SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Effects of Family History on Relative and Absolute Risks for Colorectal Cancer: A Systematic Review and Meta-Analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e159. Learning Objective–Upon completion of this activity, successful learners will be able to identify the risk for developing colorectal cancer (CRC) related to the type of family history; identify the absolute risk for developing colorectal cancer for individuals with at least one first degree relative (FDR) with CRC younger than 50 years; and define "familial colorectal cancer."

BACKGROUND & AIMS: **Guidelines recommend that individuals with familial colorectal cancer undergo colonoscopy surveillance instead of average-risk screening. However, these recommendations vary widely. To substantiate appropriate surveillance strategies, precise and valid evidence-based risk estimates are needed for individuals with a family history of colorectal cancer (CRC).**

METHODS: **We systematically searched MEDLINE, EMBASE, and Cochrane from inception to July 2018 for case–control and cohort studies investigating the effect of family history on CRC risk. We calculated summary estimates of pooled relative risks (RRs) using a random-effects model. Life tables were created to convert RR estimates into absolute risk estimates.**

RESULTS: **We screened 4417 articles and identified 42 eligible case–control and 20 cohort studies. In case–control studies, the RR for CRC in patients with 1 first-degree relative (FDR with CRC) was 1.92 (95% CI, 1.53–2.41) and 1.37 (95% CI, 0.76–2.46) for cohort studies. For individuals with 2 or more FDRs with CRC, the RR was 2.81 in case–control studies (95% CI, 1.73–4.55) and 2.40 in cohort studies (95% CI, 1.76–3.28). For individuals having a FDR diagnosed with CRC at an age younger than 50 years, the RR for CRC in their FDRs was 3.57 in case–control studies (95% CI, 1.07–11.85) and 3.26 in cohort studies (95% CI, 2.82–3.77). The cumulative absolute risks for CRC at 85 years in Western Europe were 4.8% for persons with 1 FDR with CRC (95% CI, 2.7%–8.3%), 8.2% for individuals with 2 or more FDRs (95% CI, 6.1%–10.9%), and 11% for persons with a FDR diagnosed with CRC at an age younger than 50 years (95% CI, 9.5%–12.4%).**

CONCLUSIONS: **In this systematic review and meta-analysis, we found that the RR of CRC among FDRs is lower than previously expected, especially based on cohort studies. Risk estimates are affected by the number of relatives with CRC and their age at diagnosis. Intensified colonoscopy surveillance strategies could be considered for high-risk groups. PROSPERO trial identification no: CRD42018103058.**

Keywords: Colon Cancer; Risk Factors; Detection; Family History.

Colorectal cancer (CRC) is the third most incident cancer and the second leading cause of cancer-related deaths.[1] Although the majority of CRC is sporadic, twin studies have shown that up to 30% of patients with CRC harbor a familial component.[2] However, in only 3% to 6% of all CRC cases has a genetic cause been elucidated by identification of mutations in the *APC* gene, *MuTYH* gene, and in the mismatch repair genes, among other less-common mutations.[2]

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Abbreviations used in this paper: **AR, absolute risk; CRC, colorectal cancer; FCC, familial colorectal cancer; FDR, first-degree relative; FH, family history; FIT, fecal immunochemical testing; RR, relative risk; SDR, second-degree relative; TDR, third-degree relative.**

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Familial colorectal cancer (FCC) is defined as the remaining heterogeneous group of individuals carrying an increased familial risk for developing CRC without harboring a known genetic cause. For individuals with family members with CRC, the risk of developing CRC depends on various factors, such as the degree or number of family members affected, or the age at diagnosis of CRC.[3] A recent systematic review and meta-analysis showed that the relative risk (RR) in first-degree relatives (FDRs) of developing CRC was lower than previously reported.[4] Data on the anticipated risk for second-degree relatives (SDRs) and third-degree relatives (TDRs) were not reported. Furthermore, data on case–control and cohort studies were combined and estimates of absolute risk (AR) for CRC were lacking, although important when informing individuals about their risk.

According to various clinical practice guidelines, individuals with FCC are recommended to undergo more intensive surveillance strategies than the general population, starting at an earlier age.[5–8] However, the definition of who should undergo intensified colonoscopy surveillance instead of average-risk screening varies widely.

For individuals who have a family history (FH) of CRC, evidence-based estimates of the RR and AR of developing CRC are needed to decide which patients need more intensive colonoscopy surveillance. Through a systematic review and meta-analysis we wanted to obtain summary estimates of the risk of developing CRC in asymptomatic individuals with a FH of CRC not undergoing surveillance, compared with the general population, and of the AR of developing CRC.

What You Need to Know

Background

To determine appropriate surveillance strategies, precise and valid evidence-based risk estimates are needed for individuals with a family history of colorectal cancer (CRC).

Findings

In a systematic review and meta-analysis, we found that the relative risk of CRC in individuals with 1 first-degree relative (FDR) was not even double that of persons with no relatives with CRC. Risk was higher for persons with 2 or more FDRs with CRC or with a FDR who was diagnosed with CRC at younger than age 50 years.

Implications for patient care

Colonoscopy surveillance strategies should be intensified for persons with a high risk of CRC based on family history of CRC.

Methods

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines.[9] The protocol was registered prospectively at PROSPERO (CRD42018103058).

Search Strategy for Study Identification

Ovid MEDLINE, Ovid EMBASE, and Cochrane were searched for eligible studies from inception to July 2018. The search strategy included 3 main term categories: family, colorectal neoplasm, and risk (Supplementary Appendix 1). No language, publication date, or publication status restrictions were imposed. References cited in selected articles and related meta-analyses were searched for additional eligible studies, referred to as *cross-references*.

Study Selection and Data Extraction

Three reviewers (C.M.-S., V.H.R., and L.M.-P.) independently screened all titles and abstracts. Disagreement between reviewers was solved by consensus. After selection of articles fulfilling the eligibility criteria, data extraction was performed independently by 1 of the 3 reviewers. The data extraction sheet consisted of the following: (1) characteristics of study participants; (2) type of FH: number, degree, and age at diagnosis of each family member with CRC; (3) comparator group; and (4) type of outcome measure. Data extraction was checked by 1 of the 2 other reviewers (C.M.-S. or V.H.R.).

Study Types

Case–control and cohort studies investigating the effect of a FH of CRC on the risk of developing CRC and reporting incidence data were included. A positive FH was defined as having any type of FH of CRC. Studies were included when the risk of developing CRC in adults with family members affected with CRC ($\geq$18 y) was compared with adults not having a FH of CRC.

Studies were excluded if subjects were recruited from colonoscopy surveillance programs (because surveillance decreases the risk of developing CRC), if controls had other malignant conditions, if results were based on mortality data alone, and if information about the type of FH or type of cancer was ill-defined or restricted. When multiple studies reported outcomes retrieved from the same population, only 1 study was selected, either the most applicable to our research question or the study reporting the most recent data.

Risk of Bias Assessment

The risk of bias was assessed independently by 2 reviewers (C.M.-S. and V.H.R.) using the Quality in Prognosis Studies tool.[10] Quality was analyzed based on 6 domains:

study participation; study attrition; prognostic factor measurement; outcome measurement; study confounding; and statistical analysis and reporting. Finally, studies were classified as either high quality or low quality.

Statistical Analysis

In case–control studies, the odds ratio or observed vs expected ratios were calculated. For cohort studies, estimates of RR and corresponding 95% CIs were calculated from extracted data. When crude numbers were not available, an unadjusted summary estimate was used. Odds ratios and observed vs expected ratios were considered a good estimate of the RR because the prevalence of CRC among asymptomatic subjects is considered to be low.[11] When hazard ratios were reported in cohort studies, these were considered estimates of the RR.

Because data were assumed to be heterogeneous, a random-effects meta-analysis using the generic inverse-variance weighting method was used to obtain summary estimates. To reduce heterogeneity, a stratified meta-analysis was performed using the following subgroups: number of FDRs affected (1 FDR, ≥1 FDR, and ≥2 FDRs); ≥1 SDRs, ≥1 TDRs, and age at diagnosis of the index patient. Statistical heterogeneity between studies was assessed using among-study variance (τ^2) and statistic I^2.[12]

Data for case–control and cohort studies were reported separately because case–control studies were assumed to be at higher risk of bias. A sensitivity analysis was performed that included only studies that explicitly excluded patients with Lynch syndrome.

The possibility of publication bias was assessed by inspection of funnel plots.[12] The meta-analysis was performed using Review Manager version 5.3 (The Nordic-Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Summary estimates of cohort studies were converted into AR estimates using the method proposed by Dupont.[13] We chose Western Europe and the United States as reference populations for our AR analysis. Western Europe represented the following countries: Austria, Belgium, France, Germany, Luxemburg, The Netherlands, and Switzerland. The US data were based on the National Institutes of Health and Surveillance, Epidemiology, and End Results databases. First, baseline cancer and mortality hazards were obtained with a life-table approach using age-specific CRC incidence rates of 2018 from Globocan,[14] and the most recent age-specific mortality rates available from the World Health organization[15] (Supplementary Table 1).

Then, under a proportional hazards assumption and accounting for the competing risk of all-cause mortality, absolute CRC risk estimates corresponding to specific RRs were derived (see Appendix I in Dupont[13] for technical details). Namely, we estimated ARs for the general population (RR = 1, by definition) for individuals with the following: 1 affected FDR; at least 1 affected FDR; at least 2 affected FDRs; and at least 1 FDR with CRC diagnosed before age 50 or 60 years. The cumulative AR at 85 years of age was calculated and curves for developing CRC over 10 years were shown graphically. AR data analysis was performed using R version 3.5.1 (RStudio, Inc, Boston, MA).[16]

Results

We identified 7827 articles, of which 4417 articles remained after deduplication (Figure 1). After exclusion and addition of cross-references, 160 articles remained for full-text screening. Of those, a total of 62 articles (42 case–control and 20 cohort studies) fulfilled the eligibility criteria and were included in this meta-analysis.[17–78] Characteristics of selected studies are summarized in Supplementary Tables 2 and 3. Among these, 23 studies were conducted in Europe,[17,18,20,24–26,29,31,34,36,37,39,40,42,46,57,59,60,63–65,71,77] 18 in the Asia-Pacific nations,[19,23,32,38,45,47,49,50,52,54–56,62,66,70,72,74,76] and 21 in America.[21,22,27,28,30,33,35,41,43,44,48,51,53,58,61,67–69,73,75,78] Subjects were enrolled from 1952 until 2014.

Among 42 case–control studies, 23 control groups were selected from the general population,[40–42,44,45,47–49,53,56,58,59,61,63,64,66,70,72–75,77,78] 17 control groups were hospital-based,[37,39,46,50–52,54,55,57,60,62,65,67–69,71,76] 1 consisted of patients retrieved from primary care centers,[38] and 1 study had both hospital and population-based controls.[43] Of 20 cohort studies, 11 had a retrospective design[17,18,20,22–25,27,28,31,34] 8 a prospective design,[19,21,26,30,32,33,35,36] and 1 a cross-sectional design.[29] Seventeen studies used a population-based,[17,18,21–29,31–36] 2 used a screening-based,[19,30] and 1 used a cancer database[20] as control groups. In most case–control and cohort studies the FH was assessed using questionnaires or registry-based FH data.

Risk of Colorectal Cancer According to the Degree and Number of Family Members

Individuals with at least 1 FDR with CRC (Figure 2) were 2.22 (95% CI, 2.00–2.48) times more likely to develop CRC according to 41 case–control studies[37–70,72–78] and 1.67 (95% CI, 1.52–1.82) times more likely according to 12 cohort studies.[17,19,20,26,28–32,34–36] Both case–control and cohort studies showed considerable heterogeneity (I^2 = 82% and I^2 = 100%, respectively). When having only 1 FDR, 8 case-control studies reported a pooled RR of 1.92 (95% CI, 1.53–2.41),[43,50,57,65,72,75–77] and among 3 cohort studies the pooled RR was 1.37 (95% CI, 0.76–2.46) (Figure 2).[30,32,33] Individuals with at least 2 FDRs with CRC (Figure 2) were more likely to develop CRC with a pooled RR of 2.81 (95% CI, 1.73–4.55) among 8 case–control studies,[43,50,57,65,72,75–77] and a pooled RR of 2.40 (95% CI, 1.76–3.28) in 3 cohort studies.[26,30,32] Both types of studies showed substantial heterogeneity (I^2 = 56% and I^2 = 74%, respectively).

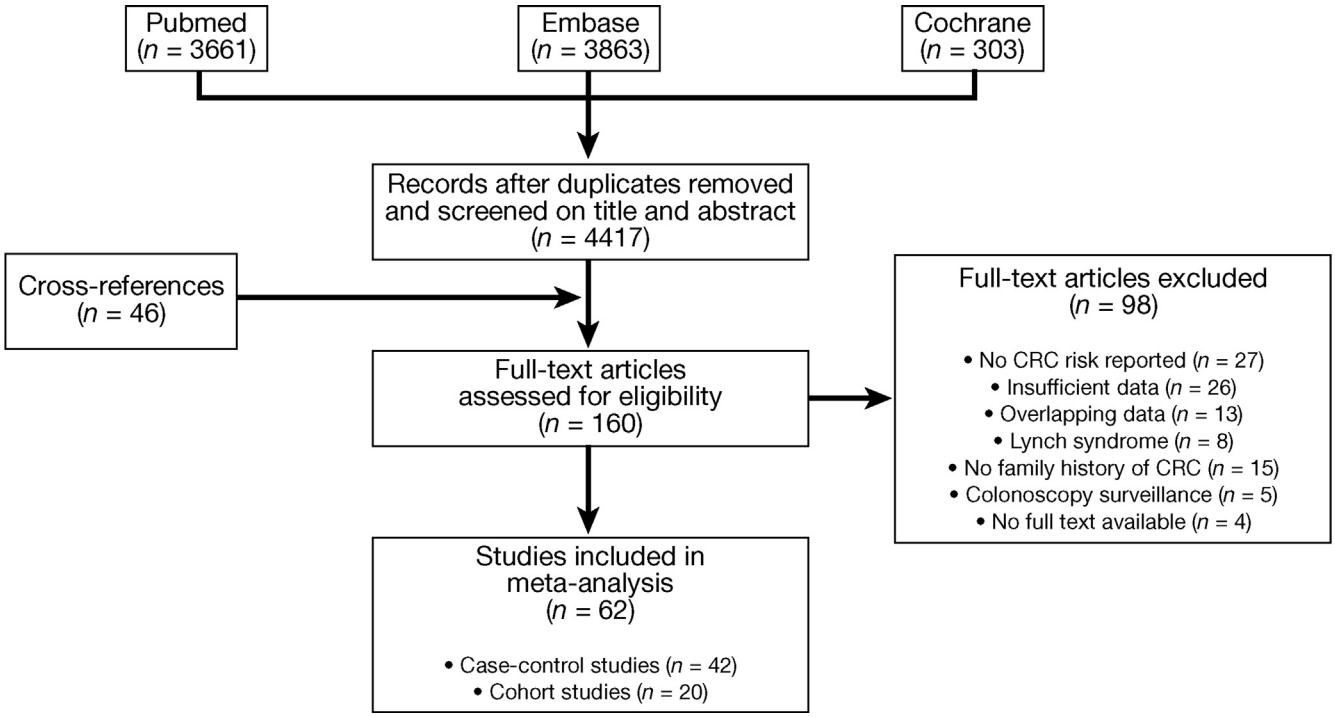

Figure 1. Flow diagram of study selection. CRC, colorectal cancer.

When having at least 1 SDR with CRC a pooled RR of 1.87 (95% CI, 1.39–2.51) was reported in 8 case–control studies,[37,38,49,55,63,72,73,77] and a pooled RR of 1.09 (95% CI, 1.03–1.15) in 3 cohort studies (Figure 2).[17,28,32]

Only 2 case–control studies evaluated the risk of developing CRC among individuals with at least 1 TDR with CRC compared with subjects with no FH, showing a RR of 2.28 (95% CI, 0.48–10.78)[38,73] and a lower pooled RR of 1.05 (95% CI, 1.02–1.08) among 2 cohort studies.[28,32]

Inspection of funnel plots both including as well as excluding Lynch syndrome patients showed asymmetry, suggesting publication bias. Smaller studies showing little or no effect seemed not to have been published (Supplementary Figure 1).

Sensitivity Analysis

In the sensitivity analysis, excluding Lynch syndrome patients, slightly higher pooled RRs were found for both case–control and cohort studies in individuals with at least 1 FDR. In contrast, for individuals with only 1 FDR or at least 2 FDRs with CRC, pooled RRs in both types of studies were lower (Supplementary Figure 2).

Risk of Colorectal Cancer According to Age at Diagnosis

Because the effect of having at least 1 affected FDR was more remarkable and robust and data regarding SDRs and TDRs were limited, we assessed the pooled effect of the age at diagnosis among FDRs using a random-effects meta-analysis model.

The meta-analysis showed that having at least 1 FDR with CRC younger than the age of 50 resulted in a pooled RR of 3.57 (95% CI, 1.07–11.85) for case–control studies[56,73] and 3.26 (95% CI, 2.82–3.77) for cohort studies.[18,21,26,32] Heterogeneity was substantial in case–control studies (I^2 = 65%) and absent in cohort studies. In contrast, among studies reporting on the CRC risk in patients older than age 50, a pooled RR of 1.88 (95% CI, 1.66–2.13)[56,73] and 1.83 (95% CI, 1.55–2.16)[21,26,32] were obtained, respectively (Figure 3).

When index patients were diagnosed at younger than 60 years of age, the pooled RR for case–control and cohort studies on the CRC risk were substantially lower: 2.40 (95% CI, 2.12–2.73)[57,65,73] and 2.02 (95% CI, 1.59–2.57),[18,21,28,30] respectively. Case–control studies showed no heterogeneity whereas cohort studies showed substantial heterogeneity (I^2 = 73%). The CRC risk when there was a relative diagnosed at older than age 60 years was similar to the risk of older than age 50 years for both case–control and cohort studies (pooled RR, 1.98; 95% CI, 1.56–2.52[57,65,73]; and pooled RR, 1.60; 95% CI, 1.35–1.90[21,28,30,32]), respectively (Figure 3).

An inspection of the funnel plot showed no signs of publication bias (Supplementary Figure 3).

Quality Assessment Among Included Studies

Results of the risk of bias assessment are provided in Supplementary Figures 4 and 5 and explained in Supplementary Table 4. The risk of bias assessment

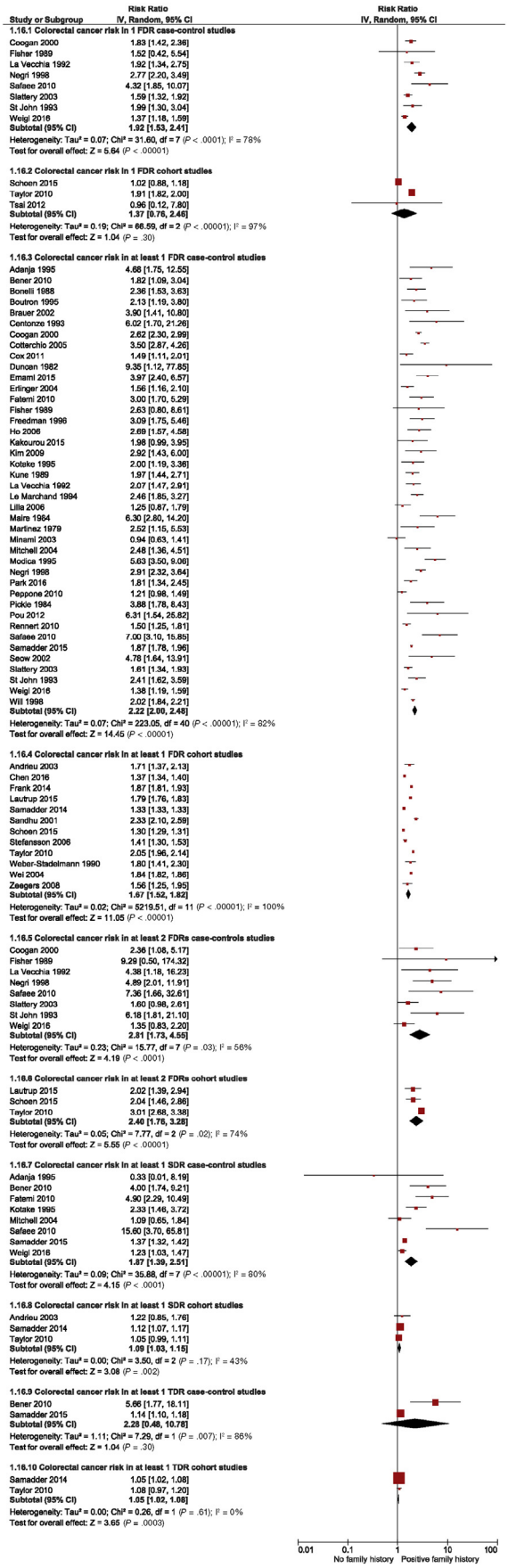

Figure 2. Forest plot degree and number of family members affected. FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.

showed that especially in case–control studies, baseline characteristics often were not well described, resulting in a high risk of bias in study participation. Study attrition, described as the loss to follow-up evaluation of the study population, often was not addressed within the studies. Furthermore, FH assessment often was not verified in the studies, especially in case–control studies. The development of CRC among index patients frequently was confirmed using either pathology reports or medical records. The majority of studies had adjusted for confounding and this was described adequately in the Methods sections, when it concerned the primary analysis of the study.

Absolute Risk Calculations

The cumulative AR of developing CRC in Western Europe at the age of 85 years was 3.5% in the general population, 4.8% (95% CI, 2.7%–8.3%) for those with 1 FDR with CRC, 5.8% (95% CI, 5.3%–6.3%) for those with at least 1 FDR, and 8.2% (6.1%–10.9%) for those with at least 2 FDRs. Regarding age at diagnosis, for those with at least 1 FDR with CRC at younger than age 60 years the cumulative AR was 6.9% (95% CI, 5.5%–8.7%), increasing to 11% (95% CI 9.5%–12.4%) for those with at least 1 FDR at younger than age 50 years (Figure 4*A*). The AR of developing CRC in the United States at age 85 years was 2.7% in the general population, 3.6% (95% CI, 2.0%–6.4%) for those with 1 FDR with CRC, 4.4% (95% CI, 4.0%–4.8%) for those with at least 1 FDR, and 6.2% (4.6%–8.4%) for those with at least 2 FDRs. Regarding the age at diagnosis, for those with at least 1 FDR with CRC at younger than age 60 years the risk of developing CRC was 5.3% (95% CI, 4.2%–6.7%), increasing to 8.3% (95% CI, 7.3%–9.5%) for those with at least 1 FDR at younger than age 50 years (Figure 4*B*).

The probability of developing CRC in the next 10 years until age 60 was less than 1% for the general population and slightly increased to reach a maximum of 1.5% for the US general population and a maximum of 2% for the Western Europe general population at 75 years. For all subgroups of individuals with a positive FH of CRC, the risk of developing CRC in the coming 10 years was less than 1% until age 40 years, and increased to 1.7% (95% CI, 1.5%–2.0%) in the United States and 1.8% (95% CI, 1.5%–2.1%) in Western Europe at 50 years for individuals with at least 1 FDR at younger than age 50 years. The risk of developing CRC per 10-year period increased to 2.0% to 2.7% (95% CI, 1.1%–3.6% and 1.5%–4.8%) between ages 75 and 85 years for individuals with 1 FDR, 3.5% to 4.7% (95% CI, 2.6%–4.7% and 3.5%–6.3%) for individuals with at least 2 FDRs, 2.9% to 4.0% (95% CI, 2.3%–3.7% and 3.1%–5.0%) for persons with at least 1 FDR at younger than age 60 years, and 4.7% to 6.3% (95% CI, 4.1%–5.4% and 5.5%–7.2%) for individuals with at least 1 FDR at younger than age 50 years (Figure 5*A* and *B*) for the US and Western Europe populations, respectively.

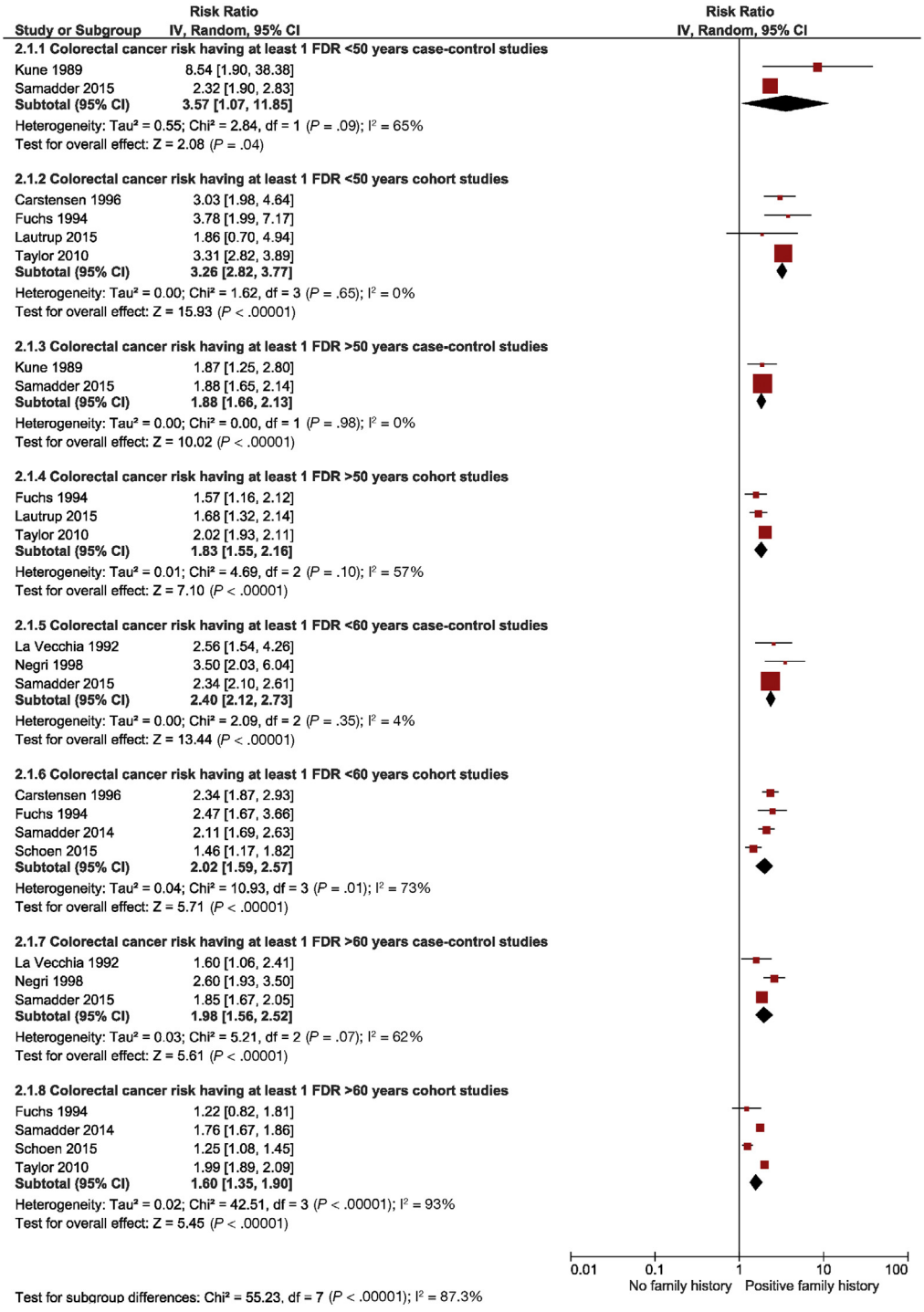

Figure 3. Forest plot age at diagnosis of CRC in FDRs. FDR, first-degree relative.

Discussion

We showed in this systematic review and meta-analysis that the risk of developing CRC in individuals with a FH of CRC is lower than previously reported, especially according to cohort studies.[4,79–81] RRs at least doubled for individuals having at least 1 FDR with CRC based on case–control studies, and almost tripled for those with at least 2 FDRs with CRC and with a FDR diagnosed with CRC before the age of 50 years. Moreover, AR estimates showed that the risk of developing CRC between 40 and 50 years was low and gradually increased at the age of 50, providing rationale for surveillance recommendations from this age onward. Therefore, we believe intensified surveillance strategies might be considered starting at age of 50 years. Our RR and AR estimates may be used to identify the high-risk groups in whom intensified colonoscopy surveillance is justified. For those individuals with a less extensive FH of CRC, average-risk screening options such as fecal immunochemical testing can be proposed.

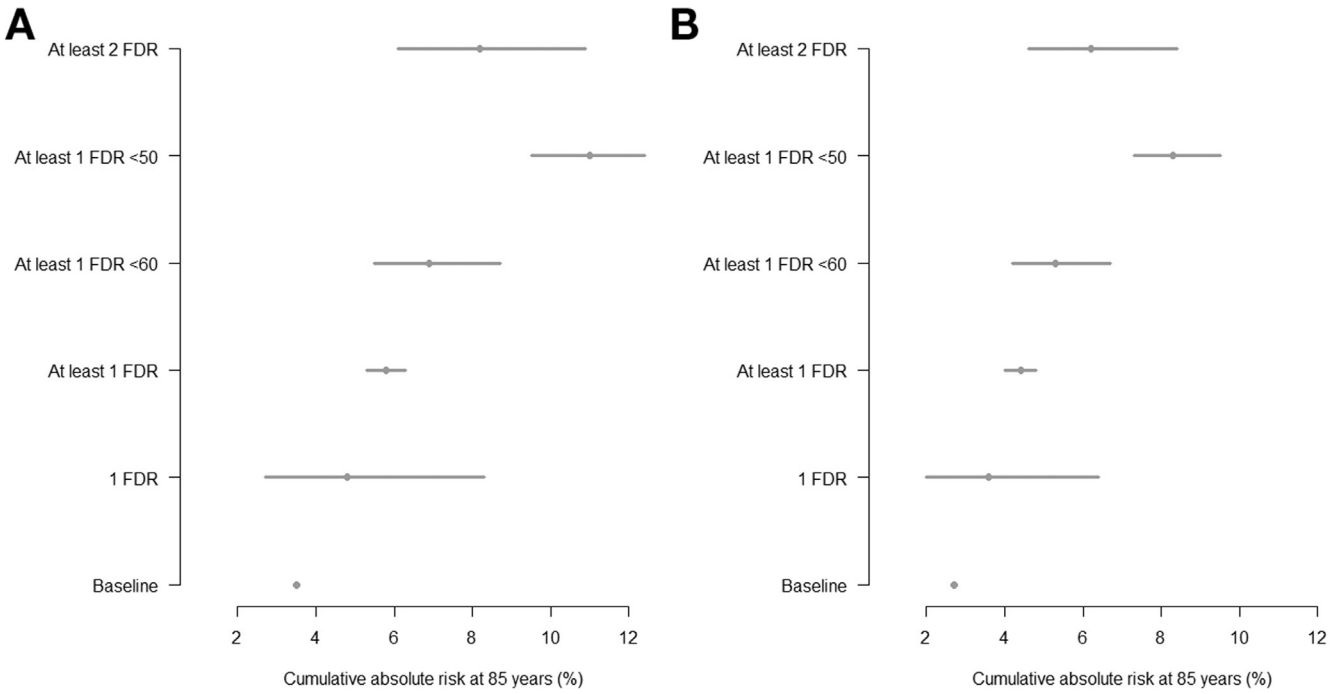

Figure 4. Cumulative absolute risk of developing CRC at 85 years in (*A*) Western Europe and (*B*) the United States. FDR, first-degree relative.

Meta-analyses published between 2001 and 2006 evaluated the risk of developing CRC in individuals with a positive FH of CRC and reported a pooled RR of having at least 1 FDR to be more than 2-fold, ranging from 2.24 to 2.26.[79–81] A more recent meta-analysis showed lower RR estimates (RR, 1.76; 95% CI, 1.57–1.97).[4] However, these previously published meta-analyses had some drawbacks and limitations: summary estimates consisted of both case–control and cohort studies, none of the studies except the study by Butterworth et al[79] addressed ARs, and the role of the inclusion of individuals with Lynch syndrome was not investigated.

In this meta-analysis we showed that the RR of developing CRC was almost tripled for individuals with at least 2 FDRs with CRC, and for individuals with a FDR with a CRC diagnosed at younger than the age of 50 a 3 to 4 times higher pooled risk was reported compared with the general population. In contrast, for individuals with 1 FDR, at least 1 FDR, or a FDR with CRC diagnosed at older than age 50, the risk of developing CRC was

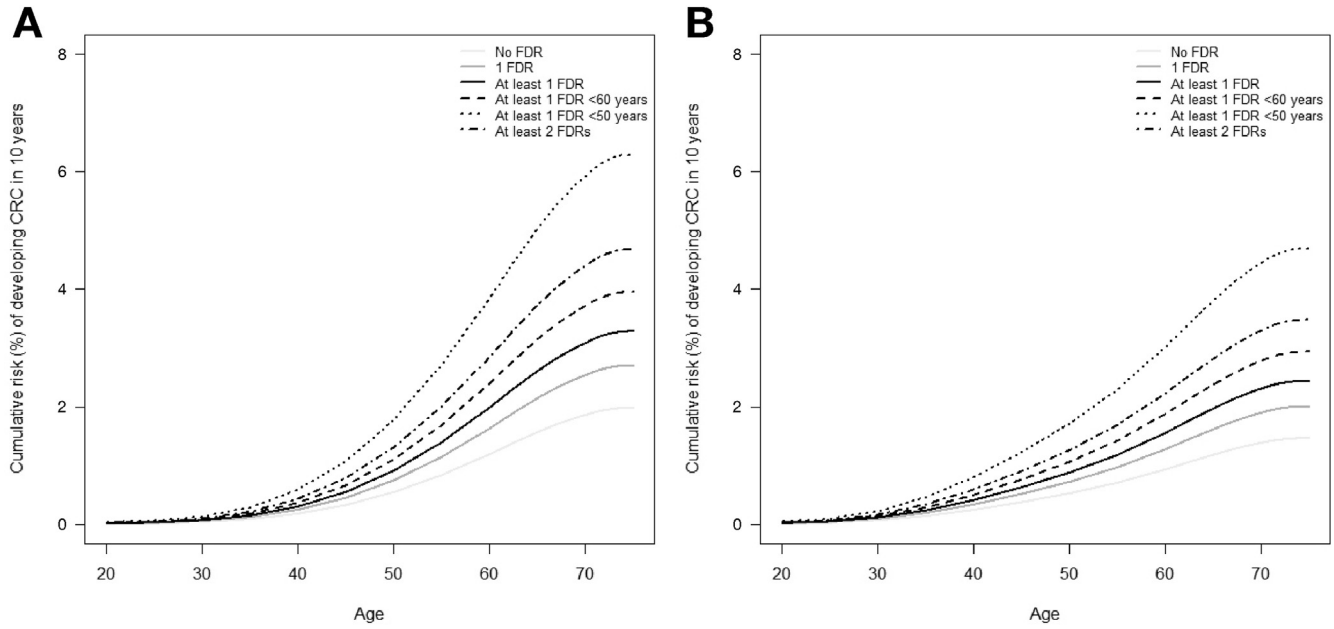

Figure 5. Cumulative absolute risk of developing CRC in 10 years in (*A*) Western Europe and (*B*) the United States. CRC, colorectal cancer; FDR, first-degree relative.

limited with a RR of approximately 2 and a cumulative AR estimate at age 85 years of less than 5%. Furthermore, we also showed just a slight increase in risk when having a SDR or TDR with CRC. Comparison of ARs showed that significantly increased risk starts at the age of 50 among FDRs, in contrast to previous reports that justified starting screening at age 40 years in people with family members with FCC.[21]

Because of the wide variation in CRC risk among individuals with a FH of CRC, it might be important to set a definition of FCC and define who should be screened more intensively. In addition, a certain level of increased RR or AR could contribute to justifying more intensive strategies. AR and 10-year risk estimates provide better insight of an individual's risk,[82] but vary widely in the world.[1] On the other hand, since fecal immunochemical testing (FIT)-based population screening programs have been implemented, FIT also has been evaluated for individuals with a FH of CRC. Quintero et al[83] showed the equivalence of repeated FIT screening annually during 3 years and colonoscopy in FDRs of patients with CRC to detect advanced neoplasia. Moreover, a recent systematic review showed that FIT performance in individuals with a FH of CRC was comparable with the performance in the average-risk population, reporting high diagnostic accuracy for CRC but moderate accuracy for advanced neoplasia.[84] Therefore, it is important to define which individuals are at a specific high risk, justifying a change in preventive measures toward specific colonoscopy surveillance. Nevertheless, future studies and policy makers, considering uptake of screening as well as diagnostic accuracy and costs, should better define for which individuals with a FH of CRC that FIT screening may replace colonoscopy surveillance. This systematic review and meta-analysis, showing both RRs and ARs, therefore may harbor a basis for this discussion.

Some limitations of our study need to be mentioned. Data on CRC risk for those individuals with at least 1 SDR or TDR were limited, as were cohort studies on CRC risk with 1 FDR and at least 2 FDRs. Furthermore, because of the limited number of studies reporting the age at diagnosis, we were not able to calculate the RR per increased unit of age. As a result, multivariable modeling using the number of relatives affected as well as age at diagnosis and age of the proband to make more refined considerations was not possible. ARs are representative for Western Europe and the United States, but can be extrapolated to other parts of the world using specific CRC incidence and all-cause mortality data. We did not address the presence of having a FH of adenomas despite current surveillance recommendations according to different clinical practice guidelines.[5–7] Imperiale and Ransohoff[85] conducted a systematic review on the CRC risk of individuals with a positive FH for adenomas and finally selected only 2 relevant studies. They concluded that there is an increased risk for CRC, however, those 2 studies harbored limitations regarding generalizability and validity. In concordance with this limited available data, the US Preventive Services Task Force recently made the recommendation not to perform more intensive surveillance for individuals with FDRs with adenomas.[86]

This review had several strengths. First, we reported a subgroup analysis per study design. Because cohort studies are less likely to contain bias, we considered these studies to produce estimates closer to the truth. We also provided AR estimates for Western Europe and the United States, which may be used to justify colonoscopy surveillance at a certain risk level. Furthermore, we showed in the sensitivity analysis that the influence of possible inclusion of Lynch syndrome patients did not change our overall estimates. This is most likely because Lynch syndrome only occurs in 2% to 3% of all CRC cases and therefore has little contribution to the overall risk estimates.[2] Finally, we reported data about SDRs and TDRs, which is important information for determining which individuals with FH of FCC are at a specific high risk.

In summary, we showed that the risk of developing CRC in individuals with a FH of CRC is lower than expected, especially according to cohort studies. Individuals with 2 or more FDRs with CRC or a FDR with CRC diagnosed before the age of 50 were at particularly increased risk because their RR almost tripled compared with the general population. Our RR estimates and AR estimates might be used to identify high-risk groups in whom specific surveillance strategies aimed to prevent CRC could be considered. In contrast, the risk of developing CRC for individuals with a less extensive FH lead to lower risk estimates and, for these individuals, average-risk screening programs might be considered an optimal method for CRC prevention.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.09.007.

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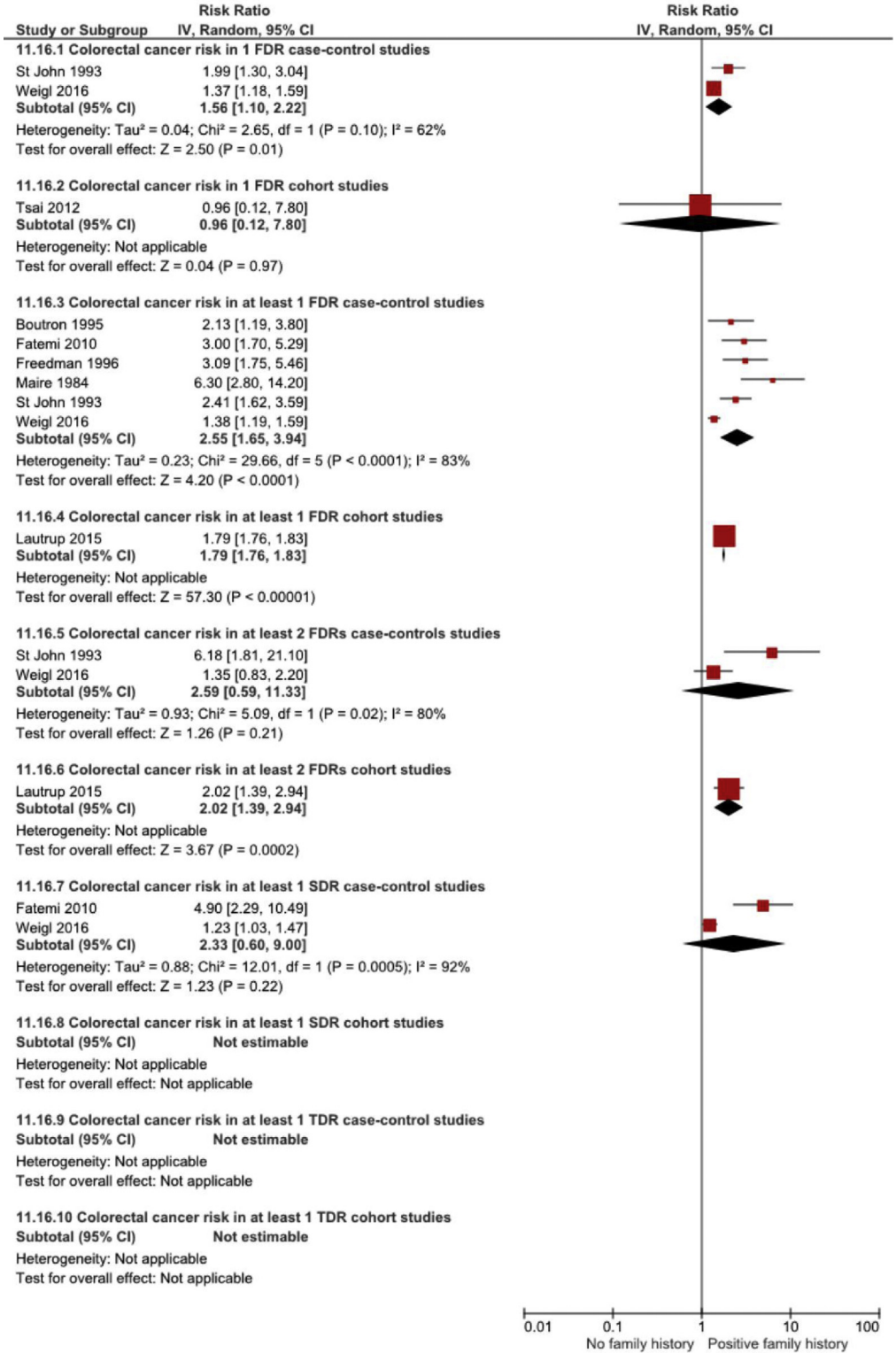
Conflicts of interest
These authors disclose the following: Evelien Dekker has received endoscopic equipment on loan from FujiFilm, a research grant from FujiFilm, honorarium for consultancy from FujiFilm, Olympus, Tillots, GI Supply, and CPP-FAP, a speakers' fee from Olympus, Roche, and GI Supply, and has served on the supervisory board of eNose; and Rodrigo Jover has received honorarium for consultancy from Norgine, Alpha-Sigma, MSD, GI supply, and CPP Pharmaceuticals. The remaining authors disclose no conflicts.

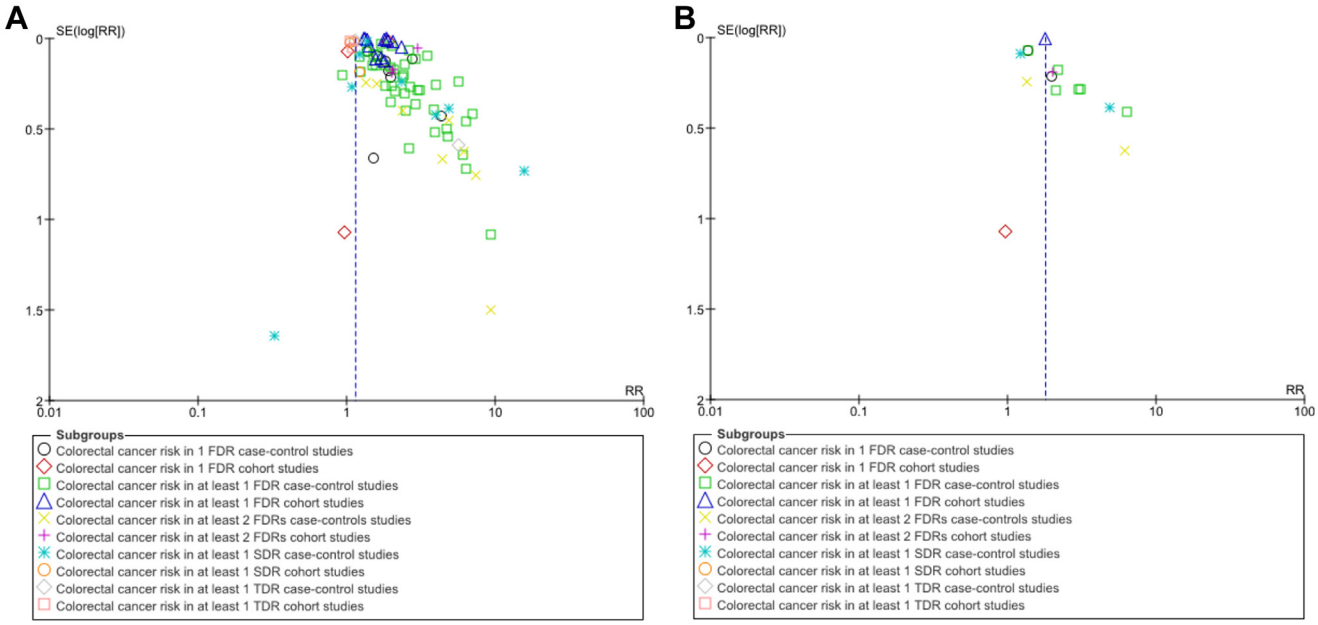
Appendix 1

Search Strategy

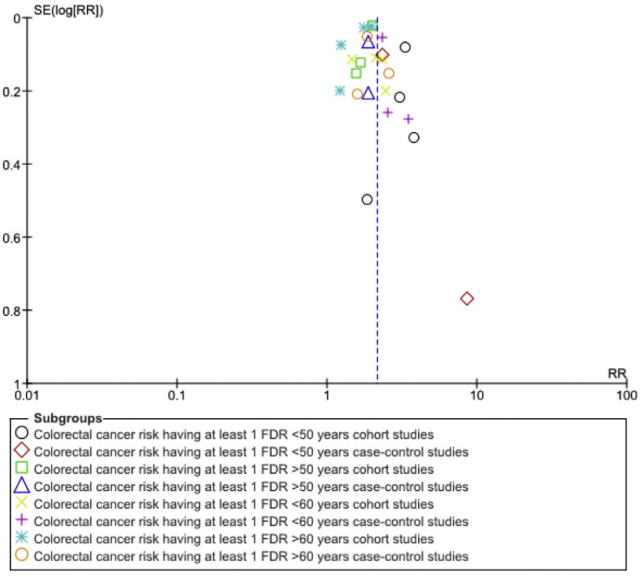
Database	Search terms	Results
PUBMED	("Family"[Mesh] OR famil*[tiab] AND (aggregation[tiab]) OR (("Family"[Mesh] OR famil*[tiab]) AND history[tiab]) OR first degree[tiab] OR second degree[tiab] OR family member[tiab] OR pedigree[tiab]) ("Colorectal Neoplasms"[Mesh] OR (colorectal[tiab] OR colonic[tiab] OR rectal[tiab] OR colon[tiab] OR rectum[tiab] OR anal[tiab] OR anus[tiab]) AND ("Neoplasms"[Mesh] OR "Carcinoma"[Mesh] OR "Adenocarcinoma"[Mesh] OR neoplas*[tiab] OR tumor* [tiab] OR tumour*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma* [tiab])) ("Risk"[Mesh] OR "Incidence"[Mesh] OR "Mortality"[Mesh] OR risk*[tiab] OR incidence[tiab] OR mortality[tiab] OR "Prevalence"[Mesh] OR "Survival"[Mesh] OR prevalence[tiab] OR survival[tiab])	3661
EMBASE	(exp family/ OR famil*.ti,ab,kw.) AND (aggregation or history).ti,ab,kw.) OR (first degree or second degree or family member or pedigree).ti,ab,kw. (exp risk/) OR (exp incidence/) OR (exp mortality/) OR ((risk* or incidence or mortality).ti,ab,kw.) (exp colorectal tumor/) OR ((colorectal or colonic or rectal or colon or rectum or anal or anus).ti,ab,kw.) AND ((exp neoplasm/) OR ((exp carcinoma/) OR (exp adenocarcinoma/) OR (neoplas* or tumor* or tumour* or cancer* or carcinoma* or adenocarcinoma*).ti,ab,kw.))	3863
COCHRANE	(([Family] OR famil*:ti,ab,kw) AND aggregation:ti,ab,kw) OR (([Family] OR famil*:ti,ab,kw) AND history:ti,ab,kw) OR first degree or second degree or family member or pedigree:ti,ab,kw [Colorectal Neoplasms] OR ([Neoplasms] OR [Carcinoma] OR [Adenocarcinoma] OR neoplas* or tumor* or tumour* or cancer* or carcinoma* or adenocarcinoma*:ti,ab,kw) AND (colorectal or colonic or rectal or colon or rectum or anal or anus:ti,ab,kw) [Risk] OR [Incidence] OR [Mortality] OR [Prevalence] OR [Survival] OR risk* or incidence or mortality or prevalence or survival:ti,ab,kw	303



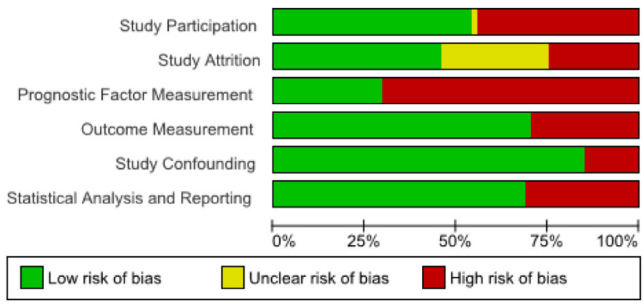
Supplementary Figure 1. Forest plot degree and number of family members affected excluding Lynch syndrome. FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.



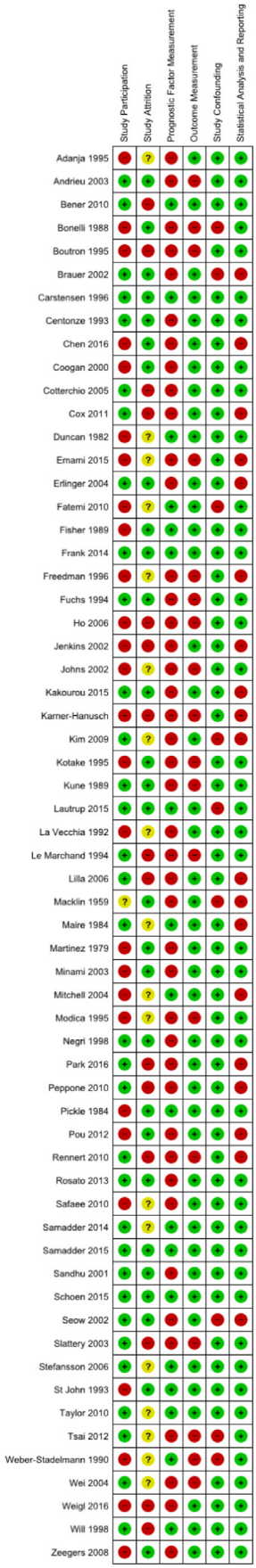
Supplementary Figure 2. (*A*) Funnel plot type of family history. (*B*) Funnel plot type of family history excluding Lynch syndrome. FDR, first-degree relative; RR, relative risk; SDR, second-degree relative; TDR, third-degree relative.



Supplementary Figure 3. Funnel plot age at diagnosis of index case. FDR, first-degree relative.



Supplementary Figure 4. Risk of bias graph.



Supplementary Figure 5. Risk of bias summary table.

Supplementary Table 1. All-Cause Mortality and Colorectal Cancer Incidence Data on Which Absolute Risk Estimates Are Based

Age group, *y*	All-cause mortality,[a] per 100,000 per year	Colorectal cancer incidence,[b] per 100,000 per year
0–4	158.4	0.0
5–9	14.9	0.1
10–14	17.2	0.4
15–19	46.3	0.7
20–24	70.5	1.1
25–29	83.7	1.3
30–34	109.1	2.8
35–39	153.8	5.5
40–44	242.4	12.7
45–49	406.6	24.6
50–54	678.2	43.4
55–59	1111.5	71.7
60–64	1700.5	109.1
65–69	2442.9	156.9
70–74	3801.1	210.0
75–79	6142.1	259.4
80–84	11,320.2	316.7
≥85	28,753.2	372.4

[a]Data are from the World Health Organization.[15]
[b]Data are from Globocan.[14]

Supplementary Table 2. Summary of Cohorts and Cross-Sectional Studies Included in the Analysis

Study	Year	Place	Date	Age of participants, *y*	Male/female ratio	Person-years of follow-up evaluation	Cohort size	Total number of relatives	Control group	Design	Family history assessment
Andrieu et al[17]	2003	France	1993–1998	25–95	NS	117,407	766	5223	Population-based	R	Registry
Carstensen et al[18]	1996	Denmark	1982–1992	<60	NS	222,634	1470	5938	Population-based	R	Registry
Chen et al[19]	2016	Taiwan	1994–2007	≥20	244,545/268,738	3,793,565	513,283	16,109	Screening-based	P	Questionnaire
Frank et al[20]	2014	Sweden	1958–2010	NS	NS	322,923	8,148,737	285,907	Cancer database	R	Registry
Fuchs et al[21]	1994	United States	1986–1992	40–75	32,085	176,093	32,085	3007	Population-based	P	Questionnaire
Fuchs et al[21]	1994	United States	1982–1990	30–55	87,031	663,936	87,031	8727	Population-based	P	Questionnaire
Goldgar et al[22]	1994	United States	1952–1992	All	NS	NS	4010	28,922	Population-based	R	Registry
Jenkins et al[23]	2002	Australia	1992–1996	18–45	NS	120,409	131	2005	Population-based	R	Registry
Johns et al[24]	2002	United Kingdom	1976–1978	<55	NS	NS	205	NS	Population-based	R	Medical reports
Karner-Hanusch et al[25]	1997	Austria	NS	26–90	NS	NS	100	NS	Population-based	R	Registry
Lautrup et al[26]	2015	Denmark	1995–1998	NS	NS	517,219	1200	4182	Population-based	P	Medical reports
Macklin et al[27]	1960	United States	1952–1955	NS	NS	NS	145	1369	Population-based	R	Questionnaire
Samadder et al[28]	2014	United States	1980–2010	22–93	9947/8835	NS	18,782	NS	Population-based	R	Registry
Sandhu et al[29]	2001	United Kingdom	1993–1997	45–74	13,663/16,690	30,202	30,353	NS	Population-based	CS	Questionnaire
Schoen et al[30]	2015	United States	1993–2001	55–74	70,669/74,100	1,588,477	144,769	NS	Screening-based	P	Questionnaire
Stefansson et al[31]	2006	Iceland	1955–2000	NS	NS	526,345	2770	23,272	Population-based	R	Registry
Taylor et al[32]	2010	Australia	2006–2008	≥45	NS	NS	2,327,327	NS	Population-based	P	NS
Tsai et al[33]	2012	United States	2005–2006	40–89	2057/2910	NS	4967	NS	Population-based	P	Medical reports
Weber-Stadelmann et al[34]	1990	Switzerland	1982–1988	28–92	100/84	NS	184	1184	Population-based	R	Medical reports
Wei et al[35]	2004	United States	1986–2000	40–75	46,632	NS	46,632	3947	Population-based	P	Questionnaire
Wei et al[35]	2004	United States	1976–2000	30–55	87,733	NS	87,733	6901	Population-based	P	Questionnaire
Zeegers et al[36]	2008	The Netherlands	1986–1999	55–69	58,279/62,573	NS	120,852	NS	Population-based	P	Questionnaire

CRC, colorectal cancer; CS, cross-sectional study; NS, not stated; P, prospective; R, retrospective.

Supplementary Table 3. Summary of Case–Control Studies Included in the Analysis

Study	Year	Place	Date	Age of participants, *y*	Male/female ratio	Cases, n	Controls, n	Control group	Family history assessment
Adanja et al[37]	1995	Serbia	Belgrade 1984–1986; Kragujevac 1990–1993	24–87	NS	286	286	Hospital-based	Registry
Bener et al[38]	2010	Qatar	2008–2009	Cases: 18–82 Controls: 19–80	249/179	146	282	Primary health care centers	Questionnaire
Bonelli et al[39]	1988	Italy	1980–1986	Cases: 25–91 Controls: 24–93	661/608	414	855	Hospital-based	Questionnaire
Boutron et al[40]	1995	France	1985–1990	30–79	NS	171	309	Population-based	Questionnaire
Brauer et al[41]	2002	Canada	1993–1996	40–79	114/497	329	282	Population-based	Questionnaire
Centonze et al[42]	1993	Italy	1987–1989	Mean, 65.9	130/108	119	119	Population-based	Questionnaire
Coogan et al[43]	2000	United States	1983–1996	<70	NS	1330	9653	Hospital-based	Questionnaire
Coogan et al[43]	2000	United States	NS	20–69	NS	1006	1090	Population-based	Questionnaire
Cotterchio et al[44]	2005	Canada	1997–2000	20–74	1542/1373	971	1944	Population-based	Questionnaire
Cox et al[45]	2011	New Zealand	2007	30–69	572/555	562	571	Population-based	Questionnaire
Duncan et al[46]	1982	United Kingdom	1981	NS	NS	50	50	Hospital-based	Medical records
Emami et al[47]	2015	Iran	NS	NS	NS	200	256	Population-based	Questionnaire
Erlinger et al[48]	2004	United States	1989–2000	>18	230/284	172	342	Population-based	Questionnaire
Fatemi et al[49]	2010	Iran	NS	NS	NS	489	249	Population-based	Questionnaire
Fisher et al[50]	1989	Australia	1975–1984	30–80	NS	146	124	Hospital-based	Medical records
Freedman et al[51]	1996	United States	1982–1993	34–84	NS	163	326	Hospital-based	Questionnaire
Ho et al[52]	2006	China	1998–2000	NS	NS	822	926	Hospital-based	Questionnaire
Kakourou et al[53]	2015	United States	1989–2000	>45	231/287	173	345	Population-based	Questionnaire
Kim et al[54]	2009	Korea	2001–2004	30–79	630/474	596	509	Hospital-based	Questionnaire
Kotake et al[55]	1995	Japan	1992–1994	NS	NS	363	363	Hospital-based	Questionnaire
Kune et al[56]	1989	Australia	1980–1981	NS	NS	702	710	Population-based	Questionnaire
La Vecchia et al[57]	1992	Italy	1985–1991	<75	1694/1304	1222	1766	Hospital-based	Questionnaire
Le Marchand et al[58]	1996	United States	1987–1991	≤84	1396/988	1192	1192	Population-based	Questionnaire
Lilla et al[59]	2006	Germany	2003–2004	30–94	635/474	505	604	Population-based	Questionnaire
Maire et al[60]	1984	France	1979–1983	20–87	NS	170	170	Hospital-based	Questionnaire
Martinez et al[61]	1979	Puerto Rico	1973–1975	≥20	253/208	461	461	Population-based	Questionnaire
Minami et al[62]	2003	Japan	1997–2001	≥40	288/200	488	2444	Hospital-based	Questionnaire
Mitchell et al[63]	2004	United Kingdom	NS	NS	NS	199	133	Population-based	Questionnaire
Modica et al[64]	1995	Italy	1984–1986	NS	NS	389	389	Population-based	Questionnaire
Modica et al[65]	1995	Italy	1988–1990	NS	NS	213	213	Population-based	Questionnaire
Negri et al[65]	1998	Italy	1992–1996	23–74	3198/2909	1953	4154	Hospital-based	Questionnaire
Park et al[66]	2016	Korea	2007–2014	NS	1875/894	923	1846	Population-based	Questionnaire
Peppone et al[67]	2010	United States	1982–1998	Cases: 40–88 Controls: 40–86	2032/1577	1203	2406	Hospital-based	Questionnaire
Pickle et al[68]	1984	United States	1970–1977	NS	129/133	86	176	Hospital-based	Medical records
Pou et al[69]	2012	Argentina	2006–2010	NS	NS	41	95	Hospital-based	Questionnaire
Rennert et al[70]	2010	Israel	1998–2006	NS	2602/2530	2468	2566	Population-based	Questionnaire

Rosato et al[71]	2013	Italy and Switzerland	1985–2009	≤45	903/787	329	1361	Hospital-based	Questionnaire
Safaee et al[72]	2010	Iran	NS	NS	426/360	393	393	Population-based	Questionnaire
Samadder et al[73]	2015	United States	1980–2010	NS	105,335/94,425	18,208	181,552	Population-based	Questionnaire
Seow et al[74]	2002	Singapore	1999–2000	≥20	145/198	121	222	Population-based	Questionnaire
Slattery et al[75]	2003	United States	1991–1994 1997–2001	30–79	2833/2214	2298	2749	Population-based	Questionnaire
St John et al[76]	1993	Australia	1952–1985	NS	NS	523	523	Hospital-based	Medical records
Weigl et al[77]	2016	Germany	2003–2014	>30	4512/2954	4313	3153	Population-based	Questionnaire
Will et al[78]	1998	United States	1959–1960	≥30	NS	15,487	848,212	Population-based	Questionnaire

NS, not stated.

Supplementary Table 4. Risk of Bias Legend

Domains	Rating	Prompting items for consideration
Study participation	High bias	No description of the source population using a baseline table
	Low bias	Adequately described source population, inclusion and exclusion criteria, and baseline table
		No or small nonsignificant differences in participants and nonparticipants are accounted for in the analysis
Study attrition	High bias	>20% Loss to follow-up evaluation owing to prognostic factors related to the outcome
	Low bias	<20% Loss to follow-up evaluation owing to prognostic factors related to the outcome
Prognostic factor measurement	High bias	The family history was not assessed for the control group or nothing was mentioned about the collection of data on family history
		Family history was assessed by questionnaire without verification
	Low bias	Family history was assessed by interview/questionnaire with verification using medical records/histology reports
Outcome measurement	High bias	Method of outcome measurement is different for cases and control groups, or no verification of outcome at all
	Low bias	Colorectal cancer based on questionnaire data and verification through medical records/histology, data were analyzed per subgroup of method of verification
Study confounding	High bias	Family history estimate is not part of the primary analysis and therefore not adjusted for confounders
		No adjustment or unequal distribution
	Low bias	Matching or adjustment for multiple relevant confounders
Statistical analysis and reporting	High bias	Family history estimate is not part of the primary analysis and therefore was not discussed in the statistical analysis of the methods
		Only a multivariate model was reported without explanation about how this was conducted
		Reported only summary estimates without raw data
	Low bias	Adjustment for factors prespecified in statistical analysis, raw data present