REVIEW

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# Risk Factors for Gastric Cancer: A Systematic Review

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## Abstract

**Objective:** Gastric cancer is one of the leading causes of death worldwide, with many influences contributing to the disease. The aim of this study was to identify the most important risk factors. **Methods:** This study was conducted in 2017 with a structured overview in the Science Directe, Scopus, PubMed, Cochrane, Web of Science (ISI) databases. In the first step, articles were extracted based on their titles and abstracts; the quality of 43 articles was evaluated using the STORBE tool. Inclusion criteria were studies carried out on human, English language (first step), year of the study and the study type (second step). **Results:** Finally, 1,381 articles were found, of which 1,269 were excluded in primary and secondary screening. In reviewing the references of the remaining 44 papers, 4 studies were added. Finally, 43 articles were selected for the quality assessment process. A total of 52 risk factors for gastric cancer were identified and classified into nine important categories: diet, lifestyle, genetic predisposition, family history, treatment and medical conditions, infections, demographic characteristics, occupational exposures and ionizing radiation'. **Conclusion:** Several environmental and genetic factors are involved in the development of gastric cancer. Regarding the role of changes in 'diet and lifestyle', considering appropriate nutrition and improving the level of education and awareness of people is vital for early diagnosis and timely treatment of this disease, especially in people with a family history and genetic predisposition.

**Keywords:** Risk factors- gastric- cancer

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## Introduction

Cancer is considered one of the leading causes of mortality in the world (Asombang and Kelly, 2012; Zali et al., 2011), and its burden is increasing in the world due to the cancer risk factors. Most of this burden occurs in developing countries; most of these cancers are preventable using knowledge and control programs based on the existing data (Jemal et al., 2011). According to evidence, 55% of the global burden of cancer in 2012 was related to six lung, breast, colorectal, prostate, gastric and liver cancers (Ferlay et al., 2015). Of them, gastric cancer is considered the most common type of upper gastrointestinal cancers (Krejs, 2010). According to Globocan 2012, this disease was the fifth most common cancer with the incidence of about one million new cases in the world. It has indicated a significant change in the incidence rate of this cancer in recent years. Concerning 723,100 deaths (8.8% of total cancer deaths), it is the third most common cause of cancer mortality in both sexes worldwide (Ferlay et al., 2015). This multifactorial disease, with both environmental and genetic factors having a role in it, is often diagnosed in the advanced stages of the disease (Carcas, 2014; Karimi et al., 2014) and its prevalence is more common in the lower socioeconomic classes, those with pernicious anemia and people with blood type A or a positive family history. In addition, high-fat, high-salt and high-nitrogen diets, a history of infection with Helicobacter pylori, EBV virus, genetic factors, pre-malignant stomach lesions and tobacco use have been reported as risk factors for gastric cancer (Gonzalez and Agudo, 2012; Dikshit et al., 2011; Matsuo et al., 2011; Nabizadeh et al., 2011; Hu et al., 2011; Babaei et al., 2010; Long et al., 2010). Therefore, different perspectives and strategies may be considered to prevent this disease.

The incidence of gastric cancer varies in different societies, with the highest incidence in East Asia, Central and South America and Eastern Europe, and the lowest incidence in Africa and North America (Nagini, 2012; Jemal et al., 2011). Therefore, although the incidence of gastric cancer is decreasing in some advanced societies due to appropriate interventions, it still remains a serious threat to health in developing countries (Khatoon et al., 2016). In this regard, since gastric cancer is a heterogeneous disease (Carcas, 2014) and since it is commonly diagnosed in its

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late stages (Lee and Derakhshan, 2013), it requires careful attention to its prevention and timely diagnosis because prevention is a vital approach in controlling this cancer and in reducing its mortality rates (Jia et al., 2016). However, due to the multidimensional nature of gastric cancer, prevention is subject to accurate identification of the risk factors and the underlying causes of this disease and the management of these factors (Yoon and Kim, 2015). According to several studies, recognizing and studying its risk factors can be an effective step in preventing and reducing the burden of this disease worldwide. Moreover, adequate knowledge of the risk factors for gastric cancer is essential to plan, monitor and evaluate national and regional plans for controlling this cancer. Therefore, the present study aimed to systematically identify and assess the risk factors for gastric cancer in 2017. Therefore, the main question of this study is to identify and investigate the risk factors for gastric cancer.

## Materials and Methods

*Study type and search strategy*

This article is a systematic review; articles related to the topic were selected and studied from texts published in authoritative scientific databases in June 2017. English-language articles on risk factors and prevention of gastric cancer were searched, collected and screened in three stages using the English keywords 'Gastric Cancer, Stomach Cancer, Gastric Neoplasm, Stomach Neoplasm, Prevention and Risk Factor (s)' in Web of Science (ISI), Scopus, Pub Med, Cochrane and Cience Directe databases using AND and OR operators to increase sensitivity (Table 1). It should be noted that no comprehensive systematic review had been conducted on the risk factors for gastric cancer (considering all the environmental and genetic factors).

*Quality Assessment and selection of articles*

All studies were evaluated by two researchers. In the first stage (title review), repeated and unrelated studies and studies on animals were excluded. In the next stage (abstract review), studies that were not relevant to the subject and purpose of the study, very old studies (before 2000) and the reviews were excluded. Finally, the quality of the remaining articles was evaluated using the STROBE tool. This tool included 22 sections: title and abstract, background/rationale, objectives, study design, setting (study place and time), participants (in two parts: methods and results), variables, data sources/ measurement, bias, study size, quantitative variables, statistical methods, descriptive data, outcome data, main results, other analyzes, key results, limitations, interpretation, generalizability and funding.

*Inclusion criteria*

The inclusion criteria in the first stage were English-language articles on the risk factors associated with gastric cancer (results related to risk factors) and on humans. In the second stage, the inclusion criteria included study year, study type and access to the full text of the studies. Finally in the third stage, studies which had good quality according to the STROBE checklist assessment criteria (7 = <score) were selected.

*Exclusion criteria*

Based on the above-mentioned checklist assessment criteria, studies with low quality were excluded. Accordingly, 5 studies were excluded after reviewing their full texts.

*Data extraction*

Extraction forms were used to extract final studies. The information on these forms included the title of the article, the first author's name, the study year, the study type, the sample size, the study place and the results of the study.

*Ethical considerations*

Ethical considerations were considered in the search for articles. Therefore, Open Access articles were used. Also the cost of purchase article in the study was paid by Shiraz University of Medical Sciences.

## Results

1,381 articles were found after searching the databases using the keywords. In the next step, repeated and unrelated studies and studies on animals (1,269) were excluded after the initial screening (title review), and 112 studies were entered into the secondary screening (abstract review) process. The screening criterion in this stage was the relevance to the study, articles published since 2000, and the exclusion of the reviews. At this stage, two researchers separately reviewed the abstracts of the articles. To improve the accuracy and quality of the study, the results of the evaluation at this stage were reviewed by two researchers in a meeting; a third assessment was carried out to resolve the differences. Following the consensus at this stage, it became clear that some of these papers were not a valid criterion to study the risk factors for gastric cancer, were not related to the study objectives, were very old (before 2000), and were reviews. Thus, the number of studies decreased to 53 articles. In searching full texts, it was tried to contact the authors of the articles which were not available (if the full texts were received, they would be included; otherwise, they would be excluded). Therefore, 44 studies were extracted. Four more related articles were extracted after reviewing the references of these papers (n=48). Then, the quality of the remaining 48 papers was reviewed. In order to assess the quality of

Table 1. The Search Strategy of the Research

| Search Strategy |
|---|
| Search Engines and Databases:, PubMed, ISI web of science, Scopus, Science Direct, Cochrane |
| Date: up to 2017, June, 5 |
| Strategy: #1 AND #2 , #1 AND #3, #1 AND #4, #1 AND #5 |
| #1 Risk factor? OR Prevention |
| #2 "Stomach cancer" |
| #3 "Gastric cancer" |
| #4 "Stomach neoplasm" |
| #5 "Gastric neoplasm" |

Table 2. The Characteristics of Articles Included in a Systematic Review

| First author's | Year | Type of study | Sample size | Place (Country) | Main results |
|---|---|---|---|---|---|
| Campanholo VM | 2014 | Case-control | 250 | Brazil | The risk of developing gastric cancer is associated with the Cox-2 genotype. Alcohol and smoking in patients with COX-2 -765G / G genotype increase the risk of gastric cancer. The 765G / G genotype and the 765G allele are associated with an increased risk of gastric cancer. |
| Zamani N | 2013 | Case-control | 837 | Iran | There was a positive correlation between the consumption of red meat and the risk of gastric cancer. The consumption of white meat at the highest quartile is associated with a reduction in the risk of gastric cancer compared to the lowest quartile. The case group (patients) had significantly higher mean age (older), mean weight (kg), BMI index, opium consumption, hot tea, daily energy intake (kilocalories), energy intake from lipids, consumption of meat, fat and oil than the control group. On the contrary, lower percentage of the case group used toothbrushes, were married and were Turkmen. Moreover, the case group received less energy from carbohydrates than the control group. |
| Chen B | 2011 | Meta-analysis | --- | --- | No association was observed between CDH1 polymorphisms and gastric cancer sensitivity. However, in the study of ethnicity subtypes, the CDH1-160C polymorphism may increase the risk of gastric cancer in Caucasians. |
| Sun CQ | 2013 | Case-control | 940 | China | Based on the results of logistics regression, smoking, consumption of hot food, alcoholic beverages, fried food, mouldy & leftover food, fast eating and family history of tumors were risk factors for gastric cancer. In contrast, the consumption of fresh fruits and vegetables, high education and high income and BMI≥25 were protective factors against gastric cancer. |
| Shen X | 2009 | Case-control | 503 | China | Results of logistic regression (a combination of environmental and genetic factors) showed that a family history of tumors, consumption of pickled foods, irregular dietary habits, no fruit consumption, genetic factors, genetic polymorphisms of CYPE1, NAT2 M1, NAT2 phenotype and XRCC1 194 were significantly associated with gastric cancer. |
| Wu Y | 2013 | A comparative study | 1024 | China | Risk factors associated with pre-cancerous gastric cancer lesions included family history of gastric cancer, frequent consumption of spicy foods, fried foods, smoked meats, fast eating, personal history of Helicobacter pylori, family history of oesophageal cancer, alcohol consumption, anxiety, depression, reflex, family and personal history of chronic gastritis, personal history of polyps and stomach ulcers, use of non-steroids, irregular food habits with no breakfast and consumption of foods rich in nitroso. |
| Nishimoto IN | 2002 | Case-control | 472 | Brazil | Non-white race, low level of education, low income were significantly higher in the case group (patients). Smoking (30 or more packets per year), low consumption of fruits and vegetables, socioeconomic status (low education and income) were identified as risk factors for gastric cancer. |
| Nomura AM | 2003 | Case-control | 746 | Hawaii | In both sexes, the case group (patients) had a higher calorie intake and lower intake of vitamins A, C, folic acid, B-carotene, totos non-steroid and vegetables (light and dark green vegetables and cruiferous) compared to the control group. Consumption of vegetables was inversely related to the risk of gastric cancer. The processed meat was mainly associated with the risk of gastric cancer in men. Smoking and family history of gastric cancer (parent or sibling) were significantly associated with gastric cancer. |
| Nemati A | 2012 | Case-control | 128 | Iran | Gastric cancer was associated with Helicobacter pylori infection, hot tea and low consumption of fresh fruits and vegetables. There was a significant reverse relationship between unsaturated fat and gastric cancer. |
| Nasır Binici D | 2009 | Case-control | 376 | Turkey | The consumption of yellow and green vegetables and fruits and refrigeration owners was significantly lower in the case group (patients) than in the control group. Conversely, cooking with boiled butter and bread baked by animal manure was higher in the case group. Yellow-green vegetables, boiled butter, and breads baked by animal manure consumptions and no refrigeration were found to be statistically significant etiologic factors for gastric carcinogenesis. |
| Bertuccio P | 2013 | Systematic review and meta-analysis | --- | --- | There was a significant difference between the risk of cancer and a healthy diet rich in fruits and vegetables or an unhealthy diet rich in meat, fats and starchy foods. A negative correlation was found between a healthy diet rich in fruits and vegetables and gastric cancer. A positive relationship was also observed between an unhealthy diet rich in meat, high fat, dairy foods, starchy foods and sweets and gastric cancer. |
| Icli F | 2011 | Case-control | 506 | Turkey | The case group (patients) had a significantly lower income and less municipal tap water than the case group; however, they smoked more and consumed more well/ village fountain water. In contrast, the control group significantly took more drugs for chronic diseases (especially antibiotics) and gall stones and consumed more fish, dried legumes (beans, peas and lentils) and tomato and cucumber in breakfast and bread. There was no significant difference in the amount and duration of smoking in both groups. However, severe smokers (two or more packets per day) were more in the patient group than in the control group, and smoking was identified as a risk factor for gastric cancer. Results of a multivariate analysis indicated that there was an inverse relationship between income level, bread consumption, frequency of coffee consumption and taking drugs for intestinal parasites and gastric cancer; however, a positive relationship was found between smoking (more than two packets per day) and gastric cancer. Moreover, animal-derived cooking oil was an independent risk factor for gastric cancer. Consumption of tomatoes and cucumbers at breakfast, fish consumption and history of gallstone and other chronic diseases was higher in the control group |

Table 2. Continued

| First author's | Year | Type of study | Sample size | Place (Country) | Main results |
|---|---|---|---|---|---|
| Lee SA | 2003 | Case-control | 268 | South Korea | Helicobacter pylori infection and high salt intake were significantly higher in the case group than in the control group. Salt consumption has a significant and positive relationship with the risk of gastric cancer ($p < 0.01$). The risk of gastric cancer decreased by the consumption of raw fruits and vegetables, clear broth, fruit and vegetable extracts and soybean curds. However, high consumption levels of salty fish and kimchi was associated with the risk of early gastric cancer. People with positive helicobacter pylori and high levels of salt were 10 times (10-fold) more at risk of early gastric cancer than those with no positive helicobacter pylori and lower levels of salt. Helicobacter pylori infection, family history of gastric cancer, intake of salt-fermented fish and kimchi and smoking were associated with an increased risk of gastric cancer. |
| Kim J | 2013 | Case-control | 974 | South Korea | Carriers of TLR4 rs10983755 A had a higher risk of intestinal-type gastric cancer than G-homozygotes.The genetic polymorphisms of innate immune genes were associated with the development of non-cardiac gastrointestinal intestinal-type gastric cancer. Infection with Helicobacter pylori was significantly more in the case group than in the control group; in addition, they smoked more. Moreover, they had lower education level and consumed less tap water ($p < 0.01$). |
| Cai M | 2017 | Case-control | 1273 | China | The percentage of smoking, alcohol consumption and Helicobacter pylori infection was significantly higher in the case group (gastric cancer patients) than in the control group. Helicobacter pylori infection, alcohol and smoking were associated with gastric cancer. Moreover, genotypes PLCE1 rs2274223, PSCA rs2294008, PSCA rs2976392, MUC1 rs4072037, SCL52A3 rs13042395 and PRKAA1 rs13361707 were related to gastric cancer. Genetic factors may be associated with some risk factors such as Helicobacter pylori infection, alcohol and smoking. |
| Sheu MJ | 2006 | Case-control | 607 | China | Patients with gastric cancer who were infected with Helicobacter Pylori infection had a higher rate of Lea+b- phenotype and a lower rate of Lea-b+ compared to the non-cancerous control group. Among patients infected with Helicobacter Pylori, the risk for gastric cancer was 3.15 times higher in patients with Lea+b- phenotype than in those with Lea-b+ phenotype. Lea+b- phenotype in a host infected with Helicobacter Pylori infection can be a risk factor for gastric carcinogenesis. |
| Zhan Z | 2013 | Case-control | 779 | China | Results of the Logistic regression showed that People who carried the AG/GG rs2237051 genotype in the exon region had an increased risk of gastric cancer compared to those with wild-type homozygous AA genotype. |
| Li H | 2012 | Case-control | 615 | China | MIF genotype was significantly higher in the case group (patients with non-cardiac gastric cancer) compared to the control group. Results of a multivariate analysis revealed that MIF-173 C and -794 non-CATT5 alleles along with Helicobacter pylori infection increased the risk of gastric cancer (Helicobacter pylori infection increased the risk of MIF polymorphism for susceptibility to gastric cancer). MIF (MIF: macrophage migration inhibitory factor) polymorphism was associated with susceptibility to non-cardiac gastric cancer. |
| Cho LY | 2012 | Case-control | 734 | South Korea | Genetic polymorphisms of CYP19A1 especially rs1004982, rs16964228, rs1902580 was associated with an increased risk of gastric cancer. |
| Yang JJ | 2012 | Case-control | 734 | South Korea | SRC rs6122566, rs6124914, c-MET rs41739, and CRK rs7208768 had a significant genetic effect on gastric cancer. The CRK rs7208768 allele increased the risk of gastric cancer at a low level of phytoestrogen. SRC, c-MET and CRK genes played a key role in gastric cancer. |
| Yaghoobi M | 2004 | Case-control | 88 | Iran | It seemed that cancer before the age of 50 was related to the family history. There was a significant relationship between the blood group O and the development of gastric cancer before the age of 50. |
| Zeng Z | 2016 | Meta-analysis | --- | --- | The proportion of HPV-positive GC (OR) was significantly higher in men than in women. Human papilloma virus could play a potential role in the pathogenesis of gastric cancer. This relationship was confirmed by the detection of HPV in pre-cancerous cells. |
| Nan HM | 2005 | Case-control | 1053 | South Korea | A reduction in the risk of gastric cancer was observed in people who consumed nonfermented alliums and nonfermented seafood. Kimchi and soybean pastes were associated with an increased risk of gastric cancer. A significant increase was observed in the risk of gastric cancer in people with CYP1A1 Ile / Val or Val / Val genotype. |
| Fang X | 2015 | Systematic review and meta-analysis | --- | --- | Total fruits and vegetables were inversely associated with a risk of gastric cancer. There was a positive correlation between the consumption of salty foods and gastric cancer. A strong influence of alcohol consumption (especially beer and liquor) was observed on the gastric cancer compared to non-drinkers. A 5-gram increase in dietary salt and a 10-gram increase in the consumption of alcohol increased the risk of gastric cancer by 12 and 5% respectively. In contrast, a 100-gram daily increase in the consumption of fruit reduced the risk of gastric cancer by 5%. Excessive consumption of alcohol and liquor was a risk factor for gastric cancer. The consumption of processed meat, salted fish, ham, bacon and sausage and high-fat diets were associated with an increased risk of gastric cancer. Vitamin C had an inverse relationship with gastric cancer. |
| Suwanrungruang K | 2008 | Case-control | 303 | Thailand | There was a significant correlation between smoking and gastric cancer. High consumption of vegetable oil and pig fat was significantly associated with gastric cancer. Consumption of salt, especially sea salt, fermented foods and family history were associated with gastric cancer. |
| Hcuch I | 2000 | Cohort | 572 | Norway | Age at Menarche was inversely associated with gastric cancer. The relationship between reproductive factors and the risk of gastric cancer should be considered separately for women before and after menopause. |

Table 2. Continued

| First author's | Year | Type of study | Sample size | Place (Country) | Main results |
|---|---|---|---|---|---|
| Lope v | 2016 | Case-control | 1421 | Spain | The case group (patients) was significantly older, had a higher BMI, less education and more children, younger children, more delayed menarche and longer lactation period than the control group. The menstrual and reproductive factors were related to gastric cancer; birth first at age was inversely related to gastric cancer (decreasing the risk by 31% for every five years increase in age at first birth). Findings showed the protective role of exogenous hormones in the risk of gastric cancer. |
| Sadjadi A | 2014 | Cohort | 928 | Iran | Opium, hookah, cigarettes as well as high salt intake, family history of gastric cancer, gastric ulcer, histological atrophic gastritis and intestinal metaplasia were related to the increased risk of gastric cancer. A multivariate analysis indicated that gastric cancer pre-cancerous lesions had a significant positive relationship with opium consumption and had a negative significant relationship with fruit and vegetable consumption. |
| Tran GD | 2005 | Cohort | 1452 | China | Age, male gender, pipe smoking, family history of oesophageal cancer and mouldy bread were positively related to the gastric cancer, while education, piped water and consumption of fresh fruits and eggs had a reverse relationship with cardiac gastric cancer. Age, gender, cigarette smoking, family history of oesophageal cancer were positively associated with non-cardiac gastric cancer; however, there was a reverse relationship between BMI and this cancer. |
| Gao Y | 2011 | Case-control | *2429 | China | A modest relationship was observed between non-cardiac gastric cancer and drinking beer. Consumption of scalding hot foods, salty meat, pickled and sour vegetables, frequent consumption of red meat and mouldy & leftover food increased the risk of cardiac and non-cardiac gastric cancer. On the contrary, consumption of fresh fruits and vegetables decreased this risk. The weekly consumption of liquor was associated with an increased risk of cardiac gastric cancer. Increased risk of cardiac and non-cardiac gastric cancer was observed in people with high levels of education (more than 10 years)! The family size of more than 4 was associated with an increased risk of cardiac gastric cancer. Corn decreased the risk of non-cardiac gastric cancer, and rice decreased the risk of cardiac gastric cancer. |
| Bonequi P | 2013 | Meta-analysis | --- | --- | Smoking, high consumption of red and processed meat, salt and alcohol were associated with a moderately increased risk of gastric cancer; conversely, high levels of education and consumption of fruits and vegetables modestly reduced gastric cancer. Polymorphism in several genes including IL1B, IL1RN, IL8, IL10, CDH1, MTHFR, PSCA, PLCE1, PTGER4, PRKAA1, and ZBTB20 was significantly associated with the risk of gastric cancer |
| Cai L | 2003 | Case-control | 603 | China | Results of a logistic regression showed that irregular dietary habits (over and fast eating), salty fish, salty vegetables, daily cigarette smoking and family history of cancer were risk factors for gastric cancer, while education level (years of study), consumption of fruits and vegetables and refrigerator were protective agents and had a negative correlation with cardiac gastric cancer. |
| Campos F | 2006 | Case-control | 647 | Columbia | Frying foods, cooking with coal, salting meals and low consumption of fruits and vegetables were associated with an increased risk of gastric cancer. The abundance of fruits and vegetables was associated with a reduction in the risk of gastric cancer. |
| Peleteiro B | 2011 | Case-control | 1071 | Portugal | Consumption of sodium-rich foods and salt intake were associated with an increased risk of stomach cancer. |
| Strumylaite L | 2006 | Case-control | 1516 | Lithuania | The case group (patients) had a significantly lower level of education, lived in villages and had a history of cancer in their parents. The risk of developing gastric cancer increased in people who consumed salt or salty foods. High intake of high-fat foods, smoked meat and smoked fish were associated with an increased risk of gastric cancer. |
| Take S | 2015 | Cohort | 1222 | Japan | Cancer in patients with successful H.pylori-positive treatment was significantly lower than that in the unsuccessful group. |
| Yu JY | 2013 | Meta-analysis | --- | --- | TNF-α 238 G/A polymorphism was significantly associated with an increase in the risk of gastric cancer. The analysis of race-based subgroups showed that the association between TNF-α 238 G/A polymorphism and gastric cancer was limited to Asiatic populations. |
| Ji J | 2006 | Cohort | 3.3 million men 2.8 million women | Sweden | Manual workers and farmers were at an increased risk of Stomach cancer. An increased risk of corpus cancer was observed for male miners and quarry workers, fishermen, construction workers, packers, loaders and warehouse workers, clerical workers and female assistant nurses and postal workers. For cardia cancer, significantly inc reased standardized incidence ratios were observed for gardeners, transport workers, bricklayers and chemical process workers among men. Cement and mineral dusts appear as major occupational risk factors. |
| Dong H | 2012 | Case-control | 1042 | China | The frequency of chromatid caused by gamma radiation was higher in the case group (patients) than in the control group. Sensitivity to gamma radiation was related to the age and cigarette status. Increased sensitivity to gamma radiation (by measuring chromatids) was associated with an increased risk of gastric cancer. The risk of gastric cancer in smokers with high sensitivity to gamma radiation was higher than that in never-smokers with high-sensitivity and smokers with low sensitivity. A higher percentage of the case group was significantly infected with Helicobacter pylori infection compared to the control group. Chromatid caused by gamma radiation in each cell was significantly higher in the case group than in the control group. |

Table 2. Continued

| First author's | Year | Type of study | Sample size | Place (Country) | Main results |
|---|---|---|---|---|---|
| Dong H | 2012 | Case-control | 1042 | China | The frequency of chromatid caused by gamma radiation was higher in the case group (patients) than in the control group. Sensitivity to gamma radiation was related to the age and cigarette status. Increased sensitivity to gamma radiation (by measuring chromatids) was associated with an increased risk of gastric cancer. The risk of gastric cancer in smokers with high sensitivity to gamma radiation was higher than that in never-smokers with high-sensitivity and smokers with low sensitivity. A higher percentage of the case group was significantly infected with Helicobacter pylori infection compared to the control group. Chromatid caused by gamma radiation in each cell was significantly higher in the case group than in the control group. |
| Singh S | 2014 | Systematic review and meta-analysis | --- | --- | Physical activity was associated with a reduction in the risk of cancer (a reverse relationship between gastric cancer and physical activity). The risk of gastric cancer was lower in people who had regular physically activity and were physically more active compared with other people with low physical activity. |
| Denova-Gutiérrez E | 2014 | Case-control | 726 | Mexico | Patients in the case group had lower levels of education (illiterate) than the control group. Moreover, alcohol consumption, Helicobacter pylori infection and energy intake (daily calories) were higher in the case group (P <0.001). The dietary pattern 1 (including fruits, vegetables and white meat in quintile 5 compared to quintile 1) was associated with a lower risk of gastric cancer. However, dietary patterns 3 (including high levels of refined grains and desserts in quintile 5 compared to quintile 1) was associated with a high risk of stomach cancer. |
| Lagergren J | 2012 | Cohort | 18912 | Sweden | A history of gastrectomy and gastric surgery (30 years after surgery) could increase the risk of gastric cancer as the level of gastric acid may decrease after surgery and might increase its sensitivity to Helicobacter Pylori. |
| Welling R | 2014 | Meta-analysis | --- | --- | Exposure to Chromium VI was associated with an increased risk of gastric cancer. |

*cases with cardiac and non-cardiac gastric cancer

the articles, each study was separately reviewed at least by two researchers (the STROBE evaluation checklist was used). Accordingly, only the articles which had been conducted appropriately based on the STORBE tool and those with scores 7 and more (out of 10) were included in the study. In addition, in the cases of differences between

Table 3. Risk Factors for Gastric Cancer

| No. | Risk factors | Subcategories | | |
|---|---|---|---|---|
| 1 | Diet | - Salt and salty diets | - Pickled vegetables and foodstuff | |
| | | - Spicy foods | - Fried foods | |
| | | - Meat (red, smoked and processed and salty) | - Irregular food habits | |
| | | - dairy foods | - Starchy foods and sweets | |
| | | - Salted and smoked fish fermented with salt | - Hot Foods | |
| | | - Hot Tea | - Lack of access to safe water | |
| | | - Mouldy and leftover bread and foods | - N-nitroso | |
| | | - Diet with limited vitamin C (vitamin C deficiency) | | |
| | | - Lack of intake or inadequate intake of fresh fruits and vegetables | | |
| | | -Rich foods | - Fat and oil | |
| | | - Refined grains | - Fermented foods | |
| 2 | Life style | -Alcohol | - Opium | |
| | | - Cigarette | - anxiety | |
| | | -Inactivity and limited physical activity - | - Hookah | |
| | | -Over and fast eating | - Get excessive daily energy | - Depression |
| 3 | Genetic talent | - Gene and Genotype Related to Gastric Cancer (The Role of Some Polymorphisms) | | |
| 4 | Family history | - Family history of the tumor | - Family history of gastric cancer | |
| 5 | Treatments and medical conditions | - History of Gastrectomy and gastric surgery | - Chronic atrophic gastritis | |
| | | - History of esophageal cancer (through the risk of pre-cancerous lesions) | | |
| | | - Blood type | - Intestinal metaplasia | |
| | | - Personal history of stomach polyp | - Reflex | - Personal |
| | | history of stomach ulcer | | |
| | | -Menstrual and reproductive factors | | |
| 6 | Infections | - Helicobacter pylori | | |
| | | - Human Papilloma Virus | | |
| 7 | Demographic characteristics | - Age | - Economic status and income level | |
| | | - Level of education (awareness and education) | - Sex | |
| | | - Race | - Place of residence | |
| 8 | Occupational exposure | - Cement | - Chrome | |
| | | - Mineral dust | | |
| 9 | Ionizing radiation | - Chromatid caused by gamma-radiation VI | | |

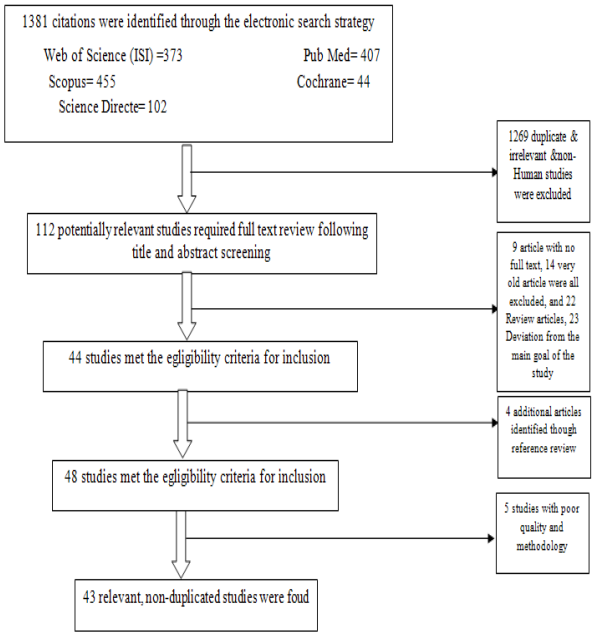


Figure 1. Flowchart for Article Screening

two researchers, a third party was asked to evaluate the quality. At this stage, 5 papers were excluded due to weak quality and methodology; the studies decreased to 43 papers. Concerning their desirability in the field of investigation, End Note software was used to extract the results (Figure 1).

Of these 43 papers (Cai et al., 2017; Lope et al., 2016; Zeng et al., 2016; Fang et al., 2015; Take et al., 2015; Welling et al., 2015; Companholo et al., 2014; Denova-Gutierrez et al., 2014; Sadjadi et al., 2014; Singh et al., 2014; Bertuccio et al., 2013; Bonequi et al., 2013; Kim et al., 2013; Yu et al., 2013; Zamani et al., 2013; Zhan et al., 2013; Sun et al., 2013; Wu et al., 2013; Cho et al., 2012; Dong et al., 2012; Li et al., 2012; Lagergren et al., 2012; Nemati et al., 2012; Yang et al., 2012; Chen et al., 2011; Gao et al., 2011; Icli et al., 2011; Peleteiro et al., 2011; Binici et al., 2009; Shen et al., 2009; Suwanrungruang et al., 2008; Campos et al., 2006; Ji and Hemminki, 2006; Sheu et al., 2006; Strumylaite et al., 2006; Nan et al., 2005; Tran et al., 2005; Yaghoobi et al., 2004; Cai et al., 2003; Lee et al., 2003; Nomura et al., 2003; Nishimoto et al., 2002; Hcuch and Kvale, 2000), 28 ones were case-control studies, 5 were meta-analysis, 3 were systematic reviews and meta-analysis, 6 were cohort studies and one was a comparative study. Of them, 9 studies were related to genetic factors, 30 were about environmental factors and 4 were related to a combination of these factors. Table 2 showed the main features of these articles.

According to the objectives of the present study and the examined studies, 52 risk factors for gastric cancer were identified and classified into nine main sections including diet (19 factors), lifestyle (9 factors), genetic predisposition, family history (2 factors), treatments and medical conditions (9 factors), infections (2 factors), demographic characteristics (6 factors), occupational exposure (3 factors) and ionizing radiation (1 factor including chromatids from gamma radiation) (Table 3).

## Discussion

The aim of this study was to identify the risk factors for gastric cancer. A total of 52 risk factors were identified in 9 sections. Some of these factors have been mentioned in numerous studies.

*Diet*

Diet and dietary habits are one of the most important factors in the incidence of gastric cancer (Amin et al., 2015; Daniyal et al., 2015; Bertuccio et al., 2013; Sadhier et al., 2013; Wu et al., 2013; Nemati et al., 2012; Compare et al., 2010; Krejs, 2010; Shen et al., 2009). Based on the results, one of the dietary risk factors mentioned in more studies (in comparison with other factors) was a salty diet which was referred to in eight studies. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has classified salt as one of the most important risk factors for gastric cancer. Fang et al. pointed to the fact that although sufficient amounts of salt were needed, excessive consumption might act as a gastric mucosa stimulant, leading to atrophic gastritis, increased DNA synthesis, and cell proliferation, thereby providing the basis for the incidence of gastric cancer (Fang et al., 2015). Evidence from previous studies showed that excessive salt intake was associated with the risk of gastric cancer. Estimates suggested that 24% of gastric cancer cases in the UK (31% in men and 12% in women) were associated with more than 6 grams of salt per day (Parkin, 2011a). Results of the meta-analysis of D'Elia et al. revealed that the risk of gastric cancer was higher in people with high salt intake than in those with low levels of consumption (D'Elia et al., 2012). Moreover, a study of cohort in Korea showed that people who were more likely to eat salty foods were at increased risk of gastric cancer (Kim J et al., 2010). In their systematic study, Ge et al. reported that high salt intake increased the risk of gastric cancer by 22% (Ge et al., 2012).

Lack of intake or inadequate intake of fresh fruit and vegetables is another risk factor for gastric cancer (reported in six studies). Nemati et al. reported in their study that low intake of fresh fruit and vegetables was a risk factor for gastric cancer (Nemati et al., 2012). In contrast, high intake of fruits and vegetables is associated with a decreased risk of gastric cancer (referred to in 9 studies) (Fang et al., 2015; Denova-Gutierrez et al., 2014; Sadjadi et al., 2014; Bonequi et al., 2013; Bertuccio et al., 2013; Sun et al., 2013; Gao et al., 2011; Campos et al., 2006; Lee et al., 2003;). In their case-control study in Shanghai, China, Epplein et al. found that there was an inverse relationship between the consumption of fruits and gastric cancer in male smokers (Epplein et al., 2010). The protective role of fruits and vegetables was observed in a Dutch cohort study with the consumption of over 156 g per day (Jarosz et al., 2011). Moreover, results of the meta-analysis of 22 cohort and case-control studies indicated that the consumption of fresh vegetables reduced the risk of gastric cancer (Kim et al., 2010). On the other hand, a cohort study showed that the risk of gastric cancer was lower in vegetarians than in meat-eaters (Key et al., 2014). Excessive consumption of red meat (Bonequi et al., 2013;

Zamani et al., 2013; Gao et al., 2011), smoked meat (Wu et al., 2013; Strumylaite et al., 2006), processed meat (Fang et al., 2015; Bonequi et al., 2013) and salty meat (Gao et al., 2011) were also reported as other risks factors of this cancer (mentioned in 8 studies). Various mechanisms may result in the production of carcinogenic compounds such as heterocyclic amines, N-nitroso compounds and polycyclic aromatic hydrocarbons which are produced during cooking or due to endogenous reactions (Ferguson, 2010).

*Lifestyle*

Lifestyle in fact refers to the interests, attitudes, behaviors, characteristics and behavioral orientations of a person, group or culture, and refers to the particular lifestyle of a person, group or community (Yassibas et al., 2012). In this study, 12 studies pointed to the role of smoking in the risk of gastric cancer (Cai et al., 2017; Campanholo et al., 2014; Sadjadi et al., 2014; Bonequi et al., 2013; Sun et al., 2013; Dong et al., 2012; Icli et al., 2011; Suwanrungruang et al., 2008; Nomura et al., 2003; Lee et al., 2003; Cai et al., 2003; Nishimoto et al., 2002). Smoking has devastating and irreversible effects on the gastric tissue which increases the risk of malignancy (Carlos et al., 2003). This agent is also known as a risk factor for gastric cancer by the IACR (International Agency for Research on Cancer) (IACR, 2017). Estimates showed that 22% of cases of gastric cancer in the UK were related to smoking (Parkin et al., 2011b). Icli, Kim and Cai et al. showed in their case control studies that the case group (patients) smoked significantly more than the control group (Cai et al., 2017; Kim et al., 2013; Icli et al., 2011). Alcoholic beverages are another risk factor reported in 7 studies (Cai et al., 2017; Fang et al., 2015; Campanholo et al., 2014; Denova-Gutierrez et al., 2014; Bonequi et al., 2013; Sun et al., 2013; Wu et al., 2013). In their meta-analysis, Ma et al. found that alcohol consumption could increase the risk of gastric cancer (odds ratio (OR) of 1.39) (Ma et al., 2017). On the other hand, Tramacere et al. reported a link between the risk of gastric cancer and alcohol consumption only in heavy (≥ 4 drinks per day) consumption (Tramacere et al., 2012). Moreover, results of the Bagnardi study showed that people who consume +50g alcohol per day were at 24% higher risks of gastric cancer compared to other people (who do not consume alcohol or consume less) (Bagnardi et al., 2015). Concerning how alcohol affects, it can be said that alcohol creates a cancer stimulating mechanism that involves a chronic inflammatory response to the toxic effects of ethanol metabolites and cytokines and thus the increased intake of nitrosamines (Bartsch and Nair, 2005).

*Genetic talent*

Genetic field which refers to the characteristics of a person at the genome level is one of the causes of human cancers. The main components of the genetic field are mutations and polymorphisms that affect by altering the expression amount or by changing the function of proteins (Dong et al., 2008). On the other hand, the genetic differences of individuals in each population are the main factors determining the susceptibility to various diseases from infectious and contagious diseases to non-communicable diseases such as cancer. When studying genetic factors which cause cancer, the focus is on mutations; however, no specific mutations have been known to predispose cancer for all types of cancer (Baroudi and Benammar-Elgaaied, 2016; Iourov et al., 2010). In addition, due to the multivariable nature of the cancer, there is a probability of the effect of genetic polymorphisms (the factor of individual differences in susceptibility to disease and response to drug therapy) along with other environmental and genetic factors in the sensitivity of the individuals to its incidence (Wang et al., 2012a; Wang et al., 2012b; Eussen et al., 2010; Johnson, 2009). In the present study, 13 studies pointed to the role of genetic factors in the incidence of cancer (Cai et al., 2017; Companholo et al., 2014; Bonequi et al., 2013; Kim et al., 2013; Zhan et al., 2013; Yu et al., 2013; Cho et al., 2012; Li et al., 2012; Yang et al., 2012; Chen et al., 2011; Shen et al., 2009; Sheu et al., 2006; Nan et al., 2005). So far, a relationship has been identified between gastric cancer and the various cytokine gene polymorphisms which are the agents of the immune system. Results of a meta-analysis on the correlation between cytokines gene polymorphisms and the risk of precancerous lesions suggested that some of them such as the IL1RNVNTR gene polymorphism were associated with the risk of these lesions (Peleteiro et al., 2010). Results of a study by Cho et al., (2012) revealed that the genetic polymorphism of CYP19A1, especially rs1004982 rs16964228 and rs1902580 was associated with an increased risk of gastric cancer. Moreover, Shen et al., (2009) stated in their study that genetic polymorphisms of CYPE1, NAT2 M1, NAT2 phenotype and XRCC1 194 were significantly associated with gastric cancer.

*Family history*

In this study, eight studies identified the family history of tumors and gastric cancer as a risk factor for gastric cancer; it can provide valuable information about the molecular genetic pathways of cancer and improve our understanding of the gastric carcinogenesis process (Choi and Kim, 2016). In this regard, Vanags et al. pointed to the first evidence of the effect of family and inheritance on the incidence of gastric cancer. As they reported in their study, the prevalence of gastric cancer was higher in people whose blood relatives (first-grade relatives) had stomach cancer (Vanags et al., 2012). Moreover, Saffaee et al. showed that the family history of gastric cancer, especially in first-grade relatives increased the risk of gastric cancer (Saffaee et al., 2012). Similarly, Yaghoobi et al., (2010) reported in their study that the risk of gastric cancer in people with a family history of this disease was 2-10 times higher than that of other people. In their study, Sadjadi et al., (2014) stated that the risk of gastric cancer was significantly higher in people with the family history of gastric cancer.

*Medical conditions and treatments*

It was reported in 7 studies that medical conditions and treatments were the effective factors in the incidence of gastric cancer. These factors included blood group (Yaghoobi et al., 2004), history of gastrectomy and

gastric surgeries (Lagergren et al., 2011), reflex (Wu et al., 2013), family history of gastric atrophy (Sadjadi et al., 2014; Wu et al., 2013), history of polyps (Wu et al., 2013) and gastric ulcer (Sadjadi et al., 2014; Wu et al., 2013), family history of esophageal cancer (Wu et al., 2013; Tran et al., 2005), intestinal metaplasia (Sadjadi et al., 2014) and some menstrual and reproductive factors (Lope et al., 2016; Hcuch and Kvale, 2000). Among the blood groups, A+ and A- were respectively the most and the least common groups in patients with gastric cancer. In a study of cohort, Edgren et al., (2010) found that people with blood type A were 20% more likely to have gastric cancer compared to those with blood type O. In contrast, Yaghoobi et al., (2004) reported in their research that there was a significant relationship between the blood type O and gastric cancer before the age of 50. According to a study by Lagergren et al., (2012) a history of gastrectomy and stomach surgery could also increase the risk of gastric cancer, as the level of gastric acid might decrease after surgery and increase its sensitivity to Helicobacter pylori. In addition, Sadjadi et al., (2014) stated in their study that gastric ulcers, histological atrophic gastritis and intestinal metaplasia were associated with an increased risk of gastric cancer. In their comparative study, Wu et al., (2013) reported that reflex, the family history, chronic atrophic gastritis, history of polyps, gastric ulcer and family history of esophageal cancers were the risk factors of precancerous lesions of gastric lesions. These lesions could pave the way for gastric cancer. Concerning menstrual and reproductive factors, the results of a Cohort study showed that gastric cancer was associated with the menopausal state and age (Green et al., 2012). Lope et al., (2016) reported in their study that the age of women at the first birth had an inverse relationship with gastric cancer. Freedman et al., (2007) found that the gastric cancer was associated with age of menopause, years of fertility (participants with less than 30 years of fertility were at increased risk compared with those with 30-36 years of fertility), years since menopause and intrauterine device use. In addition, Heuch and Kvale reported an inverse relationship between age at menarche and gastric cancer (Heuch and Kvale, 2000).

*Infections*

Infections including Helicobacter Pylori (alone or in combination with other factors such as some genetic factors, etc.) (Cai et al., 2017; Denova-Gutierrez et al., 2014; Wu et al., 2013; Dong et al., 2012; Nemati et al., 2012; Li et al., 2012; Lee et al., 2003) and the potential role of human papilloma virus are emerging risk factors (Zeng et al., 2016). Helicobacter Pylori infection which is one of the most common human infections inhabiting in the stomach is a gram-negative bacterium which affects more than 50% of the world's population (Chmiela and Gonciarz, 2017; Compare et al., 2010; Malaty, 2007). This infection can be created in childhood, but its prevalence is directly related to age, and most of the cases are asymptomatic. If the infection continues, it can lead to stomach ulcers and ultimately gastric cancer (Soltani et al., 2013) and hence it is considered a major risk factor for gastric cancer (Lu and Li, 2014). Estimates indicated that 32% of gastric cancer cases in the UK were related to Helicobacter pylori infection (Parkin, 2011c). Moreover, results of studies conducted by Kim et al., (2013), Cai et al., (2017), Dong et al., (2012) and Denova-Gutierrez et al., (2014) indicated that infection with Helicobacter pylori was significantly higher in the case (patient) group compared with the control group. In addition, a Cohort study of Take et al., (2015) showed that gastric cancer was significantly lower in patients with successful Helicobacter pylori treatment than in the unsuccessful group. Moreover, Human papilloma virus is causally related to tumorigenesis in several cancers. Results of a meta-analysis showed that human papilloma virus could play a potential role in the pathogenesis of gastric cancer (Zeng et al., 2016).

*Demographic characteristics*

In a study by Tran et al., (2005) age was positively associated with a risk of gastric cancer (cardiac and non-cardiac). Similarly, in two studies, the case group (patients) was significantly older than the control group (Lope et al., 2016; Zamani et al., 2013). Moreover, gender factor can also play a role in the biology of gastric cancer (Yao et al., 2002). Results of a study conducted by Tran et al. showed that male gender was positively associated with both cardiac and non-cardiac cancers (Tran et al., 2005). Yao et al., (2002) concluded that men were more likely to be exposed to proximal gastric cancer compared to women. In addition, in the Globocan 2012 report, age-standardized rates of stomach cancer was twice more in men than in women (12.8% and 5.7% respectively) (Ferlay et al., 2015).

The socioeconomic (income) and social (education level) status are other risk factors reported in 10 studies (Lope et al., 2016; Bonequi et al., 2013; Kim et al., 2013; Sun et al., 2013; Gao et al., 2011; Icli et al., 2011; Strumylaite et al., 2006; Tran et al., 2005; Cai et al., 2003; Nishimoto et al., 2002). Income and education which are the most important determinants of the social class are directly related to the level of health. This suggests that the social class has an impact on health (Moradilakeh and Vosooghmoghaddam, 2015). Many cancers are the result of environmental factors; socioeconomic status is one of the most important determinants of human health, and for most people, the health status is primarily determined by the rate of socioeconomic progress (Vettore et al., 2016; Eberle et al., 2010). Dar et al., (2013) as well as Torrescintron et al., (2012) found that there was an inverse relationship between the incidence of cancer and the social class. Concerning gastric cancer, although the socioeconomic status alone cannot be associated with the risk of this cancer, it can still be associated with some of its risk factors including Helicobacter Pylori and may indirectly play a role in the incidence of this cancer (Soltani et al., 2013; Nishimoto et al., 2002). In a study in Iran, higher incidence of gastric cancer was associated with lower annual income, lower annual expenditure on food, fruits and vegetables, higher unemployment rates and higher percentage of employment in agricultural and construction sectors (Mohebbi et al., 2011). Similarly, findings of studies by Nishimoto et al., (2002), Kim et al.,

(2013), Lope et al., (2016) and Strumylaite et al., (2006) showed that the case group (patients) had a significantly lower level of education than the control group. Results of a meta-analysis by Uthman et al., (2013) suggested that the risk of gastric cancer was higher in people with lower socioeconomic status, while a meta-analysis by Bonequi et al., (2013) showed that the high level of education was associated with a modest decrease in the rate gastric cancer.

*Occupational exposure*

One of the important factors determining the health of people in the community is job and occupational exposure (Moradilakeh and Vosooghmoghaddam, 2015; Saghier et al., 2013). In this study, two studies pointed to the impact of occupational exposure in increasing the risk of gastric cancer (Welling et al., 2015; Ji and Hemminki, 2006). In their study on the risk factors of occupational and socioeconomic factors, Ji and Hemminki, (2006) showed that manual workers and farmers were at higher risk for gastric cancer; cement and mineral dust were considered the most important occupational risk factors for gastric cancer. Similarly, results of a study by Welling et al., (2015) showed that the risk of gastric cancer in people with occupational exposure to chromium was 27% higher than that in others. In addition, a UK report showed that about 3% of cases of gastric cancer in men and 0.3% in women were related to occupational exposure (Bevan et al., 2012). Raj et al., (2003) referred to other occupational risk factors such as carpenters, steelworkers and tin miners. However, further studies are required to examine the role of occupational exposure in the development and incidence of gastric cancer.

*Ionizing radiation*

Ionizing radiation is another probable risk factor for gastric cancer (Lee and Derakhshan, 2013; Saghier et al., 2013) mentioned in one study (Dong et al., 2012). Among radiations, gamma radiation can play a potential role in the development of gastric cancer (Cogliano et al., 2011), with about 1% of reported cases of gastric cancer in the UK being associated with radiation (Parkin et al., 2011b). Dong et al. concluded in their research that the increased sensitivity to gamma rejection was associated with an increased risk of gastric cancer; people who were more sensitive to gamma radiation were at higher risk for gastric cancer (Dong et al., 2012).

Gastric cancer is one of multifactorial cancers, and many factors can play a role in its incidence. In the present study, several environmental and genetic factors were identified in the incidence of this cancer. It is suggested that health policy makers must take proper measures to prevent and reduce the burden of gastric cancer in order to improve nutrition and lifestyle and to promote community education and awareness. Concerning unchangeable nature of some risk factors, screening programs seem necessary for susceptible and at-risk people. Ultimately, despite many gaps that exist regarding the causes and risks of gastric cancer, studies with appropriate design are required to address some of the risk factors that may interfere with gastric cancer.

*Limitations of the study*

Considering the risk factors for gastric cancer in all types of gastric cancer are the limitation of the present study. Therefore, investigation of the risk factors for gastric cancer are suggested for each type of cancer (including cardia and non-cardia cancer) in future studies.

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*Conflict of interest*

The authors declare no conflicts of interest.

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## References

Amin MM, Kazemi A, Eskandari O, et al (2015). Geographical distribution of stomach cancer related to heavy metals in Kurdistan, Iran. *Int J Env Health Eng*, **4**, 1-5.

Asombang AW, Kelly P (2012). Gastric cancer in Africa: what do we know about incidence and risk factors?. *Trans R Soc Trop Med Hyg*, **106**, 69-74.

Babaei N, Poufarzi F, Yazdanbod A, et al (2010). Gastric cancer in Ardabil, iran- a review and update on cancer registry data. *Asian Pac J Cancer Prev*, **11**, 595 -9.

Bagnardi V, Rota M, Botteri E, et al (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*, **112**, 580-93.

Baroudi O, Benammar-Elgaaied A (2016). Involvement of genetic factors and lifestyle on the occurrence of colorectal and gastric cancer. *Crit Rev Oncol Hematol*, **107**, 72-81.

Bartsch H, Nair J (2005). Accumulation of lipid peroxidation-derived DNA lesions: potential lead markers for chemoprevention of inflammation-driven malignancies. *Mutat Res*, **591**, 34-44.

Bertuccio P, Rosato V, Andreano A, et al (2013). Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. *Ann Oncol*, **24**, 1450–8.

Bevan R, Young C, Holmes P, et al (2012). Occupational cancer in Britain. Gastrointestinal cancers: liver, oesophagus, pancreas and stomach. *Br J Cancer*, **107**, 33-40.

Binici DN, Timur K, Hakan D (2009). Dietary habits, demographical, and socio-economical risk factors of the newly diagnosed gastric cancers in the Eastern Anatolia region of Turkey: An endemic upper gastrointestinal cancer region. *Dig Dis Sci*, **54**, 2629–33.

Bonequi P, Meneses-González F, Correa P, Rabkin CS, Camargo MC (2013). Risk factors for gastric cancer in Latin-America: a meta-analysis. *Cancer Causes Control*, **24**, 217–31.

Cai L, Zheng ZL, Zhang ZF (2003). Risk factors for the gastric cardia cancer: a case-control study in Fujian Province. *World J Gastroenterol*, **9**, 214–8.

Cai M, Dai Sh, Chen W, et al (2017). Environmental factors, seven GWAS-identified susceptibility loci, and risk of gastric cancer and its precursors in a Chinese population. *Cancer Med,* **6**, 708–20.

Campanholo VM, Felipe AV, de Lima JM, et al (2014). -765 g>c

polymorphism of the cox-2 gene and gastric cancer risk in Brazilian population. *Arq Gastroenterol*, **51**, 79-83.
Campos F, Carrasquilla G, Koriyama C, et al (2006). Risk factors of gastric cancer specific for tumor location and histology in Cali, Colombia. *World J Gastroenterol*, **12**, 5772–9.
Carcas LP (2014). Gastric cancer review. J Carcinog, 13, 1-14.
Chen B, Zhou Y, Yang P, et al (2011). CDH1 _160C>A gene polymorphism is an ethnicity-dependent risk factor for gastric cancer. *Cytokine*, **55**, 266–73.
Cheng XJ, Lin JC, Tu SP (2016). Etiology and prevention of gastric cancer. *Gastrointest Tumors*, **3**, 25–36
Chmiela M, Gonciarz W (2017). Molecular mimicry in Helicobacter pylori infections. *World J Gastroenterol*, **23**, 3964–77.
Cho LY, Yang JJ, Ko KP, et al (2012). Genetic susceptibility factors on genes involved in the steroid hormone biosynthesis pathway and progesterone receptor for gastric cancer risk. *PLoS One*, **7**, e47603.
Choi YJ, Kim N (2016). Gastric cancer and family history. *Korean J Intern Med*, **31**, 1042-53.
Cogliano VJ, Baan R, Straif K, et al (2011). Preventable exposures associated with human cancers. *J Natl Cancer Inst*, **103**, 1827-39.
Compare D, Rocco A, Nardone G (2010). Risk factors in gastric cancer. *Eur Rev Med Pharmacol Sci*, **14**, 302-8.
Daniyal M, Ahmad S, Ahmad M, et al (2015). Risk factors and epidemiology of gastric cancer in Pakistan. *Asian Pac J Cancer Prev*, **16**, 4821-4.
Dar NA, Shah IA, Bhat GA, et al (2013). Socioeconomic status and esophageal squamous cell carcinoma risk in Kashmir India. *Cancer Sci*, **104**, 1231-6.
D'Elia L, Rossi G, Ippolito R, et al (2012). Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr*, **31**, 489–8.
Denova-Gutierrez E, Hernández-Ramírez RU, López-Carrillo L (2014). Dietary patterns and gastric cancer risk in Mexico. *Nutr Cancer*, **66**, 369-76.
Dikshit RP, Mathur G, Mhatre S, Yeole BB (2011). Epidemiological review of gastric cancer in India. *Indian J Med Paediatr Oncol*, **32**, 3-11.
Dong LM, Potter JD, White E, et al (2008). Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA*, **299**, 2423-36.
Dong H, Jin X, Hu J, et al (2012). High γ-radiation sensitivity is associated with increased gastric cancer risk in a Chinese Han population: A case-control analysis. *PLoS One*, **7**, e43625
Eberle A, Luttmann S, Foraita R, Pohlabeln H (2010). Socioeconomic inequalities in cancer incidence and mortality a spatial analysis in Bremen Germany. *J Public Health*, **18**, 227–35.
Edgren G, Hjalgrim H, Rostgaard K, et al (2010). Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. *Am J Epidemiol*, **172**, 1280-5.
Epplein M, Shu XO, Xiang YB, et al (2010). Fruit and vegetable consumption and risk of distal gastric cancer in the Shanghai Women's and Men's Health studies. *Am J Epidemiol*, **172**, 397-406.
Eussen SJ, Vollset SE, Hustad S, et al (2010). Vitamins B2 and B6 and genetic polymorphisms related to one-carbon metabolism as risk factors for gastric adenocarcinoma in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*, **19**, 28-38.
Fang X, Wei J, He X, et al (2015). Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Cancer*, **51**, 2820-32.
Ferguson LR (2010). Meat and cancer. *Meat Sci*, **84**, 308-13.
Ferlay J, Soerjomataram I, Dikshit R, et al (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in Globocan 2012. *Int J Cancer*, **136**, 359–86.
Freedman ND, Chow WH, Gao YT, et al (2007). Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut*, **56**, 1671-7.
Gao Y, Hu N, Han XY, et al (2011). Risk factors for esophageal and gastric cancers in Shanxi Province, China: A case-control study. *Cancer Epidemiol*, **35**, 91-9.
Ge S, Feng X, Shen L, et al (2012). Association between habitual dietary salt intake and risk of gastric cancer: A systematic review of observational studies. *Gastroenterol Res Pract*, 808120, doi:10.1155/2012/808120.
Gonzalez CA, Pera G, Agudo A, et al (2003). Smoking and the risk of gastric cancer in the European orosoective investigation into cancer and nutrition (EPIC). *Int J Cancer*, **107**, 629–34.
Gonzalez CA, Agudo A (2012). Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go. *Int J Cancer*, **130**, 745-53.
Green J, Roddam A, Pirie K, et al (2012). Reproductive factors and risk of oesophageal and gastric cancer in the million women study cohort. *Br J Cancer*, **106**, 210–6.
Hcuch I, Kvale G (2000). Menstrual and reproductive factors and risk of gastric cancer: a Norwegian cohort study. *Cancer Causes Control*, **11**, 869-74.
Hu J, La Vecchia C, Morrison H, Negri E, Mery L (2011). Salt, processed meat and the risk of cancer. *Eur J Cancer Prev*, **20**, 132-9.
Icli F, Akbulut H, Yalcin B, et al (2011). Education, economic status and other risk factors in gastric cancer: ''a case–control study of Turkish oncology group''. *Med Oncol*, **28**, 112–20.
International agency for research on cancer (2017). List of classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 116. Accessed January 2017.
Iourov IY, Vorsanova SG, Yurov YB (2010). Somatic genome variations in health and disease. *Curr Genomics*, **11**, 387-96.
Jarosz M, Sekula W, Rychlik E, Figurska K (2011). Impact of diet on long-term decline in gastric cancer incidence in Poland. *World J Gastroenterol*, **17**, 89-97.
Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.
Ji J, Hemminki K (2006). Socio-economic and occupational risk factors for gastric cancer: a cohort study in Sweden. *Eur J Cancer Prev*, **15**, 391-7.
Johnson AD (2009). Single-nucleotide polymorphism bioinformatics: a comprehensive review of resources. *Circ Cardiovasc Genet*, **2**, 530-6.
Karimi P, Islami F, Anandasabapathy Sh, D-Freedman F, Kamangar F (2014). Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev*, **23**, 700–13.
Key TJ, Appleby PN, Crowe FL, et al (2014). Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. *Am J Clin Nutr*, **100**, 378-85.
Khatoon J, Rai RP, Prasad KN (2016). Role of Helicobacter pylori in gastric cancer: Update. *World J Gastrointest Oncol*, **8**, 147-58.
Kim J, Park S, Nam BH (2010). Gastric cancer and salt preference: a population-based cohort study in Korea. *Am J Clin Nutr*, **91**, 1289–93.
Kim HJ, Lim SY, Lee JS, et al (2010). Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational

studies. *Cancer Sci*, **101**, 508-16.
Kim J, Cho YA, Choi IJ, et al (2013). Effects of polymorphisms of innate immunity genes and environmental factors on the risk of noncardia gastric cancer. *Cancer Res Treat*, **45**, 313-24.
Krejs GJ (2010). Gastric cancer: epidemiology and risk factors. *Dig Dis*, **28**, 600-3.
Lagergren J, Lindam A, Mason RM (2012). Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study. *Int J Cancer*, **131**, 1048-52.
Lee SA, Kang D, Shim KN, et al (2003). Effect of diet and helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol*, **13**, 162-8.
Lee YY, Derakhshan MH (2013). Environmental and lifestyle risk factors of gastric cancer. *Arch Iran Med*, **16**, 358-65.
Li H, Zang J, Wang P, et al (2012). Gastric cancer susceptibility in gastric cancer relatives: Attributable risks of Macrophage migration inhibitory factor promoter polymorphism and Helicobacter pylori. *Cytokine*, **60**, 346–51.
Long N, Moore MA, Chen W, et al (2010). Cancer epidemiology and control in north-East Asia - past, present and future. *Asian Pac J Cancer Prev*, **11**, 107-48.
Lope v, Fermandez Larrea N, Perez-Gomez B, et al (2016). Menstrual and reproductive factors and risk of gastric and colorectal cancer in Spain. *PLoS One*, **11**, e0164620.
Lu B, Li M (2014). Helicobacter pylori eradication for preventing gastric cancer. *World J Gastroenterol*, **20**, 5660–5.
Ma K, Baloch Z, He TT, Xia X (2017). Alcohol consumption and gastric cancer risk: A meta-analysis. *Med Sci Monit*, **23**, 238–46.
Malaty HM (2007). Epidemiology of helicobacter pylori infection. *Best Pract Res Clin Gastroenterol*, **21**, 205-14
Matsuo T, Ito M, Takata S, et al (2011). Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. *Helicobacter*, **16**, 415-9.
Mohebbi M, Wolfe R, Jolley D, et al (2011). The spatial distribution of esophageal and gastric cancer in Caspian region of Iran: An ecological analysis of diet and socio-economic influences. I*nt J Health Geogr*, **10**, 1-13.
Moradilakeh M, Vosooghmoghaddam A (2015). Health sector evolution plan in Iran; equity and sustainability concerns. *Int J Health Policy Manag*, **4**, 637-40.
Nabizadeh MM, Sima HR, Ghaffarzadehgan K, Taghizadeh Kermani A, Norouzi N (2011). Clinicopathological significance of macrophage migration inhibitory factor and its relation with p53 in gastriccancer. *J Gastrointest Cancer*, **42**, 5-10
Nagini S (2012). Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol*, **4**, 156-69.
Nan HM, Park JW, Song YJ, et al (2005). Kimchi and soybean pastes are risk factors of gastric cancer. *World J Gastroenterol*, **11**, 3175–81.
Nemati A, Mahdavi R, Naghizadeh Baghi A (2012). Case-control study of dietary pattern and other risk factors for gastric cancer. *Health Promot Perspect*, **2**, 20-7.
Nishimoto IN, Hamada GS, Kowalski LP, et al (2002). Risk factors for stomach cancer in Brazil (I): A CASE-COTROL study among non-Japanese Brazilians in sao Paulo. *Jpn J Clin Oncol*, **32**, 277-83.
Nomura AM, Hankin JH, Kolonel LN, et al (2003). Case–control study of diet and other risk factors for gastric cancer in Hawaii (United States). *Cancer Causes Control*, **14**, 547-58.
Parkin DM (2011a). 5.Cancers attributable to dietary factors in the UK in 2010. IV. Salt. *Br J Cancer*, **105**, 24-6.
Parkin DM, Boyd L, Walker LC (2011b). The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer*, **105**, 77-81.
Parkin DM (2011c). Cancers attributable to infection in the UK in 2010. *Br J Cancer*, **105**, 49-56.
Peleteiro B, Lunet N, Carrilho C, et al (2010). Association between cytokine gene polymorphisms and gastric precancerous lesions: systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **19**, 762-76.
Peleteiro B, Lopes C, Figueiredo C, Lunet N (2011). Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type. *Br J Cancer*, **104**, 198 – 207.
Raj A, Mayberry JF, Podas T (2003). Occupation and gastric cancer. *Postgrad Med J*, **79**, 252–8.
Sadjadi A, Derakhshan MH, Yazdanbod A, et al (2014). Neglected role of hookah and opium in gastric carcinogenesis: a cohort study on risk factors and attributable fractions. *Int J Cancer*, **134**, 181-8.
Safaee A, Moghimi-Dehkordi B, Fatemi SR, Maserat E, Zali MR (2012). Association of stomach cancer risk in individuals with family history of cancer. *Koomesh*, **13**, 264-8.
Saghier AA, Kabanja JH, Afreen S, Sagar M (2013) Gastric cancer: Environmental risk factors, treatment and prevention. *J Carcinogene Mutagene*, S14:008. doi: 10.4172/2157-2518. S14-008
Shen X, Zhang J, Yan Y, et al (2009). Analysis and estimates of the attributable risk for environmental and genetic risk factors in gastric cancer in a Chinese population. *J Toxicol Environ Health A*, **72**, 759-66.
Sheu MJ, Yang HB, Sheu BS, et al (2006). Erythrocyte Lewis (A+B-) host phenotype is a factor with familial clustering for increased risk of Helicobacter pylori -related non-cardiac gastric cancer. *J Gastroenterol Hepatol*, **21**, 1054-8.
Singh S, Varayil JE, Devanna S, et al (2014). Physical Activity is associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Cancer Prev Res (Phila)*, **7**, 12-22.
Soltani J, Jalil A, Soheila N, Sirous S (2013). Prevalence of helicobacter pylori infection in children, a population-based cross-sectional study in west Iran. *Iran J Pediatr*, **23**, 13-8.
Strumylaite L, Zickute J, Dudzevicius J, Dregval L (2006). Salt-preserved foods and risk of gastric cancer. *Medicina (Kaunas)*, **42**, 164-70.
Sun CQ, Chang YB, Cui LL, et al (2013). A Population-based case-control study on risk factors for gastric cardia cancer in rural areas of Linzhou. *Asian Pac J Cancer Prev*, **14**, 2897-901.
Suwanrungruang K, Sriamporn S, Wiangnon S, et al (2008). Lifestyle-related risk factors for stomach cancer in Northeast Thailan. *Asian Pac J Cancer Prev*, **9**, 71-5.
Take S, Mizuno M, Ishiki K, et al (2015). Seventeen-year effects of eradicating Helicobacter pylori on the prevention of gastric cancer in patients with peptic ulcer; a prospective cohort study. J *Gastroenterol*, **50**, 638-44.
Torrescintron M, Ortiz AP, Ortizortiz KJ, et al (2012). Using a socioeconomic position index to assess disparities in cancer incidence and mortality, Puerto Rico 1995-2004. *Prev Chronic Dis*, **9**, 212-8.
Tramacere I, Negri E, Pelucchi C, et al (2012). A metaanalysis on alcohol drinking and gastric cancer risk. *Ann Oncol*, **23**, 28-36.
Tran GD, Sun XD, Abnet CC, et al (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*, **113**, 456-63.
Uthman OA, Jadidi E, Moradi T (2013). Socioeconomic position and incidence of gastric cancer: a systematic review and meta-analysis. *J Epidemiol Community Health*, **67**, 854–60.
Vanags A, Strumfa I, Gardovskis A, et al (2012). The first

evidence of hereditary and familial gastric cancer in Latvia: Implications for prevention. *Medicina (Kaunas)*, **48**, 317-23.
Vettore MV, Faerstein E, Baker SR (2016). Social position, social ties and adult's oral health: 13-year cohort study. *J Dent,* **44**, 50-6.
Wang D, Zhou J, Wang T, et al (2012). Polymorphisms in MSH2 gene and risk of gastric cancer, and interactions with lifestyle factors in a Chinese population. *Cancer Epidemiol*, **36**, 171-6.
Wang J, Pang GS, Chong SS, Lee CG (2012). SNP web resources and their potential applications in personalized medicine. *Curr Drug Metab*, **13**, 978-90.
Welling R, Beaumont JJ, Petersen SJ, et al (2015). Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence. *Occup Environ Med*, **72**, 151-9.
Wu Y, Fan Y, Jiang Y, et al (2013). Analysis of risk factors associated with precancerous lesion of gastric cancer in patients from eastern China: A comparative study. *J Cancer Res Ther*, **9**, 205-9.
Yaghoobi M, Rakhshani N, Sadr F, et al (2004). Hereditary risk factors for the development of gastric cancer in younger patients. *BMC Gastroenterol*, **4**, doi: 10.1186/1471-230X-4-28.
Yaghoobi M, Bijarchi R, Narod SA (2010). Family history and the risk of gastric cancer. *Br J Cancer*, **102**, 237-42.
Yang JJ, Cho LY, Ko KP, et al (2012). Genetic susceptibility on CagA-interacting molecules and gene-environment interaction with phytoestrogens: A putative risk factor for gastric cancer. *PLoS One*, **7**, e31020.
Yao JC, Schnirer II, Reddy S, et al (2002). Effects of sex and racial/ethnic group on the pattern of gastric cancer localization. *J Gastric Cancer*, **5**, 208-12.
Yassibas E, Arslan P, Yalçin S (2012). Evaluation of dietary and life-style habits of patients with gastric cancer: a case-control study in Turkey. *Asian Pac J Cancer Prev*, **13**, 2291-7.
Yoon H, Kim N (2015). Diagnosis and management of high risk group for gastric cancer. *Gut Liver*, **9**, 5–17.
Yu JY, Li L, Ma H, et al (2013). Tumor necrosis factor-α 238 G/A polymorphism and gastric cancer risk: a meta-analysis. *Tumor Biol*, **34**, 3859–63.
Zali H, Rezaei-Tavirani M, Azodi M (2011). Gastric cancer: prevention, risk factors and treatment. *Gastroenterol Hepatol Bed Bench*, **4**, 175-85.
Zamani N, Hajifaraji M, Malekshah AF, et al (2013). A case-control study of the relationship between gastric cancer and meat consumption in Iran. *Arch Iran Med*, **16**, 324-9
Zeng Z, Luo EF, Zou LX, et al (2016). Human papillomavirus as a potential risk factor for gastric cancer: a meta-analysis of 1,917 cases. *Onco Targets Ther*, **9**, 7105–14.
Zhan Z, Chen Y, Wu J, et al (2013). Functional epidermal growth factor gene polymorphisms and risk of gastric cancer. *Oncol Lett*, **5**, 631–6.