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REVIEW

Epidemiologic Study of Gastric Cancer in Iran: A Systematic Review

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Background: Gastric cancer (GC) is one of the most common cancers in Iran. Knowledge of the epidemiology of the disease is essential in planning for prevention. So this study aimed to investigate the epidemiological aspects of gastric cancer including prevalence, incidence, mortality, and risk factors of Iran.

Methods: This systematic review study was based on articles published in both English and Persian languages during the years of 1970–2020 in international databases (PubMed, Web of Science, Scopus) and national databases (including SID, Magiran, and IranDoc). Papers related to epidemiological aspects of the disease including mortality, prevalence, incidence, and risk entered the final review.

Results: According to the studies, the minimum and maximum prevalence of gastric cancer in northwestern Iran (Ardabil) is between 0.2 and 100 per 100,000. Also, the death rate per 100,000 people ranged from 10.6 to 15.72 and the ASMR ranged from 4.2 to 32.2%. On the other hand, the incidence of GC was higher in men than in women (74.9 vs 4.6%). The GC risk ratio was 8-times higher in the elderly than in the other age groups (HR=8.0, 2.7–23.5). The incidence of gastric cancer in patients with *H. pylori* infection was 18-times and that of smokers 2-times higher than other populations. Low level of economic situation and food insecurity increased the odds of GC by 2.42- and 2.57-times, respectively. It should be noted that there was a direct relationship between consumption of processed red meat, dairy products, fruit juice, smoked and salty fish and legumes, strong and hot tea, and consumption of salt and gastric cancer incidence. There was also an inverse relationship between citrus consumption, fresh fruit, garlic, and gastric cancer. In addition, the mRNA genes are the most GC-related genes.

Conclusion: Given the high incidence of GC in Iran, changing lifestyle and decreasing consumption of preservatives in food, increasing consumption of fruits and vegetables, and improving the lifestyle can be effective in reducing the incidence of this disease.

Keywords: epidemiology, gastric cancer, Iran, risk factor, systematic review

Introduction

Gastric cancer is one of the most common cancers in the world,[1] with the highest incidence in the countries of Western Asia, Latin America, and the former Soviet Union. The incidence among Japanese, Korean, and Iranian males were 66.7, 64.6, and 30.4%, respectively.[2]

Gastric cancer, with an annual incidence of 7300, is one of the five most common cancers in Iranian men and women.[3] It is the first cause of cancer death in both genders in Iran as most patients are diagnosed at advanced stages of the disease.[4] Also, the 5-year survival rate in Iran is estimated to be less than 25%.[5]

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Helicobacter pylori, genetics, gastric ulcer, cigarettes, alcohol, chemical exposure, reflux, chronic anemia, gastric surgery, obesity, radiation, Epstein-Barr virus, gender, race, ethnicity, economic-social status, Type A blood groups, and food play an important role in the risk of gastric cancer.[6] Improving living standards and changing dietary habits as well as reducing *H. pylori* infection are very effective in reducing the incidence of gastric cancer.[7] Understanding the epidemiologic status of the disease and associated risk factors are essential for planning to diminish the disease, so this study aimed to investigate the epidemiological aspects of gastric cancer including prevalence, incidence, mortality, and risk factors of Iran.

Materials and Methods

Eligibility Criteria

In this study, original articles in the Iranian population which are published in Persian and English language, and published in national and international journals during the years of 1970–2020 with accessible full text, were reviewed.

Information Sources

Articles were selected from international databases (PubMed, Web of Science, Scopus) and national databases (SID, Magiran, and IranDoc).

Study Selection

Papers related to epidemiological aspects of the disease including mortality, prevalence, incidence, risk factors and genetics were reviewed. The results of the studies were presented in separate tables including mortality, prevalence, incidence, and risk factors of genetics.

It should be noted that studies lacking necessary information and links to the topic under discussion were excluded from the study.

Data Collection Process

Abstract and full text of articles, independently, by two relevant researchers, reviewing and listing information prepared for this purpose, including: author's name, year of publication, place of study, gender, sample size, age incidence, prevalence, and factors. The hazards of the genes in the articles and other cases were recorded in separate tables.

In order to increase the accuracy and reliability of the information and to reduce possible bias, the second review was performed by a second researcher and then registered by both researchers.

Summary Measures

Articles related to incidence, mortality, prevalence, risk factors, and genetics were selected in the period of 1970 to 2020 and the results are presented in separate tables.

Synthesis of Results

A total of 3461 articles were initially reviewed. It should be noted that 68 articles were not accessible to the full text, 1823 were duplicate, 822 were fully studied, 593 were irrelevant, and finally 229 were entered (Figure 1).

Results

Incidence

The incidence of gastric cancer in Iran increases due to increasing health level, lifestyle, awareness of early symptoms, and early diagnosis.[8] On the other hand, with growth of urbanization, the incidence and consequently the mortality rate will increase.[9] One of the causes of the rising incidence of gastric cancer in Iran is related to the diagnosis of end stage (non-curable stage=end stage) disease.[10,11]

Most patients are diagnosed in advanced stages and cannot be diagnosed at an early stage.[12] Studies in most parts of Iran indicate a high prevalence of this disease,[13] with the provinces located in the north and northwest as high risk areas and those located in southwestern Iran as medium risk areas.[14]

Epidemiological studies in Iran show a higher incidence of this disease in men than in women (74.9 vs 4.6), On the other hand, the sudden decrease in the incidence of disease over the age of 80 indicates the limitation of healthcare in this age group in Iran (Table 1). Increasing trend of GC is observed in the majority of men in Tehran province and most women in East Azerbaijan, Markazi, Tehran, and Yazd provinces.[15]

Non-use of refrigerator in some parts of the country, incorrect food preservation methods, high prevalence of *H. pylori*, and consumption of salty and nitrogen-containing foods, drinking hot tea, smoking and drinking contaminated water, smoking, and opium are important causes of gastric cancer in Iran.[16,17] In contrast, in the southern regions of Iran due to high consumption of dates as an antioxidant, the incidence of GC decreases.[15]

Mortality

In 2012, the rate of gastric cancer deaths in Iran was 11.4%, and it was reported as the second leading cause

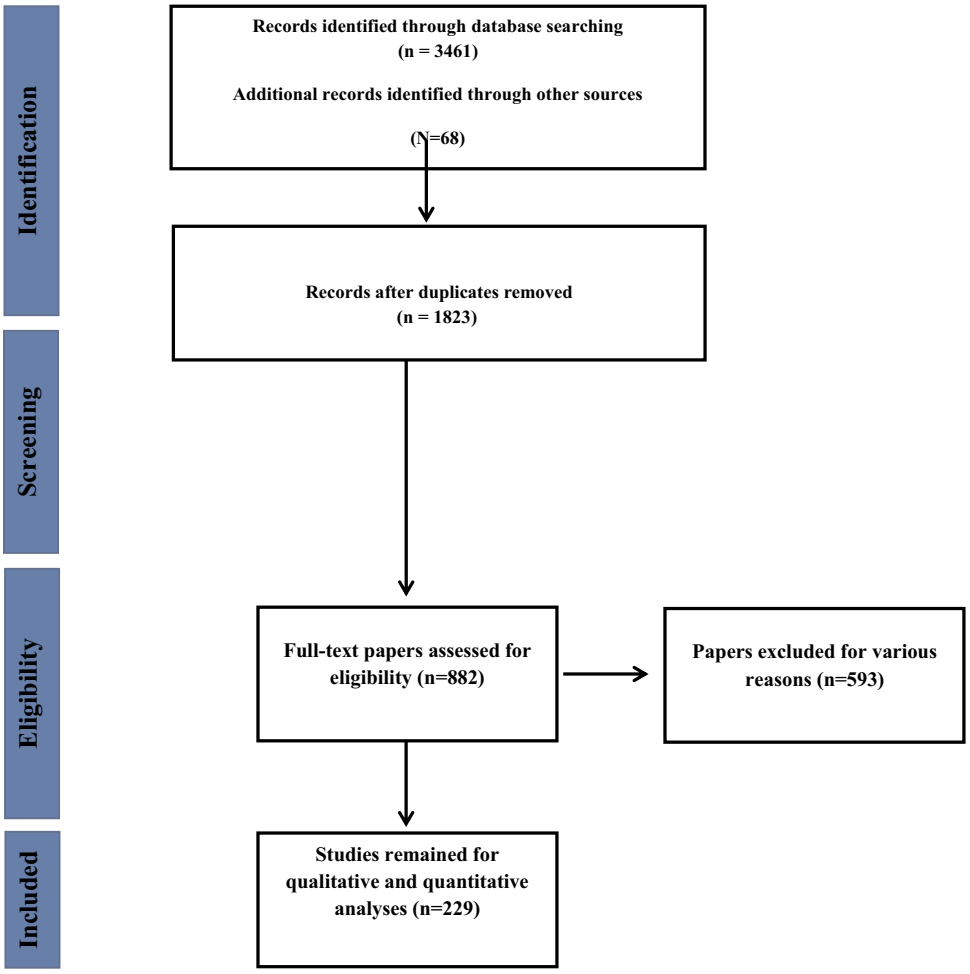

Figure 1 Flowchart of the included eligible studies in systematic review.

of death from common cancers in Iran. In fact, 15.5% of all cancer deaths in Iran are attributable to gastric cancer.[18,19] Currently, the highest mortality rate in Southwest and Central Asian countries is observable in Iran (19.9 per 100,000).[20]

GC is one of the most important causes of cancer death in Iran[21] which is due to individual or environmental factors, *H-Pylori* infection, and gastric atrophy in an Iranian population.[22] It should be noted that the incidence of GC mortality has decreased over the last five decades worldwide.[15] Thus, the number of deaths due to GC in Iranian military has been steady, which may be due to early diagnosis of this disease.[23] ASMR ranged from 4.2–32.2% (Table 2).

Prevalence

Gastric cancer is one of the most common cancers among Iranian men and women,[12] as it become the first common cancer among Iranian men.[9] The higher prevalence of males than females can be due to risky occupations such as agriculture, which may lead to exposure to nitrate-contaminated soil and chemical fertilizers as well as men's genetic susceptibility and, in turn, women's greater sensitivity to healthcare than men.[24,25] The minimum and maximum prevalence of gastric cancer in the previous studies was observed in northwestern Iran (Ardabil) between 0.2–100%. Other provinces were within the mentioned range (Table 3).

Risk Factors

H.pylori

In Iran, more than 80% of the population over 40 years have a history of *H. pylori* infection.[26,27] *H. pylori* is the most prominent risk factor for gastric cancer.[28] Age of infection seems to be very low in Iran. According to a study in southern Iran, 89% of 9-month-old children and 98% of 2-year-olds have been infected.[29] Studies have shown that *H. pylori* infection has an 18% higher

Table 1 Incidence Rate of Gastric Cancer in Iran

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
Ahmadi (2018)[72]	Chaharmahal and Bakhtiari	Retrospective	2918	
Aghaei (2013)[73]	Tehran	-	4463	-
Almasi (2015)[74]	All of Iran	Cross-sectional	35,171	7.1 15.1
Almasi (2016)[75]	All of Iran	Cross-sectional	9660	15.2
Amani (2015)[76]	Ardabil	Cross-sectional	1056	
Amoori (2014)[77]	Khuzestan	Retrospective	14,893	M=13.8 F= -
Amori (2017)[78]	All of Iran	Retrospective	301,055	M=15.02 F=7.05
Eishi (2016)[79]	Western Azerbaijan	Sectional & retrospective	2972	-
Babaei (2009)[80]	Ardabil	-	M=727 F=311	M=51.8 F=24.9
Babaei (2005)[81]	Semnan		M=936 F=796	M=36.9 F=14.8
Behnampour (2014)[65]	Golestan	Case-control	M=107 F=49	13.93
Jenab (2019)[82]	All of Iran	Ecological	4484	15.93
Hassanzade (2011)[83]	Fars	-	M=46 F=31	M=9.99 F=4.66
Chamanpara (2015)[84]	Golestan		1087	0.8–1.2
Haghdoost (2008)[85]	kerman	-	1112	
Haghigh (1971)[86]	Fars		182	
Khodadost (2015)[87]	Ardabil		857	
Sadjadi (2005)[88]	Golestan, Mazandaran, Kerman, Ardabil	-	51,000	M=26.1 F=11.1
Khazaei (2018)[89]	All of Iran	-	M=5398 F=2353	M=19.1 F=10
Masoompour (2016)[90]	Fars		-	M=5.56 F=11.21
Masoompour (2011)[91]	Fars	-	M=597 F=273	M=9.2 F=4.4
Kavousi (2015)[93]	All of Iran	Ecologic	M=20,882 F=8592	

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
Moradpour (2013)[94]	Isfahan	-	2001: Male=190 Female=104	2001: Male=9.9 Female=5.6
			2010: Male=272 Female=162	2010: Male=12.8 Female=7.9
			2015: Male=390 Female=250	2015: Male=14.7 Female=9.5
Khazaei (2016)[8]	All of Iran	Ecological	951,594	
Fateh (2013)[95]	Semnan	-	2240	15.52
Fararouei (2015)[96]	Kohgiluyeh and Boyer-Ahmad	Cohort	106	11.08
Keyghobadi (2015)[97]	Kerman	Cross-sectional	Male: 2004=671	Male: 2004=74.93
			2005=691	2005=71.43
			2006=915	2006=85.85
			2007=837	2007=79.2
			2008=1070	2008=104.22
			2009=1609	2009=131.61
			Female: 2004=572	Female: 2004=75.69
			2005=554	2005=61.79
			2006=765	2006=82.72
			2007=727	2007=78.88
			2008=851	2008=91.94
			2009=1333	2009=128.26
Faramarzi (2013)[98]	fars	Cross-sectional	Male=1652	Male=74.9
			Female=1072	Female=49.8
Mashhadi (2010)[99]	Sistan & Blouchestan	-	100	22%
Yasemi (2015)[14]	ILAM	Retrospective cross-sectional	307	
Mohebbi (2011)[100]	Mazandaran	ecologic	2665	Male=Ardabil=49.1
Yavari (2006)[101]	Ardabil and Kerman Iranian immigrants (BC Iranians)	-	-	Kerman=10.2
				Female=Ardabil=25.4
				Kerman=5.1
				BC Iranians=6.5

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
Vakili (2014)[102]	Yazd	Cross-sectional	4631	Female: 2005=3.3
				2006=4.8
				2007–4.2
				2008=4.6
				2009=4.3
				Male: 2005=7.2
				2006=8.2
				2007–7.5
				2008=9.4
				2009=8.5
Darabi (2016)[103]	All of Iran	-	Male: 2001=1105	Male: 2001=4.18
			2010=5192	2010=17.06
			Female: 2001=484	Female: 2001=2.41
			2010=2238	2010=8.85
Salehiniya (2016)[17]	Gilan, Mazandran and Golstan	Cross-sectional	Mazandran=2382	
			Gilan=1824	
			Golestan=709	
Talaiezadeh (2013)[104]	Khuzestan	Retrospective	Male=667 Female=322	Male=7.17 Female=2.34
Mohagheghi (2009)[31]	Tehran	-	Male=2119 Female=1033	Male=19.7 Female=10.0
Norouzinia (2012)[105]	Tehran, Khorasan, Lorestan, Mazandaran, Khuzestan, East Azarbaijan, Kurdestan, and Sistan and Baluchesta	Retrospective	140	Lorestan=10.24
				Tehran=5.01
				Tabriz=2.21
				Zahedan=2.31
				Sanandaj=7.07
				Sari=4.23
				Ahvaz=2.3
				Mashhad=4.48
Askarian (2014)[106]	Fars	-	1171	85.04
Sadjadi (2014)[16]	Ardabil	Cohort	928	
Norouzirad (2018)[107]	khozestan	Cross-sectional		M=10.88 F=3.29

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
Mohammadian (2016)[13]	Sistan and Baluchestan	-	255	Male: 2004=0–24 years=0
				25–29 years=1.06
				30–34 years=0
				35–39 years=1.48
				40–44 years=0
				45–49 years=2.0
				50–54 years=3.39
				55–59 years=18.42
				60–64 years=22.61
				65–69 years=11.19
				70–74 years=10.83
				75–79 years=7.47
				>80 years=0
				Female: 2004=0–29 years=0
				30–34 years=1.30
				35–39 years=1.53
				40–44 years=1.69
				45–49 years=6.88
				50–54 years=7.73
				55–74 years=0
				75–79 years=10.46
				>80 years=0
				2005: male=0–24 years=0
				25–29 years=0.97
				30–34 years=1.19
				35–39 years=4.08
				40–44 years=3.17
				45–49 years=0
				50–54 years=6.24

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
				55–59 years=20.33
				60–64 years=23.76
				65–69 years=10.29
				70–74 years=34.87
				75–79 years=20.63
				80–84 years=40.54
				>85 years=54.38
				Female: 2005=0-19 years=0
				20–24 years=0.82
				25–29 years=1.08
				30–34 years=0
				35–39 years=1.41
				40–44 years=0
				45–49 years=2.11
				50–54 years=2.37
				55–59 years=0
				60–64 years=4.44
				65–69 years=14.77
				70–74 years=5.66
				75–79 years=9.62
				>80 years=0
				2006: 0-24 years=0
				25–29 years=0.97
				30–39 years=0
				40–44 years=12.69
				45–49 years=3.68
				50–54 years=9.36
				55–59 years=6.78
				60–64 years=14.85

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
				65–69 years=17.15
				70–74 years=29.89
				80–84 years=40.54
				>85 years=0
				Female: 2006=0.14=0
				15–19 years=0.61
				20–24 years=0
				25–29 years=1.08
				30–34 years=0
				35–39 years=2.82
				40–44 years=3.11
				45–49 years=6.3
				50–54 years=4.74
				55–59 years=3.56
				60–64 years=13.33
				65–69 years=0
				70–74 years=11.32
				75–79 years=19.25
				80–84 years=0
				>85 years=29.52
				Male: 2007=0–9=0
				10–14 years=0.58
				15–19 years=0
				20–24 years=0.87
				25–39 years=0
				40–44 years=4.76
				45–49 years=3.68
				50–54 years=15.60
				55–59 years=13.55

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
				60–64 years=8.91
				70–74 years=39.85
				75–79 years=13.75
				80–84 years=60.80
				>85 years=0
				Female: 2007=0–44 years=0
				45–49 years=4.22
				50–54 years=2.37
				55–59 years=3.56
				60–64 years=0
				65–69 years=4.92
				70–74 years=5.66
				75–79 years=19.25
				80–>85 years=0
Najafi (2011)[108]	Kermanshah	-		1993=10.6
				1994=13.8
				1995=8.3
				1996=15.8
				1997=15.5
				1998=5.1
				1999=6.7
				2000=8.7
				2001=7.3
				2002=6.7
				2003=8.5
				2004=10.0
				2005=8.7
				2006=9.1
				2007=9.1

(*Continued*)

Table 1 (Continued).

First Author/ Year (Reference Number)	Province(District)	Type of Study	Sample-Size	ASR[a]
Mousavi (2009)[109]	All of Iran	-	2003–2004: Male=3088 Female=1166	2003–2004: Male=11.37 Female=5.20
			2004–2005: Male=3770 Female=1439	2004–2005: Male=13.74 Female=6.42
				2005–2006: Male=15.21 Female=6.89
Enayatrad (2014)[110]	All of Iran	-	Male: 2003=3088	Male: 2003=11.37
			2004=3770	2004=13.74
			2005=4212	2005=14.90
			2006=4299	2006=15.24
			2007=4485	2007=15.93
			2008=5398	2008=19.16
			2009=4891	2009=16.01
			Female: 2003=1166	Female: 2003=5.20
			2004=1440 2005=1624	2004=6.42 2005=6.74
			2006=167	2006=6.65
			2007=173	2007=7.38
			2008=2353	2008=10.0
			2009=1995	2009=7.78
Haidari (2012)[111]	All oflran	Cross-sectional	21,348	2000=2.8 (2.7–2.9)
				2001=2.6 (2.5–2.7)
				2002=4.6 (4.4–4.7)
				2003=7.1 (6.9–7.4)
				2004=7.9(7.7–8.1)
				2005=9.1(8.8–9.3)
Hosseintabar Marzoni (2015)[112]	Golestan	-	1122	
Rastaghi, Tohid (2019)[15]	All of Iran	Cross-sectional ecological	M=26,041 F=10,756	

Abbreviation: ASR, age standardized rate.

Table 2 The Death Rate of Gastric Cancer in Iran

First Author/ Year (Reference Number)	Province (District)	Type of Study	Sex	Sample-Size	Age-Standardized Mortality Rate per 100,000 (ASMR)	Death Number and Percent	Death per 100,000 People	RR (Relative Risk)	Cumulative Risk	Annual Mortality Rate/ 100,000
Ahmadipanah (2019)[113]	All provinces in Iran except for Tehran	Ecological study	MF	395,002	-	-	-	RR>1.75		
Aghamohammadl (2017)[114]	All provinces in Iran except for Tehran for 2006 & 2011 Isfahan & Tehran For 2007 & 2011	-	MF	2006–2011=1,172,278	-	-	Ministry of Health And Medical Education: 1385=12.20 1386=11.75 1387=11.31 1388=11.18 1389=11.06 1390=10.17 United Nations: 1385=15.05 1386=15.72 1387=15.47 1388=15.35 1389=14.80 1390=13.56	-		
Almasi (2016)[75]	All of Iran	Cross-sectional	MF	8247	12.9				1.44	
Amoori (2016)[115]	All of Iran	cross-sectional	MF	34,950	-	-	2006=11.20 2007=11.75 2008=11.31 2009=11.17 2010=11.06			
Babaei (2009)[80]	Ardabil	-	MF	M=465 F=206	M=32.2 F=16.3					
Pourhoseingholi (2013)[12]	All of Iran	-	MF							1995=1.68 1996=3.04 1997=3.38 1998=2.29 1999=5.70 2000=6.04 2001=6.47 2002=9.86 2003=9.67 2004=8.78
Hassan Zade (2011)[83]	Fars	-	MF	M=46 F=31	M=11.54 F=4.21					

(*Continued*)

Table 2 (Continued).

First Author/ Year (Reference Number)	Province (District)	Type of Study	Sex	Sample-Size	Age-Standardized Mortality Rate per 100,000 (ASMR)	Death Number and Percent	Death per 100,000 People	RR (Relative Risk)	Cumulative Risk	Annual Mortality Rate/ 100,000
Khorasani (2015)[116]	All of Iran	-	MF	M=5665 F=2582	-	M=18.8% F=11.11%				
Khazaei (2016)[8]	All of Iran	Ecological	MF	723,073			10.2			
Moradpour (2013)[94]	Isfahan	-	MF	2001: M=116 F=68 2010: M=183 F=97 2015: M=283 F=166	2001: M=7.9 f=4.2 2010: M=9.3 F=5.2 2015: M=10.6 F=6.3					
Sadjadi (2005)[88]	Golestan, Mazandaran, Kerman, Ardabil	-	MF	7843		6638				
Mousavi (2009)[109]	All of iran	-	MF				12.0			
Nalini (2018)[117]	Golestan	Cohort	MF	432		1.39%				
Mohammadi (2017)[118]	All of Iran	Cross-sectional	MF	514,550	M: 2006=16.7 2011=12.5 F: 2006=9.0 2011=6.9					

Note: Malekzadeh (2013),[119] cox hazard ratio =1.19.

chance of developing gastric cancer than those without the above-mentioned infection (OR=18.58; CI=1.63–221.520)

Cigarette Smoking and Alcohol

Studies show a 25.4% prevalence of smoking among Iranian adults. High smoking in Iran requires special attention as a risk factor for gastric cancer.[20] Furthermore, the prevalence of gastric cancer is directly related to the frequency of smoking.[9,30]

Some surveys in Iran reveal increasing prevalence of cigarette smoking at an early age and subsequently, rising trend of smoking-related cancers is similar to GC.[31] According to studies, smoking has a 2-fold chance of developing gastric cancer (OR=2.07; 1.14–3.75) (Table 4).

Opium has traditionally been used in many Southeast Asian countries, especially Iran.[32] It is noteworthy that tobacco use in the north and south of Iran is higher than in other parts of Iran.[33,34] According to some investigations in Iran, the chance of gastric cancer in smokers, especially opium consumers, is 3-times higher than those who did not consume (OR=3.0; 1.6–5.6) (Table 4). Because of the risk of hookah, especially for cancer, being less well known and the perception that tobacco is safer than cigarette smoking, the filtration of tobacco in water and the lower cost of hookah than smoking, the tendency for hookah smoking in Iran is increasing.[35] Studies show gastric cancer patients are 14% more likely to develop gastric cancer than others (OR=1.14; 0.29–4.42).

In the studies, alcohol consumption increased (OR=2.03; 0.44–9.31) times the chance of developing gastric cancer (Table 4). It should be noted that, due to the legal prohibition of alcohol consumption in Iran, under-reporting may be found in the studied investigations (Table 4).

Low Economic Level and Food Insecurity

In a survey in Iran, farmers and ranchers are considered to be high risk occupations in the prevention of gastric cancer. Findings suggest that gastric cancer is more common

Table 3 The Prevalence Rate Of Gastric Cancer In Iran

First Author/ Year (Reference Number)	Province (District)	Sample-Size	Sex	Prevalence
Ostadrahimi (2017)[120]	East-Azerbaijan	111	MF	36.9%
Islami (2004)[121]	Golestan	116	M	Gastric cardia adenocarcinoma=16% Gastric noncardia adenocarcinoma=16%
Eishi (2016)[79]	Western Azerbaijan	2972	MF	9.7%
Almasi (2015)[74]	All of Iran	35,171	MF	Male: Adenocarcinoma, Nos: 2003==68.39 2004=68.59 2005=65.17 2006=61.60 2007=59.30 2008=61.54
				Signet Ring Cell Carcinoma: 2003=9.42 2004=9.63 2005=9.90 2006=10.26 2007=11.95 2008=9.73
				Adenocarcinoma, Intestinaltype: 2003=6.80 2004=8.51 2005=10.83 2006=12.82 2007=13.94 2008=10.58
				Carcinoma, Diffuse Type: 2003=2.91 2004=3.37 2005=3.96 2006=4.07 2007=3.77 2008=4.87
				Carcinoma, Nos: 2003=2.75 2004=10.9 2005=0.28 2006=1.88 2007=0.91 2008=0.74
				Mucinous adenocarcinoma: 2003=1.91 2004=1.64 2005=2.11 2006=1.88 2007=1.87 2008=1.50 Mucin-Producing Adenocarcinoma: 2003=2.17
				2004=1.86 2005=2.04 2006=1.63 2007=1.56 2008=1.33
				F: Adenocarcinoma, Nos: =62.61 2004=65.60 2005=60.84 2006=55.33 2007=56.08 2008=58.90
				Signet Ring Cell Carcinoma: 2003=11.75 2004=12.44 2005=13.67 2006=13.60 2007=14.01 2008=12.07
				Adenocarcinoma, Intestinaltype: 2003=6.69 2004=6.46 2005=8.93 2006=12.98 2007=11.76 2008=9.14 Carcinoma, Diffuse Type: 2003=4.12 2004=3.75 2005=4.0 2006=5.61 2007=5.71 2008=5.10 Carcinoma, Nos: 2003=3.00 2004=1.46 2005=0.37 2006=1.81 2007=1.38 2008=0.72 Mucinous Adenocarcinoma:2003=1.72 2004=1.95 2005=2.59 2006=2.43 2007=1.67 2008=1.57 Mucin-Producing Adenocarcinoma: 2003=2.57 2004=1.74 2005=1.42 2006=1.37 2007=1.79 2008=1.23

(*Continued*)

Table 3 (Continued).

First Author/ Year (Reference Number)	Province (District)	Sample-Size	Sex	Prevalence
Amani (2015)[20]	Ardabil	1056	MF	Male: Ardabi)=73.1% Bilesvar=62.5 Germi=65.7 Kousar=88.9 Khalkhal=74.7 Meshkinshahr=74.3 Naming=74.4 Nir=83.9 Parsabad=84.2 Sarein=100 Other=68.2 Female: Ardabil=26.9 Bilesvar=37.5 Germi=34.3 Kousar=11.1 Khalkhal=25.3 Meshkinshahr=25.7 Naming=16.1 Nir=16.1 Parsabad=15.8 Sarein=0 Other=31.8%
Barekat (1971)[122]	Fars	M=131 F=42	MF	M=6.59 F=3.26
Bashash (2011)[123]	Ardabil	261	MF	M=70.9% F=28.7%
Pourhoseingholi (2008)[124]	Tehran	2674	MF	34.5%
Tabrizchee (1998)[125]	Kerman	2881	MF	M=9.70% F=6.30%
Tavoli (2007)[126]	Tehran	142	MF	30%
Hajmanoochehri (2013)[127]	Tehran	729	MF	64.3
Yasemi (2015)[14]	Ilam	307	MF	34.2%
Mohebbi (2008)[92]	Mazandaran	1663	MF	44.7%
Khademloo (2018)[128]	Mazandaran	1232		2008=20% 2009=23.8% 2010=20% 2011=19.5% 2012=16.7%
Tayebi (2012)[129]	Mazandaran	596	MF	4.1%
Nikfarjam (2014)[130]	Mashhad	495	MF	10.7%
Hashemi (2017)[131]	Mashhad,	30	MF	Intestinal type =90% Diffuse type =10%
Yazdizadeh (2005)[132]	Shiraz and the Tehran	1516	MF	Tehran=4% Shiraz=4%
Mehrabian (2010)[133]	–	3439	MF	
Kadivar (2016)[134]	Tehran	147	MF	32.6%
Karami (2014)[135]	Khuzestan	273	MF	1.4%
Moradpour (2013)[94]	Isfahan	2001: male=366 Female=209	MF	
		2010: male=582 female=357		
		2015: male=852 female=559		
Keyghobadi (2015)[97]	Kerman	789	MF	7.45%

(*Continued*)

Table 3 (Continued).

First Author/ Year (Reference Number)	Province (District)	Sample-Size	Sex	Prevalence
Mehrabani (2013)[9]	Fars	574	MF	<35age=8.9% 36–44=10.6% 45–54=20.7% 55–64=20.2% 65–75=27.7% >75=11.7%
Malekzadeh (2004)[22]	Ardabil	1011	MF	Erythema=68.1% Erosion=10.6 Friability=0.3 Nodularity=4.7 Polyp=0.9 Ulcer gastric=3.0 Ulcer (duodenal)=1.9 Atrophic mucosa=0.2 Raised/thickened area=0.3

in underclass and lower socioeconomic groups.[20,36] Increasing food insecurity in developing countries like Iran is due to lower economic levels and rising food costs. As the prevalence of food insecurity in Iran is estimated to be around 50%,[37] it is important to note that food insecurity is associated with low economic levels.[38] Because of the fat that income is an important factor to access adequate food in the community, people with higher economic status can have more choice in their diet.[39] For this reason, Iranian policymakers have emphasized the need to improve the economic status by the resistance economy.[40] Based on studies of low levels of economic and food insecurity, the odds of developing gastric cancer by 2.42- and 2.57-times is increasing, respectively (Table 4).

Family History and Blood Type A+

Family history is an important predictor of gastric cancer. Families with a history of gastric cancer have unique clinical manifestations.[41] Disease among young people of Iranian families with gastric cancer emphasize the role of family history in disease.[42] At the same time, family members experience similar environmental and lifestyle conditions. Family history of gastric cancer may not necessarily be related to genetic effects,[43] because environmental factors such as *H. pylori* infection play a more important role than genetic effects.[44] In the studied investigation, family history increased 2.12-times the chance of developing gastric cancer (Table 4). According to the studies, the prevalence of blood type A in an Iranian population is 30.25%.[27,45] In this survey, blood group A+ was 18.8% (Table 4).

Epstein-Barr Virus (EBV) and HTLV-1

EBV prevalence in gastric cancer patients ranged from 6.25–6.6% (Table 4). Studies in Iran show low prevalence of EBV among GC patients.[46] This is estimated to be between 3–6.66%.[47] The differences in EBV abundance reflect socio-economic, health and cultural differences in individuals,[48] hence the relationship between incidence of GC and EBV in different regions may reflect epidemiological and clinical-pathological factors, dietary habits and, ultimately, genetic differences.[49] Epidemiological studies indicate HTLV-1 is endemic in some part of Iran such as Khorasan, where HTLV are reported as around 0.77–1.7% in blood donors of different regions.[50] The prevalence of blood group A was 18.8% (Table 4).

Diet

Studies have shown an inverse relationship between citrus fruits, fresh fruits, garlic consumption, and gastric cancer (Table 4). Fruits are rich in antioxidants due to their fiber, vitamins, and minerals that can prevent initiation or progression of cancer.[51–53] Ascorbic acid and carotene in vegetables and fruits can eliminate nitrite.[54] Consuming some vegetables such as onions less than twice a week does not have any protective effect for this cancer (OR=1.28; 0.73–2.23). This is ambiguous, but may be related to the constituents of the soil (Table 4).

According to several studies, there is also a direct relationship between consumption of processed red meat, dairy products, fruit juice, smoked and salty fish, grain, strong and hot tea, and salt consumption, with a chance of incidence of gastric cancer (Table 4). Meats that are cooked at high temperatures such as frying and kebabs

Table 4 Risk Factors Associated with Gastric Cancer in Iran

First Author	Province	Sample-Size	Sex	Risk Factors	OR (Odds Ratio)
Islami (2004)[121]	Golestan	Gastric cardia=42 Gastric noncardia=40	m	Alcohol	
				Smoking	
				Nass	
				Opium (new user)	
				Opium (old user)	
				Four risk factors (alcohol, cigarette, nass or opium)	
Etemadi (2014)[42]	Ardabil, Guilan, Mazandaran, Kordestan, and West Azarbaijan	197	M&F	Blood Type A^+	-
				A^-	
				B^+	
				O^+	
				O–	
				AB^+	
				N/A Alcoholconsumpti on(yes)	
				Alcoholconsumpti on(NO)	
				Alcoholconsumpti on N/A	
				Smoking(heavy smoker)	
				Smoker	
				No smoking	
				N/A	
				Smoked food Low Moderate High N/A	
				Salty food Low Moderate High N/A	
				Nitrite Low Moderate High N/A	

(*Continued*)

Table 4 (Continued).

First Author	Province	Sample-Size	Sex	Risk Factors	OR (Odds Ratio)
				Hp Infection YES NO N/A	
Amoueian (2018)[47]	Khorasan Razavi	Case=56 Control=56	MF	Epstein–Barr virus (EBV)	-
Behnampour (2014)[65]	Golestan	M=107 F=49	MF	2.07 (1.14-3.75) Unwashed hands after defecation	History of smoking 2.61 (1.43-4.76)
				History of gastric cancer in first-degree relatives	2.46 (1.21–4.99)
				Other cancers (except for gastrointestinal cancer) in first-degree relatives	2.34 (0.92–5.96)
				Other cancers (except for gastrointestinal cancer) in second-degree relatives	4.38 (1.14-6.79)
				History of X-ray dye exposure	1.56 (0.85–2.85)
				History of CT scan encounter	2.32 (1.21-4.44)
				Charred flesh	1.65 (0.99-2.88)
				Irregular lunch-time	3.96 (0.96-6.32)
				Achalasia	76.97 (28.35-208 .92)
				Helicobacter pylori	18.58 (1.63- 211.52)
				Gastric ulcer	2.71 (1.15-6.36)
				Low mobility and lack of appropriate activities	4.78 (1.34–16.99)
Boreiri (2013)[136]	Ardabil	1011	MF	Age (years) 51–60	
				2:61	
				Family history	
				Positive smoking	
				History Histological finding (Atrophic gastritis)	
				(Intestinal metaplasia)	
				Gastric ulcer	
Paksereshtt (2011)[60]	Ardabil	Case=286 Control=304	MF	Total fat intake	1.33 (1.12–1.57)
				Carbohydrate (per 50 g)	1.00 (0.88– 1.13)
				Selenium (per 50 lg)	1.11 (0.80–1.54)
				Protein (per 10 g)	0.87 (0.76–0.99)
				Vitamin C (per 10 mg)	0.82 (0.76–0.87)
				Vitamin E (per 10 mg)	0.67 (0.44–1.03)
				0.37 (0.25–0.56)	Iron (per 5 mg)

(*Continued*)

Table 4 (Continued).

First Author	Province	Sample-Size	Sex	Risk Factors	OR (Odds Ratio)
				Zinc (per 5 mg)	0.47 (0.32–0.70)
				Energy (per 100 kcal)	0.99 (0.97–1.02)
Daneshi-Maskooni (2017)[36]	Tehran	Case=120 Control=120	MF	Food insecurity	2.57 (1.41- 4.66)
				Low economic level	2.42 (1.23- 4.76)
				Family history	1.98 (1.03- 3.80)
Safaee (2012)[43]	Tehran	746	MF	Family history	2.12 (1.72 – 3.28)
Ebrahim Tahaei (2011)[50]	Tehran	Case=201 Control=219	MF	HTLV-I antibodies	
Sadjadi (2014)[16]	Ardebil	928	MF	Family history	
				Cigarette smoking	
				Hookah smoking	
				Opium use	
				Salt intake >6 gr/day	
Moghimi-Dehkordi (2011)[137]	Tehran	FDR=113 SDR=180	MF	Having a family history	-
Zendehdel (2010)[138]	Tehran	808	MF	Family history	
Faghihloo (2014)[46]	Tehran	90	MF	Epstein-Barr virus (EBV)	
Mashhadi (2009)[56]	Sistan & Blouchestan	100	MF	Family history smoking and tobacco *H. pylori* infection	
Naghibzadeh Tahami (2014)[32]	Kerman	89	MF	Opium use Amount of daily use (>median)	3.0(1.6–5.6) 13.0 (4.2 -41.9)
				≤median	5.5 (1.0– 28.4)
				Duration (>median)	10.5 (2.4–46.1)
				≤median	6.8 (1.7–26.8)
				Cumulative use of Opium (>median)	9.2 (2.5–33.7)
				≤median	7.3 (1.2–43.0)
				Cigarette smoking Amount of daily use (>median)	1.4 (0.8–2.3) 1.9 (0.7–5.2)
				≤median	0.8 (0.2 –2.8)

(*Continued*)

Table 4 (Continued).

First Author	Province	Sample-Size	Sex	Risk Factors	OR (Odds Ratio)
				Duration (>median)	1.2 (0.3–4.2)
				≤median	1.5 (0.5–4.2)
				Cumulative use of smoking (>median)	2.4 (0.8–7.2)
				≤median	1.0 (0.2–3.8)
				Alcohol	1.2 (0.3–.4.4)
Pourfarzi (2004)[53]	Ardabil	Case=217 Control=394	MF	Tobacco Cigarette	0.90 (0.54–1.49) 0.87 (0.52–1.46)
				Hubble-bubble	1.14 (0.29–4.42)
				Current smoker	0.71 (0.41–1.25)
				Ex-smoker	1.40 (0.63–3.12)
				Age at start (years)<20 20–29 >30	0.54 (0.22–1.29) 1.28 (0.65–2.54) 0.75 (0.36–1.54)
				Average cigarette daily >20 <20	0.67 (0.35–1.30) 1.07 (0.57–1.99)
				Total smoking years–>35 21-35 <20	0.87 (0.45–1.70) 1.11 (0.51–2.46) 0.61 (0.26–1.47)
				Non-filter Filtered Both equally	0.99 (0.23–4.31) 0.86 (0.51–1.47) 0.71 (0.15–3.41)
				Smoke inhalation (Deeply) Moderately or slightly	0.51 (0.27–0.99) 1.90 (0.91–4.01)
				Alcohol	2.03 (0.44–9.31)
				Agriculture	1.96 (0.95–4.01)
				Manufacturing	0.80 (0.25–2.58)
				Construction	1.78 (0.67–4.76)
				Wholesale and retailer	1.32 (0.39–4.49)
				Raw vegetables (3 times/week) (1-2 times/week)	2.08 (1.13–3.82) 1.56 (0.89–2.73)
				Yellow-orange vegetables (3 times/week) 1–2	1.78 (0.81–3.89) 2.07 (1.15–3.70)
				Garlic (3 times/week) (1–2 times/week)	0.35 (0.13–0.95) 0.48 (0.25–0.91)

(*Continued*)

Table 4 (Continued).

First Author	Province	Sample-Size	Sex	Risk Factors	OR (Odds Ratio)
				Onion≥once per day (3–4 times/week)	0.34 (0.19–0.62) 1.28 (0.73–2.23)
				Fresh fruits≥3 times/week 1–2 times/week	0.89 (0.43–1.86) 0.44 (0.22–0.89)
				Citrus fruits (≥3 times/week) 1–2 times/week	0.31 (0.17–0.59) 0.18 (0.10–0.33)
				Juice≥ once/week	1.29 (0.73–2.29)
				Red meat≥ once/day 3–4/week	3.40 (1.79–6.46) 2.20 (1.26–3.85)
				Fresh fish≥ once/week	0.37 (0.19–0.70)
				Chicken≥once/day 3–4/week	0.93 (0.39–2.20) 1.40 (0.80–2.42)
				Dairy products ≥once/day 3–4/week	2.28 (1.23–4.22) 3.77 (1.92–7.42)
				Cheese≥once/day 3-4/week	1.16 (0.54–2.51) 1.00 (0.39–2.56)
				Smoked meats≥once/month	0.91 (0.40–2.09)
				Smoked fish≥once/month	1.09 (0.63–1.89)
				Processed meats≥once/month	1.14 (0.55–2.37)
				Salted fish≥once/month	1.08 (0.57–2.05)
				Pickled vegetables≥once/week	1.47 (0.84–2.58)
				Beans> once/week	1.04 (0.65–1.66)
				Sweets≥ once/week	0.70 (0.38–1.29)
				Seeds ≥once/month	0.96 (0.37–2.46)
				Salt preference	3.10 (1.88–5.10)
				Strength of tea	2.64 (1.45–4.80)
				Warmth of teaHot	2.85 (1.65–4.91

produce various types of carcinogens such as polycyclic aromatic hydrocarbons that cause gastric cancer.[56] Also, salt by stimulating and damaging gastric mucosal tissue is effective in the development of gastric cancer.[55] It should be noted that canned foods, spicy pickle, and animal protein are the dominant food among Iranian populations.-[56] Pickles are an important risk factor for gastric cancer due to their high salt and nitrate compounds. It should be noted that the ingredients of pickles vary from country to country due to the amount of vegetables, salt and acidity.[57]

Table 5 Genes Associated with Gastric Cancer in Iran

First Author(Year) (Reference Number)	Gene
Kulsom Ahmadi (2017)[139]	DNMT3B −579 G>T
Shirin Azarbarzin (2017)[140]	miR-383
Shirin Azarbarzin (2016)[67]	miR-299-5p
Fatemeh Azarkhazin (2017)[141]	*Casp8* and *Apaf1*
Ramin Azarhoush (2008)[142]	p53
Malek H. Asadi (2010)[143]	OCT4
Ahmad Ismaili (2015)[144]	IL-1B+3954
Saeed Mahboubi Aghdam (2014)[145]	oipA and iceA2
Hassan Akrami (2016)[146]	PI3K/Akt1 and p38MAPK
Sakineh Amoueian (2015)[147]	CD56, CD68, CD117 and CD1a
Mohammad Amini (2019)[148]	GHSR DNA
Mostafa Iranpour (2019)[149]	*PI3KCA*
Nooshin Ayremlou (2015)[150]	miR-107
Ali Basi (2012)[151]	HER2
Nader Bagheri (2013)[71]	IL-18 mRNA
Vahid Bagheri (2019)[152]	mRNA
Nader Bagheri (2014)[153]	TLR-4
Nader Bagheri (2018)[154]	MMP-3 and MMP-9
Seyedeh Zahra Bakhti (2015)[154]	vacA 3′-end
Gholam Basati (2017)[155]	PPARγ
Zeinab Basiri (2014)[156]	*vacA* d1
Ali Bahadori (2017)[157]	cagPAI and vacA
Ali Bahadori (2017)[158]	*cag*PAI and *vacA*
Bahari (2015)[159]	*MIR17HG*
Mohammadreza Beheshtizadeh (2017)[160]	*G3BP1* and *VEZT*
Shahab Bohlooli (2012)[161]	KYSE30
Modjtaba Emadi Baygi (2012)[162]	*MTDH*
Sanaz Savabkar (2013)[163]	PD-1.5C/T (rs2227981, +7785)
Ghasem Janbabai (2015)[164]	*EGFR, ErbB2* and *MET*
Naser Jafargholizadeh (2017)[165]	*LC3* mRNA
Fereshteh Jafar (2008)[166]	vacA
Milad Javanbakht (2017)[167]	Oct-4 and MUC5AC
Fereshteh Jeivad (2012)[168]	tyrosine kinas
Mina Rezaee Cherati (2017)[169]	N58E59
Nasim Hafezi (2015)[170]	CD1d
Maryam Habibzadeh (2017)[171]	TLR2-196 to -174 ins/del, Arg753Gln and Arg677Trp
Afshin Habibi (2015)[172]	CD34
Asghar Hosseinzadeh (2016)[173]	mRNA
N. R. Hussein (2010)[174]	dupA
Mohammad Reza Haghshenas (2009)[175]	(IL)-18
Khatoon Heidari (2017)[176]	*BabA2, Hpa*
Abdulkuddous Heydari-Mehrabadi (2018)[177]	*ASIC1* and *IL-6*
Fatemeh Khatami (2009)[178]	DNA methyltransferase 1
Malihea Khaleghian (2015)[179]	C-MYC
Mitra Khalili (2015)[180]	miR-302, miR-145, SOX2, c-MYC, and P21
Mitra Khalili (2012)[181]	Mir-302b
Maryam Daneshpour (2018)[182]	miR-106a and let-7a
Zohreh Salehi (2017)[183]	miRNAs
Sabahi (2010)[184]	*MDR1*
ahra Sedarat (2018)[185]	HopQ and SabA
Negar Souod (2013)[186]	cagA and vacA
Reza Safaralizadeh (2017)[187]	miR-216a and miR-217
Amin Talebi Bezmin Abadi (2011)[188]	*cagA, homA*, and *homB*
Amin Talebi Bezmin Abadi (2012)[189]	dupA
Amin Talebi Bezmin Abadi (2013)[190]	babA2
Saeid Abediankenari (2013)[191]	EGFR
Esmat Abdi (2016)[192]	*babA2*
Rana Ezzeddini (2019)[193]	HIF-1α and SREBP-1c
Hosein Effatpanah (2015)[194]	mir-21 and mir-221
Akbar Oghalaie (2016)[195]	HP0175
Hossein Dabiri (2017)[196]	vacA, cagA, cagE, oipA, iceA, babA2 and babB
Dardaei Alghalandis (2009)[197]	CEA
L. Dardaei (2011)[198]	CEA, CK20, TFF1 and MUC2
Mehdi Nikbakht Dastjerdi (2015)[199]	PLC/PRF5
Masoumeh Douraghi (2009)[200]	*vacA* intermediate region *cagA* Anti-VacA
Mahboobeh Razmkhah (2013)[201]	SDF-1alpha G801A
Masoumeh Rostami (2013)[202]	H-ras
Ali Zare (2018)[203]	miR-335, miR-124, miR-218 and miR-484
Ali Zare (2019)[204]	miR-155-5p, miR-15a, miR-15b, and miR-186
Seiran Zandi (2018)[205]	sirt2
Alireza Sadjadi (2013)[206]	Serum Ghrelin
Iraj Saadat (2001)[207]	GSTM1 and GSTT1
Azam Soleimani (2016)[208]	miR-146a
Sareh Sohrabi (2017)[209]	PTEN and CDKN1C/p57kip2
Zahra Shahhoseini (2016)[210]	rs3130932
Samaneh Saberi (2012)[211]	MTHFR C677T
Zeinab Imani-Saber (2015)[212]	PML
Mohammad Masoudi (2009)[213]	GSTM1 GSTO2 GSTT1
Mehdi Moghanibashi (2012)[214]	TFF1
Meysam Moghbeli (2014)[215]	hMLH1 and E-Cadherin
Meysam Moghbeli (2019)[216]	ErbB1 and ErbB3
Sharareh Mokmeli (2016)[217]	ERCC1 C8092A
Zahra Malek-Hosseini (2015)[218]	IL-17A
Maryam Mansoori (2015)[219]	ABCB1

(*Continued*)

Table 5 (Continued).

(*Continued*)

Table 5 (Continued).

First Author(Year) (Reference Number)	Gene
Seyedeh Habibeh Mirmajidi (2015)[220]	*bcl2*
Rouhallah Najjar Sadeghi (2010)[221]	p53
Nowruz Najafzadeh (2015)[222]	CD44
Seyedeh Elham Norollahi (2017)[223]	WNT16
Mina Noormohammad (2016)[224]	miR-222
Parvaneh Nikpour (2013)[225]	MSI1
Parvaneh Nikpour (2014)[226]	EYA1
Parvaneh Nikpour (2012)[227]	ZFX
Mohammadreza Hajjari (2013)[228]	SUZ12
Akbar Hedayatizadeh-Omran (2018)[229]	P53
Abolghasem Hadinia (2007)[230]	*CTLA-4*
Alireza Andalib (2013)[231]	anti-CCR5, anti-CXCR3, anti-CCR3 and anti-CCR4
Roya Kishani Farahani (2015)[232]	IGF-1
Shirin Farjadian (2018)[233]	HLA-G
Mahdie Hemati (2019)[234]	Q192R and L55M
Sahar Honarmand-Jahromy (2015)[235]	CagA EPIYA-C
Saeid Latifi-Navid (2013)[236]	*vacA* d1/-i1
Batool Mottaghi (2016)[236]	vacA i
M. Motovali-Bashi (2015)[238]	GT-repeat
Mojtahedi (2010)[239]	*p53*
Maedeh Mohsenzadeh (2017)[240]	*RAR-β*
Saghar Mohammadi (2017)[241]	SIRT3
Farideh Mohammadian (2016)[242]	miR-18a, miR-21 and miR-221
Ashraf Mohamadkhani (2013)[243]	Pepsinogen I, Pepsinogen II
Mohammadi (2015)[244]	mRNA
Seyed-Hamid Madani (2015)[245]	Her2-neu
Mohammad-Taher Moradi (2014)[246]	p53,MDM2 SNP309
Mohammad-Taher Moradi (2015)[247]	MnSOD Val-9Ala
Mohammad-Taher Moradi (2017)[248]	*GPX1* Pro198Leu
Hamid Ghaedi (2018)[249]	miRNAs
Nasrin Gharaati-Far (2017)[169]	cationic lipids-mediated
Ghalandary M (2015)[250]	*CBX8*
Seyed Mohammad Hossein Kashf (2015)[251]	IL-16
Dor Mohammad Kordi Tamandani (2015)[252]	*THRβ*
Elham Kalantari (2017)[253]	Lgr5, DCLK1
Behnam Kamalidehghan (2006)[254]	DmtDNA4977
Sholeh Kiani (2018)[255]	CDX1 and CDX2
Pegah Larki (2018)[256]	miR-21, miR-25, miR-93, and miR-106b
Rajeeh Mohammadian Amiri (2016)[257]	NOD1 and NOD2
Seyedeh Habibeh Mirmajidi (2016)[258]	Bcl2
Dor Mohammad Kordi-Tamandani (2014)[259]	*CTLA4*

(*Continued*)

Studies have found a direct relationship between pickling and gastric cancer (Table 4) (OR=1.47; 0.84–2.58). Some surveys in Iran show low levels of selenium in gastric cancer patients.[58] The protective effect of selenium on cancer may be due to oxidative stress and DNA damage reduction, recovery of damaged DNA and apoptosis through the p53 tumor suppressor gene and induction of Phase II enzymes to detoxify carcinogenic cells.[59] Investigations show protein intake reduces the chance of gastric cancer (Table 4). High protein intake in a low-income Iranian rural population indicates a healthy lifestyle.[60] In addition, vitamins and minerals play an important role in preventing tumorigenesis. Iron or detoxification of oxidative free radicals can prevent DNA damage.[61] Irregular food intake appears to cause gastric ulcers, which is not unexpected if gastric cancer is not treated in the long-term. The findings of the studies confirm the above (Table 4).

Age

GC is more common in people over 50 years of age[62] and is more common in people between the ages of 70 and 80 years. The incidence of GC is also increasing at ages younger than 20 and 40 years.[63] In general, the highest incidence of GC is observed in the fifth and sixth decades of life, while the risk is reduced at ages younger than 44.[15] According to some investigations, the risk ratio of GC in older people is eight times higher than in other age groups (HR=8.0; 2.7–23.5) (Table 4).

Achalasia

Achalasia is the most well-known esophageal motor disease. Many patients are treated for gastroesophageal reflux disease before detection of achalasia. Gastric adenocarcinoma is the most common malignancy causing pseudo-achalasia.[64] In

conducted surveys, patients with achalasia are 97% more likely to have GC other than those who do not have achalasia (Table 4).

Unwashed Hands After Defecation

Studies show that unwashed hands increase the odds of developing gastric cancer by 2.61-times (OR=2.61; 1.43–4.76) (Table 4). In recent decades, hand-eating has become very common in Iranian culture. Although it is good to wash your hands with water, it is not enough to eliminate contaminated microorganisms after excretion or exposure to toxic substances. Due to the frequent stool excretion and improper hand washing, the emergence of diseases associated with infected microorganisms (*H.pylori*) such as gastric ulcer or gastric cancer are expected.[65]

History of X-Ray Dye Exposure and History of CT Scan Encounter

The use of modern technology such as computed tomography and radiography in the diagnosis of diseases has been widely observed in recent decades, irrespective of its side-effects and subsequent consequences.[66] According to the study, the odds of developing gastric cancer as a consequence of advanced technology are 91% and 39%, respectively (Table 4).

Genetics

mi-RNAs are a subset of non-coding RNAs that contain approximately 22 nucleotides. They also play important functions in various cellular processes including differentiation, proliferation, and apoptosis; furthermore, they play an important role in the development of some cancers, including GC.

Disruption in the regulation of genes such as miR-383 is associated with cancer.[67] It appears that more than one-third of the genes encoding human protein are controlled by mi-RNAs and have their genetic pathways exerting their effects.[68]

In *H-pylori*-infected individuals, IL-18mRNA and IL-18 levels in gastric mucosa are increased,[69] so that IL-18 cytokines increase inflammatory conditions in chronic diseases with immune pleiotropic function,[70] and directly increase the IL-1, IL-6, and TNF-a cytokine from macrophages, promoting GC progression.[71] According to research, mi-RNAs group genes are the most GC related genes (Table 5).

Conclusion

Given the high incidence of GC in Iran, changing lifestyle and decreasing consumption of preservatives in food, increasing consumption of fruits and vegetables, and improving lifestyle can be effective in reducing the incidence of this disease.

Disclosure

The authors report no conflicts of interest in this work.

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