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Is Diabetes Mellitus an Independent Risk Factor for Colon Cancer and Rectal Cancer?

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Abstract

OBJECTIVES—Diabetes mellitus (DM) has been associated with an increased risk of colorectal cancer (CRC). The American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 recommend that clinicians be aware of an increased CRC risk in patients with smoking and obesity, but do not highlight the increase in CRC risk in patients with DM. To provide an updated quantitative assessment of the association of DM with colon cancer (CC) and rectal cancer (RC), we conducted a meta-analysis of case–control and cohort studies. We also evaluated whether the association varied by sex, and assessed potential confounders including obesity, smoking, and exercise.

METHODS—We identified studies by searching the EMBASE and MEDLINE databases (from inception through 31 December 2009) and by searching bibliographies of relevant articles. Summary relative risks (RRs) with 95% confidence intervals (CIs) were calculated with fixed- and random-effects models. Several subgroup analyses were performed to explore potential study heterogeneity and bias.

RESULTS—DM was associated with an increased risk of CC (summary RR 1.38, 95% CI 1.26–1.51; $n = 14$ studies) and RC (summary RR 1.20, 95% CI 1.09–1.31; $n = 12$ studies). The association remained when we limited the meta-analysis to studies that either controlled for smoking and obesity, or for smoking, obesity, and physical exercise. DM was associated with an increased risk of CC for both men (summary RR 1.43, 95% CI 1.30–1.57; $n = 11$ studies) and

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CONFLICT OF INTEREST

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women (summary RR 1.35, 95% CI 1.14–1.53; *n* = 10 studies). For RC, there was a significant association between DM and cancer risk for men (summary RR 1.22, 95% CI 1.07–1.40; *n* = 8 studies), but not for women (summary RR 1.09, 95% CI = 0.99–1.19; *n* = 8 studies).

CONCLUSIONS—These data suggest that DM is an independent risk factor for colon and rectal cancer. Although these findings are based on observational epidemiological studies that have inherent limitations due to diagnostic bias and confounding, subgroup analyses confirmed the consistency of our findings across study type and population. This information can inform risk models and specialty society CRC screening guidelines.

INTRODUCTION

Approximately 76,000 men and 72,000 women were diagnosed with cancer of the colon and rectum in the United States in 2009, and 49,900 died from this disease (1). Colorectal cancer (CRC) is the fourth most common cancer in the United States (2), and fourth in men and third in women worldwide (3). Understanding the risk factors for this disease is integral to the development of effective strategies for the prevention of CRC. The risk of developing CRC is influenced by both genetic and acquired risk factors. Acquired risk factors associated with CRC identified in prior studies include (4) the following: (i) dietary factors, such as low intake of fruit, vegetables, or fiber, and high intake of red meat, saturated fat, caffeine, or alcohol (5–9); (ii) lifestyle factors, such as lack of exercise, smoking, and obesity (10–12); (iii) side effects of some medical or surgical interventions, such as pelvic irradiation, cholecystectomy, and ureterocolic anastomosis (13–16); (iv) comorbid medical conditions such as Barrett's esophagus, human immunodeficiency virus infection, diabetes mellitus (DM), acromegaly, and inflammatory bowel disease (17–21). These conditions may either directly modify risk (e.g., diet) or may serve as personal markers of altered risk through shared genetic or environmental exposures, separate from any direct mechanistic link (e.g., Barrett's esophagus).

In 1910, Maynard (22) provided one of the earliest reports on the association between DM and cancer. Recently, a series of studies and meta-analyses confirmed that the risk for several solid and hematological malignancies (including liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers, and non-Hodgkin's lymphoma) is elevated in diabetic patients (23). In 1984, Williams *et al.* (24) published a retrospective analysis of three patient populations and documented a statistically significant, over 2-fold increase in the prevalence of overt DM in CRC patients compared with age-matched controls. The search for a pathological explanation for this connection has led to the so-called hyperinsulinemia hypothesis. Giovannucci (25) hypothesized that insulin, an important growth factor, may at high serum concentrations increase the risk of CRC by promoting growth of colon tumors, and acting as a cell mitogen. Other proposed explanations for the increased risk include decreased bowel transit time and elevated fecal concentrations of bile acids (26,27). Yang *et al.* (28) showed that insulin treatment may further elevate risk for CRC among patients with type 2 DM.

Although there is some heterogeneity in the published literature regarding the association between DM and CRC, a meta-analysis by Larsson *et al.* (19) in 2005 showed a relationship between DM and increased risk of CRC in both women and men by combining relative risk (RR) of colon cancer (CC) and rectal cancer (RC) (summary RR of CRC incidence 1.30, 95 % confidence interval (CI) 1.20–1.40). They also did subgroup analyses and identified elevated summary RRs of CC (summary RR 1.43, 95 % CI 1.28–1.60; *n*=7 studies) and RC (summary RR 1.33, 95 % CI 1.14–1.54; *n*=7 studies). CRC has been historically considered together; however, it is increasingly being recognized that differences in etiology and risk may exist between right CCs, left CCs, and RCs (29,30). Since the previous meta-analysis, several new studies have published separate data for CC and RC.

The American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 recommend that clinicians be aware of an increased risk of CRC in cigarette smokers and obese patients (31), but do not highlight the increased risk in patients with DM. Obesity and smoking are associated with the incidence of both type 2 DM and CRC (12,32–34); thus, they also could be important positive confounders of the association between DM and CRC. The previous meta-analysis by Larsson *et al.* (19) did not specifically evaluate for these confounders.

To provide an updated quantitative assessment of the association of DM with CC and RC risk, we conducted a meta-analysis of case–control and cohort studies. We evaluated whether the association varied by sex and study design, and calculated summary RRs separately for CC (n=14 studies) and RC (n=12 studies). We also provide the first meta-analysis to quantitatively assess the effect of certain potentially important confounding variables including obesity, smoking, and physical exercise.

METHODS

Search strategy

We identified studies by a literature search of the EMBASE and MEDLINE databases (from inception through 31 December 2009) for English-language studies with the following medical subject heading terms and/or text words: “diabetes mellitus,” “diabetes,” “colorectal cancer,” “colorectal neoplasm,” “colon cancer,” “colon neoplasm,” “rectal cancer,” “rectal neoplasm,” and “risk factor.” We also reviewed reference lists of the identified publications for additional pertinent studies.

Inclusion and exclusion criteria

Only reports fulfilling the following inclusion criteria were included in the meta-analysis. First, studies were included only if they reported an estimate of RR of colon and/or RC in individuals with DM compared with individuals without DM, with a corresponding measure of uncertainty (i.e., 95 % CI, standard error, variance, or *P* value). Studies reporting only RR for CRC were excluded. Studies were also excluded if the estimates were not adjusted by age. Second, we included case–control studies or cohort studies published as original articles; cross-sectional, ecological, and prevalence studies were excluded. Third, only studies that included distinct cohorts of patients were included. For multiple reports on the same population or subpopulation, we considered the estimates from the most recent report or the one containing the most cases.

Data extraction

The data extracted included publication data (the first author’s last name, year of publication, and country of the population studied), study design, number of cases, number of exposed and unexposed subjects (cohort studies), number of controls and the source of the controls (case–control studies), follow-up period (for cohort studies), type of DM (type 1 or 2), risk estimates with their corresponding CIs, and variables controlled for by matching or in the multivariable models. Abstractions of the data elements and the assessment of methodological quality (see below) were conducted separately by two authors (HY and CS); discordant results were resolved by consensus.

Assessment of methodological quality

We assessed the methodological “quality” of included studies based on the Newcastle-Ottawa Scale (35) for quality of case–control studies and cohort studies in meta-analysis; for this assessment, we used the Newcastle-Ottawa Scale star system (range, 0 to 9 stars). In the current study, we considered a study awarded seven or more stars as a high-quality study,

because standard validated criteria for important end points have not been established. The mean value for the six case–control studies and eight cohort studies assessed was 5.3 stars and 6.2 stars, respectively. A table containing the rankings for each study is shown in the Supplementary data online.

Statistical analysis

Summary RR estimates were calculated using both the fixed-effects inverse variance weighting method (36) and the random-effects method (37). Statistical heterogeneity between studies was evaluated with Cochran's Q-test and the I^2-statistic (38). Publication bias was assessed by constructing a funnel plot and using Egger and Begg tests (39,40). All statistical analyses were carried out with STATA, version 11.0 (Stata Corp, College Station, TX). P values that were less than 0.05 were considered statistically significant. All statistical tests were two-sided.

As it is increasingly being recognized that differences in etiology and risk may exist between right CCs, left CCs, and RCs (29,30), we calculated summary RRs separately for CC and RC. Too few studies provided separate data for the right and left CCs to calculate separate summary RRs for these.

In order to explore potential heterogeneity and evaluate different forms of possible bias, several subgroup analyses were performed. These included subgroup meta-analyses based on study design (case–control vs. cohort), sex, type of RR estimate (odds ratio, incidence rate ratio, standardized incidence ratio, and hazard ratio), and whether or not the studies adjusted for certain important potential confounders (obesity, smoking, or physical exercise).

RESULTS

Study characteristics

Detailed search steps are described in Figure 1. Briefly, from the initial literature search we identified and screened 3,966 abstracts. Sixty-nine articles were considered of interest and full text was retrieved for detailed evaluation. References cited by all 69 studies were reviewed and two additional studies were identified, for a total of 71 articles for full review. Fifty-seven of the seventy-one articles did not meet the study inclusion and were excluded. Fourteen independent studies met our predefined inclusion criteria. Of these 14 studies, 6 were case–control studies (41–46) and 8 were cohort studies (Table 1) (47–54). Three of the cohort studies calculated incidence rate ratios as the measure of RR (47–49). Of the remaining five cohort studies, three presented standardized incidence ratios (50–52) and two presented hazard ratios (53,54). In terms of the geographical settings of the studies, seven studies were conducted in the United States and Canada, five in Europe, and two in Japan. Excluded studies (26,55–64) that reported only RR for CRC are listed in Table 2. None of the cohort studies specified whether the circumstances and methods for diagnosing CC were the same for patients with DM and without DM. Only one study (by Hu *et al.* (49)) controlled for smoking, body mass index (BMI), and exercise, and also had follow-up >10 years, therefore no additional subgroup analyses were performed.

CRC incidence

Individual study results and the overall summary results are shown separately for CC and RC in Figure 2 and Figure 3, respectively. The summary RR was 1.38 (95 % CI 1.26–1.51) for the 14 studies with data on CC and 1.20 (95 % CI 1.09–1.31) for the 12 studies with data on RC. There was evidence of heterogeneity for both CC (Q=45.57, P value for heterogeneity=0.002, I^2=51.7%) and RC (Q=25.58, P value for heterogeneity=0.06,

I^2=37.5%). Bowers *et al.* (54) included only smokers and excluding this study had little impact on our results. Table 3 shows the results of subgroup meta-analyses by study design, sex, and whether studies adjusted for potential confounders (obesity, smoking, and physical exercise). The association between DM and CC incidence was similar in case–control studies (summary RR 1.36, 95% CI 1.22–1.52; *n*=11 studies) and cohort studies (summary RR 1.40, 95 % CI 1.23–1.58; *n*=12). The association between DM and RC incidence was higher in case–control studies (summary RR 1.31, 95 % CI 1.12–1.53; *n*=7) than in cohort studies (summary RR 1.16, 95 % CI 1.02–1.31; *n*=10). The results for CC were similar in men (summary RR 1.43, 95 % CI 1.30–1.57; *n*=11) and women (summary RR 1.35, 95% CI 1.14 – 1.53; *n*=10). For RC, there was a significant association between DM and cancer risk for men (summary RR 1.22, 95 % CI 1.07 – 1.40; *n*=8), but not for women (summary RR 1.09, 95% CI=0.99–1.19; *n*=8 studies).

Subgroup meta-analysis by methodological quality of the studies as ranked by the Newcastle-Ottawa Scale scale revealed a similar significant positive association in both the high-quality studies (summary RR=1.44 95% CI 1.24–1.66 *n*=9 studies for CC, summary RR=1.30 95% CI 1.10–1.54 *n*=6 studies for RC) and the low-quality studies (summary RR=1.35 95% CI 1.21–1.51; *n*=14 studies for CC, summary RR=1.17 95% CI 1.04–1.31; *n*=11 studies for RC).

Smoking and obesity are potentially the most important known confounders of the positive association between DM and CRC risk. In the meta-analysis that was restricted to the seven publications that controlled for these variables (41,43,45,48,49,53,54), the positive association of diabetes with CC (summary RR 1.34, 95% CI 1.17–1.52; *n*=12 studies) and RC (summary RR 1.28, 95% CI=1.06–1.54; *n*=9 studies) remained. In the meta-analysis that was restricted to the five publications that controlled for smoking, obesity, and physical activity (43,45,48,49,53), the positive association of DM with CC (summary RR 1.37, 95% CI 1.18–1.59; *n*=10 studies) and RC (summary RR 1.34 95% CI 1.08–1.67; *n*=7 studies) also remained.

Publication bias

Visual inspection of the Begg funnel plot for both CC and RC did not show the asymmetry typically associated with publication bias (Figure 4). Evidence of publication bias was also not seen with the Egger or Begg tests (Egger *P*=0.27 and 0.64 for CC and RC, respectively).

DISCUSSION

This meta-analysis of observational studies indicates that DM is associated with increased risks of CC and RC. To our knowledge, this meta-analysis is the first to show a statistically significant association between DM and risks of CC and RC separately after controlling for obesity, smoking, and physical exercise, which are important potential confounders. Many of the odd ratios we identified are close to 1.0; however, the very low *P* values show that these are unlikely due to chance (*P*<0.0001 for CC and *P*<0.0001 for RC).

The association of DM and cancer risk was stronger for CC than for RC (summary RR 1.38, 95 % CI 1.26 – 1.51 vs. summary RR 1.20, 95 % CI 1.09–1.31, respectively). This difference may be because the proximal colon, distal colon, and rectum have different embryological origins (65). Previous studies have found subsite variations in susceptibility to carcinogens and neoplastic transformation (66,67). Molecular biological studies also indicate that tumor suppressor genes and point mutations and genetic instability differ by subsite of the colorectum (68–71).

Type 2 DM and CC and RC share similar risk factors, including smoking and obesity (12,32–34). Thus, the increased risk of CC and RC associated with a history of DM could be the result of confounding by these risk factors. A meta-analysis by Botteri *et al.* (34) on smoking and CRC showed that the pooled risk estimate for ever vs. never smokers was 1.25 (95 % CI 1.14 – 1.37), and a meta-analysis by Moghaddam *et al.* (12) showed that the estimated RR of CRC was 1.19 (95 % CI 1.11–1.29) comparing obese (BMI>30kg/m^2) with normal weight people (BMI<25kg/m^2).

The positive association of DM with CC and RC risk did not decrease when the meta-analysis was limited to studies that controlled for smoking and BMI (summary RR for colon 1.34, 95 % CI 1.17–1.52, and summary RR for rectum 1.28, 95% CI 1.06–1.54). This suggests that the confounding effect of obesity and smoking is relatively weak, and that DM appears to be an independent risk factor for CC and RC.

Statistical heterogeneity was seen in several of our analyses, and much of this is likely due to differences in study design, study population, definition of diabetes, and statistical methods (e.g., type of RR estimate). Statistical heterogeneity was lower in our analyses of studies which adjusted for BMI, smoking, and physical activity than in the analyses of studies that did not adjust for these potential confounders. This suggests that the lack of these adjustments in some studies accounted for much of the heterogeneity observed.

Data from several sources suggest that the association between DM and the risk of CRC is biologically plausible. Type 2 DM is associated with hyperinsulinemia. Mechanistically, insulin stimulates cell proliferation through two pathways. One pathway involves direct binding of insulin to insulin or insulin-like growth factor-1 (IGF-1) receptors, and the other pathway is via inhibition of IGF-binding proteins and the resultant increase in IGF-1 availability to the IGF receptor (72). The IGF system is a potent growth regulator closely linked with carcinogenesis (73). Although not consistent across all studies, several prospective observational studies have shown an association between elevated IGF-1 levels and the risks of CRC or advanced adenoma (74–78). These data support the notion that IGF-1 has a role in the biological pathway of colorectal neoplasia, beginning at the adenoma stage.

Several limitations of this study must be considered. All of the studies that assess the association between DM and CRC are observational studies, as an intervention study addressing this question would not be ethical or feasible. Rating the scales for strength of evidence rank the quality of evidence derived from observational studies as low, especially as compared with randomized trials (79). However, there are several indications that despite the inherent limitations of observational studies, our finding that DM is associated with an increased risk of CRC may be a real association. These include comparable results for different study designs (case–control and cohort), a lack of heterogeneity among studies that adjusted for important confounders, and consistency of the results within the population-based studies, which increases the ability to generalize study results to similar large populations. These results, however, should still be viewed with caution, as the magnitude of effect found was modest; such moderate effects may be due to unmeasured confounding that persists across studies.

Most of the studies reviewed did not distinguish between type 1 and type 2 DM. Type 1 accounts for 5–10% of all cases of diabetes and type 2 accounts for 90–95 % of all DM cases (80). DM duration and insulin requirement are different in type 1 and type 2 DM, and this may affect tissue exposure to insulin in different ways. If hyperinsulinemia has a role in promoting cancer initiation and progression, it might be expected that duration of DM would

affect cancer RRs. Indeed, six studies used in this meta-analysis showed that CRC risk was higher among diabetics with longer duration of disease (42,45,47,49,51,52).

Because almost one-third of diabetics is undiagnosed (81), some degree of non-differential misclassification of exposure to diabetes is likely to have occurred in the studies, included in this meta-analysis. Although the American Diabetes Association and the World Health Organization now share identical diagnostic criteria for type 2 DM, diagnostic criteria have changed over time (82). The prevalence of DM can change as a function of diagnostic criteria used (83). The studies used in this meta-analysis did not specify which criterion for DM was used, and in most studies the DM was self-reported. Such non-differential misclassification of exposure would tend to underestimate the true relationship between DM and CRC.

Although some of the studies included in this meta-analysis controlled for obesity, smoking, or lack of physical activity, we were unable to control for other important potential confounders of the relationship between DM and CRC, including low intake of fruits and vegetables and high alcohol intake (84,85). These confounders are more prevalent in individuals of lower socioeconomic status (86). The lack of adjustment for socioeconomic status, diet, and alcohol consumption could contribute to a non-causal association between DM and CRC. However, alcohol intake and fruit and vegetable intake are likely correlated with obesity, smoking, and exercise. Because of these relationships, studies that adjusted for obesity, smoking, and exercise probably also, at least partially, adjusted for these other related factors. In addition, our finding that adjustment for obesity, smoking, and exercise had little impact on the relationship between DM and CRC suggests that further adjustment for alcohol and fruit and vegetable intake is unlikely to have a major impact on this relationship.

There are ethnic differences in the incidence of CRC in the United States. The age-adjusted incidence rates for CRC (2000–2006) are highest for blacks (both males and females), followed by non-Hispanic whites, Asian/Pacific Islanders, Hispanics, and American Indians/Alaska natives (SEER database) (1). This may distort the true relationship between DM and CRC, if these differences are not taken into account.

Another potential bias is detection bias. A person with DM is likely to have many more contacts with the health-care system than a person without DM. This might have provided more opportunities for them to have a sigmoidoscopy, colonoscopy, or fecal blood test ordered. Although the extent of this bias is unknown, it is possible that modest increases in cancer incidence could be explained solely by more intense screening in the DM group.

In this meta-analysis, no evidence of publication bias was seen in the funnel plot or in Begg or Egger tests (Egger P=0.27 and 0.64 for CC and RC, respectively). However, it should be noted that several factors other than publication bias can affect the outcome of these statistical tests, and their validity and interpretation has been debated (87).

Finally, it is widely accepted that the majority of CRCs develop slowly through polypoid growth, and endoscopists have traditionally focused on finding and removing polypoid adenomas–growths that protrude from the mucosa – during screening colonoscopy. Reports from Japan in the 1980s and 1990s suggested that nonpolypoid (flat and depressed) colorectal neoplasms were common and ominous (88,89). The likelihood that nonpolypoid (flat and depressed) colorectal neoplasms harbor serious pathology (*in situ* or submucosal carcinoma) was more than five times higher than the rate polypoid lesions after adjusting for polyp size (90). It is only recently that the existence of nonpolypoid (flat and depressed) colorectal neoplasm has been shown to contribute to the development of CRC (91). As a result, many endoscopists may not be aware of the subtle features of these lesions.

Furthermore, one study indicated that diabetic patients (irrespective of insulin use, diabetic control, or diabetic neuropathy) have a significantly poorer response to a colonoscopy bowel cleansing preparations than do nondiabetic patients (92). A recent study also suggests that optimal bowel preparation was significantly poorer in DM patients with autonomous neuropathy than in DM patients without autonomous neuropathy and controls (93). The diagnostic accuracy of the colonoscopy depends on the quality of the colon cleansing. If patients with DM are less likely to have precancerous polyps removed on colonoscopy, this may increase their risk of subsequent cancer over long periods of time. Conversely, if poor preparations lead to decreased cancer detection on short-term studies, this could underestimate the true relationship between DM and CRC.

Our results have important clinical and public health implications. The results from this meta-analysis suggest that DM is an independent risk factor of CC and RC. Although observational studies cannot exclude confounding as an explanation, especially when effect sizes are modest to moderate, the consistency of the evidence suggests a potential role for hyperinsulinemia or factors related to insulin resistance in colorectal carcinogenesis. Other data suggest that chronic insulin therapy is associated with increased colorectal adenoma risk among type 2 DM patients. These results may suggest a need for more intensive CRC screening program in patients with type 2 DM, especially those who receive chronic insulin therapy (94).

In the United States, about 23.6 million people or 7.8% of adults have DM (95), and by 2050, the number of people in the United States with diagnosed DM is estimated to grow to 48.3 million (80). Furthermore, as a recent study indicated, persons with DM and CRC may be at increased risk for CRC recurrence, non-response to chemo and radiotherapy treatment, and treatment-related complications (96). CRC deaths may be reduced through CRC screening programs. We encourage the American College of Gastroenterology to review CRC screening guidelines to determine whether diabetic status should be included as a risk factor that warrants changes in screening frequency or intensity. We also recommend that future studies on the association between DM and CRC focus on plausible causal mechanisms or mediating factors, such as obesity, smoking, physical activity, diagnostic bias, duration of diabetes, and antidiabetic therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Diabetes mellitus (DM) has been associated with an increased risk of colorectal cancer (CRC).
- The American College of Gastroenterology (ACG) Guidelines for Colorectal Cancer Screening 2008 recommend that clinicians be aware of an increased CRC risk in patients with smoking and obesity, but do not highlight the increase in CRC risk in patients with DM.
- Obesity and smoking are associated with the incidence of both type 2 DM and CRC; thus, they also could be important positive confounders of the association between DM and CRC.

WHAT IS NEW HERE

- We assess the effect of certain potentially important confounding variables, including obesity, smoking, and physical exercise.
- Our data suggest that diabetes mellitus is an independent risk factor for colon and rectal cancer.

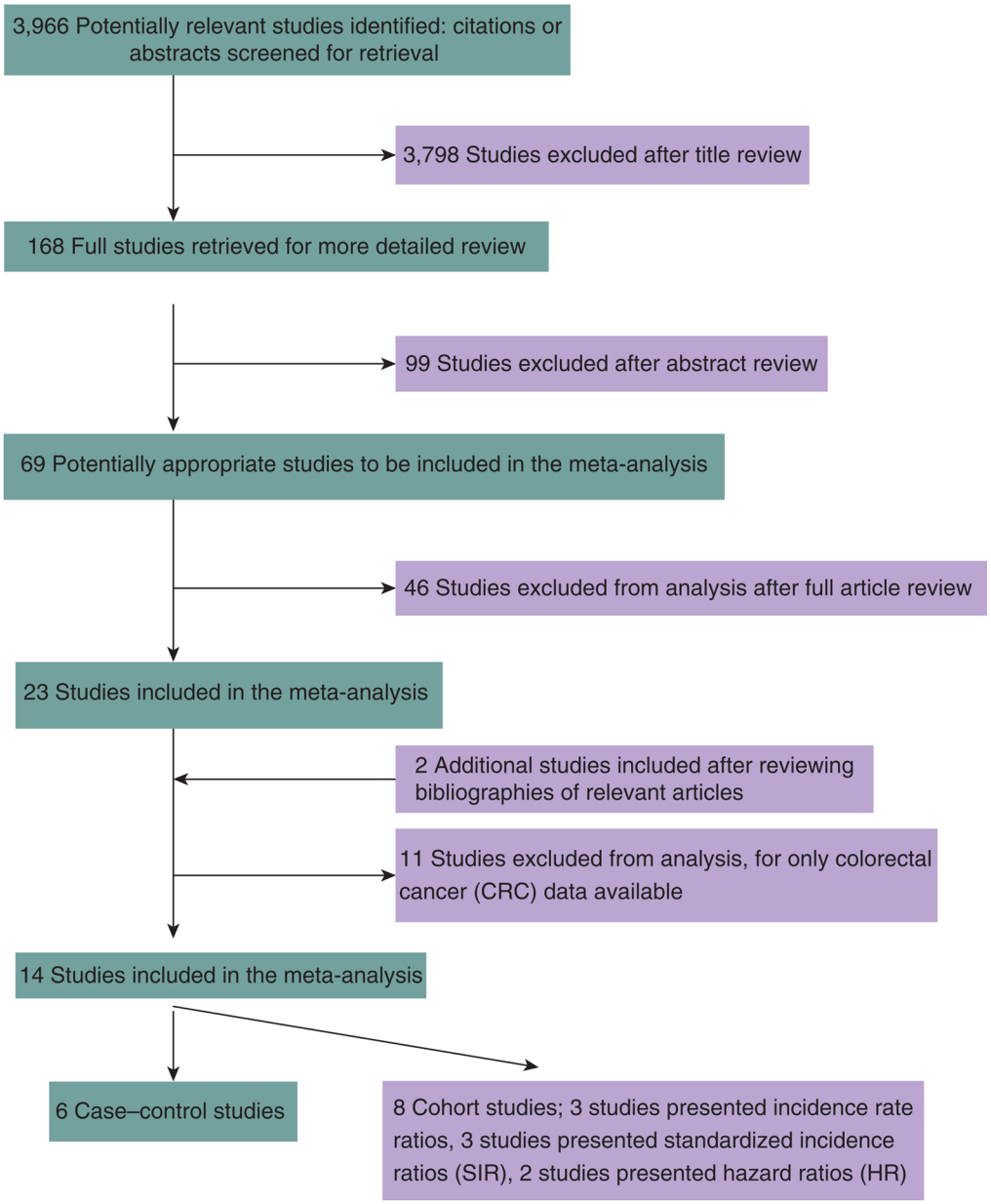

Figure 1.
Flowchart of meta-analysis.

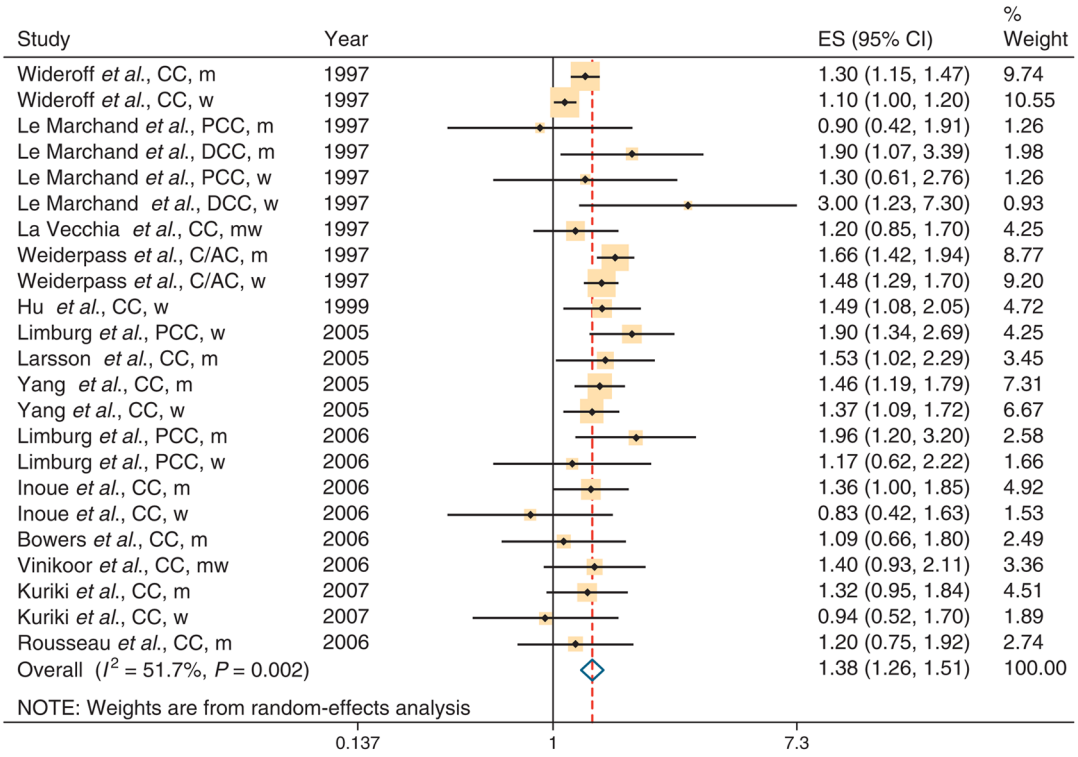

Figure 2.

Association between diabetes and colon cancer (CC) incidence in six case–control and eight cohort studies. AC, ascending colon; C, cecum; CI, confidence interval; DCC, distal colon cancer; ES, effect size; m, men; PCC, proximal colon cancer; w, women.

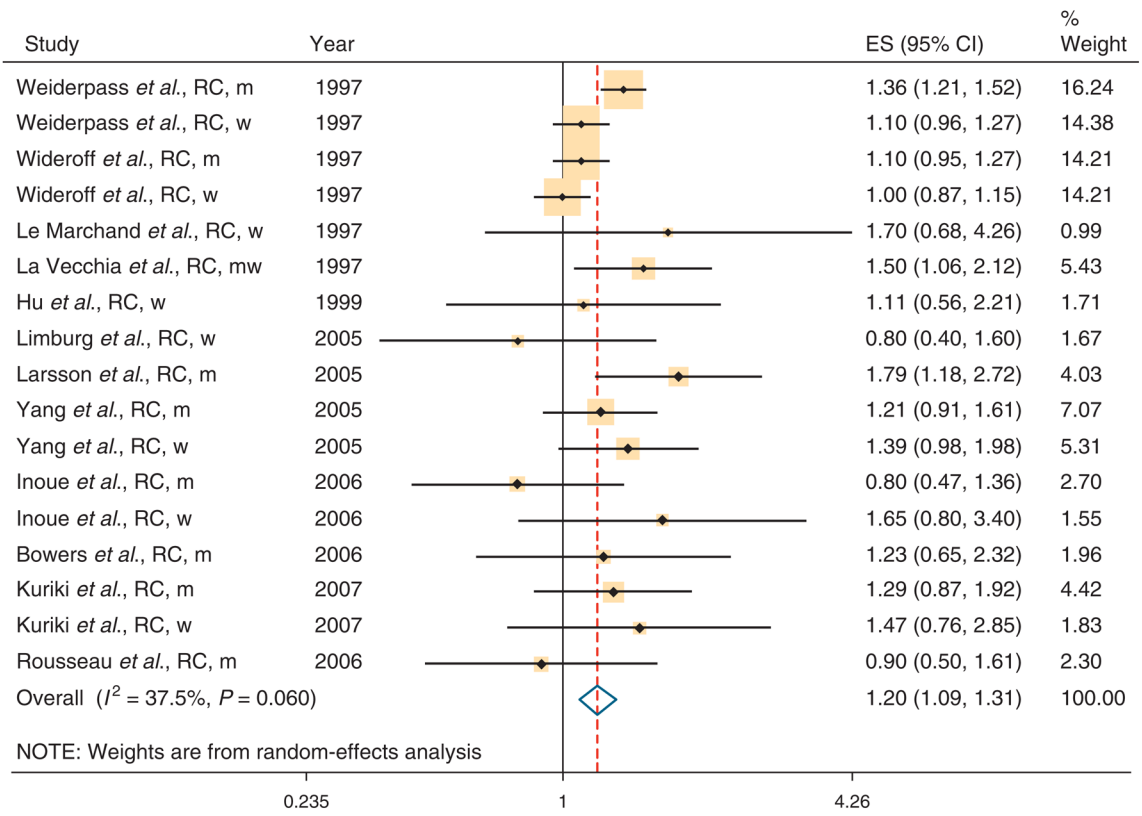

Figure 3.
Association between diabetes and rectal cancer (RC) incidence in six case–control and eight cohort studies. CI, confidence interval; m, men; w, women.

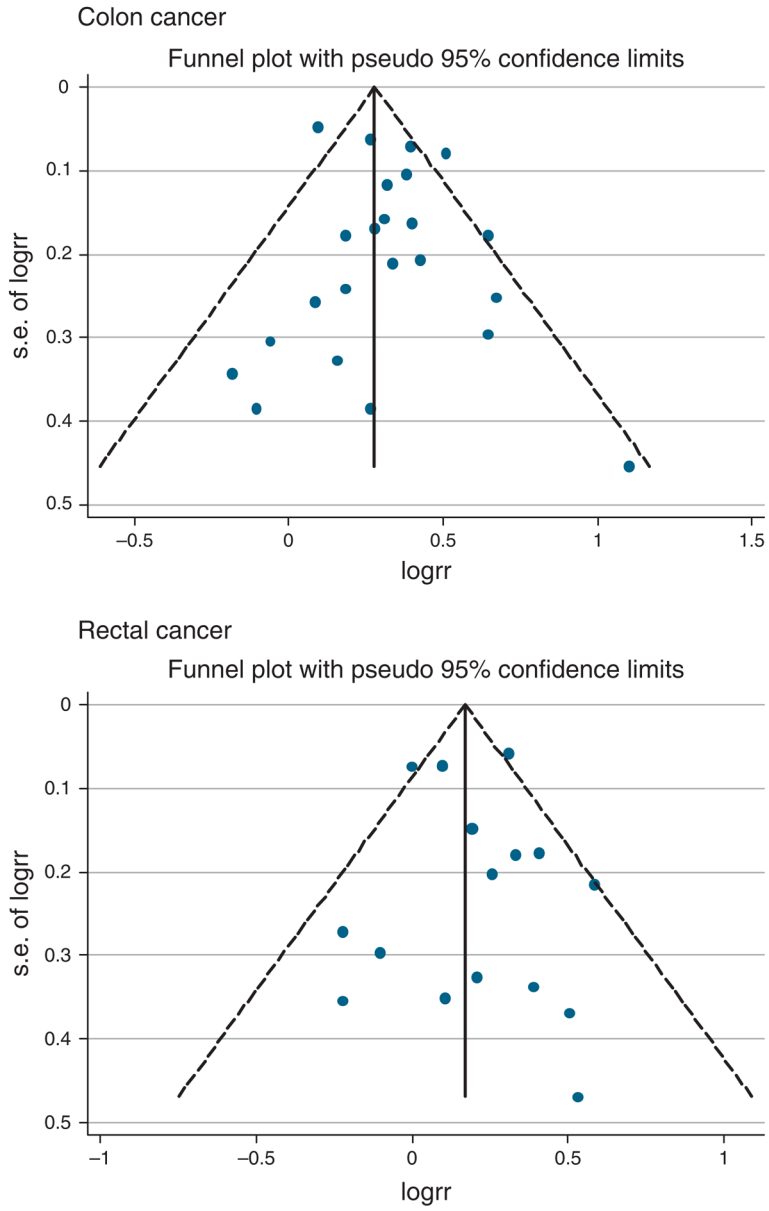

Figure 4.
Funnel plot with pseudo 95% confidence limits.

Table 1

Characteristics of studies of diabetes mellitus and colon and/or rectal cancer

Author, year (ref. no.), country	No. of case patients by cancer subsites	No. of control subjects (source of controls)	Type of diabetes	RR (95% CI), sex, cancer site	Controlled variables
Case–control studies of diabetes and colon and/or rectal cancer incidence					
Rousseau *et al.*, 2006 (41), Canada	435 CC 234 RC	509 (population controls matched by age)	Type 1 and 2 (self-reported)	1.2 (0.7–1.8), m, CC 0.9 (0.5–1.6), m, RC	Age, BMI, cigarette, calothene, marital status, family income, education
Vinikoor *et al.*, 2009 (42), U.S.A	606 CC	971 (population controls matched)	Type 1 and 2 (self-reported)	1.4 (0.93–2.12), m + w, CC	Age, BMI, family history of CRC, calcium, calorie, sex
Kuriki *et al.*, 2007 (43), Japan	382 CC 304 RC	47,768 (cancer-free controls)	Type 1 and 2 (self-reported)	1.32 (0.95–1.84), m, CC 0.94 (0.52–1.71), w, CC 1.29 (0.87–1.92), m, RC 1.47 (0.76–2.85), w, RC	Age, BMI, cigarette, exercise, alcohol, family history of CRC, family history of cancer, fruit/ vegetable, calothene
Yang *et al.*, 2005 (44), USA	6,862 CC 3,585 RC	104,429 (population controls matched)	Type 2 (medical records)	1.45 (1.25–1.70), m + w, CC 1.34 (1.08–1.68), m + w, RC	Age
Le Marchand *et al.*, 1997 (45), USA	825 CC 350 RC	1,192 (population controls matched by age, sex, and ethnicity)	Type 1 and 2 (self-reported)	0.9 (0.4–1.8), m, PCC 1.9 (1.1–3.5), m, DCC 1.3 (0.6–2.7), w, PCC 3.0 (1.2–7.1), w, DCC 0.7 (0.3–1.6), m, RC 1.7 (0.7–4.4), w, RC	Age, BMI, cigarette, exercise, family history of CRC, calcium, calorie, fiber, egg
La Vecchia *et al.*, 1997 (46), Italy	1,225 CC 728 RC	4,154 (hospital patients without cancer and gastrointestinal disease)	Type 1 and 2 (self-reported)	1.2 (0.8–1.6), m + w, CC 1.5 (1.1–2.2), m + w, RC	Age, BMI, exercise, alcohol, family history of CRC, greasy food, calorie, fiber, education, area of residence sex
Author, year (ref. no.), country, (follow-up period)	**Study population**			**RR (95% CI), sex, cancer site (number of cases)**	**Controlled variables**
Cohort studies of DM and colon and/or rectal cancer incidence based on incidence rate ratios					
Limburg *et al.*, 2005 (47), USA (1986–1999)	Exposed group: 1,900 women with self-reported DM (type 2) Comparison group: 33, 072 women without self-reported DM			1.9 (1.3 to 2.6), w, PCC (402) 1.1 (0.6 to 1.8), w, DCC (259) 0.8 (0.4 to 1.6), w, RC (196)	Age, BMI, vitamin, calcium, calorie
Larrson *et al.*, 2005 (48), Sweden (1997–2004)	Exposed group: 3,847 men with self-reported DM (type 2) Comparison group: 41,703 men without self-reported DM			1.53 (1.02–2.29), m, CC (190) 1.79 (1.18–2.73), m, RC (156)	Age, BMI, cigarette, exercise, family history of CRC, fruit/ vegetable, vitamin, NSAIDs, dairy food, meat, education
Hu *et al.*, 1999 (49), USA (1976–1994)	Exposed group: 7,069 women with self-reported DM (Type 2) Comparison group: 111, 003 women without self-reported DM			1.49 (1.09–2.06), w, CC (607) 1.11 (0.56–2.21), w, RC (176)	Age, BMI, cigarette, exercise, alcohol, family history of CRC, vitamin, NSAIDs, meat, hormonal therapy, menopausal status

Author, year (ref. no.), country	No. of case patients by cancer subsites	No. of control subjects (source of controls)	Type of diabetes	RR (95% CI), sex, cancer site	Controlled variables
Cohort studies of diabetes and colon and/or rectal cancer based on standardized incidence ratio (50–52) *and hazard ratio* (53,54)					
Limburg *et al.*, 2006 (50), USA (1971–1994)	Exposed group: 1975 Rochester residents with DM	Comparison group: Rochester population		1.96 (1.16–3.10), m, PCC (18) 1.17 (0.58–2.09), w, PCC (11)	Age
Weiderpass *et al.*, 1997 (51), Sweden (1965–1989)	Exposed group: 153,852 patients with discharge diagnosis of DM (type 1 and 2)	Comparison group: Swedish population		1.66 (1.42–1.93), m, C/AC (172) 1.48 (1.28–1.69), w, C/AC (210) 1.19 (0.87–1.59), m, TC (46) 1.31 (1.00–1.67), w, TC (63) 1.20 (0.71–1.90), m, DC (18) 1.38 (0.88–2.08), w, DC (23) 1.30 (1.09–1.54), m, SC (134) 1.30 (1.09–1.53), w, SC (140) 1.36 (1.21–1.52), m, RC (294) 1.1 (0.95–1.26), w, RC (198)	Age
Wideroff *et al.*, 1997 (52), Denmark (1977–1989)	109,581 Individuals with discharge diagnosis of DM (type 1 and 2)	Comparison group: Danish population		1.3 (1.1–1.4), m, CC (413) 1.1 (1.0–1.2), w, CC (442) 1.1 (0.9–1.2), m, RC (235) 1.0 (0.9–1.2), w, RC (167)	Age
Inoue *et al.*, 2006 (53), Japan (1994–2003)	97,771 General Japanese persons			1.36 (1.00–1.85), m, CC (491) 0.83 (0.42–1.61), w, CC (303) 0.80 (0.47–1.36), m, RC (243) 1.65 (0.80–3.39), w, RC (153)	Age, BMI, cigarette, exercise, alcohol, caffeine, fruit/vegetable, history of cerebrovascular disease/ischemic heart disease
Bowers *et al.*, 2006 (54), Finland (1985–2002)	28,983 Finish male smokers			1.09 (0.66–1.80), m, CC (10) 1.23 (0.65–2.32), m, RC (96)	Age, BMI, cigarette, HDL level

AC, ascending colon; BMI, body mass index; C, cecum; CC, colon cancer; CI, confidence interval; CRC, colorectal cancer; DC, descending colon; DCC: distal colon cancer; DM, diabetes mellitus; HDL, high-density lipoprotein; m, men; NSAIDs, non-steroidal anti-inflammatory drugs; PCC, proximal colon cancer; RC, rectal cancer; RR, relative risk; SC, sigmoid colon; TC, transverse colon; w, women.

Table 2

Characterstics of excluded studies that contain only RR of colorectal cancer

Author, year (ref. no.), country	Study design	RR (95% CI), sex
Levi *et al.*, 2002 (55), Switzerkand	Case–control study	1.3 (0.63–2.68), m 3.56 (1.05–12.11), w
Kune *et al.*, 2007 (56), Australia	Case–control study	1.28 (0.67–2.47), m 0.75 (0.35–1.61), w
Seow *et al.*, 2006 (57), Singapore	Cohort study based on incidence rate	1.5 (1.2–2.1), m 1.4 (1.0–1.9), w
Jee *et al.*, 2005 (58), Korea	Cohort study based on incidence rate	1.11 (1.0–2.4), m 1.17 (0.98–1.4), w
Khaw *et al.*, 2004 (59), UK	Cohort study based on incidence rate	3.37 (1.17–9.72), m 1.71 (0.23–12.64), w
Nielsen and Vatten, 2001 (60), Norway	Cohort study based on incidence rate	0.66 (0.35–1.24), m 1.55 (1.04–2.31), w
Schoen *et al.*, 1999 (61), USA	Cohort study based on incidence rate	1.6 (0.8–3.1), m 1.1 (0.5–2.6), w
Will *et al.*, 1998 (26), USA	Cohort study based on incidence rate	1.3 (1.03–1.65), m 1.16 (0.87–1.53), w
Steenland *et al.*, 1995 (62), USA	Cohort study based on incidence rate	1.43 (0.61–3.31), m 1.4 (0.64–3.1), w
Zendehdel *et al.*, 2003 (63), Sweden	Cohort study based on standardized incidence ratio	1.1 (0.6–1.7), m + w
Stürmer *et al.*, 2006 (64), USA	Cohort study based on hazard ratio	1.5 (1.1–2.0), m

CI, confidence interval; m, men; RR, relative risk; w, women.

Table 3

Summary RR estimates and 95% CIs for case–control and cohort studies of the association of diabetes with colon cancer and rectal cancer incidence by study design, sex, and confounders (obesity, smoking, and physical exercise)

Subgroup	No. of studies	Summary RR (95% CI), fixed-effect model	*Q*	*P*-heterogeneity	I^2-statistic %	Summary RR (95% CI), random-effect model
Colon cancer						
All studies	23	1.32 (1.26 – 1.39)	45.57	< 0.01	51.7	1.38 (1.26 – 1.51)
Study design						
Case–control	11	1.36 (1.22 – 1.52)	8.26	0.60	0.0	1.36 (1.22 – 1.52)
Cohort	12	1.31 (1.24 – 1.38)	36.90	< 0.01	70.2	1.40 (1.23 – 1.58)
Sex						
Men	11	1.42 (1.32 – 1.53)	12.10	0.28	17.3	1.43 (1.30 – 1.57)
Women	10	1.25 (1.17 – 1.34)	26.71	< 0.01	66.3	1.35 (1.14 – 1.53)
BMI/smoking adjusted						
Yes	12	1.34 (1.17 – 1.52)	10.67	0.47	0.0	1.34 (1.17 – 1.52)
No	11	1.32 (1.25 – 1.39)	34.88	< 0.01	71.3	1.41 (1.25 – 1.58)
BMI/smoking/physical exercise adjusted						
Yes	10	1.37 (1.19 – 1.58)	9.71	0.37	7.3	1.37 (1.18 – 1.59)
No	13	1.31 (1.25 – 1.39)	35.57	< 0.01	66.3	1.38 (1.24 – 1.54)
Rectal cancer						
All studies	17	1.18 (1.12 – 1.26)	25.58	0.06	37.5	1.20 (1.09 – 1.31)
Study design						
Case–control	7	1.31 (1.12 – 1.53)	3.02	0.81	0.0	1.31 (1.12 – 1.53)
Cohort	10	1.16 (1.09 – 1.24)	20.67	0.01	56.5	1.16 (1.02 – 1.31)
Sex						
Men	8	1.25 (1.15 – 1.35)	11.96	0.10	41.5	1.22 (1.07 – 1.40)
Women	8	1.09 (0.99 – 1.19)	6.95	0.43	0.0	1.09 (0.99 – 1.19)
BMI/smoking adjusted						
Yes	9	1.28 (1.06 – 1.54)	8.06	0.95	0.8	1.28 (1.06 – 1.54)
No	8	1.17 (1.10 – 1.25)	16.80	0.19	58.3	1.18 (1.05 – 1.31)
BMI/smoking/physical exercise adjusted						

Subgroup	No. of studies	Summary RR (95% CI), fixed-effect model	*Q*	*P*-heterogeneity	I^2-statistic %	Summary RR (95% CI), random-effect model
Yes	7	1.34 (1.09 – 1.65)	6.43	0.38	6.7	1.34 (1.08 – 1.67)
No	10	1.17 (1.10 – 1.25)	17.61	0.04	48.9	1.17 (1.05 – 1.29)

BMI, body mass index; CI, confidence interval; RR, relative risk.