Diabetes Mellitus and Risk of Colorectal Cancer: A Meta-Analysis

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Background: **Diabetes has been associated with an increased risk of colorectal cancer in most, but not all, studies. Findings have also been inconclusive with regard to sex and subsite in the colorectum. To resolve these inconsistencies, we conducted a meta-analysis of published data on the association between diabetes and the incidence and mortality of colorectal cancer.** *Methods:* **We identified studies by a literature search of Medline from January 1, 1966, through July 31, 2005, and by searching the reference lists of pertinent articles. Summary relative risks (RRs) with 95% confidence intervals (CIs) were calculated with a random-effects model. All statistical tests were two-sided.** *Results:* **Analysis of 15 studies (six case–control and nine cohort studies), including 2 593 935 participants, found that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes (summary RR of colorectal cancer incidence = 1.30, 95% CI = 1.20 to 1.40), without heterogeneity between studies ($P_{\text{heterogeneity}}$ = .21). These results were consistent between case–control and cohort studies and between studies conducted in the United States and in Europe. The association between diabetes and colorectal cancer incidence did not differ statistically significantly by sex (summary RR among women = 1.33, 95% CI = 1.23 to 1.44; summary RR among men = 1.29, 95% CI = 1.15 to 1.44; $P_{\text{heterogeneity}}$ = .26) or by cancer subsite (summary RR for colon = 1.43, 95% CI = 1.28 to 1.60; summary RR for rectum = 1.33, 95% CI = 1.14 to 1.54; $P_{\text{heterogeneity}}$ = .42). Diabetes was positively associated with colorectal cancer mortality (summary RR = 1.26, 95% CI = 1.05 to 1.50), but there was evidence for heterogeneity between studies ($P_{\text{heterogeneity}}$ = .04).** *Conclusions:* **Our findings strongly support a relationship between diabetes and increased risk of colon and rectal cancer in both women and men. [J Natl Cancer Inst 2005;97:1679–87]**

Type 2 diabetes mellitus and colorectal cancer are major causes of morbidity and mortality in the United States and other Western countries *(1–3)*. Dietary and lifestyle risk factors for developing insulin resistance and type 2 diabetes, such as Western diet, physical inactivity, and obesity, have also been linked to an increased risk of colon cancer *(4–7)*. On the basis of the overlapping risk factors, it has been hypothesized that diabetes itself may be a risk factor for colon cancer *(8)*.

Although epidemiologic studies of the relationship of diabetes with the risk of colorectal cancer are not entirely consistent, most studies are compatible with a positive association. In some studies, the association appeared to be stronger for colon cancer than for rectal cancer *(9–12)*, or the association was observed only in

women *(10,13,14)*. The interpretation of these findings, however, has been hampered by the low frequency at which both diseases occur in the same individual, which results in the lack of statistical power to adequately analyze this association.

To provide a quantitative assessment of the association between diabetes and risk of colorectal cancer, we conducted a meta-analysis of case–control and cohort studies. We also evaluated whether the association varied by sex and by cancer subsite (colon versus rectum and proximal colon versus distal colon).

MATERIALS AND METHODS

Search Strategy

We identified studies by a literature search of the Medline database (from January 1, 1966, through July 31, 2005) with the following medical subject heading terms and/or text words: "diabetes mellitus," "diabetes," "colorectal cancer," "colorectal neoplasm," "colon cancer," "colon neoplasm," "rectal cancer," and "rectal neoplasm." We also reviewed reference lists of the identified publications for additional pertinent studies. No language restrictions were imposed.

Inclusion and Exclusion Criteria

The 25 studies considered for inclusion in this meta-analysis were case–control and cohort studies on the association between diabetes and the incidence of or mortality from colon, rectal, or colorectal cancer *(9–33)*. Studies were excluded if they provided only an estimate of effect with no means to calculate a confidence interval or if the estimates were not adjusted by age. When there were multiple publications from the same population or cohort, only data from the most recent report were included. We excluded three candidate studies *(15–17)* because of overlapping publications and one study *(18)* that reported only crude data that were not adjusted by age.

Data Extraction

The data that we extracted included publication data (the first author's last name, year of publication, and country of population studied), study design, number of exposed and unexposed subjects, control source (in case–control studies), follow-up period (for cohort studies), type of diabetes (type 1 or 2), risk estimates with their corresponding confidence intervals, and variables controlled for by matching or in the multivariable model. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders.

Statistical Analysis

We divided epidemiologic studies of the relationship between diabetes and colorectal cancer risk into three general types according to measure of relative risk (RR): case–control studies (odds ratio), cohort studies (incidence and/or mortality rate ratio), and cohort studies with an external comparison group (standardized incidence and/or mortality ratio). We conducted separate meta-analyses of colorectal cancer incidence and mortality. The measure of effect of interest is the relative risk. Because colorectal cancer is rare, the odds ratio in case–control studies and rate ratios in cohort studies yield similar estimates of relative risk *(34)*. Cohort studies that reported standardized incidence/mortality ratio were analyzed separately.

Summary relative risk estimates with their corresponding 95% confidence intervals (CIs) were derived with the method of DerSimonian and Laird *(35)* by use of the assumptions of a random effects model, which incorporates between-study variability. We calculated a pooled relative risk and its corresponding 95% confidence interval for studies that reported only sex- and/or subsite-specific relative risks. Statistical heterogeneity between studies was evaluated with Cochran's Q test and the I^2 statistic *(36)*. Publication bias was assessed by constructing a funnel plot *(37)*, by Begg's adjusted rank correlation test, and by Egger's regression asymmetry test *(38)*.

For case–control studies and cohort studies that reported incidence rate ratios, we conducted subgroup meta-analyses to examine potential sources of heterogeneity, including study design, type of control subjects in case–control studies, sex, cancer subsite, and duration of follow-up for cohort studies. Statistical analyses were carried out with Stata, version 8.0 (Stata Corp, College Station, TX). P values that were less than .05 were considered statistically significant. All statistical tests were two-sided.

RESULTS

Study Characteristics

Twenty-one independent studies met the predefined inclusion criteria. Of these 21 studies, six were case–control studies *(10,13,19,26,27,33)* (Table 1), 11 were cohort studies that used incidence and/or mortality rate ratios as the measure of relative risk *(9,11,14,20,22–24,28,30–32)* (Table 2), and four were cohort studies that used standardized incidence and/or mortality ratio as the measure of relative risk *(12,21,25,29)* (Table 3). Eleven studies were conducted in the United States, eight in Europe, one in Australia, and one in Korea. Of the 15 cohort studies, incident colorectal cancer was the outcome in seven, mortality from colon, rectal, or colorectal cancer was the outcome in three, and colorectal cancer incidence and mortality were reported in five. In the primary meta-analysis of diabetes and colorectal cancer incidence, we included all six case–control studies *(10,13,19,26,27,33)* and the nine cohort studies that reported incidence rate ratios *(9,11,14,20,22,24,28,30,31)*. These 15 studies included a total of 2 593 935 participants. The three cohort studies *(12,21,25)* that reported standardized incidence ratio were analyzed separately. For the meta-analysis of diabetes and colorectal cancer mortality, we included the six cohort studies that reported mortality rate ratio *(11,20,23,28,30,32)*. These six studies enrolled a total of 2 523 580 participants.

Colorectal Cancer Incidence

Individual study results and the overall summary results for the six case–control and nine cohort studies of diabetes and colorectal cancer incidence are shown in Fig. 1. Eight of these 15 studies found a statistically significant positive association between diabetes and colorectal cancer incidence (range of individual RRs = 1.02 to 2.78; summary RR for all 15 studies = 1.30, 95% CI = 1.20 to 1.40). No heterogeneity among studies was found (Q = 17.9; $P_{\text{heterogeneity}}$ = .21; I^2 = 21.8%). In a sensitivity analysis in which one study at a time was excluded and the rest

Table 1. Characteristics of case–control studies of diabetes and colorectal cancer incidence*

Authors, year (ref. No.), country	No. of case patients by cancer site (subsites)	No. of control subjects (selection methods)	Type of diabetes	RR† (95% CI), sex, cancer site	Controlled variables
O'Mara et al. 1985 (26), United States	1286 CRC (612 CC, 674 RC)	4620 (hospital patients without cancer)	Type 1 and 2 (self-reported)	1.16 (0.86 to 1.57)‡§ women + men, CRC 1.29 (0.84 to 1.96)‡§ women + men, CC 1.05 (0.68 to 1.62)‡§ women + men, RC 1.15 (0.76 to 1.74)‡§ women, CRC 1.18 (0.76 to 1.83)‡§ men, CRC	Age
Kune et al, 1988 (27), Australia	714 CRC	727 (population controls matched by age and sex)	Type 1 and 2 (self-reported)	1.02 (0.62 to 1.67) women + men, CRC 0.75 (0.35 to 1.61) women, CRC 1.28 (0.67 to 2.47) men, CRC	Age
Le Marchand et al., 1997 (10), United States	1192 CRC (825 CC, 350 RC‖)	1192 (population controls matched by age, sex, and ethnicity)	Type 1 and 2 (self-reported)	1.4 (1.0 to 2.1)§ women + men, CRC 1.6 (1.0 to 2.5)§ women + men, CC 1.1 (0.6 to 1.8)§ women + men, PCC 2.2 (1.3 to 3.5)§ women + men, DCC 1.1 (0.5 to 2.6)§ women + men, RC 1.8 (1.1 to 2.8) women, CRC 1.2 (0.80 to 1.7) men, CRC	Age, BMI, physical activity, family history of colorectal cancer, smoking, and intakes of total energy, egg, dietary fiber, calcium, and alcohol
La Vecchia et al., 1997 (33), Italy	1953 CRC (1225 CC, 728 RC)	4154 (hospital patients without cancer and gastrointestinal disease)	Type 1 and 2 (self-reported)	1.3 (1.0 to 1.6) women + men, CRC 1.2 (0.8 to 1.6) women + men, CC 1.5 (1.1 to 2.2) women + men, RC 1.2 (0.8 to 1.8) women, CRC 1.4 (1.0 to 1.9) men, CRC	Age, sex, BMI, physical activity, area of residence, education, family history of colorectal cancer, and intakes of total energy, fat, dietary fiber, and alcohol
Levi et al., 2002 (13), Switzerland	287 CRC	550 (hospital patients without cancer)	Type 1 and 2 (self-reported)	1.75 (0.95 to 3.24) women + men, CRC 3.56 (1.05 to 12.11) women, CRC 1.30 (0.63 to 2.68) men, CRC	Age, sex, BMI, education, family history of colorectal cancer, smoking, alcohol intake
Yang et al., 2005 (19), United Kingdom	10447 CRC (6862 CC, 3585 RC)	104429 (population controls matched by age, enrollment date, and duration of follow-up)	Type 2 (medical records)	1.42 (1.25 to 1.62) women + men, CRC 1.45 (1.25 to 1.70) women + men, CC 1.34 (1.08 to 1.68) women + men, RC 1.38 (1.14 to 1.67) women, CRC 1.36 (1.16 to 1.61) men, CRC	Age, year of enrollment

*RR = relative risk; CI = confidence interval; RC = rectal cancer; CRC = colorectal cancer; CC = colon cancer; PCC = proximal colon cancer; DCC = distal colon cancer; BMI = body mass index; ref. = reference.

†Measure of relative risk is an odds ratio.

‡CIs were calculated from raw data reported in the article.

§RR (and its 95% CI) was derived by pooling the sex- and/or subsite-specific RRs.

‖The numbers of colon and rectal cancer cases do not add up to the total number of colorectal cancer cases because of missing information on subsite.

Table 2. Characteristics of cohort studies of diabetes and colorectal cancer incidence and mortality*

Authors, year (ref. No.), country (follow-up period)	Study population	RR† (95% CI) sex, cancer site (No. of case patients)	Controlled variables
Colorectal cancer incidence			
Steenland et al., 1995 (22), United States (1971–1987)	National Health and Nutrition Survey I Exposed group: 522 women and men with self-reported DM (type 1 and 2) Comparison group: 12532 women and men without self-reported DM	1.41 (0.79 to 2.52)‡ women + men, CRC (176) 1.40 (0.64 to 3.10) women, CRC (82) 1.43 (0.61 to 3.31) men, CRC (94)	Age, BMI, physical activity, income, smoking, alcohol intake
Will et al., 1998 (20), United States (1959–1972)	Cancer Prevention Study I Exposed group: 8258 women and 7229 men with self-reported DM (type 1 and 2) Comparison group: 502592 women and 345620 men without self-reported DM	1.24 (0.87 to 1.53)‡ women + men, CRC (7224) 1.16 (0.87 to 1.53) women, CRC (4006) 1.30 (1.03 to 1.65) men, CRC (3218)	Age, BMI, physical activity, education, race, family history of colorectal cancer, history of constipation, smoking, aspirin use, and intakes of fruits, vegetables, cereals, meat, milk, coffee, tea, and alcohol
Hu et al., 1999 (11), United States (1976–1994)	Nurses' Health Study Exposed group: 7069 women with self-reported DM (Type 2)§ Comparison group: 111003 women without self-reported DM	1.43 (1.10 to 1.87) women, CRC (892) 1.49 (1.09 to 2.06) women, CC (607) 1.64 (1.04 to 2.60) women, PCC (275) 1.38 (0.88 to 2.15) women, DCC (332) 1.11 (0.56 to 2.21) women, RC (176)	Age, BMI, physical activity, family history of colorectal cancer, smoking, menopausal status, HRT use, aspirin use, multivitamin use, and intakes of red meat and alcohol
Schoen et al., 1999 (24), United States (1989–1996)	Cardiovascular Health Study Exposed group: 638 women and 546 men with DM defined by blood glucose, medication history, and the results of oral glucose load Comparison group: 1508 women and 1106 men without DM	1.4 (0.8 to 2.4) women + men, CRC (61) 1.1 (0.5 to 2.6) women, CRC (25) 1.6 (0.8 to 3.1) men, CRC (36)	Age
Nilsen and Vatten, 2001 (14), Norway (1984–1996)	Nord-Trøndelag Health Survey Exposed group: 8202 person–years for women and 6510 person–years for men, self-reported DM (type 1 and 2) Comparison group: 376715 person-years for women and 357 person-years for men	1.05 (0.50 to 2.40)‡ women + men, CRC (726) 1.55 (1.04 to 2.31) women, CRC (367) 0.66 (0.35 to 1.24) men, CRC (359)	Age, BMI, physical activity, education, marital status
Khaw et al., 2004 (28), United Kingdom (1995–2002)	European Prospective Investigation into Cancer Norfolk Study Exposed group: 72 women and 149 men with self-reported DM (type 1 and 2) Comparison group: 5088 women and 4296 men without self-reported DM	2.78 (1.10 to 7.00) women + men, CRC (67) 1.71 (0.23 to 12.64) women, CRC (31) 3.37 (1.17 to 9.72) men, CRC (36)	Age, BMI, smoking
Limburg et al., 2005 (9), United States (1986–1999)	Iowa Women's Health Study Exposed group: 1900 women with self-reported DM (type 2)§ Comparison group: 33072 women without self-reported DM	1.4 (1.1 to 1.8) women, CRC (870) 1.5 (0.9 to 2.6)‡ women, CC (661) 1.9 (1.3 to 2.6) women, PCC (402) 1.1 (0.6 to 1.8) women, DCC (259) 0.8 (0.4 to 1.6) women, RC (196)	Age, BMI, and intakes of total energy, calcium, and vitamin E
Jee et al., 2005 (30), Korea (1993–2002)	National Health Insurance Corp Exposed group: 21056 women and 41868 men with fasting serum glucose level of ≥7.0mmol/L or self-reported treatment for DM Comparison group: 447559 Korean women and 787902 Korean men without DM	1.13 (1.03 to 1.23)‡ women + men, CRC (NA) 1.17 (0.98 to 1.40) women, CRC (NA) 1.11 (1.00 to 1.24) men, CRC (NA)	Age, smoking, and alcohol
Larsson et al., 2005 (31), Sweden (1998–2004)	Cohort of Swedish Men Exposed group: 3847 men with self-reported DM (type 2)§ Comparison group: 41703 men without self-reported DM	1.49 (1.14 to 1.96) men, CRC (411) 1.53 (1.02 to 2.29) men, CC (190) 1.68 (0.98 to 2.86) men, PCC (98) 1.40 (0.76 to 2.59) men, DCC (92) 1.79 (1.18 to 2.73) men, RC (156)	Age, BMI, physical activity, education, family history of colorectal cancer, smoking, multivitamin use, aspirin use, and intakes of fruits, vegetables, dairy foods, and red meat

(Table continues)

Table 2 (continued).

Authors, year (ref. No.), country (follow-up period)	Study population	RR† (95% CI) sex, cancer site (No. of case patients)	Controlled variables
Colorectal cancer mortality			
Smith et al., 1992 (23), United States (1967–1987)	Whitehall Study Exposed group: 224 men with plasma glucose levels of ≥200 mg/100 mL Comparison group: 17 051 men with plasma glucose levels of <96 mg/100 mL	0.62 (0.09 to 4.47) men, colon (113)‖	Age
Will et al., 1998 (20), United States (1959–1972)	Cancer Prevention Study I Exposed group: 8258 women and 7229 men with self-reported DM (type 1 and 2) Comparison group: 502 592 women and 345 620 men without self-reported DM	1.02 (0.78 to 1.32)‡ women + men, CRC (NA) 1.07 (0.71 to 1.62) women, CRC (NA) 0.98 (0.70 to 1.37) men, CRC (NA)	Age, BMI, physical activity, education, race, family history of colorectal cancer, history of constipation, smoking, aspirin use, and intakes of fruits, vegetables, cereals, meat, milk, coffee, tea, and alcohol
Hu et al., 1999 (11), United States (1976–1994)	Nurses' Health Study Exposed group: 7069 women with self-reported DM (type 2)§ Comparison group: 111 003 women without self-reported DM	1.43 (1.10 to 1.87) women, CRC (892)	Age, BMI, physical activity, family history of colorectal cancer, smoking, menopausal status, HRT use, aspirin use, multivitamin use, and intakes of red meat and alcohol
Coughlin et al., 2004 (32), United States (1982–1998)	Cancer Prevention Study II Exposed group: 26 186 women and 26 617 men with self-reported DM (type 1 and 2) Comparison group: 586 135 women and 441 305 men without self-reported DM	1.19 (1.09 to 1.31)‡ women + men, CRC (7777) 1.20 (1.05 to 1.38)‡ women, CRC (3681) 1.18 (1.05 to 1.35)‡ men, CRC (4096)	Age, BMI, physical activity, education, race, family history of colorectal cancer, smoking, HRT use, and intakes of red meat, citrus fruits and juices, vegetables, and alcohol
Khaw et al., 2004 (28), United Kingdom (1995–2002)	European Prospective Investigation into Cancer Norfolk Study Exposed group: 72 women and 149 men with self-reported DM (type 1 and 2) Comparison group: 5088 women and 4296 men without self-reported DM	3.60 (0.81 to 15.9) women + men, CRC (22)	Age, BMI, smoking
Jee et al., 2005 (30), Korea (1993–2002)	National Health Insurance Corp Exposed group: 21 056 women and 41 868 men with fasting serum glucose level of ≥7.0mmol/L or self-reported treatment for DM Comparison group: 447 559 Korean women and 787 902 Korean men without DM	1.23 (1.05 to 1.45)‡ women + men, CRC (NA) 1.11 (0.81 to 1.51) women, CRC (NA) 1.28 (1.06 to 1.55) men, CRC (NA)	Age, smoking, and alcohol

*RR = relative risk; CI = confidence interval; CRC = colorectal cancer; CC = colon cancer; RC = rectal cancer; PCC = proximal colon cancer; DCC = distal colon cancer; DM = diabetes mellitus; BMI = body mass index; HRT, hormone replacement therapy; NA = not available; ref. = reference.

†The measure of RR is a rate ratio (hazard ratio) in all studies, except for one study (11) in which the RR is a pooled odds ratio.

‡The RR (and its 95% CI) was derived by pooling the sex- and/or subsite-specific RRs.

§Excluding participants who had diabetes before age 30 years.

‖RR estimates are not available for rectal cancer because there were no cases of rectal cancer among men with diabetes.

Table 3. Characteristics of cohort studies of diabetes and colorectal cancer based on standardized incidence/mortality ratio*

Authors, year (ref. No.), country (follow-up period)	Study population	RR† (95% CI) sex, cancer site (No. of case patients among diabetics)	Controlled variables
Colorectal cancer incidence			
Raggozzino et al., 1982 *(25)*, United States (1945–1969)	Exposed group: 1135 DM patients (type 2) Comparison group: Rochester population	1.3 (0.8 to 1.9) women + men, CRC (22) 1.1 (0.5 to 2.1) women, CRC (10) 1.4 (0.7 to 2.5) men, CRC (12)	Age, sex
Wideroff et al., 1997*(12)*, Denmark (1977–1989)	Exposed group: 109 581 nationwide subjects with a discharge diagnosis of DM (type 1 and 2) Comparison group: Danish population	1.12 (1.00 to 1.25)‡ women + men, CRC (1275) 1.19 (1.01 to 1.40)‡ women + men, CC (873) 1.05 (0.95 to 1.16)‡ women + men, RC (402) 1.07 (0.98 to 1.16)‡ women, CRC (609) 1.20 (1.02 to 1.42)‡ men, CRC (666)	Age
Weiderpass et al., 1997*(21)*, Sweden (1965–1983)	Exposed group: 153 852 nationwide subjects with a discharge diagnosis of DM (type 1 and 2) Comparison group: Swedish population	1.32 (1.18 to 1.47)‡ women + men, CRC (943) 1.39 (1.31 to 1.49) women + men, CC (943) 1.42 (1.16 to 1.74)‡ women + men, PCC (491) 1.30 (1.16 to 1.45)‡ women + men, DCC (315) 1.24 (1.13 to 1.35) women + men, RC (492) 1.26 (0.98 to 1.62)‡ women, CRC (724) 1.37 (1.37 to 1.47)‡ men, CRC (711)	Age
Colorectal cancer mortality			
Kessler, 1970, *(29)*, United States (1930–1959)	Exposed group: 21 447 DM patients (type 2) Comparison group: Massachusetts population	0.81 (0.59 to 1.08)§ women + men, RC (45)	Age, sex
Weiderpass et al., 1997 *(21)*, Sweden (1965–1983)	Exposed group: 153 852 nationwide subjects with a discharge diagnosis of DM (type 1 and 2) Comparison group: Swedish population	1.54 (1.44 to 1.65)‡ women + men, CRC (NA) 1.46 (1.32 to 1.61)‡ women, CRC (NA) 1.62 (1.50 to 1.75)‡ men, CRC (NA)	Age

*RR = relative risk; CI = confidence interval; CRC = colorectal cancer; CC = colon cancer; RC = rectal cancer; PCC = proximal colon cancer; DCC = distal colon cancer; DM = diabetes mellitus; NA = not available; ref. = reference.

†The measure of RR is a standardized incidence (or mortality) ratio.

‡The RR (and its 95% CI) was derived by pooling the sex- and/or subsite-specific RRs.

§The P value reported in the article was used to calculate the CI.

were analyzed, we detected a statistically significant positive association between diabetes and colorectal cancer incidence (range of summary RRs = 1.25 to 1.36; the lower limit of the 95% CI never crossed 1.0).

We then conducted subgroup meta-analyses by study design, geographical area, sex, cancer subsite, and duration of follow-up (Table 4). The association between diabetes and colorectal cancer incidence was somewhat stronger in case–control studies (summary RR = 1.36; 95% CI = 1.23 to 1.50) than in cohort stud-

ies (summary RR = 1.29; 95% CI = 1.16 to 1.43), but there was no heterogeneity among study types ($P_\text{heterogeneity}$ = .08). In case–control studies, the source of control subjects did not statistically significantly affect the magnitude of the association. Results were consistent for studies conducted in the United States and in Europe. Results were also consistent for studies in women (summary RR among women = 1.33, 95% CI = 1.23 to 1.44) and in men (summary RR among men = 1.29, 95% CI = 1.15 to 1.44) ($P_\text{heterogeneity}$ = .26). For cancer subsites, the summary

Fig. 1. Association between diabetes and colorectal cancer incidence in case–control and cohort studies. Studies are ordered by study design and publication year. RR = relative risk; CI = confidence interval; **squares** = study-specific RR estimate (size of the **square** reflects the study-specific statistical weight, i.e., the inverse of the variance); **horizontal lines** = 95% CI; **diamond** = summary relative risk estimate and its corresponding 95% CI. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's Q test.
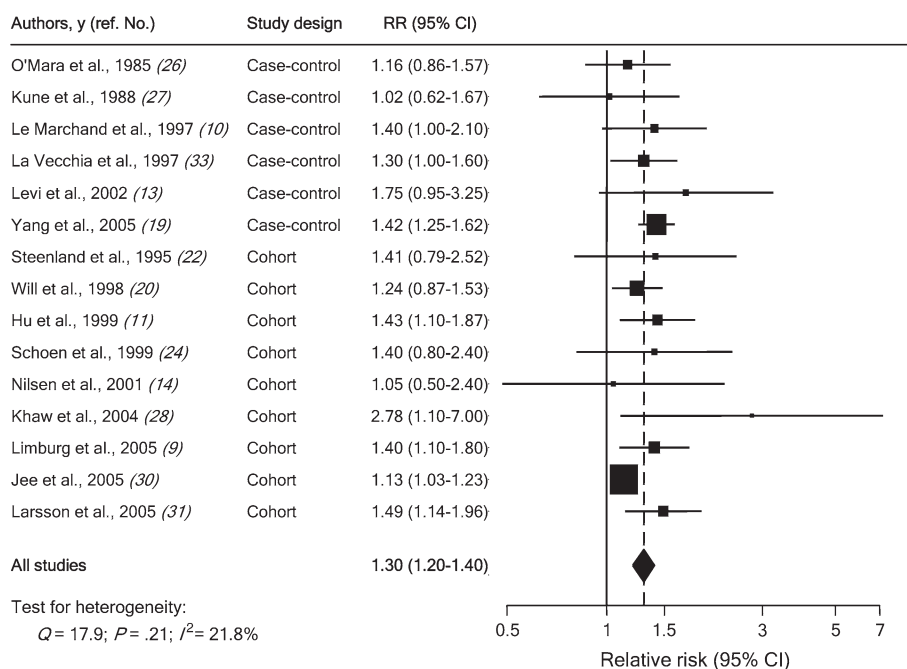

Authors, y (ref. No.)	Study design	RR (95% CI)
O'Mara et al., 1985 *(26)*	Case-control	1.16 (0.86-1.57)
Kune et al., 1988 *(27)*	Case-control	1.02 (0.62-1.67)
Le Marchand et al., 1997 *(10)*	Case-control	1.40 (1.00-2.10)
La Vecchia et al., 1997 *(33)*	Case-control	1.30 (1.00-1.60)
Levi et al., 2002 *(13)*	Case-control	1.75 (0.95-3.25)
Yang et al., 2005 *(19)*	Case-control	1.42 (1.25-1.62)
Steenland et al., 1995 *(22)*	Cohort	1.41 (0.79-2.52)
Will et al., 1998 *(20)*	Cohort	1.24 (0.87-1.53)
Hu et al., 1999 *(11)*	Cohort	1.43 (1.10-1.87)
Schoen et al., 1999 *(24)*	Cohort	1.40 (0.80-2.40)
Nilsen et al., 2001 *(14)*	Cohort	1.05 (0.50-2.40)
Khaw et al., 2004 *(28)*	Cohort	2.78 (1.10-7.00)
Limburg et al., 2005 *(9)*	Cohort	1.40 (1.10-1.80)
Jee et al., 2005 *(30)*	Cohort	1.13 (1.03-1.23)
Larsson et al., 2005 *(31)*	Cohort	1.49 (1.14-1.96)
All studies		1.30 (1.20-1.40)

Test for heterogeneity:
Q = 17.9; P = .21; I^2 = 21.8%

Relative risk (95% CI)

Table 4. Summary relative risk (RR) estimates and 95% confidence intervals (CIs) for case–control and cohort studies of the association between diabetes and colorectal cancer incidence by study design, geographical area, sex, cancer subsite, and duration of follow-up

Subgroup	No. of studies	Summary RR (95% CI)	Between studies			Between subgroups	
			Q	$P_{\text{heterogeneity}}$	I^2 statistics, %*	Q	$P_{\text{heterogeneity}}$
Study design							
Case–control	6	1.36 (1.23 to 1.50)	3.60	.61	0		
Population-based	3	1.39 (1.24 to 1.57)	1.60	.45	0		
Hospital-based	3	1.28 (1.07 to 1.53)	1.42	.49	0	0.58	.45†
Cohort studies	9	1.29 (1.16 to 1.43)	11.22	.19	16.1	3.06	.08‡
Geographical area							
United States	7	1.31 (1.18 to 1.46)	1.92	.93	0		
Europe	6	1.42 (1.28 to 1.57)	3.70	.59	0	1.04	.31
Sex							
Women	14	1.33 (1.23 to 1.44)	12.15	.52	0		
Men	13	1.29 (1.15 to 1.44)	18.60	.10	35.5	1.25	.26
Cancer subsites							
Colon	7	1.43 (1.28 to 1.60)	1.68	.95	0		
Proximal colon	4	1.64 (1.31 to 2.05)	2.73	.44	0		
Distal colon	4	1.49 (1.12 to 1.99)	3.70	.30	19	0.28	.60§
Rectum	7	1.33 (1.14 to 1.54)	6.08	.41	1.3	0.66	.42‖
Duration of follow-up							
≤10 y	4	1.35 (1.04 to 1.76)	7.50	.06	60.0		
>10 y	5	1.32 (1.17 to 1.50)	1.36	.85	0	2.44	.12

*Percentage variation due to heterogeneity between studies.

†Test for heterogeneity between population-based and hospital-based case–control studies. All statistical tests were two-sided.

‡Test for heterogeneity between case–control and cohort studies.

§Test for heterogeneity between proximal colon and distal colon cancer.

‖Test for heterogeneity between colon and rectal cancer.

estimate was similar for colon cancer (RR = 1.43, 95% CI = 1.28 to 1.60) and for rectal cancer (RR = 1.33, 95% CI = 1.14 to 1.54) ($P_{\text{heterogeneity}}$ = .42). There was also no statistically significant difference between subsites in the colon (i.e., proximal colon versus distal colon). Stratifying cohort studies by duration of follow-up resulted in no evidence of heterogeneity. Finally, the summary estimate was similar ($P_{\text{heterogeneity}}$ = .73) for studies (four case–control and four cohort) published before 2000 (RR = 1.28, 95% CI = 1.16 to 1.42) and for studies (two case–control and five cohort) published after 2000 (RR = 1.36, 95% CI = 1.17 to 1.58).

Physical activity and body mass index are potentially the most important known confounders of the positive association between diabetes and colorectal cancer risk. When we restricted the meta-analysis to studies that controlled for these variables *(10,11,14,20,22,31,33)*, we found a positive association between diabetes and colorectal cancer (summary RR = 1.34, 95% CI = 1.20 to 1.49), without statistically significant heterogeneity among studies (Q = 2.05; $P_{\text{heterogeneity}}$ = 0.91). Three studies reported both age-adjusted and multivariable-adjusted relative risks *(11,20,31)*. When we restricted the meta-analysis to those studies, the positive association between diabetes and colorectal cancer remained (summary RR adjusted for age only = 1.34, 95% CI = 1.12 to 1.60), and the estimate was identical to estimates that were adjusted for physical activity and body mass index, as well as other potential confounders (RR = 1.34, 95% CI = 1.18 to 1.53), indicating a lack of confounding.

A positive association was observed between diabetes and colorectal cancer incidence in the three cohort studies that reported standardized incidence ratios (summary RR = 1.22, 95% CI = 1.07 to 1.40) (Table 3). The test for heterogeneity among these three studies was not statistically significant (Q = 4.52; $P_{\text{heterogeneity}}$ = .10; I^2 = 55.8%).

Colorectal Cancer Mortality

Of six cohort studies of diabetes and mortality from colon *(23)* or colorectal *(11,20,28,30,32)* cancer, three *(11,30,32)* reported a statistically significant positive association, and one *(28)* observed a nonstatistically significant 3.6-fold (RR = 3.60, 95% CI = 0.81 to 15.89) increase in colorectal cancer risk associated with diabetes (Table 2). When all six studies were analyzed, a positive association between diabetes and mortality from colorectal cancer was found (summary RR = 1.26, 95% CI = 1.05 to 1.50). However, there was statistically significant heterogeneity among studies (Q = 11.59; $P_{\text{heterogeneity}}$ = .04; I^2 = 56.8%). A sensitivity analysis identified the study by Hu et al. *(11)* as contributing most to the heterogeneity. In an analysis excluding this study, the association between diabetes and mortality from colorectal cancer was weaker (summary RR = 1.19, 95% CI = 1.10 to 1.28), and the test for heterogeneity was not statistically significant (Q = 4.03; $P_{\text{heterogeneity}}$ = .40; I^2 = 0.6%). The association between diabetes and colorectal cancer mortality did not differ statistically significantly by sex (Q = 0.10; $P_{\text{heterogeneity}}$ = .75).

Of two cohort studies that reported standardized mortality ratios *(21,29)* (Table 3), one *(21)* reported a statistically significant approximately 1.5-fold increased risk of death from colorectal cancer among diabetic patients. The other study found no statistically significant association between diabetes and rectal cancer mortality *(29)*.

Publication Bias

There was no funnel plot asymmetry for the association between diabetes and colorectal cancer risk (data not shown). *P* values for Begg's adjusted rank correlation test and Egger's regression asymmetry test were .79 and .28, respectively, indicating a low probability of publication bias.

DISCUSSION

Findings from this meta-analysis indicate that individuals with diabetes have an approximately 30% increased relative risk of developing colorectal cancer compared with nondiabetic individuals. The results were consistent for case–control and cohort studies and for studies carried out in the United States and in Europe. The association was observed in both women and men and for all subsites in the colorectum.

Our analysis must be interpreted in the context of the limitations of the available data. Most of the studies did not distinguish between type 1 and type 2 diabetes. Because type 1 diabetes [which accounts for 5% to 10% of all diagnosed cases of diabetes (1)] may not be related to colorectal cancer (12,39), the magnitude of the association between diabetes and colorectal cancer risk may have been slightly underestimated. In addition, because diabetes is an underdiagnosed disease, some degree of misclassification of exposure to diabetes is likely to have occurred. Such nondifferential misclassification would also tend to attenuate the true relationship between diabetes and colorectal cancer. As in any meta-analysis, the possibility of publication bias is of concern. However, the results obtained from funnel plot analysis and formal statistical tests did not provide evidence for such bias.

Type 2 diabetes and colorectal cancer share similar risk factors, including physical inactivity and obesity (8). Thus, the observed increased risk of colorectal cancer associated with a history of diabetes may reflect confounding by these risk factors. However, a positive association between diabetes and colorectal cancer risk remained when we limited the meta-analysis to studies that controlled for physical activity and body mass index (summary RR = 1.34, 95% CI = 1.20 to 1.49).

Discrepancies among studies investigating the relationship of diabetes with colorectal cancer risk according to sex and cancer subsite may be attributable to small sample sizes that resulted in insufficient statistical power to detect some relationships in the individual studies. Because this meta-analysis included a large number of studies, we could assess the association according to sex and cancer subsite with high precision.

A relationship between diabetes and risk of colorectal cancer is biologically plausible. Type 2 diabetes is characterized by increased insulin concentrations during the early stage of the disease. Hyperinsulinemia (8) or factors related to insulin resistance, such as hyperglycemia or hypertriglyceridemia (40), have been associated with colorectal carcinogenesis. Insulin can stimulate cell proliferation through a minor pathway that involves the direct activation of the insulin receptor or insulin-like growth factor (IGF)-I receptor and a major pathway that acts through the inhibition of IGF binding proteins (in particular, IGFBP-1 and IGFBP-2), which may result in increased free and bioavailable IGF-I (41). An important role of insulin and IGF-I in colorectal carcinogenesis is supported by in vitro studies, animal models, and epidemiologic studies (41–44). Epidemiologic studies of circulating concentrations of insulin, C-peptide (a marker of insulin secretion), or IGF-I have shown two- to threefold increased risks of colorectal cancer for individuals in the highest exposure categories, compared with those in the lowest exposure categories (24,45–48). Furthermore, a recent study reported that chronic insulin therapy was associated with a statistically significant increase in colorectal cancer risk among patients with type 2 diabetes (49). Other mechanisms through which diabetes may be linked with the risk of colorectal cancer include slower bowel transit times in patients with diabetes, which could contribute to the increased exposure of colonic mucosa to potential carcinogens, and elevated concentrations of fecal bile acids associated with increased blood glucose and triglyceride concentrations (20,50–52). Fecal bile acids have been shown to promote colorectal cancer in animal models (53).

Our results have important clinical and public health implications. In the United States, about 8% of adults have diabetes (54), and it has been predicted that the number of Americans with diagnosed diabetes will increase 165%, from 11 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%) (55). Colorectal cancer is the second leading cause of cancer death in the United States and other Western countries (2,3). The prevalence of diabetes will probably increase as a result of the growing obesity epidemic, and thus this disease may contribute to the development of additional cases of colorectal cancers.

In summary, the results from this meta-analysis strongly support an association between diabetes and increased risk of colon and rectal cancer in both women and men. These findings provide evidence for a role of hyperinsulinemia or factors related to insulin resistance in colorectal carcinogenesis.

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