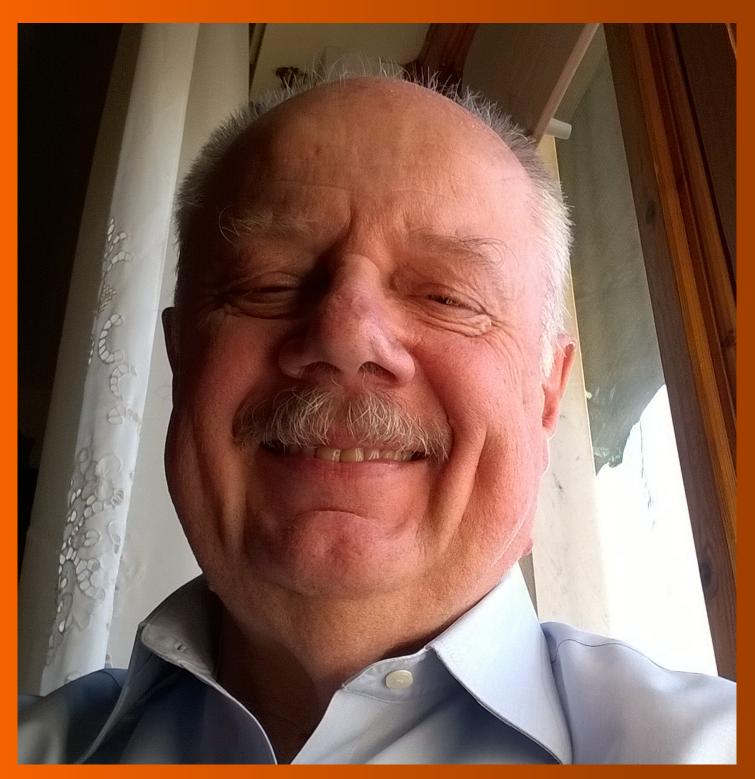
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META-ANALYSIS

What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis

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Abstract

AIM

To quantify the risk of gastric cancer in first-degree relatives of patients with the cancer.

METHODS

A comprehensive literature search was performed. Case-control trials comparing the frequency of a positive family history of gastric cancer in patients with gastric cancer, *vs* non-gastric cancer controls were retrieved. Studies with missed or non-extractable data, studies in children, abstracts, and duplicate publications were excluded. A meta-analysis of pooled odd ratios was performed using Review Manager 5.0.25. We performed subgroup analysis on Asian studies and a sensitivity analysis based on the quality of the studies, type of the outcome, sample size, and whether studies considered only first-degree relatives.

RESULTS

Thirty-two relevant studies out of 612 potential abstracts (n = 80690 individuals) were included. 19.0% of the patients and 10.9% of the controls had at least one relative with gastric cancer (P < 0.00001). The pooled relative risk for the development of gastric cancer in association with a positive family history was 2.35 (95%CI: 1.96-2.81). The Cochran Q test for heterogeneity was positive (P < 0.00001, $I^2 = 92\%$). After excluding the three outlier studies with the highest relative risks, heterogeneity remained significant (P < 0.00001, $I^2 = 90\%$). The result was not different among Asian studies as compared to others and remained



robust in several sensitivity analyses. In the 26 studies which exclusively analysed the history of gastric cancer in first-degree relatives, the relative risk was 2.71 (95%CI: 2.08-3.53; P < 0.00001).

CONCLUSION

Individuals with a first-degree relative affected with gastric cancer have a risk of about 2.5-fold for the development of gastric cancer. This could be due to genetic or environmental factors. Screening and preventive strategies should be developed for this highrisk population.

Key words: Gastric cancer; Risk, Relatives; Family history; Meta-analysis

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Core tip: Several case-control studies have found a familial predisposition for gastric cancer. Most studies suggest that first-degree relatives of patients with gastric cancer are at higher risk. In this meta-analysis we aimed to quantify this risk by including casecontrol trials comparing the frequency of a positive family history of gastric cancer in patients with gastric cancer, vs non-gastric cancer controls were retrieved. We showed that the pooled relative risk for the development of gastric cancer in association with a positive family history was 2.35 (95%CI: 1.96-2.81). We concluded that the individuals with a first-degree relative affected with gastric cancer have a risk of about 2.5-fold for the development of gastric cancer. This could be due to genetic or environmental factors. Screening and preventive strategies should be developed for this high-risk population.

Yaghoobi M, McNabb-Baltar J, Bijarchi R, Hunt RH. What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis. *World J Gastroenterol* 2017; 23(13): 2435-2442 Available from: URL: http://www.wjgnet. com/1007-9327/full/v23/i13/2435.htm DOI: http://dx.doi. org/10.3748/wjg.v23.i13.2435

INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and is the second most frequent cause of death from cancer, accounting for 10.4% of all cancer deaths^[1]. Approximately 700000 people die from gastric cancer each year^[2]. In 2008, about threequarters of cases and deaths from stomach cancer occurred in low- and middle-income and middle-income countries (LMIC). Rates are also elevated in Eastern Europe including Russia, as well as certain parts of Latin America and East Asia^[3]. Both environmental and genetic factors are believed to play a part in the development of gastric cancer. Environmental factors include diet and infection with Helicobacter pylori (H. pylori) have been shown to contribute to gastric cancer^[4]. The incidence of gastric cancer is declining globally, principally because of the improvements in socio-economic status and partly due to widespread use of eradication therapy for *H. pylori*^[2]. An increased intake of nitrites and nitrosamines, as well as of salted foods have also been other suggested environmental factors^[5,6]. Familial predisposition has also long been considered an important factor. Several case-control studies have reported a higher rate of gastric cancer among relatives of patients than among relatives of controls, however, no guideline defines the assessment of the family history in patients with gastric cancer. A systematic review on the studies investigating the rates of genetic assessment and referral for 11 different types of familial cancer did not include gastric cancer^[7]. This indicates an apparent lack of awareness of the extent of genetic susceptibility to gastric cancer. The only meta-analysis on the risk of gastric cancer in the first degree relatives of patients scrutinized the role of *H. pylori* concluded that first-degree relatives of patients with gastric cancer may be at higher risk of developing gastric cancer, due to indirect evidence such as higher prevalence of H. pylori, gastric atrophy and intestinal metaplasia^[8]. We have shown an increased risk of developing gastric cancer in first degree relatives of patients by systematically reviewing the literature, however, we did not aim to perform a statistical analysis to estimate the risk^[9]. The goal of this study was to measure the risk of gastric cancer in family members, by conducting a meta-analysis of published case-control studies.

MATERIALS AND METHODS

Search strategy

Electronic searches were conducted using OVID MEDLINE (1946 to December 2013), EMBASE (1980 to December 2013) and Cochrane library, and ISI Web of knowledge from 1980 to December 2013. Articles were selected using a highly sensitive search strategy, with a combination of MeSH headings and text words that included (1) gastric cancer; (2) risk factor; or (3) family history. Recursive searches and crossreferencing were carried out using a "similar articles" function; bibliography of the articles identified after an initial search were also manually reviewed. The search was not restricted to any specific language.

Inclusion/exclusion criteria

Case-control studies were included if they included cases diagnosed with gastric cancer and controls with diagnoses other than gastric cancer. The outcome of interest was a positive family history of gastric cancer in first or second-degree relatives. Studies with missed



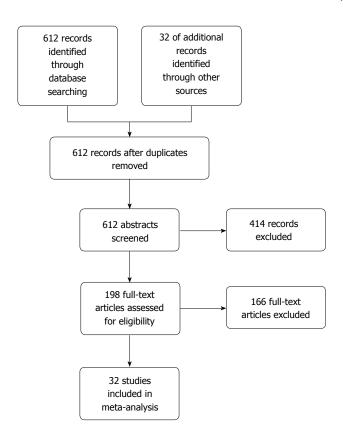


Figure 1 PRISMA diagram.

or non-extractable data, studies in children, abstracts, and duplicate publications were excluded.

Publication bias

No restrictions were applied in terms of language, geographical location or quality of studies. A funnel plot model was applied to explore the likelihood of publication bias. Asymmetry of funnel plot implies likelihood of publication bias.

Reliability

One of the *a priori* concerns was the possibility of selection bias in retrieving and evaluating the included studies. In order to reduce this bias, two independent reviewers performed the search, quality assessment and data extraction. A third reviewer was involved when a consensus could not be achieved.

Heterogeneity

Variation in the patient populations and the quality of studies was considered as an *a priori* source of heterogeneity. Subgroup analyses were predicted *a priori* to investigate each source.

Quality assessment

Two reviewers retrieved the data. The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses was applied to evaluate the quality of observational studies^[10]. The total score for this assessment tool ranged from 0 to 9. No studies

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were excluded based on the quality score. Studies with a score of > 5 were considered as of higher quality.

Statistical analysis

A meta-analysis of pooled relative risk was performed using the Mantel-Haenszel method and Review Manager 5.0.25. The random effect model was applied. A P value of 0.05 was applied as criterion for statistical significance. I^2 was generated to assess heterogeneity and was interpreted as previously described^[11]. Test of heterogeneity was considered significant if the P value less than 0.10. All results are reported with 95%CI when applicable. Subgroup analysis was done on studies in patients with Asian ethnicity vs studies of patients with non-Asian origins. The following sensitivity analyses were also conducted: (1) studies with higher quality score vs those with lower quality score; (2) studies with the question of family history in gastric cancer as the primary objective vs studies in which it was a secondary objective; (3) Studies with a sample size of more than 1000; and (4) Studies on positive family history of gastric cancer in first degree relatives.

RESULTS

A total of 612 potential studies were identified. Thirty two studies were found to be eligible and were included in the meta-analysis (nine from Europe, nineteen from East Asian countries, one from India, one from Iran, one from Peru and one from the United States). Figure 1 depicts the PRISMA flow diagram. All but three of the studies were published in English, one in Spanish and one was in Korean. The results of one of the included studies were published separately for siblings and parents^[12,13] and one publication included two different studies on hospital- and community-based populations^[14]. The primary objective of seventeen studies was to estimate the risk of gastric cancer in relatives of patients. This was a secondary objective in fifteen other studies. Table 1 lists the characteristics of the included studies. Figure 2 depicts the Funnel plot of the study. No visual asymmetry was observed in the Funnel plot.

In total, 17306 cases with gastric cancer and 63384 controls. 19.0% of the cases and 10.9% of the controls had at least one relative with a diagnosis of gastric cancer (P < 0.00001). The random model Mantel-Haenszel meta-analysis showed a relative risk for the development of gastric cancer in individuals with a positive family history in a first- or second-degree relative, compared to controls was 2.35 (95%CI: 1.96-2.81) (Figure 3). The Cochran Q test for heterogeneity was positive (P < 0.00001, $I^2 = 92\%$).

After excluding the three outlier studies with the highest relative risks, heterogeneity remained significant (P < 0.00001, $I^2 = 90\%$). When we considered the 26 studies which exclusively analysed the history of gastric cancer in first-degree relatives, the relative risk was 2.71



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Ref.	Year	Country	Controls	Type of outcome	Family history	Quality score (0-9)
Bakir <i>et al</i> ^[11,12]	2000 2003	Turkey	HB, NC, NGC	Primary	1^{st}	4
Brenner et al ^[25]	2000	Germany	HB, NGC	Primary	1^{st}	5
Chen et al ^[26]	2004	Taiwan	HB, NC, GC, NGI	Primary	1^{st}	6
Chirinos et al ^[27]	2012	Peru	HB, NC	Primary	Unclear	5
Chow et al ^[28]	1999	Poland	CB, Healthy	Secondary	Unclear	7
Chung et al ^[29]	2010	South Korea	HB, NGC	Primary	1^{st}	5
Dhillon <i>et al</i> ^[30]	2001	United States	PB, Healthy	Primary	1^{st}	7
Ennishi <i>et al</i> ^[31]	2011	Japan	HB, NGC	Secondary	1^{st}	6
Eto et al ^[32]	2006	Japan	HB, NGC	Primary	1^{st}	4
Foschi et al ^[33]	2008	Italy	HB, NC	Primary	1^{st}	6
Gajalakshmi <i>et al</i> ^[34]	1996	India	HB, NGC	Secondary	Unclear	5
Garcia-Gonzalez <i>et al</i> ^[35]	2012	Spain	CB, NGI	Secondary	1^{st}	6
Gong et al ^[36]	2013	South Korea	HB, NGC	Primary	1^{st}	5
García-González et al ^[37]	2007	Spain	HB, NC, NGC	Secondary	$1^{\rm st}/2^{\rm nd}$	6
Hong et al ^[38]	2006	South Korea	HB, NC, NGC	Secondary	1^{st}	4
Huang et al ^[39]	1999	Japan	HP, NGC	Secondary	1^{st}	5
Ikeguchi et al ^[40]	2001	Japan	HB, NC, NGC, NGI	Primary	1 st -3 rd	4
La Vecchia <i>et al</i> ^[41]	1992	Italy	HB, NC, NGC, NGI	Primary	1^{st}	3
Lee et al ^[42]	2009	South Korea	HB, NGC	Primary	Unclear	5
Li et al ^[43]	2010	China	HB, NGI	Secondary	1^{st}	6
Mao et al ^[44]	2011	China	HB, NGC	Secondary	1^{st}	5
Minami et al ^[45]	2003	Japan	HP, NC, NGC	Secondary	1^{st}	5
Nagase <i>et al</i> ^[46]	1996	Japan	HB, NC, NGC	Primary	1^{st}	5
Palli et al ^[47]	1994	Italy	CB, healthy	Primary	1^{st}	6
Presson <i>et al</i> ^[13]	2009	Sweden	HB, CB, NC	Secondary	$1^{\text{st}}/2^{\text{nd}}$	7
Safaee <i>et al</i> ^[48]	2011	Iran	HB, Healthy	Primary	1^{st}	6
Shen <i>et al</i> ^[49]	2009	China	HB, NGC	Primary	1^{st}	6
Shin et al ^[50]	2010	South Korea	HB, NGC	Primary	1^{st}	6
Wen et al ^[51]	2014	China	HB + CB, NGC	Secondary	1^{st}	7
Yi et al ^[52]	2010	China	HB, NGC	Secondary	1^{st}	5
Zhang et al ^[53]	2009	China	HB, NC	Secondary	1^{st}	6
Zhang et al ^[54]	2008	China	HB, NC	Secondary	1^{st}	6

HB: Hospital-based; CB: Community-based; NC: Non-cancer; NGI: Non gastrointestinal disorder; NGC: Non-gastric cancer.

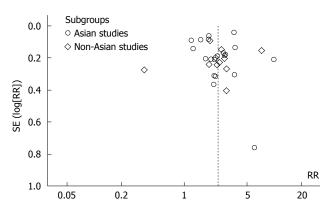


Figure 2 Funnel plot of included studies (n = 19).

(95%CI: 2.08-3.53; *P* < 0.00001).

Subgroup analysis

Asian and non-Asian populations: There was no significant difference in studies on Asian as compared to those on non-Asian population in random model Mantel-Haenszel meta-analysis (P = 0.82). The relative risk in Asian studies was 2.38 (95%CI: 1.91-2.97, P < 0.00001). The test of heterogeneity was significant

within this subgroup of seven studies (P < 0.00001, $I^2 = 93\%$). In non-Asian population, the relative risk was 2.27 (95%CI: 1.56-3.30; P < 0.00001). There was evidence for heterogeneity in this analysis (P < 0.00001, $I^2 = 91\%$).

A sensitivity analysis was performed after excluding all studies with a total number of included individuals less than 1000 and showed that the difference between two groups remained unchanged (P = 0.31).

Sensitivity analyses

High quality *vs* **low quality studies:** Heterogeneity persisted among thirteen studies that were scored as high quality (P < 0.00001, $I^2 = 73\%$) as well as among studies with lower quality scores (P < 0.00001, $I^2 = 95\%$). Random model Mantel-Haenszel meta-analysis showed no significant difference (P = 0.50) between the high quality [RR = 2.21 (95%CI: 1.84-2.64)] as compared to low quality studies [RR = 2.47 (95%CI: 1.87-3.27)].

Family history being the primary *vs* **secondary outcome:** Heterogeneity persisted among seventeen studies that used family history as the primary outcome

Cases Control Risk ratio Risk ratio Study or subgroup Events Total Events Total Weight M-H, random, 95%CI M-H, random, 95%CI Asian studies Ennishi 2011 1.19 (1.00, 1.42) 155 703 270 1462 3.8% Mao 2011 200 1.25 (0.95, 1.66) 74 59 200 3.6% Minami 2003 140 614 369 2444 3.8% 1.51 (1.27, 1.80) Zhang 2009 46 236 36 320 3.3% 1.73 (1.16, 2.59) Huang 1999 207 887 3608 28619 3.9% 1.85 (1.64, 2.09) Ikeguchi 2001 216 926 254 2025 3.8% 1.86 (1.58, 2.19) Gong 2013 61 327 31 327 3.3% 1.97 (1.31, 2.95) Nagase 1996 21 136 10 136 2.4% 2.10 (1.03, 4.29) Li 2012 32 138 12 110 2.7% 2.13 (1.15, 3.93) Lee 2009 54 183 27 199 3.3% 2.17 (1.43, 3.30) Zhang 2008 31 414 14 414 2.7% 2.21 (1.20, 4.10) Shin 2010 90 428 33 368 3.4% 2.34 (1.61, 3.41) Shen 2009 112 503 41 503 3.5% 2.73 (1.95, 3.82) Wen 2014 92 308 33 308 3.4% 2.79 (1.94, 4.02) Chen 2004 47 176 54 579 3.4% 2.86 (2.01, 4.07) Eto 2006 543 1400 1475 13467 3.9% 3.54 (3.26, 3.84) Yi 2010 41 140 12 147 2.8% 3.59 (1.97, 6.54) 252 Chung 2010 3242 64 3000 3.6% 3.64 (2.78, 4.77) Gajalakshmi 1996 12 388 2 388 1.1% 6.00 (1.35, 26.63) Hong 2006 94 108 21 238 3.3% 9.86 (6.51, 14.94) Subtotal (95%CI) 55254 65.0% 2.38 (1.91, 2.97) 11457 Total events 2320 6425 Heterogeneity: Tau² = 0.21, χ^2 = 287.39, df = 19 (*P* < 0.00001); I^2 = 93% Test for overall effect: *Z* = 7.70 (*P* < 0.00001) Non-Asian studies Chirinos 2012 14 96 39 96 2.9% 0.36 (0.21, 0.62) Presson 2009 49 286 22 242 3.1% 1.88 (1.17, 3.02) Palli 1994 213 1016 177 1623 3.8% 1.92 (1.60, 2.31) Dhillon 2001 70 695 3.3% 2.21 (1.49, 3.27) 629 35 Foschi 2008 30 230 31 547 3.1% 2.30 (1.43, 3.71) Chow 1999 59 25 480 3.2% 2.44 (1.56, 3.83) 464 La Vecchia 1992 79 628 87 1776 3.6% 2.57 (1.92, 3.43) Garcia-Gonzalez 2012 81 446 29 446 3.3% 2.79 (1.87, 4.18) Brenner 2000 10 68 12 239 2.2% 2.93 (1.32, 6.48) 53 746 18 746 3.0% 2.94 (1.74, 4.98) Safaee 2011 Bakir 2000, 2003 316 1240 44 1240 3.5% 7.18 (5.29, 9.75) Subtotal (95%CI) 2.27 (1.56, 3.30) 5849 8130 35.0% Total events 974 519 Heterogeneity: Tau² = 0.35, χ^2 = 107.30, df = 10 (*P* < 0.00001); I^2 = 91% Test for overall effect: Z = 4.27 (P < 0.0001)Total (95%CI) 17306 63384 100.0% 2.35 (1.96, 2.81) 3294 6944 Total events Heterogeneity: Tau² = 0.22, χ^2 = 390.94, df = 30 (P < 0.00001); I^2 = 92% Test for overall effect: Z = 9.23 (P < 0.00001) 0.05 0.2 1 5 20 Test for subgroup differences: $\chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$ Control Cases

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Figure 3 The Mantel-Haenszel meta-analysis of all included studies (n = 32) with subgroup analysis of Asian vs non-Asian population.

 $(P < 0.00001, I^2 = 91\%)$ as well as among studies that used it as secondary outcome $(P < 0.00001, I^2 = 89\%)$. Random model Mantel-Haenszel meta-analysis showed no significant difference (P = 0.66) between two subgroups [RR = 2.43 (95%CI: 1.95-3.05) and RR = 2.26 (95%CI: 1.75-2.91)], respectively.

Effect of the sample size on outcome: Heterogeneity persisted among thirteen studies with a total included individuals greater than 1000 (P < 0.00001, $I^2 = 96\%$). Random model Mantel-Haenszel meta-analysis showed a relative risk of 2.68 (95%CI: 2.08-3.45, P < 0.00001).

DISCUSSION

To our knowledge, this is the first meta-analysis exploring the relative risk for the development of gastric cancer among the relatives of patients. Overall, the risk is approximately 2.5 times greater in those with an affected first-degree relative than in relatives of unaffected controls. However, we observed significant heterogeneity between studies. This heterogeneity could be the result of variations in population sampling or in experimental design, but could also reflect inherent differences in the genetic composition of the studied populations. The relative risk of gastric cancer is elevated to a similar extent for first-degree relatives of patients in the different studies, but the actual risk will depend on the ethnic group and the country of residence. For example, the lifetime risk of gastric cancer is approximately 1% in Canada and the United States, but exceeds 4% in regions of China, Japan and Korea^[15]. Rates are also high in Colombia, Ecuador and Costa Rica and in parts of southern and Eastern Europe, including Italy, Portugal, Latvia and Estonia. In parts of Japan, the lifetime risk of gastric cancer exceeds 10% in males and 4% in females and if the relative risk of 2.5 is applied to relatives of patients in these populations, the lifetime risk may approach 25%. In contrast, in Canada a male with a first-degree relative with gastric cancer faces a lifetime risk of about 3%^[2].

Among environmental factors H. Pylori infection is directly related to gastric cancer. In a metaanalysis of prospective (cohort) studies, the OR for the association between H. Pylori infection and the subsequent development of gastric cancer was 2.36 (95%CI: 1.98-2.81)^[16]. A comprehensive literature search identified 16 gualified studies with 2284 cases and 2770 controls. H. pylori and cagA seropositivity significantly increased the risk for gastric cancer by 2.28- and 2.87-fold, respectively. Among H. pylori -infected populations, infection with cagA-positive strains further increased the risk for gastric cancer by 1.64-fold (95%CI: 1.21-2.24) overall and by 2.01-fold (95%CI: 1.21-3.32) for noncardiac gastric cancer^[17]. Another meta-analysis of three randomized controlled studies also showed a reduction in the risk of gastric cancer following the eradication of H. pylori infection (OR = 0.67; 95%CI: 0.42-1.07)^[4]. Other environmental risk factors include a high intake of foods containing nitrite and nitrosamine, salted foods as well as decreased consumption of fresh fruits and vegetables^[5,6].

The genetic factors which are responsible for the familial aggregation of gastric cancer are largely unknown. Gastric cancer is one of several inherited cancer predisposition syndromes, including hereditary non-polyposis colon cancer, familial adenomatous polyposis, Peutz-Jeghers syndrome, Cowden disease, and the Li-Fraumeni syndrome^[18,19]. Hereditary diffuse gastric cancer (HDGC) is a rare, form of gastric cancer with an autosomal dominant inheritance, which presents with early-onset, poorly differentiated, highgrade, diffuse gastric cancer that can be caused by germline mutations in CDH1 or p53 in half to two thirds of the cases^[20,21]. Microsatellite instability was significantly associated with antral tumors and a positive family history of gastric cancer^[20]. Increased gastric cancer risk has also been associated with polymorphic variants in interleukin-1-beta (IL-1 β) and N-acetyltransferase-1 (NAT1). In one study, individuals carrying the IL-1 β -31 T polymorphism were at a higher risk of gastric cancer after *H. pylori* infection^[22,23]. This might indicate the potential interaction between

environmental and genetic factors.

Our study has the limitations inherent to most case-control studies. We could not completely exclude publication bias. Although we did not limit the language of study publication and we used several search sources, all but one of our included studies is in English and some publications may have been overlooked. Unpublished data might be another source of bias. We have also provided a funnel plot to visually assess this possibility. Several studies adjusted their analyses for the effects of known or presumed environmental factors. However, in our meta-analysis it was not possible to consider possible confounders because we did not have access to the original data.

Although different case-control studies have shown a higher rate of gastric cancer among relatives of patients, no guidelines have been developed to assess systematically the family histories of individual patients with gastric cancer. In 2008 Asia-Pacific consensus guideline on preventing gastric cancer considered a positive family history of gastric cancer an important risk factor^[24]. A systematic review on cancer genetic assessment provided risk assessment and referral rates for 11 types of cancer known to show evidence of familial clustering but did not include gastric cancer^[7]. This indicates a possible lack of awareness of the extent of genetic susceptibility for gastric cancer.

In summary, there is strong evidence that gastric cancer has a familial component. The relative risk of 2.5 reported here is larger than that observed for most adult forms of solid cancers, with the exception of ovarian cancer. Improving socioeconomic status and eradication of *H. pylori* infection might, in long term, decrease the risk however molecular epidemiology studies, such as genome-wide association studies, may help to identify the responsible genetic factors.

COMMENTS

Background

Gastric cancer is the fourth most common cancer worldwide and is the second most frequent cause of death from cancer responsible for approximately 700000 death each year. The risk of development of gastric cancer in relatives of patients with this cancer is not clear.

Research frontiers

The estimated risk of gastric cancer will help in development of preventive and screening strategies for the relatives of patients.

Innovations and breakthroughs

This is the first meta-analysis in quantifying the risk of developing gastric cancer in relatives of patients with this cancer.

Applications

The obtained information could be used in developing screening guidelines.

Peer-review

Congratulations for the quality of the work. In my opinion there was an overestimation of *Helicobacter pylori* and no reference to alcohol abuse and the tobacco dependency.



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