Quantitative risk of positive family history in developing colorectal cancer: A meta-analysis

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Abstract

BACKGROUND
Positive family history is a risk factor for development of colorectal cancer. Despite numerous studies on the topic, the absolute risk in patients with a positive family history remains unclear and therefore studies are lacking to validate non-invasive screening methods in individuals with positive family history.

AIM
To quantify the risk of colorectal cancer in individuals with a positive family history.

METHODS
A comprehensive electronic literature search was performed using PubMed from January 1955 until November 2017, EMBASE from 1947 until 2018, and Cochrane Library without date restrictions. Two independent reviewers conducted study selection, data extraction and quality assessment. A meta-analysis of Mantel-Haenzel relative risks was performed using the random effects model. Newcastle-Ottawa scale was used to score the quality of selected papers. Funnel plot and Egger's regression test was performed to detect publication bias. Subgroup analysis was performed comparing Asian and non-Asian studies. Sensitivity analyses were performed to rule out the effect of the timing of the study, overall quality, the main outcome and the effect of each individual study in overall result.

RESULTS
Forty-six out of 3390 studies, including 906981 patients were included in the final

analysis. 41 of the included studies were case-control and 5 were cohort. A positive family history of colorectal cancer in first-degree relatives was associated with significantly increased risk of colorectal cancer with a relative risk of 1.87 (95%CI: 1.68-2.09; $P < 0.00001$). Cochrane Q test was significant ($P < 0.00001$, $I^2 = 90\%$). Egger's regression test showed asymmetry in the funnel plot and therefore the Trim and Fill method was used which confirmed the validity of the results. There was no difference between Asian versus non-Asian studies. Results remained robust in sensitivity analyses.

CONCLUSION
Individuals with a positive family history of colorectal cancer are 1.87 times more likely to develop colorectal cancer. Screening guidelines should pay specific attention to individuals with positive family history and further studies need to be done on validating current screening methods or developing new modalities in this high-risk population.

Key words: Colorectal cancer; Risk; Family history

Core tip: The increased risk of developing colorectal cancer in individuals with a positive family history remains unknown. Many independent studies have provided different numerical risks with relatively large differences between the values. Here, we have performed a systematic review and meta-analysis to provide a more accurate estimate of this increased risk in an attempt to aid future guideline making and help implement preventative measures for at-risk individuals.

INTRODUCTION

Colorectal cancer is the third most common cancer and the fourth leading cancer-related cause of death worldwide[1]. Most colorectal cancer seems to have a stepwise progression from precancerous lesions[2]. As an example, the number, size and physical characteristics of adenomas can determine the likelihood of malignant transformation[3]. Presence of advanced colorectal adenomas characterized by a large size (greater than 1 cm), high multiplicity (more than 3 adenomas), villous morphology and high grade dysplasia results in higher risk of developing colorectal cancer[4]. The incidence of colorectal cancer is expected to increase in the future, leading to an additional 1.1 million deaths by the year 2030[5]. Given the morbidity and mortality associated with this cancer, it is important for clinicians to understand the quantitative risk associated with various risk factors.

Several environmental and hereditary factors are known as the risk factors for colorectal cancer[6]. Some of these include previous history of inflammatory bowel diseases (ulcerative colitis and Crohn's disease), high amounts of processed meat in the diet, high body fat, cigarette smoking and low fruit and vegetable consumption[7]. In addition, patients with inherited conditions such as, hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) as well those with a positive family history of colorectal cancer in relatives are at a higher risk of developing this condition[8]. An old meta-analysis of 27 studies attempted to determine the risk associated with colorectal cancer in individuals with a positive family history of the condition, however, many newer studies have been published and the recommended methodology to perform conventional meta-analysis has since significantly changed specially in the area of risk of bias assessment[9].

Several case-control and cohort studies from different regions around the world have attempted to quantify the risk of familial colorectal cancer[9]. However, substantial variability is present amongst the estimated risks in different publications.

Therefore, despite availability of multiple screening modalities for colorectal precancerous and cancerous lesions such as colonoscopy, fecal occult blood test (FOBT), and fecal immunochemical test (FIT), guidelines either lack specific recommendations for preventative screening in individuals with a positive family history of colorectal cancer or make conditional recommendation based upon quality evidence[10-12]. Therefore, the aim of this study was to systematically review these papers and perform a meta-analysis according to Cochrane Group Methodology to provide a more accurate estimate for the risk of colorectal cancer associated with a positive family history of the disease in first-degree relatives of the patient[13].

MATERIALS AND METHODS

Registration
The study protocol was registered (CRD42018094964) in the International prospective register of systematic reviews (PROSPERO).

Search strategy
Comprehensive electronic searches of PubMed from January 1955 until November 2017, EMBASE from 1947 until 2018, and Cochrane Library without date restrictions were performed using a highly sensitive search strategy to identify studies with MeSH headings and text words which included (1) Family, (2) Colorectal Cancer, (3) Medical History. No language restriction was applied. In addition, the bibliography of selected articles were manually searched to find any additional studies for our meta-analysis.

Inclusion criteria
Case-control studies were included if they involved colon, rectal or colorectal cancer patients as cases and non-colorectal cancer patients as controls. The exposure of interest was a positive family history of colorectal cancer in first-degree relatives of patients. Additionally, cohort studies were eligible for inclusion if they followed individuals with positive and negative family history of colorectal cancer in first-degree relatives and assessed the patients for the outcome of colorectal cancer. Studies which did not clearly define relatives as first-degree relatives were also included, however, we planned to do a sensitivity analysis to investigate their effect on overall result.

Exclusion criteria
Abstracts, studies with insufficient data that did not allow for independent calculation of relative risk, paediatric studies, as well as duplicate studies were excluded. Moreover, we excluded studies which relied on the same patient databases and medical records during overlapping patient recruitment periods to avoid du-plications. Studies which included patients with known hereditary conditions (FAP and HNPCC) or inflammatory bowel diseases were excluded. Studies that reported family history without specifying colorectal cancer were not included in the analysis.

Outcome measure
The main outcome of interest in this meta-analysis was the relative risk of colorectal cancer in first-degree relatives of patients. We independently calculated relative risk based on original data presented in the studies[14].

Reliability
In order to reduce the risk of selection bias, two independent reviewers performed the literature search, data extraction and quality assessment. In cases where an agreement could not be reached, a third reviewer was involved.

Risk of bias
Newcastle-Ottawa scale (NOS) for the assessment of risk of bias in non-randomized studies was sued to assess the quality of the included studies[15]. The score ranged from 0 to 9 based on three categories: Selection, comparability and exposure/outcome[15]. We defined a score greater than 5 as high quality and any score equal or less than 5 was considered low.

Publication bias
We did not restrict our search strategy based on language, risk of bias, sample size or geographical location of the study. A funnel plot analysis was also performed to assess the likelihood of publication bias[16]. Egger's regression test was also performed to detect asymmetries in the funnel plot[17]. Comprehensive Meta-analysis Version 3.0

was used for Egger's regression analysis for assessing asymmetries in the funnel plot and for Trim and Fill sensitivity analysis[18]. *P* values less than 0.05 were considered significant for the significance of asymmetry.

Statistical analysis

Review Manager 5.3 was used to perform a meta-analysis of random model Mantel-Haenzel relative risk for case control and cohort studies[18]. *P* values less than 0.05 were considered to be statistically significant. Higgins I^2 and Cochran's Q were used to measure heterogeneity as recommended by Cochrane Collaboration[19]. Additional subgroup and sensitivity analyses were planned *a priori* to investigate sources of heterogeneity in the result. Subgroup analysis was performed based on the geographical location of the study by separately analyzing Asian and non-Asian studies. Several sensitivity analyses were also conducted by excluding the largest included trial as well as each included study by turn to ensure none single study has significantly changed the conclusion of the study. *P* values less than 0.10 were considered statistically significant for heterogeneity. Additional subgroup and sensitivity analyses were planned *a priori* to investigate sources of heterogeneity in the result. Subgroup analysis was performed based on the geographical location of the study by separately analyzing Asian and non-Asian studies given different prevalence of colorectal in these two areas. Several sensitivity analyses were also conducted by excluding the largest included trial as well as each included study by turn to ensure none single study has significantly changed the conclusion of the study. results were presented with 95% confidence intervals whenever possible.

RESULTS

Characteristics of included studies

Of 3390 studies identified, 46 studies including 906981 patients were included in the final analysis. All studies with exception of one were written in the English[20]. Figure 1 depicts the PRISMA diagram for our literature search. 41 of the included studies were case control and 5 were prospective and retrospective cohort. In total, there were 47898 colorectal cancer patients and 320360 control subjects included in the case control studies. In addition, there were 68345 patients with a positive family history of colorectal cancer, and 470378 subjects without a family history of colorectal cancer. Table 1 contains detailed information about the studies included. We observed small visual asymmetry in the funnel plot (Figure 2) and Egger's regression for the detection of asymmetry (Figure 3) in the funnel plot was statistically significant (*P* = 0.047).

Relative risk of colorectal cancer in first-degree relatives

The relative risk of developing colorectal cancer in first-degree relatives of patients was 1.87 (95%CI: 1.68-2.09; *P* < 0.00001) using the random effects model to account for detected heterogeneity (Figure 4). We performed a subgroup analysis between Asian and non-Asian studies as hypothesized *a priori*. 18 studies were conducted in Asian countries and 28 studies were conducted in non-Asian countries. The relative risk of colorectal cancer in first-degree relatives was 1.83 (95%CI: 1.54-2.16; *P* < 0.00001) in Asian studies as compared to 1.88 (95%CI: 1.63-2.17; *P* < 0.00001) in non-Asian studies. Heterogeneity remained in both subgroups (*P* < 0.00001, I^2 = 72 and I^2 = 93% respectively). There was no significant difference in the relative risk between the subgroups (*P* = 0.78). Figure 4 depicts this meta-analysis.

Sensitivity analysis

Family history as the primary objective: Thirteen studies reported information about family history as their primary outcome and 33 studies reported information as their secondary outcomes. Heterogeneity persisted in studies with family history as primary or secondary outcome. The Mantel-Haenzel random effect relative risk was not significantly different between the two subgroups (*P* = 0.28).

Risk of bias: There were 23 high-quality studies and 23 low-quality studies. Heterogeneity was unaffected by quality of the included studies. The Mantel-Haenzel random effects relative risk was not significantly different between the two subgroups (*P* = 0.99).

Case control studies versus cohort studies: There were 41 case control studies and 5 cohort studies with non-significant difference in relative risk between the groups (*P* = 0.27). Design of studies did not affect the heterogeneity in the results.

Timing of the study: There were 12 studies published prior the year 2000 and 34

Table 1 Characteristics of the included studies (*n* = 46)

Study author	Year of publication	Type of study	Country of origin	Type of family history	Study period (start-end)	Type of outcome	Nos quality scale
Arafa *et al*[33]	2011	Case control	Jordan	FDR	2008-2009	Secondary	6
Bener *et al*[34]	2010	Case control	Qatar	FDR	2003-2008	Primary	7
Bonelli *et al*[35]	1988	Case control	Italy	FDR	1980-1986	Primary	4
Castiglione *et al*[36]	2012	Case control	Italy	FDR	1995-2009	Primary	4
Centonze *et al*[37]	1993	Case control	Italy	FDR	1987-1989	Primary	8
Crockett *et al*[38]	2012	Case control	United States	FDR	2001-2006	Secondary	7
Emami *et al*[39]	2015	Case control	Iran	FDR	N/A	Secondary	5
Fernandez *et al*[40]	2002	Case control	Italy	FDR	1985-1992	Secondary	5
Freedman *et al*[41]	1996	Case control	United States	FDR	1982-1992	Secondary	6
Fuchs (health professional cohort) *et al*[42]	1994	Prospective	United States	FDR	1986-1992	Primary	3
Fuchs (nurse health cohort)	1994	Prospective	United States	FDR	1982-1990	Primary	3
Grosso *et al*[43]	2014	Case control	Italy	Unclear	2000-2012	Secondary	7
Guo *et al*[44]	2010	Case control	China	At least one FDR or two or more SDR	2007	Secondary	7
Huang *et al*[45]	2004	Case control	Japan	FDR	1988-1998	Secondary	2
Ibáñez-sanz *et al*[46]	2017	Case control	Spain	FDR, SDR, TDR	2008-2013	Secondary	7
Il'yasova *et al*[47]	2003	Case control	United States	Unclear	1996-2000	Secondary	7
Jia *et al*[20]	2007	Case control	China	FDR	2003-2005	Secondary	7
Jo *et al*[48]	2012	Case control	South Korea	Unclear	2004-2007	Secondary	3
Kampman *et al*[49]	2000	Case control	United States	FDR	1991-1994	Secondary	6
Kim *et al*[50]	2009	Case control	South Korea	FDR	2001-2004	Secondary	4
Kotake *et al*[51]	1995	Case control	Japan	FDR	1992-1994	Primary	6
Kune *et al*[52]	2009	Case control	Australia	FDR	1980-1981	Primary	7
La vecchia *et al*[53]	1996	Case control	Italy	FDR	1985-1992	Secondary	4
Le merchand *et al*[54]	1999	Case control	United States	FDR	1987-1991	Secondary	8
Lee *et al*[55]	2014	Retrospective	Sweden	FDR: Sibling only	1958-2009	Primary	5
Lohsoonthorn *et al*[26]	1995	Case control	Thailand	FDR: Parents only	N/A	Primary	7
Mahmoudi *et al*[56]	2014	Case control	Iran	Unclear	2009-2012	Secondary	4
Mahmoudi *et al*[57]	2016	Case control	Iran	Unclear	2008-2012	Secondary	4
Minami *et al*[58]	2003	Case control	Japan	FDR	1997-2001	Secondary	5
Morois *et al*[59]	2014	Prospective	France	FDR	1990-2008	Secondary	4
Newcomb *et al*[60]	1999	Case control	United States	FDR	1990-1991	Primary	7
Otani *et al*[61]	2006	Case control	Japan	Unclear	1990-2003	Secondary	7
Pou *et al*[61]	2012	Case control	Argentina	FDR	2006-2010	Secondary	7
Rennert *et al*[62]	2010	Case control	Israel	FDR	N/A	Secondary	5
Rosenberg *et al*[63]	1998	Case control	United States	FDR	1992 -1994	Secondary	8
Russo *et al*[64]	1998	Case control	Italy	Unclear	1992-1996	Secondary	4
Samadder *et al*[65]	2016	Case control	United States	FDR	2000-2010	Secondary	7
Schoen *et al*[66]	2015	Prospective	United States	FDR	1993-2001	Primary	5

Senda-nakagawa herpacc (i) *et al*[67]	2017	Case control	Japan	FDR	1988-2000	Secondary	5
Senda-nakagawa herpacc (ii)	2017	Case control	Japan	FDR	2001-2005	Secondary	5
Seow *et al*[68]	2002	Case control	China	FDR	1999-2000	Secondary	4
Shang *et al*[69]	2016	Case control	Australia, Canada, United States	FDR	1997-2012	Secondary	6
Sun *et al*[70]	2012	Case control	Canada	Unclear	1997-2003	Secondary	7
Turati *et al*[71]	2013	Case control	Italy, Switzerland	FDR	1991-2009	Primary	3
Weigl *et al*[72]	2016	Case control	Germany	FDR	2003-2014	Secondary	7
Wells *et al*[73]	2014	Case control	United States	FDR: colon cancer only (not rectal)	1993-1996	Secondary	5

FDR: First-degree relative; SDR: Second degree relative; TDR: Third degree relative; NOS: Newcastle Ottawa scale.

studies published after. The Mantel-Haenzel random effects relative risk was not significantly different between the subgroups (P = 0.14). Heterogeneity was not significant in studies published before 2000 (P = 0.16, I^2 = 29%), and significant in studies published after 2000 (P < 0.00001, I^2 = 92%).

Proximity of relative with positive history: Thirty-five studies reported family history only in first-degree relatives and 11 studies were either unclear or included other groups. Heterogeneity was unaffected by the family history information. The relative risk between the two subgroups was not statistically significant (P = 0.30).

Excluding each study in turn: Excluding none of the included studies significantly changed the results.

Trim and fill analysis: The adjusted Mantel-Haenzel random effects relative risk was 1.66 (95%CI: 1.47-1.87) in Trim and Fill analysis, which is not substantially different from the crude value for the measure. Figure 3 shows the visual representation of the funnel plot after the inclusion of imputations for possible missing studies.

DISCUSSION

Our meta-analysis of case control and cohort studies showed that patients with a positive family history of colorectal cancer in first-degree relatives have a 1.87-fold chance for the development of this condition compared to those without a family history. To our knowledge, this is the first comprehensive published meta-analysis estimating the relative risk for development of colorectal cancer in the context of positive family history in the last 15 years including more than 900000 patients. The only published meta-analysis included 26 studies published before the year 2000 to estimate the relative risk of colorectal cancer to be 2.25 in patients with a positive family history[9]. However, the authors only searched MEDLINE as opposed to multiple databases which could have led to selection bias. On the other hand they did not assess the studies for the risk of bias. In our study a subgroup analysis showed the risk of colorectal cancer to be 2.06 in a sensitivity analysis of studies published before the year 2000. These results could indicate the possibility of time lag publication bias whereby over time, with newer studies available, evidence indicates that the initial risk for familial colorectal cancer may have been overestimated[21]. Moreover, it is possible that studies published before the year 2000 included patients with hereditary conditions such as FAP and HNPCC due to lack of awareness or technological advances to detect those patients, therefore contributing to the overestimation of colorectal cancer risk in individuals with a positive family history. However, a sensitivity analysis did not show a significant difference in the overall risk in studies published before 2000 as compared to those published afterward.

We performed subgroup analysis based on the location of the study conducted. This subgroup analysis was based on the fact that colorectal cancer has a higher incidence in Europe and North America and it is less common in South and Central Asia[22]. According to the 2018 global burden of cancer report published by the World Health Association, the age standardized incidence of colorectal cancer is 17.7 per 100000 in Asia as opposed to 26.2 in North America, and 30 in Europe[22]. Additionally, the Western diet has been associated with an increased risk of colorectal
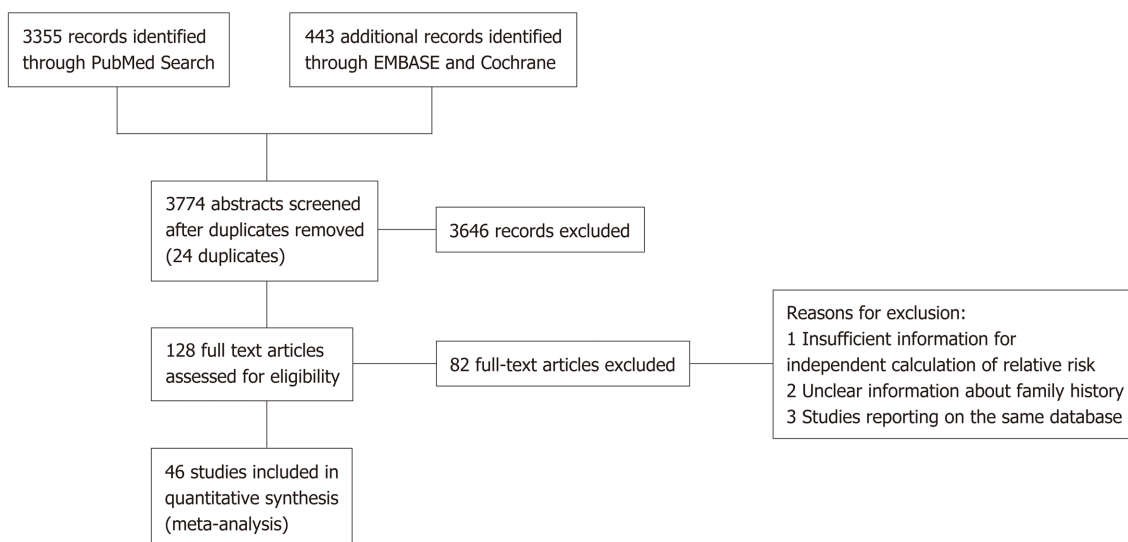
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│ 3355 records identified │     │ 443 additional records  │
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        │ 128 full text articles │   │ 82 full-text articles │   │ Reasons for exclusion:               │
        │ assessed for eligibility├──┤ excluded              ├───┤ 1 Insufficient information for       │
        │                        │   └───────────────────────┘   │ independent calculation of relative  │
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                                                                  │ 2 Unclear information about family   │
        ┌────────────────────────┐                                │ history                              │
        │ 46 studies included in │                                │ 3 Studies reporting on the same      │
        │ quantitative synthesis │                                │ database                             │
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Figure 1 PRISMA diagram of the literature search conducted.

cancer especially for those diagnosed at a younger age[23]. However, our analysis revealed that there was no significant difference between the two subgroups that may indicate that the role of family history has equal importance in Asian as compared to non-Asian populations. This finding may play an important role in developing recommendations regarding individuals with family history of colorectal cancer in screening guideline in Asian populations. One should note that the absolute risk might still be lower in an individual with Asian background given the overall lower prevalence despite similar relative risk.

We observed substantial heterogeneity in the results which persisted despite various sensitivity analyses except for the subgroup of studies published before the year 2000. We used random model effect analysis to reduce the effect of heterogeneity on our results. We also performed several sensitivity analyses to explain the statistical heterogeneity. Several factors may explain the observed heterogeneity. Various environmental and lifestyle factors such as physical activity, smoking and alcohol consumption also impact the likelihood of developing colorectal cancer[7]. Our meta-analysis was limited by the primary information provided and we were not able to calculate an adjusted relative risk for familial colorectal cancer based on the abovementioned factors. Consequently, it is possible that inherent differences between the study subjects in other risk factors could have led to the presence of heterogeneity in the results as one might expect from such a large meta-analysis. In addition, evidence from previous studies shows that the familial risk of colorectal cancer may also be site dependent which could have also contributed to heterogeneity in the results[9]. Moreover, the familial risk of colorectal cancer is also dependent on the number of relatives affected which could have led to heterogeneity in the results[9].

There are other possible shortcomings in this study due to intrinsic nature of each meta-analysis. Firstly, there is a possibility for selection bias. Although we did not restrict the language of the initial literature search and used a sensitive strategy to include all the critical studies, it is possible that some eligible studies may not have been included. Only one of the included studies was not published in the English language[20]. However, in this case we were able to access duplicate publication of the same results in English[24]. In addition to selection bias, given that most of the included studies were retrospective in design, there is a possibility of recall bias. It is possible that patients may have provided incorrect family history information[25]. Indeed, the Newcastle-Ottawa scale tool revealed that only 1 included study used a blinded trained interview as a method of determining patient family history information[26].

Another potential source of bias is publication bias which led us to perform Trim and Film sensitivity analysis. We limited our search to published articles and excluded abstracts. We observed small visual asymmetry in the funnel plot and Egger's test was significant for asymmetry. It is important to mention that the presence of asymmetry in a funnel plot does not necessarily indicate publication bias and could be caused by other reporting biases[17]. Since we were unable to offer other possibilities than publication bias for the asymmetry of the funnel plot, we decided to perform Trim and Fill analysis. Our results remained robust with the Trim and Fill analysis with the adjusted relative risk overlapping greatly with the crude relative
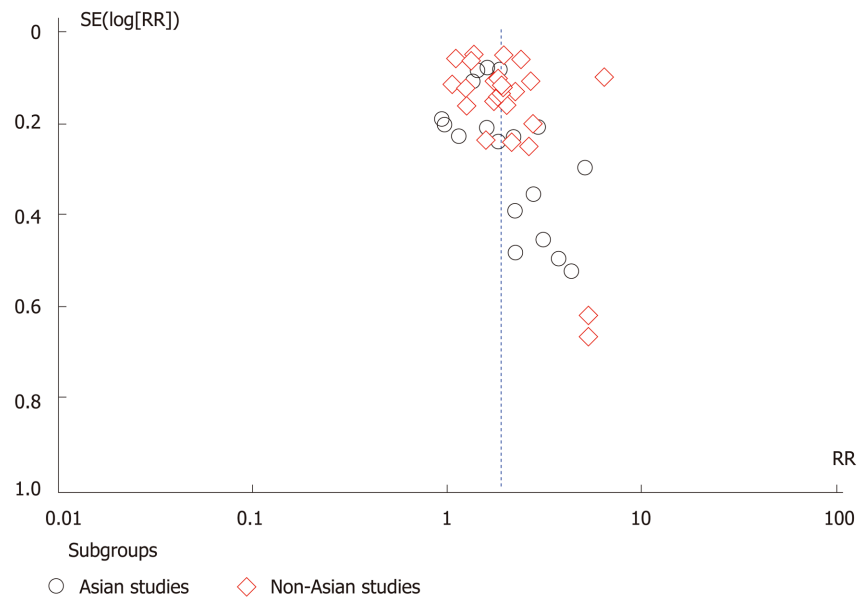
Figure 2 Funnel plot of included studies separated based on the country of origin (Asian *vs* non-Asian).

risk. These analyses indicate that although publication bias is a possibility in this meta-analysis, it could not have substantially affected the results.

The cause for the increased risk of colorectal cancer in patients with a positive family history is not well defined, but it can be attributed to both genetic and environmental factors[27]. Some known environmental factors for colorectal cancer include poor nutritional practices such as a diet rich in fats and red meat, smoking, obesity, low physical activity and heavy alcohol consumption[27]. Recent advances in cancer research has recognized the individual variability in biological markers in cancer patients, leading to the emergence of pathological molecular epidemiology[28,29]. According to this emerging field, it is possible that specific environmental factors such as dietary choices, physical activity and alcohol consumption contribute to the incidence and prognosis of specific forms of colorectal cancer categorized through the presence or absence of pathological molecular markers. For instance, it is well established that mutations within *KRAS* and *BRAF* oncogenes lead to an increased risk of developing colorectal cancer through the activation of the epidermal growth factor receptor. A recent case case-control study of 959 Chinese CRC cases found that one's mutational status is associated with variables such as sex, smoking status, serum carbohydrate antigen 19-9 and carcinoembryonic antigen[30]. According to the findings of this paper, colorectal cancer tumours with mutated *KRAS* or *BRAF* were associated with higher levels of serum carbohydrate antigen 19-9 and carcino-embryonic antigen which are considered to be indicative of poor prognosis and survival in CRC patients[30]. Moreover, another pathological molecular epidemiology study determined that having a first degree relative with CRC is significantly associated with having wild type *KRAS*[31]. Many of the studies looking at specific subsets of CRC patients are recent and still substantial variability between individual papers is present, making it exceedingly difficult to perform a meta-analysis with high clinical importance. Over the next decade, as newer studies in the field of molecular pathological epidemiology become available, an updated meta-analyses can potentially examine specific subsets of colorectal cancer, such as those with mutated *KRAS* and *BRAF* to further explore the role of family history as compared or in combination of other factors demonstrated by molecular epidemiology studies.

Future studies should aim to determine how these environmental factors act in conjunction with genetic factors to affect patients with a family history.

In conclusion, we have found that patients with a positive family history of colorectal cancer in first-degree relatives are at a significantly higher risk of developing the disease. These findings could be used for the development of guidelines for screening and preventative programs for patients of colorectal cancer relatives in all populations. The development of such guidelines could yield population-wide health benefits, as national organizations such as the American Cancer Society, currently focus on individuals at an average risk of colorectal cancer as opposed to those at an increased risk for their guidelines[32]. In addition, although
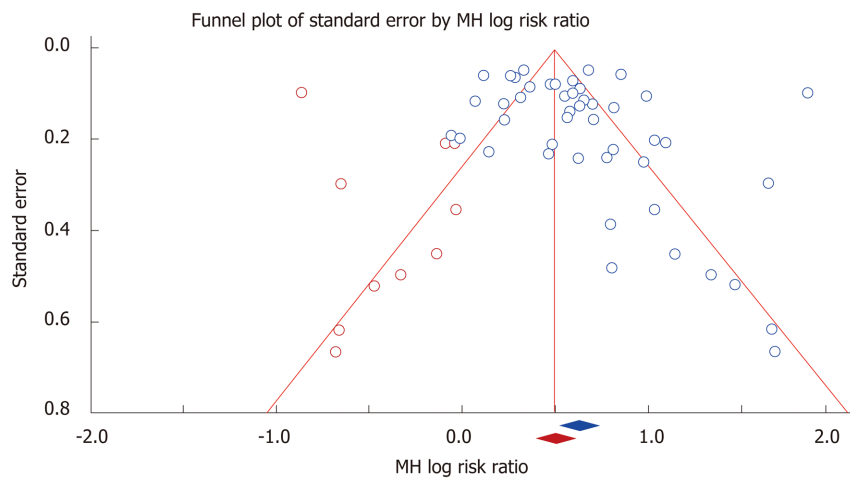
Figure 3 Trim and Fill analysis of the funnel plot to adjust for asymmetries. Red dots indicate studies which were imputed.

some organizations, such as United States. Multi-society Task Force on Colorectal Cancer, have produced guidelines directed at high-risk populations, they require further validation by more recent studies[12]. Despite development of multiple non-invasive modalities to screen average-risk individuals, none has been validated in a rigorous study in individuals with positive family history. Therefore, the results of our meta-analysis might provide grounds for future studies to develop better screening methods as compared to colonoscopy in this population[10-12].

Study or subgroup	Cases Events	Total	Controls Events	Total	Weight	Risk ratio M-H, Random, 95%CI
1.1.1 Asian Studies						
Arafa 2011	20	220	9	220	1.2%	2.22 [1.03, 4.77]
Bener 2010	33	146	39	282	2.1%	1.63 [1.08, 2.48]
Emami 2015	67	200	26	231	2.1%	2.98 [1.97, 4.99]
Guo 2010	20	167	6	157	1.0%	3.13 [1.29, 7.60]
Huang 2004	124	1352	2456	50706	2.7%	1.89 [1.59, 2.25]
Jia 2007	38	345	33	670	2.0%	2.24 [1.43, 3.50]
Jo 2012	21	187	21	976	1.6%	5.22 [2.91, 9.36]
Kim 2009	33	596	10	509	1.4%	2.82 [1.40, 5.66]
Kotake 1995	45	363	24	363	1.9%	1.88 [1.17, 3.01]
Lohsoonthorn 1995	19	279	5	279	0.9%	3.80 [1.44, 10.03]
Mahmoudi 2014	39	303	46	354	2.1%	0.99 [0.67, 1.47]
Mahmoudi 2016	32	261	36	339	2.0%	1.15 [0.74, 1.81]
Minami 2003	30	488	159	2444	2.2%	0.94 [0.65, 1.38]
Otani 2006	9	375	8	750	0.9%	2.25 [0.88, 5.78]
Rennert 2010	295	2566	204	2566	2.7%	1.45 [1.22, 1.71]
Senda-Nakagawa HERPACC（Ⅰ）2017	179	1867	557	9335	2.7%	1.61 [1.37, 1.89]
Senda-Nakagawa HERPACC（Ⅱ）2017	96	829	347	4145	2.6%	1.38 [1.12, 1.71]
Seow 2002	12	121	5	222	0.8%	4.40 [1.59, 12.21]
Subtotal (95% CI)		10665		74548	33.0%	1.83 [1.54, 2.16]
Total events	1112		3991			

Heterogeneity: Tau^2 = 0.07; Chi^2 = 61.16, df = 17 (*P*<0.00001); I^2 = 72%

Test for overall effect: *Z* = 6.97 (*P*<0.00001)
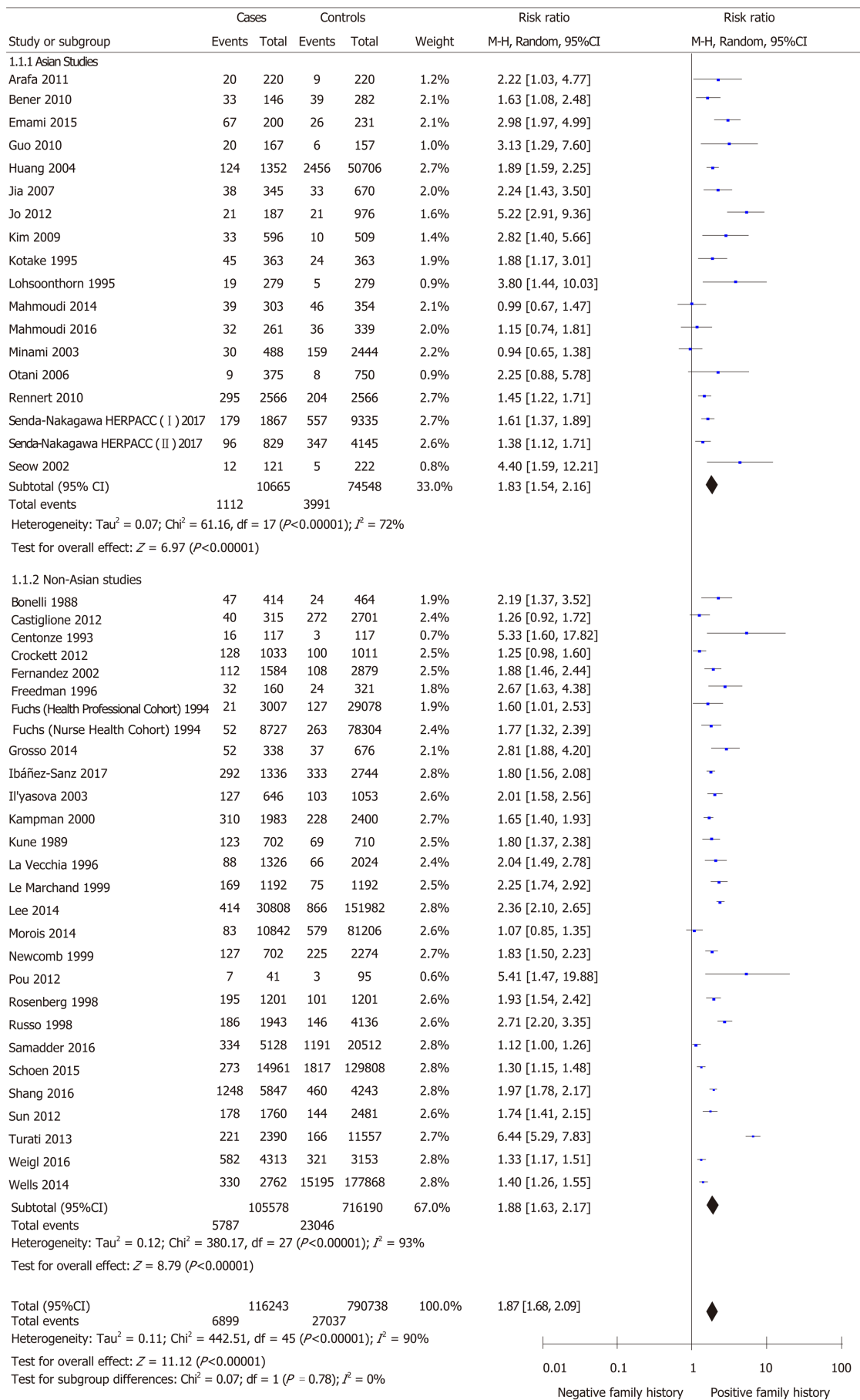
Study or subgroup	Cases Events	Total	Controls Events	Total	Weight	Risk ratio M-H, Random, 95%CI
1.1.2 Non-Asian studies						
Bonelli 1988	47	414	24	464	1.9%	2.19 [1.37, 3.52]
Castiglione 2012	40	315	272	2701	2.4%	1.26 [0.92, 1.72]
Centonze 1993	16	117	3	117	0.7%	5.33 [1.60, 17.82]
Crockett 2012	128	1033	100	1011	2.5%	1.25 [0.98, 1.60]
Fernandez 2002	112	1584	108	2879	2.5%	1.88 [1.46, 2.44]
Freedman 1996	32	160	24	321	1.8%	2.67 [1.63, 4.38]
Fuchs (Health Professional Cohort) 1994	21	3007	127	29078	1.9%	1.60 [1.01, 2.53]
Fuchs (Nurse Health Cohort) 1994	52	8727	263	78304	2.4%	1.77 [1.32, 2.39]
Grosso 2014	52	338	37	676	2.1%	2.81 [1.88, 4.20]
Ibáñez-Sanz 2017	292	1336	333	2744	2.8%	1.80 [1.56, 2.08]
Il'yasova 2003	127	646	103	1053	2.6%	2.01 [1.58, 2.56]
Kampman 2000	310	1983	228	2400	2.7%	1.65 [1.40, 1.93]
Kune 1989	123	702	69	710	2.5%	1.80 [1.37, 2.38]
La Vecchia 1996	88	1326	66	2024	2.4%	2.04 [1.49, 2.78]
Le Marchand 1999	169	1192	75	1192	2.5%	2.25 [1.74, 2.92]
Lee 2014	414	30808	866	151982	2.8%	2.36 [2.10, 2.65]
Morois 2014	83	10842	579	81206	2.6%	1.07 [0.85, 1.35]
Newcomb 1999	127	702	225	2274	2.7%	1.83 [1.50, 2.23]
Pou 2012	7	41	3	95	0.6%	5.41 [1.47, 19.88]
Rosenberg 1998	195	1201	101	1201	2.6%	1.93 [1.54, 2.42]
Russo 1998	186	1943	146	4136	2.6%	2.71 [2.20, 3.35]
Samadder 2016	334	5128	1191	20512	2.8%	1.12 [1.00, 1.26]
Schoen 2015	273	14961	1817	129808	2.8%	1.30 [1.15, 1.48]
Shang 2016	1248	5847	460	4243	2.8%	1.97 [1.78, 2.17]
Sun 2012	178	1760	144	2481	2.6%	1.74 [1.41, 2.15]
Turati 2013	221	2390	166	11557	2.7%	6.44 [5.29, 7.83]
Weigl 2016	582	4313	321	3153	2.8%	1.33 [1.17, 1.51]
Wells 2014	330	2762	15195	177868	2.8%	1.40 [1.26, 1.55]
Subtotal (95%CI)		105578		716190	67.0%	1.88 [1.63, 2.17]
Total events	5787		23046			

Heterogeneity: Tau^2 = 0.12; Chi^2 = 380.17, df = 27 (*P*<0.00001); I^2 = 93%

Test for overall effect: *Z* = 8.79 (*P*<0.00001)

Total (95%CI)		116243		790738	100.0%	1.87 [1.68, 2.09]
Total events	6899		27037			

Heterogeneity: Tau^2 = 0.11; Chi^2 = 442.51, df = 45 (*P*<0.00001); I^2 = 90%

Test for overall effect: *Z* = 11.12 (*P*<0.00001)

Test for subgroup differences: Chi^2 = 0.07; df = 1 (*P* = 0.78); I^2 = 0%

0.01   0.1   1   10   100

Negative family history   Positive family history

Figure 4 Relative risk of developing colorectal cancer in individuals with a first-degree relative. Subgroup analysis is conducted based on the geographical location where the study was conducted (Asian *vs* non-Asian).

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is one of the most common and dangerous malignancies which is likely caused by a combination of environmental and genetic factors. Although it has been long known that individuals with a positive family history of colorectal cancer are at an increased risk of developing this cancer, a robust quantitative estimate of this increased risk is not available in the medical literature with large variability between individual studies.

Research motivation

Estimating the increased risk of individuals with a positive family history of colorectal cancer could be crucial for the development of preventative and screening guidelines for these individuals. The currently existing screening guidelines for individuals with a positive family history are not based on high quality evidence or absent all-together.

Research objectives

The objective of this report was to accurately estimate the risk of developing colorectal cancer in patients with a positive family history.

Research methods

This project was a meta-analysis of case-control and cohort studies of colorectal cancer patients. Data from individual papers was extracted to independently calculate a relative risk of colorectal cancer in patients with a positive family history.

Research results

We found that a positive family history of colorectal cancer in first-degree relatives is associated with significantly increased risk of colorectal cancer with a relative risk of 1.87 (95%CI: 1.68-2.09; *P* < 0.00001). Future research should aim to determine the influence of environmental factors such as diet and exercise on the familial risk of developing colorectal cancer.

Research conclusions

We found that individuals with a positive family history of colorectal cancer have almost 2-fold higher chance of developing this cancer. To our knowledge, this is the first manuscript in the past decade which estimated the risk of familial colorectal cancer. Our results can substantially contribute to the development of new screening guidelines for individuals with a positive family history.

Research perspective

More research is required to gain a better understanding of the influence of environmental factors on the familial risk of colorectal cancer. In addition, future projects should determine whether the number of first degree relatives affected and their age of initial diagnosis has an effect on the increased risk of this cancer.

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