, Yu et al. 1996). Several hypotheses have been proposed to explain variation in the results including difference in anatomical sub-sites and histopathology of GC, variation in the virulence of bacteria as well as effect modification by other environmental factors. In addition, diagnostic methods are very important factors which may alter results. These techniques vary in terms of accuracy.

While literature on the association of GC with *H. pylori* is inconclusive, there is much debate on the association of *H. pylori* with different anatomical sub-sites and histopathology of GC. In relation to anatomical sub-sites, a higher risk of non-cardia cancer was reported in *H. pylori* infected people (Martin-de-Argila, Boixeda et al. 1997;

Hansen, Melby et al. 1999; Limburg, Qiao et al. 2001). A meta-analysis has also suggested an exclusive association with non-cardia cancer. This study reported a relative risk of 5.9 for non-cardia cancer among *H. pylori* infected people while there was no association with cardia cancer (Helicobacter and Cancer Collaborative 2001). This difference was also shown in a meta-analysis for cardia versus non-cardia cancer (1.23 vs. 3.08; p = 0.003) respectively by Huang, Sridhar et al. (1998). However, some of the articles did not report heterogeneity between sub-sites of GC in relation to the *H. pylori* infection (Archimandritis, Bitsikas et al. 1993; Lin, Wang et al. 1994; Menegatti, Vaira et al. 1995). On the other hand a nested case-control study found a negative association between *H. pylori* infection and non-cardia GC (OR = 0.4; 95% CI, 0.20 – 0.77) (Hansen, Melby et al. 1999). Therefore it is expected to find a higher proportion of non-cardia GC in those geographic areas with high prevalence of *H. pylori* infection. The situation of Ardabil province differs from this statement as there is a high prevalence of both *H. pylori* infection and cardia cancer (Mikaeli, Malekzadeh et al. 2000; Yazdanbod, Arshi et al. 2001).

It has also been reported that intestinal type of GC tended to occur in *H. pylori* infected people more than diffuse type particularly in non-cardia (Parsonnet, Vandersteen et al. 1991; Buruk, Berberoglu et al. 1993; Endo, Ohkusa et al. 1995; Martin-de-Argila, Boixeda et al. 1997; Wu, Chen et al. 1997). A meta-analysis also showed a slight difference between these two sub-types (OR 1.14; 95% CI: 1.05 – 1.25) in favor of intestinal type of GC (Eslick, Lim et al. 1999), however the majority of studies showed that both intestinal and diffuse sub-types of GC are equally associated with *H. pylori* infection (Hu, Mitchell et al. 1994; Kato, Saito et al. 1994; Lin, Wang et al. 1994) which is in accordance with another meta-analysis (Huang, Sridhar et al. 1998).

The African enigma and other reports on the imbalance between prevalence of *H. pylori* and GC make investigators suspicious enough to study whether there are other sub-types or strains of *H. pylori* which are responsible for this association. These investigators have found several strains of *H. pylori*, of which cagA and vacA are the most reported strains. They have sought the association between these strains and gastroduodenal diseases in which conflicting results were found in different geographic areas. Some of the published articles have reported an increased risk of GC among cagA positive patients (Blaser, Perez-Perez et al. 1995; Enroth, Kraaz et al. 2000; Miehlke, Kirsch et al. 2000) particularly in non-cardia GC (Queiroz, Mendes et al. 1998; Huang, Zheng et al. 2003; Wu, Crabtree et al. 2003). It has been even suggested using seropositivity tests of cagA and vacA to identify people at high risk of developing GC (Grimley, Holder et al. 1999; Huang, Zheng et al. 2003). However, some issues should be taken into account in interpreting their results. Firstly, it was shown that despite the high prevalence of a virulent strain of *H. pylori* in people from sub-Saharan African who are mostly positive for cagA and vacA, there was a low prevalence of gastroduodenal diseases as well as GC (Segal, Ally et al. 2001). This is in agreement with some other reports which showed a high risk of cagA regardless of GC prevalence in their community (Miehlke, Go et al. 1998; Bernstein, McKeown et al. 1999). A current study in Iran showed that the virulent type of *H. pylori* constitutes the majority of infections in both high and low incidence areas (Siavoshi, Malekzadeh et al. 2004). These inconsistent findings along with those other studies which have not found any association between cagA and GC, argue against this association. These researchers believe that the cagA gene is not a more important factor than overall *H. pylori* infection (Mitchell, Hazell et al. 1996; Matsukura, Onda et al. 1997; Miehlke, Go et al. 1998; Kikuchi, Crabtree et al. 1999). The Eurogast study showed that variation in the

seroprevalence of cagA did not explain geographic variation in GC rates any better than *H. pylori* alone (Webb, Crabtree et al. 1999).

Interaction between *H. pylori* and other environmental factors is another conflicting area of discussion. Some of the environmental factors have been reported to have either a synergic or antagonistic interaction with *H. pylori*. A synergistic interaction was reported between *H. pylori* and smoking (Siman, Forsgren et al. 2001; Brenner, Arndt et al. 2002) and diet, especially salt (Lee, Kang et al. 2003; Machida-Montani, Sasazuki et al. 2004). On the other hand, consumption of vitamin C has been hypothesized to play a protective role among *H. pylori* infected people (Zhang, Wakisaka et al. 1997). It is believed that geographic differences in the rate of GC and *H. pylori* infection may be due to different lifestyle and dietary habits (Lunet and Barros 2003).

Finally, further questions arise from the lack of conclusive findings from randomized controlled trials. If *H. pylori* infection increases the risk of GC, its eradication should reduce development of GC. However reduction of GC risk has not been observed in all studies in which *H. pylori* was eradicated. For instance a population-based prospective, randomized, placebo-controlled study in a high risk area of China reported no benefit of *H. pylori* eradication in prevention of GC (Wong, Lam et al. 2004). However, timing of eradication is an important issue which could alter results of *H. pylori* eradication trial. The older the group recruited, the less likely treatment prevents development to GC (Feldman, 2001).

Although causal mechanism/s for *H. pylori* have not been well established, several possible mechanisms have been suggested. It has been shown that infection with *H. pylori* causes an inflammation in the gastric mucosal layer. Chronic inflammation can

lead to the production of chemical intermediates, such as nitric oxide and superoxide which can form reactive oxygen and nitrosamines which are believed to be carcinogenic (Marshall 1994; Wink, Vodovotz et al. 1998). Free oxygen metabolites could damage DNA and play a mutagenic role (Correa 1992). In addition, *H. pylori* infection causes atrophic gastritis which results in reduced acid secretion in the stomach. An overgrowth of bacteria may occur due to hypoacidity which subsequently transforms nitrate to nitrite and increase formation of carcinogenic nitrosamine (Sobala, Pignatelli et al. 1991).

In summary, infection with *H. pylori* is strongly associated with an increased risk of precancerous lesions in the stomach. However, most of the infected people with *H. pylori* with precancerous conditions will never develop to GC. More than 50% of world's population is infected with *H. pylori*, while 10% – 20% develop to gastroduodenal diseases and less than 1% of patients with gastroduodenal diseases progress to GC. This means there is not a simple and direct causative association between these two factors. Most studies and meta-analyses have shown a positive association between GC and *H. pylori*, whereas some researchers do not accept a direct and significant relationship between them (Archimandritis, Bitsikas et al. 1993; Muszynski, Dzierzanowska et al. 1995; Kim, Cho et al. 1997; Broutet, Sarasqueta et al. 1999; Fujioka, Fahey et al. 2001). This group argues that gastric carcinogenesis is a multi step and multi factorial process, therefore onset of GC could not be related to one single factor but rather to a series of different variables. In addition to this inconsistency about a general association there are some other controversies among those reporting a positive association. These inconsistencies are about cardia versus non-cardia, intestinal versus diffuse and developed versus developing countries as well as virulence of

bacteria. Therefore, because of such inconsistencies, the “African enigma”, those studies reporting no or inverse association and inconclusiveness of reports on benefits of eradication therapy, this association needs to be re-examined to address the question of what role *H. pylori* plays in GC especially in areas of high cardia cancer rate such as Ardabil province. Therefore despite a large number of studies, *H. pylori* remains an important world wide health problem which needs to be further studied.

2.6.3.5 Assessment methods

Several laboratory tests have been introduced to examine whether someone is infected by *H. pylori* or not. These methods are divided into two categories of invasive and non-invasive techniques. The invasive method refers to those tests requiring endoscopy and biopsy [(histology, culture and rapid urease test (RUT)]. On the other hand, the non-invasive method refers to those without invasive procedures including serological tests, urea breath test (UBT) and detection of *H. pylori* antigen in a stool specimen. These methods have different degrees of accuracy which need to be considered. Choosing between them is not easy, and several issues need to be considered such as local availability and the clinical circumstances of patients, as well as cost.

Histology is the most sensitive test which is preferred for patients who require endoscopy. In this method, biopsied specimens can be investigated for both cell abnormality and *H. pylori* infection. Currently it is performed either separately, or in combination with other diagnostic tests, as a second gold standard after culture. Sensitivity and specificity of over 95% have been reported for histology (Vaira, Gatta et al. 2002). However, sensitivity can be improved by getting at least two specimens, one from the body and the other from the antrum of the stomach (Dixon, Genta et al. 1996). Culture is a definitive marker of infection in all infectious diseases. However, culture is

not a common method for diagnosis of *H. pylori* and is only performed in specific conditions. It has been recommended to use this method when there is a failure of previous treatment, allergy to the antibiotic and antibiotic resistance which needs to determine antibiotic sensitivity (Marshall 1994). Although this test is the gold standard for *H. pylori* infection, it is not technically available everywhere. RUT is currently used in combination with histology. This test is based on the urease activity of *H. pylori*. It is a rapid and cheap test compared to the other invasive methods and results can be seen while the patient is in the clinic. A high accuracy has been reported for this test (sensitivity 93% – 98% and specificity 98%), however, accuracy of test depends on size and location of the biopsy (Midolo and Marshall 2000).

Serological testing is one of the non-invasive diagnostic methods. The mechanism of this test is based on the detection of specific anti-*H. pylori* either IgG or IgA antibodies in the patient's serum. Host cells produce an immunological response to the *H. pylori* infection and produce IgG and IgA. Presence of both antibodies in serum and saliva has been used for the serological diagnosis of infection (Hirschl, Brandstatter et al. 1993; Marshall 1994). A prospective study stressed the value of IgA antibody (Aromaa, Kosunen et al. 1996). Although both antibody levels fall after eradication, IgA falls faster than IgG. IgG is more sensitive than IgA and long-lasting in the blood even after treatment (Hirschl, Brandstatter et al. 1993). Therefore it demonstrates a history of chronic infection which is preferred for retrospective studies. It has also been shown that a positive anti *H. pylori* IgG antibody is a sensitive test in diagnosing chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) (Sitas, Smallwood et al. 1993). CAG was shown to be a major pathological precursor of GC (Correa and Ruiz 1989; Sitas and Forman 1989). Serological testing is simple to perform, non-invasive and

reasonably cheap but a positive result is not always due to acute infection. Since IgG antibodies persist in the blood circulation for a long period of time after treatment, a positive result should be regarded as positive history of exposure rather than an acute infection (Vaira, Gatta et al. 2002). Antibodies can be detected by different types of serological assays including hemaglutination, complement fixation test (CFT) and bacterial agglutination and ELISA (Marshall, McGechie et al. 1984; Kaldor, Tee et al. 1986). Several commercially available serological kits have been used as an alternative to endoscopy for the diagnosis of *H. pylori* infection but they vary widely in their accuracy. It is recommended that ELISA kits be validated locally, because the antigenic properties of local bacterial strains may differ to those used in the tests (Sacket, Haynes et al. 1991; Lam and Talley 1998; Szeto, Lee et al. 2001; Obata, Kikuchi et al. 2003). UBT measures the activity of *H. pylori* urease enzyme. It is highly specific (98%) and very sensitive (95%) and can indicate cure rate of *H. pylori* infection four weeks after antibiotic therapy (Marshall 1994).

There are some other methods for detecting *H. pylori* infection, however most of them are only performed in research and are not technically available everywhere. These methods include PCR (polymerase chain reaction), near-patient tests and other immunological tests of saliva and urine and stool antigen, as well as immunoblast which is used to detect an immunological memory of the infection long after the bacterium has disappeared (Enroth, Kraaz et al. 2002). Near patient tests were developed to be used in the management of dyspeptic people, particularly when laboratory based tests are not available. Its accuracy has been compared in several studies which found different validity (Duggan, Logan et al. 1996). However it is not yet recommended to be used in primary care because of its poorer accuracy (Duggan, Elliott et al. 1999). Similarly a

Chinese study did not find it as a sensitive test in a general practice setting for the test-and-treat approach (Wong, Wong et al. 2000). It is believed that the estimation of risk for the association between *H. pylori* and GC risk is to some extent related to the diagnostic method used to detect *H. pylori* infection. It has also been reported that culture and immunohistochemistry may reveal generally a weaker and statistically non-significant association between *H. pylori* infection and GC compared to the serological tests (Enroth, Kraaz et al. 2002). Therefore a serological test is the most appropriate non-invasive test for measurement of exposure to the *H. pylori* in the epidemiological study of GC.

2.6.4 Lifestyles

Lifestyle related habits vary between nations and populations. These habits could expose people to some substances which may play a carcinogenic role. Among lifestyle factors tobacco and alcohol drinking are the most widely investigated factors, as well as snuff dipping and tobacco chewing which were subjects of interest in a few studies in epidemiology of GC.

2.6.4.1 Tobacco

Tobacco is widely used in the world in its various types and different methods. At the beginning of the 21st century about one-third of adults in the world, including increasing numbers of women, used tobacco. Almost one billion men and 250 million women in the world smoke. Smoking is more common in men living in less-developed than more developed countries with prevalence of 50% and 35% respectively, while this rate is reversed for females with a higher rate of smoking in more-developed compared to less-developed countries with prevalences of 22% and 9% respectively (Mackay, Eriksen et al. 2002). Tobacco smoking has decreased by about 1% annually in more-developed

countries, whereas it is increasing 1% – 2% in the less-developed countries. This means that the smoking burden in the less-developed countries is higher than in more-developed countries. Therefore smoke related cancers will be an increasingly major health problem in developing countries. It was reported that 15.3% of Iranian adults smoke. The smoking rate in men is about ten times more than women, 27.2% and 3.4% respectively (Mackay, Eriksen et al. 2002). A recent study in Ardabil has reported a general smoking rate of about 30% (Sadjadi, Malekzadeh et al. 2003).

Several studies examined the association of GC and smoking before 1986 when IARC evaluated them (IARC 1986). IARC Working Group on the Evaluation of Carcinogenic Risks to Humans did not conclude that the associations noted in some studies were causal. Following this monograph several other studies reported an association between GC and smoking. IARC evaluated new evidence in 2002 and updated its previous monographs (WHO and IARC 2004). In current monographs, tobacco smoking was classified as a group I carcinogen which means tobacco smoking and tobacco smoke are carcinogenic to humans. It has been estimated in a meta-analysis that the proportion of GC attributable to smoking was 11% and 4% among men and women in developing countries respectively while this rate was 17% and 11% among men and women in developed countries (Tredaniel, Boffetta et al. 1997). The risk of GC was reported to be 50% – 60% higher, on average, in smokers than in non-smokers (RR = 1.5 –1.6). This association was higher in “current smoker” than “never smoker” in the evaluation of 44 case-control and 27 cohort studies (Vineis, Alavanja et al. 2004).

Almost all of the studies published after the IARC monograph (2004) have reported a positive association between smoking and GC (Sasazuki, Sasaki et al. 2002; Engel, Chow et al. 2003; Gonzalez, Pera et al. 2003; Minami and Tateno 2003; Koizumi,

Tsubono et al. 2004; Wu, Chen et al. 2004). It is shown that those classified as "ever smokers" are approximately twice at risk of the development of GC compared to those who never smoked. In addition, the category of "current smokers" were at higher risk than "ex-smokers" (Sasazuki, Sasaki et al. 2002; Koizumi, Tsubono et al. 2004). However, a Japanese cohort study which reported a significant increase in the risk of GC among "ever smokers" (RR = 2.01; 95% CI 1.1 – 3.7), failed to show a dose dependency (Sasazuki, Sasaki et al. 2002). Another case-control study in Japan also found a weak association only in males (OR = 1.31; 95% CI: 1.02 – 1.67) (Minami and Tateno 2003). In addition, a prospective study in ten European countries with 521,468 participants did not show a significant trend in relation to the number of cigarettes smoked (Gonzalez, Pera et al. 2003). Finally, it is thought that deep smoking may increase risk compared to the those who do not swallow smoke (Chen, Chiou et al. 2000). While it has been claimed that using a filter in the cigarette can reduce exposure to the potential chemical in cigarette, it has been shown to have little effect (Chow, Swanson et al. 1999).

While there is a lack of evidence in terms of dose dependency, it has been suggested that smoking may have a different effect in the GC of different sub-sites and histopathologies. A large case-control study in Canada reported about twice higher risk of GC in cardia with smoking compared to the distal GC (Mao, Hu et al. 2002). This study has shown a dose dependency for smoking in cardia cancer, while there was no consistent dose dependency for distal cancer. Several other studies have also shown a sub-site association in favor of cardia cancer (Gammon, Schoenberg et al. 1997; Wu, Wan et al. 2001). This difference was not observed in a recent cohort study in Japan (Koizumi, Tsubono et al. 2004). There are also several other studies in which no

difference was observed between two sub-sites (Ye, Ekstrom et al. 1999; Okabayashi, Gotoda et al. 2000). A similar inconsistency has also been shown for histopathologic classification (Ye, Ekstrom et al. 1999). The lack of evidence in dose dependency and debate on the difference between sub-sites and histopathologies could be due to effect modification with alcohol drinking and *H. pylori* infection (De Stefani, Boffetta et al. 1998a; Chen, Chiou et al. 2000; Zaridze, Borisova et al. 2000; Siman, Forsgren et al. 2001).

The mechanism by which tobacco smoke causes GC is not fully understood. Cigarette smoke contains a complex mixture of over 4000 chemicals, about 60 of which are known or suspected to be carcinogenic. Some possible mechanisms have been hypothesized. Tobacco smoke consists of several chemicals which may damage the gastric mucosa layer by direct contact or indirectly through the blood stream. N- nitroso compounds are well known carcinogens which have been reported in cigarette smoke (Tricker and Preussmann 1992). It was also observed that smoking-related DNA adducts can be seen in smokers more than non-smokers because of binding of tobacco carcinogens to the gastric mucosal DNA (Dyke, Craven et al. 1992) . In addition, tobacco smoking may increase gastric acidity and pepsin which could damage the gastric mucosal layer (Lanas and Hirschowitz 1992; Endoh and Leung 1994).

2.6.4.2 Tobacco habits other than smoking

Tobacco could be consumed by methods other than smoking: snuff, chewing and nass. Snuff comprises powdered tobacco and a variety of additives and can be consumed by inhalation or dipping. In the inhalation this powder is taken in nasally but in the dipping, snuff is placed between cheek and gum and is sucked. Although snuff has been reported to increase the risk of cancer of the nasal cavity, sinus, tongue and gum and pharynx

(Winn, Blot et al. 1981; Elbeshir, Abeen et al. 1989; Sankaranarayanan, Duffy et al. 1989), no association was shown with GC (Ye, Ekstrom et al. 1999; Lagergren, Bergstrom et al. 2000). Tobacco can also be chewed as an alternative method to smoking. However an association was not observed between GC and tobacco chewing (Gajalakshmi and Shanta 1996; Mathew, Gangadharan et al. 2000; Mao, Hu et al. 2002; Rao, Ganesh et al. 2002). Tobacco may also be taken orally in a mixture with other substances such as ash, lime and cotton seed oil. This composition, which is common in central Asia, northern Iran and part of Pakistan and Afghanistan is called nass. It has been reported to possibly play a causative role in oral leukoplakia and, most probably, oral and esophageal cancer (Zaridze, Blettner et al. 1986; Evstifeeva and Zaridze 1992) but its role has not been examined for GC. The carcinogenic role of these habits were evaluated by IARC but no association was concluded (IARC 1985).

2.6.4.3 Alcohol

Alcohol consumption has been reported in nearly all societies. However a declining rate was shown in most of the more-developed countries, whereas it is rising in many of the less-developed countries and the countries of Central and Eastern Europe. Based on a report by WHO (2001), alcohol causes as much death and disability as measles and malaria, and far more years of life lost to death and disability than tobacco or illegal drugs. There is not conclusive information to estimate how much people are drinking, since home, illegal and small commercial products may not be estimated. The most common products are wine, beer and spirits. The main components of all alcoholic beverages are water and ethanol. Wine generally ranges in strength from 10% to 14% alcohol. Beer can range from 0.5% to as high as 14% alcohol and distilled spirits, which

may contain as low as 20% but usually have upwards of 35% pure alcohol (WHO, 2001).

The association of GC with alcoholic beverages has been examined in several studies. The results of these studies were controversial as a wide range of associations from negative to positive have been reported in different countries in which high alcohol consumption was prevalent, such as USA (Gammon, Schoenberg et al. 1997) Mexico (Lopez-Carrillo, Lopez-Cervantes et al. 1998), Germany (Boeing, Frentzel-Beyme et al. 1991), Russia (Zaridze, Borisova et al. 2000) and China (Ji, Chow et al. 1996) . Results vary between gender (Agudo, Gonzalez et al. 1992; Zaridze, Borisova et al. 2000), sub-sites (Ji, Chow et al. 1996; Zaridze, Borisova et al. 2000) and histopathologies and even between different form of drinks (Boeing, Frentzel-Beyme et al. 1991; Lopez-Carrillo, Lopez-Cervantes et al. 1998). An evaluation was made by IARC in which a causal association was not accepted between GC and alcohol (IARC 1988).

The association of substance abuse with cancer has been examined in several studies and shown to be related to cancer of the bladder, esophagus and larynx (Kmet 1978; Hewer 1979; Behmard, Sadeghi et al. 1981; Dowlatshahi and Miller 1985; Ghavamzadeh, Moussavi et al. 2001; Mousavi, Damghani et al. 2003). While there are some studies which found an association between opium use and aerodigestive tract, it has not been investigated for GC.

In summary, the role of smoking and alcohol drinking has been examined in many studies. While role of smoking in development to GC was accepted by IARC, several well designed studies did not find a dose-dependency. The results on the association of GC and alcohol are more inconsistent with the majority reporting no association. It was

also shown that the interaction between tobacco and alcohol may synergistically increase the risk of GC. On the other hand, there was no evidence in the literature to support any association between GC and snuff, tobacco chewing, nass and opium.

2.6.5 Occupation

A large part of adult life is spent in the workplace. Work environment may influence workers' health status by exposing them to risk factors. The workers could be exposed directly or indirectly to the occupational hazards including physical, chemical and biologic agents. Occupational exposures are important to the cancer epidemiologist from different points of view: scientific, social, and public health. As a scientific issue, the workplace offers a unique possibility for epidemiological studies because of the possibility for long term follow up. As a social issue, work has special place in most cultures and political systems. Occupational illnesses, including cancer, deserve a special legal compensation system. Therefore, scientific answers are needed from exploring the links between exposure and disease. Finally, as a public health issue, occupational cancer is theoretically preventable, so it offers a crucial opportunity for intervention and primary prevention (Frumkin 1997).

The carcinogenic role after workplace exposures was first reported in 18th century where employment in particular occupations was found to potentially increase the risk of cancer (Pott 1775 cited in Greenwald, Kramer et al. 1995). This was followed by several studies conducted by occupational epidemiologists. Although the majority of such studies have focused on lung cancer, a number of studies have reported that other cancers such as GC may be linked to certain industries and occupations. It is unclear to what extent cancer is occupational, although estimates of 2% – 20% have been reported (Fox and Adelstein 1978; Nurminen and Karjalainen 2001). The most widely cited

article estimated that 2% – 8% of cancer is attributed to occupational exposure in the USA (Doll and Peto 1981).

A higher proportion of cancer is attributed to occupation in less-developed compared to more developed countries (Frumkin 1997). It is believed that the intensity of exposures may be higher in less-developed countries due to inadequate controls by authorities and governments. The duration of exposure may also be longer in less-developed countries, on a weekly basis because of longer work schedules, and over a lifetime because of the prevalence of child labor. Workplaces close to residential areas, even within the same structures, increase the opportunities for population exposure and extend the potential exposures from the workforce to family members and others. Many of the workforce in developing nations are employed in small firms with few technical and financial resources to reduce exposures and are beyond the reach of inspection authorities. Therefore epidemiological studies in developing countries play an important role in prevention programs. As seen in Appendix J, despite this higher risk in less developed countries the majority of occupational studies on GC have been conducted in more developed countries. Meanwhile, people working in the same industries and occupations but different geographic areas may have different risk. This inconsistency in the results could be partly explained by difference in the dose and nature of exposures or by assessment methods. In Iran, like other developing countries, work takes place in small industries without using safety equipment such as protective clothing, gloves, and respirators and usually involves minimally trained and educated employees. These workplaces are geographically far from the control of the health department.

Thirty five studies and one meta-analysis relating to occupation and GC were found by a Medline search and cross-reference checking (Appendix J). Specific attention was

paid to the articles published during the last ten years after considering a review which comprehensively examined related studies in 1996 (Cocco, Ward et al.). In this section published articles are examined in two sections of industry and occupation by using the Industrial Classification of All Economic Activities (ISIC) (Appendix K) and International Standard Classification of Occupations (ISCO-88) (Appendix L) (International Labour Office. 1990; United Nations. Statistical Division 2004). However, these two categories cannot be completely separated. As Appendix I shows all of these studies except two studies in Taiwan and Brazil were conducted in more developed countries (Yang, Chiu et al. 1997; Medrado-Faria, Rodrigues de Almeida et al. 2001).

2.6.5.1 Industrial classification

Industries have been categorized into 17 categories and 60 sub-categories based on ISIC. Of these, 13 categories have been investigated in the reviewed studies which are discussed in this section. These categories include (A) agriculture, hunting and forestry, (B) fishing, (C) mining and quarrying, (D) manufacturing, (F) construction, (G) wholesale and retail trade, repair of motor vehicles, motorcycles and personal and households goods, (I) transport, storage and communications, (J) financial intermediation, (K) real estate, renting and business activities, (M) education, (N) health and social work, (O) other community, social and personal services activities and (P) private households with employed persons.

Agriculture, hunting and forestry have been examined in several studies (Burns and Swanson 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Ekstrom, Eriksson et al. 1999; Engel, Vaughan et al. 2002; Bucchi, Nanni et al. 2004; Krstev, Dosemeci et al. 2005). A case-control study in which the phone interview was used to

measure exposure, reported an OR of 2.4 (95% CI: 1.0 – 6.1) only for white men (Burns and Swanson 1995). This association was also observed in a cohort study which observed a modest increase in people working in agriculture (Bucchi, Nanni et al. 2004). However, when time periods of mortality were categorized, this association remained significant for only the time period of "1969 – 1976" and other time periods "1977 – 1984" and "1985 – 1993" became non-significant. This finding shows that the pattern of exposure might have changed over time. It is thought that exposure to dust, pesticide, herbicides and other chemicals may be responsible for this association. However, most of the studies did not support this association. A meta-analysis did not find an association between these factors (Acquavella, Olsen et al. 1998), although it was an extension of another meta-analysis which had reported a weak association (Blair, Zahm et al. 1992). In addition, no difference was observed between the anatomical sub-sites in relation to work in agriculture (Engel, Vaughan et al. 2002). This inconsistency of findings was also reported in a review by Cocco, Ward et al (1996).

A positive association has been reported between GC and mining and quarrying (Raj, Mayberry et al. 2003). Some studies have categorized mining based on the mined material in which an inconsistent positive association was reported for gold mining (Kusiak, Ritchie et al. 1993) and coal mining (Gonzalez, Sanz et al. 1991b). A Swedish cohort study described this association as caused by exposure to dust in the workplace (Aragones, Pollan et al. 2002). In this study risk was higher for long term employment compared to general cohort (RR = 1.91; 95% CI: 1.40 – 2.61) and (RR = 1.55; 95% CI: 1.25 – 1.93) respectively. Direct damage of gastric mucosa layer was suggested as a possible mechanism in development to GC. In a study of coal miners it

was shown that people with mild pneumoconiosis or normal lung develop GC more than those with severe pneumoconiosis. Authors believed that inhaled dust could be cleared out from the respiratory tract and swallowed in the case of a normal clearance system (Swaen, Meijers et al. 1995). This swallowed dust may play a carcinogenic role by local damage to the gastric mucosa.

The most widely examined category is manufacturing which was the subject of interest in several studies. This category covers the highest number of sub-categories in ISIC. An inconsistent positive association has been reported for five subcategories of manufacturing: (a) food and beverage industries, (b) basic metal manufacture, (c) paper and paper products, (d) publishing and printing and (e) rubber and plastic products. Working in food and beverage industries may increase the risk of GC by about two fold (Burns and Swanson 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Boffetta, Gridley et al. 2000; Engel, Vaughan et al. 2002). However association was statistically significant in only two articles. In addition a higher risk was reported for cardia GC compared to all sub-sites, (OR = 2.6; 95% CI: 1.1 – 6.2) and (OR = 1.6; 95% CI: 1.1 – 2.3) respectively, and among meat industry workers (Boffetta, Gridley et al. 2000). Metal manufacturing was also examined in six studies and was shown to be significantly associated with GC in three studies (Park and Mirer 1996; Ekstrom, Eriksson et al. 1999; Engel, Vaughan et al. 2002). Risk was particularly high for working duration of more than ten years (OR = 1.65; 95% CI: 1.17 – 2.32) compared to "ever workers" (OR = 1.46; 95% CI: 1.10 – 1.94) (Ekstrom, Eriksson et al. 1999). Sub-categories of paper, paper products and publishing and printing showed about two fold increase in the risk of GC (Cocco, Ward et al. 1998; Engel, Vaughan et al. 2002). The findings of these two studies were inconsistent regarding anatomical sub-sites of GC.

Finally, the rubber industry is a suspect in GC (Tomatis, Kaldor et al. 1996; Straif, Chambless et al. 1999). According to the IARC monographs, GC may occur in excess in various product areas and departments of rubber industry, but no consistent excess is seen across the various studies (IARC 1987). The majority of the studies after IARC monographs did not report any significant association between GC and this sub-category (Cocco, Ward et al. 1998; Straughan and Sorahan 2000; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). No significant association has been reported between GC and furniture and wood manufacturing industries, motor vehicles and trailers, textile and leather manufacturering.

Construction category was examined in five studies (Burns and Swanson 1995; Cocco, Ward et al. 1998; Ekstrom, Eriksson et al. 1999; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). These studies showed no significant association between GC and working in the construction industry, with the exception of a Swedish study which reported a modest increase in the risk of GC among those working in the construction industry (Aragones, Pollan et al. 2002). Moreover, an increase of risk which was found in a population-based case-control study disappeared after adjustment for age, gender and socioeconomic status (Ekstrom, Eriksson et al. 1999).

Five studies examined the association between GC and category of transport, four of which reported a significant increase in risk among sub-category of land transport (Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). They reported about 20% – 80% increase in the risk of GC among workers in this industry. All of these reports were about men and only one of them found a sub-site specific association for cardia cancer (Engel, Vaughan et al. 2002).

A significant association has not been observed for the remaining industrial categories: wholesale and retail trade, health and social work (Burns and Swanson 1995; Engel, Vaughan et al. 2002), private households with employed persons (Burns and Swanson 1995; Cocco, Ward et al. 1998; Ekstrom, Eriksson et al. 1999; Aragones, Pollan et al. 2002), other community, social and personal service activities (Burns and Swanson 1995; Engel, Vaughan et al. 2002), education and fishing (Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002) and financial intermediation and real estate, renting and business activities (Cocco, Ward et al. 1998; Aragones, Pollan et al. 2002).

2.6.5.2 Occupational classification

Occupations were classified in ten major, 28 sub-major and 116 minor groups based on International Standard Classification of Occupations (International Labour Office. 1990). These groups have been arranged in order from non-manual to heavy manual work titled from 0 - 9 (Appendix L).

The first major group is legislators, senior officials and managers, which were examined in four studies (Kang, Burnett et al. 1997; Cocco, Ward et al. 1998; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002), two of which showed an increased risk of GC. Cocco, Ward et al (1998) reported that white men working as financial managers were at higher risk compared to the control group (RR = 6.1; 95% CI: 1.3 – 28.8), but this interpretation was just based on six cases. On the other hand, a protective role which was reported for administrative and managerial workers among men, was attenuated after adjustment for age, period of diagnosis, geographic risk area and occupational sectors (Aragones, Pollan et al. 2002).

The third group of occupation, technician and associate professionals, were examined in five studies (Burns and Swanson 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Ekstrom, Eriksson et al. 1999; Engel, Vaughan et al. 2002), two of which reported about a two fold increase in the risk of development of GC among electricians (Parent, Siemiatycki et al. 1998; Engel, Vaughan et al. 2002). The latter found a sub-site association for non-cardia adenocarcinoma of stomach (OR = 2.4; 95% CI: 1.0 – 6.1). In addition, it was reported that those who had worked more than ten years in the minor group of safety and quality inspectors were at 2 – 3 times higher risk of GC (Burns and Swanson 1995).

In relation to the major group of clerks, a Swedish cohort study reported a slight increase for the minor sub-group of cashiers, tellers and related clerks but it was attenuated after adjustment to the age, period of diagnosis, geographic risk area and occupational sectors (Aragones, Pollan et al. 2002).

Five studies also examined the major group of plant and machine operators and assemblers and its sub-groups (Burns and Swanson 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002), four of which showed an increasing risk between 1.2 and 1.8 times for the sub-major group of drivers and mobile plant operators and related minor groups particularly in motor vehicle drivers. Meanwhile a positive association was shown for assemblers among white men (OR = 2.0; 95% CI: 1.1 – 3.4) and black women (OR = 5.4; 95% CI: 1.3 – 22.0) (Burns and Swanson 1995) and white male pulp and paper mills worker (OR = 2.0; 95% CI, 1.0-37), and newspaper publishing and printing men (OR = 2.6; 95% CI, 1.0-6.3) (Cocco, Ward et al. 1998).

Major group seven covers occupations related to craft and related trades workers. This was the most widely examined group during the last ten years and the subject of 14 articles (Burns and Swanson 1995; Swaen, Meijers et al. 1995; Pang, Burges et al. 1996; Park and Mirer 1996; Robinson, Petersen et al. 1996; Xu, Brown et al. 1996; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Ekstrom, Eriksson et al. 1999; Boffetta, Gridley et al. 2000; Wong and Harris 2000; Park 2001; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). For food products an increased risk of 1.3 – 4.0 was reported among different food-related occupations including butchery, bakery and food workers (Burns and Swanson 1995; Cocco, Ward et al. 1998; Parent, Siemiatycki et al. 1998; Boffetta, Gridley et al. 2000; Aragones, Pollan et al. 2002). The second sub-major group which was shown to link to GC is metal and machinery and related trades workers where there may be an increase in the risk up to five times. This sub-major group covers the minor groups of welders and solderers, roofers and pavers and nickel platers, lead smelter and steel workers (Burns and Swanson 1995; Pang, Burges et al. 1996; Park and Mirer 1996; Xu, Brown et al. 1996; Cocco, Ward et al. 1998; Ekstrom, Eriksson et al. 1999; Wong and Harris 2000; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002). For wood workers, no association was reported with the exception of one article which reported an increasing risk of about 80% (Robinson, Petersen et al. 1996). Miners were also shown to have a positive association with GC in the reviewed articles. Accordingly, working as a miner was reported to increase the risk about 50% (Swaen, Meijers et al. 1995; Aragones, Pollan et al. 2002).

Elementary occupations which covers most of the occupants who are working as labourers in different industries were examined in 11 studies since 1995 (Burns and Swanson 1995; Xu, Brown et al. 1996; Vaughan, Stewart et al. 1997; Cocco, Ward et al.

1998; Parent, Siemiatycki et al. 1998; Straif, Chambless et al. 1999; Tsuda, Mino et al. 2001; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002; Stucker, Meguellati et al. 2003; Bucchi, Nanni et al. 2004). Some of the minor groups have been inconsistently reported to link to GC including manufacturing labourers with 90% – 220 % excess in the risk of GC (Burns and Swanson 1995; Xu, Brown et al. 1996; Parent, Siemiatycki et al. 1998; Straif, Chambless et al. 1999), driver sales (OR = 3.8; 95% CI: 1.6 – 9.0) (Burns and Swanson 1995) as well as construction, transport labourers and freight handlers and launderers and cleaners (Cocco, Ward et al. 1999; Aragones, Pollan et al. 2002). Those people working in this latter group for more than ten years were at higher risk than those working less than ten years.

The majority of reviewed papers did not report any significant increase for major, sub-major and minor groups of professionals (Cocco, Ward et al. 1998; Ekstrom, Eriksson et al. 1999; Engel, Vaughan et al. 2002), excluding a study which reported an increase in the risk for minor sub-group of nursing and midwifery professionals among women (Aragones, Pollan et al. 2002). According to this study risk of GC was higher in those with job history of more than ten years compared to the general cohort (RR = 1.49; 95% CI: 1.22 – 1.81) and (RR = 1.66; 95% CI: 1.20 – 2.29) respectively. On the other hand, this study showed an inverse association between GC and the major group of professional and technical work in both men and women (RR = 0.77; 95% CI: 0.73 – 0.82) and (RR = 0.85; 95% CI: 0.77 – 0.95) respectively. In addition a negative association was reported for minor groups of engineering, medical, educational and legal professionals among men. Furthermore there was not any significant association among service workers and shop and market sales workers and its sub-groups in four reviewed studies (Burns and Swanson 1995; Ekstrom, Eriksson et al. 1999; Aragones,

Pollan et al. 2002; Engel, Vaughan et al. 2002). In the reviewed studies no association was shown for group 0: armed forces (Cocco, Ward et al. 1998; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002).

Some issues should be considered before interpreting the above reviewed papers. First, as seen in Appendix J, the majority of occupational studies have been based on death certificates, cancer registry information or company records. Since these sources of information usually provide information just on job titles, they may cause some problems in the classification of the industries and occupations. In these records normally only a job title is recorded without their duties and working history. Occupational histories are often collected from next of kin and recorded by a funeral officer so it may cause occupational misclassification. Histopathologic classification could not be extracted from such records. As a result a proportion of deaths may have been wrongly classified. Death certificates normally record the most common and recent job rather than lifetime work history. It may result in an important loss of information on exposures experienced in other jobs, mainly among short term workers who usually experience the highest workplace exposures.

Secondly, confounding is a critical issue throughout occupational epidemiology which was not considered in some of the above discussed studies. Therefore, estimates of risks can differ widely between similar studies. As a result of these weaknesses occupational risks of GC remain the subject of debate (Raj, Mayberry et al. 2003). Age is an important confounder, since cancer varies greatly with age, but was omitted or at least not reported in some articles (Pang, Zhang et al. 1997; Zeka, Eisen et al. 2004). Gender and race may be important and are routinely adjusted in the studies of occupational cancer. Another important confounder in occupational epidemiology is social class.

Workers who experience carcinogenic exposures mostly belong to the specific working class, or are sometimes poor. There is a complex relationship between social class and cancer, which was not considered in some of the reviewed articles (Kang, Burnett et al. 1997; Kazerouni, Thomas et al. 2000; Aragones, Pollan et al. 2002; Bucchi, Nanni et al. 2004; Zeka, Eisen et al. 2004). Social class is itself a surrogate for a range of other behaviors and exposures, including the most suspected environmental risk factor, smoking. In fact, smoking prevalence has long been known to vary by occupational category and social class (Giovino, Henningfield et al. 1995; Frumkin 1997). *H. pylori* infection and diet have been shown to play an important role in the etiology of GC. Although these two factors have been important confounders and they may interact with occupational exposure, they were not often adjusted in the reviewed studies (Kang, Burnett et al. 1997; Cocco, Ward et al. 1998; Marsh, Gula et al. 1999; Boffetta, Gridley et al. 2000; Kazerouni, Thomas et al. 2000; Aragones, Pollan et al. 2002; Engel, Vaughan et al. 2002; Bucchi, Nanni et al. 2004).

Interaction is another important problem in occupational cancer epidemiology. This phenomenon occurs when the joint effect of two or more carcinogens is different to what would have been predicted based on the individual effects. It may be synergistic or antagonistic, in which joint effects can increase or decrease the combined individual effects. In some cases, interaction may be nothing more than the combined effects of two carcinogens acting through different mechanisms, such as an initiator and a promoter. Individually these substances may be predicted to have a certain degree of effect, but in combination they may be far more potent (Frumkin 1997). Ames (1983) found a risk excess in miners who had prolonged exposure to both coal mine dust and cigarette smoke, suggesting an interaction between these factors but it has not been

examined in the reviewed articles (Kang, Burnett et al. 1997; Cocco, Ward et al. 1998; Marsh, Gula et al. 1999; Boffetta, Gridley et al. 2000; Kazerouni, Thomas et al. 2000; Bucchi, Nanni et al. 2004; Zeka, Eisen et al. 2004).

2.6.5.3 Assessment methods

Exposure assessment during a person's work history is a critical component of studies focusing on the effects of occupational exposures. Prospective exposure assessment is ideally the best method in occupational epidemiology. However, it is difficult to follow people for a long time as cancer always occurs some time after exposure. Therefore, retrospective exposure assessment is generally used in occupational epidemiology either by case-control or cohort studies. The most common method for assessment of occupational exposure includes questionnaire, medical records, death certificates and administrative data sources (Teschke, Olshan et al. 2002). Data on occupation and industry, whether from questionnaires or records, is usually derived from self reports or, when a subject is dead or in some way incapable, by next of kin. Self-reports were shown as a valid and reliable method of exposure assessment in several studies with reliability of 70% – 90%. In these studies, results of self-reported work history were compared with government records (Baumgarten, Siemiatycki et al. 1983) , company records (Bond, Bodner et al. 1988) and re-interview (Brower and Attfield 1998). Since such records did not exist in Iran, self report work history was utilized as the only possible method of exposure assessment.

In summary, epidemiological studies have examined the influence of working in different industries and occupations on GC. They have shown an inconsistent positive association between GC and some particular industries including agriculture, mining, transport, food industry and metal and paper product manufacturing. A non-significant

increase in the risk among construction works was also reported. Meanwhile some other studies have focused on the role of occupation. These investigators showed an increasing risk in assemblers, pulp and paper workers and white males in publishing and printing as well as motor transport vehicle drivers. A positive association has been reported with elementary works which cover most of the labourers' job such as construction, transport, freight handler, launderer and cleaner and driver sales. A higher risk of GC has also been reported in food, metal and machinery products workers and miners. Some of these studies reported a sub-site specific association, such as cardia in the food and transport workers and non-cardia among electricians, metal, publishing and paper product workers, however it remains uncertain because of inconsistency between studies.

2.6.6 Other risk factors

Several other factors have been stated to link to GC. An inconsistent increasing risk of GC was found among people with higher BMI especially in cardia GC (Chow, Blot et al. 1998; Lagergren, Bergstrom et al. 1999b; Wu, Wan et al. 2001), Epstein-Barr virus (Neugut, Hayek et al. 1996; Shinohara, Miyazaki et al. 1998; Corvalan, Koriyama et al. 2001), exposure to radiation (Neugut, Hayek et al. 1996; Nomura 1996; Kai, Luebeck et al. 1997) whereas an inverse association was reported for non-steroid anti inflammatory drugs (NSAID) (Farrow, Vaughan et al. 1998; Sorensen, Friis et al. 2003; Wang, Huang et al. 2003; Gammon, Terry et al. 2004). However these findings are controversial and require further work before being considered in primary prevention.

CHAPTER THREE: RESEARCH DESIGN AND METHODS

As it was discussed in chapter one, the aim of this research is to investigate whether there is an association between environmental factors and GC in Ardabil province. In other words, whether or not GC patients have been exposed to environmental risk factors more than those who are cancer free. Several factors are thought to contribute to GC as discussed earlier namely; dietary habits, *H. pylori* infection, lifestyle and occupation as well as familial history. Although many studies have been carried to explore the relationship between these risk factors and GC, there is still controversy about the findings and little has been done in Iran. The main hypothesis was mentioned in chapter one as "There are modifiable factors of dietary habits, *H. pylori* infection and possibly lifestyle and occupation which contribute toGC". Corresponding questions arise from these hypotheses, which are stated below.

1. Do people who have developed GC have a history of higher consumption of red meat, dairy products and preserved food than people who do not have this disease?
2. Do people who have not developed GC have a higher consumption of eating fresh fruits and vegetables than GC patients?
3. Do people who have a preference for higher salt intake or strong and hot tea develop GC more than those without these habits?
4. Is there an association between GC and a history of working in a particular industry or occupation?
5. Is an increased risk of GC associated with lifestyle (e.g. smoking, drinking alcoholic beverage and opium use)?

6. Is the risk of GC increased by *H. pylori* infection?
7. Is there any difference between anatomical sub-sites of GC (cardia and non-cardia) in relation to exposure to the environmental factors?
8. Is there any difference between histopathological classifications of GC (intestinal and diffuse) in relation to exposure to the environmental factors?

In order to find answers for these questions a study was conducted in the Northwest of Iran. The method is explained in this chapter.

3.1 Study design

Ideally, the most powerful study design to answer these questions is an interventional study. However, it is not feasible for this research because of ethical considerations and time limitation. In medical research the approach often is limited to observational methods namely; cohort, case-control, ecological and cross sectional studies. A cohort study can provide precise information about cause and effect but it would need a very large number of people to be followed for long term to find a similar risk ratio to that of a case-control study. Therefore case-control method is especially preferred for evaluating the etiology of rarer diseases. A case-control study is relatively inexpensive and can be carried out in a short period of time. In addition, it allows the examination of the effects of multiple etiological risk factors (Schlesselman 1982). In this method patients who have developed a disease are identified and their past exposures to the suspected etiological factors are compared with those controls who do not have the disease. For these reasons a case-control approach was selected to answer the questions of this study. This is a population-based case-control study as both cases and controls were selected from the community base.

3.2 Geographic and demographic description of the study area

Ardabil province is located in Northwest of Iran (Figure 3.1) and has an area of about 17,881 square kilometers (1.09% of Iran area). The province was formerly districts of East Azerbaijan province and was established in 1995. It is a mountainous area in which Sabalan is the highest peak with an altitude of 4811 meters. Sabalan is a volcanic mountain which has been dormant for a long period. It borders the Republic of Azerbaijan (part of former Soviet Union) in the north and Zanjan, Guilan and East Azerbaijan provinces in the south, east and west respectively. There is a wide climate variation between the different Ardabil districts. Districts in north of the province (Parsabad, Bilesavar and Germi) have a hot summer and temperate winter, whereas Ardabil and Meshghin in central and Khalkhal in southern part of province have a very cold winter and mild weather in summer (Statistical Centre of Iran 2002).

Figure 3. 1: Geographic situation and incidence rates of GC (ASR) in Ardabil province, Iran and nearby countries

(M) male and (F) female

incidences from (Ferlay, Bray et al. 2004)

Ardabil's population was 1,204,410 (1.84% of Iran's population) in 2002 (Statistical Centre of Iran 2003). According to the latest National Census, 51.2% of the Ardabil population was urban residents (Statistical Centre of Iran 1996). The population is comparatively young; 40% under 15 years old (Figure 3.2), thus the incidence of GC which is age related may increase during the next decades due to the aging of the population. The population is from Arian Caucasoid ancestry and speak Azari language (Sadjadi, Malekzadeh et al. 2003).

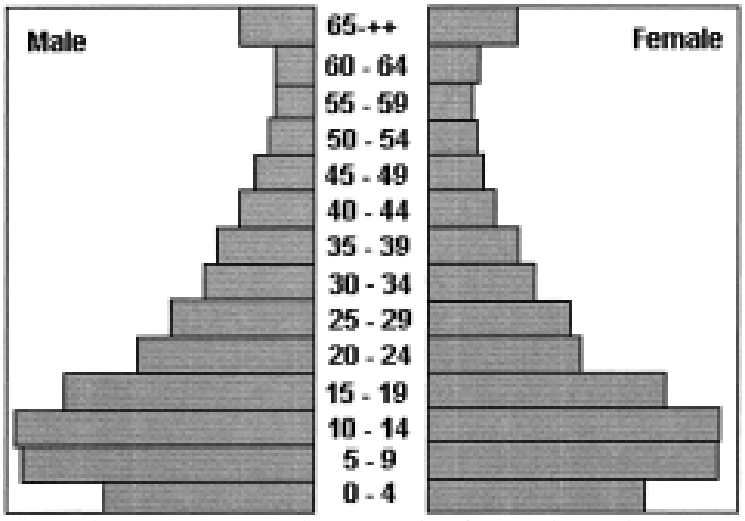


Figure 3. 2: Population pyramid of Ardabil province
from (Sadjadi et al., 2003)

3.3 Study population

In order to examine the risk factors proposed earlier and explore the relationship between the selected variables to GC, subjects were recruited in two groups of cases and controls.

3.3.1 Definition and Selection of Cases

Cases were defined as adults who had been diagnosed histopathologicaly as having GC. They were diagnosed by pathologists in five private laboratories and two hospitals. The

general inclusion criteria for cases were as follows: (1) Ardabil residents for at least five years prior to diagnosis; (2) aged more than 18 years (3) have not had previous gastric surgery prior to diagnosis of GC and (4) a positive histopathologic report. Cases were identified from the Ardabil Cancer Registry. This registry was established in 1999 and is run by Ardabil University of Medical Sciences and supervised by the Digestive Diseases Research Center (Tehran University of Medical Science). A specific data collection form was distributed from the cancer registry to all laboratories, hospitals and private and public clinics working in Ardabil province. All cancers were reported to the cancer registry using this form which contained information on name, age, gender, address and histopathologic diagnosis of cancer. However, a specific active surveillance was arranged for GC by the cancer registry to ensure completeness of case ascertainment. In that surveillance program all hospitals, public and private clinics, particularly those of three gastroentrologists, were regularly visited. All reported cases were classified according to the International Classification of Disease for Oncology (ICD-O code 160-9) and entered in a database which was used for case findings (Appendix M). The histologic sub-types and anatomical sub-sites of cancer were also considered where such information was available from the pathology reports.

After identification of the incident cases, they were informed by the Ardabil health department about the study which asked them whether they wished to participate in the study or not (Appendix N). In the case of their acceptance they were introduced to the researcher. For those cases who agreed to participate but were not ready on that day due to time or place inappropriateness, another session was arranged to suit the participant. Meanwhile those cases who refused to participate were excluded from the study. A form was completed for these refusal cases which contained information on age, gender and

reason for non-participation (Appendix O). The process of case recruitment is shown in Figure 3.3.

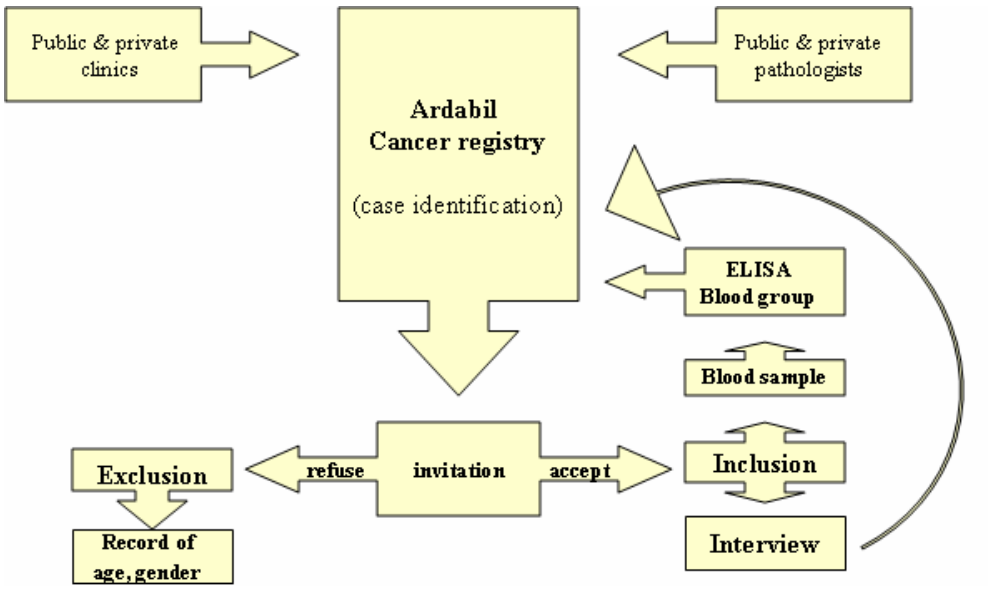


Figure 3. 3: Procedure of case recruitment

3.3.2 Definition and Selection of Controls

Controls were sought from community samples assumed to be cancer free based on their records at the health center. The health department of Ardabil University of Medical Science was contacted to provide a sampling frame derived from the annual household survey. Generally, each province has a medical university which is responsible for medical education as well as providing health care for all inhabitants via a provincial health department. Primary health care is provided by this department to people via urban and rural health centers. Each center normally covers 9000 – 15000 individuals. At the beginning of each year information is collected about household inhabitants, newborns and deaths through direct, home-to-home visits by health professionals from rural and urban health centers. Each household is allocated a unique household number during this home visit. This information is sent to the district health

centers which compile information in a database to be sent to the provincial health department. The database in the provincial health department was used to select random household numbers using an internet based program named Research Randomizer (Urbaniak and Plous 1997). Five hundred and fifty random numbers were generated by Research Randomizer which were considered as household number. This list contained almost one and half times the predetermined number of controls to be replaced in case of refusals. Controls also had to be a resident of Ardabil province for at least five years and had the same criteria as cases except for being a GC patient. Ideally, selection of equal numbers of cases and controls will make a study most efficient, however due to the rarity of GC, two controls were drawn for each case, frequency matched on 5-year age groups and gender, to increase the power of study.

In relation to recruitment of controls, predetermined households were visited by health professionals seeking eligible individuals who satisfied the inclusion and matching criteria. If such a person was not available at that home or did not satisfy inclusion criteria, the immediate neighbor to the right hand side was referred to for eligible control. This process continued for a maximum of three households including the first predetermined household. If an eligible control could not be found, the primary list of random controls was used to choose another subject. In the next step, eligible controls were given an information letter from the local health authority which invited them to join this study. After agreeing to take part in the study, similar steps were performed as the cases in relation to the interview and blood sampling. This procedure is shown in Figure 3.4. The interviews were administered either in the local (Azari) or Persian language, depending on subjects' preference.

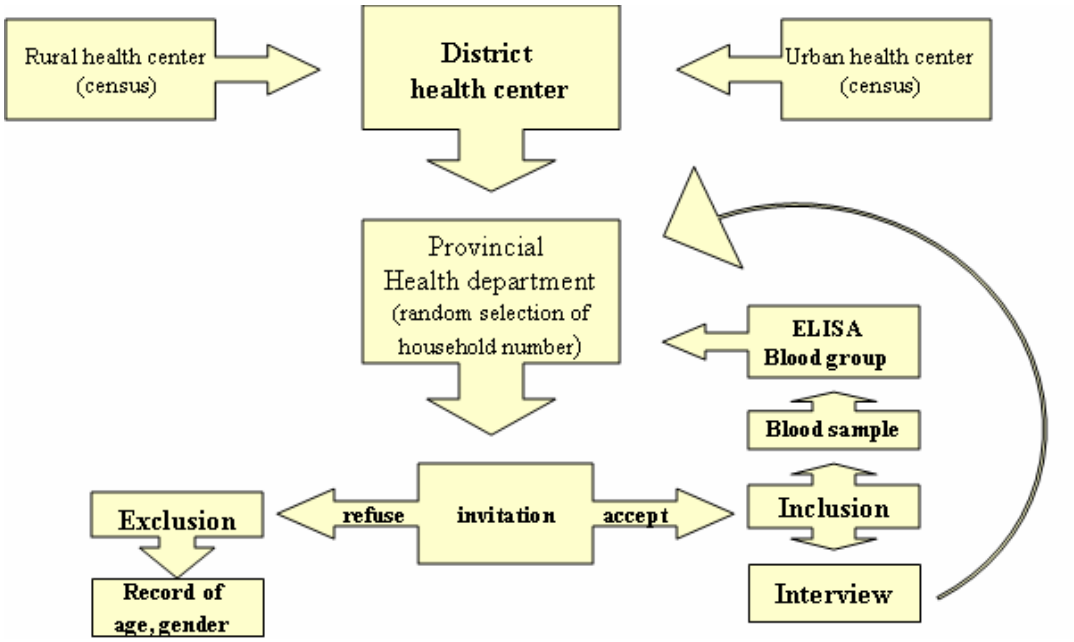


Figure 3. 4: Procedure of control recruitment

3.4 Sample size

Selection of an adequate number of subjects is an essential factor which must be considered in all studies. This is an important issue in gaining statistically significant results. Selection of sufficient samples will result in avoiding two types of errors, type I and II. Type I error (α) is the probability of finding an association between disease and exposure while they are not actually related to each other. Type II error (ß) is the probability of rejecting the association between exposure and disease where there is an association. The power of the study can be measured using (1- ß).

To calculate the sample size in this study using equation 3.1, four factors were considered. These were firstly "P_0" which shows the proportion of exposure in the control group, secondly "R" that was denoted for relative risk for hypothesized association of the exposure and disease. Odds ratio "ψ" is often used instead of relative risk "R" in case-control studies, thirdly "α" which denotes level of significance and finally the power of the study which can be calculated from "ß" (Schlesselman 1982).

$$n = 2\bar{p}\bar{q}\frac{\left(Z_{\alpha} + Z_{\beta}\right)^2}{\left(p_1 - p_0\right)^2} \qquad \textbf{(Equation 3. 1)}$$

$$\bar{p} = \frac{p_1 + p_0}{2} \quad , \quad \bar{q} = 1 - \bar{p} \qquad \textbf{(Equation 3. 2)}$$

$$p_1 = \frac{p_0 \times R}{\left[1 + p_0\left(R - 1\right)\right]} \qquad \textbf{(Equation 3. 3)}$$

The quantities of Z_{α} and Z_{β} are values from the standard normal distribution corresponding to α and β. Considering predetermined α and β which were 0.05 and 0.10 respectively, their values are $Z_{\alpha} = 1.96$ and $Z_{\beta} = 1.28$ for two-sided test of the hypothesis. In equation 3.1 "n" denotes the sample size for each group when there is equity in the number of case and control. To calculate sample size, the proportion of exposure in the control $\left(p_0\right)$ was estimated at 70% for *H. pylori* infection, although a wide variation was reported in different parts of Iran. P_0 was assumed to be 30% for smoking based on available information (Malekzadeh, Sotoudeh et al. 2004). By considering the above equation, the minimum number of cases were 250 and 190 patients to find a doubling in the risk of GC for *H. pylori* and smoking respectively. However, due to the limited time of study and the rarity of disease, it was intended to have multiple controls per case therefore another equation 3.4 was employed for an adjustment of sample size. In this equation "c" denotes the number of controls per case.

$$n' = \frac{\left(c + 1\right) \times n}{2c} \qquad \textbf{(Equation 3. 4)}$$

Therefore, by assuming a prevalence of 70% and 30% for *H. pylori* infection and smoking among controls, a matched design, $\alpha = 0.05$ (two-sided), and having two controls per case 187 and 143 subjects would be the minimum number of cases to find a doubling of GC risk. Table 3.2 presents the number of subjects in various prevalences of exposure and control/ case ratios to find an OR ranging 1.5 - 2.0. Therefore based on the Table 3.1, recruitment of 200 cases and 400 controls was deemed to be sufficient sample size to provide a good power of study (> 90%) for these exposures.

Table 3. 1: Required cases to detect OR of 1.5 – 2.0 with various case: control ratios alpha = 0.05 and power of study = 90%

		Case: control (1: 1)			Case: control (1: 2)			Case: control (1: 3)			Case: control (1: 4)		
P_0	OR	1.5	1.75	2.0	1.5	1.75	2.0	1.5	1.75	2.0	1.5	1.75	2.0
0.20		716	364	231	537	273	173	478	242	154	448	227	144
0.30		570	294	190	427	221	142	380	196	126	356	184	119
0.40		520	273	178	390	205	134	346	182	119	325	170	112
0.50		520	277	184	390	208	138	346	185	122	325	173	115
0.60		563	305	205	423	229	154	376	203	136	352	191	128
0.70		670	367	250	502	276	187	446	245	166	418	230	156
0.80		913	508	349	685	381	262	609	339	233	571	317	218

P_0 = Prevalence of exposure in control
OR = Odds ratio

3.5 Research instruments

Two research instruments were utilized to measure exposure to the predefined factors. These research instruments were a structured questionnaire and a biological specimen. The questionnaire ascertained information on demographic characteristics, socioeconomic status, smoking history and beverage consumption, medical history, occupation and eating habits. In the next step their blood was collected and stored in two tubes by a trained laboratorist who immediately transferred them to the laboratory. The first tube which contained citrated blood specimen was used for blood grouping and the second tube was centrifuged and serums were parted. These serums were kept in the

–60 °C freezer to be further used for detecting IgG antibody against *H. pylori* using Enzyme-Linked Immunosorbent Assay (ELISA).

3.5.1 Questionnaire

A questionnaire is the most commonly used instrument for measurement of personal characteristics and exposure to environmental factors. It can be either by interview or self-administered. Both methods have advantages and disadvantages, however, interview administered questionnaire is normally preferred. For this study a person to person interview was selected because of high illiteracy in older people. Moreover a personal interview can promote a subject's collaboration and reduce misunderstanding, although it may cause interviewer bias. To minimize this bias an instruction guide was prepared to be used by interviewers.

The study questionnaire was based on a previously administered questionnaire in Ardabil (Malekzadeh, Sotoudeh et al. 2004). Some modification was made to the original questionnaire after considering principles of questionnaire design to collect detailed information about time and dose of exposure particularly in the consumption of tobacco, opium and alcohol (Silva 1999; Armitage, Matthews et al. 2002). For instance, in the original questionnaire, subjects were asked about the starting and finishing date of exposure to calculate duration of exposure. Since there was a possibility of smoking cessation, another question was added asking about possible smoking cessation time. In addition, due to possible variation between week-days and week-end smoking, separate questions were asked about smoking during week-days and the week-end. This was not considered in the original questionnaire. The same modification was done for consumption of alcohol and opium and other substance use.

The modified questionnaire was pre-tested with ten Iranians to find any ambiguous or unclear wording as well as average interview time. The average time was 54 minutes and no changes were made in wording, however, two extra choices were added to the multiple choice questions. First a "Do not know" choice was given to be used in the case of unclearness of answer for participants. Secondly, an "other" choice with opportunity to specify was added in case their response was not found within provided choices.

Validity of questionnaire is a fundamental issue in the study. The term of validity is used in two ways namely external and internal. The term of external validity is defined as if the study is repeated in the same population using the same methods and measures, approximately the same results will be obtained. Another way in which the term validity is used is whether a measure of exposure or outcome actually measures that exposure or outcome. This is referred as an internal validity. To measure internal validity, an absolute measure is needed to be compared with study measure (Margetts and Nelson 1991). The administered questionnaire was a modified version of an already administered questionnaire in Ardabil province. Internal validity of this questionnaire could not be measured as there was not a reference method. However, it showed a good reliability. For assessment of reliability, the questionnaire was administered twice for a subset of subjects (23 individuals) within a one month interval using the final version of questionnaire. The responses given on the first and second interviews were compared in order to check for consistency of response using statistical analysis of proportion of agreement, Kappa coefficient (κ), and correlation coefficient. These analyses are shown in Appendix P and Q for categorized and continuous variables respectively. Among those questions having similar format those of higher importance was stated. As results

show there was a good agreement for most of the questions $\kappa > 0.60$ but for two other questions measuring consumption of garlic and salted fish a moderate agreement $\kappa = 0.40$ to 0.60 was observed. However, in general all questions had an acceptable level of agreement ($\kappa > 0.50$). In addition, there was a high correlation between two interviews in relation to the continuous variables.

3.5.1.1 Structure of questionnaire

Questions were structured in eight sections including (A) introduction for proxy interview, (B) demographic information, (C) socio-economic status, (D) smoking, (E) beverage consumption, (F) medical and family history, (G) work history and (H) eating habits (Appendix R). In most of the sections it was intended to ask a general question at first and then follow with detailed questions. For example "have you smoked tobacco regularly?" (Regular means smoking of at least one cigarette per day for six months or more). If the answer was positive then they were asked details about dose, duration and type of smoking as well as any withdrawal. In the case of negative response the rest of related questions were skipped.

3.5.1.1.1 Introduction for proxy interview

This was an optional section which was filled in only in the case of death or serious illness in the cases. Information was collected about the reasons for a proxy interview, relation of surrogate to the case and duration of time living with GC case.

3.5.1.1.2 Demographic and socioeconomic status

Demographic characteristics and socioeconomic status were evaluated in section "B" and "C". Section "B" was designed to collect data about age, gender, birth and living place, marital status, and religion and ethnicity. Section "C" collected information on

socio-economic status. It focused on income and expenses, domestic condition, access to facilities at home and education. Questions in this section were similar to the questions used in the Iranian National Census (Statistical Centre of Iran 1996). This allowed a comparison between socioeconomic status of our subjects with those of the census.

3.5.1.1.3 Lifestyle

Section “D” and “E” collected information on lifestyle related habits including smoking and substances and beverage consumption. This part was intended to collect information on various methods of tobacco smoking. A smoker was defined as someone who had ever smoked at least once per day for six months or more. Dose and time of smoking as well as using a smoking filter were also noted. In addition to tobacco consumption, subjects were questioned about substance use and drinking alcoholic beverages. Alcohol drinkers and substance users were defined as an individual who consumed these items at least once a week for six months or more. Subjects were also asked about time and dose of exposure. In the beverage part, subjects were also asked about their drinking habits in relation to tea and coffee.

3.5.1.1.4 Medical and family history

In section “F”, subjects were asked about their medical history and any history of cancer particularly upper GI malignancy in their first-degree relatives.

3.5.1.1.5 Work history

In section “G”, subjects’ work history were explored. This section included life time work history since age 16 years. Subjects were asked to explain the job title, activities, industry, and duration of work and full time / part time status for each job held for at

least one year. In addition, a subject's main activity during the last ten years was included. Information on occupational history was collected from age 16 years up to the interviewing time for controls and diagnosis date for cases. Occupational exposures were ascertained by self reported work history. Alternative methods of ascertainment such as company or government records were not applicable for our subjects as such records did not exist for all subjects. Reliability and validity of self-reported work histories have been examined in several studies (Baumgarten, Siemiatycki et al. 1983; Rona and Mosbech 1989; Rosenberg 1993; Booth-Jones, Lemasters et al. 1998). These studies reported it as an accurate method particularly where subjects tend to be stable and employed long-term, as exists in Ardabil.

3.5.1.1.6 Dietary habits

Eating habits were ascertained in section "H" by asking people about the consumption frequency of dietary items during the last ten years. The most informative food items were included in the food list on the basis of prior information. The dietary section included 20 food items plus other dietary practices of subjects. The selection of food items includes vegetables (raw, yellow-orange, onion, garlic); fruits and juice (total and citrus fruits and fresh juice), meat (red meat, fish and poultry), preserved food and vegetables (smoked red meat, smoked and salted fish, processed meat and pickled vegetables) grain (beans and seeds) and dairy products and sweets. Dietary practices include the preference of subjects for salt and warmth and strength when drinking tea. The frequency of food intake was measured in six categories ranging from "never" to "2 – 3 daily". While the controls were asked about their dietary habits over the last ten years, the cases were asked about their dietary habits during ten years prior to the diagnosis. Subjects were also questioned about any possible changes in their habitual

diet in the last ten years ago for controls or the ten years prior to diagnosis for cases. In the FFQ special attention was given to food items rather than dietary constituents. As it is now generally agreed, any suggestion to reduce risk of chronic diseases as well as cancer should be expressed in terms of food group and drinks. Dietary constituents could be addressed in the next step. This policy could allow more practical recommendations (WCRF and AICR1997). In addition, to the best of my knowledge, there is not a food composition table in Iran to measure food constituents. Therefore by considering the two above reasons the major suspect food groups were examined in this study.

Several methods have been used to investigate the role of diet in development to GC. It is known that development to cancer does not occur in a short period of time but needs a long time of exposure to the environmental factors such as dietary factors. Therefore past dietary habits are important determinants in cancer development. The association between diet and GC could be examined by either prospective or retrospective approaches. Each of these approaches has its strengths and limitations. Ideally the best ways of investigating dietary effects are randomized trials and prospective studies. However these methods are time and cost consuming and sometimes are not ethical. Therefore looking to the past history of exposure is more feasible. There are four basic methods for assessing dietary intake: dietary recalls, food records, diet histories and FFQ. The first two methods focus on current intake whereas diet histories and FFQ focus on usual intake over a period of time (Block 1982). FFQ was selected to collect information on past exposure to the dietary items during last ten years.

In addition to the above-mentioned sections there was another section (J) in which the interviewer was asked to comment about the reliability of the general interview and

each separate section. After the interview, the subject's weight and height were measured to be used for the calculation of BMI. BMI was calculated using the subject's weight, prior to the occurrence of signs and symptoms, in kilograms and height in centimeters, using following equation.

$$BMI = \frac{Weight(kg)}{Height^2(m)}$$

Results in kilogram per squared meter (kg / m^2) were divided in four categories; underweight = BMI below 18.5 kg / m^2; normal = BMI of 18.5 – 24.9 kg / m^2; over weight = BMI of 25.0 – 29.9 kg / m^2 and obese = BMI of 30 and above kg / m^2 based on CDC classification (Centers for Disease Control and Prevention 2005). In addition, subjects were asked about their normal weight before signs and symptoms were noticed. To help them to answer accurately to this question they were asked whether they have currently had a weight loss or not.

3.5.1.2 Laboratory test

Ten milliliters (ml) of blood were collected from each of the cases and controls. One ml of this was collected in a citrated anticoagulant tube for blood grouping. The rest of the blood specimen was centrifuged and serum was separated and divided in two different tubes. These specimens were transferred to the Aras clinic in Ardabil and kept at – 60^o C to be further analyzed with all the other samples at once to minimize measurement error. All tubes were labeled by a unique identification number (ID) which had already been assigned for subjects. This ID was the same as the questionnaire number.

3.5.1.2.1 Blood grouping

In this study, a blood typing was done for all cases to define their blood types (ABO and Rh). Blood typing was determined by adding anti-serum “A”, “B” and “D” into the blood samples. The determination of blood group and Rh was specified by guideline stated in Table 3.2.

Table 3. 2: The guideline for determination of blood groups and Rh

Blood type	Definition
Blood type A	Blood sample clotted when anti-A serum was added.
Blood type B	Blood sample clotted when anti-B serum was added.
Blood type AB	Blood sample clotted when both anti-A and anti-B serum were added.
Blood type O	Blood sample did not clot when either anti-A or anti-B serum were added.
Rh Positive	Blood sample clotted when anti-Rh serum was added.
Rh Negative	Blood sample did not clot when anti-Rh serum was added.

3.5.1.2.2 ELISA test

A serological test was carried out to detect antibody against *H. pylori* IgG using an ELISA test. To select an accurate ELISA kit from those of available in Iran, a validation study was carried out using four commercially available kits. These kits had been manufactured by Genesis, IBL, Biohit and DIA.PRO. This study is discussed in Appendix S but briefly serum of 83 patients who had been referred for upper endoscopy due to dyspepsia were selected. Forty of these subjects were positive and the remaining were negative for *H. pylori* based on results of the gold standard (positive results of histology and rapid urease test). Serums were examined using the four kits. The kit manufactured by Biohit showed a satisfactory level of accuracy for the selected subjects. The respective sensitivity, specificity and positive and negative predictive values for the kit manufactured by Biohit were 92.5%, 90.7%, 90.2% and 92.9%.

In the final stage of data collection, all frozen serums were transferred into the refrigerator to be de-frosted. All serums were examined together by a laboratorist experienced in serological tests particularly ELISA. She was blinded to the subjects' diagnosis. Results were reported to the researcher by the ID number which had been given to subjects.

3.6 Data collection and data entry

Data collection was conducted between June 2003 and April 2005 aiming to include all incident cases of GC in the Ardabil province. Cases were mainly identified from the Ardabil Cancer Registry. In addition, active surveillance was conducted in public and private hospitals and laboratories as well as gastroenterologists clinic to ensure completeness of case ascertainment. Two controls per case from the general population of Ardabil province were identified randomly from a database which is kept in the health department. Controls were frequency matched to the cases by gender and 5-year age group. Eligible cases and controls were invited to participate in this study. In the case of their acceptance and signing the consent letter they were included in the study.

Subjects were interviewed by me and three of my colleagues in the health department. These three health professionals had already been involved in several surveys including a study where the original questionnaire was derived (Sadjadi, Malekzadeh et al. 2003). An instruction guide was prepared for interview which was discussed in a training workshop. Following this workshop five interviews were conducted by the investigator followed by six interviews by my colleagues (two interviews by each interviewer) while all interviewers attended in the interview session. To ensure about accuracy of interviews, ten questionnaires were selected and subjects re-interviewed in which results were comparable.

The collected information from questionnaires and laboratory results were coded and entered into a database which had been developed using the Microsoft Access program. To double check the accuracy of data entry, 40 questionnaires were randomly selected by the investigator and compared with existing information in the database. All information in the database was completely similar to the questionnaires. Following this double check, the file was exported to the Microsoft Excel program and finally imported into the SPSS 13.0 for windows (Statistical Package for the Social Sciences) (SPSS Inc 2004).

3.7 Statistical analysis

The analysis was started by evaluating subjects' datasets during the data collection period when the researcher checked each questionnaire to ensure that no questions were unanswered. This allowed us to follow any incomplete questionnaire, either by phone call or home visit, to be completed. Following data entry, statistical analysis commenced with general descriptive analysis followed by multivariate analysis. All analyses were conducted using SPSS for windows version 13.0 (SPSS Inc 2004).

3.7.1 Descriptive analysis

Preliminary assessment of the dataset was performed to look at any missing variables and outliers. This assessment allowed us to follow whether these missing variables or outliers had been correctly coded or not. The frequency of variables in the control group was also compared to the results of the national census and other available information where it was applicable. This could help to judge whether controls are likely to represent the Ardabil population where the study case arose. In the next step, the distribution of GC was examined by gender, age group, histopathology and anatomical

sub-sites. Subjects were recruited in two groups of cases and controls. These two groups were firstly compared in relation to the continuous variables by looking to the mean, mode, median and standard deviation. Differences between cases and controls in relation to continuous variables were assessed using unpaired t-tests. Continuous variables were converted to categorical variables and distributions of these categories were compared between cases and controls similar to the other categorical variables in this study. These variables were firstly compared visually by graphing them. Then a cross-tabulation was run between dependent variables of subjects' status (case or control) and each independent variable. Differences between them were examined for significance using t-test for continuous variables and chi-square for categorical variables. Chi-square test was used to compare the difference between case and control in relation to the categorical variables. Following these descriptive analyses of overall cases, similar analyses were conducted for each anatomical sub-sites (cardia and non-cardia) and histopathologic sub-types (intestinal and diffuse) of GC. In addition, distribution of histopathology was examined for sub-sites of GC. Finally, reliability of the questionnaire was assessed using proportion of agreement, Kappa statistics and correlation coefficient.

In addition population attributable risk percent was calculated to estimate burden of each risk factors in community level. PAR percent was calculated using following equation.

$$PAR = \frac{P(RR-1)}{P(RR-1)+1} \times 100$$

To calculate PAR, two factors were considered. These were firstly “P” which shows the proportion of exposure in the control group, secondly “RR” that was denoted for calculated relative risk. However, Odds ratio was used instead of RR.

3.7.2 Multivariate analysis

This analysis was started by binary logistic regression analysis between outcome and each variable separately. In all these analyses age group and gender were included. These analyses were conducted in two steps. In the first step, all cases were included in the analyses whereas in the second step proxy interviews were excluded. This allows us to see whether collected information from proxy interviews is comparable to case interviews. The results of these analyses led to conducting multivariate analyses. Multivariate analyses proceeded via logistic regressions to estimate risk in exposure adjusted for covariates. This analysis was used to analyze the relationship between dichotomous dependent variables and a set of predictor or independent variables. It was performed to identify those environmental etiologic factors associated with GC. This analysis was commenced with inclusion of all relevant variables in the logistic regression model. The next step was continued with removing of variables from the full model using a backward logistic regression. All variables which remained significant after removing of non-significant variables except age group and gender were removed from this model one by one. Those variables which made a significant contribution to GC were kept in the model. Age group and gender were always kept in the model. Trends of ordinal variables were ascertained by considering them as continuous variables in the logistic regression model. The contribution of environmental variables to the anatomical sub-sites and histopathological sub-types of GC were also examined using the same model which was used for all cases.

3.8 Predictive model

To determine the final model, three strategies were employed by considering 18 variables which were found to be associated with GC in univariate analysis.

Firstly, in the main categories of SES, two variables (educational level and availability of hot shower at home) showed an association with GC in univariate analysis. However, using these two variables together in the multivariate logistic regression, the association of hot shower and GC disappeared. Therefore of these two variables, education was considered as a determinant of SES and was kept in the model. After excluding availability of hot shower, 17 variables remained significant.

To avoid over adjustment, a second strategy, logistic regression analyses were used by a backward elimination approach to select the best subset of risk factors. In this method all variables with significant univariate association with GC were included in the analysis including age groups and gender. Six variables were excluded in the backward logistic regression in seven steps. The excluded variables included consumption of poultry, education, BMI, family history of GC, main job and consumption of fresh fruits. After excluding those six variables a model including preference for salt intake, warmth and strength of tea, consumption of garlic, onion, fish, citrus fruits, red meat, dairy products, opium use and *H. pylori* infection was found to be statistically a significant logistic regression model.

To avoid more over adjustment a third strategy was conducted. In this strategy, the above mentioned variables were excluded one by one from the main model to look at the impact of each of them in the model. Theoretically, a confounder is an extraneous variable that satisfies both of two conditions: (1) being a risk factor for study disease

and (2) being associated with the study exposure but not a consequence of exposure. However, in practice it has been recommended that if an adjustment for a variable makes no substantive difference in the analysis, then it can be ignored even if the variable is "significantly" associated with both outcome and exposure (Schlesselman 1982). Hence, opium use was excluded from the final model, because this exclusion did not change the significance of the predictive model. Meanwhile there was no association between opium use and some of associated variables including education, *H. pylori* infection and consumption of dietary factors such as citrus fruits, onion, red meat, fish and dairy products. Therefore opium use could not theoretically play confounding role in the final model. On the other hand, if the adjustment for the variable yields a substantive difference in the analysis, then it can be adjusted even if the variable is not significantly associated with exposure or disease (Schlesselman 1982). For this reason, two variables of education and family history of GC were added to this model. Both of these variables have already been reported to be important confounders. Considering above strategies and the practical guidance of Schlesselman (1982), a model including preference for salt, warmth and strength of tea, seropositivity for *H. pylori* and consumption of garlic, onion, citrus fruits, red meat, fish and dairy products, family history of GC and education as well as age groups and gender were taken in account in the final logistic regression model for gastric carcinogenesis.

3.9 Ethical considerations

The Study protocol and informed consent used for this investigation were approved by both the ethics committees of UNSW and Ardabil Medical University prior to the study. For the benefit of ethical considerations, it was ensured that there would be no compulsion in the participation of the survey. The participation was totally voluntary

and all subjects were invited to participate in the study, in writing, by the health department. Those subjects willing to participate were asked to sign a consent letter (Appendix T and U) and let us interview them and collect their blood. A four-digit sequential ID code was assigned to each participant so their names would not be a part of the survey. All questionnaires bound with the signed consent letter were kept in a cabinet in the Ardabil Cancer Registry under the supervision of the researcher. In the next step the collected data was entered in the database which was developed using Microsoft Access program by the director of Ardabil Cancer Registry. This database was secured, and the data were accessible only to me and Director of Cancer Registry. Data were backed up frequently. Finally this file was exported to SPSS software for future analysis (SPSS Inc 2004). All computer files, questionnaires and laboratory findings have been kept confidential and strictly secure in the Ardabil Cancer Registry. This information will be kept securely for a minimum of seven years in accordance with the Human Ethics Research Committee (HREC) regulation of the study.

CHAPTER FOUR: FINDINGS

A population-based case-control study was conducted in Ardabil province in Northwest of Iran in which a high incidence of GC had been reported. This study aimed to examine association of GC with environmental factors including dietary habits, *H. pylori* infection, lifestyle and occupation. Findings of this study are presented in this chapter in six sections. The first section explains recruitment and interview of subjects. The second section discusses definition of cases and controls. In the next section, univariate analysis carried out between GC and each factor is explained. Multivariate analysis discusses a predictive model in the etiology of GC using logistic regression approach. The final section explains subgroup analysis in relation to the anatomical sub-sites and histopathological sub-types of GC.

4.1 Recruitment and interview of subjects

A total number of 231 cases of GC were histopathologicaly diagnosed and reported to the Ardabil Cancer Registry, of these cases nine did not satisfy study inclusion criteria because they were not resident of Ardabil province during the last five years prior to the diagnosis (East Azerbaijan 2, Guilan 5 and Tehran 2). After excluding them, 222 cases were invited to participate in the study. However, five of them could not be recruited because of refusal in two cases and an unidentifiable contact address in three cases. Finally, 217 cases (97.8% of eligible cases) were included in the analysis. As described in chapter three, it was planned to recruit two controls per each case. A total of 434 households were randomly selected from a database of the provincial health department to find eligible controls. Four hundred and fifteen eligible controls agreed to participate

in the study, of which 21 persons refused to give a blood sample. Finally, 394 controls (90.8% of eligible controls) agreed to participate in the study and give a blood sample. Non-participants tended to be older (67.3 vs. 64.7) than controls but the difference was not significant ($p = 0.18$). Refusal was higher in males than females (12.3% vs. 2.3%).

Cases and controls were interviewed by the investigator and three health professionals using a structured questionnaire. In general, subjects were mainly interviewed in their home and private and public health centers (61%, 18% and 13%). However this proportion was different between cases and controls. The majority of cases (61.9%) were interviewed in two private clinics of gastroenterologists and the Aras special clinic which had been established for gastrointestinal diseases while controls were mostly interviewed at home (79.5%) (Table 4.1). In 16 cases (7.4%), interviews were carried out with next of kin due to subject's death (13) or disability (3). These surrogates had lived with the subjects for 26.4 years on average before diagnosis with a range of 10 – 55 years. The remainder of cases and all controls were interviewed in person. Interviews were conducted either in the local language (Azari) or in Persian, depending on the subject's preference. The average time for general interview was 41.0 ± 15.5 minutes.

4.2 Definition of cases and controls

The demographic characteristics of subjects are summarized in Table 4.2. Of 217 cases, 151 (69.6%) were male and 66 (30.4%) female which showed a male / female ratio of 2.3. This ratio was 2.1 among controls which is not statistically different than the observed ratio for cases ($p = 0.56$). The average age of the cases was 66.0 ± 11.6 years which was non-significantly higher for males compared to females 66.7 ± 10.4 and 64.3 ± 14.1 respectively. Controls tended to be younger than cases, 64.7 and 66.0 years respectively ($p = 0.19$). Gastric cancer was not common in those aged less than 50

years, however, it started to rise from age 50 and peaked in age groups 65 – 74. While the number of cases in age below 40 was small, it was seen in females more than males (Figure 4.1).

More than half of the cases were rural residents (52.5%) whereas controls were more likely to be urban dwellers (51.8%) which corresponds closely to the result of the last national census in Ardabil province which showed that 51.2% of the population were urban residents (Statistical Centre of Iran 1996). This difference was not statistically significant ($p = 0.31$). In addition, cases and controls were similar in term of marital status ($p = 0.30$).

4.3 Histopathology and anatomical sub-sites of GC

Adenocarcinoma constituted 96.3% of GC. In relation to the Lauren (1965) histopathological classification, intestinal type constituted more than half of the cases with 116 subjects (53.5%), followed by the diffuse type 70 (32.3%) and mixed type 14 (6.4%). In addition, nine (4.1%) cases were identified as undifferentiated adenocarcinoma (Figure 4.2). In relation to the sub-site analysis, cardia was the most common sub-site of GC compared to the non-cardia with 115 (53.0%) and 81 (37.3%) cases respectively. In 21 (9.7%) of the cases the location of malignancy could not be identified (Figure 4.3).

In relation to the Lauren histopathologic classification, intestinal type was the more common type in both males and females 53.0% and 54.5%, which is similar to the proportion of overall cases. Both sub-types were also similar in average age of diagnosis. After categorization by age a higher risk of diffuse type was observed in those aged less than 50 years and 60 – 64 years compared to the other age groups (Table

4.3). For anatomical sub-sites, cardia cancer was more common in males than females (62.1% vs. 49%). In addition, the average age of both sub-sites was approximately 66 years (Table 4.4). As seen in Table 4.5 intestinal type was the common type of GC in both anatomical sub-sites.

4.4 Univariate analysis

A univariate analysis was conducted between GC and each variable. In all analyses, age and gender were included. Univariate analysis was conducted twice. In the first step, all cases were considered in the analysis. In the second step, analysis was conducted by excluding the proxy interview.

4.4.1 Socioeconomic status

Socioeconomic indicators are presented in Table 4.6. As seen in the table, illiteracy was high in both groups of cases and controls, however cases were significantly less educated than controls, with an average 0.9 and 1.9 years of schooling respectively ($p < 0.01$). A higher proportion of controls had completed at least one grade in the educational system (26.9%) compared to the cases (13.4%). This showed a significant inverse association for completing at least one grade in the education system with odds ratio (OR) of 0.33. Cases and controls were approximately similar in economic status. As seen in Table 4.6 there was no significant difference between cases and controls in term of monthly income and expenses. People in the lowest categories of income and expenses did not show a higher risk compared to those at highest level of income and expenses with OR of 1.07 and 1.24 respectively. Exclusion of proxy interviews did not change these results.

In domestic related indicators, cases and controls reported almost similar numbers of family members (5.5 ± 2.7 and 5.2 ± 2.9), number of occupied rooms (2.5 ± 1.0 and 2.6 ± 1.1) as well as the home area (114.8 ± 85.8 and 125.4 ± 87.4 m^2) respectively (Table 4.7). Furthermore, categorization of these variables did not reveal any difference between the two groups. Cases and controls were also compared in term of access to facilities at home. They reported approximately equal access to piped water, electricity, telephone with 92%, 99% and 83% respectively. Central heating system was not commonly used by both groups of cases and controls. On the other hand, controls reported a significantly higher access rate to the hot shower and piped gas at home compared to the controls. Access to the hot shower facility at home appeared to be a better determinant of economic status, since differences in the access rate to the piped gas could be due to unavailability of piped gas, as it is not available everywhere in the province. Results remained almost the same after excluding proxy interviews but association of GC with piped gas became non-significant.

4.4.2 Medical and family history and BMI

In this section cases and controls were compared regarding their medical and family history of cancer as body size. These factors included body mass index (BMI), ABO blood groups, Rh and family history of cancer (Table 4.8). The original four categories of BMI were re-categorized into two categories of over weight = BMI $\geq$ 25 and not over weight = BMI < 25 kg / m^2 because the number of people in the underweight and obese people were too small and approximately similar in cases and controls (Figure 4.4). A higher proportion of cases were overweight than controls showing an OR = 1.77.

Cases and controls were compared for "ABO" blood grouping system. Blood group "O" was considered as the reference group. Blood group "A" was slightly higher in the cases than controls, however, no significant association was observed between any blood groups and GC. Cases and controls were also compared in term of IgD which did not show a significant difference (OR = 1.47; 95% CI: 0.84 – 2.56).

In relation to the family history of cancer, 100 subjects reported a positive background of cancer in their first degree relatives. Fifty five of them were GC and 45 subjects reported other types of cancer in their first degree relatives. Subjects were divided into three categories of positive history for GC, other types of cancer or no background of familial cancer as the reference group. A significant increase in the risk was noted for those with a positive family history of GC (OR = 2.64). Although this association reduced after exclusion of proxies, there still remained a significant positive association. There was no association between GC and family history of other types of cancer.

4.4.3 Diet

As was explained in chapter three, frequency of consumption was measured in six categories, however by considering distribution of consumption among controls, it was re-categorized to form more meaningful categories of exposure. In this section association of GC with diet is presented in five subsections of vegetables and fruits, meat and dairy products, preserved foods and preservation methods, other dietary items and eating and drinking preferences.

4.4.3.1 Vegetables and fruits

In this sub-section, associations of GC with intake of vegetables and fruits were examined. There was no significant difference between cases and controls in

consumption of raw vegetables. For both cases and controls, more than 50% had consumed at least one serve per week of raw vegetables. Similarly no significant association was found between GC and the highest versus lowest consumption category of yellow-orange vegetables (Table 4.9).

An association was observed between GC and consumption of allium vegetables. Controls reported consuming allium vegetables twice as often as cases, although consumption of garlic was less common than onion. Those who consumed garlic more than three times per week were at lower risk than those who never or infrequently consumed it (OR = 0.42; p for trend < 0.01). Similarly a lower rate was observed among those who ate onion at least once per day compared to those eating less than twice per week (OR = 0.35; p for trend < 0.01) (Table 4.9).

A reduced risk was also observed for consumption of fruits overall, and citrus fruits in particular. Those who consumed fresh fruits at least three times per week had approximately 50% lower risk compared to those who never or infrequently ate them (OR = 0.45). A significant dose dependency was also observed (p < 0.01). However a greater inverse association was observed for consumption of citrus fruits than all fruits as general. Those who ate citrus fruits more than three times per week had approximately 70% lower risk than those who never or infrequently ate this group of fruits (OR = 0.28; p for trend < 0.01). No association was found for drinking juice with GC (Table 4.9).

4.4.3.2 Meats and dairy products

Associations of different types of animal protein including red meat, fish and poultry as well as dairy products are shown in Table 4.10. A high intake of red meat was

associated with an approximately 2.5 fold increased risk of GC. Those people consuming red meat at least once per day were at higher risk than those consuming it less than twice per week, with a significant dose dependency (OR = 2.71; p for trend < 0.01). This risk was greater after excluding the collected information from proxy interviews. In addition, cases tended to consume dairy products more frequently than controls. People who ate any dairy products more than once per day were at higher risk than those who consumed it less than twice per week (OR = 2.16). An increasing trend of risk was seen by increasing frequency of intake ($p < 0.01$). An increasing risk, but not significant, was also observed for consumption of cheese alone. In addition, a positive association was observed for consumption of chicken and poultry, however there was no dose dependency ($p < 0.11$). On the other hand, consumption of fresh fish was inversely associated with GC. Those people who ate fresh fish more than once per week had approximately 80% lower risk compared to those who never or infrequently ate it (OR = 0.22).

4.4.3.3 Preserved foods and preservation methods

Association of GC with intake of preserved foods including smoked meat and fish, salted fish, processed meat and pickled vegetables are presented in Table 4.11. Little variation was seen in the consumption frequency of the above mentioned items in this population, hence only two levels of intake were formed. No significant association was found between GC and consumption of any of these food items. In addition, there was no difference between cases and controls in term of their access to the refrigerator (OR = 1.10).

4.4.3.4 Other dietary items

Association of GC with beans, seeds and sweets are shown in Table 4.12. Cases and controls reported approximately similar frequency of intake for these dietary items. A significant association was not observed between GC and any of these dietary items. Results were similar for all cases whether proxies were included or not.

4.4.3.5 Drinking and eating preferences

The majority of subjects (> 99%) drank tea as the most common beverage after water in Ardabil province. This rate was similar in both groups of cases and controls. Almost all of the subjects drank black tea except seven subjects who drank green tea (five cases and two controls) and two drank herbal tea (one case and one control). While cases and controls were similar in term of frequency of drinking tea, cases drank hot and strong tea more than controls. Those who drank hot tea were significantly at higher risk than those drinking tea at mild temperatures (OR = 4.05). Similarly, cases drank strong tea significantly more than controls (OR = 3.89) (Table 4.13).

In addition, risks of GC rose with a high preference for the consumption of salt compared to non salty food. People with a preference for higher salt intake were approximately four times greater at risk of GC than those who prefer non-salty food (OR = 4.21) (Table 4.13).

4.4.4 Helicobacter pylori

In total, apart from 16 proxies who obviously were not able to give blood specimens, 595 subjects donated a blood specimen for laboratory tests. As was explained in chapter three, these collected blood specimens were centrifuged and serums were stored at –60°C until analysis. In the analysis, eight blood specimens, which had been collected

from controls, could not be identified because of unclear ID number in three subjects and missing in five subjects. Therefore 587 serums were analyzed using ELISA test (Biohit Corporation 2005) with sensitivity and specificity of 92.5% and 90.7% respectively.

One hundred and fifty five patients with GC and 269 control subjects were considered positive for *H. pylori* infection after considering the results of ELISA. The overall prevalence of *H. pylori* infection was 68.3% in the control subjects while it was 71.4% in the cases. However this prevalence was greater for the cases if the ratio was calculated against the existing number of serum. This means, after exclusion of proxies, prevalence of *H. pylori* infection was 77.1% (155 /201) for the cases. The prevalence was also higher for controls after excluding unidentified samples (269 / 386) which was 69.7%. In addition, 17 subjects had equivocal results, nine of which were cases and eight were controls. People with a positive result of *H. pylori* infection were at higher risk than those without (OR = 1.72; 95% CI: 1.12 – 2.63) (Table 4.14).

4.4.5 Lifestyles

Among lifestyles factors that may be related to GC, smoking, drinking alcoholic beverage and substance use were examined and the results are presented in this section.

4.4.5.1 Smoking

Subjects were asked about their history of ever smoking and whether they are currently smoking or not. Two hundred and forty four subjects had ever smoked tobacco at least once daily for 6 months or more. Sixty five of ever smokers had quit smoking and 179 were currently smoking. Seventy of current smokers were cases and 109 controls. Prevalence of current smoking in the controls was 27.7% which is close to the reported

prevalence in the study by Malekzadeh, Sotoudeh et al. (2004) in Ardabil. In this study a community based survey was conducted looking into the prevalence of gastric precancerous lesions in subjects aged 40 and above in the Ardabil and reported that 29.9% of subjects were smokers. Cigarettes were the most commonly used form of tobacco smoking (224 / 244) followed by hubble-bubble (smoking pipe that uses water to filter smoke) (19 / 244). One of the subjects reported using a special traditional pipe which is locally named "Chopogh". Cases were slightly more ever smoker (92 / 217) than controls (152 / 394) with a prevalence rate of 42.4% compared to 38.6% respectively, but this difference was not significant.

The influence of smoking on GC was examined in three steps. In the first step, cases and controls were compared in terms of ever smoking of different forms of tobacco. There was no significant association between GC and both methods of smoking: cigarette and hubble-bubble. Ever smokers were categorized as current and ex-smokers to find whether there was a risk difference between them or not. No significant association was observed between GC and both current and ex-smoking for overall tobacco smoking with OR of 1.22 and 0.97 respectively. Similarly no association was observed between GC and both current and ex-smoker of cigarettes with OR of 1.10 and 0.93 respectively (Table 4.15).

The next step examined the role of dose dependency by looking at the starting age of smoking, average cigarettes per day and total smoking years. The average age for starting smoking was 26.2 versus 26.3 for cases and controls respectively which was not statistically different ($p = 0.92$). The starting age of cigarette smoking was divided into three categories of below 20, 20 – 29 and 30 or more years and compared to those who had never smoked. As seen in Table 4.15 there was no significant association between

age of starting cigarettes and GC. The number of cigarettes smoked was assessed for week-days and week-ends separately. These numbers were summed up and the average number of cigarettes per day was calculated. These numbers were categorized into two groups of less than 20 and 20 or more per day and neither were significantly associated to GC (OR = 0.93) and (OR = 1.19) respectively. Total years of smoking were also calculated by subtracting the starting age from current age or age at cessation by considering duration of cessation which may have occurred between starting age and current age. Total years of smoking was divided into three categories of more than 35, 21 – 35 and 20 or less years and compared to the never smokers. This analysis did not also reveal any significant difference between cases and controls.

In the final step, cases and controls were compared regarding the intensity of smoke inhalation and using filtered cigarettes. Intensity of inhalation was categorized into two levels of deep and moderate to slight, and was compared with non-smokers. No significant association was observed between intensity of smoking and GC. In addition, risk in those using filtered cigarettes was compared to those without. Non-filtered cigarettes were rarely smoked by both groups of cases and controls. Although cases tended to use non-filtered cigarettes more than controls, this difference was not statistically significant (OR = 1.62; 95% CI: 0.63 – 4.14). In all analyses relating to smoking, exclusion of proxy interviews did not change the direction or significance of association (Table 4.15).

Since male smokers constituted the majority of smokers, a separate analysis was performed looking on the male smokers which are presented in Table 4.16. As seen in this table, results were approximately similar with those of all subjects.

4.4.5.2 Alcoholic beverage and opium

Thirty two participants answered "yes" to the question asking about their history of opium use by smoking. A higher proportion of cases (18 / 217) 8.3% were opium users than controls (14 / 394) 3.6%. There are several sources which have reported prevalence of drug use in Iran (Ministry of Health and Medical Education, Islamic Republic of Iran Police) with different prevalences ranging from 1.6% to 5.5%. In this study, 3.6% of controls were drug users (mostly opium) which is in the above mentioned range and also compatible with the latest report by the United Nations. In this report annual prevalence of opiate abuse was 2.8% of the population aged 15 – 64 (United Nations Office for Drug Control and Crime Prevention. 2004). Univariate analysis showed approximately 2.5 time increases in the risk of development to GC among opium users (OR = 2.45; 95% CI: 1.18 – 5.07). As seen in Table 4.17 both groups of cases and controls were approximately similar in the duration of drug abuse, about 12 years (p = 0.85). In relation to consumption of alcoholic beverages only 12 people reported a history of drinking. No statistical difference was observed between cases and controls in terms of alcohol drinking.

4.4.6 Occupation

As mentioned in chapter three, each job and industry reported by a subject was coded according to the International Standard Industrial Classification of all Economic Activities (ISIC) and International Standard Classification of Occupations (ISCO-88) respectively (International Labour Office. 1990; United Nations. Statistical Division 2004). However there were not a sufficient number of subjects in 6 / 10 of occupational categories (Figure 4.5). Similarly a sufficient number of subjects for statistical analysis were observed in only four industrial categories (Figure 4.6). Therefore the subject's

main activity was taken into account for analysis corresponding to the ISIC grouping scheme which is compatible to that classification which had been used in the Iranian National Census (Statistical Centre of Iran 1996). For the purposes of this analysis, jobs were compressed into five groups; agriculture, manufacturing, construction, wholesale and retail trade and other activities, and compared to the reference group. The group of unexposed included financial intermediation, real estate, public administration, education and private households with employed persons. The individuals who had worked in these industries plus those who had never worked or worked as home duties were grouped as the reference group.

Table 4.18 presents distributions of main activities among subjects showing only groups with at least five cases and controls. In general, except for 13 subjects who reported no history of work, the remainder reported a work history for at least six months, although 139 of them were home duties. Agricultural work was the most common job in both groups of cases (114 / 217) and controls (135 / 394) followed by construction, wholesale and retail trade as well as manufacturing. Four main activities of agriculture, constructions, wholesale and retail trade and manufacturing constituted about 75% of occupations which is close to the result of the national census in Ardabil that had reported 80% of people who had ever worked were in these four groups (Statistical Centre of Iran 1996).

An increasing risk of GC was observed among those working in agriculture and construction. People who were mainly working in agriculture and construction were approximately three times at higher risk than the reference group (OR = 3.13; 95% CI: 1.87 – 5.23) and (OR = 2.78; 95% CI: 1.38 – 5.62) respectively. No association was found between GC and working in the manufacturing and wholesale and retail trade.

Since the numbers of subjects were small, a separate analysis was not conducted for different subgroup of manufacturing and wholesale and retail trades (Table 4.18). A separate analysis was conducted for male workers as they constituted the majority of occupants in which a higher risk was found for both agriculture and construction. There was still no association between GC and other activities (Table 4.19).

4.5 Multivariate analysis

As discussed in chapter three, the final predictive model was constructed by considering the results of univariate analyses. Based on univariate analyses 18 variables were associated with GC. Two of these variables (education and access to hot shower at home) were indicators of SES. The association of these two variables with GC was examined in logistic regression in which education was significantly associated with GC. In the next step, full related variables (17 variables) were included in the logistic regression model. Six of these variables were removed from the model based on the result of backward logistic regression. The final predictive model included 12 variables: preference for salt intake, warmth and strength of tea, seropositivity for *H. pylori* and consumption of garlic, onion, citrus fruits, red meat, fish and dairy products, family history of GC and education as well as age groups and gender. In the following section results are presented in two sections. Firstly findings about those variables in the final predictive model are presented. The second section examines those variables which have been previously reported as possible risk factors for GC by adding them separately to the final model, although no association was found between them and GC in univariate analysis. A similar model was used for examining association of environmental factors with anatomical sub-sites and histopathologic sub-types of GC.

4.5.1 Variables included in the final predictive model

The final predictive model is presented in Table 4.20. The inverse association which was observed between GC and consumption of garlic, onion, citrus fruits and fresh fish, remains significant after adjustment for confounders. Risk of GC was approximately 65% lower in those who ate garlic more than three times per week compared to those who ate never or infrequently (OR = 0.35). The trend of this association was significant ($p < 0.01$). This inverse association was also observed among those who ate garlic 1 – 2 times per week, even though it was not as high as the highest category of consumption. Similarly, an inverse association was found for onion intake among those who consumed at least once a day (OR = 0.34; p for trend = 0.02). An inverse association which was found in univariate analysis between GC and consumption of fresh and citrus fruits remained only significant for citrus fruits intake after adjustment for confounders. Those who ate citrus fruits at least three times per week were at lower risk compared to those who ate them never or infrequently (OR = 0.31; p for trend < 0.01). Finally, consumption of fresh fish showed an inverse association with GC. People who ate fresh fish at least once a week were approximately 60% at lower risk than those never or infrequently ate fish (OR = 0.37; p for trend < 0.01).

In contrast to the consumption of allium vegetables, citrus fruits and fresh fish which had inverse association with GC, an increasing risk was observed for consumption of fresh red meat and dairy products. The value of OR for consumption of red meat, which was seen in univariate analysis, increased after adjustment for confounders. People who had at least one serve of red meat in their daily meal were 3.5 times at higher risk than those with less than two serves per week (p for trend < 0.01). Similarly a higher risk was found for those who consumed any dairy products at least once a day with a

significant dose dependency (OR = 2.28; p for trend < 0.01). In addition to red meat and dairy products, several dietary and drinking practices were also positively associated with GC. People who reported a preference for higher salt intake were approximately three times at higher risk than those who did not prefer salty food, although risk was attenuated after adjustment for confounders (OR = 3.10). Strength and warmth of tea were also positively associated with GC. People who drank hot tea were three times at higher risk compared to those drinking non-hot tea (OR = 2.85). This risk was 2.64 times in those who drank strong tea rather than light tea (Table 4.20).

In addition to the diet, an association was observed between GC and *H. pylori* infection and a positive history of GC in the first degree relatives. A positive association which was observed between GC and *H. pylori* infection became stronger after adjustment for confounders (OR = 2.41). In addition, people who had a positive history of GC were approximately 2.3 times at higher risk than those without a positive background. A positive history for cancer other than GC was not associated with GC (Table 4. 20)

4.5.2 Variables not included in the final predictive model

Other variables which did not show an association with GC in univariate analysis were also examined separately in the model. In relation to the dietary items, no significant associations were found between GC and preserved foods, sweets, seeds, beans, chicken and cheese. An inverse risk was observed between the second category of fresh fruit intake and GC, while this association was not observed for the highest category of intake (p for trend = 0.32). On the other hand an increasing risk was observed for high consumption of raw vegetables (≥ 3 times per week vs. never or infrequently) (Table 4. 21).

In relation to lifestyle related behaviors, associations between GC and smoking and alcoholic beverage still remained non-significant. Tobacco smoking overall and cigarette smoking in particular were not related to GC. A positive association which was observed between opium use and GC became just non-significant after adjustment for confounders (OR = 2.83; 95% CI: 0.99 – 8.08) (Table 4. 22).

An increasing risk which was observed among those who work in agriculture and construction was attenuated after adjustment for confounders. Although people working in these categories had approximately two times greater risk than those people working in the reference group, these associations were not statistically significant (OR = 1.96; 95% CI: 0.95 – 4.01) and (OR = 1.78; 95% CI: 0.67 – 4.76) for agriculture and construction respectively (Table 4. 23).

In relation to other factors, an inverse association was found between blood group "AB" and GC but it was not significant. Rh was also positive in cases twice as much as controls, however this difference was non-significant. There was also a non-significant increase of risk in those who were overweight (Table 4. 24).

4.6 Sub-sites analysis

The associations of environmental factors were examined in relation to the anatomical sub-sites of GC. The same model as overall analysis was used for this analyses. Findings are presented here in two sections. The first section examines those variables which were associated with GC in overall analysis, which is followed by another section presenting those variables which were not associated to GC in overall analysis.

4.6.1 Variables in the model

Allium vegetables (garlic and onion) were inversely associated with both cardia and non-cardia GC. However the association of onion was greater for non-cardia than cardia cancer. An inverse association was also observed between consumption of citrus fruits and both anatomical sub-sites, although association with non-cardia GC was non-significant. Consumption of fresh fish was also inversely associated with GC in both sub-sites but this association was not significant (Table 4. 25).

On the other hand, in the sub-site analysis, there was an association between consumption of red meat with both cardia and non-cardia cancer. However the magnitude of risk for cardia was approximately twice more than non-cardia cancer. People who ate fresh red meat at least once daily were 5.8 times at higher risk of GC in the cardia compared to those who ate red meat less than twice a week, whereas this risk was 2.9 for non-cardia cancer. In addition, consumption of dairy products showed a significantly increased risk of cardia cancer but not in non-cardia cancer. People who had consumed dairy products at least once a day were 3.1 times at greater risk of GC in cardia than those who ate less than twice a week, while this risk was 1.9 for non-cardia GC (Figure 4. 25).

Similar to the risk in the combined analysis, there was an increasing risk with strength of tea for both cardia and non-cardia. However, the magnitude of association was higher for cardia than non-cardia cancer with OR of 3.29 versus 2.68 respectively. Warmth of tea was also related to GC in both sub-sites; however, association was higher for the non-cardia than cardia cancer with OR of 4.38 versus 3.06 respectively. There was a preference for higher salt intake among those with non-cardia than cardia GC with OR of 4.94 versus 2.83 (Table 4.25).

A difference was observed between cardia and non-cardia GC in term of *H. pylori* infection and family history of GC. A higher rate of seropositivity was seen in both sub-sites compared to the control groups, but risk was greater for non-cardia GC than cardia with OR of 3.25 versus 2.02 respectively. This association was statistically significant only for non-cardia GC. The magnitude of this association was greater than that which was calculated for all cases. In addition, a strong increasing risk was observed for non-cardia cancer (OR = 5.28) in relation to the family history of GC which was twice as much as that of combined cases. This association was not found between cardia GC and history of GC in first degree relatives (Table 4. 25).

4.6.2 Variables not in the model

Sub-sites analysis was also conducted for other variables which were not in the model. Among dietary factors, no significant association was found between GC of both anatomical sub-sites and the remainder of dietary items with the exception for raw vegetables. Consumption of raw vegetables was positively associated to GC in both sub-sites. People who ate raw vegetables at least three times per week were at higher risk of GC than those who never or infrequently ate them (Table 4. 26). No significant association was observed between remaining dietary factors and anatomical sub-sites of GC.

In relation to lifestyle factors, there was no association between either overall tobacco or cigarette smoking and GC of both sub-sites. Categorization of smokers as current and ex-smokers also did not reveal any association. A higher risk of GC in both anatomical sub-sites was seen among those people who were opium users, even though it was not statistically significant. Sub-sites analysis was not performed for alcoholic beverages,

because the number of subjects who reported drinking alcohol was too small to be divided in two groups (Table 4. 27).

In relation to occupation, sub-site analysis did not reveal any significant association between GC of both sub-sites and any of the related categories although, the value of OR for non-cardia GC was at least twice greater than cardia among those who had worked in agriculture, construction and whole sales and retail trades (Table 4. 28).

Finally a sub-site analysis was performed for BMI and blood group. As seen in Table 4. 29, there was no difference between cardia and non-cardia GC in relation to the BMI. ABO blood group and Rh also did not show a significant association with both sub-sites, even though there was a variation of OR between these two anatomical sub-sites of GC.

4.7 Histopathologic analysis

Histopathologic analyses were conducted similar to those analyses which were performed for anatomical sub-sites. Results are reported in this section separately for those variables in the predictive models and those which were not.

4.7.1 Variables in the model

In relation to the dietary items which were in the model, an inverse association was observed between consumption of allium vegetables, citrus fruits and fresh fish and both histopathologic types of GC. Consumption of garlic and onion had an inverse association with both intestinal and diffuse types, however the magnitude of these inverse associations was greater in the diffuse than intestinal type of GC. In addition, the association of intestinal type of GC with consumption of garlic was not statistically significant. For citrus fruits, a negative association was observed for both

histopathologies which were close to the calculated risk of overall cases. Consumption of fresh fish was also inversely associated with both sub-types of GC, although it was statistically significant for only intestinal type (Table 4. 30).

On the other hand, two other dietary items of red meat and dairy products showed an increasing risk of GC in both histopathologic types. People who ate fresh red meats at least once daily were three times at higher risk of intestinal type of GC compared to those who had consumed meat less than twice per week. The magnitude of this association was lower and non-significant for diffuse type. In contrast to the red meat, dairy products showed a greater association with risk of diffuse type of GC, although both were significant (Table 4. 30).

In relation to drinking and dietary preferences, an increasing risk of both intestinal and diffuse type was observed among those who had high preference for drinking of hot and strong tea. However the risk in the intestinal type was slightly less than the diffuse type and also non-significant for strength of tea. For salt preference, there was an increasing risk of development to the both intestinal and diffuse type. However, the magnitude of risk was higher for intestinal than diffuse type with OR of 4.39 versus 2.25 respectively (Table 4. 30).

In relation to the non-dietary factors, no difference was found between intestinal and diffuse type of GC in term of *H. pylori* infection and a positive family history of GC. Those people infected with *H. pylori* were at twice the risk of both sub-types of cancer than uninfected people but these associations were non-significant. In addition, a positive history of GC in first degree relatives increased risk of both GC sub-types by three times, although this risk was non-significant for diffuse type (Table 4. 30).

4.7.2 Variables not in the model

Subgroup analysis was also conducted for other variables which were not in the model. Among dietary factors no significant association was found between GC of both histopathologic types and the remaining of dietary items, with the exception of yellow-orange vegetables. An increasing risk was only observed for highest versus lowest consumption of yellow-orange vegetables with intestinal type of GC. This association was marginally significant (OR = 2.70; 95% CI: 1.05 – 6.96) (Table 4. 31).

In relation to lifestyle, there was no association between either overall tobacco or cigarette smoking and GC of both intestinal and diffuse type. Categorization of smokers as current and ex-smokers did not also reveal any association. There was an increasing risk of intestinal type of GC among opium users but it was not significant. Risk could not be calculated for diffuse type in relation to the opium use, because there were only four opium users who developed to GC. This subgroup analysis could not be performed for alcoholic beverages due to the small number of subjects in each subgroup (Table 4.32).

In relation to the histopathologic classification, subgroup analysis did not reveal any significant association between GC of both intestinal and diffuse and none of the work-related categories (Table 4.33).

Finally association of BMI and blood groups was examined with different types of GC. Although a positive association was observed between the intestinal types of GC with BMI, this association was statistically non-significant. ABO blood group and Rh also did not show a significant association with both histopathologic types, although there was a variation of OR between these two types (Table 4. 34).

4.8 Population attributable risk

Population attributable risks (PAR) were calucalted for main risk factors of H. pylori infection, dietary items and preference for salt and warmth and strength of tea (Table 4.35). As shown in table the highest PAR was found for *H. pylori* infection followed by dairy products and preference for high salt intake.

In summary, *H. pylori* infection and diet were the major environmental determinants in the etiology of GC. In addition to these environmental factors, a positive history of GC in first degree relatives was also associated with increased risk of GC. Among dietary items, high consumption of red meat and dairy products increased the risk of GC. In addition, a preference for higher salt intake and drinking of hot and strong tea were positively associated with risk of GC. By contrast, an inverse association was found between GC and consumption of allium vegetables (garlic and onion), citrus fruits and fresh fish. Finally, non-cardia GC was more associated with environmental factors compared to cardia GC, although this difference was not observed for all environmental factors. No specific pattern was found to show a meaningful difference between intestinal and diffuse type of GC in term of risk factors.

Table 4. 1: Place of interview for cases and controls

Place of interview	Subjects				Total	%
	Case	%	Control	%		
Aras clinic	24	11.1	2	0.5	26	4.3
Home	59	27.2	313	79.5	372	60.9
Health center	6	2.8	75	19.0	81	13.2
Hospital	17	7.8	2	0.5	19	3.1
Work	1	0.4	2	0.5	3	0.5
Private clinics	110	50.8	0	0.0	110	18.0
Total	**217**	**100.0**	**394**	**100.0**	**611**	**100.0**

Table 4. 2: Demographic characteristics of cases and controls

Characteristics	Cases (%) (No: 217)	Controls (%) (No: 394)	P - value
Gender			
Male	151 (69.6)	265 (67.3)	
Female	66 (30.4)	129 (32.7)	a
Age groups (years)			
Less than 50	17 (7.8)	32 (8.1)	
50 – 59	35 (16.1)	68 (17.3)	
60 – 64	33 (15.2)	59 (15.0)	a
65 – 69	41 (18.9)	73 (18.5)	
70 – 74	41 (18.9)	71 (18.0)	
75 and more	50 (23.1)	91 (23.1)	
Average age (overall) ± SD	66.0 ± 11.6	64.7 ± 11.6	
Male	66.7 ± 10.4	65.0 ± 11.0	a
Female	64.3 ± 14.1	64.0 ± 12.8	
Residence			
Urban	103 (47.5)	204 (51.8)	0.31[b]
Rural	114 (52.5)	190 (48.2)	
Marital status			
Never married	3 (1.4)	6 (1.5)	
Married	184 (84.8)	316 (80.2)	0.30[b]
Widowed	29 (13.4)	72 (18.3)	
Missing	1 (0.4)	0 (0.0)	

(a) not tested because matched , (b) adjusted for gender and age group

Table 4. 3: Demographic characteristics in relation to the Lauren histopathologic classification of GC

Characteristics	Intestinal (No: 116)		Diffuse (No: 70)		Other (No: 31)		P - value
	No	%	No	%	No	%	
Gender							
Male	80	69.0	54	77.1	17	54.8	0.23[a]
Female	36	31.0	16	22.9	14	45.2	
Age groups							
Less than 50	5	4.3	7	10.0	5	16.1	0.39[a]
50 – 59	21	18.1	8	11.4	6	19.3	
60 – 64	17	14.7	14	20.0	2	6.5	
65 – 69	22	19.0	16	22.9	3	9.7	
70 – 74	22	19.0	11	15.7	8	25.8	
75 and more	29	25.0	14	20.0	7	22.6	
Average age ± SD	67.3 ± 9.9		64.7 ± 13.2				0.12[a]

a: not significant for intestinal vs. diffuse

Table 4. 4: Demographic characteristics in relation to the anatomical sub-sites of GC

Characteristics	Cardia (No: 115)		Non-cardia (No: 81)		Other (No: 21)		P - value
	No	%	No	%	No	%	
Gender							
Male	74	64.3	64	79.0	13	62.0	0.03
Female	41	35.7	17	21.0	8	38.0	
Age groups							
Less than 50	7	6.1	7	8.6	3	14.3	0.46
50 – 59	21	18.2	10	12.3	4	19.1	
60 – 64	17	14.8	14	17.3	2	9.5	
65 – 69	27	23.5	12	14.8	2	9.5	
70 – 74	20	17.4	16	19.8	5	23.8	
75 and more	23	20.0	22	27.2	5	23.8	
Average age ± SD	66.1 ± 9.9		66.4 ± 13.1				0.87[a]

a: not significant for cardia vs. non-cardia

Table 4. 5: Lauren histopathologic classification in relation to the anatomical sub-sites of GC

Histopathologic sub-types	Anatomical sub-sites					
	Cardia	%	Non-cardia	%	Other	%
Intestinal	64	55.7	50	61.7	2	9.5
Diffuse	26	22.6	28	34.6	16	76.2
Mix	13	11.3	0	0.0	1	4.8
Undifferentiated	12	10.4	3	3.7	2	9.5
Total	115	100.0	81	100.0	21	100.0

Table 4. 6: Socioeconomic indicators among cases and controls

Variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95 % CI)	OR[2] (95 % CI)	p - value
Highest level of education					
Literate	29 (13.4)	106 (26.9)	0.33 (0.20 – 0.55)	0.33 (0.20 – 0.56)	
Illiterate	188 (86.6)	288 (73.1)	1.00	1.00	
Schooling years ± SD	0.9 ± 2.8	1.9 ± 3.8			< 0.01
Monthly income ± SD	1,252,212 ± (1,323,095)	1,273,185 ± (1,714,505)			0.88
Income (Rials)					
≤ 500,000	47 (21.7)	93 (23.6)	1.07 (0.63 – 1.83)	1.05 (0.60 – 1.81)	
500,001 – 1,000,000	105 (48.4)	153 (38.8)	1.45 (0.91 – 2.31)	1.48 (0.92 – 2.37)	
1,000,001 – 1,500,000	27 (12.4)	68 (17.3)	0.84 (0.46 – 1.52)	0.80 (0.43 – 1.48)	
> 1,500,000	38 (17.5)	80 (20.3)	1.00	1.00	
Monthly expenses ± SD	1,265,645 ± (1,274,106)	1,332,652 ± (1,699,919)			0.61
Expenses (Rials)					
≤ 500,000	43 (19.8)	82 (20.8)	1.24 (0.72 – 2.15)	1.23 (0.70 – 2.17)	
500,001 – 1,000,000	106 (48.8)	147 (37.3)	1.69 (1.07 – 2.67)	1.78 (1.11 – 2.85)	
1,000,001 – 1,500,000	30 (13.8)	76 (19.3)	0.92 (0.52 – 1.63)	0.91 (0.50 – 1.65)	
> 1,500,000	38 (17.5)	89 (22.6)	1.00	1.00	

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)

Table 4. 7: Domestic related indicators among cases and controls

Variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95 % CI)	OR[2] (95 % CI)	p - value
Home area (m^2) ± SD	114.8 ± 85.8	125.4 ± 87.4			0.15
Home area (m^2)					
≤ 75	60 (27.6)	92 (23.3)	1.38 (0.85 – 2.23)	1.39 (0.85 – 2.30)	
76 – 100	72 (33.2)	121 (30.7)	1.25 (0.79 – 1.98)	1.31 (0.82 – 2.10)	
101 – 140	36 (16.6)	85 (21.6)	0.89 (0.53 – 1.51)	0.90 (0.52 – 1.55)	
> 140	46 (21.2)	96 (24.4)	1.00	1.00	
Missing	3 (1.4)	0 (0.0)	a	a	
Number of rooms ± SD	2.5 ±1.0	2.6 ± 1.1			0.52
Family members ± SD	5.5 ± 2.7	5.2 ± 2.9			0.30
Family members					
≤ 3	52 (24.0)	122 (31.0)	0.76 (0.45 – 1.29)	0.81 (0.47 – 1.38)	
4 – 5	56 (25.8)	103 (26.1)	1.00 (0.60 – 1.66)	1.00 (0.59 – 1.69)	
6 – 7	69 (31.8)	96 (24.4)	1.32 (0.80 – 2.18)	1.39 (0.83 – 2.34)	
> 7	39 (18.0)	72 (18.3)	1.00	1.00	
Missing	1 (0.4)	1 (0.2)	a	a	
Facilities at home					
Piped water					
Yes	198 (91.2)	366 (92.9)	0.80 (0.43 – 1.47)	0.73 (0.39 – 1.34)	
No	19 (8.8)	28 (7.1)	1.00	1.00	
Electricity					
Yes	215 (99.1)	392 (99.5)	0.55 (0.08 – 3.96)	0.50 (0.07 – 3.62)	
No	2 (0.9)	2 (0.5)	1.00	1.00	
Piped gas					
Yes	97 (44.7)	214 (54.3)	0.68 (0.48 – 0.95)	0.72 (0.51 – 1.01)	
No	120 (55.3)	180 (45.7)	1.00	1.00	
Hot shower					
Yes	121 (55.8)	265 (67.3)	0.61 (0.43 – 0.86)	0.61 (0.43 – 0.87)	
No	96 (44.2)	129 (32.7)	1.00	1.00	
Telephone					
Yes	186 (85.7)	326 (82.7)	1.26 (0.79 – 2.00)	1.20 (0.75 – 1.92)	
No	31 (14.3)	68 (17.3)	1.00	1.00	
Central heating					
Yes	2 (0.9)	2 (0.5)	a	a	
No	215 (99.1)	392 (99.5)			

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 8: Odds ratios (ORs) and 95% confidence interval (CI) of GC in relation to family and medical history

Variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
BMI (Before symptoms)				
Over weight	135 (62.2)	191 (48.5)	1.77 (1.25 – 2.49)	1.92 (1.35 – 2.73)
Not overweight	81 (37.3)	200 (50.8)	1.00	1.00
Don't know	1 (0.5)	3 (0.7)	a	a
BMI (Before symptoms)				
Obese	26 (12.0)	52 (13.2)	1.46 (0.14 – 14.88)	1.40 (0.14 – 14.33)
Over weight	109 (50.2)	139 (35.3)	2.30 (0.24 – 22.63)	2.19 (0.22 – 21.58)
Underweight	3 (1.4)	10 (2.5)	0.88 (0.06 – 12.06)	0.90 (0.07 – 12.43)
Normal	78 (35.9)	190 (48.2)	1.00	1.00
Don't know	1 (0.5)	3 (0.8)	a	a
Blood group				
A	76 (35.1)	121 (30.7)	1.43 (0.94 – 2.18)	b
B	48 (22.1)	93 (23.6)	1.18 (0.75 – 1.88)	
AB	7 (3.2)	30 (7.6)	0.52 (0.21 – 1.24)	
O	61 (28.1)	139 (35.3)	1.00	
Unknown	25 (11.5)	11 (2.8)	a	
Rh				
Positive	173 (79.7)	330 (83.8)	1.47 (0.84 – 2.56)	b
Negative	19 (8.8)	53 (13.4)	1.00	
Unknown	25 (11.5)	11 (2.8)	a	
Family history of cancer				
Gastric cancer	31 (14.3)	24 (6.1)	2.64 (1.49 – 4.68)	2.29 (1.27 – 4.15)
Other type of cancer	16 (7.4)	29 (7.4)	1.10 (0.58 – 2.08)	1.01 (0.52 – 1.98)
No cancer	170 (78.3)	341 (86.5)	1.00	1.00

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five
b: Was not calculated because blood samples were not collected from surrogates

Table 4. 9: ORs and 95% CI of GC in relation to the consumption of vegetables and fruits

variables	Cases (%) (No: 217)	Controls (%) (N0: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Raw vegetables				
≥ 3 times / week	58 (26.7)	95 (24.2)	1.31 (0.86 – 1.99)	1.37 (0.90 – 2.11)
1 – 2 times / week	70 (32.3)	113 (28.7)	1.33 (0.89 – 1.98)	1.27 (0.84 – 1.93)
Never or infrequently	88 (40.6)	184 (46.7)	1.00	1.00
Don't know	0 (0.0)	1 (0.2)	a	a
Missing	1 (0.4)	1 (0.2)	a	a
P for trend			0.13	0.12
Yellow-orange vegetables				
≥ 3 times / week	27 (12.4)	43 (10.9)	1.39 (0.82 – 2.37)	1.54 (0.90 – 2.63)
1 – 2 times / week	65 (30.0)	84 (21.3)	1.72 (1.16 – 2.54)	1.75 (1.17 – 2.62)
Never or infrequently	122 (56.2)	264 (67.0)	1.00	1.00
Don't know	2 (0.9)	1 (0.3)	a	a
Missing	1 (0.5)	2 (0.5)	a	a
P for trend			0.01	< 0.01
Garlic				
≥ 3 times / week	13 (6.0)	46 (11.7)	0.42 (0.22 – 0.81)	0.41 (0.21 – 0.81)
1 – 2 times / week	27 (12.5)	91 (23.1)	0.43 (0.27 – 0.69)	0.40 (0.25 – 0.66)
Never or infrequently	173 (79.7)	254 (64.5)	1.00	1.00
Don't know	2 (0.9)	2 (0.5)	a	a
Missing	2 (0.9)	1 (0.2)	a	a
P for trend			< 0.01	< 0.01
Onion				
≥ once per day	38 (17.5)	160 (40.6)	0.35 (0.23 – 0.55)	0.29 (0.18 – 0.46)
3 – 4 / week	78 (35.9)	86 (21.8)	1.36 (0.91 – 2.03)	1.22 (0.81 – 1.84)
≤ 2 times / week	98 (45.2)	147 (37.3)	1.00	1.00
Missing	3(1.4)	1 (0.3)	a	a
P for trend			< 0.01	< 0.01
Fresh fruits (total)				
≥ 3 times / week	68 (31.3)	137 (34.8)	0.45 (0.29 – 0.68)	0.46 (0.30 – 0.71)
1 – 2 times / week	58 (26.7)	172 (43.7)	0.30 (0.20 – 0.46)	0.30 (0.19 – 0.46)
Never or infrequently	89 (41.0)	82 (20.8)	1.00	1.00
Don't know	1 (0.5)	1 (0.2)	a	a
Missing	1 (0.5)	2 (0.5)	a	a
P for trend			< 0.01	< 0.01
Citrus fruits				
≥ 3 times / week	42 (19.4)	126 (32.0)	0.28 (0.18 – 0.44)	0.30 (0.19 – 0.47)
1 – 2 times / week	45 (20.7)	154 (39.1)	0.25 (0.16 – 0.38)	0.24 (0.16 – 0.37)
Never or infrequently	127 (58.5)	109 (27.7)	1.00	1.00
Don't know	2 (0.9)	4 (1.0)	a	a
Missing	1 (0.5)	1 (0.2)	a	a
P for trend			< 0.01	< 0.01
Juice				
≥ once / week	73 (33.6)	125 (31.7)	1.10 (0.77 – 1.57)	1.13 (0.79 – 1.63)
Never or infrequently	138 (63.6)	260 (66.0)	1.00	1.00
Don't know	5 (2.3)	8 (2.0)	a	a
Missing	1 (0.5)	1 (0.3)	a	a

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 10: ORs and 95% CI of GC in relation to the consumption of meat and dairy products

variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Fresh red meat				
≥ once / day	67 (30.9)	70 (17.8)	2.71 (1.75 – 4.20)	3.16 (2.01 – 4.96)
3 – 4 / week	76 (35.0)	125 (31.7)	1.71 (1.15 – 2.56)	2.05 (1.35 – 3.11)
≤ 2 times / week	70 (32.3)	195 (49.5)	1.00	1.00
Don't know	2 (0.9)	3 (0.8)	a	a
Missing	2 (0.9)	1 (0.2)	a	a
P for trend			< 0.01	< 0.01
Fresh fish				
≥ once / week	22 (10.1)	133 (33.8)	0.22 (0.14 – 0.36)	0.22 (0.13 – 0.36)
Never or infrequently	188 (86.6)	256 (65.0)	1.00	1.00
Don't know	6 (2.8)	4 (1.0)	a	a
Missing	1 (0.5)	1 (0.2)	a	a
Chicken				
≥ once / day	30 (13.8)	32 (8.1)	1.92 (1.11 – 3.33)	2.06 (1.18 – 3.60)
3 – 4 / week	74 (34.1)	134 (34.0)	1.12 (0.77 – 1.61)	1.19 (0.82 – 1.73)
≤ 2 times / week	111 (51.1)	226 (57.3)	1.00	1.00
Don't know	1 (0.5)	1 (0.3)	a	a
Missing	1 (0.5)	1 (0.3)	a	a
P for trend			0.11	0.05
Dairy products				
≥ once / day	107 (49.3)	182 (46.2)	2.16 (1.38 – 3.40)	2.07 (1.31 – 3.28)
3 – 4 / week	71 (32.7)	85 (21.6)	3.09 (1.88 – 5.07)	2.85 (1.72 – 4.73)
≤ 2 times / week	34 (15.7)	124 (31.5)	1.00	1.00
Don't know	4 (1.8)	2 (0.5)	a	a
Missing	1 (0.5)	1 (0.2)	a	a
P for trend			< 0.01	< 0.01
Cheese				
≥ once / day	163 (75.1)	292 (74.2)	1.56 (0.88 – 2.77)	1.75 (0.95 – 3.23)
3 – 4 / week	34 (15.7)	50 (12.7)	1.93 (0.96 – 3.89)	2.21 (1.06 – 4.61)
≤ 2 times / week	18 (8.3)	50 (12.7)	1.00	1.00
Don't know	0 (0.0)	1 (0.2)	a	a
Missing	2 (0.9)	1 (0.2)	a	a
P for trend			0.22	0.15

OR[1]: Adjusted for age groups and gender (all cases)
OR[2:] Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 11: ORs and 95% CI of GC in relation to the consumption of preserved foods and refrigerator use

variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Smoked meats				
≥ once / month	20 (9.2)	33 (8.4)	1.13 (0.63 – 2.02)	1.09 (0.60 – 1.99)
Never	189 (87.1)	350 (88.8)	1.00	1.00
Don't know	7 (3.2)	10 (2.5)	a	a
Missing	1 (0.5)	1 (0.3)	a	a
Smoked fish				
≥ once / month	59 (27.2)	112 (28.4)	0.94 (0.65 – 1.37)	0.97 (0.66 – 1.41)
Never	152 (70.0)	272 (69.0)	1.00	1.00
Don't know	5 (2.3)	9 (2.3)	a	a
Missing	1 (0.5)	1 (0.3)	a	a
Processed meats				
≥ once / month	23 (10.6)	50 (12.7)	0.84 (0.49 – 1.43)	0.80 (0.46 – 1.40)
Never	188 (86.6)	338 (85.8)	1.00	1.00
Don't know	5 (2.3)	5 (1.3)	a	a
Missing	1 (0.5)	1 (0.2)	a	a
Salted fish				
≥ once / month	35 (16.1)	74 (18.8)	0.84 (0.54 – 1.31)	0.76 (0.48 – 1.21)
Never	174 (80.2)	310 (78.7)	1.00	1.00
Don't know	7 (3.2)	9 (2.3)	a	a
Missing	1 (0.5)	1 (0.2)	a	a
Pickled vegetables				
≥ once / week	63 (29.0)	129 (32.7)	0.87 (0.61 – 1.26)	0.85 (0.58 – 1.23)
Never or infrequently	147 (67.8)	261 (66.3)	1.00	1.00
Don't know	5 (2.3)	3 (0.7)	a	a
Missing	2 (0.9)	1 (0.3)	a	a
Refrigerator				
Yes	202 (93.1)	364 (92.4)	1.10 (0.58 – 2.12)	1.02 (0.53 – 1.96)
No	15 (6.9)	30 (7.6)	1.00	1.00

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 12: ORs and 95% CI of GC in relation to the consumption of other food items

variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Beans				
≥ once / week	109 (50.2)	183 (46.4)	1.20 (0.85 – 1.68)	1.16 (0.82 – 1.64)
Never or infrequently	105 (48.4)	207 (52.6)	1.00	1.00
Don't know	2 (0.9)	3 (0.7)	a	a
Missing	1 (0.5)	1 (0.3)	a	a
Sweets				
≥ once / week	37 (17.0)	98 (24.9)	0.74 (0.49 – 1.12)	0.75 (0.49 – 1.14)
Never or infrequently	177 (81.6)	292 (74.1)	1.00	1.00
Missing	3 (1.4)	4 (10.0)	a	a
Seeds				
≥ once / week	13 (6.0)	34 (8.6)	0.69 (0.35 – 1.36)	0.64 (0.31 – 1.31)
Never or infrequently	200 (92.2)	357 (90.6)	1.00	1.00
Don't know	3 (1.4)	1 (0.3)	a	a
Missing	1 (0.4)	2 (0.5)	a	a

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects were less than five

Table 4. 13: ORs and 95% CI of GC in relation to the dietary habits

variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Strength of tea				
Strong tea	87 (40.1)	57 (14.5)	3.89 (2.63 – 5.78)	3.94 (2.64 – 5.87)
Not strong	129 (59.4)	327 (83.0)	1.00	1.00
Don't know	1 (0.5)	10 (2.5)	a	a
Warmth of tea				
Hot	106 (48.8)	74 (18.8)	4.05 (2.80 – 5.86)	3.94 (2.70 – 5.75)
Not hot	109 (50.3)	308 (78.1)	1.00	1.00
Don't know	2 (0.9)	12 (3.1)	a	a
Salt preference				
Salty	121 (55.8)	92 (23.4)	4.21 (2.93 – 6.03)	4.57 (3.16 – 6.62)
Not salty	95 (43.8)	299 (75.9)	1.00	1.00
Missing	1 (0.4)	3 (0.7)	a	a

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 14: ORs and 95% CI of GC in relation to the *H. pylori* infection

Helicobacter pylori	Cases (%) (No: 217)	Controls (%) (No: 394)	OR (95% CI)
Seropositivity			
Positive	155 (71.4)	269 (68.3)	1.72 (1.12 – 2.63)
Negative	37 (17.1)	109 (27.7)	1.00
Equivocal	9 (4.1)	8 (2.0)	a
Unknown	16 (7.4)	8 (2.0)	a

a: Was not calculated

Table 4. 15: ORs and 95% CI of GC in relation to the smoking

Variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Tobacco smoking				
Yes	92 (42.4)	152 (38.6)	1.15 (0.80 – 1.65)	1.27 (0.85 – 1.8 9)
No	125 (57.6)	242 (61.4)	1.00	1.00
Smoking methods				
Cigarette	82 (37.8)	142 (36.1)	1.10 (0.76 – 1.59)	1.12 (0.77 – 1.62)
Hubble-bubble	9 (4.1)	10 (2.5)	1.71 (0.66 – 4.39)	1.61 (0.61 – 4.27)
Other	1 (0.5)	0 (0.0)	a	a
Never	125 (57.6)	242 (61.4)	1.00	1.00
Tobacco smoking status				
Current smoker	70 ((32.3)	109 (27.7)	1.22 (0.83 – 1.81)	1.27 (0.85 – 1.89)
Ex-smoker	22 (10.1)	43 (10.9)	0.97 (0.55 – 1.71)	0.90 (0.49 –1.63)
Never smoker	125 (57.6)	242 (61.4)	1.00	1.00
Cigarette smoking				
Yes	82 (37.8)	142 (36.0)	1.05 (0.73 – 1.50)	1.07 (0.74 – 1.54)
No	135 (62.2)	252 (64.0)	1.00	1.00
Cigarette smoking status				
Current smoker	60 (27.7)	99 (25.1)	1.10 (0.74 – 1.65)	1.16 (0.77 – 1.74)
Ex-smoker	22 (10.1)	43 (10.9)	0.93 (0.53 – 1.63)	0.86 (0.48 – 1.55)
Never smoker	135 (62.2)	252 (64.0)	1.00	1.00
Age at Start (year)				
< 20	17 (7.8)	37 (9.4)	0.85 (0.45 – 1.58)	0.92 (0.49 – 1.73)
20 – 29	41 (18.9)	53 (13.4)	1.41 (0.88 – 2.28)	1.34 (0.82 – 2.20)
≥ 30	24 (11.1)	52 (13.2)	0.84 (0.49 – 1.44)	0.90 (0.53 – 1.55)
Never	135 (62.2)	252 (64.0)	1.00	1.00
Average cigarette per day				
≥ 20	41 (18.9)	79 (20.0)	0.93 (0.59 – 1.46)	0.90 (0.56 – 1.44)
< 20	41 (18.9)	63 (16.0)	1.19 (0.76 – 1.88)	1.27 (0.80 –2.01)
Never	135 (62.2)	252 (64.0)	1.00	1.00
Total smoking year				
> 35	46 (21.2)	62 (15.7)	1.36 (0.86 – 2.15)	1.35 (0.8 5 –2.16)
21 – 35	21 (9.7)	39 (9.9)	1.00 (0.55 – 1.81)	0.99(0.54 –1.84)
≤ 20	15 (6.9)	41 (10.4)	0.67 (0.35 – 1.26)	0.73 (0.39 – 1.38)
Never	135 (62.2)	252 (64.0)	1.00	1.00
Non-filtered VS. Filtered				
Non-filter	9 (4.2)	10 (2.5)	1.62 (0.63 – 4.14)	1.52 (0.58 – 4.01)
Filtered	68 (31.3)	125 (31.7)	0.99 (0.68 – 1.45)	1.04 (0.71 – 1.53)
Both equally	5 (2.3)	7 (1.8)	1.29 (0.40 – 4.17)	0.81 (0.20 – 3.24)
Never	135 (62.2)	252 (64.0)	1.00	1.00
Smoke inhalation				
Deeply	33 (15.2)	93 (23.6)	0.64 (0.40 – 1.02)	0.67 (0.42 – 1.08)
Moderately or slightly	49 (22.6)	48 (12.2)	1.87 (1.16 – 2.93)	1.84 (1.15– 2.95)
Never	135 (62.2)	252 (64.0)	1.00	1.00
Missing	0 (0.0)	1 (0.2)	a	a

OR[1] : Adjusted for age groups and gender (all cases)
OR[2] : Adjusted for age groups and gender (excluding proxies)
a : Was not calculated because number of subjects was less than five

Table 4. 16: ORs and 95% CI of GC in relation to the smoking among males

Variables	Cases (%) (No: 151)	Controls (%) (No: 265)	OR[1] (95% CI)	OR[2] (95% CI)
Tobacco smoking				
Yes	83 (55.0)	129 (48.7)	1.29 (0.86 – 1.93)	1.31 (0.87 – 1.99)
No	68 (45.0)	136 (51.3)	1.00	1.00
Smoking methods				
Cigarette	74 (49.0)	119 (44.9)	1.25 (0.83 – 1.89)	1.28 (0.84 – 1.96)
Hubble-bubble	8 (5.3)	10 (3.8)	1.59 (0.59 – 4.25)	1.50 (0.54 – 4.17)
Other	1 (0.7)	0 (0.0)	a	a
Never	68 (45.0)	136 (51.3)	1.00	1.00
Tobacco smoking status				
Current smoker	62 (41.1)	96 (36.2)	1.30 (0.84 – 2.01)	1.34 (0.86 –2.09)
Ex-smoker	21 (13.9)	33 (12.5)	1.27 (0.68 – 2.37)	1.24 (0.65 –2.36)
Never smoker	68 (45.0)	136 (51.3)	1.00	1.00
Cigarette smoking				
Yes	74 (49.0)	119 (44.9)	1.18 (0.79 – 1.77)	1.22 (0.81 – 1.84)
No	77 (51.0)	146 (55.1)	1.00	1.00
Cigarette smoking status				
Current smoker	53 (35.1)	86 (32.5)	1.18 (0.75 – 1.83)	1.23 (0.78 – 1.9 4)
Ex-smoker	21 (13.9)	33 (12.5)	1.20 (0.65 –2.23)	1.18 (0.63 –2.23)
Never smoker	77 (51.0)	146 (55.1)	1.00	1.00
Age at Start (year)				
< 20	16 (10.6)	33 (12.5)	0.94 (0.48 – 1.82)	1.02 (0.52 –2.00)
20 – 29	38 (25.2)	47 (17.7)	1.54 (0.92 – 2.57)	1.50 (0.89 – 2.55)
≥ 30	20 (13.2)	39 (14.7)	0.97 (0.53 – 1.77)	1.04 (0.57 – 1.92)
Never	77 (51.0)	146 (55.1)	1.00	1.00
Average cigarette per day				
≥ 20	39 (25.8)	69 (26.0)	1.06 (0.65 – 1.73)	1.07 (0.65 – 1.75)
< 20	35 (23.2)	50 (18.9)	1.35 (0.81 – 2.26)	1.43 (0.85 – 2.42)
Never	77 (51.0)	146 (55.1)	1.00	1.00
Total smoking year				
> 35	43 (28.5)	55 (20.8)	1.49 (0.91 – 2.43)	1.53 (0.9 3 –2.53)
21 – 35	18 (11.9)	33 (12.4)	1.05 (0.54 – 2.04)	1.01 (0.5 1 – 2.03)
≤ 20	13 (8.6)	31 (11.7)	0.79 (0.39 – 1.60)	0.85 (0.42 – 1.76)
Never	77 (51.0)	146 (55.1)	1.00	1.00
Non-filtered VS. Filtered				
Non-filter	8 (5.3)	9 (3.4)	1.65 (0.61 – 4.49)	1.57 (0.56 – 4.41)
Filtered	62 (41.1)	103 (38.9)	1.15 (0.75 – 1.75)	1.21 (0.79 – 1.86)
Both equally	4 (2.6)	7 (2.6)	a	a
Never	77 (51.0)	146 (55.1)	1.00	1.00
Smoke inhalation				
Deeply	32 (21.2)	77 (29.0)	0.79 (0.48 – 1.30)	0.83 (0.50 – 1.38)
Moderately or slightly	42 (27.8)	41 (15.5)	1.94 (1.16 – 3.24)	1.96 (1.16 –3.31)
Never	77 (51.0)	146 (55.1)	1.00	1.00
Missing	0 (0.0)	1 (0.4)	a	a

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)
a: Was not calculated because number of subjects was less than five

Table 4. 17: ORs and 95% CI of GC in relation to the alcohol drinking and opium use

variables	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Alcohol				
Yes	5 (2.3)	7 (1.8)	1.30 (0.40 – 4.20)	1.45 (0.45 –4.71)
No	212 (97.7)	387 (98.2)	1.00	1.00
Opium				
Yes	18 (8.3)	14 (3.6)	2.45 (1.18 – 5.07)	2.39 (1.12 –5.03)
No	199 (91.7)	380 (96.4)	1.00	1.00
Average years of drug use ± SD	12.67 ± 13.1	11.82 ± 11.3		

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)

Table 4. 18: ORs and 95% CI of GC in relation to the main job during last ten years

Main activities	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Main job during last 10 years				
Agriculture	114 (52.5)	135 (34.3)	3.13 (1.87 – 5.23)	3.22 (1.89 –5.48)
Manufacturing	9 (4.1)	30 (7.6)	1.13 (0.47 – 2.72)	1.14 (0.45 – 2.85)
Construction	28 (12.9)	40 (10.2)	2.78 (1.38 – 5.62)	3.03 (1.47 – 6.22)
Wholesale and retail trades	11 (5.1)	30 (7.6)	1.46 (0.62 – 3.44)	1.63 (0.d8 – 3.89)
Other	7 (3.2)	21 (5.3)	1.25 (0.47 – 3.32)	1.42 (0.53 – 3.79)
Reference group	48 (22.1)	138 (35.0)	1.00	1.00

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)

Table 4. 19: ORs and 95% CI of GC in relation to the main job among males

Main activities	Cases (%) (No: 217)	Controls (%) (No: 394)	OR[1] (95% CI)	OR[2] (95% CI)
Main job during last 10 years				
Agriculture	89 (58.9)	114 (43.0)	3.74 (1.62 – 8.66)	3.96 (1.63 – 9.59)
Manufacturing	9 (6.0)	26 (9.8)	1.65 (0.55 – 4.90)	1.68 (0.53 – 5.28)
Construction	28 (18.5)	40 (15.1)	3.34 (1.33 – 8.40)	3.70 (1.41 – 9.70)
Wholesale and retail trades	11 (7.3)	30 (11.3)	1.74 (0.61 – 4.96)	2.00 (0.68 – 5.89)
Other	6 (4.0)	19 (7.2)	1.47 (0.44 – 4.91)	1.70 (0.50 – 5.83)
Reference group	8 (5.3)	36 (13.6)	1.00	1.00

OR[1]: Adjusted for age groups and gender (all cases)
OR[2]: Adjusted for age groups and gender (excluding proxies)

Table 4. 20: Multivariate analysis for variables included in the predictive model

Variables	OR[1] (95% CI)	P for trend	OR[2] (95% CI)	P for trend
Garlic				
≥ 3 times / week	0.42 (0.22 – 0.81)	< 0.01	0.35 (0.13 – 0.95)	< 0.01
1 – 2 times / week	0.43 (0.27 – 0.69)		0.48 (0.25 – 0.91)	
Never or infrequently	1.00		1.00	
Onion				
≥ once per day	0.35 (0.23 – 0.55)	< 0.01	0.34 (0.19 – 0.62)	0.02
3 – 4 / week	1.36 (0.91 – 2.03)		1.28 (0.73 – 2.23)	
≤ 2 times / week	1.00		1.00	
Citrus fruits				
≥ 3 times / week	0.28 (0.18 – 0.44)	< 0.01	0.31 (0.17 – 0.59)	< 0.01
1 – 2 times / week	0.25 (0.16 – 0.38)		0.18 (0.10 – 0.33)	
Never or infrequently	1.00		1.00	
Fresh red meat				
≥ once / day	2.71 (1.75 – 4.20)	< 0.01	3.40 (1.79 – 6.46)	< 0.01
3 – 4 / week	1.71 (1.15 – 2.56)		2.20 (1.26 – 3.85)	
≤ 2 times / week	1.00		1.00	
Fresh fish				
≥ once / week	0.22 (0.14 – 0.36)	a	0.37 (0.19 – 0.70)	a
Never or infrequently	1.00		1.00	
Dairy products				
≥ once / day	2.16 (1.38 – 3.40)	< 0.01	2.28 (1.23 – 4.22)	< 0.01
3 – 4 / week	3.09 (1.88 – 5.07)		3.77 (1.92 – 7.42)	
≤ 2 times / week	1.00		1.00	
Salt preference				
Salty	4.21 (2.93 – 6.03)	a	3.10 (1.88 – 5.10)	a
Not salty	1.00		1.00	
Strength of tea				
Strong tea	3.89 (2.63 – 5.78)	a	2.64 (1.45 – 4.80)	a
Not strong	1.00		1.00	
Warmth of tea				
Hot	4.05 (2.80 – 5.86)	a	2.85 (1.65 – 4.91)	a
Not hot	1.00		1.00	
***H. pylori* seropositivity**				
Positive	1.72 (1.12 – 2.63)	a	2.41 (1.35 – 4.32)	a
Negative	1.00		1.00	
Equivocal and unknown	a		a	
Family history of cancer				
Gastric cancer	2.64 (1.49 – 4.68)	a	2.32 (1.11 – 4.85)	a
Other type of cancer	1.10 (0.58 – 2.08)		0.82 (0.33 – 2.01)	
No cancer	1.00		1.00	

OR[1]: Adjusted for gender and age group
OR[2]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*
a: was not calculated

Table 4. 21: Multivariate analysis for dietary variables which were not included in the predictive model

Variables	OR[1] (95% CI)	P for trend	OR[2] (95% CI)	P for trend
Raw vegetables				
≥ 3 times / week	1.31 (0.86 – 1.99)		2.08 (1.13 – 3.82)	
1 – 2 times / week	1.33 (0.89 – 1.98)	0.13	1.56 (0.89 – 2.73)	0.02
Never or infrequently	1.00		1.00	
Yellow-orange vegetables				
≥ 3 times / week	1.39 (0.82 – 2.37)		1.78 (0.81 – 3.89)	
1 – 2 times / week	1.72 (1.16 – 2.54)	0.01	2.07 (1.15 – 3.70)	0.01
Never or infrequently	1.00		1.00	
Fresh fruits (total)				
≥ 3 times / week	0.45 (0.29 – 0.68)		0.89 (0.43 – 1.86)	
1 – 2 times / week	0.30 (0.20 – 0.46)	< 0.01	0.44 (0.22 – 0.89)	0.32
Never or infrequently	1.00		1.00	
Juice				
≥ once / week	1.10 (0.77 – 1.57)	a	1.29 (0.73 – 2.29)	a
Never or infrequently	1.00		1.00	
Chicken				
≥ once / day	1.92 (1.11 – 3.33)		0.93 (0.39 – 2.20)	
3 – 4 / week	1.12 (0.77 – 1.61)	0.11	1.40 (0.80 – 2.42)	0.41
≤ 2 times / week	1.00		1.00	
Cheese				
≥ once / day	1.56 (0.88 – 2.77)		1.16 (0.54 – 2.51)	
3 – 4 / week	1.93 (0.96 – 3.89)	0.22	1.00 (0.39 – 2.56)	0.71
≤ 2 times / week	1.00		1.00	
Smoked meats				
≥ once / month	1.13 (0.63 – 2.02)	a	0.91 (0.40 – 2.09)	a
Never	1.00		1.00	
Smoked fish				
≥ once / month	0.94 (0.65 – 1.37)	a	1.09 (0.63 – 1.89)	a
Never	1.00		1.00	
Processed meats				
≥ once / month	0.84 (0.49 – 1.43)	a	1.14 (0.55 – 2.37)	a
Never	1.00		1.00	
Salted fish				
≥ once / month	0.84 (0.54 – 1.31)	a	1.08 (0.57 – 2.05)	a
Never	1.00		1.00	
Pickled vegetables				
≥ once / week	0.87 (0.61 – 1.26)	a	1.47 (0.84 – 2.58)	a
Never or infrequently	1.00		1.00	
Refrigerator				
Yes	1.10 (0.58 – 2.12)	a	1.07 (0.41 – 2.80)	a
No	1.00		1.00	
Beans				
≥ once / week	1.20 (0.85 – 1.68)	a	1.04 (0.65 – 1.66)	a
Never or infrequently	1.00		1.00	
Sweets				
≥ once / week	0.74 (0.49 – 1.12)	a	0.70 (0.38 – 1.29)	a
Never or infrequently	1.00		1.00	
Seeds				
≥ once / week	0.69 (0.35 – 1.36)	a	0.96 (0.37 – 2.46)	a
Never or infrequently	1.00		1.00	

OR[1]: Adjusted for gender and age group
OR[2]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*
a: was not calculated

Table 4. 22: Multivariate analysis for lifestyle related variables

Variables	OR[1] (95% CI)	P for trend	OR[2] (95% CI)	P for trend
Tobacco smoking				
Yes	1.15 (0.80 – 1.65)	a	0.90 (0.54 – 1.49)	a
No	1.00		1.00	
Smoking methods				
Cigarette	1.10 (0.76 – 1.59)		0.87 (0.52 – 1.46)	
Hubble-bubble	1.71 (0.66 – 4.39)	a	1.14 (0.29 – 4.42)	a
Other	a		b	
Never	1.00		1.00	
Tobacco smoking status				
Current smoker	1.22 (0.83 – 1.81)		0.77 (0.44 – 1.34)	
Ex-smoker	0.97 (0.55 – 1.71)	a	1.42 (0.63 – 3.18)	a
Never smoker	1.00		1.00	
Cigarette smoking				
Yes	1.05 (0.73 – 1.50)	a	0.86 (0.52 – 1.42)	a
No	1.00			
Cigarette smoking status				
Current smoker	1.10 (0.74 – 1.65)		0.71 (0.41 – 1.25)	
Ex-smoker	0.93 (0.53 – 1.63)	a	1.40 (0.63 – 3.12)	a
Never smoker	1.00		1.00	
Age at Start (year)				
< 20	0.85 (0.45 – 1.58)		0.54 (0.22 – 1.29)	
20 – 29	1.41 (0.88 – 2.28)	0.84	1.28 (0.65 – 2.54)	0.51
≥ 30	0.84 (0.49 – 1.44)		0.75 (0.36 – 1.54)	
Never	1.00		1.00	
Average cigarette per day				
≥ 20	0.93 (0.59 – 1.46)	0.58	0.67 (0.35 – 1.30)	0.35
< 20	1.19 (0.76 – 1.88)		1.07 (0.57 – 1.99)	
Never	1.00		1.00	
Total smoking year				
> 35	1.36 (0.86 – 2.15)		0.87 (0.45 – 1.70)	
21 – 35	1.00 (0.55 – 1.81)	0.53	1.11 (0.51 – 2.46)	0.80
≤ 20	0.67 (0.35 – 1.26)		0.61 (0.26 – 1.47)	
Never	1.00		1.00	
Non-filtered VS. Filtered				
Non-filter	1.62 (0.63 – 4.14)		0.99 (0.23 – 4.31)	
Filtered	0.99 (0.68 – 1.45)	a	0.86 (0.51 – 1.47)	a
Both equally	1.29 (0.40 – 4.17)		0.71 (0.15 – 3.41)	
Never	1.00		1.00	
Smoke inhalation				
Deeply	0.64 (0.40 – 1.02)	0.39	0.51 (0.27 – 0.99)	
Moderately or slightly	1.87 (1.16 – 2.93)		1.90 (0.91 – 4.01)	0.29
Never	1.00		1.00	
Alcohol				
Yes	1.30 (0.40 – 4.20)	a	2.03 (0.44 – 9.31)	a
No	1.00		1.00	
Opium				
Yes	2.45 (1.18 – 5.07)	a	2.83 (0.99 – 8.08)	a
No	1.00		1.00	

OR[1]: Adjusted for gender and age group
OR[2]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*
a: was not calculated

Table 4. 23: Multivariate analysis for occupational variables

Variables	OR[1] (95% CI)	OR[2] (95% CI)
Main job during last 10 years		
Agriculture	3.13 (1.87 – 5.23)	1.96 (0.95 – 4.01)
Manufacturing	1.13 (0.47 – 2.72)	0.80 (0.25 – 2.58)
Construction	2.78 (1.38 – 5.62)	1.78 (0.67 – 4.76)
Wholesale and retail trades	1.46 (0.62 – 3.44)	1.32 (0.39 – 4.49)
Other	1.25 (0.47 – 3.32)	0.71 (0.17 – 3.01)
Reference group	1.00	1.00

OR[1:] Adjusted for gender and age group
OR[2]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 24: Multivariate analysis for BMI and blood groups

Variables	OR[1] (95% CI)	OR[2] (95% CI)
BMI (Before symptoms)		
Over weight	1.77 (1.25 – 2.49)	1.57 (0.98 – 2.54)
Not overweight	1.00	1.00
Blood group		
A	1.43 (0.94 – 2.18)	1.44 (0.81 – 2.55)
B	1.18 (0.75 – 1.88)	1.15 (0.60 – 2.20)
AB	0.52 (0.21 – 1.24)	0.46 (0.14 – 1.49)
O	1.00	1.00
Rh		
Positive	1.47 (0.84 – 2.56)	2.08 (0.97 – 4.52)
Negative	1.00	1.00

OR[1]: Adjusted for gender and age group
OR[2]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 25: ORs and 95% CI of GC sub-sites in relation to the variables included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Garlic							
≥ 3 times / week	46 (11.7)	8 (6.9)	0.30 (0.09 – 1.07)	4 (4.9)	0.29 (0.05 – 1.92)	13 (6.0)	0.35 (0.13 – 0.95)
1 – 2 times / week	91 (23.1)	9 (7.8)	0.20 (0.08 – 0.54)	16 (19.8)	0.78 (0.33 – 1.87)	27 (12.5)	0.48 (0.25 – 0.91)
Never or infrequently	254 (64.5)	96 (83.5)	1.00	60 (74.1)	1.00	173 (79.7)	1.00
Don't know	2 (0.5)	1 (0.9)		0 (0.0)		2 (0.9)	
Missing	1 (0.2)	1 (0.9)		1 (1.2)		2 (0.9)	
Onion							
≥ once per day	160 (40.6)	21 (18.3)	0.38 (0.18 – 0.81)	11 (13.6)	0.14 (0.06 – 0.37)	38 (17.5)	0.34 (0.19 – 0.62)
3 – 4 / week	86 (21.8)	40 (34.7)	1.65 (0.83 – 3.30)	26 (32.1)	0.70 (0.31 – 1.59)	78 (35.9)	1.28 (0.73 – 2.23)
≤ 2 times / week	147 (37.3)	54 (47.0)	1.00	43 (53.1)	1.00	98 (45.2)	1.00
Missing	1 (0.3)	0 (0.0)		1 (1.2)		3(1.4)	
Citrus fruits							
≥ 3 times / week	126 (32.0)	24 (20.9)	0.28 (0.12 – 0.65)	16 (19.8)	0.43 (0.17 – 1.08)	42 (19.4)	0.31 (0.17 – 0.59)
1 – 2 times / week	154 (39.1)	24 (20.9)	0.22 (0.11 – 0.45)	20 (24.7)	0.22 (0.09 – 0.53)	45 (20.7)	0.18 (0.10 – 0.33)
Never or infrequently	109 (27.7)	66 (57.4)	1.00	43 (53.1)	1.00	127 (58.5)	1.00
Don't know	4 (1.0)	1 (0.8)		1 (1.2)		2 (0.9)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	
Fresh red meat							
≥ once / day	70 (17.8)	44 (38.3)	5.75 (2.52–13.08)	22 (27.2)	2.91 (1.13 – 7.54)	67 (30.9)	3.40 (1.79 – 6.46)
3 – 4 / week	125 (31.7)	37 (32.2)	2.15 (1.04 – 4.44)	34 (42.0)	3.19 (1.40 – 7.29)	76 (35.0)	2.20 (1.26 – 3.85)
≤ 2 times / week	195 (49.5)	33 (28.7)	1.00	22 (27.1)	1.00	70 (32.3)	1.00
Don't know	3 (0.8)	0 (0.0)		2 (2.5)		2 (0.9)	
Missing	1 (0.2)	1 (0.8)		1 (1.2)		2 (0.9)	
Fresh fish							
≥ once / week	133 (33.8)	12 (10.5)	0.45 (0.19 – 1.03)	10 (12.3)	0.38 (0.14 – 1.01)	22 (10.1)	0.37 (0.19 – 0.70)
Never or infrequently	256 (65.0)	102 (88.6)	1.00	67 (82.7)	1.00	188 (86.6)	1.00
Don't know	4 (1.0)	1 (0.9)		3 (3.7)		6 (2.8)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 25 (continued): ORs and 95% CI of GC sub-sites in relation to the variables included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Dairy products							
≥ once / day	182 (46.2)	63 (54.8)	3.05 (1.38 – 6.74)	39 (48.2)	1.87 (0.74 – 4.71)	107 (49.3)	2.28 (1.23 – 4.22)
3 – 4 / week	85 (21.6)	35 (30.4)	4.51 (1.88 –	24 (29.6)	2.62 (0.96 – 7.18)	71 (32.7)	3.77 (1.92 – 7.42)
≤ 2 times / week	124 (31.5)	17 (14.8)	10.82)	13 (16.1)	1.00	34 (15.7)	1.00
Don't know	2 (0.5)	0 (0.0)	1.00	4 (4.9)		4 (1.8)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	
Salt preference							
Salty	92 (23.4)	65 (56.5)	2.83 (1.54 – 5.20)	52 (64.2)	4.94 (2.43 – 10.05)	121 (55.8)	3.10 (1.88 – 5.10)
Not salty	299 (75.9)	50 (43.5)	1.00	28 (34.6)	1.00	95 (43.8)	1.00
Missing	3 (0.7)	0 (0.0)		1 (1.2)		1 (0.4)	
Strength of tea							
Strong tea	57 (14.5)	50 (43.5)	3.29 (1.61 – 6.71)	33 (40.8)	2.68 (1.14 – 6.34)	87 (40.1)	2.64 (1.45 – 4.80)
Not strong	327 (83.0)	65 (56.5)	1.00	47 (58.0)	1.00	129 (59.4)	1.00
Don't know	10 (2.5)	0 (0.0)		1 (1.0)		1 (0.5)	
Warmth of tea							
Hot	74 (18.8)	56 (48.7)	3.06 (1.57 – 5.96)	42 (51.9)	4.38 (2.02 – 9.52)	106 (48.8)	2.85 (1.65 – 4.91)
Not hot	308 (78.1)	58 (50.6)	1.00	38 (46.9)	1.00	109 (50.3)	1.00
Don't know	12 (3.1)	1 (0.8)		1 (1.2)		2 (0.9)	
***H. pylori* seropositivity**							
Positive	269 (68.3)	83 (72.2)	2.02 (0.98 – 4.16)	59 (72.8)	3.25 (1.27 – 8.33)	155 (71.4)	2.41 (1.35 – 4.32)
Negative	109 (27.7)	22 (19.1)	1.00	12 (14.8)	1.00	37 (17.1)	1.00
Equivocal and unknown	16 (4.0)	10 (8.7)		10 (12.3)		25 (11.5)	a
Family history of cancer							
Gastric cancer	24 (6.1)	12 (10.4)	0.94 (0.33 – 2.70)	15 (18.5)	5.28 (1.94 – 14.36)	31 (14.3)	2.32 (1.11 – 4.85)
Other type of cancer	29 (7.4)	10 (8.7)	0.61 (0.18 – 2.04)	5 (6.2)	1.02 (0.30 – 3.52)	16 (7.4)	0.82 (0.33 – 2.01)
No cancer	341 (86.5)	93 (80.9)	1.00	61 (75.3)	1.00	170 (78.3)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 26: ORs and 95% CI of GC sub-sites in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Raw vegetables							
≥ 3 times / week	95 (24.1)	33 (28.7)	2.20 (1.03 – 4.71)	22 (27.2)	2.89 (1.11 – 7.49)	58 (26.7)	2.08 (1.13 – 3.82)
1 – 2 times / week	113 (28.7)	38 (33.0)	1.93 (0.95 – 3.89)	25 (30.9)	1.43 (0.62 – 3.28)	70 (32.3)	1.56 (0.89 – 2.73)
Never or infrequently	184 (46.7)	44 (38.1)	1.00	33 (40.7)	1.00	88 (40.6)	1.00
Don't know	1 (0.2)	0 (0.0)		0 (0.0)		0 (0.0)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.4)	
Yellow-orange vegetables							
≥ 3 times / week	43 (10.9)	14 (12.2)	2.01 (0.72 – 5.61)	11 (13.6)	2.12 (0.67 – 6.73)	27 (12.4)	1.78 (0.81 – 3.89)
1 – 2 times / week	84 (21.3)	38 (33.0)	2.21 (1.09 – 4.49)	21 (25.9)	1.71 (0.71 – 4.12)	65 (30.0)	2.07 (1.15 – 3.70)
Never or infrequently	264 (67.0)	63 (54.8)	1.00	47 (58.1)	1.00	122 (56.2)	
Don't know	1 (0.3)	0 (0.0)		1 (1.2)		2 (0.9)	1.00
Missing	2 (0.5)	0 (0.0)		1 (1.2)		1 (0.5)	
Fresh fruits (total)							
≥ 3 times / week	137 (34.8)	35 (30.4)	0.65 (0.25 – 1.69)	29 (35.8)	1.08 (0.35 – 3.32)	68 (31.3)	0.89 (0.43 – 1.86)
1 – 2 times / week	172 (43.7)	33 (28.7)	0.48 (0.20 – 1.17)	20 (24.7)	0.24 (0.08 – 0.77)	58 (26.7)	0.44 (0.22 – 0.89)
Never or infrequently	82 (20.8)	46 (40.0)	1.00	31 (38.3)	1.00	89 (41.0)	1.00
Don't know	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Missing	2 (0.5)	0 (0.0)		1 (1.2)		1 (0.5)	
Juice							
≥ once / week	125 (31.7)	38 (33.0)	1.31 (0.65 – 2.67)	33 (40.7)	1.00 (0.44 – 2.30)	73 (33.6)	1.29 (0.73 – 2.29)
Never or infrequently	260 (66.0)	76 (66.1)	1.00	45 (55.6)	1.00	138 (63.6)	1.00
Don't know	8 (2.0)	1 (0.9)		2 (2.5)		5 (2.3)	
Missing	1 (0.3)	0 (0.0)		1 (1.2)		1 (0.5)	
						217 (100.0)	
Chicken							
≥ once / day	32 (8.1)	18 (15.6)	1.02 (0.37 – 2.79)	11 (13.6)	1.01 (0.28 – 3.66)	30 (13.8)	0.93 (0.39 – 2.20)
3 – 4 / week	134 (34.0)	39 (33.9)	1.25 (0.62 – 2.51)	34 (42.0)	2.12 (0.94 – 4.80)	74 (34.1)	1.40 (0.80 – 2.42)
≤ 2 times / week	226 (57.5)	58 (50.5)	1.00	35 (43.2)	1.00	111 (51.1)	1.00
Don't know	1 (0.2)	0 (0.0)		0 (0.0)		1 (0.5)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 26 (continued): ORs and 95% CI of GC sub-sites in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Smoked meats							
≥ once / month	33 (8.4)	12 (10.4)	0.75 (0.25 – 2.22)	7 (8.6)	0.90 (0.27 – 3.01)	20 (9.2)	0.91 (0.40 – 2.09)
Never	350 (88.8)	102 (88.7)	1.00	70 (86.4)	1.00	189 (87.1)	1.00
Don't know	10 (2.5)	1 (0.9)		3 (3.7)		7 (3.2)	
Missing	1 (0.3)	0 (0.0)		1 (1.2)		1 (0.5)	
Smoked fish							
≥ once / month	112 (28.4)	38 (33.0)	1.72 (0.86 – 3.47)	18 (22.2)	0.56 (0.24 – 1.30)	59 (27.2)	1.09 (0.63 – 1.89)
Never	272 (69.0)	77 (67.0)	1.00	59 (72.9)	1.00	152 (70.0)	1.00
Don't know	9 (2.3)	0 (0.0)		3 (3.7)		5 (2.3)	
Missing	1 (0.3)	0 (0.0)		1 (1.2)		1 (0.5)	
Processed meats							
≥ once / month	50 (12.7)	13 (11.3)	1.23 (0.50 – 3.05)	8 (9.9)	0.69 (0.22 – 2.24)	23 (10.6)	1.14 (0.55 – 2.37)
Never	338 (85.8)	102 (88.7)	1.00	69 (85.2)	1.00	188 (86.6)	1.00
Don't know	5 (1.3)	0 (0.0)		3 (3.7)		5 (2.3)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	
Salted fish							
≥ once / month	74 (18.8)	15 (13.0	1.17 (0.49 – 2.81)	16 (19.8)	1.30 (0.54 – 3.12)	35 (16.1)	1.08 (0.57 – 2.05)
Never	310 (78.7)	99 (86.1)	1.00	60 (74.1)	1.00	174 (80.2)	1.00
Don't know	9 (2.3)	1 (0.9)		4 (4.9)		7 (3.2)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	
Pickled vegetables							
≥ once / week	129 (32.7)	38 (33.1)	2.01 (0.99 – 4.09)	16 (19.8)	0.52 (0.22 – 1.26)	63 (29.0)	1.47 (0.84 – 2.58)
Never or infrequently	261 (66.2)	74 (64.3)	1.00	62 (76.5)	1.00	147 (67.8)	1.00
Don't know	3 (0.8)	3 (2.6)		1 (1.2)		5 (2.3)	
Missing	1 (0.3)	0 (0.0)		2 (2.5)		2 (0.9)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 26 (continued): ORs and 95% CI of GC sub-sites in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Cheese							
≥ once / day	292 (74.2)	91 (79.1)	2.79 (0.95 – 8.21)	61 (75.3)	0.69 (0.23 – 2.08)	163 (75.1)	1.16 (0.54 – 2.51)
3 – 4 / week	50 (12.7)	17 (14.8)	1.80 (0.50 – 6.50)	10 (12.4)	0.57 (0.14 – 2.27)	34 (15.7)	1.00 (0.39 – 2.56)
≤ 2 times / week	50 (12.7)	6 (5.2)	1.00	9 (11.1)	1.00	18 (8.3)	1.00
Don't know	1 (0.2)	0 (0.0)		0 (0.0)		0 (0.0)	
Missing	1 (0.2)	1 (0.9)		1 (1.2)		2 (0.9)	
Beans							
≥ once / week	183 (46.4)	58 (50.4)	1.11 (0.61 – 2.01)	44 (54.4)	1.21 (0.60 – 2.45)	109 (50.2)	1.04 (0.65 – 1.66)
Never or infrequently	207 (52.6)	56 (48.7)	1.00	36 (44.4)	1.00	105 (48.4)	1.00
Don't know	3 (0.8)	1 (0.9)		0 (0.0)		2 (0.9)	
Missing	1 (0.2)	0 (0.0)		1 (1.2)		1 (0.5)	
Sweets							
≥ once / week	98 (24.9)	20 (17.4)	0.90 (0.42 – 1.94)	12 (14.8)	0.41 (0.15 – 1.12)	37 (17.0)	0.70 (0.38 – 1.29)
Never or infrequently	292 (74.1)	94 (81.7)	1.00	67 (82.7)	1.00	177 (81.6)	1.00
Missing	4 (1.0)	1 (0.9)		2 (2.5)		3 (1.4)	
Seeds							
≥ once / week	34 (8.6)	5 (4.3)	0.81 (0.22 – 3.01)	6 (7.4)	1.12 (0.32 – 3.89)	13 (6.0)	0.96 (0.37 – 2.46)
Never or infrequently	357 (90.6)	108 (93.9)	1.00	74 (91.4)	1.00	200 (92.2)	1.00
Don't know	1 (0.3)	2 (1.7)		0 (0.0)		3 (1.4)	
Missing	2 (0.5)	0 (0.0)		1 (1.2)		1 (0.4)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 27: ORs and 95% CI of GC sub-sites in relation to the lifestyle related variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Tobacco smoking							
Yes	152 (38.6)	44 (38.3)	0.87 (0.45 – 1.67)	40 (49.4)	0.93 (0.44 – 1.98)	92 (42.4)	0.90 (0.54 – 1.49)
No	242 ((61.4)	71 (61.7)	1.00	41 (50.6)	1.00	125 (57.6)	1.00
Tobacco smoking status							
Current smoker	109 (27.7)	31 (27.0)	0.63 (0.30 – 1.30)	31 (38.3)	0.78 (0.34 – 1.78)	70 ((32.3)	0.77 (0.44 – 1.34)
Ex-smoker	43 (10.9)	13 (11.3)	2.05 (0.77 – 5.44)	9 (11.1)	1.68 (0.49 – 5.68)	22 (10.1)	1.42 (0.63 – 3.18)
Never smoker	242 (61.4)	71 (61.7)	1.00	41 (50.6)	1.00	125 (57.6)	1.00
Cigarette smoking							
Yes	142 (36.0)	39 (33.9)	0.82 (0.42 – 1.58)	37 (45.7)	1.01 (0.48 – 2.10)	82 (37.8)	0.86 (0.52 – 1.42)
No	252 (64.0)	76 (66.1)	1.00	44 (54.3)	1.00	135 (62.2)	1.00
Cigarette smoking status							
Current smoker	99 (25.1)	26 (22.6)	0.55 (0.26 – 1.18)	28 (34.6)	0.85 (0.38 – 1.91)	60 (27.7)	0.71 (0.41 – 1.25)
Ex-smoker	43 (10.9)	13 (11.3)	2.01 (0.76 – 5.30)	9 (11.1)	1.73 (0.51 – 5.84)	22 (10.1)	1.40 (0.63 – 3.12)
Never smoker	252 (64.0)	76 (66.1)	1.00	44 (54.3)	1.00	135 (62.2)	1.00
Opium							
Yes	14 (3.6)	6 (5.2)	2.11 (0.46 – 9.76)	10 (12.3)	2.27 (0.57 – 9.03)	18 (8.3)	2.83 (0.99 – 8.08)
No	380 (96.4)	109 (94.8)	1.00	71 (87.7)	1.00	199 (91.7)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 28: ORs and 95% CI of GC sub-sites in relation to the occupational variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Main job during last 10 years							
Agriculture	135 (34.3)	61 (53.0)	1.53 (0.64 – 3.65)	42 (51.8)	2.91 (0.91 – 9.37)	114 (52.5)	1.96 (0.95 – 4.01)
Manufacturing	30 (7.6)	4 (3.5)	0.36 (0.07 – 1.80)	5 (6.2)	1.46 (0.29 – 7.41)	9 (4.1)	0.80 (0.25 – 2.58)
Construction	40 (10.2)	13 (11.3)	1.18 (0.34 – 4.04)	14 (17.3)	2.52 (0.56 – 11.37)	28 (12.9)	1.78 (0.67 – 4.76)
Wholesale and retail trade	30 (7.6)	3 (2.7)	0.72 (0.12 – 4.30)	8 (9.9)	2.68 (0.52 – 13.95)	11 (5.1)	1.32 (0.39 – 4.49)
Other	21 (5.3)	5 (4.3)	0.38 (0.06 – 2.34)	1 (1.2)	1.03 (0.08 – 13.49)	7 (3.2)	0.71 (0.17 – 3.01)
Reference group	138 (35.0)	29 (25.2)	1.00	11 (13.6)	1.00	48 (22.1)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 29: ORs and 95% CI of GC sub-sites in relation to the BMI and blood groups were not included in the predictive model

Variables	Controls (%) (No: 394)	Cardia		Non-cardia		Total	
		Cases (%) (No: 115)	OR[1] (95%CI)	Cases (%) (No: 81)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
BMI (Before symptoms)							
Over weight and more	191 (48.5)	74 (64.3)	1.52 (0.84 – 2.75)	49 (60.5)	1.51 (0.72 – 3.15)	135 (64.0)	1.57 (0.98 – 2.54)
Normal and underweight	200 (50.8)	40 (34.8)	1.00	32 (39.5)	1.00	81(35.5)	1.00
Don't know	3 (0.7)	1 (0.9)		0 (0.0)		1 (0.5)	
Blood group							
A	121 (30.7)	39 (33.9)	1.07 (0.53 – 2.16)	30 (37.0)	1.86 (0.74 – 4.72)	76 (35.1)	1.44 (0.81 – 2.55)
B	93 (23.6)	24 (20.9)	0.64 (0.27 – 1.49)	22 (27.2)	2.25 (0.86 – 5.90)	48 (22.1)	1.15 (0.60 – 2.20)
AB	30 (7.6)	4 (3.5)	0.26 (0.6 – 1.14)	3 (3.7)	1.00	7 (3.2)	0.46 (0.14 – 1.49)
O	139 (35.3)	38 (33.0)	1.00	19 (23.5)		61 (28.1)	1.00
Unknown	11 (2.8)	10 (8.7)		7 (8.6)		25 (11.5)	
Rh							
Positive	330 (83.8)	98 (85.2)	2.95 (0.91 – 9.55)	64 (79.0)	1.31 (0.48 – 3.56)	173 (79.7)	2.08 (0.97 – 4.52)
Negative	53 (13.5)	7 (6.1)	1.00	10 (12.3)	1.00	19 (8.8)	1.00
Unknown	11 (2.8)	10 (8.7)		7 (8.6)		25 (11.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 30: ORs and 95% CI of GC histopathologies in relation to the variables were included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 116)	OR[1] (95%CI)	Cases (%) (No:70)	OR[1] (95%CI)	Cases (%) (No: 217)	OR[1] (95%CI)
Garlic							
≥ 3 times / week	46 (11.7)	8 (6.9)	0.59 (0.18 – 1.94)	2 (2.9)	0.05 (0.00 – 0.78)	13 (6.0)	0.35 (0.13 – 0.95)
1 – 2 times / week	91 (23.1)	13 (11.2)	0.40 (0.17 – 0.93)	6 (8.6)	0.16 (0.04 – 0.58)	27 (12.5)	0.48 (0.25 – 0.91)
Never or infrequently	254 (64.5)	93 (80.2)	1.00	61 (87.1)	1.00	173 (79.7)	1.00
Don't know	2 (0.5)	0 (0.0)		1 (1.4)		2 (0.9)	
Missing	1 (0.2)	2 (1.7)		0 (0.0)		2 (0.9)	
Onion							
≥ once per day	160 (40.6)	21 (18.1)	0.39 (0.19 – 0.82)	12 (17.2)	0.20 (0.07 – 0.58)	38 (17.5)	0.34 (0.19 – 0.62)
3 – 4 / week	86 (21.8)	41 (35.3)	1.42 (0.71 – 2.84)	31 (44.3)	1.81 (0.78 – 4.21)	78 (35.9)	1.28 (0.73 – 2.23)
≤ 2 times / week	147 (37.3)	53 (45.7)	1.00	26 (37.1)	1.00	98 (45.2)	1.00
Missing	1 (0.3)	1 (0.9)		1 (1.4)		3(1.4)	
Citrus fruits							
≥ 3 times / week	126 (32.0)	25 (21.6)	0.30 (0.13 – 0.69)	9 (12.9)	0.25 (0.09 – 0.68)	42 (19.4)	0.31 (0.17 – 0.59)
1 – 2 times / week	154 (39.1)	28 (24.1)	0.27 (0.13 – 0.54)	10 (14.3)	0.09 (0.03 – 0.28)	45 (20.7)	0.18 (0.10 – 0.33)
Never or infrequently	109 (27.7)	62 (53.4)	1.00	49 (70.0)	1.00	127 (58.5)	1.00
Don't know	4 (1.0)	0 (0.0)		2 (2.8)		2 (0.9)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Fresh red meat							
≥ once / day	70 (17.8)	39 (33.6)	3.05 (1.34 – 6.94)	11 (15.7)	1.54 (0.54 – 4.41)	67 (30.9)	3.40 (1.79 – 6.46)
3 – 4 / week	125 (31.7)	42 (36.3)	2.68 (1.30 – 5.55)	27 (38.6)	1.92 (0.85 – 4.35)	76 (35.0)	2.20 (1.26 – 3.85)
≤ 2 times / week	195 (49.5)	33 (28.5)	1.00	30 (42.9)	1.00	70 (32.3)	1.00
Don't know	3 (0.8)	1 (0.8)		1 (1.4)		2 (0.9)	
Missing	1 (0.2)	1 (0.8)		1 (1.4)		2 (0.9)	
Fresh fish							
≥ once / week	133 (33.8)	10 (8.6)	0.33 (0.14 – 0.80)	5 (7.1)	0.29 (0.08 – 1.02)	22 (10.1)	0.37 (0.19 – 0.70)
Never or infrequently	256 (65.0)	104 (89.6)	1.00	60 (85.8)	1.00	188 (86.6)	1.00
Don't know	4 (1.0)	1 (0.9)		5 (7.1)		6 (2.8)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 30 (continued): ORs and 95% CI of GC histopathologies in relation to the variables were included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 116)	OR [1] (95%CI)	Cases (%) (No:70)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Dairy products							
≥ once / day	182 (46.2)	65 (56.0)	2.41 (1.10 – 5.29)	23 (32.9)	3.71 (1.27 – 10.89)	107 (49.3)	2.28 (1.23 – 4.22)
3 – 4 / week	85 (21.6)	30 (25.9)	2.62 (1.09 – 6.28)	34 (48.6)	1.32 (0.32 – 5.33)	71 (32.7)	3.77 (1.92 – 7.42)
≤ 2 times / week	124 (31.5)	18 (15.5)	1.00	11 (15.7)	1.00	34 (15.7)	1.00
Don't know	2 (0.5)	2 (1.7)		2 (2.8)		4 (1.8)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Salt preference							
Salty	92 (23.4)	72 (62.1)	4.39 (2.37 – 8.13)	30 (42.9)	2.25 (1.05 – 4.87)	121 (55.8)	3.10 (1.88 – 5.10)
Not salty	299 (75.9)	43 (37.1)	1.00	40 (57.1)	1.00	95 (43.8)	1.00
Missing	3 (0.7)	1 (0.9)		0 (0.0)		1 (0.4)	
Strength of tea							
Strong tea	57 (14.5)	48 (41.4)	2.00 (0.98 – 4.08)	24 (34.3)	2.49 (1.01 – 6.17)	87 (40.1)	2.64 (1.45 – 4.80)
Not strong	327 (83.0)	68 (58.6)	1.00	45 (64.3)	1.00	129 (59.4)	1.00
Don't know	10 (2.5)	0 (0.0)		1 (1.4)		1 (0.5)	
Warmth of tea							
Hot	74 (18.8)	62 (53.4)	3.64 (1.87 – 7.08)	28 (40.0)	3.94 (1.69 – 9.18)	106 (48.8)	2.85 (1.65 – 4.91)
Not hot	308 (78.1)	53 (45.7)	1.00	41 (58.6)	1.00	109 (50.3)	1.00
Don't know	12 (3.1)	1 (0.9)		1 (1.4)		2 (0.9)	
***H. pylori* seropositivity**							
Positive	269 (68.3)	82 (70.7)	1.93 (0.92 – 4.01)	47 (67.1)	1.95 (0.81 – 4.70)	155 (71.4)	2.41 (1.35 – 4.32)
Negative	109 (27.7)	24 (20.7)	1.00	12 (17.1)	1.00	37 (17.1)	1.00
Equivocal and unknown	16 (4.0)	10 (8.6)		11 (15.7)		25 (11.5)	a
Family history of cancer							
Gastric cancer	24 (6.1)	21 (18.1)	3.11 (1.29 – 7.51)	8 (11.4)	3.05 (0.92 – 10.14)	31 (14.3)	2.32 (1.11 – 4.85)
Other type of cancer	29 (7.4)	8 (6.9)	0.80 (0.24 – 2.64)	5 (7.2)	1.32 (0.32 – 5.33)	16 (7.4)	0.82 (0.33 – 2.01)
No cancer	341 (86.5)	87 (75.0)	1.00	57 (81.4)	1.00	170 (78.3)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 31: ORs and 95% CI of GC histopathologies in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 115)	OR [1] (95%CI)	Cases (%) (No: 81)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Raw vegetables							
≥ 3 times / week	95 (24.1)	32 (27.6)	1.75 (0.81 – 3.78)	14 (20.0)	2.41 (0.89 – 6.50)	58 (26.7)	2.08 (1.13 – 3.82)
1 – 2 times / week	113 (28.8)	32 (27.6)	0.99 (0.48 – 2.05)	28 (40.0)	3.21 (1.31 – 7.91)	70 (32.3)	1.56 (0.89 – 2.73)
Never or infrequently	184 (46.7)	51 (44.0)	1.00	28 (40.0)	1.00	88 (40.6)	1.00
Don't know	1 (0.2)	0 (0.0)		0 (0.0)		0 (0.0)	
Missing	1 (0.2)	1 (0.8)		0 (0.0)		1 (0.4)	
Yellow-orange vegetables							
≥ 3 times / week	43 (10.9)	19 (16.5)	2.70 (1.05 – 6.96)	4 (5.7)	1.70 (0.39 – 7.45)	27 (12.4)	1.78 (0.81 – 3.89)
1 – 2 times / week	84 (21.3)	26 (22.4)	1.41 (0.65 – 3.09)	28 (40.0)	6.33 (2.47 – 16.23)	65 (30.0)	2.07 (1.15 – 3.70)
Never or infrequently	264 (67.0)	69 (59.5)	1.00	37 (52.9)	1.00	122 (56.2)	
Don't know	1 (0.3)	1 (0.8)		1 (1.4)		2 (0.9)	1.00
Missing	2 (0.5)	1 (0.8)		0 (0.0)		1 (0.5)	
Fresh fruits (total)							
≥ 3 times / week	137 (34.8)	41 (35.4)	1.15 (0.44 – 2.97)	17 (24.3)	0.58 (0.18 – 1.83)	68 (31.3)	0.89 (0.43 – 1.86)
1 – 2 times / week	172 (43.7)	27 (23.3)	0.33 (0.13 – 0.87)	17 (24.3)	0.39 (0.14 – 1.14)	58 (26.7)	0.44 (0.22 – 0.89)
Never or infrequently	82 (20.8)	46 (39.7)	1.00	36 (51.4)	1.00	89 (41.0)	1.00
Don't know	1 (0.2)	1 (0.8)		0 (0.0)		1 (0.5)	
Missing	2 (0.5)	1 (0.8)		0 (0.0)		1 (0.5)	
Juice							
≥ once / week	125 (31.7)	39 (33.6)	0.89 (0.43 – 1.84)	18 (25.7)	1.34 (0.51 – 3.47)	73 (33.6)	1.29 (0.73 – 2.29)
Never or infrequently	260 (66.0)	76 (65.6)	1.00	49 (70.0)	1.00	138 (63.6)	1.00
Don't know	8 (2.0)	0 (0.0)		3 (4.3)		5 (2.3)	
Missing	1 (0.3)	1 (0.8)		0 (0.0)		1 (0.5)	
Chicken							
≥ once / day	32 (8.1)	18 (15.5)	0.78 (0.27 – 2.24)	8 (11.4)	1.51 (0.40 – 5.70)	30 (13.8)	0.93 (0.39 – 2.20)
3 – 4 / week	134 (34.0)	42 (36.2)	1.29 (0.65 – 2.58)	16 (22.9)	0.94 (0.38 – 2.35)	74 (34.1)	1.40 (0.80 – 2.42)
≤ 2 times / week	226 (57.4)	55 (47.4)	1.00	45 (64.3)	1.00	111 (51.1)	1.00
Don't know	1 (0.2)	0 (0.0)		1 (1.4)		1 (0.5)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 31 (continued): ORs and 95% CI of GC histopathologies in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 115)	OR [1] (95%CI)	Cases (%) (No: 81)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Smoked meats							
≥ once / month	33 (8.4)	9 (7.8)	0.58 (0.19 – 1.76)	8 (11.4)	0.98 (0.28 – 3.44)	20 (9.2)	0.91 (0.40 – 2.09)
Never	350 (88.8)	103 (88.8)	1.00	59 (84.3)	1.00	189 (87.1)	1.00
Don't know	10 (2.5)	3 (2.6)		3 (4.3)		7 (3.2)	
Missing	1 (0.3)	1 (0.8)		0 (0.0)		1 (0.5)	
Smoked fish							
≥ once / month	112 (28.4)	33 (28.4)	1.23 (0.61 – 2.48)	15 (21.4)	0.76 (0.31 – 1.87)	59 (27.2)	1.09 (0.63 – 1.89)
Never	272 (69.0)	81 (69.8)	1.00	51 (72.9)	1.00	152 (70.0)	1.00
Don't know	9 (2.3)	1 (0.9)		4 (5.7)		5 (2.3)	
Missing	1 (0.3)	1 (0.9)		0 (0.0)		1 (0.5)	
Processed meats							
≥ once / month	50 (12.7)	8 (6.9)	0.43 (0.14 – 1.26)	9 (12.9)	1.28 (0.40 – 4.05)	23 (10.6)	1.14 (0.55 – 2.37)
Never	338 (85.8)	106 (91.3)	1.00	57 (81.4)	1.00	188 (86.6)	1.00
Don't know	5 (1.3)	1 (0.9)		4 (5.7)		5 (2.3)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Salted fish							
≥ once / month	74 (18.8)	19 (16.4)	1.27 (0.56 – 2.89)	13 (18.6)	1.16 (0.44 – 3.05)	35 (16.1)	1.08 (0.57 – 2.05)
Never	310 (78.7)	94 (81.0)	1.00	52 (74.3)	1.00	174 (80.2)	1.00
Don't know	9 (2.3)	2 (1.7)		5 (7.1)		7 (3.2)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Pickled vegetables							
≥ once / week	129 (32.7)	34 (29.3)	1.40 (0.69 – 2.83)	19 (27.1)	0.86 (0.35 – 2.12)	63 (29.0)	1.47 (0.84 – 2.58)
Never or infrequently	261 (66.2)	79 (68.1)	1.00	48 (68.6)	1.00	147 (67.8)	1.00
Don't know	3 (0.8)	1 (0.9)		3 (4.3)		5 (2.3)	
Missing	1 (0.3)	2 (1.7)		0 (0.0)		2 (0.9)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 31 (continued): ORs and 95% CI of GC histopathologies in relation to the dietary variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 115)	OR [1] (95%CI)	Cases (%) (No: 81)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Cheese							
≥ once / day	292 (74.2)	88 (75.9)	1.92 (0.65 – 5.67)	48 (68.6)	0.38 (0.13 – 1.12)	163 (75.1)	1.16 (0.54 – 2.51)
3 – 4 / week	50 (12.7)	19 (16.4)	1.83 (0.51 – 6.59)	11 (15.7)	0.21 (0.05 – 0.85)	34 (15.7)	1.00 (0.39 – 2.56)
≤ 2 times / week	50 (12.7)	7 (6.0)	1.00	11 (15.7)	1.00	18 (8.3)	1.00
Don't know	1 (0.2)	0 (0.0)		0 (0.0)		0 (0.0)	
Missing	1 (0.2)	2 (1.7)		0 (0.0)		2 (0.9)	
Beans							
≥ once / week	183 (46.4)	63 (54.3)	1.21 (0.66 – 2.19)	31 (44.3)	0.86 (0.41 – 1.83)	109 (50.2)	1.04 (0.65 – 1.66)
Never or infrequently	207 (52.6)	52 (44.8)	1.00	37 (52.9)	1.00	105 (48.4)	1.00
Don't know	3 (0.8)	0 (0.0)		2 (2.8)		2 (0.9)	
Missing	1 (0.2)	1 (0.9)		0 (0.0)		1 (0.5)	
Sweets							
≥ once / week	98 (24.9)	16 (13.8)	0.46 (0.19 – 1.08)	12 (17.1)	0.98 (0.36 – 2.63)	37 (17.0)	0.70 (0.38 – 1.29)
Never or infrequently	292 (74.1)	99 (85.3)	1.00	56 (80.0)	1.00	177 (81.6)	1.00
Missing	4 (1.0)	1 (0.9)		2 (2.9)		3 (1.4)	
Seeds							
≥ once / week	34 (8.6)	6 (5.1)	0.96 (0.28 – 3.33)	4 (5.7)	0.47 (0.09 – 2.54)	13 (6.0)	0.96 (0.37 – 2.46)
Never or infrequently	357 (90.6)	108 (93.1)	1.00	64 (91.4)	1.00	200 (92.2)	1.00
Don't know	1 (0.3)	1 (0.9)		2 (2.9)		3 (1.4)	
Missing	2 (0.5)	1 (0.9)		0 (0.0)		1 (0.4)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 32: ORs and 95% CI of GC histopathologies in relation to the lifestyle related variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 116)	OR [1] (95%CI)	Cases (%) (No:70)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Tobacco smoking							
Yes	152 (38.6)	49 (42.2)	0.93 (0.49 – 1.76)	34 (48.6)	1.13 (0.52 – 2.46)	92 (42.4)	0.90 (0.54 – 1.49)
No	242 ((61.4)	67 (57.8)	1.00	36 (51.4)	1.00	125 (57.6)	1.00
Tobacco smoking status							
Current smoker	109 (27.7)	36 (31.0)	0.73 (0.36 – 1.48)	27 (38.6)	1.03 (0.44 – 2.38)	70 ((32.3)	0.77 (0.44 – 1.34)
Ex-smoker	43 (10.9)	13 (11.2)	1.87 (0.69 – 5.06)	7 (10.0)	1.61 (0.42 – 6.17)	22 (10.1)	1.42 (0.63 – 3.18)
Never smoker	242 (61.4)	67 (57.8)	1.00	36 (51.4)	1.00	125 (57.6)	1.00
Cigarette smoking							
Yes	142 (36.0)	43 (37.1)	0.83 (0.43 – 1.57)	31 (44.3)	1.06 (0.49 – 2.29)	82 (37.8)	0.86 (0.52 – 1.42)
No	252 (64.0)	73 (62.9)	1.00	39 (55.7)	1.00	135 (62.2)	1.00
Cigarette smoking status							
Current smoker	99 (25.1)	30 (25.9)	0.61 (0.30 – 1.27)	24 (34.3)	0.94 (0.40 – 2.19)	60 (27.7)	0.71 (0.41 – 1.25)
Ex-smoker	43 (10.9)	13 (11.2)	1.80 (0.67 – 4.83)	7 (10.0)	1.57 (0.41 – 5.97)	22 (10.1)	1.40 (0.63 – 3.12)
Never smoker	252 (64.0)	73 (62.9)	1.00	39 (55.7)	1.00	135 (62.2)	1.00
Opium							
Yes	14 (3.6)	12 (10.3)	2.76 (0.75–10.18)	4 (5.7)	a	18 (8.3)	2.83 (0.99 – 8.08)
No	380 (96.4)	104 (89.7)	1.00	66 (94.3)		199 (91.7)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

b: was not calculated

Table 4. 33: ORs and 95% CI of GC histopathologies in relation to the occupational variables were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 116)	OR [1] (95%CI)	Cases (%) (No:70)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
Main job during last 10 years							
Agriculture	135 (34.3)	60 (51.7)	1.53 (0.64 – 3.67)	42 (60.0)	2.13 (0.53 – 8.48)	114 (52.5)	1.96 (0.95 – 4.01)
Manufacturing	30 (7.6)	4 (3.4)	0.48 (0.10 – 2.27)	2 (2.8)	0.27 (0.03 – 2.84)	9 (4.1)	0.80 (0.25 – 2.58)
Construction	40 (10.2)	21 (18.1)	1.80 (0.55 – 5.89)	7 (10.0)	0.97 (0.17 – 5.37)	28 (12.9)	1.78 (0.67 – 4.76)
Wholesale and retail trade	30 (7.6)	5 (4.3)	0.57 (0.10 – 3.34)	3 (4.3)	1.36 (0.18 – 10.39)	11 (5.1)	1.32 (0.39 – 4.49)
Other	21 (5.3)	3 (2.6)	0.41 (0.05 – 3.44)	2 (2.9)	2.22 (0.26 – 19.11)	7 (3.2)	0.71 (0.17 – 3.01)
Reference group	138 (35.0)	23 (19.8)	1.00	14 (20.0)	1.00	48 (22.1)	1.00

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 34: ORs and 95% CI of GC histopathologies in relation to the BMI and blood groups were not included in the predictive model

Variables	Controls (%) (No: 394)	Intestinal		Diffuse		Total	
		Cases (%) (No: 116)	OR [1] (95%CI)	Cases (%) (No:70)	OR [1] (95%CI)	Cases (%) (No: 217)	OR [1] (95%CI)
BMI (Before symptoms)							
Over weight and more	191 (48.4)	78 (67.2)	1.98 (1.09 – 3.61)	37 (52.9)	1.13 (0.52 -2.45)	135 (64.0)	1.57 (0.98 – 2.54)
Normal and underweight	200 (50.8)	38 (32.8)	1.00	32 (45.7)	1.00	81(35.5)	1.00
Don't know	3 (0.8)	0 (0.0)		1 (1.4)		1 (0.5)	
Blood group							
A	121 (30.7)	42 (36.2)	1.44 (0.70 – 2.96)	22 (31.4)	1.09 (0.43 – 2.76)	76 (35.1)	1.44 (0.81 – 2.55)
B	93 (23.6)	31 (26.7)	1.46 (0.66 – 3.26)	13 (18.6)	0.84 (0.29 – 2.39)	48 (22.1)	1.15 (0.60 – 2.20)
AB	30 (7.6)	2 (1.7)	0.15 (0.02 – 1.11)	2 (2.9)	0.22 (0.02 – 2.08)	7 (3.2)	0.46 (0.14 – 1.49)
O	139 (35.3)	33 (28.5)	1.00	21 (30.0)	1.00	61 (28.1)	1.00
Unknown	11 (2.8)	8 (6.9)		12 (17.1)		25 (11.5)	
Rh							
Positive	330 (83.8)	98 (84.5)	2.31 (0.85 – 6.26)	51 (72.9)	1.36 (0.45 – 4.17)	173 (79.7)	2.08 (0.97 – 4.52)
Negative	53 (13.4)	10 (8.6)	1.00	7 (10.0)	1.00	19 (8.8)	1.00
Unknown	11 (2.8)	8 (6.9)		12 (17.1)		25 (11.5)	

OR[1]: Adjusted for gender, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*

Table 4. 35: Population attributable risk percent for risk factors

Risk factors	P (%)	OR	PAR %
H. pylori (positive vs. negative)	69.7	2.41	49.6
Red meat (≥ 1/ day vs. ≤ 2 / week)	17.8	3.40	29.9
Dairy products (≥ 1/ day vs. ≤ 2 / week)	74.2	2.28	48.7
Preference for salt (high vs. low)	23.4	3.10	32.9
Strngth of tea (strong vs. mild)	14.5	2.64	19.2
Warmth of tea (hot vs. mild)	18.8	2.85	25.8

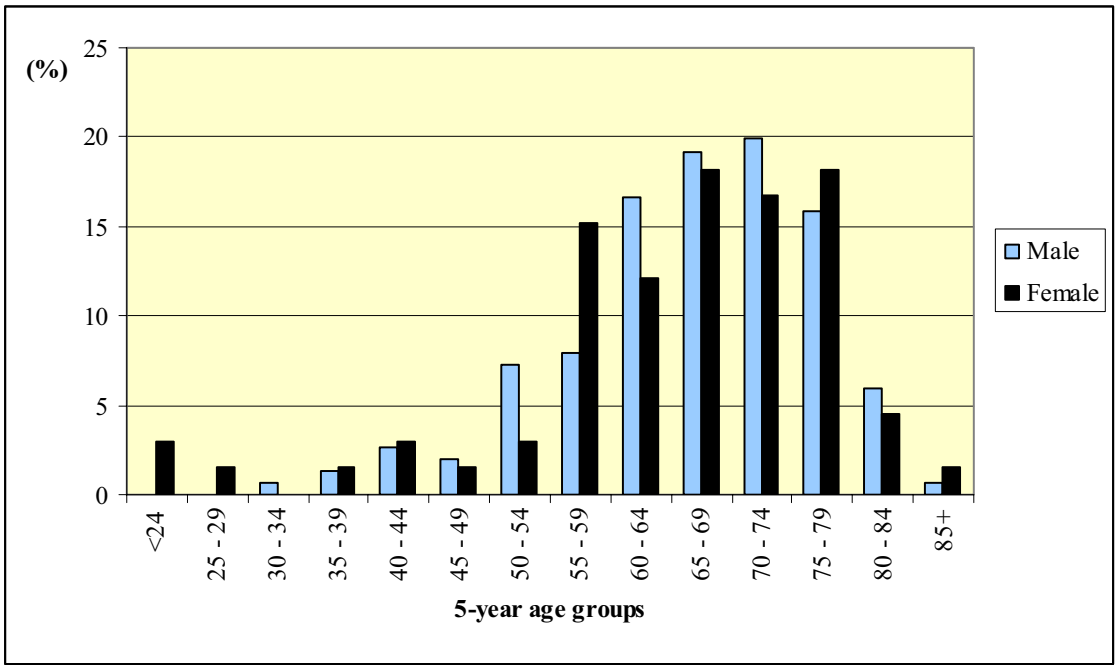


Figure 4. 1: Proportion of cases in each age group among males and females

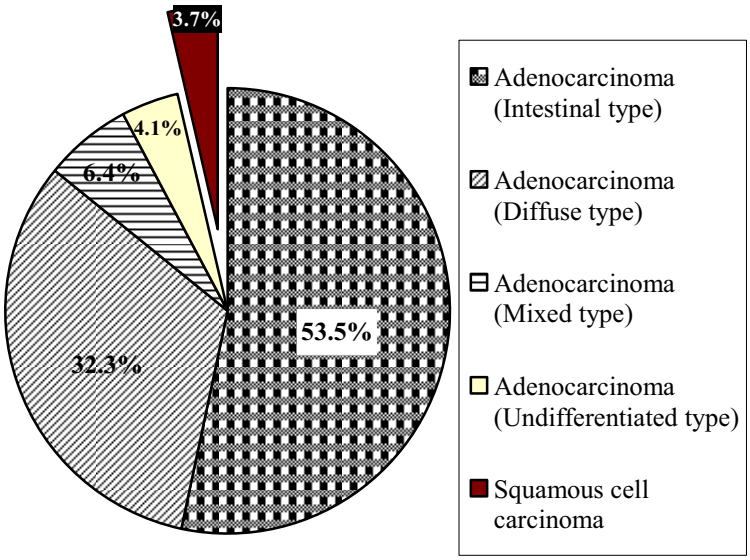


Figure 4. 2: Histopathological classification of GC in study cases

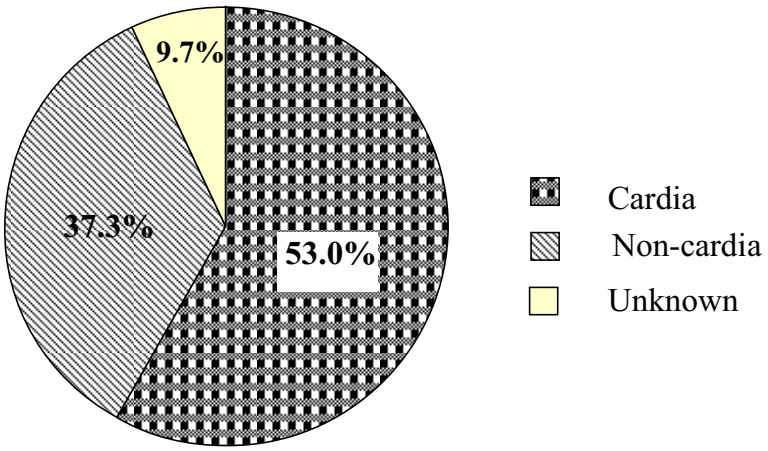


Figure 4. 3: Anatomical sub-sites of GC in study cases

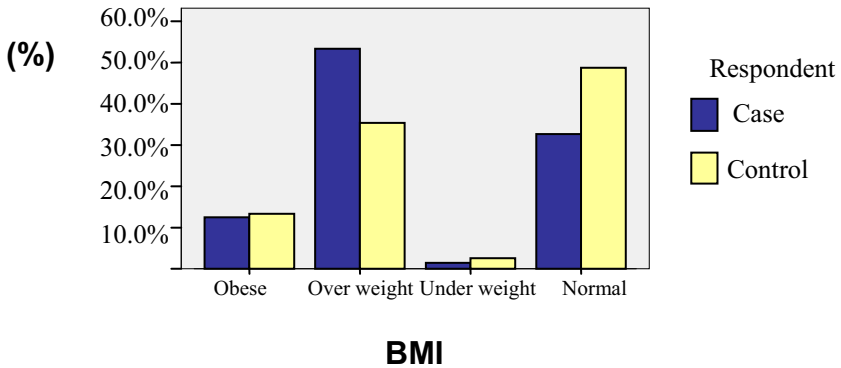


Figure 4. 4: BMI of subjects before occurrence of symptoms and signs

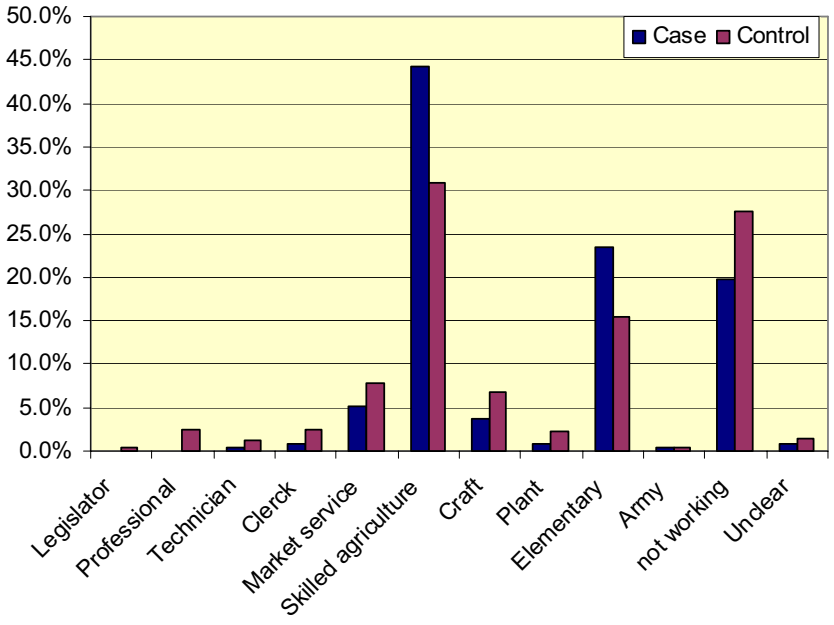


Figure 4. 5: Distribution of occupation among cases and controls based on ISCO – 88

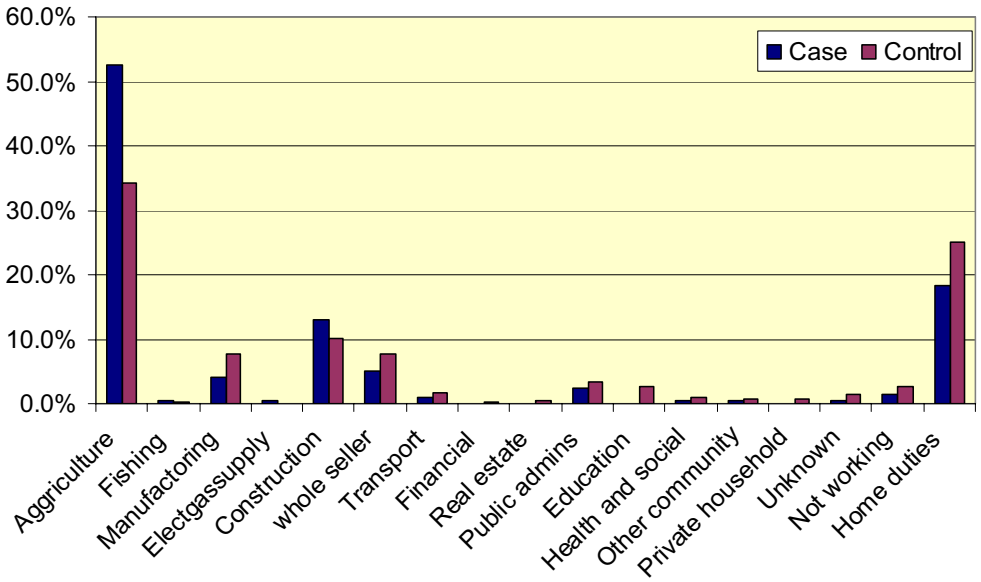


Figure 4. 6: Distribution of industries among cases and controls based on ISIC

CHAPTER FIVE: DISCUSSION

This study is the first case-control study of GC in Iran to investigate the associations between environmental factors and GC. The study factors include diet, *H. pylori* infection, lifestyle and occupation. In this section, methodological issues are considered followed by discussion of the study findings. The final section draws conclusions from the study, and in particular public health implications and recommendations which need to be examined in future studies.

5.1 Methodological issues

While each study provides more information about the mystery of the causes and prevention of GC, each has strengths and limitations which need to be taken into account when interpreting their findings.

5.1.1 Strength of study

The main strength of this study is that subjects have been recruited from the community. It is generally accepted that population-based case-control studies are less prone to selection bias than hospital based case-control studies. It is also believed that cases and controls from hospital may not be representative of the population (Lasky and Stolley 1994). Another strength of this study is completeness of case ascertainment as collaboration with the Ardabil Cancer Registry enabled reliable case ascertainment. This registry covers all private and public hospitals, clinics and laboratory in which cases can be diagnosed. The next strength of this study is a high participation rate among both groups of cases and controls, 97.8% and 90.8% respectively. Histologic

confirmation of diagnosis is another important strength of this study. This will minimize misclassification bias. Another strength of the current study is that *H. pylori* infection was determined using an ELISA kit which was validated for the local community in this study. It is believed that those kits which are imported have to be validated locally (Sacket, Haynes et al. 1991; Lam and Talley 1998; Szeto, Lee et al. 2001; Duggan 2003; Obata, Kikuchi et al. 2003). In addition, in this study a more accurate self reported work history was used rather than death certificates for measurement of occupational exposures. This study is also the first case-control study on GC in Iran which provides a considerable amount of important information which can be used as a baseline in future studies.

5.1.2 Limitations

Limitations inherent to this study are those that generally exist in case-control studies but some of them are specific to this study, although all attempts were made to minimize the impact of these factors. These limitations are discussed in the following section. There are several possible types of bias which could have occurred in case-control studies: selection and information bias.

5.1.2.1 Selection bias

There are several potential sources of selection bias which may have occurred in this case-control study. The first source of selection bias arises when different sampling frameworks are used for identification of subjects. The study cases were identified from the Ardabil Cancer Registry which covers all possible places in which cases could be diagnosed. In addition, controls seem to be representative of the community because they were randomly selected from a database which covers all dwellers of the province with the exception of those who have moved into the province after the census.

However, this was not problematic in this study as all subjects had to be resident of Ardabil province during the last five years.

Another source of selection bias arises when prevalent cases rather than incident cases are included in the study. Inclusion of prevalent cases may result in identification of factors which have prolonged the disease rather than only those causative factors. Therefore, only those GC cases that had been newly diagnosed were recruited to overcome this possible source of bias.

Poor prognosis of GC may cause another selection bias as it is possible that cases die before recruitment. This bias could be introduced when a surrogate is interviewed, in deceased or disabled cases. In this study 16 proxy interviews were conducted with surrogates of deceased or disabled cases. However proxy interviews constitute a small proportion of all case interviews (16 / 217) because of active surveillance which had been performed by the Ardabil Cancer Registry. The remainder of cases were identified within one month of diagnosis. As seen in chapter four, risk estimates of all cases were comparable to the index cases (that is after excluding proxies). This similarity indicates that the proxy interview is less likely to be a source of selection bias in this study.

Another source of selection bias originates from low participation rates which may result in difference of characteristics between participants and those who refused. However, the participation rate was very high for both groups of case and control corresponding to 98% and 91% respectively. About 9% of controls did not accept to participate in the study which may have resulted in selection bias. However interviewed and non-interviewed controls were similar in terms of age although refusal was higher in males which could be a source of selection bias. However by considering a

comparable prevalence of exposure between controls and general population in relation to the smoking and occupation, it can be assumed that controls are representative of the community. Refusal in the cases was too small to distort risk estimates. In addition, all analyses were adjusted for age and gender. There was no information on the exposure to the environmental factors for those who refused.

5.1.2.2 Misclassification of outcome

Cases were included in the study after they had been diagnosed with GC. Therefore, it is unlikely to misclassify a non GC patient as a case. However, it has been shown that there is a possibility of misclassifying an esophagus cancer as cardia and vice versa (Ekstrom, Signorello et al. 1999). While it is thought that these two cancers are similar in relation to the risk factors (Zhang, Kurtz et al. 1996; Gammon, Schoenberg et al. 1997), several researchers have argued against this hypothesis (Lagergren, Bergstrom et al. 1999b; Corley and Buffler 2001; El-Serag, Mason et al. 2002). However, if these cancers are similar in etiology then inclusion of lower esophageal cancer as GC will have a tiny impact on risk measurement. In contrast, if cancer of cardia and lower esophagus are separate in relation to the risk factors, inclusion of lower esophageal cancer would possibly result in shifting risk estimate to the null. Therefore estimated risk should be considered as minimum risk. Furthermore GC could be histologically misclassified as intestinal and diffuse. It was shown that a certain percentage (approximately 10%) of intestinal type tumors could be misclassified as diffuse type and the same percentage of misclassification of diffuse type tumors as intestinal type (Hansson, Lindgren et al. 1996). The impact of this misclassification on the estimates of risk is not predictable and it may change the risk estimate in both directions. Therefore findings in relation to the histopathologic classification should be cautiously considered.

Finally, it is possible that some cases were misclassified as controls because they are in early stage of GC and have not been diagnosed yet. After considering that GC has a low incidence rate, this misclassification, if it exists, will not be an important source of bias in this study.

5.1.2.3 Information bias

The majority of case-control studies measure exposure by using an interview or self-administered questionnaires and medical records. Information ascertained from questionnaires mostly relies on personal recall which can cause recall bias. In this study, exposures to the environmental factors were measured using a structured questionnaire and blood specimen. The validity of information partly depends on the questionnaire design and partly on the interview administration. As stated in chapter three, there was an acceptable level of agreement between repeated interviews ($\kappa > 0.50$) which represents a good external validity. Internal validity of the questionnaire could not be evaluated. However, if there is a measurement error in the evaluation of exposure to the environmental factors, it should be a non-differential error which results in biasing risks towards the null. Thus any discussed associations are likely to be underestimated. In addition, a recognized ELISA test was used as a measurement instrument to test seropositivity against *H. pylori*. A validation study was conducted to find an accurate ELISA kit using available kits in Iran. An ELISA kit manufactured by Biohit (Bio-hit Corporation 2005) was selected for this study with a sensitivity and specificity of 92.5% and 90.7% respectively (Appendix S). It is believed that *H. pylori* infection causes chronic gastritis which may lead to atrophic gastritis (Marshall, 1994). Sometimes, this bacterium could not be found in *H. pylori* induced atrophic gastritis. This is termed as false-negative results (Uemura, 2002). However a cross sectional endoscopic screening

study did not support this statement (Malekzadeh, Sotoudeh, et al. 2004). In this study a high prevalence of both *H. pylori* infection and atrophic gastritis was found in Ardabil. In addition a positive association was reported between *H. pylori* infection and precursors of GC (You, Blot, et al. 1993).

Recall bias is a major source of information error which may distort estimation of exposures. It was thought that self-reported family history of cancer may bias results because of differential recall between cases and controls. However, it was shown that cases can identify 83% of primary site of cancer correctly (Love, Evans, et al. 1985). In addition, people could remember information such as where they were born and lived better than occupational history and dietary habits, especially if they are asked about exposure from a long time ago. This bias could not be prevented as exposures were measured based on the memory of exposure by subjects. Exposure to risk factors under study may be under or over expressed by subjects. The problem arises when cases or controls report exposures different from each other. This difference may occur when one of these groups is familiar with the hypothesis. For example information bias may occur when cases over expressed consumption of food items thought to be protective or under-report consumption of promoter factors. This is most likely to occur when cases are familiar with various hypotheses such as association between GC and vegetables, fruits or other factors. However, it is unlikely to be a major source of bias in this study because of high illiteracy in subjects, especially in cases, and lack of media reports on GC and related risk factors.

There was a possibility of interviewer bias because subjects' status in relation to their disease was known to interviewers. Cases were aware of their cancer and explained it to the interviewers. Therefore interviewers were trained to interview subjects similarly

regardless of being cases or controls. They were provided with an instruction guide for interviews.

Another limitation is that, because of problems which arise from using a long FFQ, we have just focused on the intake frequency of those food items which had already been suggested to contribute to GC. This may reduce interview time, as a long interview could decrease the attention of participants as well as affect the accuracy of collected information. In addition, because of the short FFQ which was used in this study it was not possible to calculate energy intake. Furthermore, because of short FFQ, a full dietary history could not be collected. Therefore caution should be made in the interpretation of dietary findings.

5.1.2.4 Confounders

Confounding variables were dealt with at the study design and analysis stages. In the study design, data was collected on all factors which may potentially confound the association between GC and environmental factors such as SES. Age and gender as important confounders were taken in account in the study design by matching controls to the cases in relation to these factors. In addition, these two factors were always included in univariate and multivariate analysis. In the analysis stage, Mantel Henszel procedures were used to calculate age and gender adjusted OR for each variables. In univariate analysis association was found between GC and 18 study variables. The associated factors were *H. pylori* infection, diet (Garlic, Onion, fresh fruits, citrus fruits, red meats, fish, poultry, dairy products, salt preference, warmth and strength of tea), opium use, occupation as well as SES (education and access to hot shower at home), family history of GC and BMI. A logistic regression model was constructed including full relevant variables. Six variables were eliminated from this model using backward

logistic regression. As explained in section 3.8, the final model included variables of salt intake, warmth and strength of tea, *H. pylori* infection and consumption of garlic, onion, citrus fruits, red meat, fish and dairy products, family history of GC and education as well as age groups and gender.

Socioeconomic status has been reported as one of the important confounders in epidemiological studies. An association was reported between *H. pylori* infection and SES which is consistent with the pattern of GC (Sitas, Forman et al. 1991). SES is generally considered as an indicator of social class and economic condition. Although different factors are used as an indicator of SES in different countries, occupation, education and income are the most important of them. There is not a specific indicator of SES in Iran. However, information on different indicators such as education, income and domestic related factors are collected in 10 yearly national census. Similar questions were included in the questionnaire of this study and the education was selected as the best indicator of SES. In this study, risk estimates were adjusted for education as a determinant of SES. Among other variables which were eliminated from this model, smoking has been suggested to play a confounding role in the association between GC and *H. pylori* infection (Siman, Forsgren et al. 2001; Brenner, Arndt et al. 2002). However in this study, smoking was not a confounder. As seen in the table no significant association was seen between GC and smoking when it was examined in the final model. Similarly, occupation which was reported to be a confounder in the association between GC and salt intake was not a confounder in this study (Ngoan and Yoshimura 2003).

In this situation when several factors are adjusted, regression modeling techniques are more efficient. However it cannot remove the effect of confounding completely. It does

not solve all problems and there is a possibility of residual confounding which may arise from unmeasured or unknown variables and measurement error. However all attempts were made to minimise measurement errors. Finally, the contribution of environmental variables to the anatomical sub-sites and histopathological sub-types of GC were examined using the same model that was used for all cases. Although this model might not be the best model, it allowed us to compare general analysis to the histopathological sub-types and anatomical sub-sites analyses.

5.2 Study findings

In this study the influence of environmental factors on GC was examined. The main focus was on diet, *H. pylori* infection, lifestyle and occupation. The impact of socioeconomic status, family and medical history were also considered. In the following section, findings of this study are discussed. These findings were briefly presented in Table 5.1.

5.2.1 Histopathology and anatomical sub-sites

Intestinal type constitutes 53% of all GC followed by diffuse type (32.3%). This finding is in agreement with results of several other studies which reported that intestinal type is the common histopathogy in GC with rate of 50% – 75% (Boeing, Jedrychowski et al. 1991; Harrison, Zhang et al. 1997; Parsonnet, Friedman et al. 1997; Akre, Ekstrom et al. 2001; Uemura, Okamoto et al. 2001; Nomura, Hankin et al. 2003). Diffuse types tended to occur in males more than females and at slightly younger age compared to intestinal types. Diffuse type was also more common in age under 50 than intestinal type (8.6% vs. 6.1%). However significant differences were not found between intestinal and diffuse type in terms of age and gender (Table 4.3).

More than half of the GC occurred in cardia whereas this rate was 37% for non-cardia. This is in agreement with another study in Ardabil in which 49.5% of GC were diagnosed in cardia (Yazdanbod, Arshi et al. 2001). Cardia and non-cardia was significantly different in term of gender as non-cardia cancer was observed in males more than females. Some studies have reported a strong male predominance in cardia cancer but not all (Gammon, Schoenberg, et al.1997; Mao, Hu, et al. 2002; Cai, Zheng, et al. 2003). However, a male / female ratio of 1.8 was observed in this study is in range of 1.6 – 2.5 which have been reported in several other studies (Huang, Tajima, et al. 1999; Corvalan, Koriyama, et al. 2001; Yazdanbod, Arshi, et al. 2001; Ye and Nyren 2003; Chen, Wu, et al. 2004). The average age of diagnosis was similar for both anatomical sub-sites.

5.2.2 Socioeconomic status

An association was observed between education and GC. Educational level and schooling years were lower in cases than controls. This finding is in agreement with the findings of several other studies (Hansson, Baron et al. 1994; La Vecchia, D'Avanzo et al. 1995b; van Loon, Goldbohm et al. 1998; Munoz, Plummer et al. 2001; Fujino, Tamakoshi et al. 2002; Nomura, Hankin et al. 2003). No significant association was observed between GC and residence area (rural vs. urban) which has been reported (Cipriani, Buiatti et al. 1991). We also did not find any association between GC and other SES indicators: income, expenses, family size and access to facilities at home. These indicators have been inconsistently reported to link to GC (Smith, Taylor et al. 1996; Gammon, Schoenberg et al. 1997; Munoz, Plummer et al. 2001; Nishimoto, Hamada et al. 2002).

5.2.3 Family and medical history

An increasing risk of GC was observed among those with a positive history of GC in their first degree relatives. Those with a positive family history of GC were at 2.3 times greater risk of development of GC. This finding is in agreement with several other studies which reported that the risk of GC may increase the risk of this malignancy in first degree relatives approximately 1.5 – 4.0 times compared to the general population (La Vecchia, Negri et al. 1992; Palli, Galli et al. 1994; Inoue, Tajima et al. 1998b; Lissowska, Groves et al. 1999; Munoz, Plummer et al. 2001; Yatsuya, Toyoshima et al. 2002; Nomura, Hankin et al. 2003). However it is not clear whether this risk is due to genetic factors or similarity in exposure to the shared environmental risk factors among family members. In relation to blood groups, this study did not find an association between GC and ABO blood groups and Rh. This finding is in agreement with a large scale case-control study that reported no association between blood groups and GC (Palli, Galli et al. 1994).

5.2.4 Diet

In this study an inverse association was found between GC and consumption of fresh fruits particularly citrus fruits. The association of fresh fruits and GC has been one of the most investigated dietary factors in epidemiological studies. During the last ten years, 26 case-control and ten cohort studies have been published. The majority of these studies reported a protective role for high consumption of fruits, although some of the reported associations were not significant. Fruits are rich in fiber, vitamin and minerals and some other bioactive compounds. Some of these compounds have been reported to inhibit initiation or progression to cancer (WCRF and AICR 1997). While the mechanism by which fruits inhibit GC is not yet clear, antioxidant activity has been

frequently cited as a possible mechanism. Antioxidants and other bioactive compounds lower the risk of GC possibly by preventing DNA damage (Smith - Warner and Giovannucci 1999). It has been suggested that reactive oxidative compounds including superoxide, hydrogen peroxide, and singlet oxygen may play a carcinogenic role by intermediation of DNA damage (Cerutti 1985). This oxidant load can be increased by chronic infection such as *H. pylori*, while antioxidants which reduce this load may play a protective role. We found that consumption of citrus fruits is more protective than all fruits in the development of GC. It is thought that much of the benefit of fruits and vegetables has been attributed to ascorbic acid and β-carotene (Blackburn, Go et al. 1999). Another hypothesis about the mechanism of ascorbic acid is that it acts as a scavenger of nitrite which could be transformed to the N-nitroso compounds which are thought to be gastric carcinogens (Drake, Davies et al. 1996). A protective role for citrus fruit has been reported in several case-control and a few cohort studies (Buiatti, Palli et al. 1989; Boeing, Frentzel-Beyme et al. 1991; Jansen, Bueno-de-Mesquita et al. 1999; De Stefani, Correa et al. 2001; De Stefani, Correa et al. 2004). A randomized, controlled chemoprevention trial also reported a statistically significant increase in the rates of regression of two precancerous lesions of non-metaplastic atrophy and intestinal metaplasia by ascorbic acid treatment (Correa, Fontham et al. 2000).

In relation to vegetables, an inverse association was observed for the highest versus the lowest consumption of allium vegetables (garlic and onion). People consuming allium vegetables more frequently, experienced a significantly lower risk of GC. Our finding is in agreement with reports of several case-control studies (You, Blot et al. 1989; Gao, Takezaki et al. 1999; De Stefani, Correa et al. 2001; Munoz, Plummer et al. 2001). Prospective study on allium vegetables and GC is limited to a cohort study which

reported an inverse association between onion and GC (Dorant, van den Brandt et al. 1996). While it is not clear which components of allium vegetables are responsible for this protective role, it has been shown that allium vegetables, particularly garlic may prevent development to GC. This may suggest some mechanisms; garlic organosulfur compounds may scavenge free radicals, modulate the immune system, inhibit carcinogen-induced DNA binding and adduct formation, modulate enzymes of the detoxification system, and inhibit the initiation and promotion processes of carcinogenesis (Dorant, van den Brandt et al. 1993).

Moreover, this study did not find any evidence to support a protective role for raw vegetables. Although the majority of studies reported an inverse association between GC and raw vegetables, some studies similar to this study did not find a protective role for consumption of vegetables (Gonzalez, Sanz et al. 1991a; Lee, Park et al. 1995; Galanis, Kolonel et al. 1998; Kim, Chang et al. 2002; Hara, Hanaoka et al. 2003). The reasons why these vegetables were not associated with reduced risk of GC are unclear.

No association was found between GC and consumption of preserved foods and vegetables. Consumption of salted and smoked meat and pickled vegetables were not risk factors in Ardabil province. This finding is in agreement with several other studies (Harrison, Zhang et al. 1997; Ward, Sinha et al. 1997; Galanis, Kolonel et al. 1998; Mathew, Gangadharan et al. 2000; McCullough, Robertson et al. 2001; Ito, Inoue et al. 2003; van den Brandt, Botterweck et al. 2003; Lissowska, Gail et al. 2004) but not all (Ward and Lopez-Carrillo 1999; Ngoan, Mizoue et al. 2002). It has been hypothesized that food preservation may increase the formation of N-nitroso compounds which are gastric carcinogens (WCRF and AICR 1997). N-nitroso compounds are experimentally shown to be carcinogenic in animals (Sugimura and Fujimura 1967; Sugimura, Tanaka

et al. 1971; Eisenbrand, Schmahl et al. 1976). Following these reports, they have been hypothesized as possible gastric carcinogens in human. N-nitroso compounds present in cured meats and fish and fried or grilled bacon (Sen 1972; Wasserman, Fiddler et al. 1972) or can be formed endogenously. Endogenous nitrosation occurs by chemical reaction between nitrite and secondary nitrogen. Nitrite which is used as a preservative of fish and meat is the possible source of nitrite. However it is known that the level of nitrite in these foods declines rapidly from the time of processing and it would be less than 10 ppm at the time of serving (Yamaguchi and Abe 1999). Nitrate in food and drinking water is the main source of nitrite. After ingestion of nitrate, it is absorbed in the small intestine and then 25% of that is excreted in saliva and gastric juice. Vegetables are the most important source of nitrate (Yamaguchi and Abe 1999). Bacteria are also suggested as playing a role in the reduction of nitrate into nitrite in achlorhydria in the stomach. This hypothesis has been examined by several researchers who reported inconsistent positive association (Zhang, Deng et al. 1991; La Vecchia, D'Avanzo et al. 1995a; Palli, Saieva et al. 2001).

An increasing risk was observed among those who drink hot and strong tea. Although a causative role for hot tea has been reported in the development of esophageal cancer (Munoz and Day 1996), to the best of my knowledge it was examined in only one study in relation to GC. A large case-control study in Mongolia on 1,263 cases and 2,526 healthy controls reported approximately three times increased risk with drinking hot tea (Dorzhgotov 1989). Although the mechanism by which hot tea increases the risk is not clear, cellular damage may explain this association. Some case-control studies have suggested that the heat of food plays a role in development to GC by thermal irritation (La Vecchia, Negri et al. 1990; Gao, Takezaki et al. 1999). In addition, a positive

association was observed between GC and drinking of strong tea. Tea has been inconsistently reported to reduce the risk of GC in case-control studies (Chow, Swanson et al. 1999; Takezaki, Gao et al. 2001; Rao, Ganesh et al. 2002; De Stefani, Correa et al. 2004), even though some findings were not significant or only significant for males. This inverse association was not observed in one cohort study (Goldbohm, Hertog et al. 1996). A further argument was made against this negative association in a cohort study which showed an increasing risk of GC with drinking of tea, although this study did not adjust for SES (Kinlen, Willows et al. 1988). While over 400 volatile compounds and several other nonvolatile components have been identified in black tea it is not clear which compound/s are responsible for this suggested association (WHO and IARC 1991).

We found an increasing risk of GC among those who had a preference for higher salt intake. This is in agreement with several epidemiological studies. It is also in accordance with the Correa model (1992). According to the Correa model, salt may cause irritation and mucosal damage and superficial gastritis in the stomach. This gastritis may progress to atrophic gastritis which is a precursor of GC. An interaction between salt intake and *H. pylori* infection was observed in a study which reported 14 times increase in the risk of non-cardia GC among those infected cases with *H. pylori* consuming high amounts of salt (Machida-Montani, Sasazuki et al. 2004). This might indicate that bacterial infection is a co-factor with salt, which enhances carcinogenesis after the gastric epithelium is damaged (Joossens, Hill et al. 1996). Animal studies showed a synergistic effect of salt and *H. pylori* in development to GC. It was shown that excessive salt intake enhances *H. pylori* colonization in mice and induces development to GC (Fox, Dangler et al. 1999).

In relation to animal products, our data suggests that frequent consumption of red meat and dairy products could increase the risk of development of GC. On the other hand a protective role was found for the consumption of fresh fish. The association between red meat and GC has already been shown in some case-control studies (Ward, Sinha et al. 1997; De Stefani, Boffetta et al. 1998b; Hamada, Kowalski et al. 2002). Although this association has not been shown in prospective studies, it may be attributed to some component of meat and cooking methods. High-temperature cooking of meats could produce a variety of carcinogenic compounds such as polycyclic aromatic hydrocarbons that may promote gastric carcinogenesis. Among cooking methods, frying, grilling and barbecuing have been reported to produce these compounds (Howard and Fazio 1970). These chemicals have been experimentally shown to be carcinogenic in animals when administered orally (Rigdon and Neal 1969).

In addition to red meat, dairy products were also found to increase the risk of GC. This finding is in agreement with two case-control studies which reported 2.4 – 3.0 times increase in the risk with dairy product consumption (Mathew, Gangadharan et al. 2000; Munoz, Plummer et al. 2001). However this association was not observed in other case-control and cohort studies. The real cause behind this association is not clear, however, this association could be a consequence rather than a cause of the disease, because cases may drink more milk to control symptoms of the disease such as dyspepsia.

On the other hand an inverse association was observed between consumption of fresh fish and GC. This protective role has been inconsistently reported in some case-control studies although some of these findings were marginally non-significant (Munoz, Plummer et al. 2001; Ito, Inoue et al. 2003; De Stefani, Correa et al. 2004; Lissowska, Gail et al. 2004). It is thought that polyunsaturated fatty acid (PUFA) may inhibit gastric

carcinogenesis. This inhibitory role was experimentally shown in mice (Karmali, Marsh et al. 1984). An inverse association was reported between consumption of polyunsaturated fat and GC with a significant dose dependency (Lopez-Carrillo, Lopez-Cervantes et al. 1999). Our findings do not suggest any association between GC and other dietary items.

5.2.5 Helicobacter pylori

In this case-control study an increased risk of GC was found for *H. pylori* infection. The risk of GC was 2.4 times greater in seropositives compared to seronegatives. This association is in agreement with the result of a follow-up study in UK which reported 2.8 times increase in the risk of GC in those with a history of infection with *H. pylori*. (Forman, Newell et al. 1991). This finding also supports role of *H. pylori* infection in the etiology of GC which was stated by IARC as a type I carcinogen (IARC 1994). This finding is also in agreement with 6 meta-analyses which reported that *H. pylori* infected people may develop GC 2 - 4 times more than uninfected people (Forman, Webb et al. 1994; Huang, Sridhar et al. 1998; Danesh 1999; Eslick, Lim et al. 1999; Helicobacter and Cancer Collaborative 2001; Xue, Xu et al. 2001). Several mechanisms have been hypothesized for the carcinogenesis effect of *H. pylori*, however, the real causal mechanisms are still unclear. It has been hypothesized that *H. pylori* infection could cause a superficial gastritis (Correa 1992). This gastritis may develop to atrophic gastritis, intestinal metaplasia and eventually to GC in the presence of *H. pylori* and other environmental factors, including specific dietary factors and lifestyle (Parsonnet, Friedman et al. 1991). In addition, the gastric carcinogenic effect of *H. pylori* has been experimentally shown in animals (Honda, Fujioka et al. 1998; Watanabe, Tada et al. 1998; Touati, Michel et al. 2003).

Although mechanisms of this association are unclear, several hypotheses have been postulated: (a) cell division of stomach epithelia due to ammonia which is produced by urease activity (b) gastric epithelial cell damage by phospholipase activity of *H. pylori* and (c) virulent strains of *H. pylori* having vacuolating cytotoxic activity may expose epithelial cells to carcinogens by impairing defense capabilities (Forman, Webb et al. 1994). Meanwhile, it has been suggested that people infected with *H. pylori* have a lower level of ascorbic acid in their gastric juice (Sobala, Schorah et al. 1993; Correa, Malcom et al. 1998). The lower level of antioxidative in gastric juice may be another possible mechanism in the gastric carcinogenesis.

Despite the bulk of studies reporting a positive association between GC and *H. pylori* infection, some researchers could not find an association between these two factors, especially in Asian countries such as Taiwan (Lin, Wang et al. 1993; Lin, Wang et al. 1995), India (Sivaprakash, Rao et al. 1996), China (Webb, Yu et al. 1996) Korea (Kim, Cho et al. 1997) and Japan (Blaser, Kobayashi et al. 1993; Kato, Onda et al. 1996). This inconsistency in the result could be explained due to the small sample sizes of these studies. A large sample size is needed in these countries with high prevalences of *H. pylori* infection, but most of these studies recruited small number of cases (< 100). Statistical analysis methods may be another reason for differences in the results. Non-adjustment or inadequate adjustment for potential confounders in these studies may impact on the magnitude of association. For instance there are several studies which did not adjust for confounders (Lin, Wang et al. 1993) or only adjusted for age and gender (Estevens, Fidalgo et al. 1993; Kuipers, Gracia-Casanova et al. 1993; Asaka, Kato et al. 1995). In addition, variation in the virulence of *H. pylori* is suspected as a possible reason for inconsistency of the results. It was thought that some specific virulent strains

of *H. pylori* including cagA and vacA may be responsible for the progression to GC, although it was not shown in many studies reporting a high risk of cagA regardless of GC prevalence in their community (Miehlke, Go et al. 1998; Bernstein, McKeown et al. 1999). Finally, the difference in the results might have occurred due to difference in diagnostic methods for *H. pylori*. Several methods, including histology, culture, RUT, UBT and serology have been used to determine *H. pylori* infection. These diagnostic methods vary in relation to their accuracy and validity (Vaira, Gatta et al. 2002). For instance a study was conducted by Kim, Cho et al. (1997) to examine the association of *H. pylori* with GC. They used RUT and / or histology to determine *H. pylori* infection and did not find an association between these two factors. However, in another study in Korea, an association was found by these investigators using serology (Chang, Kim et al. 2001). Serological tests have been found to be an appropriate method for epidemiologic studies looking at the role of *H. pylori* infection, because positive results show a past infection rather than an acute ongoing infection (Vaira, Gatta et al. 2002). Several types of ELISA kits are available worldwide but their accuracy needs to be measured in the study population. For this study we compared the accuracy of four available ELISA kits in Iran using positive histology and RUT as gold standard. An ELISA kit manufactured by Biohit was selected for this study and showed a high sensitivity and specificity compared to the other kits.

In sub-sites analysis, the association between GC and *H. pylori* was stronger in non-cardia cancer whereas it was non-significant for cardia cancer. This finding supported the idea that cardia and non-cardia cancer are possibly attributed to different environmental factors. The influence of *H. pylori* has been examined for sub-sites and histopathological classification in several studies. For cardia versus non-cardia, a higher

association was reported for non-cardia cancer (Martin-de-Argila, Boixeda et al. 1997; Hansen, Melby et al. 1999; Limburg, Qiao et al. 2001) and was emphasized in a combined analysis of 12 case-control studies nested within prospective cohorts which suggested a relative risk of 5.9 for non-cardia cancer and *H. pylori* (Helicobacter and Cancer Collaborative 2001). This difference was also shown for cardia versus non-cardia cancer (1.23 vs. 3.08; $p = 0.003$) respectively in a meta-analysis by Huang, Sridhar et al. (1998).

In histopathologic analysis, a similar increasing risk was observed for both intestinal and diffuse types of GC, although the association was statistically non-significant. Non-significant increased risk might be explained as due to the relatively small sample size in each histopathologic sub-type. This is in contrast to the finding of some studies which suggested that intestinal type of GC is associated with environmental factors compared to diffuse type (Parsonnet, Vandersteen et al. 1991; Buruk, Berberoglu et al. 1993; Wu, Chen et al. 1997). However, the majority of studies showed that both intestinal and diffuse types of GC are similarly associated with *H. pylori* infection (Hu, Mitchell et al. 1994; Kato, Saito et al. 1994). This is in accordance with a meta-analysis which showed that both intestinal and diffuse cancer are equally related to *H. pylori* infection (Huang, Sridhar et al. 1998).

By considering a causative association between *H. pylori* and GC, investigators have hypothesized that GC could have been prevented after eradication of *H. pylori* infection by elimination of *H. pylori* (Uemura, Mukai et al. 1997; Shimizu, Ikehara et al. 2000; Hahm, Song et al. 2003; Nozaki, Shimizu et al. 2003; Leung, Lin et al. 2004). This prevention was reported to be effective in those carriers without precancerous lesions whereas there was no difference in the development of the GC in those who have

already developed the precancerous lesions (Wong, Lam et al. 2004). Therefore an early detection of infection may play an important role in the prevention of GC. All of these findings emphasize role of *H. pylori* infection in the etiology of GC.

5.2.6 Lifestyle

In this study no association was observed between GC and ever versus never smoking. Further analysis by dividing "ever smoker" in two categories of "current smoker" and "ex-smoker" did not reveal any significant association. In addition, there was also no significant difference between cases and controls in relation to starting age, average daily smoking and cessation. The IARC working group in 1986 evaluated this association and were not convinced about the causal association between GC and smoking (IARC 1986). However, the influence of smoking on GC was accepted after considering new studies by IARC in 2004 (WHO and IARC 2004).

In addition to the evaluation by IARC, a positive association has been reported between GC and smoking in several articles (Ji, Chow et al. 1996; Chow, Swanson et al. 1999; Sitas, Urban et al. 2004; Vineis, Alavanja et al. 2004). However our findings do not support this association. This conflict could be explained by two possibilities. The first possibility is that smoking is not an independent causative factor for GC. This possibility is supported by results of several case-control and cohort studies which could not find a significant association between smoking and GC (Buiatti, Palli et al. 1989; Boeing, Frentzel-Beyme et al. 1991; Guo, Blot et al. 1994; Engeland, Andersen et al. 1996). Results of these studies should not be discounted as some of them had recruited a large sample size with an appropriate design and analysis. A cohort study with 28 year follow-up of 26,000 Norwegian men and women did not find any association (Engeland, Andersen et al. 1996). This inconsistency in the results on GC and smoking

has been explained in a review by Correa, Piazuelo et al. (2004). In addition to the above mentioned articles, a few studies which have been published after the IARC evaluation have failed to show a dose dependency. A Japanese cohort study which has reported a significant increase in the risk of GC among "ever smokers" (RR = 2.01; 95% CI 1.1 – 3.7), failed to show a dose dependency (Sasazuki, Sasaki et al. 2002). Another multi-centric case-control study in Japan also found a weak association only in males (OR = 1.31; 95% CI: 1.02 – 1.67) (Minami and Tateno 2003). Finally a prospective study in ten European countries with more than 521,000 participants did not show a significant dose dependency in terms of number of cigarettes smoked (Gonzalez, Pera et al. 2003).

The second explanation is that our subjects have had an inconsistent exposure to smoking. This may be supported by the fact that tobacco was banned because of Fatva (religiously endorsed recommendation) in Iran about 100 years ago. Therefore, the majority of study subjects have grown up in a family with anti smoking beliefs. As seen in Table 4.15, about 20% of smokers started to smoke at less than 20 years of age while this rate is higher in several studies in which a positive association was observed. For instance the rate was 36% in Taiwan (Chen, Chiou et al. 2000), 40% in Uruguay (De Stefani, Boffetta et al. 1998a) and even 56% in Poland (Chow, Swanson et al. 1999). Therefore interpretation of results should be regarded by considering the specific context of each nation.

Similar to the combined analysis, no difference was observed in histopathologic classification and anatomical sub-sites of GC in relation to smoking. A further analysis in relation to filtered cigarettes also did not show any difference between cases and controls. Although it was claimed that filters may reduce exposure to the potential

chemical in cigarettes, little effect was shown by using filters (Chow, Swanson et al. 1999).

In relation to alcohol consumption, no association was found between drinking alcohol and GC. There are several studies examining this association but the majority of them did not report a significant excess risk (Gammon, Schoenberg et al. 1997; Chow, Swanson et al. 1999; Ye, Ekstrom et al. 1999; Wu, Chen et al. 2004). IARC Working Group on the Evaluation of the Carcinogenic Risk to Humans (1988) evaluated 13 cohort and 12 case-control studies, of which one cohort and three case-control studies found an increasing risk between alcohol consumption and GC. Therefore, they concluded that the available data is inadequate to suggest a causal role for drinking of alcoholic beverages in GC.

We found about 2.5 times increased risk of GC with opium use. The magnitude of the risk increased after adjustment for confounders but it became marginally non-significant. However, opium use was excluded from final model because it did not satisfy confounding criteria. No association was found between opium use and some of related factors including education, H. pylori infection and consumption of dietary factors such as citrus fruits, onion, red meat, fish and dairy products. In addition, to the best of my knowledge there have been no reports on the association between such substance use and GC in the literature. However, further investigations are needed to examine its effect on development to the GC as there are some reports on association between opium use and cancer of bladder, esophagus and larynx (Kmet 1978; Hewer 1979; Behmard, Sadeghi et al. 1981; Dowlatshahi and Miller 1985; Ghavamzadeh, Moussavi et al. 2001; Mousavi, Damghani et al. 2003). In anatomical sub-site and histopathologic analyses an increasing risk was also observed for both anatomical sub-

sites and intestinal type by opium use. Since the number of subjects with diffuse type was small, the risk could not be accurately measured. The association between opium use and anatomical subsites and intestinal type needs to be further investigated as the number of cases in each group was not adequate to measure risk with high power of study.

5.2.7 Occupation

Working in four main industries of agriculture, construction, wholesale and retail trade and manufacturing constitute about 75% of occupations in this study. In this study, an association was observed between GC and agriculture and construction in univariate analysis. However after adjustment for confounders this association became non-significant. For the two other categories of wholesale and retail trade and manufacturing, no significant association was observed between GC with either of these activities. Among these four activities, agriculture and construction have been inconsistently reported to increase risk of GC. Our study does not support those findings. There are some studies reporting an increasing risk of GC among those working in agriculture (Burns and Swanson 1995). A meta-analysis also reported a weak association between GC and farmers (Blair, Zahm et al. 1992). This association was postulated due to exposures to herbicides, pesticides, and fertilizers, however other studies similar to this study did not find an association between GC and agriculture (Gonzalez, Sanz et al. 1991b; Parent, Siemiatycki et al. 1998; Krstev, Dosemeci et al. 2005) or exposure to pesticides, herbicides, insecticides and fungicides (Cocco, Ward et al. 1999; Ekstrom, Eriksson et al. 1999). A large scale cohort study also did not find an association between these factors (Aragones, Pollan et al. 2002). In addition, another

meta-analysis which evaluated 29 studies did not show a significant association (Acquavella, Olsen et al. 1998).

Construction is the next most common industry in Ardabil and was also not related to GC. While a Swedish cohort study reported a modest increase in the risk of GC in those working in the construction category (Aragones, Pollan et al. 2002), our result is in agreement with findings of several other studies which did not find an association (Gonzalez, Sanz et al. 1991b; Burns and Swanson 1995; Parent, Siemiatycki et al. 1998; Ekstrom, Eriksson et al. 1999; Engel, Vaughan et al. 2002).

This study also did not find a significant association between GC and wholesale and retail trade and manufacturing. This finding supports the results of the Swedish cohort study, in which no association was observed between GC and wholesale and retail trade (Aragones, Pollan et al. 2002). The category of manufacturing has been investigated in several studies. These studies have inconsistently reported a positive association between GC and some subcategories of manufacturing including (a) food and beverage industries, (b) basic metal manufacturer, (c) paper and paper products, (d) publishing and printing and (e) rubber and plastic products. However, our study could not examine the association of GC with these subcategories because of the small number of cases who reported a work history in manufacturing (nine cases).

On the other hand some occupations including work in mining, transport, basic metal manufacturing and paper products and printing which have previously reported to link to GC do not exist in Ardabil province or the numbers are too small to be evaluated.

5.2.8 Anatomical sub-sites and histopathologic analysis

As seen in Table 5.1 both anatomical sub-sites and histopathological sub-types of GC are attributed to environmental factors. In sub-site analysis, there was a variation between anatomical sub-sites of GC in relation to some dietary factors. Non-cardia cancer is related to the preference for higher salt intake, drinking hot tea and *H. pylori* infection as well as history of GC in first degree relatives more than cardia cancer, whereas cardia cancer is related to the consumption of animal products such as red meat and dairy products more than non-cardia GC. Meanwhile drinking strong tea was a greater risk for cardia than non-cardia GC. In addition, both intestinal and diffuse types were related to environmental factors in our population. This similarity was shown for intestinal and diffuse histopathological classification in most other studies (Harrison, Zhang et al. 1997; Ward and Lopez-Carrillo 1999; Ekstrom, Serafini et al. 2000) although there are some articles which reported a greater association between environmental factors and intestinal type (Parsonnet, Vandersteen et al. 1991; Buruk, Berberoglu et al. 1993; Wu, Chen et al. 1997).

5.3 Conclusion and public health implications

In conclusion, our study found that *H. pylori* infection and dietary habits were the most important factors associated with GC. The study found that regular consumption of allium vegetables and fruits, especially citrus fruits, could reduce the risk of GC by more than half. In addition to fruits and allium vegetables, consumption of fresh fish was found to play a protective role in development to GC.

On the other hand, several food items and dietary habits were found to increase the risk of GC in this high risk population. Regular consumption of red meat and dairy products were associated with more than doubled risk of GC. Other dietary practices were also

found to be important factors in the etiology of GC. People who had a preference for higher salt intake and drinking of strong and hot tea were at higher risk than those who did not.

The presence of antibodies indicated past *H. pylori* infection was also related to GC. A history of *H. pylori* infection was associated with a doubling of the risk of GC.

We also found that lifestyle related factors, particularly smoking which has been previously suggested as a risk factor, may be not applicable in this high risk area. However the association between GC and opium use needs to be further studied. Finally, people with a positive history of GC in their first degree relative may develop GC more than twice those without this history.

We found that anatomical sub-sites of GC differ in relation to their association with some environmental factors, as well as with family aggregation. We also found that cardia GC differs from non-cardia GC in term of gender. These findings suggest that these two sub-sites of GC are distinct in terms of risk factors, although it needs to be re-evaluated in studies with larger sample sizes in each sub-site. In contrast to the difference between cardia and non-cardia cancer, our findings could not support a different etiology for intestinal versus diffuse type. Both histopathologic sub-types of GC were similar in demographic characteristics. There was neither a consistent difference between them in relation to the environmental exposure nor family history. However our results should be cautiously considered for histopathologic analysis and anatomical sub-sites because of the small sample sizes in these subgroups.

These findings have important implications in planning preventive strategies for this malignancy, which is a major health problem in Iran particularly in Northwest. It has

been recommended that every country needs to establish a national cancer control program (NCCP) according to their priorities. On the W.H.O guidelines for NCCP development, four principal approaches are recommended: prevention, early detection, diagnosis and treatment and palliative care (2002). It is believed that cancer prevention deserves continuing high priority in term of both research and application (Vainio 2003). The first step in prevention involves studies looking into the etiology of cancer as we have done. Our study provided basic and original information about GC and associated factors in the Iranian context. However, further studies could provide confirmatory evidence for GC prevention. Once an association is strongly established, it is necessary for it to be translated into effective intervention at the community level. However before a general campaign is implemented, intervention should be trialed on a smaller scale.

By considering the above mentioned findings further studies are recommended especially in relation to diet and *H. pylori*. Studies on diet could use both observational and interventional methods. Observational studies especially case-control and cohort are recommended using a long form of FFQ to investigate the impact of nutrients in the etiology of GC. These studies could also re-examine the effect of drinking hot and strong tea as well as opium use on GC. Meanwhile, interventional studies investigating the benefit of food supplements such as antioxidants can provide precise information about the causal effect of these supplements. Further studies may examine the effect of *H. pylori* eradication on prevention of GC. In Iran a randomized control trial could be used to examine the efficacy of *H. pylori* eradication on the prevention of both GC and its precursors such as CAG. In the meantime the efficacy of different types of treatment could be examined using observational method.

Given the findings of this study, primary prevention would be the best approaches for our community. The other three approaches, in the NCCP guidelines, namely the early detection, diagnosis and treatment of cancer and palliative care are beyond the scope of our findings. Indeed, primary prevention is probably more cost effective and feasible than treatment in developing countries like Iran where cases are diagnosed in late stages of GC.

5.3.1 Primary prevention

Efficacy of primary prevention has been reported in ecological studies but further studies are needed before suggesting it for the individual and community level (Hakama 1997). Primary prevention is defined as eliminating or minimizing exposure to the causes of cancer (WHO 2002). In primary prevention, the main approach could be health promotion campaign. Several developed countries such as Australia have conducted health and lifestyle campaigns which focus on tobacco control, promotion of appropriate diet by increasing intake of fresh fruits and vegetables and avoidance of excess sun exposure (National Health Priority Action Council., Cancer Strategies Group. et al. 2001; Stewart and Coates 2005). These campaigns have been associated with a decrease of chronic diseases including cancer. Such general campaigns might be useful if modified to the Iranian context. This campaign would be based generally on the modification of diet by establishment of a national dietary recommendation which could cover not only GC but also other noncommunicable disease such as diabetes, cardiovascular diseases and other type of cancers. This integrated prevention program has been reported as an effective national strategy on disease prevention (World Health Organization. 2002). This campaign could recommend a diet rich in fruits and vegetables especially allium vegetables and less consumption of red meat. It has already

been reported that vegetables and fruits contain substances that may protect against some cancers. It was also indicated that excessive amounts of animal products in the diet, such as red meat, may increase the risk of some cancers (WCRF and AICR, 1997). Meanwhile a modification could be suggested in drinking hot and strong tea as well as high salt intake. However, the feasibility of these strategies needs to be evaluated on small scale at first.

Other primary prevention strategies should be in relation to *H. pylori*. These strategies vary before and after infection. A vaccine may ultimately be the best prevention method as studies on animal models have shown its ability to protect against infection (Ferrero, Thiberge et al. 1995; Raghavan, Hjulstrom et al. 2002). Until development of such a human vaccine, health promotion campaigns to improve hygiene practices could possibly reduce person to person transmission, but this requires further investigations. This suggestion could be especially focussed on the rural areas which are more deprived, because it has been shown that *H. pylori* infection is related to SES (Sitas, Forman et al. 1991). Two strategies could be considered for the management of symptomatic *H. pylori* infection: referral for endoscopy or eradicating *H. pylori* and referring only those people with persistent symptoms after eradication (Duggan 2003). Obviously treatment of all *H. pylori* infected people is not practical nor currently scientifically indicated in our community, as no randomized trial has been done to confirm its efficacy. Therefore we recommend a health economic evaluation of these strategies for those at higher risk, such as those with a positive family history of GC and dietary exposure. This recommendation can be supported by calculated PAR for *H. pylori* (69.7%). It means 70% of GC could be prevented in the population by elimination of *H. pylori* infection (Table 4.35).

In summary, this study has provided important and original information to add to knowledge about GC etiology, particularly in the Iranian context. It suggests that there is sufficient information about causative mechanism to develop a cancer prevention policy and develop a health promotion strategy. However a demonstration on a small scale is suggested before introduction of a community based campaign. It also suggests that models of *H. pylori* eradication be investigated further. In the long term, action is needed by individuals, families and the health system to improve their health and reduce the death rate and morbidity associated with GC.

Table 5. 1: Comparative risk estimate of family history and environmental factors for combined, anatomical sub-sites and histopathologic classification of GC

Factors	Combined	Intestinal	Diffuse	Cardia	Non-cardia
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
BMI (Before symptoms)					
Over weight and more	1.57 (0.98 – 2.54)	1.98 (1.09 – 3.61)	1.13 (0.52 -2.45)	1.52 (0.84 – 2.75)	1.51 (0.72 – 3.15)
Normal and underweight	1.00	1.00	1.00	1.00	1.00
Family history of cancer					
Gastric cancer	2.32 (1.11 – 4.85)	3.11 (1.29 – 7.51)	3.05 (0.92 – 10.14)	0.94 (0.33 – 2.70)	5.28 (1.94 – 14.36)
Other type of cancer	0.82 (0.33 – 2.01)	0.80 (0.24 – 2.64)	1.32 (0.32 – 5.33)	0.61 (0.18 – 2.04)	1.02 (0.30 – 3.52)
No cancer	1.00	1.00	1.00	1.00	1.00
Helicobacter pylori					
Positive	2.41 (1.35 – 4.32)	1.93 (0.92 – 4.01)	1.95 (0.81 – 4.70)	2.02 (0.98 – 4.16)	3.25 (1.27 – 8.33)
Negative	1.00	1.00	1.00	1.00	1.00
Salt preference					
Salty	3.10 (1.88 – 5.10)	4.39 (2.37 – 8.13)	2.25 (1.05 – 4.87)	2.83 (1.54 – 5.20)	4.94 (2.43 – 10.05)
Normal or less salty	1.00	1.00	1.00	1.00	1.00
Strength of tea					
Strong tea	2.64 (1.45 – 4.80)	2.00 (0.98 – 4.08)	2.49 (1.01 – 6.17)	3.29 (1.61 – 6.71)	2.68 (1.14 – 6.34)
Regular	1.00	1.00	1.00	1.00	1.00
Warmth of tea					
Hot	2.85 (1.65 – 4.91)	3.64 (1.87 – 7.08)	3.94 (1.69 – 9.18)	3.06 (1.57 – 5.96)	4.38 (2.02 – 9.52)
Mild to warm	1.00	1.00	1.00	1.00	1.00
Fresh red meat					
≥ once daily	3.40 (1.79 – 6.46)	3.05 (1.34 – 6.94)	1.54 (0.54 – 4.41)	5.75 (2.52 – 13.08)	2.91 (1.13 – 7.54)
3 – 4 weekly	2.20 (1.26 – 3.85)	2.68 (1.30 – 5.55)	1.92 (0.85 – 4.35)	2.15 (1.04 – 4.44)	3.19 (1.40 – 7.29)
Less than 1 – 2 weekly	1.00	1.00	1.00	1.00	1.00
Fresh fish					
≥ once per week	0.37 (0.19 – 0.70)	0.33 (0.14 – 0.80)	0.29 (0.08 – 1.02)	0.45 (0.19 – 1.03)	0.38 (0.14 – 1.01)
Never or infrequently	1.00	1.00	1.00	1.00	1.00
Dairy products					
≥ once daily	2.28 (1.23 – 4.22)	2.41 (1.10 – 5.29)	3.71 (1.27 – 10.89)	3.05 (1.38 – 6.74)	1.87 (0.74 – 4.71)
3 – 4 weekly	3.77 (1.92 – 7.42)	2.62 (1.09 – 6.28)	1.32 (0.32 – 5.33)	4.51 (1.88 – 10.82)	2.62 (0.96 – 7.18)
≤ 1 – 2 weekly	1.00	1.00	1.00	1.00	1.00

Adjusted for age groups, gender, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, salt preference and *H. pylori*

Table 5. 1 (continued): Comparative risk estimate of environmental factors for combined, anatomical sub-sites and histopathologic classification of GC

Factors	Combined	Intestinal	Diffuse	Cardia	Non-cardia
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Raw vegetables					
≥ 3 – 4 weekly	2.08 (1.13 – 3.82)	1.75 (0.81 – 3.78)	2.41 (0.89 – 6.50)	2.20 (1.03 – 4.71)	2.89 (1.11 – 7.49)
1 – 2 weekly	1.56 (0.89 – 2.73)	0.99 (0.48 – 2.05)	3.21 (1.31 – 7.91)	1.93 (0.95 – 3.89)	1.43 (0.62 – 3.28)
Never or infrequently	1.00	1.00	1.00	1.00	1.00
Yellow-orange vegetables					
≥ 3 – 4 weekly	1.78 (0.81 – 3.89)	2.70 (1.05 – 6.96)	1.70 (0.39 – 7.45)	2.01 (0.72 – 5.61)	2.12 (0.67 – 6.73)
1 – 2 weekly	2.07 (1.15 – 3.70)	1.41 (0.65 – 3.09)	6.33 (2.47 – 16.23)	2.21 (1.09 – 4.49)	1.71 (0.71 – 4.12)
Never or infrequently	1.00	1.00	1.00	1.00	1.00
Garlic					
≥ 3 – 4 weekly	0.35 (0.13 – 0.95)	0.59 (0.18 – 1.94)	0.05 (0.00 – 0.78)	0.30 (0.09 – 1.07)	0.29 (0.05 – 1.92)
1 – 2 weekly	0.48 (0.25 – 0.91)	0.40 (0.17 – 0.93)	0.16 (0.04 – 0.58)	0.20 (0.08 – 0.54)	0.78 (0.33 – 1.87)
Never or infrequently	1.00	1.00	1.00	1.00	1.00
Onion					
≥ once daily	0.34 (0.19 – 0.62)	0.39 (0.19 – 0.82)	0.20 (0.07 – 0.58)	0.38 (0.18 – 0.81)	0.14 (0.06 – 0.37)
3 – 4 weekly	1.28 (0.73 – 2.23)	1.42 (0.71 – 2.84)	1.81 (0.78 – 4.21)	1.65 (0.83 – 3.30)	0.70 (0.31 – 1.59)
Less than 1 – 2 weekly	1.00	1.00	1.00	1.00	1.00
Fresh fruits					
≥ 3 – 4 weekly	0.89 (0.43 – 1.86)	1.15 (0.44 – 2.97)	0.58 (0.18 – 1.83)	0.65 (0.25 – 1.69)	1.08 (0.35 – 3.32)
1 – 2 weekly	0.44 (0.22 – 0.89)	0.33 (0.13 – 0.87)	0.39 (0.14 – 1.14)	0.48 (0.20 – 1.17)	0.24 (0.08 – 0.77)
Never or infrequently	1.00	1.00	1.00	1.00	1.00
Citrus fruits					
≥ 3 – 4 weekly	0.31 (0.17 – 0.59)	0.30 (0.13 – 0.69)	0.25 (0.09 – 0.68)	0.28 (0.12 – 0.65)	0.43 (0.17 – 1.08)
1 – 2 weekly	0.18 (0.10 – 0.33)	0.27 (0.13 – 0.54)	0.09 (0.03 – 0.28)	0.22 (0.11 – 0.45)	0.22 (0.09 – 0.53)
Never or infrequently	1.00	1.00	1.00	1.00	1.00

Adjusted for age groups, gender, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, salt preference and *H. pylori*

REFERENCES:

Acquavella, J., Olsen, G., et al. (1998). "Cancer among farmers: a meta-analysis." Annals of Epidemiology **8**(1): 64-74.

Adamson, R. H. (1990). Mutagens and carcinogens formed during cooking of food and methods to minimize their formation. Cancer Prevention. DeVita, V. T., Hellman, S. and Rosenberg, S. A. Philadelphia, JB Lippincott.

Agha, A. and Graham, D. Y. (2005). "Evidence-based examination of the African enigma in relation to Helicobacter pylori infection." Scandinavian Journal of Gastroenterology **40**(5): 523-9.

Agudo, A., Gonzalez, C. A., et al. (1992). "Consumption of alcohol, coffee, and tobacco, and gastric cancer in Spain." Cancer Causes & Control. **3**(2): 137-43.

Aird, I., Bentall, H. H., et al. (1953). "A relationship between cancer of stomach and the ABO blood groups." British Medical Journal **i**: 799-801.

Akre, K., Ekstrom, A. M., et al. (2001). "Aspirin and risk for gastric cancer: a population-based case-control study in Sweden." British Journal of Cancer. **84**(7): 965-8.

Al-Dabbagh, S., Forman, D., et al. (1986). "Mortality of nitrate fertiliser workers." British Journal of Industrial Medicine **43**(8): 507-15.

Al-Moagel, M. A., Evans, D. G., et al. (1990). "Prevalence of Helicobacter (formerly Campylobacter) pylori infection in Saudia Arabia, and comparison of those with and without upper gastrointestinal symptoms." American Journal of Gastroenterology. **85**(8): 944-8.

Ames, R. G. (1983). "Gastric cancer and coal mine dust exposure. A case-control study." Cancer. **52**(7): 1346-50.

Amorosi, A., Bianchi, S., et al. (1988). "Gastric cancer in a high-risk area in Italy. Histopathologic patterns according to Lauren's classification." Cancer **62**(10): 2191-6.

Aragones, N., Pollan, M., et al. (2002). "Stomach cancer and occupation in Sweden: 1971-89." Occupational & Environmental Medicine **59**(5): 329-37.

Archimandritis, A., Bitsikas, J., et al. (1993). "Non-cardia gastric adenocarcinoma and Helicobacter pylori infection." Italian Journal of Gastroenterology **25**(7): 368-71.

Ardabil University of Medical Science (2000). Ardabil health branch annual report. Ardabil, Ardabil University of Medical Science.

Armitage, P., Matthews, J. N. S., et al. (2002). Statistical methods in medical research. Oxford ; Malden, MA, Blackwell Science.

Aromaa, A., Kosunen, T. U., et al. (1996). "Circulating anti-Helicobacter pylori immunoglobulin A antibodies and low serum pepsinogen I level are associated with increased risk of gastric cancer." American Journal of Epidemiology. **144**(2): 142-9.

Asaka, M., Kato, M., et al. (1995). "Relationship between Helicobacter pylori infection, atrophic gastritis and gastric carcinoma in a Japanese population." European Journal of Gastroenterology & Hepatology **7 Suppl 1**: S7-10.

Asaka, M., Kimura, T., et al. (1994). "Possible role of Helicobacter pylori infection in early gastric cancer development." Cancer **73**(11): 2691-4.

Banatvala, N., Mayo, K., et al. (1993). "The cohort effect and Helicobacter pylori." Journal of Infectious Diseases **168**(1): 219-21.

Barreto-Zuniga, R., Maruyama, M., et al. (1997). "Significance of Helicobacter pylori infection as a risk factor in gastric cancer: serological and histological studies." Journal of Gastroenterology. **32**(3): 289-94.

Battisti, C., Formichi, P., et al. (2000). "Vitamin E serum levels and gastric cancer: results from a cohort of patients in Tuscany, Italy." Cancer Letters **151**(1): 15-8.

Baumgarten, M., Siemiatycki, J., et al. (1983). "Validity of work histories obtained by interview for epidemiologic purposes." American Journal of Epidemiology **118**(4): 583-91.

Behmard, S., Sadeghi, A., et al. (1981). "Positive association of opium addiction and cancer of the bladder. Results of urine cytology in 3,500 opium addicts." Acta Cytologica **25**(2): 142-6.

Bernstein, C. N., McKeown, I., et al. (1999). "Seroprevalence of Helicobacter pylori, incidence of gastric cancer, and peptic ulcer-associated hospitalizations in a Canadian Indian population." Digestive Diseases & Sciences **44**(4): 668-74.

Bizzozero, G. (1892). "Sulle ghiandole tubulari del tubo gastro-enterico e sui rapporti del loro epitelio coll'epitelio di rivestimento della mucosa." Atti della Reale Accademia delle Scienze di Torino **28**: 233-51.

Bjelke, E. (1974). "Epidemiologic studies of cancer of the stomach, colon, and rectum; with special emphasis on the role of diet." Scandinavian Journal of Gastroenterology **Supplement 31**: 1-235.

Blackburn, G. L., Go, V. L. W., et al. (1999). Nutritional oncology. London, Academic.

Blair, A., Zahm, S. H., et al. (1992). "Clues to cancer etiology from studies of farmers." Scandinavian Journal of Work, Environment & Health **18**(4): 209-15.

Blaser, M. J., Kobayashi, K., et al. (1993). "Helicobacter pylori infection in Japanese patients with adenocarcinoma of the stomach." International Journal of Cancer **55**(5): 799-802.

Blaser, M. J., Perez-Perez, G. I., et al. (1995). "Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach." Cancer Research **55**(10): 2111-5.

Block, G. (1982). "A review of validations of dietary assessment methods." American Journal of Epidemiology **115**(4): 492-505.

Blot, W. J., Devesa, S. S., et al. (1991). "Rising incidence of adenocarcinoma of the esophagus and gastric cardia." JAMA **265**(10): 1287-9.

Boeing, H., Frentzel-Beyme, R., et al. (1991). "Case-control study on stomach cancer in Germany." International Journal of Cancer. **47**(6): 858-64.

Boeing, H., Jedrychowski, W., et al. (1991). "Dietary risk factors in intestinal and diffuse types of stomach cancer: a multicenter case-control study in Poland." Cancer Causes & Control. **2**(4): 227-33.

Boffetta, P., Gridley, G., et al. (2000). "Employment as butcher and cancer risk in a record-linkage study from Sweden." Cancer Causes & Control **11**(7): 627-33.

Bond, G. G., Bodner, K. M., et al. (1988). "Validation of work histories obtained from interviews." American Journal of Epidemiology **128**(2): 343-51.

Booth-Jones, A. D., Lemasters, G. K., et al. (1998). "Reliability of questionnaire information measuring musculoskeletal symptoms and work histories." American Industrial Hygiene Association Journal **59**(1): 20-4.

Botterweck, A. A., Schouten, L. J., et al. (2000). "Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries." International Journal of Epidemiology **29**(4): 645-54.

Botterweck, A. A., van den Brandt, P. A., et al. (1998). "A prospective cohort study on vegetable and fruit consumption and stomach cancer risk in The Netherlands." American Journal of Epidemiology. **148**(9): 842-53.

Botterweck, A. A., van den Brandt, P. A., et al. (2000). "Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma: results from a prospective study after 6.3 years of follow-up." Cancer **88**(4): 737-48.

Braunwald, E. (2001). Harrison's principles of internal medicine. New York, McGraw-Hill.

Brenner, H., Arndt, V., et al. (2002). "Risk of gastric cancer among smokers infected with Helicobacter pylori." International Journal of Cancer. **98**(3): 446-9.

Broutet, N., Sarasqueta, A. M., et al. (1999). "Is there a link between the variation in gastric cancer mortality and differences in Helicobacter pylori prevalence in different regions of France?" Gastroenterologie Clinique et Biologique **23**(6-7): 754-60.

Brower, P. S. and Attfield, M. D. (1998). "Reliability of reported occupational history information for US coal miners, 1969-1977." American Journal of Epidemiology **148**(9): 920-6.

Brown, J., Harding, S., et al. (1998). "Longitudinal study of socio-economic differences in the incidence of stomach, colorectal and pancreatic cancers." Population Trends(94): 35-41.

Bruckner, H., Morris, J., et al. (2003). Neoplasms of the Stomach. Cancer medicine. Kufe, D., Holland, J., Bast, R.et al. Hamilton, Ont. ; London, Decker**:** 2 v. (xxiv, 2699 p.).

Bucchi, L., Nanni, O., et al. (2004). "Cancer mortality in a cohort of male agricultural workers from northern Italy." Journal of Occupational & Environmental Medicine **46**(3): 249-56.

Buiatti, E., Palli, D., et al. (1991). "A case-control study of gastric cancer and diet in Italy. III. Risk patterns by histologic type." International Journal of Cancer. **48**(3): 369-74.

Buiatti, E., Palli, D., et al. (1989). "A case-control study of gastric cancer and diet in Italy." International Journal of Cancer. **44**(4): 611-6.

Burns, P. B. and Swanson, G. M. (1995). "Stomach cancer risk among black and white men and women: the role of occupation and cigarette smoking." Journal of Occupational & Environmental Medicine **37**(10): 1218-23.

Buruk, F., Berberoglu, U., et al. (1993). "Gastric cancer and Helicobacter pylori infection." British Journal of Surgery **80**(3): 378-9.

Cai, L., Zheng, Z. L., et al. (2003). "Risk factors for the gastric cardia cancer: a case-control study in Fujian Province." World Journal of Gastroenterology **9**(2): 214-8.

Centers for Disease Control and Prevention (2005). BMI - Body Mass Index: BMI for Adults, Department of Health and Human Services (HHS). **2005**.

Cerutti, P. A. (1985). "Prooxidant states and tumor promotion." Science **227**(4685): 375-81.

Chang, W. K., Kim, H. Y., et al. (2001). "Association between Helicobacter pylori infection and the risk of gastric cancer in the Korean population: prospective case-controlled study." Journal of Gastroenterology. **36**(12): 816-22.

Chao, A., Thun, M. J., et al. (2002). "Cigarette smoking, use of other tobacco products and stomach cancer mortality in US adults: The Cancer Prevention Study II." International Journal of Cancer **101**(4): 380-9.

Chen, H., Tucker, K. L., et al. (2002). "Nutrient intakes and adenocarcinoma of the esophagus and distal stomach." Nutrition & Cancer **42**(1): 33-40.

Chen, H., Ward, M. H., et al. (2002). "Dietary patterns and adenocarcinoma of the esophagus and distal stomach." American Journal of Clinical Nutrition **75**(1): 137-44.

Chen, K., Qiu, J. L., et al. (2003). "Nutrient intake and gastric cancer in residents of Zhoushan Islands, China." Digestive & Liver Disease **35**(12): 912-3.

Chen, M. J., Chiou, Y. Y., et al. (2000). "Lifestyle habits and gastric cancer in a hospital-based case-control study in Taiwan." American Journal of Gastroenterology. **95**(11): 3242-9.

Chen, M. J., Wu, D. C., et al. (2004). "Personal history and family history as a predictor of gastric cardiac adenocarcinoma risk: a case-control study in Taiwan." American Journal of Gastroenterology **99**(7): 1250-7.

Choi, M. A., Kim, B. S., et al. (1999). "Serum antioxidative vitamin levels and lipid peroxidation in gastric carcinoma patients." Cancer Letters **136**(1): 89-93.

Chow, W. H., Blot, W. J., et al. (1998). "Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia." Journal of the National Cancer Institute **90**(2): 150-5.

Chow, W. H., Swanson, C. A., et al. (1999). "Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland." International Journal of Cancer. **81**(6): 871-6.

Cipriani, F., Buiatti, E., et al. (1991). "Gastric cancer in Italy." Italian Journal of Gastroenterology. **23**(7): 429-35.

Cocco, P., Ward, M. H., et al. (1996). "Occupational risk factors for gastric cancer: an overview." Epidemiologic Reviews **18**(2): 218-34.

Cocco, P., Ward, M. H., et al. (1998). "Occupational risk factors for cancer of the gastric cardia. Analysis of death certificates from 24 US states." Journal of Occupational & Environmental Medicine. **40**(10): 855-61.

Cocco, P., Ward, M. H., et al. (1999). "Risk of stomach cancer associated with 12 workplace hazards: analysis of death certificates from 24 states of the United States with the aid of job exposure matrices." Occupational & Environmental Medicine. **56**(11): 781-7.

Corley, D. A. and Buffler, P. A. (2001). "Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database." International Journal of Epidemiology **30**(6): 1415-25.

Corley, D. A. and Kubo, A. (2004). "Influence of site classification on cancer incidence rates: An analysis of gastric cardia carcinomas." Journal of National Cancer Institute **96**(18): 1383-7.

Cornee, J., Pobel, D., et al. (1995). "A case-control study of gastric cancer and nutritional factors in Marseille, France." European Journal of Epidemiology. **11**(1): 55-65.

Correa, P. (1988). "A human model of gastric carcinogenesis." Cancer Research **48**(13): 3554-60.

Correa, P. (1992). "Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention." Cancer Research **52**(24): 6735-40.

Correa, P., Fontham, E. T., et al. (2000). "Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy." Journal of the National Cancer Institute **92**(23): 1881-8.

Correa, P., Fox, J., et al. (1990). "Helicobacter pylori and gastric carcinoma : Serum antibody prevalence in populations with contrasting cancer risk." Gastric Cancer **66**: 2569 -74.

Correa, P., Haenszel, W., et al. (1975). "A model for gastric cancer epidemiology." Lancet **2**: 58 -60.

Correa, P., Malcom, G., et al. (1998). "Review article: Antioxidant micronutrients and gastric cancer." Alimentary Pharmacology & Therapeutics **12 Suppl 1**: 73-82.

Correa, P., Piazuelo, M. B., et al. (2004). "The future of gastric cancer prevention." Gastric Cancer **7**(1): 9-16.

Correa, P. and Ruiz, B. (1989). Campylobacter pylori and gastric cancer. Campylobacter pylori and gastroduodenal disease. Rathbone, B. J. and Heatley, R. V. Oxford, Blackwell**:** 139-45.

Corvalan, A., Koriyama, C., et al. (2001). "Epstein-Barr virus in gastric carcinoma is associated with location in the cardia and with a diffuse histology: a study in one area of Chile." International Journal of Cancer **94**(4): 527-30.

Czene, K., Lichtenstein, P., et al. (2002). "Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database." International Journal of Cancer **99**(2): 260-6.

Danesh, J. (1999). "Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies." Alimentary Pharmacology & Therapeutics. **13**(7): 851-6.

De Stefani, E., Boffetta, P., et al. (2000a). "Dietary carotenoids and risk of gastric cancer: a case-control study in Uruguay." European Journal of Cancer Prevention. **9**(5): 329-34.

De Stefani, E., Boffetta, P., et al. (1998a). "Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay." Cancer Causes & Control. **9**(3): 321-9.

De Stefani, E., Boffetta, P., et al. (1999). "Carbohydrates and risk of stomach cancer in Uruguay." International Journal of Cancer. **82**(4): 618-21.

De Stefani, E., Boffetta, P., et al. (1998b). "Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay." Nutrition & Cancer **30**(2): 158-62.

De Stefani, E., Boffetta, P., et al. (2000b). "Plant sterols and risk of stomach cancer: a case-control study in Uruguay." Nutrition & Cancer. **37**(2): 140-4.

De Stefani, E., Correa, P., et al. (2004). "Dietary patterns and risk of gastric cancer: a case-control study in Uruguay." Gastric Cancer **7**(4): 211-20.

De Stefani, E., Correa, P., et al. (2001). "Plant foods and risk of gastric cancer: a case-control study in Uruguay." European Journal of Cancer Prevention. **10**(4): 357-64.

De Stefani, E., Ronco, A., et al. (2001). "Meat consumption and risk of stomach cancer in Uruguay: a case-control study." Nutrition & Cancer **40**(2): 103-7.

Devesa, S. S., Blot, W. J., et al. (1998). "Changing patterns in the incidence of esophageal and gastric carcinoma in the United States." Cancer **83**(10): 2049-53.

Dixon, M. F., Genta, R. M., et al. (1996). "Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994." American Journal of Surgical Pathology. **20**(10): 1161-81.

Doenges, J. L. (1939). "Spirochetes in gastric glands of Macacus rhesus and of man without related disease." Arch. Pathol. **27**: 469-77.

Doll, R., Payne, P., et al. (1966). Cancer incidence in five continents. A technical report. Genaeve, International Union against Cancer.

Doll, R. and Peto, R. (1981). "The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today." Journal of the National Cancer Institute **66**(6): 1191-308.

Dorant, E., van den Brandt, P. A., et al. (1993). "Garlic and its significance for the prevention of cancer in humans: a critical view." British Journal of Cancer **67**(3): 424-9.

Dorant, E., van den Brandt, P. A., et al. (1996). "Consumption of onions and a reduced risk of stomach carcinoma." Gastroenterology **110**(1): 12-20.

Dorzhgotov, B. (1989). "Les facteurs de risque dans la manifestation de cinq formes principales de cancer, en Republique Populaire de Mongolie." Sante Publique **32**(4): 361-7.

Dowlatshahi, K. and Miller, R. J. (1985). "Role of opium in esophageal cancer: a hypothesis." Cancer Research **45**(4): 1906-7.

Drake, I. M., Davies, M. J., et al. (1996). "Ascorbic acid may protect against human gastric cancer by scavenging mucosal oxygen radicals." Carcinogenesis. **17**(3): 559-62.

Duggan, A. (2002). "Helicobacter pylori: when is treatment now indicated?" Internal Medicine Journal **32**(9-10): 465-9.

Duggan, A. (2003). "Management of dyspepsia at the beginning of the twenty-first century." Internal Medicine Journal **33**(12): 604-9.

Duggan, A., Logan, R., et al. (1996). "Accuracy of near-patient blood tests for Helicobacter pylori." Lancet **348**(9027): 617.

Duggan, A. E., Elliott, C., et al. (1999). "Testing for Helicobacter pylori infection: validation and diagnostic yield of a near patient test in primary care." BMJ **319**(7219): 1236-9.

Dyke, G. W., Craven, J. L., et al. (1992). "Smoking-related DNA adducts in human gastric cancers." International Journal of Cancer **52**(6): 847-50.

Eisenbrand, G., Schmahl, D., et al. (1976). "Carcinogenicity in rats of high oral doses of N-nitroso-carbaryl, a nitrosated pesticide." Cancer Letters **1**(5): 281-4.

Ekstrom, A. M., Eriksson, M., et al. (1999). "Occupational exposures and risk of gastric cancer in a population-based case-control study." Cancer Research. **59**(23): 5932-7.

Ekstrom, A. M., Serafini, M., et al. (2000). "Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the intestinal and diffuse types: a population-based case-control study in Sweden." International Journal of Cancer. **87**(1): 133-40.

Ekstrom, A. M., Signorello, L. B., et al. (1999). "Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence." Journal of the National Cancer Institute **91**(9): 786-90.

Elbeshir, E. I., Abeen, H. A., et al. (1989). "Snuff dipping and oral cancer in Sudan: a retrospective study." British Journal of Oral & Maxillofacial Surgery **27**(3): 243-8.

El-Serag, H. B., Mason, A. C., et al. (2002). "Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA." Gut **50**(3): 368-72.

Endo, S., Ohkusa, T., et al. (1995). "Detection of Helicobacter pylori infection in early stage gastric cancer. A comparison between intestinal- and diffuse-type gastric adenocarcinomas." Cancer. **75**(9): 2203-8.

Endoh, K. and Leung, F. W. (1994). "Effects of smoking and nicotine on the gastric mucosa: a review of clinical and experimental evidence." Gastroenterology **107**(3): 864-78.

Engel, L. S., Chow, W. H., et al. (2003). "Population attributable risks of esophageal and gastric cancers." Journal of the National Cancer Institute **95**(18): 1404-13.

Engel, L. S., Vaughan, T. L., et al. (2002). "Occupation and risk of esophageal and gastric cardia adenocarcinoma." American Journal of Industrial Medicine. **42**(1): 11-22.

Engeland, A., Andersen, A., et al. (1996). "Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women." Cancer Causes & Control **7**(5): 497-506.

Enroth, H., Kraaz, W., et al. (2000). "Helicobacter pylori strain types and risk of gastric cancer: A case-control study." Cancer Epidemiology, Biomarkers & Prevention **9**(9): 981-5.

Enroth, H., Kraaz, W., et al. (2002). "Does the method of Helicobacter pylori detection influence the association with gastric cancer risk?" Scandinavian Journal of Gastroenterology **37**(8): 884-90.

Eslick, G. D., Lim, L. L., et al. (1999). "Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis." American Journal of Gastroenterology **94**(9): 2373-9.

Estevens, J., Fidalgo, P., et al. (1993). "Anti-Helicobacter pylori antibodies prevalence and gastric adenocarcinoma in Portugal: report of a case-control study." European Journal of Cancer Prevention. **2**(5): 377-80.

Evstifeeva, T. V. and Zaridze, D. G. (1992). "Nass use, cigarette smoking, alcohol consumption and risk of oral and oesophageal precancer." European Journal of Cancer Part B, Oral Oncology **28B**(1): 29-35.

Farrow, D. C., Vaughan, T. L., et al. (1998). "Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer." Cancer Epidemiology, Biomarkers & Prevention. **7**(2): 97-102.

Feldman, R. A. (2001). "Review article: would eradication of Helicobacter pylori infection reduce the risk of gastric cancer?" Alimentary Pharmacology & Therapeutics. **15**(Suppl 1): 2-5.

Ferlay, J., Bray, F., et al. (2004). GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. Lyon, IARC Press,.

Ferrero, R. L., Thiberge, J. M., et al. (1995). "The GroES homolog of Helicobacter pylori confers protective immunity against mucosal infection in mice." Proceedings of the National Academy of Sciences of the United States of America **92**(14): 6499-503.

Fitzgerald, O. and Murphy, P. (1950). "Studies on the physiological chemistry and clinical significance of urease and urea with special reference to the stomach." Irish Journal of Medical Science. **292**: 97 - 159.

Fontana, V., Decensi, A., et al. (1998). "Socioeconomic status and survival of gastric cancer patients." European Journal of Cancer **34**(4): 537-42.

Forman, D., Al-Dabbagh, S., et al. (1985). "Nitrates, nitrites and gastric cancer in Great Britain." Nature **313**(6004): 620-5

Forman, D., Newell, D. G., et al. (1991). "Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation." BMJ **302**(6788): 1302-5.

Forman, D., Sitas, F., et al. (1990). "Geographic association of Helicobacter pylori antibody prevalence and gastric cancer mortality in rural China." International Journal of Cancer **46**(4): 608-11.

Forman, D., Webb, P., et al. (1994). "H pylori and gastric cancer." Lancet. **343**(8891): 243-4.

Fox, A. J. and Adelstein, A. M. (1978). "Occupational mortality: work or way of life?" Journal of Epidemiology & Community Health **32**(2): 73-8.

Fox, J. G., Dangler, C. A., et al. (1999). "High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice." Cancer Research. **59**(19): 4823-8.

Freedberg, A. S. and Barron, L. E. (1940). "The presence of spirochetes in human gastric mucosa." American Journal of Digestive Diseases **7**: 443-5.

Fritz, A. G. (2000). International classification of diseases for oncology = ICD-O. Geneva, World Health Organization.

Frumkin, H. (1997). "Cancer epidemiology and the workplace." Salud Publica de Mexico **39**(4): 356-69.

Fu, H. and Boffetta, P. (1995). "Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data." Occupational & Environmental Medicine **52**(2): 73-81.

Fuchs, C. S. and Mayer, R. J. (1995). "Gastric Carcinoma." The New England Journal of Medicine **333**(1): 32-41.

Fujino, Y., Tamakoshi, A., et al. (2002). "Prospective study of educational background and stomach cancer in Japan." Preventive Medicine **35**(2): 121-7.

Fujioka, N., Fahey, M. T., et al. (2001). "Serological Immunoglobulin G antibody titers to Helicobacter pylori in Japanese Brazilian and Non-Japanese Brazilian gastric cancer patients and controls in Sao Paulo." Japanese Journal of Cancer Research. **92**(8): 829-35.

Fukuda, H., Saito, D., et al. (1995). "Helicobacter pylori infection, serum pepsinogen level and gastric cancer: a case-control study in Japan." Japanese Journal of Cancer Research. **86**(1): 64-71.

Gajalakshmi, C. K. and Shanta, V. (1996). "Lifestyle and risk of stomach cancer: a hospital-based case-control study." International Journal of Epidemiology. **25**(6): 1146-53.

Galanis, D. J., Kolonel, L. N., et al. (1998). "Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study." International Journal of Epidemiology **27**(2): 173-80.

Gammon, M. D., Schoenberg, J. B., et al. (1997). "Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia." Journal of the National Cancer Institute. **89**(17): 1277-84.

Gammon, M. D., Terry, M. B., et al. (2004). "Nonsteroidal anti-inflammatory drug use associated with reduced incidence of adenocarcinomas of the esophagus and gastric cardia that overexpress cyclin D1: a population-based study." Cancer Epidemiology, Biomarkers & Prevention **13**(1): 34-9.

Gao, C. M., Takezaki, T., et al. (1999). "Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China." Japanese Journal of Cancer Research. **90**(6): 614-21.

Garcia-Closas, R., Gonzalez, C. A., et al. (1999). "Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain." Cancer Causes & Control **10**(1): 71-5.

Ghavamzadeh, A., Moussavi, A., et al. (2001). "Esophageal cancer in Iran." Seminars in Oncology **28**(2): 153-7.

Giovino, G. A., Henningfield, J. E., et al. (1995). "Epidemiology of tobacco use and dependence." Epidemiologic Reviews **17**(1): 48-65.

Glober, G. A., Cantrell, E. G., et al. (1971). "Interaction between ABO and rhesus blood groups, the site of origin of gastric cancers, and the age and sex of the patient." Gut **12**(7): 570-3.

Goldbohm, R. A., Hertog, M. G., et al. (1996). "Consumption of black tea and cancer risk: a prospective cohort study." Journal of the National Cancer Institute **88**(2): 93-100.

Gonzalez, C. A., Pera, G., et al. (2003). "Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC)." International Journal of Cancer **107**(4): 629-34.

Gonzalez, C. A., Sanz, J. M., et al. (1991a). "Dietary factors and stomach cancer in Spain: a multi-centre case-control study." International Journal of Cancer. **49**(4): 513-9.

Gonzalez, C. A., Sanz, M., et al. (1991b). "Occupation and gastric cancer in Spain." Scandinavian Journal of Work, Environment & Health. **17**(4): 240-7.

Goodwin, C. S., Armstrong, J. A., et al. (1989). "Transfer of Campylobacter pylori and Campylobacter mustelae to Helicobacter gen. nov. as Helicobacter pylori comb. nov. and Helicobacter mustelae comb. nov., respectively." International Journal of Systematic Bacteriology **39**(4): 397-405.

Greenwald, P., Kramer, B. S., et al. (1995). Cancer Prevention and Control. New York, M. Dekker.

Grimley, C. E., Holder, R. L., et al. (1999). "Helicobacter pylori-associated antibodies in patients with duodenal ulcer, gastric and oesophageal adenocarcinoma." European Journal of Gastroenterology & Hepatology **11**(5): 503-9.

Guarner, J., Mohar, A., et al. (1993). "The association of Helicobacter pylori with gastric cancer and preneoplastic gastric lesions in Chiapas, Mexico." Cancer **71**(2): 297-301.

Guo, W., Blot, W. J., et al. (1994). "A nested case-control study of oesophageal and stomach cancers in the Linxian nutrition intervention trial." International Journal of Epidemiology. **23**(3): 444-50.

Habibi, A. (1965). "Cancer in Iran. A survey of the most common cases." Journal of National Cancer Institute **34**: 553-69.

Haenszel, W. and Kurihara, M. (1968). "Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States." Journal of National Cancer Institute **40**: 43 - 68.

Haenszel, W., Kurihara, M., et al. (1976). "Stomach cancer in Japan." Journal of National Cancer Institute **56**: 265-274.

Hahm, K. B., Song, Y. J., et al. (2003). "Chemoprevention of Helicobacter pylori-associated gastric carcinogenesis in a mouse model: is it possible?" Journal of Biochemistry & Molecular Biology **36**(1): 82-94.

Hakama, M. (1971). "Epidemiologic evidence for multi-stage theory of carcinogenesis." International Journal of Cancer **7**(3): 557-64.

Hakama, M. (1972). "Trends in stomach cancer incidence for male cohorts in Finland." Annals of Clinical Research **4**(5): 300-3.

Hakama, M. (1997). "Chemoprevention research in Europe." International Journal of Cancer **Supplement 10**: 30-3.

Hakama, M. and Saxen, E. A. (1967). "Cereal consumption and gastric cancer." International Journal of Cancer **2**(3): 265-8.

Hamada, G. S., Kowalski, L. P., et al. (2002). "Risk factors for stomach cancer in Brazil (II): a case-control study among Japanese Brazilians in Sao Paulo." Japanese Journal of Clinical Oncology **32**(8): 284-290.

Hanley, A. J., Choi, B. C., et al. (1995). "Cancer mortality among Chinese migrants: a review." International Journal of Epidemiology. **24**(2): 255-65.

Hansen, S., Melby, K. K., et al. (1999). "Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study." Scandinavian Journal of Gastroenterology. **34**(4): 353-60.

Hansson, L. E., Baron, J., et al. (1994). "Early-life risk indicators of gastric cancer. A population-based case-control study in Sweden." International Journal of Cancer. **57**(1): 32-7.

Hansson, L. E., Engstrand, L., et al. (1993). "Helicobacter pyloriinfection: independent risk indicator of gastric adenocarcinoma." Gastroenterology **105**: 1098-1103.

Hansson, L. E., Lindgren, A., et al. (1996). "Can endoscopic biopsy specimens be used for reliable Lauren classification of gastric cancer?" Scandinavian Journal of Gastroenterology **31**(7): 711-5.

Hansson, L. R., Engstrand, L., et al. (1995). "Prevalence of Helicobacter pylori infection in subtypes of gastric cancer." Gastroenterology **109**(3): 885-8.

Hara, M., Hanaoka, T., et al. (2003). "Cruciferous vegetables, mushrooms, and gastrointestinal cancer risks in a multicenter, hospital-based case-control study in Japan." Nutrition & Cancer **46**(2): 138-47.

Harrison, L. E., Zhang, Z. F., et al. (1997). "The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S." Cancer. **80**(6): 1021-8.

Helicobacter and Cancer Collaborative, G. (2001). "Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts." Gut. **49**(3): 347-53.

Henson, D. E., Dittus, C., et al. (2004). "Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type." Archives of Pathology & Laboratory Medicine **128**(7): 765-70.

Hewer, T., Rose, E., et al. (1978). "Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus." Lancet **2**(8088): 494-6.

Hewer, T. F. (1979). "Opium and oesophageal cancer in Iran." Lancet **1**(8106): 45.

Hirschl, A. M., Brandstatter, G., et al. (1993). "Kinetics of specific IgG antibodies for monitoring the effect of anti-Helicobacter pylori chemotherapy." Journal of Infectious Diseases. **168**(3): 763-6.

Holcombe, C. (1992). "Helicobacter pylori: the African enigma." Gut **33**(4): 429-31.

Holcombe, C., Omotara, B. A., et al. (1992). "H. pylori, the most common bacterial infection in Africa: a random serological study." American Journal of Gastroenterology. **87**(1): 28-30.

Honda, S., Fujioka, T., et al. (1998). "Development of Helicobacter pylori-induced gastric carcinoma in Mongolian gerbils." Cancer Research **58**(19): 4255-9.

Hoshiyama, Y., Kawaguchi, T., et al. (2002). "A prospective study of stomach cancer death in relation to green tea consumption in Japan." British Journal of Cancer **87**(3): 309-13.

Hoshiyama, Y., Kawaguchi, T., et al. (2004). "A nested case-control study of stomach cancer in relation to green tea consumption in Japan." British Journal of Cancer **90**(1): 135-8.

Howard, J. W. and Fazio, T. (1970). "A review of polycyclic aromatic hydrocarbons in foods." IMS - Industrial Medicine & Surgery **39**(10): 435-40.

Howson, C., Hiyama, T., et al. (1986). "The decline in gastric cancer: epidemiology of an unplanned triumph." Epidemiologic Reviews **8**: 1 - 27.

Hu, P. J., Mitchell, H. M., et al. (1994). "Association of Helicobacter pylori with gastric cancer and observations on the detection of this bacterium in gastric cancer cases." American Journal of Gastroenterology **89**(10): 1806-10.

Huang, J. Q., Sridhar, S., et al. (1998). "Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer." Gastroenterology **114**(6): 1169-79.

Huang, J. Q., Zheng, G. F., et al. (2003). "Meta-analysis of the relationship between cagA seropositivity and gastric cancer." Gastroenterology **125**(6): 1636-44.

Huang, X., Tajima, K., et al. (1999). "Effect of life styles on the risk of subsite-specific gastric cancer in those with and without family history." Journal of Epidemiology **9**(1): 40-5.

Huang, X. E., Tajima, K., et al. (2000). "Effects of dietary, drinking, and smoking habits on the prognosis of gastric cancer." Nutrition & Cancer. **38**(1): 30-6.

IARC Working Group on the Evaluation of the Carcinogenic Risk to Humans (1988). Alcohol drinking. Lyon, France, International Agency for Research on Cancer.

Inoue, M., Ito, L. S., et al. (2002). "Height, weight, menstrual and reproductive factors and risk of gastric cancer among Japanese postmenopausal women: analysis by subsite and histologic subtype." International Journal of Cancer. **97**(6): 833-8.

Inoue, M., Tajima, K., et al. (1998a). "Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan." 209-16.

Inoue, M., Tajima, K., et al. (1996). "Protective factor against progression from atrophic gastritis to gastric cancer--data from a cohort study in Japan." International Journal of Cancer. **66**(3): 309-14.

Inoue, M., Tajima, K., et al. (1998b). "Family history and subsite of gastric cancer: data from a case-referent study in Japan." International Journal of Cancer **76**(6): 801-5.

International Agency for Research on Cancer (1986). Tobacco smoking. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (1987). Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (1994). Infection with Helicobacter pylori. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer. (1985). Tobacco habits other than smoking : betel-quid and areca-nut chewing and some related nitrosamines. Lyon, France, International Agency for Research on Cancer.

International Labour Office. (1990). International Standard Classification of Occupations : ISCO-88. Geneva, International Labour Office.

Ito, L. S., Inoue, M., et al. (2003). Dietary factors and the risk of gastric cancer among Japanese women: a comparison between the differentiated and non-differentiated subtypes. Annals of Epidemiology. **13:** 24-31.

Jakobsson, K., Mikoczy, Z., et al. (1997). "Deaths and tumours among workers grinding stainless steel: a follow up." Occupational & Environmental Medicine **54**(11): 825-9.

Jansen, M. C., Bueno-de-Mesquita, H. B., et al. (1999). "Consumption of plant foods and stomach cancer mortality in the seven countries study. Is grain consumption a risk factor? Seven Countries Study Research Group." Nutrition & Cancer **34**(1): 49-55.

Jedrychowski, W., Popiela, T., et al. (2001). "Nutrient intake patterns in gastric and colorectal cancers." International Journal of Occupational Medicine & Environmental Health **14**(4): 391-5.

Ji, B. T., Chow, W. H., et al. (1996). "The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China." Cancer **77**(12): 2449-57.

Ji, B. T., Chow, W. H., et al. (1998). "Dietary habits and stomach cancer in Shanghai, China." International Journal of Cancer. **76**(5): 659-64.

Joossens, J. V., Hill, M. J., et al. (1996). "Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group." International Journal of Epidemiology **25**(3): 494-504.

Kaaks, R., Tuyns, A. J., et al. (1998). "Nutrient intake patterns and gastric cancer risk: a case-control study in Belgium." International Journal of Cancer. **78**(4): 415-20.

Kai, M., Luebeck, E. G., et al. (1997). "Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis." Radiation Research **148**(4): 348-58.

Kaldor, J., Tee, W., et al. (1986). "Immunoblot confirmation of immune response to Campylobacter pyloridis in patients with duodenal ulcers." Medical Journal of Australia **145**(3-4): 133-5.

Kampschoer, G. H., Fujii, A., et al. (1989). "Gastric cancer detected by mass survey. Comparison between mass survey and outpatient detection." Scandinavian Journal of Gastroenterology. **24**(7): 813-7.

Kang, S. K., Burnett, C. A., et al. (1997). "Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures." American Journal of Industrial Medicine **31**(6): 713-8.

Karmali, R. A., Marsh, J., et al. (1984). "Effect of omega-3 fatty acids on growth of a rat mammary tumor." Journal of the National Cancer Institute **73**(2): 457-61.

Kasper, D. L. and Harrison, T. R. (2005). Harrison's principles of internal medicine. New York, McGraw-Hill, Medical Pub. Division.

Kasum, C. M., Jacobs, D. R., Jr., et al. (2002). "Dietary risk factors for upper aerodigestive tract cancers." International Journal of Cancer. **99**(2): 267-72.

Kato, M., Asaka, M., et al. (2004). "Relationship between Helicobacter pylori infection and the prevalence, site and histological type of gastric cancer." Alimentary Pharmacology & Therapeutics **20 Suppl 1**: 85-9.

Kato, S., Onda, M., et al. (1996). "Genetic polymorphisms of the cancer related gene and Helicobacter pylori infection in Japanese gastric cancer patients. An age and gender matched case-control study." Cancer. **77**(8 Suppl): 1654-61.

Kato, T., Saito, Y., et al. (1994). "Helicobacter pylori infection in gastric carcinoma." European Journal of Gastroenterology & Hepatology **6 Suppl 1**: S93-6.

Kazerouni, N., Thomas, T. L., et al. (2000). "Mortality among workers exposed to cutting oil mist: update of previous reports." American Journal of Industrial Medicine **38**(4): 410-6.

Ke, L. and Shunzhang, Y. (1999). "Economic status and occupational correlates of stomach cancer in the rubber industry." International Journal of Occupational Medicine & Environmental Health **12**(4): 345-52.

Kikuchi, S., Crabtree, J. E., et al. (1999). "Association between infections with CagA-positive or -negative strains of Helicobacter pylori and risk for gastric cancer in young adults. Research Group on Prevention of Gastric Carcinoma Among Young Adults." American Journal of Gastroenterology. **94**(12): 3455-9.

Kim, H. J., Chang, W. K., et al. (2002). "Dietary factors and gastric cancer in Korea: a case-control study." International Journal of Cancer. **97**(4): 531-5.

Kim, H. Y., Cho, B. D., et al. (1997). "Helicobacter pylori infection and the risk of gastric cancer among the Korean population." Journal of Gastroenterology & Hepatology **12**(2): 100-3.

Kim, M. K., Sasaki, S., et al. (2004). "Prospective study of three major dietary patterns and risk of gastric cancer in Japan." International Journal of Cancer **110**(3): 435-42.

Kinlen, L. J., Willows, A. N., et al. (1988). "Tea consumption and cancer." British Journal of Cancer **58**(3): 397-401.

Klein, P. D., Graham, D. Y., et al. (1991). "Water source as risk factor for Helicobacter pylori infection in Peruvian children. Gastrointestinal Physiology Working Group." Lancet. **337**(8756): 1503-6.

Kmet, J. (1978). "Opium and oesophageal cancer in Iran." Lancet **2**(8104-5): 1371-2.

Kneller, R. W., Guo, W. D., et al. (1992). "Risk factors for stomach cancer in sixty-five Chinese counties." Cancer Epidemiology, Biomarkers & Prevention **1**(2): 113-8.

Kobayashi, M., Tsubono, Y., et al. (2002). "Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC Study Cohort I." International Journal of Cancer **102**(1): 39-44.

Koea, J. B., Karpeh, M. S., et al. (2000). "Gastric cancer in young patients: demographic, clinicopathological, and prognostic factors in 92 patients." Annals of Surgical Oncology **7**(5): 346-51.

Koizumi, Y., Tsubono, Y., et al. (2004). "Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan." International Journal of Cancer **112**(6): 1049-55.

Koizumi, Y., Tsubono, Y., et al. (2003). "No association between green tea and the risk of gastric cancer: pooled analysis of two prospective studies in Japan." Cancer Epidemiology, Biomarkers & Prevention **12**(5): 472-3.

Kono, S. and Hirohata, T. (1996). "Nutrition and stomach cancer." Cancer Causes & Control. **7**(1): 41-55.

Krienitz, W. (1906). "Uber das Auftreten von Spirochaeten verschiedener Form im Mageninhalt bei Carcinoma Ventriculi." Deutsche Medizinische Wochenschrift **22**: 872.

Krstev, S., Dosemeci, M., et al. (2005). "Occupation and risk of stomach cancer in Poland." Occupational & Environmental Medicine **62**(5): 318-24.

Kubota, H., Kotoh, T., et al. (2000). "Impact of screening survey of gastric cancer on clinicopathological features and survival: retrospective study at a single institution." Surgery **128**(1): 41-47.

Kuipers, E., Gracia-Casanova, M., et al. (1993). "Helicobacter pylori serology in patients with gastric carcinoma." Scandinavian Journal of Gastroenterology. **28**: 433-437.

Kuipers, E. J., Uyterlinde, A. M., et al. (1995). "Long-term sequelae of Helicobacter pylori gastritis." Lancet **345**(8964): 1525-8.

Kurosawa, M., Kikuchi, S., et al. (2000). "Helicobacter pylori infection among Japanese children." Journal of Gastroenterology & Hepatology. **15**(12): 1382-5.

Kusiak, R. A., Ritchie, A. C., et al. (1993). "Mortality from stomach cancer in Ontario miners." British Journal of Industrial Medicine **50**(2): 117-26.

La Vecchia, C., Bosetti, C., et al. (1998). "Refined sugar intake and the risk of gastric cancer." International Journal of Cancer. **78**(1): 130-1.

La Vecchia, C., D'Avanzo, B., et al. (1995a). "Nitrosamine intake and gastric cancer risk." European Journal of Cancer Prevention. **4**(6): 469-74.

La Vecchia, C., D'Avanzo, B., et al. (1995b). "Attributable risks for stomach cancer in northern Italy." International Journal of Cancer. **60**(6): 748-52.

La Vecchia, C., Ferraroni, M., et al. (1995). "Number of siblings and subsequent gastric cancer risk." European Journal of Cancer Prevention. **4**(1): 69-72.

La Vecchia, C., Munoz, S. E., et al. (1997). "Diet diversity and gastric cancer." International Journal of Cancer. **72**(2): 255-7.

La Vecchia, C., Negri, E., et al. (1990). "Food temperature and gastric cancer." International Journal of Cancer. **46**(3): 432-4.

La Vecchia, C., Negri, E., et al. (1992). "Family history and the risk of stomach and colorectal cancer." Cancer. **70**(1): 50-5.

Lagergren, J., Bergstrom, R., et al. (1999a). "Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma." New England Journal of Medicine. **340**(11): 825-31.

Lagergren, J., Bergstrom, R., et al. (2000). "The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia." International Journal of Cancer. **85**(3): 340-6.

Lagergren, J., Bergstrom, R., et al. (1999b). "Association between body mass and adenocarcinoma of the esophagus and gastric cardia." Annals of Internal Medicine. **130**(11): 883-90.

Lam, S. K. and Talley, N. J. (1998). "Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection." Journal of Gastroenterology & Hepatology **13**(1): 1-12.

Lanas, A. and Hirschowitz, B. I. (1992). "Influence of smoking on basal and on vagally and maximally stimulated gastric acid and pepsin secretion." Scandinavian Journal of Gastroenterology **27**(3): 208-12.

Langenberg, W., Rauws, E. A., et al. (1990). "Patient-to-patient transmission of Campylobacter pylori infection by fiberoptic gastroduodenoscopy and biopsy." Journal of Infectious Diseases. **161**(3): 507-11.

Lasky, T. and Stolley, P. D. (1994). "Selection of cases and controls." Epidemiologic Reviews **16**(1): 6-17.

Lauren, P. (1965). "The two histological main types of gastric cancer: diffuse and so- called intestinal type carcinoma: an attempt at a histo-clinical classification." Acta Pathologica et Microbiologica Scandinavica **64**: 31 - 49.

Lauren, P. (1991). "Histogenesis of intestinal and diffuse types of gastric carcinoma." Scandinavian Journal of Gastroenterology **Supplement 180**: 160-4.

Lauren, P. A. and Nevalainen, T. J. (1993). "Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas.[see comment]." Cancer **71**(10): 2926-33.

Layton, D. W., Bogen, K. T., et al. (1995). "Cancer risk of heterocyclic amines in cooked foods: an analysis and implications for research." Carcinogenesis **16**(1): 39-52.

Lee, J. K., Park, B. J., et al. (1995). "Dietary factors and stomach cancer: a case-control study in Korea." International Journal of Epidemiology. **24**(1): 33-41.

Lee, S. A., Kang, D., et al. (2003). "Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer." Journal of Epidemiology **13**(3): 162-8.

Lehtola, J. (1978). "Family study of gastric carcinoma; With special reference to histological types." Scandinavian Journal of Gastroenterology **Supplement 50**: 3-54.

Lehtola, J. (1981). "Family behaviour of gastric carcinoma." Annals of Clinical Research **13**(3): 144-8.

Leung, W. K., Lin, S. R., et al. (2004). "Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication." Gut **53**(9): 1244-9.

Lichtenstein, P., Holm, N. V., et al. (2000). "Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland." New England Journal of Medicine **343**(2): 78-85.

Lieber, C. S. and Lefevre, A. (1957). "Effect of oxytetracycline on acidity, amonia and urea in gastric juice in normal and uremic subjects." CR Soc Biol **151**: 1038-42.

Limburg, P., Qiao, Y., et al. (2001). "Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China." Journal of the National Cancer Institute. **93**(3): 226-33.

Lin, J. T., Wang, J. T., et al. (1993). "Helicobacter pylori infection in a randomly selected population, healthy volunteers, and patients with gastric ulcer and gastric adenocarcinoma. A seroprevalence study in Taiwan." Scandinavian Journal of Gastroenterology **28**(12): 1067-72.

Lin, J. T., Wang, J. T., et al. (1994). "Seroprevalence study of Helicobacter pylori infection in patients with gastroduodenal diseases." Journal of the Formosan Medical Association **93**(2): 122-7.

Lin, J. T., Wang, L. Y., et al. (1995). "A nested case-control study on the association between Helicobacter pylori infection and gastric cancer risk in a cohort of 9775 men in Taiwan." Anticancer Research **15**(2): 603-6.

Ling, A. M., Horwath, C., et al. (1998). "Validation of a short food frequency questionnaire to assess consumption of cereal foods, fruit and vegetables in Chinese Singaporeans." European Journal of Clinical Nutrition **52**(8): 557-64.

Lissowska, J., Gail, M. H., et al. (2004). "Diet and Stomach Cancer Risk in Warsaw, Poland." Nutrition and Cancer **48**(2): 149-159.

Lissowska, J., Groves, F. D., et al. (1999). "Family history and risk of stomach cancer in Warsaw, Poland." European Journal of Cancer Prevention. **8**(3): 223-7.

Lopez-Carrillo, L., Lopez-Cervantes, M., et al. (1998). "Alcohol consumption and gastric cancer in Mexico." Cadernos de Saude Publica. **14**(Suppl 3): 25-32.

Lopez-Carrillo, L., Lopez-Cervantes, M., et al. (2003). "Capsaicin consumption, Helicobacter pylori positivity and gastric cancer in Mexico." International Journal of Cancer **106**(2): 277-82.

Lopez-Carrillo, L., Lopez-Cervantes, M., et al. (1999). "Nutrient intake and gastric cancer in Mexico." International Journal of Cancer. **83**(5): 601-5.

Love, R. R., Evans, A. M. et al. (1985). "The accuracy of patient reports of a family history of cancer." Journal of Chronic Diseases **38**(4): 289-93.

Lucet, M. (1910). "Sur la presence de Spirochètes dans un cas de gastro-entèrite hémorragique chez le chien." Compt. Rend. Acad. Sci. **151**: 260 -262.

Luger, A. (1917). "Uber Spirochaten und fusiforme Bazillen im darm, miteinem Beitrag zur Frag der Lamblien-enteritis." Wein Klin Wocheenschr **52**: 1643 -7.

Lunet, N. and Barros, H. (2003). "Helicobacter pylori infection and gastric cancer: facing the enigmas." International Journal of Cancer **106**(6): 953-60.

MacDonald, W. C. and MacDonald, J. B. (1987). "Adenocarcinoma of the esophagus and/or gastric cardia." Cancer **60**(5): 1094-8.

Machida-Montani, A., Sasazuki, S., et al. (2004). "Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan." Gastric Cancer **7**(1): 46-53.

Mackay, J., Eriksen, M., et al. (2002). The tobacco atlas. Geneva, World Health Organization.

Mahboubi, E., Kmet, J., et al. (1973). "Oesophageal cancer studies in the Caspian Littoral of Iran: the Caspian cancer registry." British Journal of Cancer **28**(3): 197-214.

Malaty, H. M. and Graham D. Y., (1994). "Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection." Gut **35**(6): 742-5.

Malekzadeh, R., Sotoudeh, M., et al. (2004). "Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the northwest of Iran." Journal of Clinical Pathology **57**(1): 37-42.

Mao, Y., Hu, J., et al. (2002). "Active and passive smoking and the risk of stomach cancer, by subsite, in Canada." European Journal of Cancer Prevention **11**(1): 27-38.

Margetts, B. M. and Nelson, M. (1991). Design Concepts in Nutritional Epidemiology. New York, Oxford University Press.

Marsh, G. M., Gula, M. J., et al. (1999). "Mortality among chemical plant workers exposed to acrylonitrile and other substances." American Journal of Industrial Medicine **36**(4): 423-36.

Marshall, B. J. (1994). "Helicobacter pylori." American Journal of Gastroenterology. **89**(8 Suppl): S116-28.

Marshall, B. J. (2002). Helicobacter pioneers : firsthand accounts from the scientists who discovered Helicobacters, 1892-1982. Carlton, Vic., Blackwell Science Asia.

Marshall, B. J., McGechie, D. B., et al. (1984). "Pyloric campylobacter serology." Lancet **2**(8397): 281.

Martin-de-Argila, C., Boixeda, D., et al. (1997). "Relation between histologic subtypes and location of gastric cancer and Helicobacter pylori." Scandinavian Journal of Gastroenterology. **32**(4): 303-7.

Massarrat, S., Saberi-Firoozi, M., et al. (1995). "Peptic ulcer disease, irritable bowel syndrome and constipation in two populations in Iran." European Journal of Gastroenterology & Hepatology **7**: 427-433.

Mathew, A., Gangadharan, P., et al. (2000). "Diet and stomach cancer: a case-control study in South India." European Journal of Cancer Prevention. **9**(2): 89-97.

Matsukura, N., Onda, M., et al. (1997). "Cytotoxin genes of Helicobacter pylori in chronic gastritis, gastroduodenal ulcer and gastric cancer: an age and gender matched case-control study." Japanese Journal of Cancer Research **88**(6): 532-6.

Mayne, S. T., Risch, H. A., et al. (2001). "Nutrient intake and risk of subtypes of esophageal and gastric cancer." Cancer Epidemiology, Biomarkers & Prevention. **10**(10): 1055-62.

McCullough, M. L., Robertson, A. S., et al. (2001). "A prospective study of diet and stomach cancer mortality in United States men and women." Cancer Epidemiology, Biomarkers & Prevention **10**(11): 1201-1205.

McFarlane, G., Forman, D., et al. (2001). "A minimum estimate for the incidence of gastric cancer in Eastern Kenya." British Journal of Cancer. **85**(9): 1322-5.

Medrado-Faria, M. A., Rodrigues de Almeida, J. W., et al. (2001). "Gastric and colorectal cancer mortality in an urban and industrialized area of Brazil." Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo **56**(2): 47-52.

Megraud, F. (1992). Epidemiology of Helicobacter pylori infection. Helicobacter pylori and Gastroduodenal Disease. Rathbone, B. J. and Heatley, R. V. Oxford, Blackwell Scientific Publications**:** 107-23.

Megraud, F., Brassens-Rabbe, M. P., et al. (1989). "Seroepidemiology of Campylobacter pylori infection in various populations." Journal of Clinical Microbiology. **27**(8): 1870-3.

Mendall, M. A., Goggin, P. M., et al. (1992). "Childhood living conditions and Helicobacter pylori seropositivity in adult life.[comment]." Lancet. **339**(8798): 896-7.

Menegatti, M., Vaira, D., et al. (1995). "Helicobacter pylori in patients with gastric and nongastric cancer." American Journal of Gastroenterology. **90**(8): 1278-81.

Midolo, P. and Marshall, B. J. (2000). "Accurate diagnosis of Helicobacter pylori. Urease tests." Gastroenterology Clinics of North America. **29**(4): 871-8.

Miehlke, S., Go, M. F., et al. (1998). "Serologic detection of Helicobacter pylori infection with cagA-positive strains in duodenal ulcer, gastric cancer, and asymptomatic gastritis." Journal of Gastroenterology **33**(Suppl 10): 18-21.

Miehlke, S., Kirsch, C., et al. (2000). "The Helicobacter pylori vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany." International Journal of Cancer **87**(3): 322-7.

Mikaeli, J., Malekzadeh, R., et al. (2000). "Prevalence of helicobacter pylori in two Iranian provinces with high and low incidence of gastric carcinoma." Archives of Iranian Medicine **3**(1): 6-9

Minami, Y. and Tateno, H. (2003). "Associations between cigarette smoking and the risk of four leading cancers in Miyagi Prefecture, Japan: a multi-site case-control study." Cancer Science **94**(6): 540-7.

Mitchell, H. M., Hazell, S. L., et al. (1996). "Serological response to specific Helicobacter pylori antigens: antibody against CagA antigen is not predictive of gastric cancer in a developing country." American Journal of Gastroenterology **91**(9): 1785-8.

Mitchell, H. M., Lee, A., et al. (1989). "Increased incidence of Campylobacter pylori infection in gastroenterologists: further evidence to support person-to-person transmission of C. pylori." Scandinavian Journal of Gastroenterology **24**(4): 396-400.

Miyaji, H., Azuma, T., et al. (2000). "Helicobacter pylori infection occurs via close contact with infected individuals in early childhood." Journal of Gastroenterology & Hepatology. **15**(3): 257-62.

Moayyedi, P., Axon, A. T. R., et al. (2002). "Relation of adult lifestyle and socioeconomic factors to the prevalence of Helicobacter pylori infection." International Journal of Epidemiology June **31**(3): 624-631.

Morgenstern, H. (1998). Ecologic Studies. Modern epidemiology. Rothman, K. J. and Greenland, S. Philadelphia, PA, Lippincott-Raven**:** 459 - 80.

Mosane, T. W., Malope, B. I., et al. (2004). "Seroprevalence of Helicobacter pylori immunoglobulin G antibodies in South African mothers and their children." European Journal of Gastroenterology & Hepatology **16**(1): 113-4.

Mousavi, M. R., Damghani, M. A., et al. (2003). "Opium and risk of laryngeal cancer." Laryngoscope **113**(11): 1939-43.

Munoz, N., Correa, P., et al. (1968). "Histologic types of gastric carcinoma in high- and low-risk areas." International Journal of Cancer **3**(6): 809-18.

Munoz, N. and Day, N. E. (1996). Esophageal cancer. Cancer epidemiology and prevention. Schottenfeld, D. and Fraumeni, J. F. New York, Oxford University Press**:** 681–706.

Munoz, N., Plummer, M., et al. (2001). "A case-control study of gastric cancer in Venezuela." International Journal of Cancer. **93**(3): 417-23.

Muszynski, J., Dzierzanowska, D., et al. (1995). "Is Helicobacter pylori infection a real risk factor for gastric carcinoma?" Scandinavian Journal of Gastroenterology **30**(7): 647-51.

Nagano, J., Kono, S., et al. (2001). "A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan)." Cancer Causes & Control **12**(6): 501-8.

Nagata, C., Takatsuka, N., et al. (2002). "A prospective cohort study of soy product intake and stomach cancer death." British Journal of Cancer **87**(1): 31-6.

Naghavi, M. (2000). Death report from 10 provinces in Iran. Tehran, Ministry of Health and Medical Education.

Naghavi, M. (2003). Situation of Mortality in 18 Provinces of Iran. Tehran, Ministry of Health and Medical Education.

National Health Priority Action Council., Cancer Strategies Group., et al. (2001). Priorities for action in cancer control : 2001-2003. [Canberra], Dept. of Health and Ageing.

Neugut, A. I., Hayek, M., et al. (1996). "Epidemiology of gastric cancer." Seminars in Oncology. **23**(3): 281-91.

Ngoan, L. T., Mizoue, T., et al. (2002). "Dietary factors and stomach cancer mortality." British Journal of Cancer **87**(1): 37-42.

Ngoan, L. T. and Yoshimura, T. (2003). "Work, salt intake and the development of stomach cancer." Medical Hypotheses **60**(4): 552-6.

Nishimoto, I. N., Hamada, G. S., et al. (2002). "Risk factors for stomach cancer in Brazil (I): a case-control study among non-Japanese Brazilians in Sao Paulo." Japanese Journal of Clinical Oncology **32**(8): 277-283.

Nomura, A. (1996). Stomach cancer. Cancer Epidemiology and Prevention. Schottenfeld, D. and Fraumeni, J. F. New York, Oxford University Press**:** 707-724.

Nomura, A., Stemmermann, G. N., et al. (1991). "Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii." New England Journal of Medicine **325**(16): 1132-6.

Nomura, A. M., Hankin, J. H., et al. (2003). "Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States)." Cancer Causes & Control **14**(6): 547-58.

Norat, T. and Riboli, E. (2002). "Fruit and vegetable consumption and risk of cancer of the digestive tract: meta-analysis of published case-control and cohort studies." IARC Scientific Publications **156**: 123-5.

Nozaki, K., Shimizu, N., et al. (2003). "Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils." Cancer Science **94**(3): 235-9.

Nurminen, M. and Karjalainen, A. (2001). "Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland." Scandinavian Journal of Work, Environment & Health **27**(3): 161-213.

Nyren, O. and Adami, H. O. (2002). Stomach Cancer. Textbook of cancer epidemiology. Adami, H.-O., Hunter, D. J. and Trichopoulos, D. Oxford ; New York, N.Y., Oxford University Press**:** 162 - 87.

Obata, Y., Kikuchi, S., et al. (2003). "Diagnostic accuracy of serological kits for Helicobacter pylori infection with the same assay system but different antigens in a Japanese patient population." Journal of Medical Microbiology **52**(Pt 10): 889-92.

Okabayashi, T., Gotoda, T., et al. (2000). "Early carcinoma of the gastric cardia in Japan: is it different from that in the West?" Cancer **89**(12): 2555-9.

Paik, D. C., Saborio, D. V., et al. (2001). "The epidemiological enigma of gastric cancer rates in the US: was grandmother's sausage the cause?" International Journal of Epidemiology **30**(1): 181-2.

Palli, D. (1997). "Gastric cancer and Helicobacter pylori: a critical evaluation of the epidemiological evidence." Helicobacter **2 Suppl 1**: S50-5.

Palli, D., Bianchi, S., et al. (1992). "A case-control study of cancers of the gastric cardia in Italy." British Journal of Cancer. **65**(2): 263-6.

Palli, D., Decarli, A., et al. (1993). "Helicobacter pylori antibodies in areas of Italy at varying gastric cancer risk." Cancer Epidemiology, Biomarkers & Prevention. **2**(1): 37-40.

Palli, D., Galli, M., et al. (1994). "Family history and risk of stomach cancer in Italy." Cancer Epidemiology, Biomarkers & Prevention. **3**(1): 15-8.

Palli, D., Russo, A., et al. (2001). "Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy." Cancer Causes & Control. **12**(2): 163-72.

Palli, D., Saieva, C., et al. (2001). "O6-alkylguanines, dietary N-nitroso compounds, and their precursors in gastric cancer." Nutrition & Cancer. **39**(1): 42-9.

Pang, D., Burges, D. C., et al. (1996). "Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93." Occupational & Environmental Medicine **53**(10): 714-7.

Pang, Z. C., Zhang, Z., et al. (1997). "Mortality from a Chinese asbestos plant: overall cancer mortality." American Journal of Industrial Medicine **32**(5): 442-4.

Parent, M. E., Siemiatycki, J., et al. (1998). "Occupational exposures and gastric cancer." Epidemiology. **9**(1): 48-55.

Park, R. M. (2001). "Mortality at an automotive engine foundry and machining complex." Journal of Occupational & Environmental Medicine **43**(5): 483-93.

Park, R. M. and Mirer, F. E. (1996). "A survey of mortality at two automotive engine manufacturing plants." American Journal of Industrial Medicine **30**(6): 664-73.

Parkin, D. M., Bray, F. I., et al. (2001). "Cancer burden in the year 2000. The global picture." European Journal of Cancer. **37**(Suppl 8): S4-66.

Parkin, D. M., Whelan, S. L., et al. (2005). Cancer Incidence in Five Continents, Vol. I to VIII. Lyon, IARC.

Parsonnet, J., Friedman, G. D., et al. (1997). "Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection." Gut. **40**(3): 297-301.

Parsonnet, J., Friedman, G. D., et al. (1991). "Helicobacter pylori infection and the risk of gastric carcinoma." New England Journal of Medicine. **325**(16): 1127-31.

Parsonnet, J., Vandersteen, D., et al. (1991). "Helicobacter pylori infection in intestinal- and diffuse-type gastric adenocarcinomas." Journal of the National Cancer Institute **83**(9): 640-3.

Perez-Perez, G. I., Taylor, D. N., et al. (1990). "Seroprevalence of Helicobacter pylori infections in Thailand." Journal of Infectious Diseases. **161**(6): 1237-41.

Pisani, P., Bray, F., et al. (2002). "Estimates of the world-wide prevalence of cancer for 25 sites in the adult population." International Journal of Cancer. **97**(1): 72-81.

Plato, N., Westerholm, P., et al. (1995). "Cancer incidence, mortality and exposure-response among Swedish man-made vitreous fiber production workers." Scandinavian Journal of Work, Environment & Health **21**(5): 353-61.

Pott, P. (1775). Chirurgical Observations. London, Clarke and Collins.

Pounder, R. E. and Ng, D. (1995). "The prevalence of Helicobacter pylori infection in different countries." Alimentary Pharmacology & Therapeutics. **9**(Suppl. 2): 33-39.

Queiroz, D. M., Mendes, E. N., et al. (1998). "cagA-positive Helicobacter pylori and risk for developing gastric carcinoma in Brazil." International Journal of Cancer **78**(2): 135-9.

Raghavan, S., Hjulstrom, M., et al. (2002). "Protection against experimental Helicobacter pylori infection after immunization with inactivated H. pylori whole-cell vaccines." Infection & Immunity **70**(11): 6383-8.

Raj, A., Mayberry, J. F., et al. (2003). "Occupation and gastric cancer." Postgraduate Medical Journal **79**(931): 252-8.

Rao, D. N., Ganesh, B., et al. (2002). "A case-control study of stomach cancer in Mumbai, India." International Journal of Cancer. **99**(5): 727-31.

Rathbone, B. J. and Heatley, R. V. (1992). The historical associations between bacteria and peptic-ulcer disease. Helicobacter pylori and Gastroduodenal Disease. Rathbone, B. J. and Heatley, R. V. Oxfords, Blackwell Scientific Publications**:** 1-4.

Rigdon, R. H. and Neal, J. (1969). "Relationship of leukemia to lung and stomach tumors in mice fed benzo (a) pyrene." Proceedings of the Society for Experimental Biology & Medicine **130**(1): 146-8.

Rios-Castellanos, E., Sitas, F., et al. (1992). "Changing pattern of gastric cancer in Oxfordshire." Gut. **33**(10): 1312-7.

Rix, B. A., Villadsen, E., et al. (1997). "Cancer incidence of sulfite pulp workers in Denmark." Scandinavian Journal of Work, Environment & Health **23**(6): 458-61.

Robinson, C. F., Petersen, M., et al. (1996). "Mortality of Carpenters' Union members employed in the U.S. construction or wood products industries, 1987-1990." American Journal of Industrial Medicine **30**(6): 674-94.

Romundstad, P., Andersen, A., et al. (2001). "Cancer incidence among workers in the Norwegian silicon carbide industry." American Journal of Epidemiology **153**(10): 978-86.

Rona, R. J. and Mosbech, J. (1989). "Validity and repeatability of self-reported occupational and industrial history from patients in EEC countries." International Journal of Epidemiology **18**(3): 674-9.

Rosenberg, C. R. (1993). "An analysis of the reliability of self reported work histories from a cohort of workers exposed to polychlorinated biphenyls." British Journal of Industrial Medicine **50**(9): 822-6.

Rotterdam, H. (1989). Carcinoma of the stomach. Pathology of the stomach and duodenum. Rotterdam, H. and Enterline, H. T. New York, Springer-Verlag**:** 142 - 204.

Rustgi, A. K. (2001). Neoplasms of the stomach. Cecil essentials of medicine. Cecil, R. L. and Andreoli, T. E. Philadelphia, W.B. Saunders**:** 738-741.

Sacket, D. L., Haynes, B. R., et al. (1991). Clinical epidemiology: a basic science for medicine. Boston, Little Brown.

Sadjadi, A., Malekzadeh, R., et al. (2003). "Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran." International Journal of Cancer **107**(1): 113-8.

Sakaki, N., Momma, K., et al. (1995). "The influence of Helicobacter pylori infection on the progression of gastric mucosal atrophy and occurrence of gastric cancer." European Journal of Gastroenterology & Hepatology **7 Suppl 1**: S59-62.

Salomon, H. (1896). "Ueber das Spirillium des Saugetiermagens und sein Verhalten zu den Bellegzellen." Zentralblatt fur Bakteriologie **19**: 433-442.

Sankaranarayanan, R., Duffy, S. W., et al. (1989). "Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India." British Journal of Cancer **60**(4): 638-43.

Sasako, M. and Sugimura, T. (1997). Gastric cancer. New York, Oxford University Press.

Sasazuki, S., Sasaki, S., et al. (2002). "Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type." International Journal of Cancer **101**(6): 560-6.

Schlesselman, J. (1982). Case-control studies :design, conduct, analysis. New York, Oxford University Press.

Schottenfeld, D. (1996). Principles and applications of cancer prevention. Cancer epidemiology and prevention. Schottenfeld, D. and Fraumeni, J. F. New York, Oxford University Press**:** 1391-1409.

Schottenfeld, D. and Fraumeni, J. F. (1996). Cancer epidemiology and prevention. New York, Oxford University Press.

Segal, I., Ally, R., et al. (2001). "Gastric cancer in sub-Saharan Africa." European Journal of Cancer Prevention **10**(6): 479-82.

Selvin, H. C. (1958). "Durkheim's suicide and problems of empirical research." American Journal of Sociology **63**: 607 - 19.

Sen, N. P. (1972). "The evidence for the presence of dimethylnitrosamine in meat products." Food & Cosmetics Toxicology **10**(2): 219-23.

Serafini, M., Bellocco, R., et al. (2002). "Total antioxidant potential of fruit and vegetables and risk of gastric cancer." Gastroenterology. **123**(4): 985-91.

Shimizu, N., Ikehara, Y., et al. (2000). "Eradication diminishes enhancing effects of Helicobacter pylori infection on glandular stomach carcinogenesis in Mongolian gerbils." Cancer Research **60**(6): 1512-4.

Shinohara, K., Miyazaki, K., et al. (1998). "Gastric diseases related to Helicobacter pylori and Epstein-Barr virus infection." Microbiology & Immunology **42**(6): 415-21.

Siavoshi, F., Malekzadeh, R., et al. (2004). "Association Between Helicobacter pylori Infection in Gastric Cancer, Ulcers and Gastritis in Iranian Patients." Helicobacter **9**(5): 470-470.

Silva, I. d. S. (1999). Cancer epidemiology : principles and methods. Lyon, France, International Agency for Research on Cancer.

Siman, J. H., Forsgren, A., et al. (2001). "Tobacco smoking increases the risk for gastric adenocarcinoma among Helicobacter pylori-infected individuals." Scandinavian Journal of Gastroenterology. **36**(2): 208-13.

Sitas, F. (1993). "Helicobacter pylori and gastric cancer." The Southern African Journal of Epidemiology and Infection **8**(2): 32 - 35.

Sitas, F. and Forman, D. (1989). The Epidemiology of Chronic Active Gastritis. Topics of Gastroenterology. Jewell, D. P. and Snook, A. Oxford, Blackwells.

Sitas, F., Forman, D., et al. (1991). "Helicobacter pylori infection rates in relation to age and social class in a population of Welsh men." Gut **32**(1): 25-8.

Sitas, F., Sathar, M. A., et al. (1997). "Helicobacter pylori seroprevalence in the African adult population of the Cape Peninsula." The Southern African Journal of Epidemiology and Infection **12**(4): 111 - 114.

Sitas, F., Smallwood, R., et al. (1993). "Serum anti-Helicobacter pylori IgG antibodies and pepsinogens A and C serological markers of chronic atrophic gastritis." Cancer Epidemiol Biomarkers Prev **2**: 119-123.

Sitas, F., Urban, M., et al. (2004). "Tobacco attributable deaths in South Africa." Tobacco Control **13**(4): 396-9.

Sivaprakash, R., Rao, U. A., et al. (1996). "Investigation for the prevalence of Helicobacter pylori infection in patients with gastric carcinoma in Madras, India." Japanese Journal of Medical Science & Biology **49**(2): 49-56.

Skog, K., Steineck, G., et al. (1995). "Effect of cooking temperature on the formation of heterocyclic amines in fried meat products and pan residues." Carcinogenesis **16**(4): 861-7.

Smith - Warner, S. A. and Giovannucci, E. (1999). Fruit and Vegetable Intake and Cancer. Nutritional oncology. Blackburn, G. L., Go, V. L. W., Heber, D. and Cancer Treatment Research Foundation (U.S.). San Diego, Calif. ; London, Academic**:** xix,632 p.

Smith, D., Taylor, R., et al. (1996). "Socioeconomic differentials in cancer incidence and mortality in urban New South Wales, 1987-1991." Australian & New Zealand Journal of Public Health **20**(2): 129-37.

Sobala, G. M., Pignatelli, B., et al. (1991). "Levels of nitrite, nitrate, N-nitroso compounds, ascorbic acid and total bile acids in gastric juice of patients with and without precancerous conditions of the stomach." Carcinogenesis **12**(2): 193-8.

Sobala, G. M., Schorah, C. J., et al. (1993). "High gastric juice ascorbic acid concentrations in members of a gastric cancer family." Carcinogenesis **14**(2): 291-2.

Sokoloff, B. (1938). "Predisposition to cancer in the Bonaparte family." American Journal of Surgery. **40**: 973-8.

Sorensen, H. T., Friis, S., et al. (2003). "Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study." British Journal of Cancer **88**(11): 1687-92.

SPSS Inc (2004). SPSS version 13.0. Chicago, Illinois, SPSS Inc.

Statistical Centre of Iran (1996). National Census of Population & Housing.

Statistical Centre of Iran (2002). Iran statistical year book 1381 [2002-2003]. Tehran, Statistic Centre of Iran.

Statistical Centre of Iran (2003). Selected Data. Tehran, Statistical Centre of Iran. **2004**.

Steer, H. W. and Colin-Jones, D. G. (1975). "Mucosal changes in gastric ulceration and their response to carbenoxolone sodium." Gut **16**(8): 590-7.

Stewart, B. W. and Coates, A. S. (2005). "Cancer prevention: a global perspective." Journal of Clinical Oncology **23**(2): 392-403.

Straif, K., Chambless, L., et al. (1999). "Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment." International Journal of Epidemiology. **28**(6): 1037-43.

Straif, K., Keil, U., et al. (2000). "Exposure to nitrosamines, carbon black, asbestos, and talc and mortality from stomach, lung, and laryngeal cancer in a cohort of rubber workers." American Journal of Epidemiology **152**(4): 297-306.

Straif, K., Weiland, S. K., et al. (1998). "Workplace risk factors for cancer in the German rubber industry: Part 2. Mortality from non-respiratory cancers." Occupational & Environmental Medicine **55**(5): 325-32.

Straughan, J. K. and Sorahan, T. (2000). "Cohort mortality and cancer incidence survey of recent entrants (1982-91) to the United Kingdom rubber industry: preliminary findings." Occupational & Environmental Medicine **57**(8): 574-6.

Stucker, I., Meguellati, D., et al. (2003). "Cohort mortality study among French asphalt workers." American Journal of Industrial Medicine **43**(1): 58-68.

Sugimura, T. and Fujimura, S. (1967). "Tumour production in glandular stomach of rat by N-methyl-N'-nitro-N-nitrosoguanidine." Nature **216**(118): 943-4.

Sugimura, T., Tanaka, N., et al. (1971). "Production of stomach cancer in dogs by N-methyl-N'-nitro-N-nitrosoguanidine." Gann **62**(1): 67.

Sullivan, P. B., Thomas, J. E., et al. (1990). "Helicobacter pylori in Gambian children with chronic diarrhoea and malnutrition." Archives of Disease in Childhood. **65**(2): 189-91.

Sunny, L., Yeole, B. B., et al. (2004). "Decreasing trend in the incidence of stomach cancer in Mumbai, India, during 1988 to 1999." Asian Pacific Journal of Cancer Prevention: Apjcp **5**(2): 169-74.

Swaen, G. M., Meijers, J. M., et al. (1995). "Risk of gastric cancer in pneumoconiotic coal miners and the effect of respiratory impairment." Occupational & Environmental Medicine **52**(9): 606-10.

Szeto, M. L., Lee, C. K., et al. (2001). "Evaluation of five commercial serological tests for the detection of Helicobacter pylori infection in Chinese." Alimentary Pharmacology & Therapeutics. **15**(5): 703-6.

Takezaki, T., Gao, C. M., et al. (2001). "Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area." Japanese Journal of Cancer Research **92**(11): 1157-65.

Talley, N. J., Zinsmeister, A. R., et al. (1991). "Gastric adenocarcinoma and Helicobacter pylori infection." Journal of the National Cancer Institute **83**(23): 1734-9.

Terry, P., Lagergren, J., et al. (2001a). "Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers." European Journal of Cancer Prevention **10**(4): 365-9.

Terry, P., Lagergren, J., et al. (2000). "Antioxidants and cancers of the esophagus and gastric cardia." International Journal of Cancer **87**(5): 750-4.

Terry, P., Lagergren, J., et al. (2001b). "Inverse association between intake of cereal fiber and risk of gastric cardia cancer." Gastroenterology. **120**(2): 387-91.

Terry, P., Nyren, O., et al. (1998). "Protective effect of fruits and vegetables on stomach cancer in a cohort of Swedish twins." International Journal of Cancer **76**(1): 35-7.

Terry, P. D., Lagergren, J., et al. (2003). "Dietary intake of heterocyclic amines and cancers of the esophagus and gastric cardia." Cancer Epidemiology, Biomarkers & Prevention **12**(9): 940-4.

Teschke, K., Olshan, A. F., et al. (2002). "Occupational exposure assessment in case-control studies: opportunities for improvement." Occupational & Environmental Medicine **59**(9): 575-93; discussion 594.

The EUROGAST STUDY GROUP (1993). "An international association between Helicobacter pylori infection and gastric cancer." Lancet. **341**(8857): 1359-62.

Thomas, R. J., Lade, S., et al. (1996). "Incidence trends in oesophageal and proximal gastric carcinoma in Victoria." Australian & New Zealand Journal of Surgery **66**(5): 271-5.

Tomatis, L., Kaldor, J., et al. (1996). Experimental studies in the assessment of human risk. Cancer epidemiology and prevention. Schottenfeld, D. and Fraumeni, J. F. New York, Oxford University Press**:** xxi, 1521 p.

Touati, E., Michel, V., et al. (2003). "Chronic Helicobacter pylori infections induce gastric mutations in mice." Gastroenterology **124**(5): 1408-19.

Tredaniel, J., Boffetta, P., et al. (1997). "Tobacco smoking and gastric cancer: review and meta-analysis." International Journal of Cancer. **72**(4): 565-73.

Tricker, A. R. and Preussmann, R. (1992). "Volatile N-nitrosamines in mainstream cigarette smoke: occurrence and formation." Clinical Investigator **70**(3-4): 283-9.

Tsubono, Y., Nishino, Y., et al. (2001). "Green tea and the risk of gastric cancer in Japan." New England Journal of Medicine **344**(9): 632-6.

Tsuda, T., Mino, Y., et al. (2001). "A case-control study of the relationships among silica exposure, gastric cancer, and esophageal cancer." American Journal of Industrial Medicine. **39**(1): 52-7.

Tsugane, S., Sasazuki, S., et al. (2004). "Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women." British Journal of Cancer **90**(1): 128-34.

Uemura, N. (2002). "The magnitude of association between Helicobacter pylori infection and the development of gastric cancer." Scandinavian Journal of Gastroenterology **37**(8): 869-70.

Uemura, N., Mukai, T., et al. (1997). "Effect of Helicobacter pylori eradication on subsequent development of cancer after endoscopic resection of early gastric cancer." Cancer Epidemiology, Biomarkers & Prevention. **6**(8): 639-42.

Uemura, N., Okamoto, S., et al. (2001). "Helicobacter pylori infection and the development of gastric cancer." New England Journal of Medicine. **345**(11): 784-9.

United Nations Office for Drug Control and Crime Prevention. (2004). World drug report 2004, United Nations (UN).

United Nations. Statistical Division (2004). International Standard industrial classification of all economic activities (ISIC). New York, United Nations.

Urbaniak, G. C. and Plous, S. (1997). Research Randomizer, Social Psycology Network, Wesleyan University. **2003**.

Vainio, H. (2003). "Social responsibility in cancer prevention research: IARC as a 'Global Science Force'." Asian Pacific Journal of Cancer Prevention: Apjcp **3**(3): 267-272.

Vaira, D., Gatta, C., et al. (2002). "Review Article: Diagnosis of Helicobacter pylori Infection." Alimentary Pharmacology & Therapeutics. **16**(Suppl. 1): 16-23.

van den Brandt, P. A., Botterweck, A. A., et al. (2003). "Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence: a prospective cohort study (Netherlands)." Cancer Causes & Control **14**(5): 427-38.

van Loon, A. J., Botterweck, A. A., et al. (1997). "Nitrate intake and gastric cancer risk: results from the Netherlands cohort study." Cancer Letters **114**(1-2): 259-61.

van Loon, A. J., Botterweck, A. A., et al. (1998). "Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study." British Journal of Cancer **78**(1): 129-35.

van Loon, A. J., Goldbohm, R. A., et al. (1998). "Socioeconomic status and stomach cancer incidence in men: results from The Netherlands Cohort Study." Journal of Epidemiology & Community Health **52**(3): 166-71.

Vaughan, T. L., Stewart, P. A., et al. (1997). "Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus." Occupational & Environmental Medicine **54**(9): 692-5.

Videbaek, A. and Mosbech, J. (1954). "The etiology of gastric carcinoma elucidated by a study of 302 pedigrees." Acta Med Scand **149**: 137-159.

Vineis, P., Alavanja, M., et al. (2004). "Tobacco and cancer: recent epidemiological evidence." Journal of the National Cancer Institute **96**(2): 99-106.

Wang, H. H., Antonioli, D. A., et al. (1986). "Comparative features of esophageal and gastric adenocarcinomas: recent changes in type and frequency." Human Pathology **17**(5): 482-7.

Wang, R. T., Wang, T., et al. (2002). "Helicobacter pylori infection and gastric cancer: evidence from a retrospective cohort study and nested case-control study in China." World Journal of Gastroenterology **8**(6): 1103-7.

Wang, W. H., Huang, J. Q., et al. (2003). "Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: A systematic review and meta-analysis." Journal of the National Cancer Institute **95**(23): 1784-1791.

Wangensteen, O. H. (1956). Cancer of the esophagus and the stomach. New York, American Cancer Society.

Ward, M. H. and Lopez-Carrillo, L. (1999). "Dietary factors and the risk of gastric cancer in Mexico City." American Journal of Epidemiology **149**(10): 925-32.

Ward, M. H., Sinha, R., et al. (1997). "Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference." International Journal of Cancer **71**(1): 14-9.

Warren, J. R. and Marshall, B. J. (1983). "Unidentified curved bacilli on gastric epithelium in active chronic gastritis." Lancet **1**: 1273-5.

Wasserman, A. E., Fiddler, W., et al. (1972). "Dimethylnitrosamine in frankfurters." Food & Cosmetics Toxicology **10**(5): 681-4.

Watanabe, T., Tada, M., et al. (1998). "Helicobacter pylori infection induces gastric cancer in mongolian gerbils." Gastroenterology. **115**(3): 642-8.

Watanabe, Y., Kurata, J. H., et al. (1997). "Helicobacter pylori infection and gastric cancer. A nested case-control study in a rural area of Japan." Digestive Diseases & Sciences. **42**(7): 1383-7.

Webb, P. M., Crabtree, J. E., et al. (1999). "Gastric cancer, cytotoxin-associated gene A-positive Helicobacter pylori, and serum pepsinogens: an international study. The Eurogst Study Group." Gastroenterology **116**(2): 269-76.

Webb, P. M., Yu, M. C., et al. (1996). "An apparent lack of association between Helicobacter pylori infection and risk of gastric cancer in China." International Journal of Cancer **67**(5): 603-7.

Willett, W. (1998). Nutritional epidemiology. New York, Oxford University Press.

Wink, D., Vodovotz, Y., et al. (1998). "The multifaceted roles of nitric oxide in cancer." Carcinogenesis **19**(5): 711-721.

Winn, D. M., Blot, W. J., et al. (1981). "Snuff dipping and oral cancer among women in the southern United States." New England Journal of Medicine **304**(13): 745-9.

Wiseman, R. (1676). Several Chirurgicall Treatises. London, Flesher and Macock.

Wizla-Derambure, N., Michaud, L., et al. (2001). "Familial and community environmental risk factors for Helicobacter pylori infection in children and adolescents." Journal of Pediatric Gastroenterology & Nutrition. **33**(1): 58-63.

Wong, B. C., Lam, S. K., et al. (2004). "Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial." JAMA **291**(2): 187-94.

Wong, B. C., Wong, W., et al. (2000). "An evaluation of whole blood testing for Helicobacter pylori infection in the Chinese population." Alimentary Pharmacology & Therapeutics. **14**(3): 331-5.

Wong, O. and Harris, F. (2000). "Cancer mortality study of employees at lead battery plants and lead smelters, 1947-1995." American Journal of Industrial Medicine **38**(3): 255-70.

World Cancer Research Fund and American Institute for Cancer Research (1997). Food, nutrition and the prevention of cancer : a global perspective. Washington, World Cancer Research Fund / American Institute for Cancer Research.

World Health Organization (2001). Global Status Report on Alcohol Summary, World Health Organization**:** 14.

World Health Organization and International Agency for Research on Cancer (2004). Tobacco smoke and involuntary smoking. Lyon, France, International Agency for Research on Cancer.

World Health Organization. (2002). National cancer control programmes : policies and managerial guidelines. Geneva, World Health Organization.

World Health Organization. and International Agency for Research on Cancer. (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. Lyon, France, IARC.

Wu, A. H., Crabtree, J. E., et al. (2003). "Role of Helicobacter pylori CagA+ strains and risk of adenocarcinoma of the stomach and esophagus." International Journal of Cancer **103**(6): 815-21.

Wu, A. H., Wan, P., et al. (2001). "A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States)." Cancer Causes & Control **12**(8): 721-32.

Wu, M. S., Chen, S. Y., et al. (1997). "Increased prevalence of Helicobacter pylori infection among patients affected with intestinal-type gastric cancer at non-cardiac locations." Journal of Gastroenterology & Hepatology **12**(6): 425-8.

Wu, M. T., Chen, M. C., et al. (2004). "Influences of lifestyle habits and p53 codon 72 and p21 codon 31 polymorphisms on gastric cancer risk in Taiwan." Cancer Letters **205**(1): 61-8.

Xu, Z., Brown, L. M., et al. (1996). "Cancer risks among iron and steel workers in Anshan, China, Part II: Case-control studies of lung and stomach cancer." American Journal of Industrial Medicine. **30**(1): 7-15.

Xue, F. B., Xu, Y. Y., et al. (2001). "Association of H. pylori infection with gastric carcinoma: a Meta analysis." World Journal of Gastroenterology **7**(6): 801-4.

Yamaguchi, N. and Abe, K. (1999). Gastric cancer. Nutritional oncology. Blackburn, G. L., Go, V. L. W., Heber, D. and (U.S.), C. T. R. F. San Diego, Calif. ; London, Academic.

Yamaoka, Y., Kodama, T., et al. (1999). "Antibody against Helicobacter pylori CagA and VacA and the risk for gastric cancer." Journal of Clinical Pathology. **52**(3): 215-8.

Yang, C. Y., Chiu, H. F., et al. (1997). "Cancer mortality and residence near petrochemical industries in Taiwan." Journal of Toxicology & Environmental Health **50**(3): 265-73.

Yatsuya, H., Toyoshima, H., et al. (2002). "Family history and the risk of stomach cancer death in Japan: differences by age and gender." International Journal of Cancer **97**(5): 688-94.

Yazdanbod, A., Arshi, S., et al. (2001). "Gastric Cardia Cancer; The Most Common Type of Upper Gastrointestinal Cancer in Ardabil, Iran: An Endoscopy Clinic Experience." Archives of Iran Medicine. **4**(2): 76-79.

Ye, W., Ekstrom, A. M., et al. (1999). "Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type." International Journal of Cancer. **83**(2): 223-9.

Ye, W. and Nyren, O. (2003). "Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia." Gut **52**(7): 938-41.

You, W. C., Blot, W. J., et al. (1989). "Allium vegetables and reduced risk of stomach cancer." Journal of the National Cancer Institute **81**(2): 162-4.

You, W. C., Blot, W. J. et al. (1993). "Precancerous gastric lesions in a population at high risk of stomach cancer." Cancer Research **53**(6): 1317-21.

You, W. C., Ma, J. L., et al. (2000). "Blood type and family cancer history in relation to precancerous gastric lesions." International Journal of Epidemiology. **29**(3): 405-7.

Yu, G. P., Hsieh, C. C., et al. (1995). "Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China." Cancer Causes & Control **6**(6): 532-8.

Zanghieri, G., Di Gregorio, C., et al. (1990). "Familial occurrence of gastric cancer in the 2-year experience of a population-based registry." Cancer **66**(9): 2047-51.

Zaridze, D., Borisova, E., et al. (2000). "Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia." Cancer Causes & Control. **11**(4): 363-71.

Zaridze, D. G., Blettner, M., et al. (1986). "The effect of nass use and smoking on the risk of oral leukoplakia." Cancer Detection & Prevention **9**(5-6): 435-40.

Zeka, A., Eisen, E. A., et al. (2004). "Risk of upper aerodigestive tract cancers in a case-cohort study of autoworkers exposed to metalworking fluids." Occupational & Environmental Medicine **61**(5): 426-31.

Zhang, H. M., Wakisaka, N., et al. (1997). "Vitamin C inhibits the growth of a bacterial risk factor for gastric carcinoma: Helicobacter pylori." Cancer **80**(10): 1897-903.

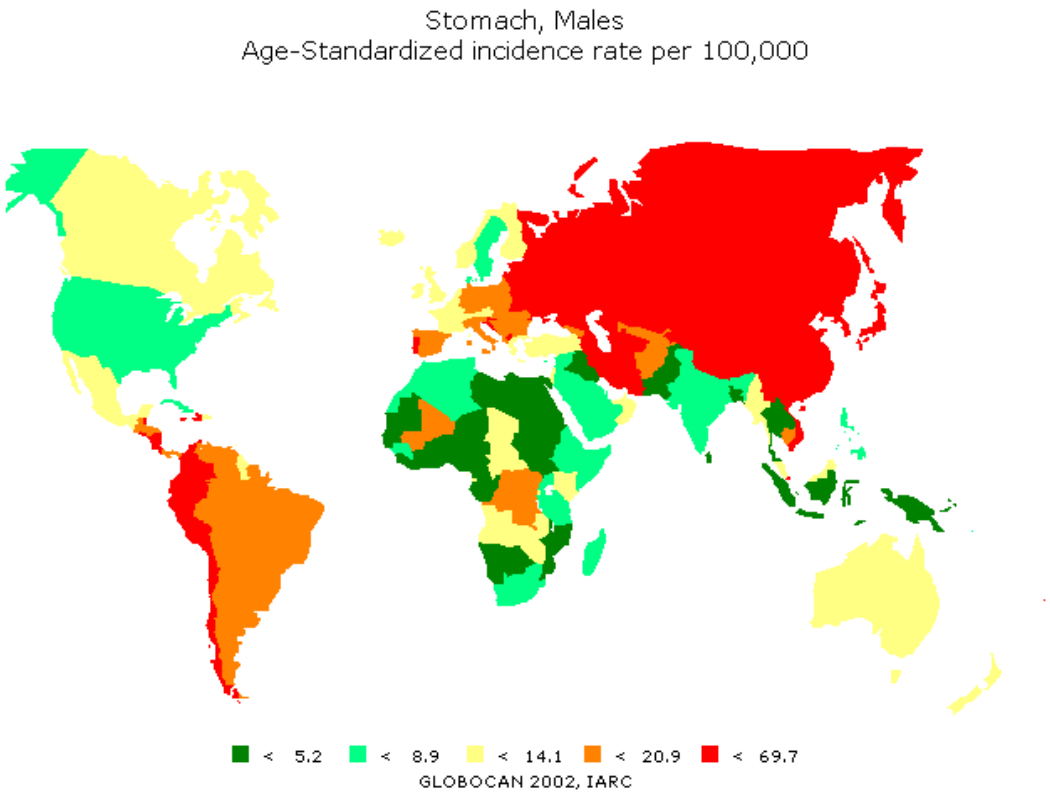
Zhang, R. F., Deng, D. J., et al. (1991). "Role of nitrosamides in the high risk for gastric cancer in China." IARC Scientific Publications(105): 152-7.

Zhang, Z. F., Kurtz, R. C., et al. (1996). "Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors." Cancer Epidemiology, Biomarkers & Prevention **5**(10): 761-8.

Zhang, Z. F., Kurtz, R. C., et al. (1997). "Adenocarcinomas of the esophagus and gastric cardia: the role of diet." Nutrition & Cancer **27**(3): 298-309.

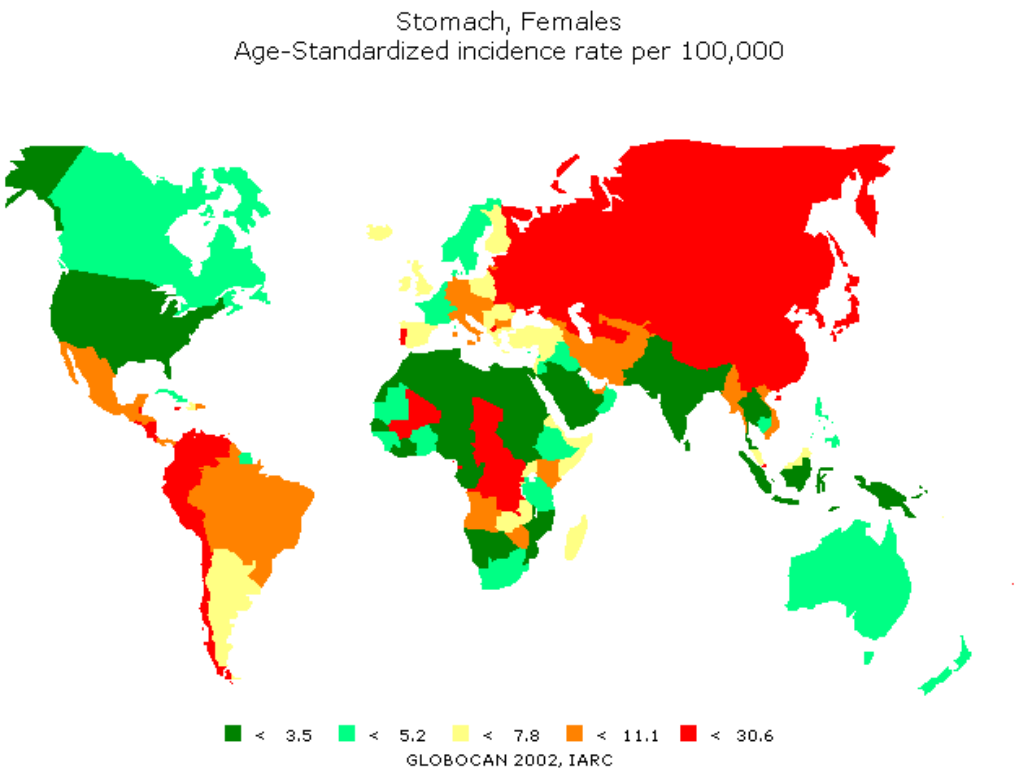
APPENDICES

Appendix A: Incidence of GC (ASR) among males



from (Ferlay, Bray et al. 2004)

Appendix B: Incidence of GC (ASR) among females



from (Ferlay, Bray et al. 2004)

Appendix C: Incidence and mortality of GC (ASR) among males and females in different regions

Males			Females		
Country/Region	**Incidence**	**Mortality**	**Incidence**	**Mortality**	**Country/Region**
Eastern Africa	**7.4**	**7**	**5.5**	**5.2**	**Eastern Africa**
Mauritius	14	10.1	13	12.4	Rwanda
Mozambique	0.9	0.8	0.8	0.8	Malawi
Middle Africa	**13.4**	**12.6**	**12.7**	**12**	**Middle Africa**
Congo	18.9	17.9	17.8	16.8	Congo
Cameroon	0.6	0.5	0.6	0.5	Gabon
Northern Africa	**4.4**	**4.1**	**2.5**	**2.4**	**Northern Africa**
Algeria	5.9	5.6	3.1	3	Algeria
Sudan	3.2	3.1	2	1.9	Egypt
Southern Africa	**8.2**	**7.2**	**3.7**	**3.2**	**Southern Africa**
South African Republic	8.8	7.6	3.9	3.4	South African Republic
Namibia	2.6	2.5	1.7	1.6	Namibia
Western Africa	**3.4**	**3.2**	**3.6**	**3.4**	**Western Africa**
Mali	17.2	16.1	19.5	18.3	Mali
Nigeria	1.8	1.6	2	1.9	Nigeria
Carribean	**13.6**	**11.5**	**6.7**	**5.3**	**Carribean**
Haiti	28.8	25.1	11.6	9.2	Jamaica
Cuba	7.1	6.9	4.3	3.6	Cuba
Central America	**15.2**	**11.7**	**10.8**	**8.3**	**Central America**
Costa Rica	41.2	30.1	22.1	17	Costa Rica
Mexico	13.1	9.9	9.5	7.2	Mexico
South America	**24.3**	**18.1**	**12.2**	**9.3**	**South America**
Chile	46.1	32.5	30.6	24.1	Peru
Guyana	13.9	10	4.7	3.4	Suriname
Northern America	**7.4**	**4.2**	**3.4**	**2.2**	**Northern America**
Canada	9.1	5.9	4	2.8	Canada
United States of America	7.2	4	3.3	2.2	United States of America

Appendix C (continued): Incidence and mortality of GC (ASR) per 100,000 among males and females in different regions

Males			Females		
Country/Region	**Incidence**	**Mortality**	**Incidence**	**Mortality**	**Country/Region**
Eastern Asia	**46.1**	**32.5**	**20.6**	**14.8**	**Eastern Asia**
Korea	69.7	37.1	26.8	15	Korea
Mongolia	39.2	33.4	19.2	15.1	China
South-Eastern Asia	**8.6**	**7.4**	**4.5**	**3.9**	**South-Eastern Asia**
Singapore	22.3	17.8	11.1	8.5	Singapore
Lao	3.2	2.7	1.9	1.6	Lao
South-Central Asia	**6.9**	**5.9**	**3.6**	**3**	**South-Central Asia**
Kazakhstan	41.5	34.6	18.4	15.4	Kazakhstan
Iran, Islamic Republic of	26.1	22.4	11.1	9.4	Iran, Islamic Republic of
Bangladesh	1.6	1.4	0.9	0.8	Sri Lanka
Western Asia	**11.7**	**9.8**	**6.4**	**5.4**	**Western Asia**
Azerbaijan	36	30.1	15.6	13.1	Azerbaijan
Iraq	4.5	3.8	3	2.6	Kuwait
Central &Eastern Europe	**29.6**	**25.2**	**12.8**	**10.8**	**Central &Eastern Europe**
Belarus	41.9	33	16.9	13.4	Belarus
Czech Republic	14.8	12.1	6.8	6.6	Romania
Northern Europe	**12.4**	**9.2**	**6**	**4.6**	**Northern Europe**
Estonia	30.5	24.1	15.2	11.4	Estonia
Denmark	7.9	5.5	3.9	3.3	Denmark
Southern Europe	**18**	**12.9**	**8.7**	**6.3**	**Southern Europe**
Macedonia	28.5	20.4	13.6	10.1	Portugal
Greece	12	8.9	5	4.4	Malta
Western Europe	**12.8**	**8.9**	**6.6**	**5**	**Western Europe**
Germany	15.1	10.4	8.8	6.4	Germany
Belgium	9.4	8.1	4.1	3.1	France
Australia/New Zealand	**9.9**	**6**	**4.2**	**3**	**Australia/New Zealand**
New Zealand	10.3	8	4.5	4.1	New Zealand
Australia	9.8	5.7	4.1	2.8	Australia

Based on GLOBOCAN 2002 (Ferlay, Bray et al. 2004)

Appendix D: Case-control studies of GC and diet published since 1995

	References	Country	Number of cases and controls (study base)
	(Ji, Chow et al. 1998)	China	1124 cases / 1451controls (population)
	(Gao, Takezaki et al. 1999)	China	153 Cases / 234 referent (population)
	(Chen, Qiu et al. 2003)	China	103 cases / 103 controls (population)
	(Takezaki, Gao et al. 2001)	China	187 cases / 333 controls (population)
	(Yu, Hsieh et al. 1995)	China	711 cases / 711 controls (population)
	(Cai, Zheng et al. 2003)	China	191 cardia and 190 non-cardia cases / 222 control (hospital)
	(Mathew, Gangadharan et al. 2000)	India	194 cases / 305 controls (hospital)
	(Rao, Ganesh et al. 2002)	India	170 cases / 2184 controls (hospital)
	(Hoshiyama, Kawaguchi et al. 2004)	Japan	157 cases / 285 controls (nested)
	(Ito, Inoue et al. 2003)	Japan	508 female cases / 36,490 referents (hospital)
	(Inoue, Tajima et al. 1998a)	Japan	893 cases / 21,128 referents (hospital)
	(Hara, Hanaoka et al. 2003)	Japan	149 cases / 287 controls (hospital)
	(Machida-Montani, Sasazuki et al. 2004)	Japan	122 non- cardia cases /235 controls (hospital)
	(Inoue, Ito et al. 2002)	Japan	365 women / 1,825 Controls (hospital)
	(Lee, Park et al. 1995)	Korea	213 cases / equal controls (hospital)
	(Choi, Kim et al. 1999)	Korea	59 cases / 44 controls (hospital)
	(Kim, Chang et al. 2002)	Korea	136 cases / equal controls (hospital)
	(Lee, Kang et al. 2003)	Korea	69 cases / 199 controls (hospital)
[1]	(Zhang, Kurtz et al. 1997)	USA	95 cases / 132 controls (hospital)
[1]	(Harrison, Zhang et al. 1997)	USA	91 cases / 132 controls (hospital)
	(Mayne, Risch et al. 2001)	USA	255 cardia and 352 non- cardia cancer / 687 controls (population)
[2]	(Ward, Sinha et al. 1997)	USA	176 cases / 502 controls (population)
[2]	(Chen, Tucker et al. 2002)	USA	170 cases / 449 controls or their proxy (population)
[2]	(Chen, Ward et al. 2002)	USA	124 cases / 449 controls or their proxy (population)
	(Nomura, Hankin *et al.* 2003)	USA	300 cases / 446 controls (Population)
	(Nishimoto, Hamada et al. 2002)	Brazil	236 cases/equal controls (population)
	(Hamada, Kowalski et al. 2002)	Brazil	96 cases / 192 controls (hospital)
	(Lopez-Carrillo, Lopez-Cervantes et al. 2003)	Mexico	234 cases / 468 controls (hospital)
[3]	(Ward and Lopez-Carrillo 1999)	Mexico	220 cases / 752 Controls (population)
[3]	(Lopez-Carrillo, Lopez-Cervantes et al. 1999)	Mexico	220 cases / 752 controls (population)
	(Munoz, Plummer et al. 2001)	Venezuela	292 cases / 485 controls (neighbor)

Appendix D (continued): Case-control studies of GC and diet published since 1995

	References	Country	Number of cases and controls (study base)
	(De Stefani, Boffetta et al. 1998b)	Uruguay	340 cases / 698 controls (hospital)
4	(De Stefani, Boffetta et al. 1999)	Uruguay	88 cases / 351 controls (hospital)
4	(De Stefani, Boffetta et al. 2000a)	Uruguay	128 cases / 372 controls (hospital)
4	(De Stefani, Boffetta et al. 2000b)	Uruguay	120 cases / 360 controls (hospital)
4	(De Stefani, Correa et al. 2001)	Uruguay	160 cases / 320 controls (hospital)
4	(De Stefani, Ronco et al. 2001)	Uruguay	123 cases / 282 controls (hospital)
4	(De Stefani, Correa et al. 2004)	Uruguay	240 cases / 960 controls (hospital)
	(Kaaks, Tuyns et al. 1998)	Belgium	301 cases / 2851 controls (population)
	(Cornee, Pobel et al. 1995)	France	92 cases / 128 controls (hospital)
5	(La Vecchia, Bosetti et al. 1998)	Italy	769 cases /2081 controls (Hospital)
5	(La Vecchia, Munoz et al. 1997)	Italy	746 cases / 2053 controls (Hospital)
5	(La Vecchia, D'Avanzo et al. 1995a)	Italy	746 cases / 2053 controls (Hospital)
	(Palli, Russo et al. 2001)	Italy	382 cases / 561 controls (Population)
	(Battisti, Formichi et al. 2000)	Italy	51 cases and 49 controls (NA)
	(Garcia-Closas, Gonzalez et al. 1999)	Spain	354 cases / 354 controls (hospital)
6	(Chow, Swanson et al. 1999)	Poland	464 cases / 480 controls (population)
6	(Lissowska, Gail et al. 2004)	Poland	274 cases / 463 controls (population)
	(Jedrychowski, Popiela et al. 2001)	Poland	80 cases / equal controls (hospital)
7	(Ekstrom, Serafini et al. 2000)	Sweden	567 cases / 1165 controls (population)
7	(Serafini, Bellocco et al. 2002)	Sweden	505 cases / 1116 controls (population)
8	(Terry, Lagergren et al. 2001a)	Sweden	262 cases / 815 controls (population)
8	(Terry, Lagergren et al. 2000)	Sweden	258 cases / 815 controls (population)
8	(Terry, Lagergren et al. 2001b)	Sweden	262 cases / 815 controls (population)
8	(Terry, Lagergren et al. 2003)	Sweden	258 cases / 815 controls (population)
8	(Lagergren, Bergstrom et al. 1999a)	Sweden	262 cases / 820 controls (population)
8	(Lagergren, Bergstrom et al. 2000)	Sweden	262 cases / 820 controls (population)

1, 2, 3, 4, 5, 6, 7, 8 have been published from the same studies

Appendix E: Cohort studies of GC and diet published since 1995

	References	Country	Number of subjects
	(Ngoan, Mizoue *et al.* 2002)	Japan	13,000 subjects, 116 died from GC after 10.5 years follow up
	(Tsugane, Sasazuki *et al.* 2004)	Japan	39065 subjects, 486 cases after 12 years follow up
1	(Tsubono, Nishino *et al.* 2001)	Japan	26311subjects, 419 cases
1	(Koizumi, Tsubono *et al.* 2003)	Japan	2 cohort: cohort 1: 26311 subjects, 419 case after 9 year follow up Cohort 2: 39604 subjects, 314 cases after 7 years follow up
	(Kobayashi, Tsubono *et al.* 2002)	Japan	40,293 subjects followed up 10 years and 404 GC cases
	(Hoshiyama, Kawaguchi *et al.* 2002)	Japan	72851 subjects followed up 8 years follow up 359 were died of GC
	(Kim, Sasaki *et al.* 2004)	Japan	42112 subjects, 400 cases after 10 year follow up
	(Fujino, Tamakoshi *et al.* 2002)	Japan	127,477 subjects, 379 deaths from GC after about 7 years follow up
	(Inoue, Tajima et al. 1996)	Japan	5,373 subjects, 69 cases after an average of 6 years of follow-up,
	(Nagata, Takatsuka et al. 2002)	Japan	30,304 subjects, 121 death Over 7 years of follow-up
	(Nagano, Kono *et al.* 2001)	Japan	38450 subjects, 901 GC cases after about 13 years follow up
	(McCullough, Robertson *et al.* 2001)	USA	1.2 million subjects, 1349 death of GC after 14 years follow up
	(Kasum, Jacobs *et al.* 2002)	USA	34651 postmenopausal women, 56 cases after 14 years follow up
	(Chao, Thun *et al.* 2002)	USA	1055841 subjects, 1505 death from GC after 15 years follow up
	(Galanis, Kolonel *et al.* 1998)	USA	11,907 Japanese residents of Hawaii, 108 cases of GC in 14.8 years follow up
2	(van den Brandt, Botterweck *et al.* 2003)	Netherlands	120,852 subjects, 282 cases / 3123 sub cohort after 6.3 years follow up
2	(Botterweck, van den Brandt *et al.* 2000)	Netherlands	120,852 subjects, 282 cases after 6.3 years follow up
2	(van Loon, Botterweck *et al.* 1997)	Netherlands	120,852 subjects 203 cases/ 3500 sub cohort
2	(van Loon, Botterweck *et al.* 1998)	Netherlands	120,852 subjects, 282 cases/ 3500 sub cohort after 6.3 years follow up
2	(Dorant, van den Brandt *et al.* 1996)	Netherlands	120,852 subjects, 139 cases/ 3123 sub cohort after 3.3 years follow up
2	(Botterweck, van den Brandt *et al.* 1998)	Netherlands	120,852 subjects, 282 cases after 6.3 years follow up
	(Terry, Nyren *et al.* 1998)	Sweden	11546 subjects, 116 cases after 21 years follow up
	(Jansen, Bueno-de-Mesquita *et al.* 1999)	7 countries	12000 men

1, 2 have been published from the same studies

Appendix F: Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(Ji, Chow et al. 1998) China	1124 cases / 1451controls (Population)	Yellow-green vegetables Total vegetables Fresh fruits Preserved vegetable foods Allium vegetables	Highest vs. lowest quartile	0.5 (0.4–0.7) p < 0.0001[1] 0.4 (0.3–0.5) p < 0.0001 0.4 (0.3–0.6) p < 0.0001[2] 1.9 (1.3–2.8) p = 0.002[3] 0.8 (0.6–1.1) p < 0.08	Age, income, education, smoking (males only) and alcohol drinking (males only)
(Takezaki, Gao et al. 2001) China	187 cases / 333 controls (Population)	Pickled vegetables Vegetables Raw vegetables Fruit Garlic Onion	Highest vs. lowest quartile	1.62 (0.82–3.20) p = 0.399 0.50 (0.29–0.87) p = 0.002 0.183 0.62 (0.30–1.25) p = 0.047 0.66 (0.37–1.17) p = 0.077 1.48 (0.83–2.62) p = 0.035	Age, sex, and smoking and drinking
(Cai, Zheng et al. 2003) China	191 cardia and 190 non-cardia GC cases / 222 control (Hospital)	Fresh fruit intake[4] Pickled vegetables fresh vegetables,		0.2 (0.1–0.5) 1.8 (1.0–3.0) 0.4 (0.2–0.9)	Age, gender, drinking and family cancer history in the first degree relatives
(Gao, Takezaki et al. 1999) China	153 cases / 234 referent (Population)	Raw vegetables Fruit Pickled vegetables Garlic Onion	Highest / lowest tertile	0.07 (0.04–0.13)[5] 0.88 (0.47–1.67)[5] 2.37 (1.75–3.20)[5] 0.31 (0.22–0.44) 0.17 (0.08–0.36)	Age, sex, income, smoking, drinking, tea consumption, intake of leftover gruel, pickled vegetables, meat, fruit, tomatoes, eggs and snap beans
(Mathew, Gangadharan et al. 2000) India	194 cases / 305 controls (Hospital)	Vegetables[6]	Daily vs. never	0.6 (0.3–1.0) p = 0.01[7]	Age, sex, religion, education, income, smoking, alcohol

[1] Was significant for men not women
[2] This was 0.5 (0.3-0.8) p = 0.0006 for women
[3] Was significant for women not men
[4] Gastric cardia cancer
[5] Adjusted for age and sex
[6] Except leafy vegetables
[7] Not significant for leafy vegetables

Appendix F (continued): Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(Inoue, Ito et al. 2002) Japan	365 postmenopausal women cases /1,825 controls (Hospital)	Raw vegetables	Daily vs. Less	0.67 (0.53–0.86) $p < 0.05$	Age, year and season of interview, family history of GC, smoking and cooked fish intake.
(Machida-Montani, Sasazuki *et al.* 2004) Japan	122 non- cardia cases /235 controls (Hospital)	Total fruit Total Vegetables Pickled vegetables	Highest / Lowest tertile	1.1 (0.5–2.4) NS 0.9 (0.4–2.2) NS 0.6 (0.3–1.3) NS	*H. Pylori*, smoking, family history of GC, (total vegetable and fruit intake/ pickled vegetables), salt intake, and total energy intake
(Ito, Inoue et al. 2003) Case referent Japan	508 female cases / 36,490 outpatients referents	Raw vegetables Fruit Green vegetables Pickled vegetables Salted vegetables	Highest / lowest quartile	0.50 (0.36–0.71) $p < 0.001$[8] 0.68 (0.40–1.16) $p < 0.001$ 0.60 (0.43–0.83) $p < 0.001$[8] 1.04 (0.74–1.47) n.s.[9] 1.07 (0.81–1.40) n.s.[9]	Age, year, season at first hospital visit, smoking habit and family history of GC.
(Hara, Hanaoka et al. 2003) Japan	149 cases / 287 controls (Hospital)	Total vegetables Vegetables containing carotenes[10]	Highest vs. lowest tertile	1.12 (0.61–2.05) P=0.70 NS 1.41 (0.76–2.62)	Smoking, family history of GC, salt intake and total energy intake
(Lee, Park et al. 1995) Korea	213 cases / equal controls (Hospital)	Salt preferences Fresh vegetables Pickled vegetables	High / low	3.7 (1.1–12.5) NS 1.2 (0.8–1.9) NS 3.8 (2.3–6.5) $p < 0.001$	Age, sex, education, economic status, residence and other dietary factors
(Terry, Lagergren et al. 2001a) Sweden	262 cases / 815 controls (Population)	Fruit and vegetables Vegetables Fruit	Highest / lowest quartile	NS for adenocarcinoma of the gastric cardia.	
(Lee, Kang et al. 2003) Korea	69 cases / 199 controls (Hospital)	Raw vegetables Fruits Fruit & vegetables juice	High / low	0.2 (0.1–0.5) $p < 0.01$ 0.3 (0.1–0.7) $p < 0.01$ 0.5 (0.2–1.2) $p < 0.01$	Age, sex, education, family history, smoking, *H. pylori*

[8] reverse association was higher for differentiated than non-differentiated
[9] NS for both differentiated and non-differentiated sub-type
[10] Carotenes ≥600 µg/100 g carotenes ≥ 600

Appendix F (continued): Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(Kim, Chang et al. 2002) Korea	136 cases / equal controls (Hospital)	Garlic Fruit juice Total vegetables Raw vegetables Cooked vegetables Salted vegetables Total fruits Citrus fruits	High/Low	0.53 (0.27–1.02) p < 0.05 0.55 (0.28–1.07) NS 0.64 (0.31–1.32) p = 0.0249 0.55 (0.28–1.09) p = 0.1579 0.98 (0.50–1.90) p = 0.6734 1.48 (0.76–2.88) p = 0.2855 0.67 (0.33–1.39) p = 5578 0.66 (0.31–1.41) p = 2666	Sex, age, socioeconomic status, family history and refrigerator use
(Nishimoto, Hamada et al. 2002) Brazil	236 cases / equal controls (Population)	Fruit Green vegetables Yellow vegetables Other vegetables	Daily / less than once a week	0.4 (0.2–0.8) p = 0.005[11] 0.6 (0.3–1.1) p = 0.10 0.4 (0.2–0.8) p = 0.04[11] 0.4 (0.2–0.8) p = 0.004	Race and education
(Hamada, Kowalski et al. 2002) Brazil	96 cases / 192 controls (Hospital)	Pickled vegetables Green vegetables Yellow vegetables Other vegetables Fruits	Daily / less than once per week	1.0 (0.5–1.9) p = 0.89 0.9 (0.4–1.9) p = 0.73 0.5 (0.1–1.5) p = 0.47 0.9 (0.3–3.0) p = 0.45 0.5 (0.3–1.1)	Country of birth
(Munoz, Plummer et al. 2001) Venezuela	292 cases / 485 controls (Neighbor)	Vegetables Fruits Garlic Onion	Highest / lowest quartile	0.35 (0.21–0.59), p < 0.001 2.27 (1.40–3.70) p = 0.001 0.5 (0.3–0.8) p = 0.006[12] 0.4 (0.3–0.7) p = 0.002 [12]	Age, sex, tobacco, alcohol, total calories and SES.
(Harrison, Zhang et al. 1997) USA	91 cases / 132 controls (Hospital)	Fruits Citrus and juices Citrus Non- citrus Vegetables Cruciferous Dark green Dark yellow Raw vegetables		0.5, (0.3–0.9) p < 0.05[13] 0.8, (0.5–1.3) [14] 0.7, (0.4–1.3) [14] 0.6, (0.3–0.97) [15] 0.8, (0.5–1.3) [16] 0.8, (0.5–1.5) NS 0.6, (0.3–1.1) NS [16] 0.8, (0.4–1.7) NS [16] 0.6, (0.4–1.1) NS [16]	Caloric intake, age, gender, race, education, pack-years of smoking, alcohol drinking, and body mass index.

[11] After extra adjustment for smoking and fruit and vegetables intake association was slightly attenuated

12 Adjusted for age, sex and SES.

[13] This is for intestinal type however there was no difference for diffuse type

Appendix F (continued): Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(Lissowska, Gail et al. 2004) Poland	274 cases / 463 controls (population)	Vegetables (total) Fruits (excluding juice) Allium vegetables Raw vegetables Pickled vegetables	Highest / lowest quartile	0.83 (0.52–1.33) p < 0.22 0.57 (0.32–1.05) p = 0.02 0.78 (0.50–1.22) p = 0.20 0.81 (0.52–1.26) p = 0.26 0.98 (0.61–1.56) p = 0.81	Age, sex, smoking, education, calories.
(De Stefani, Correa et al. 2004)	240 cases / 960 controls (Hospital)	Raw vegetables Cooked vegetables Total vegetables Citrus fruits Total fruits	Highest / lowest tertile	0.38 (0.26– 0.57) p < 0.01 1.01 (0.70–1.47) p = 0.94 0.60 (0.41–0.88) p = 0.01 0.45 (0.30–0.68) p < 0.01 0.51 (0.35–0.74) p < 0.01	Age, sex, residence, urban/rural, education, BMI and total energy intake
(De Stefani, Correa et al. 2001) Uruguay	160 cases / 320 controls (Hospital)	Raw vegetables Cooked vegetables Allium vegetables Cruciferous vegetables Green leafy vegetables All fruits Citrus fruits Other fruits All vegetables and fruits Onion Garlic		0.52 (0.31–0.86) p = 0.01 0.93 (0.57–1.51) p = 0.81 0.46 (0.29–0.76) p = 0.002 1.59 (0.88–2.86) p = 0.34 0.73 (0.46–1.18) p = 0.19 0.33 (0.20–0.56) p < 0.001 0.51 (0.31–0.85) p = 0.01 0.34 (0.20–0.57) p < 0.001 0.33 (0.19–0.55) p < 0.001 0.20 (0.06–0.68) 0.57 (0.33–0.98)	Age, sex, residence, urban/ rural status, education, body mass index, and total energy intake.
(Chen, Ward et al. 2002) USA	124 cases / 449 controls or their proxy (Population)	All vegetables Dark-green vegetables Dark-yellow vegetables Onions Citrus fruit and juices	Highest / Lowest quartile	0.63 (0.29–1.4) NS 1.2 (0.57–2.5) NS 1.8 (0.78–4.0) NS 2.1 (0.90–4.7) NS 0.84 (0.40–1.7) NS	Age, sex, energy intake, respondent type, BMI, alcohol, tobacco, education, family history, and vitamin supplement

[14] Non significant for both intestinal and diffuse
[15] Significant for intestinal but non significant for diffuse
[16] It was significant when adjusted for caloric intake, age, and gender. But after extra adjustment for race, education, pack-years of smoking, alcohol drinking, and body mass index the results became non significant.

Appendix F (continued): Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(Zhang, Kurtz et al. 1997) USA	95 cases / 132 controls (Hospital)	Total fruits Citrus fruit and juice Citrus Non- citrus Total vegetables Dark green vegetables Dark yellow vegetables Raw vegetables	Highest / lowest quartile	0.7 (0.4–1.0) p = 0.0559[17] 1.2 (0.8–1.6) p = 0.3786 0.8 (0.5–1.3) p = 0.3695 0.5 (0.3–0.8) p = 0.0051 0.8 (0.6–1.2) p = 0.2945 0.6 (0.3–0.96) p = 0.0339 1.1 (0.7–1.7) p = 0.6041 0.7 (0.4–1.0) p = 0.0548	Age, sex, race, education and total calories intake
(Nomura, Hankin et al. 2003) USA	300 cases / 446 controls (Population)	Total vegetables Dark green vegetables Light green vegetables Yellow vegetables Cruciferous vegetables	Highest/lowest tertile	0.4 (0.2–0.6) p < 0.001 [18] 0.3 (0.2–0.6) p < 0.001[18] 0.4 (0.3–0.7) p < 0.001 [18] 0.4 (0.3–0.7) p < 0.001[18] 0.6 (0.4–1.0) p = 0.07 NS	Age, ethnicity, smoking, education, history of gastric ulcer, SAID family history of GC, total calories.
(Ward and Lopez-Carrillo 1999) Mexico	220 cases / 752 Controls (Population)	All vegetables Dark green vegetables Yellow / orange vegetables All fruits Citrus fruits Other fruits	Highest / lowest frequency	0.3 (0.1–0.6) p = 0.001 1.0 (0.6–1.8) p = 0.90 0.2 (0.1–0.3) p < 0.001 1.0 (0.5–2.2) p = 0.67 0.7 (0.3–1.5) p = 0.07 1.2 (0.6–2.4) p = 0.54	Age, gender, total calories, chili pepper, salt, history of peptic ulcer, smoke, SES
(Cornee, Pobel et al. 1995) France	92 cases / 128 controls (Clinic)	Fresh fruit Citrus fruit Non- citrus fruit Total vegetables Raw vegetables Cooked vegetables Dried vegetables	Highest / lowest tertile	0.5 (0.25–1.03) p = 0.02 0.57 (0.26–1.25) p = 0.17 0.63 (0.31–1.26) p = 0.03 0.77 (0.37–1.60) p = 0.68 0.41 (0.19–0.88) p = 0.02 1.06 (0.53–2.13) p = 0.51 0.8 (0.39–1.67) p = 0.97	Age, sex, occupation, total energy intake

[17] After extra adjustment for smoking, alcohol and body mass index it becomes NS OR=0.8 (0.5-1.2) p=0.2332

[18] Inverse association were seen for both genders

Appendix F (continued): Summary of case-control studies of GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects (base)	Type of vegetables and fruit	Comparison	OR (95% CI) p for trend	Adjustment for
(La Vecchia, Munoz et al. 1997) Italy	746 cases / 2053 controls (Hospital)	Vegetables Fruit	Highest /lowest frequency	0.5 (0.4–0.7) p<0.001 0.6 (0.5–0.8) p< 0.001	Age, sex, residence, education, family history of GC, BMI and total energy intake
(De Stefani, Boffetta et al. 1998b) Uruguay	340 cases / 698 controls (Hospital)	Fruits Vegetables		0.43 (0.35–0.51) 0.43 (0.36–0.52)	Age, sex, residence, urban/rural, smoking, alcohol, mate consumption
(Ekstrom, Serafini et al. 2000) Sweden	567 cases / 1165 controls (Population)	Total vegetable intake Dark green vegetables3 Cruciferous vegetables Allium vegetables Onion Garlic Total fruit intake Fruit juice Citrus fruit	Highest/lowest frequency	0.5 (0.3–1.1) p = 0.05 cardia[19] 0.4 (0.2–0.9) p < 0.01 cardia[20] 0.7 (0.3–1.4) p = 0.24 cardia[15] 0.9 (0.5–1.9) p = 0.49 cardia [21] 0.6 (0.3–1.2) p = 0.13 cardia [16] 0.9 (0.5–1.6) p = 0.82 cardia [22] 0.5 (0.2–1.0) p = 0.03 cardia[23] 0.5 (0.2–1.0) p = 0.04 cardia[20] 0.8 (0.4–2.0) p = 0.26 cardia[16]	Age, sex, total caloric intake, tobacco use, BMI, geographic risk area, number of siblings, SES, number of meals/day, Multivitamin supplements, table salt use, and urban environment

[19] 0.7 (0.5–1.0) p=0.02 for non cardia
[20] NS for non cardia
[21] Significant for non cardia
[22] Not significant for both cardia and non cardia
[23] Significant for non cardia as well 0.6 (0.4–0.8) p < 0.01

Appendix G: Summary of Cohort studies on GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects	Type of vegetables and fruit	Comparison	RR (95% CI) p for trend	Adjustment for
(Ngoan, Mizoue et al. 2002) Japan	13,000 subjects, 116 died from GC after 10.5 years follow up	Green and yellow vegetables Other vegetables Fruit	High / low	0.4 (0.2–0.9) p < 0.05[24] NS for both gender NS for both gender	Age, sex, smoking, processed meat, liver, cooking or salad oil, suimono, and pickled food.
(McCullough, Robertson et al. 2001) USA	1.2 million subjects, 1349 death of GC after 14 years follow up	Citrus fruits and juice Vegetables	Highest/lowest tertile	0.75 (0.64–0.87) p<0.001 [25] 0.76(0.65–0.89) p<0.001 [25]	Age-adjusted[26]
(Kasum, Jacobs et al. 2002) USA	34651 women, 56 cases after 14 years follow up	Yellow/orange vegetables	Highest /lowest tertile	HRR = 0.63 and significant	
(Tsugane, Sasazuki et al. 2004) Japan	39065 subjects, 486 cases after 12 years follow up	Pickled vegetables	Highest / lowest quartile	2.35 (1.57–3.54) P <0.001[27] men and 1.74 (0.89–3.41) p=0.05 for women	Age, cigarette smoking and fruit, non-green – yellow vegetable intake
(Dorant, van den Brandt et al. 1996) Netherland	139 cases/ 3123 sub-cohort	Onions	Highest/ Lowest quartile	0.50 (0.26–0.95) p<0.02[28]	Adjusted for age, alcohol intake, vitamin C intake, and b-carotene and sex, smoking status, education, history of stomach disorders, and family history of GC
(Botterweck, van den Brandt et al. 1998) Netherland	120,852 subjects, 282 cases after 6.3 years follow up	Total vegetable and fruit Total vegetables Prepared vegetables Raw vegetables Total fruits Citrus fruits	Highest /lowest quintile	0.64(0.43–0.97) p = 0.04[29] 0.79 (0.55–1.14) p = 0.10 0.79(0.55–1.14) p = 0.18 0.81 (0.55–1.19) p = 0.33 0.83(0.56–1.23) 0 = 0.14 0.75 (0.51–1.11) p = 0.03[29]	Age and sex

[24] After excluding the first three year follow up
[25] This is for men but it was NS for women
[26] After extra adjustment for education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, and family history the association was attenuated
[27] This was still significant after extra adjustment for salt intake
[28] association for non cardia was reverse association but for cardia it increase the risk but NS
[29] After extra adjustment there was still reverse association but NS

Appendix G (continued): Summary of Cohort studies on GC and Vegetables and fruits since 1995

Authors, year, place	No of subjects	Type of vegetables and fruit	Comparison	RR (95% CI) p for trend	Adjustment for
(Kobayashi, Tsubono et al. 2002) Japan	40,293 subjects followed up 10 years and 404 GC cases	Green vegetables Yellow vegetables White vegetables Pickled vegetables Fruit	Highest/lowest quartile	0.77 (0.40–1.46) p= 0.62 0.66 (0.43–1.01) p=0.03 0.59 (0.31–1.12) p=0.57 0.86 (0.57–1.28) p=0.57 0.70 (0.48–1.01) p=0.25	Age, gender, area, education, smoking, BMI, alcohol intake, use of vitamin A, C, E supplement, total energy intake, salted food intake, history of peptic ulcer and family history of GC
(Galanis, Kolonel et al. 1998) USA	11,907 Japanese residents of Hawaii, 108 cases of GC in 14.8 years follow up	Fresh fruits Raw vegetables Fresh fruits, raw vegetables Pickled vegetables	Highest /lowest frequency of consumption	0.6 (0.4–0.9) 0.8 (0.5–1.2) 0.5 (0.3–0.8) p=0.02[30] 1.1 (0.7–1.8)	Age, year of education, Japanese place of birth and gender
(Jansen, Bueno-de-Mesquita et al. 1999) 7 countries	12000 men	Fruits and vegetables Fruits Citrus fruits Non- citrus fruits Vegetables		0.90 (0.82–0.98) 0.96 (0.91–0.99) significant 0.95 (0.92–0.98) significant 0.98 (0.94–1.01) 0.96 (0.82–1.11) NS	Energy and smoking
(Terry, Nyren et al. 1998) Sweden	11546 subjects, 116 cases after 21 years follow up	Fruit and vegetable intake	Lowest / highest quartile	5.53 (1.67–18.31) p <0.05	

[30] This association was NS for women

Appendix H: Summary of case-control studies of GC and Meat, poultry, fish, egg since 1995

Authors, year, place	No of subjects (base)	Type of meat products	Comparison	OR (95% CI) p for trend	Adjustment for
(Ji, Chow et al. 1998) China	1124 cases / 1451controls (Population)	Fresh red meats Poultry Fish Eggs	Highest vs. lowest quartile	Male 0.9 (0.6–1.2) NS[31] Male 0.7 (0.5–0.9) p=0.0005 [32] Male 0.8 (0.6–1.1) NS [31] Male 0.6 (0.4–0.8) p=0.001[31]	Age, income, education, smoking (males only) and alcohol drinking (males only)
(Takezaki, Gao et al. 2001) China	187 cases / 333 controls (Population)	Meat Fish Poultry Egg	Highest vs. lowest quartile	1.31 (0.60–2.85) NS 1.42 (0.67–3.04) NS 1.42 (0.62–3.25) p=0.005 1.55 (0.86–2.79) NS	Age, sex, and smoking and drinking
(Gao, Takezaki et al. 1999) China	153) Cases / 234 referent (Population)	Meat Egg	Highest / lowest tertile	0.70 (0.30–1.64) NS 3.79 (2.20–7.10)	Age, sex,
(Rao, Ganesh et al. 2002) India	170 cases / 2184 controls (Hospital)	Dry fish Fresh fish Mutton Chicken Liver	Highest / lowest frequency	4.59 (3.1–6.8) p<0.001 1.4 (0.95–2.0) p=0.055 1.4 (0.9–2.2) p=0.067 1.4 (0.9–2.1) p=0.04 0.7 (0.4–1.0) p=0.03	Habits, 5 age groups, and sex
(Mathew, Gangadharan et al. 2000) India	194 cases / 305 controls (Hospital)	Fresh water fish Dried fish Sea fish Beef Chicken Mutton Egg	Highest / lowest frequency	0.8 (0.4 – 1.7) NS 1.6 (0.4 – 2.9) NS 1.4 (0.5 – 4.3) p=0.03 0.7 (0.3 – 1.4) NS 1.4 (0.8 – 2.3) NS 2.0 (0.8 – 5.4) NS 1.7 (0.7 – 4.3) NS	Age, sex, religion, education, income, smoking and alcohol habit
(Inoue, Ito et al. 2002) Japan	365 postmenopausal Women cases /1,825 controls (Hospital)	Cooked fish intake	Highest / lowest frequency	0.83 (0.65–1.06)[33] NS	Age, interview time family history of GC, smoking, cooked fish intake.

[31] Approximately the same for female
[32] NS for female
[33] There was no difference between sub sites (all NS) but non differentiated histological type was inversely associated with cooked fish OR = 0.7 (0.52 – 0.95) p<0.05

Appendix H (continued): Summary of case-control studies of GC and Meat, poultry, fish, egg since 1995

Authors, year, place	No of subjects (base)	Type of meat products	Comparison	OR (95% CI) p for trend	Adjustment for
(Ito, Inoue et al. 2003) Case referent Japan	508 female cases / 36,490 outpatients referents	Salted fish Cooked fish Chicken Beef Eggs Processed meat	Highest / lowest quartile	0.60 (0.29–1.21) n.s.[34] 0.60 (0.40–0.90) $p < 0.05$[35] 0.69 (0.39–1.23) n.s.[34] 0.97 (0.39–2.39) n.s.[34] 1.05 (0.76–1.44) n.s.[34] 0.50 (0.22–1.13) n.s.[34]	Age, year, season at first hospital visit, smoking habit and family history of GC.
(Lee, Park et al. 1995) Korea	213 cases / equal controls (Hospital)	Broiled fish	High / low	7.7 (2.4 – 24.7) $p < 0.01$	Age, sex, education, economic status, residence and other dietary factors
(Lee, Kang et al. 2003) Korea	69 cases / 199 controls (Hospital)	Salt-fermented fish	High / low	2.4 (1.0–5.7) significant	Age, sex, education, family history, smoking, *H. pylori*
(Kim, Chang et al. 2002) Korea	136 cases / equal controls (Hospital)	Charcoal grilled beef Charcoal grilled meats Total beef Salted fish and shellfish Fried meats and fish	High/Low	2.11 (1.17–3.82) $p < 0.05$ 1.58 (0.80–3.10) NS 1.67 (0.86–3.27) $p = 0.0660$ 0.78 (0.39–1.56) NS 0.73 (0.36–1.48) NS	Sex, age, socioeconomic status, family history and refrigerator use
(Nishimoto, Hamada et al. 2002) Brazil	236 cases / equal controls (Population)	Beef Fish Egg	Daily / less than once a week	1.1 (0.6–1.7) NS 1.1 (0.5–2.4) NS 3.2 (1.7–6.0) $p < 0.001$	Race and education, smoking, fruit and vegetables
(Hamada, Kowalski et al. 2002) Brazil	96 cases / 192 controls (Hospital)	Beef Fish	Highest / Lowest quartile	2.2 (1.0–4.8) $p=0.04$ 0.3 (0.1–2.2) NS	Country of birth Excluding volunteer controls
(Munoz, Plummer et al. 2001) Venezuela	292 cases / 485 controls (Neighbor)	Meat Fish Eggs	Highest / lowest quartile	0.31 (0.18–0.53) $p < 0.001$ 0.36 (0.22–0.60) $p < 0.001$ 0.83 (0.52–1.34) $p = 0.53$	Age, sex, tobacco, alcohol, total calories and SES.

[34] No differences for histopathological classification (non differentiated / differentiated)
[35] Was significant for all cases and non-differentiated but NS for differentiated

Appendix H (continued): Summary of case-control studies of GC and Meat, poultry, fish, egg since 1995

Authors, year, place	No of subjects (base)	Type of meat products	Comparison	OR (95% CI) p for trend	Adjustment for
(De Stefani, Boffetta et al. 1998b) Uruguay	340 cases / 698 controls (Hospital)	Red meat Barbecue Salted meat Processed meat		1.4 (1.1–1.70) NS 2.02 (1.66–2.47) 1.71 (1.39–2.08) 1.04 (0.86–1.25) NS	Age, sex, residence, urban/rural, smoking, alcohol, mate consumption
(De Stefani, Correa et al. 2001) Uruguay	160 cases / 320 controls (Hospital)	Red meat, White meat, Processed meat, Total meat,	Highest / Lowest tertile	1.8 (0.8–4.3) NS 1.0 (0.6–1.8) NS 1.9 (1.1–3.5) p = 0.02 1.7 (0.7–4.0) NS	Age, sex, residence, urban/ rural status, education, body mass index, and total energy intake.
(Lissowska, Gail et al. 2004) Poland	274 cases / 463 controls (population)	Meat, poultry, fish Fish Red meat Sausages Smoked meat / fish	Highest / lowest quartile	1.40 (0.84 – 2.35), p = 0.55 0.62 (0.37 – 1.02) p = 0.13 1.51 (0.90 – 2.51) p = 0.28 1.23 (0.79 – 1.93) p = 0.81 1.30 (0.86 – 1.96) p = 0.31	Age, sex, smoking, education, calories.
(Chen, Ward et al. 2002) USA	124 cases / 449 controls or their proxy (Population)	Total meat Processed meat Red meat Poultry Fish	Highest / Lowest quartile	0.97 (0.40, 2.3) NS 1.7 (0.72, 3.9) NS 2.0 (0.85, 4.7) p = 0.05 0.88 (0.35, 2.2) NS 0.58 (0.25, 1.4) NS	Age, sex, energy intake, respondent type, BMI, alcohol, tobacco, education, family history, vitamin supplement
(Zhang, Kurtz et al. 1997) USA	95 cases / 132 controls (Hospital)	Total meat, poultry and fish Poultry and fish Red meat Processed meats	Highest / lowest quartile	0.9 (0.6 – 1.2) NS 0.7 (0.5 – 1.0) p = 0.049[36] (0.8 – 1.6) NS 1.2 (0.9 – 1.7) NS	Age, sex, race, education and total calories intake,
(Ward, Sinha et al. 1997) USA	176 cases / 502 controls (Population)	Total red meat Processed meats Beef (steaks/roasts, hamburgers)	Highest / Lowest quartile	2.4 (1.3–4.8) p < 0.001 1.6 (0.9–2.9) p = 0.06 1.6 (0.9–3.0) p = 0.06	Gender and year of birth

[36] After extra adjustment for smoking alcohol use and BMI result became non significant

Appendix H (continued): Summary of case-control studies of GC and Meat, poultry, fish, egg since 1995

Authors, year, place	No of subjects (base)	Type of meat products	Comparison	OR (95% CI) p for trend	Adjustment for
(Harrison, Zhang et al. 1997) USA	91 cases / 132 controls (Hospital)	Meat, fish and poultry overall Poultry and fish Red meat Processed meat	Intestinal vs. diffuse	1.1 (0.7–1.6) vs. 1.1 (0.7–1.7) NS 0.8 (0.5–1.2) vs. 0.9 (0.5–1.5) NS 1.2 (0.9–1.7) vs. 1.2 (0.8–1.6) NS 1.4 (0.9–2.0) vs. 1.3 (0.8–2.1) NS	Caloric intake, age, gender, race, education, pack-years of smoking, alcohol drinking, and BMI
(De Stefani, Correa et al. 2004)	240 cases / 960 controls (Hospital)	Red meat Poultry Fish Salted meat Total meat Egg	Highest / lowest tertile	1.10 (0.71–1.71) p=0.67 0.98 (0.67–1.44) p=0.96 0.73 (0.5 1–1.03) p=0.08 1.98 (1.35–2.90) p<0.01 1.19(0.77–1.84) p=0.42 0.48 (0.33–0.69) p<0.01	Age, sex, residence, urban/rural, education, BMI and total energy intake
(Nomura, Hankin et al. 2003) USA	300 cases / 446 controls (Population)	Processed meats Poultry	Highest/lowest tertile	2.0 (1.2–3.3) p=0.03 male[37] 0.5 (0.3–0.8) p=0.008 male[38]	Age, ethnicity, cigarette smoking, education, history of gastric ulcer, NSAID use, family history of GC, and total calories.
(Ward and Lopez-Carrillo 1999) Mexico	220 cases / 752 Controls (Population)	Fresh meat Processed meats Fish	Highest / lowest quartile	3.1 (1.6 – 6.2) p=0.001[39] 3.2 (1.5 - 6.6) p=0.002 2.2 (1.2 – 3.8) p=0.001	Age, gender, total calories, chili pepper, salt, history of peptic ulcer, smoke and SES
(Cornee, Pobel et al. 1995) France	92 cases / 128 controls (Clinic)	Total meat products Meat Poultry Ham Salami Fish Egg	Highest / lowest tertile	1.80 (0.89 – 3.66) NS 0.57 (0.28 – 1.19) NS 0.69 (0.34 – 1.36) NS 1.59 (0.77 – 3.29) NS 1.02 (0.50 – 2.09) NS 0.97 (0.48 – 1.96) NS 0.84 (0.42 – 1.68) NS	Age, sex, occupation, total energy intake

[37] NS for women
[38] significant for both sexes
[39] Risks with consumption of fresh meat, processed meat, and dairy products were greater for the intestinal type of gastric cancer compared with risks for the diffuse type. For frequent consumption of fish, similar risks were observed for intestinal and diffuse types.

Appendix I: Summary of cohort studies of GC and Meat, poultry, fish, egg since 1995

Authors, year, place	No of subjects	Type of meat products	Comparison	RR (95% CI) p for trnd	Adjustment for
(Ngoan, Mizoue et al. 2002) Japan	13,000 subjects, 116 died from GC after 10.5 years follow up	Fresh meat[40] Processed meat Fresh fish[40] Processed fish[40] Eggs[40]	High / low Male / female	1.8 (0.9–3.7) vs. 0.5 (0.1–4.0) NS 3.4 (1.4–8.1) NS 1.5 (0.7–3.1) vs. 0.6 (0.2–1.7) NS 2.1 (0.9–4.9) vs. 1.4 (0.3–7.3) NS 0.8 (0.4–1.6) vs. 1.1 (0.9–1.3) NS	Age, sex, smoking, processed meat, liver, cooking or salad oil, suimono, and pickled food.
(McCullough, Robertson et al. 2001) USA	1.2 million subjects, 1349 death of GC after 14 years follow up	Processed meat	Highest/lowest tertile	1.20 (0.97–1.47) 0.09 Male 1.12 (0.89–1.41) 0.39 Female	Age[41]
(Kasum, Jacobs et al. 2002) USA	34651 women, 56 cases after 14 years follow up	Red meat	Highest /lowest tertile	No association (data not shown).	
(Tsugane, Sasazuki et al. 2004) Japan	39065 subjects, 486 cases after 12 years follow up	Dried or salted fish	Highest / lowest quartile	2.23 (1.37 –3.63) p=0.007	Age, smoking and fruit and non-green – yellow vegetable
(Galanis, Kolonel et al. 1998) USA	11,907 Japanese residents of Hawaii, 108 cases of GC in 14.8 years follow up	Dried or salted fish Processed meat High salt intake	Highest /lowest frequency of consumption	1.0 (0.6 – 1.7) NS 1.0 (0.6 – 1.7) NS 1.1 (0.7 – 1.8) NS	Age, year of education, Japanese place of birth and gender
(van den Brandt, Botterweck et al. 2003) Netherlands	120,852 subjects, 282 cases / 3123 sub cohort after 6.3 years follow up	Bacon in the hot meal Smoked sausage in hot meal Total sliced cold meats Boiled ham Smoked beef, pork loin roll Other sliced cold meat	Highest / lowest amount	1.33 (1.03–1.71) 0.95 (0.67–1.35) NS 1.33 (0.85–2.09) NS 0.77 (0.56–1.07) NS 0.92 (0.71–1.19) NS 1.29 (0.96–1.72) NS	age, sex, smoking status, level of education, stomach disorders and GC in the family

[40] NS for both gender

[41] After extra adjustment for education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, and family history the association was attenuated

Appendix J: Studies of GC and occupation published since 1995

Reference	Country	Methodology	Exposure assessment
(Aragones, Pollan et al. 2002)	Sweden	Cohort	Work history by interview
(Boffetta, Gridley et al. 2000)	Sweden	Cohort	Work history by interview
(Ekstrom, Eriksson et al. 1999)	Sweden	Case- control	Work history by interview
(Jakobsson, Mikoczy et al. 1997)	Sweden	Cohort	Work history from records
(Plato, Westerholm et al. 1995)	Sweden	Cohort	Work history from records
(Bucchi, Nanni et al. 2004)	Italy	Cohort	Work history from records
(Gonzalez, Sanz et al. 1991b)	Spain	Case- control	Work history by interview
(Pang, Burges et al. 1996)	UK	Cohort	Work history from records
(Straughan and Sorahan 2000)	UK	Cohort	Work history from records
(Rix, Villadsen et al. 1997)	Denmark	Cohort	Work history from records
(Straif, Chambless et al. 1999)	Germany	Cohort	Work history from records
(Straif, Keil et al. 2000)	Germany	Cohort	Work history from records
(Straif, Weiland et al. 1998)	Germany	Cohort	Work history from records
(Stucker, Meguellati et al. 2003)	French	Cohort	Work history from records
(Swaen, Meijers et al. 1995)	Netherlands	Cohort	Work history from records
(Romundstad, Andersen et al. 2001)	Norway	Cohort	Job exposure matrix
(Krstev, Dosemeci et al. 2005)	Poland	Case- control	Work history by interview
(Burns and Swanson 1995)	USA	Case- control	Work history by interview
(Cocco, Ward et al. 1998)	USA	Case- control	Death certificate
(Cocco, Ward et al. 1999)	USA	Case- control	Death certificate
(Wong and Harris 2000)	USA	Cohort- nested case-control	Work history by interview
(Engel, Vaughan et al. 2002)	USA	Case- control	Work history by interview
(Fu and Boffetta 1995)		Meta-analysis	
(Marsh, Gula et al. 1999)	USA	Cohort	Occupational hygienist
(Park and Mirer 1996)	USA	Descriptive	Work history from records
(Zeka, Eisen et al. 2004)	USA	Case-cohort	Work history by interview
(Robinson, Petersen et al. 1996)	USA	Descriptive	Work history by interview
(Kang, Burnett et al. 1997)	USA	Descriptive	Death certificate
(Kazerouni, Thomas et al. 2000)	USA	Cohort	Work history from records
(Vaughan, Stewart et al. 1997)	USA	Case- control	Work history by interview
(Parent, Siemiatycki et al. 1998)	Canada	Case- control	Work history by interview
(Medrado-Faria, Rodrigues de Almeida et al. 2001)	Brazil	Ecological	Death certificate
(Tsuda, Mino et al. 2001)	Japan	Case- control	Death certificate
(Ke and Shunzhang 1999)	China	Case- cohort	Work history from records
(Pang, Zhang et al. 1997)	China	Cohort	Work history from records
(Blair, Zahm et al. 1992)		Meta-analysis	
(Acquavella, Olsen et al. 1998)		Meta- analysis	
(Xu, Brown et al. 1996)	China	Nested case-control	Work history by interview
(Yang, Chiu et al. 1997)	Taiwan	Ecological	Records

Appendix K: International Standard Industrial Classification of all Economic Activities (ISIC) Third Revision

Category A: Agriculture, hunting and forestry

01 Agriculture, hunting and related service activities

02 Forestry, logging and related service activities

Category B: Fishing

05 Fishing, operation of fish hatcheries and fish farms; service activities incidental to fishing

Category C: Mining and quarrying

10 Mining of coal and lignite; extraction of peat

11 Extraction of crude petroleum and natural gas; service activities incidental to oil and gas extraction, excluding surveying

12 Mining of uranium and thorium ores

13 Mining of metal ores

14 Other mining and quarrying

Category D: Manufacturing

15 Manufacture of food products and beverages

16 Manufacture of tobacco products

17 Manufacture of textiles

18 Manufacture of wearing apparel; dressing and dyeing of fur

19 Tanning and dressing of leather; manufacture of luggage, handbags, saddlery, harness and footwear

20 Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials

21 Manufacture of paper and paper products

22 Publishing, printing and reproduction of recorded media

23 Manufacture of coke, refined petroleum products and nuclear fuel

24 Manufacture of chemicals and chemical products

25 Manufacture of rubber and plastic products

26 Manufacture of other non-metallic mineral products

27 Manufacture of basic metals

28 Manufacture of fabricated metal products, except machinery and equipment

29 Manufacture of machinery and equipment NEC (not elsewhere classified)

30 Manufacture of office, accounting and computing machinery

31 Manufacture of electrical machinery and apparatus NEC

32 Manufacture of radio, television and communication equipment and apparatus

33 Manufacture of medical, precision and optical instruments, watches and clocks

34 Manufacture of motor vehicles, trailers and semi-trailers

35 Manufacture of other transport equipment

36 Manufacture of furniture; manufacturing NEC

37 Recycling

Category E: Electricity, gas and water supply

40 Electricity, gas, steam and hot-water supply

41 Collection, purification and distribution of water

Appendix K (continued): International Standard Industrial Classification of all Economic Activities (ISIC) Third Revision

Category F: Construction

45 Construction

Category G: Wholesale and retail trade; repair of motor vehicles, motorcycles and personal and household goods

50 Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel

51 Wholesale trade and commission trade, except of motor vehicles and motorcycles

52 Retail trade, except of motor vehicles and motorcycles; repair of personal and household goods

Category H: Hotels and restaurants

55 Hotels and restaurants

Category I: Transport, storage and communications

60 Land transport; transport via pipelines

61 Water transport

62 Air transport

63 Supporting and auxiliary transport activities; activities of travel agencies

64 Post and telecommunications

Category J: Financial intermediation

65 Financial intermediation, except insurance and pension funding

66 Insurance and pension funding, except compulsory social security

67 Activities auxiliary to financial intermediation

Category K: Real estate, renting and business activities

70 Real estate activities

71 Renting of machinery and equipment without operator and of personal and household goods

72 Computer and related activities

73 Research and development

74 Other business activities

Category L: Public administration and defence; compulsory social security

75 Public administration and defence; compulsory social security

Category M: Education

80 Education

Category N: Health and social work

85 Health and social work

Category O: Other community, social and personal service activities

90 Sewage and refuse disposal, sanitation and similar activities

91 Activities and membership organizations NEC

92 Recreational, cultural and sporting activities

93 Other service activities

Category P: Private households with employed persons

95 Private households with employed persons

Category Q: Extra-territorial organizations and bodies

99 Extra-territorial organizations and bodies

Appendix L: International Standard Classification of Occupations (ISCO – 88)

Major group 1: Legislators, senior officials and managers

11 Legislators and senior officials

111 Legislators

112 Senior government officials

113 Traditional chiefs and heads of villages

114 Senior officials of special interest organizations

12 Corporate managers

121 Directors and chief executives

122 Production and operations department managers

123 Other departmental managers

13 General managers

131 General managers

Major group 2: Professionals

21 Physical, mathematical and engineering science professionals

211 Physicists, chemists and related professionals

212 Mathematicians, statisticians and related professionals

213 Computing professionals

214 Architects, engineers and related professionals

22 Life science and health professionals

221 Life science professionals

222 Health professionals (except nursing)

223 Nursing and midwifery professionals

23 Teaching professionals

231 College, university and higher education teaching professionals

232 Secondary education teaching professionals

233 Primary and pre-primary education teaching professionals

234 Special education teaching professionals

235 Other teaching professionals

24 Other professionals

241 Business professionals

242 Legal professionals

243 Archivists, librarians and related information professionals

244 Social sciences and related professionals

245 Writers and creative or performing artists

246 Religious professionals

Appendix L (continued): International Standard Classification of Occupations (ISCO – 88)

Major group 3: Technicians and associate professionals

31 Physical and engineering science associate professionals

311 Physical and engineering science technicians

312 Computer associate professionals

313 Optical and electronic equipment operators

314 Ship and aircraft controllers and technicians

315 Safety and quality inspectors

32 Life science and health associate professionals

321 Life science technicians and related associate professionals

322 Modern health associate professionals (except nursing)

323 Nursing and midwifery associate professionals

324 Traditional medicine practitioners and faith-healers

33 Teaching associate professionals

331 Primary education teaching associate professionals

332 Pre-primary education teaching associate professionals

333 Special education teaching associate professionals

334 Other teaching associate professionals

34 Other associate professionals

341 Finance and sales associate professionals

342 Business services agents and trade brokers

343 Administrative associate professionals

344 Customs, tax and related government associate professionals

345 Police inspectors and detectives

346 Social work associate professionals

347 Artistic, entertainment and sports associate professionals

348 Religious associate professionals

Major group 4: Clerks

41 Office clerks

411 Secretaries and keyboard-operating clerks

412 Numerical clerks

413 Material-recording and transport clerks

414 Library, mail and related clerks

419 Other office clerks

42 Customer service clerks

421 Cashiers, tellers and related clerks

422 Client information clerks

Major group 5: Service workers and shop and market sales workers

51 Personal and protective services workers

511 Travel attendants and related workers

Appendix L (continued): International Standard Classification of Occupations (ISCO – 88)

512 Housekeeping and restaurant services workers

513 Personal care and related workers

514 Other personal service workers

515 Astrologers, fortune-tellers and related workers

516 Protective services workers

52 Models, salespersons and demonstrators

521 Fashion and other models

522 Shop salespersons and demonstrators

523 Stall and market salespersons

Major group 6: Skilled agricultural and fishery workers

61 Market-oriented skilled agricultural and fishery workers

611 Market gardeners and crop growers

612 Market-oriented animal producers and related workers

613 Market-oriented crop and animal producers

614 Forestry and related workers

615 Fishery workers, hunters and trappers

62 Subsistence agricultural and fishery workers

621 Subsistence agricultural and fishery workers

Major group 7: Craft and related trades workers

71 Extraction and building trade workers

711 Miners, shot-firers, stonecutters and carvers

712 Building frame and related trades workers

713 Building finishers and related trades workers

714 Painters, building structure cleaners and related trade workers

72 Metal, machinery and related trades workers

721 Metal moulders, welders, sheet-metalworkers, structural-metal preparers and related trades workers

722 Blacksmiths, toolmakers and related trades workers

723 Machinery mechanics and fitters

724 Electrical and electronic equipment mechanics and fitters

73 Precision, handicraft, printing and related trades workers

731 Precision workers in metal and related materials

732 Potters, glass-makers and related trades workers

733 Handicraft workers in wood, textile, leather and related materials

734 Printing and related trades workers

74 Other craft and related trades workers

741 Food processing and related trades workers

742 Wood treaters, cabinet-makers and related trades workers

743 Textile, garment and related trades workers

744 Felt, leather and shoemaking trades workers

Appendix L (continued): International Standard Classification of Occupations (ISCO – 88)

Major group 8: Plant and machine operators and assemblers

81 Stationary plant and related operators
811 Mining and mineral-processing plant operators
812 Metal-processing plant operators
813 Glass, ceramics and related plant operators
814 Wood processing and papermaking plant operators
815 Chemical processing plant operators
816 Power production and related plant operators
817 Automated assembly-line and industrial robot operators
82 Machine operators and assemblers
821 Metal and mineral products machine operators
822 Chemical products machine operators
823 Rubber and plastic products machine operators
824 Wood products machine operators
825 Printing, binding and paper products machine operators
826 Textile, fur and leather products machine operators
827 Food and related products machine operators
828 Assemblers
829 Other machine operators and assemblers
83 Drivers and mobile plant operators
831 Locomotive engine-drivers and related workers
832 Motor vehicle drivers
833 Agricultural and other mobile plant operators
834 Ships' deck crews and related workers

Major group 9: Elementary occupations

91 Sales and services elementary occupations
911 Street vendors and related workers
912 Shoe cleaning and other street services' elementary occupations
913 Domestic and related helpers, cleaners and launderers
914 Building caretakers, window and related cleaners
915 Messengers, porters, doorkeepers and related workers
916 Garbage collectors and related labourers
92 Agricultural, fishery and related labourers
921 Agricultural, fishery and related labourers
93 Labourers in mining, construction, manufacturing and transport
931 Mining and construction labourers
932 Manufacturing labourers
933 Transport labourers and freight handlers

Major group 0: Armed forces

01 Armed forces
011 Armed forces

Code	Description
C16.0	Cardia
C16.1	Fundus of Stomach Gastric fundus
C16.2	Body of Stomach Corpus of Stomach Gastric corpus
C16.3	Gastric antrum Antrum of Stomach Pyloric antrum
C16.5	Lesser curvature of Stomach, NOS (not classifiable to C16.1 to C16.4)
C16.6	Greater curvature of Stomach, NOS (not classifiable to C16.0 to C16.4)
C16.8	Overlapping lesion of Stomach Anterior wall of Stomach, NOS (not classifiable to C16.0 to C16.4) Posterior wall of Stomach, NOS (not classifiable to C16.0 to C16.4)
C16.9	Stomach, NOS Gastric, NOS

Appendix N: Invitation letter from Ardabil health department to subjects

P.O.BOX: 56135 – 316
IRAN - ARDABIL
TEL: 3351020
FAX: (0098-451) 3351054

Mr. / Mrs.: ……

A research team is planning to do a study in gastric cancer by collaboration of researchers from University of New South Wales in Australia and Ardabil university of Medical Science. A detail of study is attached. If you are interested to participate in this research would you please sign attached consent letter and return it to the address which was printed in the attached reply-paid envelope. Please do not hesitate to call us if you have any further questions

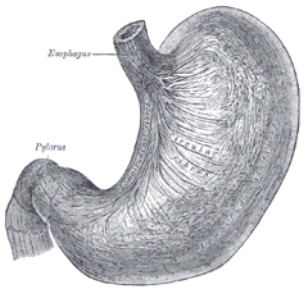
Ardabil Health Department

Cancer Registry

Appendix O: Administered questionnaire for those refusing to participate

THE UNIVERSITY OF NEW SOUTH WALES
THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
DIGESTIVE DISEASE RESEARCH CENTER

The influence of environmental factors on gastric cancer in Iran - Ardabil



Non- participant classification:
1-☐ Case 2-☐ Control

Date of interview: |__|__|__|__| |__|__| |__|__|
YYYY MM DD

Sex (Interviewer record but do not ask sex of study subject) 1. ☐Male 2. ☐Female

Age |__|__| years Interviewer:

Place of interview:
1. ☐ Aras clinic 2.☐ Home 3. ☐ Clinic of Doctor ……4.☐ Other (specify) ……

What is the reason for non-participation?
1-☐ Was board or uninterested
2-☐ Was inhibited by others around her/him
3-☐ Other (specify)

Appendix P: Reliability of questionnaire in measurement of continuous variables

Section	Questions	Interview 1		Interview 2		Correlation coefficients		p
		Mean	SD	Mean	SD	Pearson	Spearman	
C	Income	1297830	840250	1312170	894020	0.98	0.99	< 0.01
C	Expenses	1332610	850880	1295650	873460	0.89	0.85	< 0.01
D	Smoking years	6.30	11.2	6.0	10.6	0.95	0.99	< 0.01
D	Average smoke per day	3.6	6.7	3.5	6.1	0.98	0.99	< 0.01
G	Working years	7.1	9.7	7.4	9.9	0.99	0.99	< 0.01

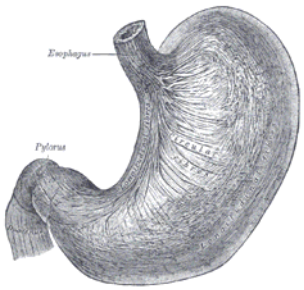
Appendix Q: Reliability of questionnaire in measurement of categorical variables

Section	Questions	Agreement between answers		PA %	Kappa coefficient
		Yes	No		
D	Have you ever smoked cigarettes?	23	0	100	1.0
E	Preference for strong tea	18	5	78.3	0.65
E	Preference for hot tea	18	5	78.3	0.66
F	Have you ever had any firs-degree relatives with cancer?	23	0	100.0	1.0
G	What was your main job during last ten years?	23	0	100.0	1.0
H	Preference for salt intake	21	2	91.3	0.84
H	Raw vegetables intake	19	4	82.6	0.71
H	Fresh fruits intake	22	1	95.7	0.93
H	Garlic intake	15	8	65.2	0.51
H	Onion intake	20	3	87.0	0.79
H	Diary products intake	18	5	78.3	0.69
H	Pickled vegetables intake	18	5	78.3	0.68
H	Red meats	18	5	78.3	0.66
H	Cured meat	18	5	78.3	0.64
H	Salted fish	16	7	69.6	0.56

Appendix R: Administered questionnaire

THE UNIVERSITY OF NEW SOUTH WALES
THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
DIGESTIVE DISEASE RESEARCH CENTER

The influence of environmental factors on gastric cancer in Iran - Ardabil



Given name: Family name: ID: |__|__|__|__|

Present address:

Contact phone number

Respondent: 1-☐ Case 2-☐ Control 3-☐ Proxy

Date of interview: |__|__|__|__| |__|__| |__|__|
YYYY MM DD

Time interview began: |__|__| : |__|__| AM PM

Time interview ended: |__|__| : |__|__| AM PM

Total interview time: |__|__|__| MINUTES

Interviewer:

Place of interview:
1. ☐ Aras clinic 2.☐ Home 3. ☐ Clinic of Doctor ……4.☐ Other (specify) ……

Appendix R (continued): Administered questionnaire

In all instances, code 9, 99, etc. should be used for missing information

A. INTRODUCTION FOR PROXY INTERVIEWS

What is the reason for proxy interview?

1-☐ Subject's death 2-☐Disability of case 3-☐Other (specify)……...

What is your relation to Mr./ Ms. ……..?

11-☐Wife 12-☐Husband 13-☐Daughter 14-☐ Son 15-☐Mother
16-☐ Father 17-☐Sister 18-☐Brother 19-☐Other

How old are you? |__|__| Years

How many years (have you been/ were you) lived in the same household? |__|__| Years
NEVER ……00

B. DEMOGRAPHIC CHARACTERISTICS

First, we need some basic information about you

Sex (Interviewer record but do not ask sex of study subject)

1. ☐Male 2. ☐Female

Date of birth: |__|__|__|__| : |__|__| : |__|__| OR Age(completed years): |__|__|
YYYY M M DD

Where were you born?

1- Province 2- District 3- City 4- Village

Where have you lived during last fifteen years (15 years before starting symptoms)? (write from the last place)

Province	District	City	Village	From age	To age

What is your current marital status? (Mark only one answer.)

1-☐ Single (never married) 2-☐ Married 3-☐ Divorced 4- ☐ Widowed
5-☐ Other (specify) ……

What is your ethnicity?

1-☐ Turk 2-☐ Lor 3-☐ Arab 4-☐ Kord
5-☐ Fars 6-☐ Turkoman 7-☐ Baluch 8-☐ Other …….

What is your religion?

1-☐ Muslim 2-☐ Christian 3-☐ Jewish 4-☐ Zoroastrian
5-☐ Other ……

Appendix R (continued): Administered questionnaire

C. SOCIO-ECONOMIC STATUS

Now I have some questions about lifestyle practices you may have.

How much were your income monthly during last year? (Including income provided by you, your spouse and any other person living in your household)

☐☐,☐☐☐,☐☐☐ Rials

How much were your expenditure monthly during last year? (Including expenditure of you, your spouse and any other person living in your household)

☐☐,☐☐☐,☐☐☐ Rials

How many people, including you, were supported by this income during the last calendar year?

|__|__|

How many meters is your living home? |__|__|__| m2

What type of theses facilities have you had in your home?

1-☐ Pipe water
2-☐ Electricity
3-☐ Piped gas
4-☐ Hot shower
5-☐ Telephone
6-☐ Central heating

What is the highest level of education you have completed? (Mark only one answer.)

1-☐ Nil
2-☐ Fifth grade or less
3-☐ Beyond fifth grade, but not high school (RAHNEMAEI)
4-☐ High school graduate or Diploma
5-☐ FOGH DIPLOMA
6-☐ Finished an University program (BA, Master, Doctorate.) OR (HOOZEE)

Numbers of years schooling? |__|__|

Appendix R (continued): Administered questionnaire

D. SMOKING

Have you ever smoked cigarettes, pipe regularly? (at least one per day for 6 months or more)
1-☐ Yes 2-☐No

If yes please ask about each products

Product	1-Yes 2-No	**A** From age	**B** To age	How many years in total between age (A, B) did you not smoke cigarette?	How many years altogether did you smoke?	Quantity per day		When you have smoked, how was your inhalation? 1- Slightly (mouth only) 2-Moderately (mouth and throat) 3-Deeply (Chest)
						Week-days	Week-ends	
Cigarettes								
Pipe								
Galyan								
Chopogh (traditional pipe)								
Chewing tobacco								
Other. ……								

During the smoking years, did you usually smoke filtered or non-filtered cigarettes?
1-☐ Filtered 2-☐ Non-filtered 3-☐ Both equally

Whether or not you smoke, about how many hours per week have you been exposed to the smoke of others during last ten years (ten years before symptoms)? (If not exposed please put 00)

At home? ___	At work? ___	In other place? ___

Have you ever used opium or nass regularly? (At least once per week for 6 months or more)
1-☐ Yes 2-☐ No

If yes please ask about each products

Type	**1- Yes 2- No**	**From age**	**To age**	**How many years altogether?**	**Quantity per day**	**Duration of placement (min)**
Opium (Taryak)	☐					
Cannabis	☐					
Nass	☐					
Sokhteh	☐					
SHIREH	☐					
HEROIN	☐					
Other (specify)	☐					

Appendix R (continued): Administered questionnaire

E. BEVERAGE CONSUMPTION…

What is your most likely drinking beverage? (Except water)
1-☐ Tea 2-☐ Coffee 3-☐ Other (specify) …….

Have (you / subject) ever drunk coffee, tea and soft drink beverage regularly? (at least once a week for more than 6 months) 1-☐ YES 2-☐ NO

If yes please answer to these questions.

Product	Yes No	B From age	A To age	How many years in total between age (A, B) did you not drink?	How many years altogether did you drink?1	How many times per week?	How many cups per time?
Coffee	☐						
Tea	☐						
Soft drink	☐						

What kind of tea do you drink most often?
1-☐ Black tea 2-☐ Green tea 3-☐ Herbal tea (specify)……
4-☐ All of the three 5-☐ Other (Specify) ……

How did you like strength of drinking tea? (Please read the following.)
1-☐ Strong 2-☐ Regular 3-☐ Light 4-☐ Unclear

How did you like warmth of drinking tea?
1-☐ Extremely hot 2-☐ Hot 3-☐ Warm 4-☐ Unclear

Now I have some questions about (your/subject's) beverage consumption. Please think about (your/subject's) habits over most of (your/subject's) adult life, that is, before any recent changes (you / subject) may have made for any reason, such as an illness or a change in lifestyle. Although I would like you to be as accurate as possible, if you don't remember exactly, please give me your best guess, as that information would be better than no information at all.

Have you ever drunk alcoholic beverage regularly? (at least once a week for more than 6 months)
1-☐ YES 2-☐ NO (GO TO SECTION F)

If yes please answer to these questions

Product	1-Yes 2- No	B From age	A To age	How many years in total between age (A, B) did you/ not drink?	How many years altogether did you drink?[1]	How many times per week?	Average ml in every time
	☐						
	☐						
	☐						
	☐						

[1] Do not include any periods during which subject may have quit

F. MEDICAL AND FAMILY HISTORY

Height in cm |__|__|__| cm

Current weight |__|__|__| kg

What was your Weight prior to the symptoms and signs? |__|__|__| kg

Have you ever had any sort of disease changing your occupation, personal habits and normal food habits?

1-☐ YES 2-☐NO

If yes what was the nature of the problem? (i. e. hypertension, diabetes, ….)

1- ……. 2 - ……

3 - ……

Have you ever been diagnosed with a cancer?

1- ☐YES 2- ☐NO

If yes at what age? |__|__|

At which site?

1-☐ Respiratory system (specify) ……
2-☐ Neurological system (specify) …….
3-☐ Gastro intestinal system (specify)…….
4-☐ Immuno-hematological system (specify)……..
5-☐ Cardiovascular system (specify)……
6-☐ Genito-urinary system (specify)……
7-☐ Dermatological system (specify0 ……..
8-☐ Other (specify)……

Now I have a few questions about the health of some of (your/subject) blood relatives. I am only interested in your relatives who are related by blood. Do not include adopted or foster relatives. I will be asking about your mother, your father, any sisters and brothers you have, and any children.
How many daughter, son, brother and sister do you/ have, including both living and deceased?

Daughter	☐☐
Son	☐☐
Sister	☐☐
Brother	☐☐

Do (you / subject) have any first-degree relatives who ever had a diagnosis of cancer?

1- ☐ YES 2- ☐ NO 3-☐ Don't know [2 and 3 SKIP TO SECTION G]

No	Which relative was this? 1-Father 2- Mother 3-Brother 4- Sister 5-Son 6- Daughter	What type of cancer did (s/he) has? (RECORD VERBATIM)	What was the age at diagnosis?	Is (s/he)? Alive Deceased
1	☐			☐
2	☐			☐
3	☐			☐

Appendix R (continued): Administered questionnaire

G. WORK HISTORY

Now I'd like to ask about your/subject's work history?

Since age 16, did you ever work for 12 months or more in one position or job?
1- ☐ YES 2- ☐ NO [SKIP TO SECTION H]

G2. At what age did (you / subject) start working? |__|__|

G3. At what age did (you / subject) stop working? |__|__|
CURRENTLY WORKING ……..96

How many years have you worked between G.2 and G.3? (Please do not include any periods during which you may have quit.) |__|__|

What was your main job during last ten years (10 years before symptoms)?
1-☐ Agriculture 2-☐ Labour 3-☐ Public adminstration
4-☐ Animal breeding 5-☐ Housekeeper 6-☐ Other (specify)
…….

List all jobs in which you have employed for at least one year starting from the last job. We are interested in every job, full or part-time, paid or unpaid, that (you / subject) held for a total of one year or longer.

No	A[42] Job title, occupation	B What was the type of the industries for which you worked?	C What was the main activity or product?	D Duration of Work (Years)	E Was this job full-time (40 h or more per week or part time? 1-F 2-P
1				☐☐	☐
2				☐☐	☐
3				☐☐	☐
4				☐☐	☐
5				☐☐	☐

[42] If you held exactly the same position at more than one place, report these multiple jobs as one job, if you did not hold a different type of job in between. Some examples are moving from one location to another as a teacher, temporary worker, nurse's aide, hospital worker or child care worker. On the other hand, if you held more than one position at a company, we will talk about each position separately if you held that job for one year or longer). Also, please include any job in the military, jobs (you / subject) may have performed at home and volunteer job at which you worked for a period of one year or longer.

Appendix R (continued): Administered questionnaire

H. EATING HABITS

What is your main food at home?

1-☐ Rice 2-☐ Wheat bread 3-☐ Barley bread

Have you made any changes to your diet in the last ten years?

1-☐ YES because of illness 2-☐ YES because of other reasons
3-☐ Can't remember 4-☐ NO

If yes how did it change? ……
…….

How salty did you usually prefer to eat your food prior to any possible change?

1-☐ Very salty 2-☐ Salty 3-☐ Normal
4-☐ Not salty 5-☐ Don't know

Do you have a refrigerator?
1-☐ YES 2-☐ NO

If yes from how many years ago? |__|__|

Do you have a freezer?
1-☐ YES 2-☐ NO

If yes from how many years ago? |__|__|

Appendix R (continued): Administered questionnaire

How frequently do (you / subject) usually eat the following foods? (refer to the last ten years, before any recent changes)

No	Food items	Seldom or Never	1 – 2 per month	1 – 2 per week	3 – 4 per week	Once daily	2 – 3 times daily	Don't know
1	Raw vegetables							
2	Yellow-orange vegetables (Pumpkin, squashes, carrots, ..							
3	Garlic							
4	Onion							
5	Pickled vegetables							
6	Soy beans, baked beans, green peas, etc							
7	Fresh fruits							
8	Citrus fruits (orange, lemon, ….)							
9	Juice (fresh or canned)							
10	Fresh meat							
11	Smoked meat							
12	rocessed meat (sausage, hamburger, salami, …)							
13	Fresh fish							
14	Salted fish							
15	Smoked fish							
16	Chicken, and poultry							
17	Diary products (milk, butter, … except cheese)							
18	Cheese							
19	Sweet, Jam, etc							
20	Seeds (sunflower							

Appendix R (continued): Administered questionnaire

I. LABORATORY FINDING

I. 1 Pathology of cancer

1-☐ Diffuse adenocarcinoma 2-☐ Intestinal adenocarcinoma
3-☐ Lymphoma 4-☐other (specify) …….

I. 2 Topography of cancer

1-☐ Cardia 2-☐ Fundus
3-☐ Antrum 4-☐ other (specify) …….

I. 3 Blood group

1-☐ A 2-☐ B
3-☐ AB 4-☐ O

I. 4 Rh

1-☐ Positive 2-☐ Negative

I. 5 ELISA

1-☐ Positive 2-☐ Negative

J. INTERVIEWER REMARKS

RESPONDENT'S COOPERATION WAS:
1-☐VERY GOOD 2-☐GOOD 3-☐FAIR 4-☐POOR

THE QUALITY OF THE INTERVIEW IS: (COMPLETE FOR EACH SECTION)

SECTION	UNSATIS-FACTORY	QUESTION-ABLE	GENERALLY RELIABLE	HIGH QUALITY
A. INTRODUCTION FOR PROXY INTERVIEWS				
B. DEMOGRAPHIC INFORMATION				
C. SOCIOECONOMIC STATUS				
D. SMOKING HISTORY				
E. BEVERAGE CONSUMPTION				
F. MEDICAL HISTORY				
G. OCCUPATION				
H. EATING HABITS				
I. LABORATORY FINDING				

THE OVERALL QUALITY OF THIS INTERVIEW IS:
1-☐ UNSATISFACTORY 2-☐ QUESTIONABLE
3-☐ GENERALLY RELIABLE (END/COMMENTS) 4- ☐ HIGH QUALITY

THE REASON(S) FOR UNSATISFACTORY OR QUESTIONABLE QUALITY OF INFORMATION (WAS/WERE) BECAUSE THE RESPONDENT: (CIRCLE ALL THAT APPLY)

1-☐ WAS BORED OR UNINTERESTED
2-☐ WAS UPSET, DEPRESSED, OR ANGRY
3-☐ HAD POOR HEARING OR SPEECH
4-☐ WAS INHIBITED BY OTHERS AROUND HER OR HIM
5-☐ WAS EMBARRASSED BY THE SUBJECT MATTER
6-☐ WAS EMOTIONALLY UNSTABLE
7-☐ WAS PHYSICALLY ILL
8-☐ OTHER (SPECIFY)

Comments:
……...
……
……

Appendix S: Validation of ELISA kit

Evaluation of Commercially available ELISA Kits for Detection of *Helicobacter Pylori* infection in Iran

Introduction

Helicobacter pylori (*H. pylori*) infection occurs worldwide, however prevalence of infection varies between different regions. Infection rate is higher in developing countries compared to developed countries. It is estimated that about one-third of the adults in the more developed countries are infected while this rate is about two-thirds of the adults in less developed countries (Pounder and Ng 1995). It has been reported that about 80% of the Iranian population is infected with *H. pylori* with infection rate particularly high in the Northwest (Massarrat, Saberi-Firoozi et al. 1995; Mikaeli, Malekzadeh et al. 2000). *H.pylori* infection can be diagnosed by invasive methods requiring endoscopy and biopsy (histological examination, culture and polymerase chain reaction (PCR)) or by non-invasive techniques (serology, urea breath test (UBT) and detection of *H.pylori* antigen in stool specimen). Choosing among them is not easy, and several issues need to be considered such as local availability and clinical circumstances of patients as well as tests' cost. When one of these methods is chosen for either clinical or research objective, it has to be validated locally (Sacket, Haynes et al. 1991; Lam and Talley 1998; Szeto, Lee et al. 2001; Obata, Kikuchi et al. 2003) because the antigenic properties of local bacterial strains may differ to those used in the tests. This study was conducted to evaluate the accuracy of four imported ELISA kits in Iran in order to select a method of *H. pylori* diagnosis to use in a case- control study of gastric cancer in NorthWest Iran.

METHODS:

Aras clinic has been established as a special referral clinic for gastrointestinal diseases. Eligible subjects were selected among those who had been referred to this clinic due to

dyspepsia. Those patients who had received prior *H. pylori* eradication or proton-pump inhibitor within the past month were excluded. All patients underwent a routine upper GI endoscopy. Three endoscopic specimens were taken from all referred patients, two from the antrum and one from the fundus. One antral specimen was used for the rapid urea test (RUT) and the remainders were used for histological Giemsa staining. RUTs were read at 30 minutes after adding specimen to tube however we were waiting 3 hours before listing a patient's result as negative based on kit instruction. Gold standard diagnosis of *H. pylori* infection was considered when results were positive for both histological examination and RUT. In addition to the endoscopy, approximately 10 ml of subjects' blood were collected. These blood specimens were centrifuged to separate serum which was stored in – 60 ^{o} C. All serum were examined for *H. pylori* specific IgG using four following enzyme linked immunosorbent assay (ELISA) kits; Hp-G Screen (Genesis Diagnostics, UK), HP IgG (DIA.PRO, Italy), Helicobacter pylori IgG (IBL, Germany) and Helicobacter pylori IgG (Biohit, Finland). Results of these four kits were compared to those of gold standard to calculate sensitivity, specificity, positive and negative predictive value. All participants had been asked to sign an informed consent letter prior to the including in the study.

RESULTS:

Eighty three subjects were investigated in this study of whom 45 (54.2%) were male and 38 (45.8%) female. Average age of participants was 47.7 ± 18.2 years. Forty of participants were positive and 43 negative based on predetermined gold standard. All negative results of *H. pylori* by histopathology were negative in RUT but two subjects who were negative in RUT were diagnosed positive histopathologicaly. However they

were considered as positive because bacteria had been seen in histopathology. In addition all subjects were free of any intestinal metaplasia.

The results of the serological kits compared with the gold standard of histology and RUT are presented in table 1. In general all kits showed a good accuracy, however, the kit manufactured by Biohit showed the highest accuracy (88.0%).

Table 1: distribution of serological results among kits and their accuracy

Test	Number of seronegative (true negative = 43)	Number of seropositive (true positive = 40)	Number of equivocal result	General accuracy (%)
Biohit (Finland)	39	37	0	88.0
Diapro (Italy)	28	38	0	79.5
Genesis (UK)	28	33	2	73.5
IBL (Germany)	33	28	0	73.5

The sensitivity and specificity and positive and negative predictive value were calculated for the four kits which are shown in Table 2. HP IgG (DIA.PRO) showed the highest sensitivity (95.0%) compared to the other three kits. However, specificity of this kit was low in the studied population (65.1%). ELISA kit manufactured by Biohit was found to have higher accuracy in this setting. In addition, as seen in the table it has a higher positive and negative predictive value.

Table 2: Sensitivity, specificity, positive and negative predictive values and 95% CIs of serology kits

Test	Sensitivity % (95% CI)	Specificity % (95% CI)	positive predictive value % (95% CI)	negative predictive value % (95% CI)
Biohit (Finland)	92.5 (84.3 – 100.7)	90.7 (82.0 – 99.4)	90.2 (81.1 – 99.3)	92.9 (85.1 – 100.7)
Diapro (Italy)	95.0 (88.2 – 101.8)	65.1 (50.9 – 79.3)	71.7 (59.6 – 83.8)	93.3 (84.4 – 102.2)
Genesis (UK)	82.5 (70.7 – 94.3)	65.1 (50.9 – 79.3)	68.8 (55.7 – 81.9)	84.8 (72.6 – 97.0)
IBL (Germany)	70.0 (55.8 – 84.2)	76.7 (64.1 – 89.3)	73.7 (59.7 – 87.7)	73.3 (60.4 – 86.2)

Conclusion: Serological tests are a reliable test which can be used instead of invasive method of diagnosis. However these tests need to be validated prior to use in the epidemiological and the clinical investigations.

Appendix T: Consent letter for cases

Approval No .....

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Cases)
(Title of project: The influence of environmental factors on gastric cancer)

You are invited to participate in the study of gastric cancer and its related risk factors. We hope to discover the effect of diet, personal habit, and *Helicobacter pylori* Infection on gastric cancer. You were selected as a possible participant in this study because you have been diagnosed as someone with gastric cancer.

About study

Gastric cancer is the second most common malignancy in the world. At the same time it is the most common malignancy in the Iran and Ardabil Province as well. We are planning to compare various factors between those with and those without this malignancy, attempting to find the cause(s) of gastric cancer. This research may help us in reducing the occurrence of gastric cancer in this area and the other parts of the world.

For this purpose, we are asking you and several hundred other people to participate in a study that will help us have a better understanding of the causes of gastric cancer in Ardabil Province. If you decide to participate, the researcher and his associates will administer a questionnaire. The questionnaire will contain questions about your age, education, occupation, family history, personal habits and diet. Our trained personnel will collect 10 ml of your blood. The collected blood will be used to define blood grouping and any relationship with a particular organism, *Helicobacter pylori*. The collected blood samples will be used for two above-mentioned tests and it will not be used for further analysis or research. All of this process will be completed in about 1 hour. There are no expected risks from answering our questionnaire. You will feel a small needle stick in your arm while your blood will be collected.

Confidentiality and disclosure of information

The results of your participation, including all your answers to the questionnaire, all analysis or testing we do on your blood sample, will be kept strictly confidential and your identity will never be made public **except as required by law**. We will add your information to that of others, and it will not be possible to identify you as an individual, as all the information will be pooled. If you give us your permission by signing this document, we plan to discuss the pooled results with the health department in Iran. The study results may be published in related medical and health journals and presented in related seminars. In any publication, information will be provided in such a way that you cannot be identified.

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Cases)
(Title of project: The influence of environmental factors on gastric cancer)

Complaints may be directed to the Ardabil health center (director office), Azadi Shahrak, Sadsale Square (phone 0451 7713116, fax 0451 7713117).

Your consent

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales, University of Health and Medical Science of Ardabil and Hospital or my medical attendants. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later, Dr Farhad Pourfarzi (Tel: (Australia) 0417426799 and (Iran) 09114511861) will be happy to answer them.

You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the information provided above, you have decided to participate.

Signature of subject	**Signature of witness**
Please PRINT name	**Please PRINT name**
Date	**Nature of Witness**

Signature(s) of investigator(s)

Please PRINT Name

Appendix T (continued): Consent letter for cases

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Cases)
(Title of project: The influence of environmental factors on gastric cancer)
REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the University of New South Wales and University of Ardabil Health and Medical Science and Hospital or my medical attendants.

Signature **Date**

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Dr. Anna Whelan
Room 224, Second floor, Samuels Building
School of Public Health and Community Medicine
University of New South Wales
Sydney, NSW 2052, Australia
Telephone: +61(2) 9385 5393
Mobile: 0402 985532
Fax: +61(2) 9385 1036
E-mail: a.whelan@unsw.edu.au

Appendix U: Consent letter for controls

Approval No .....

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Controls)
(Title of project: The influence of environmental factors on gastric cancer)

You are invited to participate in the study of gastric cancer and its related risk factors. We hope to discover the effect of diet, personal habit, and *Helicobacter pylori* Infection on gastric cancer. You were selected as a possible participant in this study because you have been randomly chosen from your file in the health center as a sample from general population. We will compare you as a person without gastric cancer with those with gastric cancer.

About study

Gastric cancer is the second most common malignancy in the world. At the same time it is the most common malignancy in the Iran and Ardabil Province as well. We are planning to compare various factors between those with and those without this malignancy, attempting to find the cause(s) of gastric cancer. This research may help us in reducing the occurrence of gastric cancer in this area and the other parts of the world.

For this purpose, we are asking you and several hundred other people to participate in a study that will help us have a better understanding of the causes of gastric cancer in Ardabil Province. If you decide to participate, the researcher and his associates will administer a questionnaire. The questionnaire will contain questions about your age, education, occupation, family history, personal habits and diet. Our trained personnel will collect ten ml of your blood. The collected blood will be used to define blood grouping and any relationship with a particular organism, *Helicobacter pylori*. The collected blood samples will be used for two above-mentioned tests and it will not be used for further analysis or research. All of this process will be completed in about 1 hour. There are no expected risks from answering our questionnaire. You will feel a small needle stick in your arm while your blood will be collected.

Confidentiality and disclosure of information

The results of your participation, including all your answers to the questionnaire, all analysis or testing we do on your blood sample, will be kept strictly confidential and your identity will never be made public **except as required by law**. We will add your information to that of others, and it will not be possible to identify you as an individual, as all the information will be pooled. If you give us your permission by signing this document, we plan to discuss the pooled results with the health department in Iran. The study results may be published in related medical and health journals and presented in related seminars. In any publication, information will be provided in such a way that you cannot be identified.

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Controls)
(Title of project: The influence of environmental factors on gastric cancer)

Complaints may be directed to the Ardabil health center (director office), Azadi Shahrak, Sadsale Square (phone 0451 7713116, fax 0451 7713117).

Your consent

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales, University of Health and Medical Science of Ardabil and Hospital or my medical attendants. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later, Dr Farhad Pourfarzi (Tel: (Australia) 0417426799 and (Iran) 09114511861) will be happy to answer them.

You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the information provided above, you have decided to participate.

Signature of subject **Signature of witness**

Please PRINT name **Please PRINT name**

Date **Nature of Witness**

Signature(s) of investigator(s)

Please PRINT Name

Appendix U (continued): Consent letter for controls

THE UNIVERSITY OF NEW SOUTH WALES AND THE UNIVERSITY OF ARDABIL HEALTH AND MEDICAL SCIENCE
SUBJECT INFORMATION STATEMENT AND CONSENT FORM
(For Controls)
(Title of project: The influence of environmental factors on gastric cancer)
REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the University of New South Wales and University of Ardabil Health and Medical Science and Hospital or my medical attendants.

Signature **Date**

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Dr. Anna Whelan
Room 224, Second floor, Samuels Building
School of Public Health and Community Medicine
University of New South Wales
Sydney, NSW 2052, Australia
Telephone: +61(2) 9385 5393
Mobile: 0402 985532
Fax: +61(2) 9385 1036
E-mail: a.whelan@unsw.edu.au

Appendix V: Consent letter for cases in Persian

دانشگاه نیوساوت ولز استرالیا
دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل
مرکز تحقیقات بیماریهای گوارش و کبد

بیان موضوع و رضایت نامه
(مخصوص Case)

موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

بدینوسیله شما برای شرکت در مطالعه مربوط به کانسر معده و عوامل خطر مرتبط دعوت میشوید. ما امیدواریم که در این مطالعه تاثیر رژیم غذایی ، عادات شخصی ، شغل و عفونت باکتریایی هلیکوباکتر پیلوری را بر روی کانسر معده بررسی کنیم. شما با توجه به بیماری گوارشی که داشته اید بعنوان شرکت کننده در این مطالعه انتخاب شده اید.

موضوع مورد مطالعه:

در این مطالعه محقق و همکارانش برای شما یک پرسشنامه تکمیل خواهند کرد. این پرسشنامه شامل سئوالاتی در مورد سن شما ، تحصیلات ، شغل ، تاریخچه فامیلی ، عادات شخصی و رژیم غذایی تان خواهد بود. همینطور پرسنل دوره دیده ما از شما مقداری خون خواهند گرفت که جهت آزمایش عفونت گوارشی با هلیکو باکتر پیلوری و تعیین گروه خون مورد استفاده قرار خواهد گرفت. پیش بینی میشود تمام این مراحل کمتر از یکساعت از وقت شما را بگیرد.

امانت داری و عدم افشاء اسرار شخصی:

تمام اطلاعات جمع آوری شده در رابطه با این تحقیق کاملا محرمانه خواهد بود. اگر شما با امضا این رضایت نامه اجازه بدهید نتایج در مجلات بهداشتی و پزشکی منتشر خواهد شد و همینطور موضوع در سمینارهای مرتبط مطرح خواهد شد.

توضیحا اینکه اطلاعات بدست آمده به گونه ای مورد بحث قرار خواهد گرفت که اطلاعات شخصی و نام شما محفوظ بماند.

Appendix V (continued): Consent letter for cases in Persian

دانشگاه نیوساوت ولز استرالیا
دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل
مرکز تحقیقات بیماریهای گوارش و کبد

بیان موضوع و رضایت نامه

موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

نظرات خود را میتوانید به مرکز بهداشت اردبیل به آدرس اردبیل شهرک آزادی میدان شهید صدساله (دفترمدیریت) ارسال کنید و یا به تلفن ۰۴۵۱ ۷۷۱۳۱۱۶ و یا فاکس ۰۴۵۱ ۷۷۱۳۱۱۶۷ اطلاع داده شود..

رضایت نامه شما:

رضایت شما در مورد شرکت کردن یا نکردن در تحقیق هیچگونه تاثیری در ارتبـــاط شما با دانشگاه علوم پزشکی اردبیل و مراکز بهداشتی و درمانی و بیمارستان نخواهد داشت. اگر شما در این مطالعه شرکت نمائید آزاد خواهید بود که در هر مرحله این اجازه نامه را باطل و یا همکاری خود را در مطالعه ناتمام بگذارید.

در صورت وجود هرگونه سئوال در تمام مراحل دکتر پورفرضی خوشحال خواهد بود که در شماره تلفن های ۰۹۱۱۴۵۱۱۸۶۱ در ایران و یا ۰۰۶۱۴۱۷۴۲۶۷۹۹ در استرالیا جوابگوی سئوالات شما باشد. یک کپی از این رضایت نامه بشما داده خواهد شد.

امضا شما بیانگر این خواهد بود که شما اطلاعات بالا را خوانده اید و تصمیم به شرکت دارید.

امضا شرکت کننده	امضا شاهد
نام و نام خانوادگی	نام و نام خانوادگی
تاریخ	نسبت شاهد

امضا محقق

نام و نام خانوادگی

صفحه ۲ از ۳

Appendix V (continued): Consent letter for cases in Persian

دانشگاه نیوساوت ولز استرالیا
دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل
مرکز تحقیقات بیماریهای گوارش و کبد

بیان موضوع و رضایت نامه

موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

لغو رضایت نامه

من اینجا لغو رضایت نامه ام را برای شرکت در طرح تحقیق با عنوان توصیف شده در بالا اعلام میکنم و آگاهی دارم که این عمل هیچگونه تاثیری در رابطه من با دانشگاه نیوساوت ولز و یا دانشگاه علوم پزشکی اردبیل و مراکز بهداشتی و درمانی و بیمارستان نخواهد داشت.

_____ _____

امضا تاریخ

_____

نام و نام خانوادگی

این قسمت برای لغو رضایت نامه باید به آدرس زیر ارسال شود.

دکتر آنا ویلن
دانشگاه نیوساوت ولز – ساختمان ساموئل – دانشکده بهداشت عمومی و پزشکی اجتماعی
طبقه دوم اطاق ۲۲۴
استرالیا – سیدنی – کدپستی ۲۰۵۲
تلفن : ۶۱۲۹۳۸۵۵۳۹۳ +
موبایل : ۶۱۴۰۲۹۸۵۵۳۲ +
فاکس : ۶۱۲۹۳۸۵۱۰۳۶ +
پست الکترونیکی: a.whelan@unsw.edu.au

Appendix W: Consent letter for controls in Persian

دانشگاه نیوساوت ولز استرالیا
دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل
مرکز تحقیقات بیماریهای گوارش و کبد
بیان موضوع و رضایت نامه
(مخصوص Control)
موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

بدینوسیله شما برای شرکت در مطالعه مربوط به کانسر معده و عوامل خطر مرتبط دعوت میشوید. ما امیدواریم که در این مطالعه تاثیر رژیم غذایی ، عادات شخصی ، شغل و عفونت باکتریایی هلیکوباکتر پیلوری را بر روی کانسر معده بررسی کنیم. شما با توجه پرونده بهداشتی موجود بصورت تصادفی و بعنوان شرکت کننده ممکن در این مطالعه انتخاب شده اید.

موضوع مورد مطالعه:

در این مطالعه محقق و همکارانش برای شما یک پرسشنامه تکمیل خواهند کرد. این پرسشنامه شامل سئوالاتی در مورد سن شما ، تحصیلات ، شغل ، تاریخچه فامیلی ، عادات شخصی و رژیم غذایی تان خواهد بود. همینطور پرسنل دوره دیده ما از شما مقداری خون خواهند گرفت که جهت آزمایش عفونت گوارشی با هلیکو باکتر پیلوری و تعیین گروه خون مورد استفاده قرار خواهد گرفت. پیش بینی میشود تمام این مراحل کمتر از یکساعت از وقت شما را بگیرد.

امانت داری و عدم افشاء اسرار شخصی:

تمام اطلاعات جمع آوری شده در رابطه با این تحقیق کاملا محرمانه خواهد بود. اگر شما با امضا این رضایت نامه اجازه بدهید نتایج در مجلات بهداشتی و پزشکی منتشر خواهد شد و همینطور موضوع در سمینارهای مرتبط مطرح خواهد شد.
توضیحا اینکه اطلاعات بدست آمده به گونه ای مورد بحث قرار خواهد گرفت که اطلاعات شخصی و نام شما محفوظ بماند.

Appendix W (continued): Consent letter for controls in Persian

دانشگاه نیوساوت ولز و دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل و مرکز تحقیقات بیماریهای گوارش و کبد

بیان موضوع و رضایت نامه

موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

نظرات خود را میتواند به مرکز بهداشت اردبیل به آدرس اردبیل شهرک آزادی میدان شهید صدساله (دفترمدیریت) ارسال کنید و یا به تلفن ۷۷۱۳۱۱۶ ۰۴۵۱ و یا فاکس ۷۷۱۳۱۱۶۷ ۰۴۵۱ اطلاع داده شود..

رضایت نامه شما:

رضایت شما در مورد شرکت کردن یا نکردن در تحقیق هیچگونه تاثیری در ارتبـــاط شما با دانشگاه نیوساوت ولز و یا دانشگاه علوم پزشکی اردبیل مراکز بهداشتی و درمانی و بیمارستان نخواهد داشت. اگر شما شرکت نمائید آزاد خواهید بود که در هر مرحله این اجازه نامه را باطل و یا همکاری خود را در مطالعه ناتمام بگذارید.

در صورت وجود هرگونه سئوال در تمام مراحل دکتر پورفرضی خوشحال خواهد بود که در شماره تلفن های ۰۹۱۱۴۵۱۱۸۶۱ در ایران و یا ۰۰۶۱۴۱۷۴۲۶۷۹۹ در استرالیا جوابگوی سئوالات شما باشد. یک کپی از این رضایت نامه بشما داده خواهد شد.

امضا شما بیانگر این خواهد بود که شما اطلاعات بالا را خوانده اید و تصمیم به شرکت دارید.

_____	_____
امضا شرکت کننده	امضا شاهد
_____	_____
نام و نام خانوادگی	نام و نام خانوادگی
_____	_____
تاریخ	نسبت شاهد

_____

امضا محقق

_____

نام و نام خانوادگی

Appendix W (continued): Consent letter for controls in Persian

دانشگاه نیوساوت ولز و دانشگاه علوم پزشکی و خدمات بهداشتی، درمانی اردبیل و مرکز تحقیقات بیماریهای گوارش و کبد

بیان موضوع و رضایت نامه

موضوع پروژه : بررسی تاثیر عوامل محیطی در بروز کانسر معده

لغو رضایت نامه

من اینجا لغو رضایت نامه ام را برای شرکت در طرح تحقیق با عنوان توصیف شده در بالا اعلام میکنم و آگاهی دارم که این عمل هیچگونه تاثیری در رابطه من با دانشگاه نیوساوت ولز و یا دانشگاه علوم پزشکی اردبیل و مراکز بهداشتی و درمانی و بیمارستان نخواهد داشت.

_____ _____

امضا تاریخ

_____

نام و نام خانوادگی

این قسمت برای لغو رضایت نامه باید به آدرس زیر ارسال شود.

دکتر آنا ویلن

دانشگاه نیوساوت ولز – ساختمان ساموئل – دانشکده بهداشت عمومی و پزشکی اجتماعی

طبقه دوم اطاق ۲۲۴

استرالیا – سیدنی – کدپستی ۲۰۵۲

تلفن : ٦١٢٩٣٨٥٥٣٩٣ +

موبایل : ٦١٤٠٢٩٨٥٥٣٢ +

فاکس : ٦١٢٩٣٨٥١٠٣٦ +

پست الکترونیکی: a.whelan@unsw.edu.au