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REVIEW

Colorectal Cancer Outcomes, Recurrence, and Complications in Persons With and Without Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract
Background Diabetes mellitus increases the risk of incident colorectal cancer, but it is less clear if pre-existing diabetes mellitus influences mortality outcomes, recurrence risk, and/or treatment-related complications in persons with colorectal cancer.
Methods We performed a systematic review and meta-analysis comparing colorectal cancer mortality outcomes, cancer recurrence, and treatment-related complications in persons with and without diabetes mellitus. We searched MEDLINE and EMBASE through October 1, 2008, including hand-searching references of qualifying articles. We included studies in English that evaluated diabetes mellitus and cancer treatment outcomes, prognosis, and/or mortality. The initial search identified 8,208 titles, of which 15 articles met inclusion criteria. Each article was abstracted by one author using a standardized form and re-reviewed by another author for accuracy. Authors graded quality based on pre-determined criteria.

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Results We found significantly increased short-term perioperative mortality in persons with diabetes mellitus. In the meta-analysis of long-term mortality, persons with diabetes mellitus had a 32% increase in all-cause mortality compared to those without diabetes mellitus (95% CI: 1.24, 1.41). Although data on other outcomes are limited, available studies suggest that pre-existing diabetes mellitus predicts increased risk of some post-operative complications as well as 5-year cancer recurrence. In contrast, there is little evidence that diabetes confers increased risk for long-term cancer-specific mortality.

Conclusions Patients with colorectal cancer and pre-existing diabetes mellitus have an increased risk of short- and long-term mortality. Future research should determine whether improvements in prevention and treatment of diabetes mellitus will improve outcomes for colorectal cancer patients.

Keywords Colorectal carcinoma · Diabetes mellitus · Mortality · Treatment outcome · Fatal outcome

Introduction

Colorectal cancer is the fourth most common cancer in the United States [1], with >80% of incident disease diagnosed in persons aged >50 years [2]. Many cases of colorectal cancer occur in adults with pre-existing diabetes, since type 2 diabetes is highly prevalent after age 50 and appears to be an independent risk factor for the development of colorectal cancer [3]. Possible explanations for the increased risk include hyperinsulinemia, decreased bowel transit time, and elevated fecal concentrations of bile acids [3–5].

Diabetes mellitus is also an independent risk factor for fatal colon cancer in both men and women [5]. Diabetes mellitus might influence survival following colorectal cancer due to insulin-stimulated growth of colorectal cancer cells or inadequate treatment of persons with concomitant disease. However, the relationship of diabetes mellitus to overall mortality in persons with colorectal cancer has not been systematically reviewed. We therefore sought to perform a systematic review and meta-analysis to determine if persons with pre-existing diabetes mellitus and a diagnosis of colorectal cancer have an increased risk for all-cause short- and long-term mortality, cancer-specific mortality, cancer recurrence, and treatment-related outcomes and complications, as compared to persons without diabetes mellitus.

Methods

Selection of Studies

We identified studies by searching EMBASE and MEDLINE from inception through October 1, 2008 for human, English-language studies of diabetes mellitus and cancer treatment outcomes, prognosis, and/or mortality. Table 1 shows the detailed search strategy. We also searched references of included studies for further articles.

We then narrowed the search to articles that investigated colorectal cancer mortality outcomes, cancer recurrence outcomes, and/or treatment-related outcomes or complications. Studies were excluded if they (1) included non-cancer patients or excluded non-diabetic patients, (2) did not analyze data regarding a clinical outcome, (3) did not report original data, or (4) did not report risk associated with pre-existing diabetes mellitus.

At this point, articles were eligible for inclusion in our systematic review. To be included in the formal meta-analysis, articles had to meet two additional criteria: (1) report risk estimate [e.g., hazard ratio (HR) or relative risk (RR)] relating pre-existing diabetes to subsequent death using survival analysis regression models, and (2) report an estimate of precision, such as a standard error or 95% confidence interval. We included articles that failed to report precision directly, but from which we could reconstruct an estimate of precision using *P* values and other study data.

Data Abstraction

Articles were abstracted using a standardized form designed by the authors and piloted for completeness and

Table 1 Details of search strategy

Database	Years included	Search terms
MEDLINE EMBASE	1966 to October 1, 2008 1980 to October 1, 2008	((‘diabetes mellitus’/exp OR ‘diabetes mellitus’ OR ‘diabetes’) OR (‘glucose intolerance’/exp OR ‘glucose intolerance’) OR (‘impaired glucose tolerance’/exp OR ‘impaired glucose tolerance’) OR (‘insulin resistance’/exp OR ‘insulin resistance’) OR (‘hyperinsulinism’/exp OR ‘hyperinsulinism’ OR ‘hyperinsulinemia’) OR (‘metabolic syndrome x’/exp OR ‘metabolic syndrome’)) AND ((‘neoplasm subdivided by anatomical site’) OR (‘malignant neoplastic disease’/exp OR ‘malignant neoplastic disease’) OR (‘cancer’ or ‘neoplasm’)) AND ((mortality’/exp OR ‘mortality’) OR (‘death’/exp OR ‘death’) OR (‘survival analysis’/exp OR ‘survival analysis’) OR (‘survival’/exp OR ‘survival’) OR (‘disease course’/exp OR ‘prognosis’ OR ‘cancer recurrence’ OR ‘tumor recurrence’ OR ‘metastasis’ OR ‘case fatality rate’))

understandability. Details abstracted from each study included author's name, publication year, country of study location, type of cancer and cancer characteristics, study design, data source, inclusion and exclusion criteria, diabetes mellitus exposure, outcomes, confounders considered, characteristics of study participants with diabetes mellitus and without diabetes mellitus (age, gender, race, body-mass index), and statistical results by outcome and quality assessment. Each stage of the abstraction process was conducted independently by two authors and disputes were settled by consensus or a third reviewer.

To grade methodological quality, we used elements of the STROBE checklist for cohort studies, including inclusion/exclusion criteria, estimated internal and external validity of the study design, method of diabetes and outcome ascertainment, whether diabetes mellitus was the primary exposure variable or one of a group of prognostic variables, and the statistical methods, including the use of survival analysis and adjustment for confounding [6].

We checked publications for overlapping patient populations. When we found overlap, we included the study with the most comprehensive analysis of pre-existing diabetes mellitus on colorectal cancer mortality outcomes, cancer recurrence, or treatment-related outcomes or complications. We excluded three articles from the long-term, all-cause mortality meta-analysis due to overlapping patient populations [7–9].

Statistical Analysis

We defined short-term mortality as death occurring within 30 days of operative management for colorectal cancer. We considered studies reporting risk ratios for mortality outcomes quantitatively and those not reporting risk ratios qualitatively. In addition, due to heterogeneity of study outcomes, we reported cancer-specific mortality, cancer recurrence outcomes, and treatment-related outcome and complications qualitatively.

For the meta-analysis, potential sources of heterogeneity between studies were assessed using Cochran Q statistics and I^2 statistics. We calculated a pooled hazard ratio using the DerSimonian–Laird method since there was significant between-study heterogeneity and to allow for variable effects across studies. Publication bias was evaluated using both the Begg's and Egger's funnel plots. We performed sensitivity analysis including only observational, cohort study designs and excluding the one study that was designed as a randomized, controlled trial. We also performed influence analyses to estimate the effect of each study on the pooled risk estimate. Analyses were conducted using STATA, version 10 (College Station, TX, USA).

Results

Of the 8,208 titles identified in our search, we reviewed 735 abstracts and 102 manuscripts that met our inclusion and exclusion criteria. Agreement between observers on which studies to include was excellent. Fifteen of these articles evaluated mortality outcomes, cancer recurrence, and/or treatment-related complications for diabetes mellitus and colorectal cancer and are included in this analysis. Figure 1 shows the details of the literature search.

Description and Quality of Studies

The details of the short-term and long-term mortality studies included in our meta-analysis and systematic review are summarized in Tables 2 and 3, respectively. Of the 15 articles, 4 evaluated short-term mortality, 8 evaluated long-term mortality, 4 evaluated cancer-specific mortality, 4 evaluated treatment-related complications, 1 evaluated treatment-related response, and 1 evaluated cancer recurrence; some articles examined more than one outcome. Eight of the studies included patients with colorectal cancer, five studies included patients with colon cancer, one study included patients with rectal cancer, and one study evaluated patients with colon and rectal cancer, separately. One study evaluated participants from a randomized, controlled trial; the other studies were observational cohort studies of patients undergoing routine cancer care. Most studies were set in the United States (ten studies), but some were set in

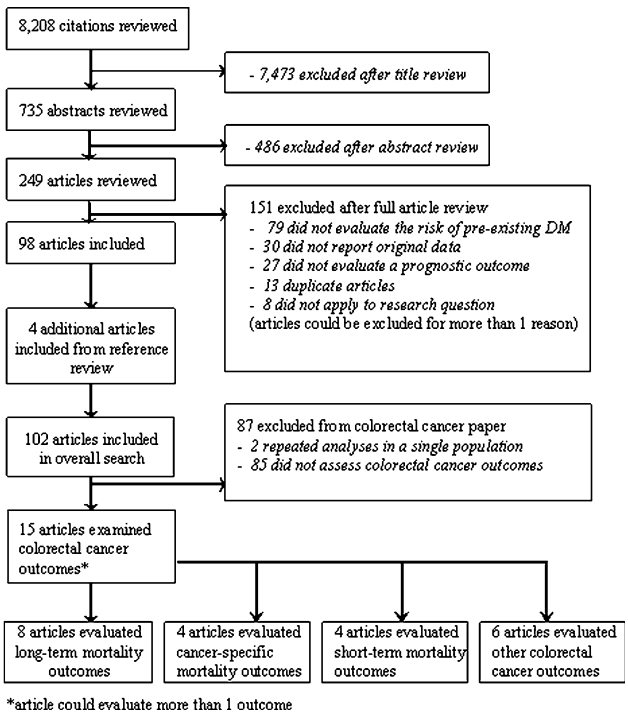

Fig. 1 Details of the literature search

Table 2 Overview of short-term follow-up studies

Study	Year, country	Type of cancer	Overall sample size (*N*)	Number with DM (*N*)	Confounders considered	Study characteristics	Mortality outcome	Other outcome
Davila [13]	2005, USA	Colorectal	32,621	Not reported	Age, race, marital status, other comorbid diseases	VA hospitals (98% male, 77% white); mean age 68 years	HR 1.19 (95% CI, 1.04–1.36) for DM versus non-DM	Increased acute myocardial infarction ($P = 0.01$) Increased anastomotic complications ($P = 0.02$)
Little [12]	2002, USA	Colorectal	727	61	None	Hepatic resection for colorectal cancer at single institution; median age 62 years, 57% male	DM: 8% Non-DM: 2.4%	30-day post-operative complications: 39 vs 39% (*P* value NS) Infective complications: 29.2 vs 15.3% (*P* value NS) Cardiovascular complications: 6.1 vs 10.1% (*P* value NS) Post-operative hepatic decompensation: 21.2 vs 2.5% (*P* value not reported)
Koperna [10]	1997, Austria	Colon	99	11	None	Emergency surgery for colon cancer at single institution, included only patients >70 years of age (mean 81.5 years); 63% female	DM: 90.9% Non-DM: 45.4%	–
Tsugawa [11]	2002, Japan	Colon	71	10	None	Emergency surgery for colon cancer at single institution, included only patients >70 years of age (mean 75.4 years); 54% female	DM: 80% Non-DM: 49.2%	–

Death within 30 days of operative management for colorectal cancer

DM Diabetes mellitus, *NS* non-significant, *VA* veterans' affairs

Table 3 Overview of studies evaluating long-term mortality and other prognostic outcomes

Study	Year, country	Type of cancer	Overall sample size (*N*)	Number with DM (*N*)	Confounders considered	Study characteristics	Mortality outcome	Other outcome
Caudle [23]	2008, USA	Rectal	110	17	Age, gender, body-mass index	Retrospective review of patients at a single institution with a diagnosis of rectal cancer (1995–2006) and received neoadjuvant chemoradiotherapy, DM group 88% male, 12% female, median age 56 years; non-DM group 60% male, 40% female, median age 56 years	–	Any downstaging, DM 65% versus non-DM 66% (*P* value NS) Local progression, DM 24% versus non-DM 5% ($P = 0.046$) Complete pathologic response, DM 0% versus non-DM 23% ($P = 0.039$); association remained after adjustment for age, BMI, or gender ($P = 0.02$)
Gross [14]	2006, USA	Colorectal	29,733	17.8%	Age, gender, sociodemographic characteristics, comorbid conditions, and cancer-specific characteristics, including stage, grade, tumor location	SEER-Medicare database of Stage 1–3 colorectal cancer (1993–1999), included only patients >67 years of age (mean 77.8 years); 55% female, median follow-up 4.1 years	HR 1.26 (95% CI, 1.18, 1.28)	–
Gross [9]	2007, USA	Colon	5,330	950	Age, gender, sociodemographic characteristics, comorbid conditions, number of physician visits, and cancer-specific characteristics, including grade, tumor location, number of positive lymph nodes	SEER-Medicare database of Stage III colon cancer (1993–1999), included only patients >67 years of age (median 76 years); 59.5% female, 87% white	–	Hospitalizations (all-cause): DM versus non-DM $P = 0.85$ Hospitalizations related to chemotherapy toxicity: OR 1.67 (1.16–2.41) for DM and OR 1.80 (1.51–2.16) for non-DM ($P = 0.35$) Chemotherapy completion: DM 71.5% versus non-DM 74.2% $P = 0.17$
Little [12]	2002, USA	Colorectal	727	61	None	Hepatic resection for colorectal cancer at single institution (1990–1999); median age 62 years, 57% male	Median survival: DM 42 months; non-DM 43 months 5-year survival: DM 30%; non-DM 35%	–

Table 3 continued

Study	Year, country	Type of cancer	Overall sample size (*N*)	Number with DM (*N*)	Confounders considered	Study characteristics	Mortality outcome	Other outcome
Meyerhardt [19]	2003, USA	Colon	3,759	287	Age, sex, race, body-mass index, bowel obstruction, bowel perforation, baseline performance status, disease stage, presence of peritoneal implants, completion of assigned chemotherapy	Cohort study of randomized, controlled trial of different adjuvant chemotherapy regimens for Stage II–Stage III colon cancer at multiple locations (1988–1992). Diabetes mellitus mean age, 65.5 years, 61% male; non-diabetes mellitus mean age 61.6 years, 54% male. Median follow-up: 9.4 years	HR 1.42 (95% CI, 1.22, 1.67)	Recurrence-free survival (HR 1.21, 95% CI 1.00, 1.46) >Grade 3 toxicity: 56 vs 57%, *P* value NS Treatment-related death, 1.3 vs 1.1% ($P = 0.56$) Treatment-related diarrhea, 29 vs 20% ($P < 0.001$)
Park [15]	2006, Korea	Colorectal	14,578	1,223	Age, alcohol consumption, body-mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, other comorbid diseases	Male participants in the National Health Examination Program starting in 1996 with incident colon cancer identified in Korean Central Cancer Registry; mean age 50.8 years; mean follow-up 3 years	HR 1.18 (95% CI 0.85, 1.63)	–
Payne [22]	1995, Australia	Colorectal	207	15	None	Retrospective review of consecutive colorectal surgical patients admitted to single institution over 16-year period (1971–1988), mean age 75, predominantly male	–	Median survival (excluding colorectal cancer deaths): DM 68 months, non-DM 160 months ($P = 0.014$)
Polednak [17]	2006, USA	Colorectal	9,395	1,014	Age, sex, race, extent of disease, lymph node involvement, poverty rate	Connecticut residents diagnosed 1994–1999 with invasive colorectal cancer; 95% white, 52% female	HR 1.38 (95% CI 1.27, 1.49)	Non-cancer mortality: HR 1.84 (95% CI 1.65, 2.06)
Shonka [18]	2006, USA	Colon	1,853	255	Gender, age, smoking status, family history, date of diagnosis, pathologic stage	Diagnosis of colon cancer at single institution 1986–2003; median age of diabetics, 72 years; median age of non-diabetics, 71 years; 52% female	HR 1.08 ($P = 0.46$)	–

Table 3 continued

Study	Year, country	Type of cancer	Overall sample size (*N*)	Number with DM (*N*)	Confounders considered	Study characteristics	Mortality outcome	Other outcome
Siddiqui [20]	2008, USA	Colorectal	269	155	None	Retrospective review of colorectal cancer patients at the Veterans Affairs North Texas Health Care System 1997–2001; mean age of diabetics 68.3 years, 65.8% Caucasian; mean age of non-diabetics 70.5 years, 77.2% Caucasian	5-year survival: DM 65.2%; non-DM 64.0%	5-year cancer-specific survival: poorly-controlled DM (HbA1c >7.5%) 52%; well-controlled DM (HbA1c <7.5%) 74%; non-DM 64% ($P < 0.05$)*
Van de Poll-Franse [16]	2007, The Netherlands	Colon	5,273	609	Age, gender, stage, treatment, cardiovascular disease	Patients diagnosed with colon cancer in Eindhoven Cancer Registry, 1995–2002; mean age of diabetics, 72.9, 44% male; mean age of non-diabetics, 68.4, 51% male	HR 1.28 (95% CI 1.14, 1.42)	–
Van de Poll-Franse [16]	2007, The Netherlands	Rectal	3,055	304	Age, gender, stage, treatment, cardiovascular disease	Patients diagnosed with rectal cancer in Eindhoven Cancer Registry, 1995–2002; mean age of diabetics, 71.6, 55% male; mean age of non-diabetics, 66.3, 60% male	HR 1.48 (95% CI 1.28, 1.73)	–
Will [21]	1998, USA	Colorectal	7,224	161	Age, race, body-mass index, education, smoking status, exercise, family history of colorectal cancer, eats cereal daily, eats meat daily, eats fruit daily, coffee consumption, eats cooked veggies daily, eats green salad daily, eats fried foods daily, cups of tea daily, cups of milk daily, alcoholic drinks daily, aspirin consumption, pregnancies for women, pipe/cigar smoking for men	Participants of the Cancer Prevention Study from 1959–1972 who developed colorectal cancer during 13-year follow-up, mean age 57 years, 55% female	–	Colorectal cancer death: Men: IDR 0.98 (95% CI 0.70, 1.37) Women: IDR 1.07 (95% CI 0.71, 1.62)

IDR Incidence density ratio, *DM* diabetes mellitus, *HR* hazard ratio, *NS* non-significant

* *P* value from log-rank test comparing persons with well-controlled DM and non-DM to persons with poorly controlled DM

Western Europe (two studies), Southeast Asia (two studies), and Australia (one study).

Four articles focused on short-term mortality: two assessed mortality after emergency surgery in persons aged >70 years [10, 11], one examined mortality after hepatic metastasis resection at a single institution [12], and one examined 30-day operative mortality using the Veterans' Affairs (VA) database [13].

Eight articles focused on long-term mortality. Three used regional or national databases, including the Surveillance, Epidemiology and End Result (SEER)-Medicare database in the United States [14], the Korean Central Cancer Registry linked to the National Health Examination Program [15], and the Eindhoven Cancer Registry in The Netherlands [16]. The other five included a state cancer registry population [17], two retrospective evaluations of colorectal cancer at single institutions [12, 18], a randomized, controlled trial for colorectal cancer at multiple locations throughout the United States [19], and a retrospective evaluation of colorectal cancer at a regional Veterans' Affairs Health System [20]. All six of the long-term mortality studies included in the meta-analysis reported adjusted risk estimates and five adjusted for age and cancer stage.

Four articles reported on cancer-specific mortality: one was the state cancer registry study [17], another was a prospective cohort study in the US [21], the third was a retrospective evaluation of surgical patients at a single institution in Australia [22], and the fourth was a retrospective evaluation of colorectal cancer patients at a regional Veterans' Affairs Health System [20]. Four articles examined treatment-related complications: two studies were retrospective studies of post-operative complications [12, 13], one was a randomized-controlled trial [19], and one was a prospective cohort in the United States [9]. Additionally, one article focused on treatment response at a single institution in the US [23], and a second article evaluated cancer recurrence using a randomized, controlled trial for colorectal cancer at multiple locations throughout the United States [19].

Study quality was heterogeneous. Ascertainment of diabetes mellitus was primarily from medical records (12 studies) [9–11, 13, 14, 16–18, 20, 22, 23], but also included laboratory data (2 studies) [12, 15], and patient report (1 study) [21]. Eight of the articles focused on diabetes mellitus as the primary exposure, whereas the other seven articles evaluated diabetes mellitus among other prognostic factors. Table 4 details the quality characteristics of each article.

Short-Term Mortality

Due to the heterogeneity of the four short-term mortality studies, we report the results of these studies qualitatively. The two studies that assessed mortality after emergency surgery in patients older than 70 years with colon cancer showed a significantly increased risk of mortality in patients with pre-existing diabetes mellitus as compared to their non-diabetic counterparts. One study evaluated 99 colon cancer patients (10% with diabetes mellitus, all requiring insulin treatment) aged >70 years and found an unadjusted 30-day operative mortality of 90.9% in patients with diabetes as compared to 45.4% in patients without diabetes mellitus ($P = 0.005$) [10]. A second study evaluated emergency surgery in 71 colon cancer patients (14% with diabetes mellitus) aged >70 years and found an unadjusted 30-day operative mortality of 80% in patients with diabetes mellitus as compared to 49.2% in patients without diabetes mellitus ($P = 0.006$) [11].

The other two studies evaluated postoperative mortality after surgery for colorectal cancer. Both showed significantly increased risk of death among patients with pre-existing diabetes mellitus. A study in 32,621 VA patients found an overall 30-day postoperative mortality rate of 3.9% after colorectal cancer resection with a 1.19 increased hazard (95% CI: 1.04, 1.36) in patients with diabetes mellitus as compared to patients without diabetes mellitus [13]. The second study evaluated 788 patients (8.4% with diabetes mellitus) undergoing hepatic resection for metastatic colorectal cancer and found an unadjusted 30-day operative mortality of 8% in patients with diabetes mellitus as compared to 2.4% in patients without diabetes mellitus (HR 3.63, $P = 0.02$) [12].

Long-Term Mortality

We combined six articles in a meta-analysis that reported long-term, all-cause mortality outcomes with hazard risk estimates and 95% confidence intervals from a Cox proportional hazards model (Fig. 2). We found a 32% increased risk for long-term, all-cause mortality in persons with colorectal cancer and diabetes mellitus as compared to persons without diabetes mellitus (HR 1.32, 95% CI: 1.24, 1.41). Heterogeneity was significant by the Q statistic (14.6 on 6 df, $P = 0.02$) and the I^2 statistic (52.4%, $P = 0.050$). We did not find evidence of publication bias when evaluated by Begg's test ($P = 0.76$) or Egger's test ($P = 0.47$).

We performed a sensitivity analysis including the five articles that used an observational, cohort design, but excluding the randomized, controlled trial [19]. The risk estimate for long-term, all-cause mortality was similar to inclusion of all articles (HR 1.31, 95% CI: 1.22, 1.38). Influence analyses showed that no study had substantial influence on the overall estimate and a significant risk persisted when studies were removed one at a time.

Two studies reporting long-term, all-cause mortality as unadjusted percentages were not included in the meta-analysis. One found a non-significant difference in 5-year

Table 4 Quality assessment

Study	Population source		Diabetes ascertainment			Outcome ascertainment			Degree of focus on diabetes mellitus		Statistical analysis	
	Population-based cohort	Clinic-based cohort	Blood test	Medical records	Self-report	Death registry	Medical record	Study follow-up	Primary exposure	One of multiple exposures	Adjusted models	Adjusted for age and cancer severity
Caudle [23]		■		■			■		■		■	
Davila [13]	■			■			■			■	■	■
Gross [14]	■			■		■				■	■	■
Gross [9]	■			■		■				■	■	■
Little [12]		■	■				■		■			
Koperna [10]		■		■			■			■		
Meyerhardt [19]	■			■				■	■		■	■
Park [15]	■		■			■				■	■	
Payne [22]		■					■			■		
Polednak [17]	■			■		■			■		■	■
Shonka [18]		■		■			■		■		■	■
Siddiqui [20]		■		■			■		■			
Tsugawa [11]		■		■			■			■		
Van de Poll-Franse [16]	■			■		■			■		■	■
Will [21]	■				■	■		■	■		■	

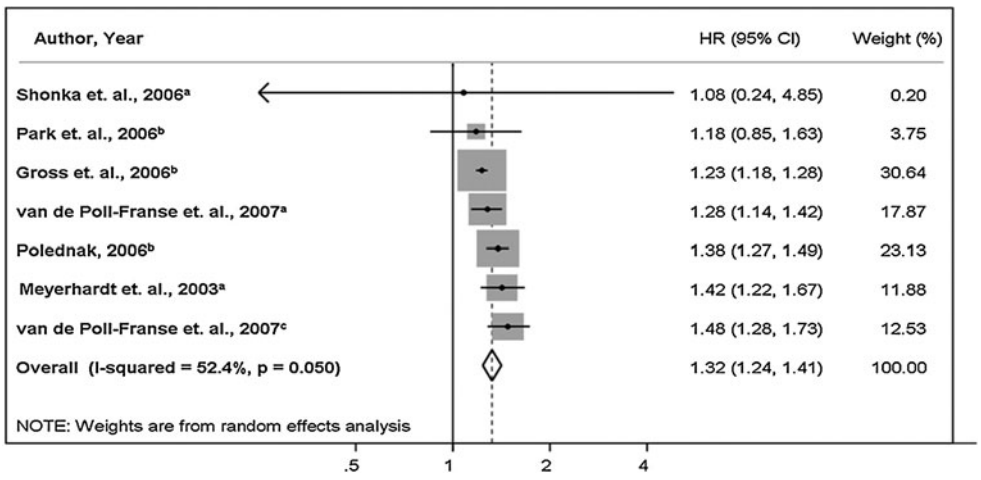

Fig. 2 Meta-analysis of long-term mortality studies. [a]Colon cancer only, [b]colorectal cancer, [c]rectal cancer only

survival between persons with diabetes mellitus (65.2%) and persons without diabetes mellitus (64%) [20]. The second found no significant difference in 5-year survival rates after hepatic resection for colorectal cancer in persons with diabetes mellitus (30%) versus persons without diabetes mellitus (35%) [12].

Cancer-Specific Mortality

Four studies evaluated long-term colorectal cancer-specific mortality. Only one of the four found an association between poorly-controlled, pre-existing diabetes mellitus and the risk of death attributed to colorectal cancer, and two found an elevated risk of non-cancer death. This study evaluated 269 persons with colorectal cancer at the Veterans Affairs North Texas Health Care System and found an unadjusted 64% cancer-specific survival among persons without diabetes mellitus as compared to 74 and 52% cancer-specific survival among persons with well-controlled diabetes mellitus (glycosylated hemoglobin, HbA1c <7.5%) and poorly-controlled diabetes mellitus (HbA1c >7.5%), respectively ($P < 0.05$) [20]. A second study utilized a state cancer registry of 9,395 persons diagnosed with colorectal cancer and found a HR 1.06 (95% CI: 0.94–1.20) for colorectal cancer mortality. The presence of comorbid diabetes mellitus, however, was associated with increased mortality from non-cancer causes (HR 1.84, 95% CI: 1.65, 2.06) [17]. A third study evaluated 7,224 persons with colorectal cancer in the Cancer Prevention Study, and reported no association between diabetes mellitus and subsequent death from colorectal cancer in males (incidence density ratio (IDR) 0.98, 95% CI: 0.70, 1.37) or in females (IDR 1.07, 95% CI: 0.71, 1.62). This study did not evaluate non-colorectal cancer death in the subcohort of participants with a colorectal cancer diagnosis [21]. A fourth study of 207 colorectal cancer patients operated on at a single institution reported a median survival, excluding colorectal cancer deaths, of 160 months in persons without diabetes mellitus and 68 months in persons with diabetes mellitus ($P = 0.014$). The decreased survival of persons with diabetes mellitus was not related to post-operative complications [22].

Complications

Few studies have evaluated treatment-related complications in persons with colorectal cancer and diabetes mellitus. A cohort study of 3,759 patients with stage II and stage III colon cancer who had entered a randomized, controlled trial of chemotherapy reported a higher incidence of severe treatment-related diarrhea in persons with diabetes mellitus as compared to persons without diabetes mellitus (29 vs 20%, $P < 0.001$). There were no significant differences in other major toxicities, including severe nausea, vomiting, stomatitis, leucopenia, fever, or infection. Additionally, there was no difference in grade 3 or greater toxicity (56 vs 57%) or treatment-related death (1.3 vs 1.1%, $P = 0.56$) between persons with diabetes mellitus and those without diabetes mellitus, respectively [19]. A second study found no difference in 30-day post-operative complications after hepatic resection for metastatic colorectal cancer in 727 patients at a single institution (39.3 vs 39.3%). There was no significant difference in the incidence of infectious complications (29.2 vs 15.3%) or cardiovascular complications (6.1 vs 10.1%) in persons with diabetes mellitus as compared to persons without diabetes mellitus. Persons with diabetes mellitus, however, were at much higher risk of postoperative hepatic decompensation as compared to persons without diabetes mellitus (21.2 vs 2.5%) [12]. A third study of post-operative VA patients with colorectal cancer found a higher risk of acute myocardial infarction ($P = 0.01$) and anastomotic complications ($P = 0.02$) in persons with diabetes mellitus [13]. Finally, a study of 5,330 stage III colon cancer patients in

the SEER-Medicare database found that persons with diabetes mellitus receiving adjunct chemotherapy had the same rate of hospitalizations as their non-diabetic counterparts ($P = 0.85$). Additionally, among patients who started an adjunct chemotherapy regimen, there was no significant difference in completion by diabetes mellitus status [9].

Treatment Response

One study evaluated the impact of diabetes mellitus on response to chemoradiotherapy treatment for rectal cancer and found no difference in tumor downstaging between persons with diabetes mellitus (65%) and those without diabetes mellitus (66%). However, the study did report a difference in local tumor progression of 24% in persons with diabetes mellitus and 5% in persons without diabetes mellitus ($P = 0.046$). Additionally, there was a 0% complete pathologic response in persons with diabetes mellitus as compared to 23% in persons without diabetes mellitus ($P = 0.039$). When the complete pathologic response was individually adjusted for age, gender, and body-mass index, the strength of the association between diabetes mellitus and a complete pathologic response was strengthened ($P = 0.02$ for each individual adjustment) [23].

Cancer Recurrence

One study evaluated the impact of diabetes mellitus on cancer recurrence and reported that persons with diabetes mellitus experienced a 5-year recurrence-free survival of 56% as compared to 64% for persons without diabetes mellitus ($P = 0.012$). Moreover, during the study follow-up, persons with diabetes mellitus were more likely to die of recurrent disease (41 vs 33%, $P = 0.006$) [19].

Discussion

Our systematic review and meta-analysis suggest that pre-existing diabetes is a risk factor for short-term and long-term mortality in adults who develop colorectal cancer. Pre-existing diabetes may also increase the risk of some complications of chemotherapy and increase the risk of colorectal cancer recurrence.

Previous series have shown emergency surgery for colorectal cancer to have an overall short-term mortality of 15–36% [24], but in elderly patients it has been associated with a >50% mortality rate [25]. Given that most deaths from emergency surgery are related to pre-existing comorbid conditions or thromboembolic disease, the high mortality rates found in the studies of emergency surgery in elderly persons with diabetes mellitus was not unexpected. Although these studies do not describe the mechanism of death in patients with diabetes mellitus, the study of VA patients found persons with diabetes mellitus had a higher risk for post-operative acute myocardial infarction and anastomotic complications [13]. Additionally, the higher risk of hepatic decompensation after hepatic lobectomy in persons with diabetes mellitus has been described in hepatic resection for hepatocellular carcinoma, and may reflect the inability of the liver to withstand major hepatic resection and regenerate in persons with diabetes mellitus [12]. More rigorous studies are required to better estimate of the short-term mortality risk conferred by the concomitant diagnoses of diabetes mellitus and colorectal cancer in emergent and non-emergent operative management.

In our meta-analysis of long-term mortality, we estimated that adults with pre-existing diabetes who develop colorectal cancer were 32% more likely to die than their non-diabetic counterparts. Our review of cause-specific mortality suggests that this stems from the general effects of diabetes on mortality risk rather than from a specific interaction with colorectal cancer or its treatment. However, one must interpret cause-specific mortality with caution, since attribution of cause of death in cancer patients is often problematic [26, 27]. All-cause mortality averts the problem of misattribution and is certainly relevant to patients and physicians.

A strength of our study is a comprehensive search strategy with two reviewers abstracting each article. A second strength is the high quality studies included in the long-term mortality meta-analysis with five of the six articles adjusting for key confounding variables in an adjusted hazard analysis.

Nonetheless, several limitations of our study deserve comment. First, the heterogeneity of ascertainment of diabetes mellitus in the studies may have led to an under-ascertainment of diabetes mellitus, resulting in a hazard estimate closer to the null. Second, there was heterogeneity in length of follow-up in the long-term mortality studies; however, the majority of studies had follow-up for greater than 5 years. Third, lack of adjustment in the multivariate models between studies may have biased the results, especially in the short-term mortality studies. Only one of the studies included in the short-term mortality systematic review performed an adjusted analysis [13]. In contrast, all the studies included in the long-term mortality meta-analysis included sociodemographic confounders in an adjusted analysis, and most included information on disease status and other comorbid medical disease. Fourth, eight studies combined patients with colon and rectal cancers despite different surgical procedure and radiation treatment for the two cancers. Studies have shown a higher proportion of proximal colon cancers in persons with diabetes mellitus

[28–30]; thus, the combination of these two cancers may bias the risk estimate.

In conclusion, we found an increased risk of short- and long-term mortality in patients with diabetes mellitus and colorectal cancer. Although much of the long-term risk appears to be attributed to causes other than cancer, available evidence also suggests that persons with diabetes mellitus and colorectal cancer may be at increased risk for colorectal cancer recurrence, non-response to chemoradiotherapy treatment, and treatment-related complications. Future research should investigate pathways of diabetes-related risk and determine the whether improved diabetes care can improve short and long-term outcomes for patients with colon cancer.

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