Published in final edited form as:
Dis Colon Rectum. 2013 November ; 56(11): 1304–1319. doi:10.1097/DCR.0b013e3182a479f9.

"Diabetes and colorectal cancer prognosis: a meta-analysis"

Katherine T Mills, MSPH,
Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

Charles F Bellows, MD,
Department of Surgery, Tulane University School of Medicine, New Orleans, Louisiana, USA

Aaron E Hoffman, PhD,
Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

Tanika N Kelly, PhD, and
Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

Giuseppe Gagliardi, MD
Department of Surgery, Tulane University School of Medicine, New Orleans, Louisiana, USA

Abstract

Background—Diabetes mellitus is associated with an increased incidence of colorectal cancer, but the impact of diabetes on colorectal cancer prognosis is not clear.

Objective—We conducted a meta-analysis of observational studies to examine the association between pre-existing diabetes and colorectal cancer all-cause mortality, cancer-specific mortality and recurrence.

Data Sources—Medline and Embase were searched through August 22, 2012.

Study Selection—We included studies reporting all-cause mortality, cancer-specific mortality, disease-free survival, or recurrence in colorectal cancer patients according to diabetic status.

Intervention—Meta-analyses performed using random effects models.

Main Outcome Measures—All-cause mortality, cancer-specific mortality, diseases free survival.

CORRESPONDING AUTHOR: Dr. Giuseppe Gagliardi, Department of Surgery, Tulane University School of Medicine, New Orleans, Louisiana, 1340 Tulane Avenue, New Orleans LA 70112, USA, Tel: (504) 284-8613; Fax: (504) 988-5516, gagliarg@yahoo.com.

CONFLICT OF INTERST
The authors have no conflict of interest to disclose.

CONTRIBUTION OF EACH AUTHOR
KT Mills=Data collection, data analysis, drafting of the article
CF Bellows=Study design, critical review of the manuscript
AE Hoffmann=Study design, critical review of the manuscript
TN Kelly=Drafting of the article, data analysis
G Gagliardi=Study design, data collection, drafting of the article

Results—Twenty-six articles met our inclusion criteria. Colorectal cancer patients with diabetes had a 17% increased risk of all-cause mortality (RR = 1.17; 95% CI: 1.09-1.25) and a 12% increased risk of cancer-specific mortality (RR = 1.12; 95% CI: 1.01-1.24) compared to those without diabetes. Those with diabetes also had poorer disease-free survival (RR = 1.54; 95% CI: 1.08-2.18) compared to their non-diabetic counterparts. In subgroup analyses, diabetes was associated with all-cause mortality in both rectal (RR = 1.24; 95% CI: 1.07-1.29) and colon cancer patients (RR = 1.17; 95% CI: 1.07-1.29). Sensitivity analyses including only patients with non-metastatic disease identified stronger associations between diabetes and both all-cause (RR = 1.32; 95% CI: 1.21-1.44) and cancer-specific (RR = 1.27; 95% CI: 1.06-1.52) mortality.

Limitations—Some studies had short follow-up or did not report mean or median follow-up. The included studies were heterogeneous in study population, diabetes diagnostic criteria and outcome ascertainment.

Conclusion—Colorectal cancer patients with diabetes are at greater risk for all-cause and cancer-specific mortality and have worse disease-free survival compared to those without diabetes. Studies are warranted to determine if proper treatment could attenuate the excess mortality among diabetic colorectal cancer patients.

Keywords

Colorectal neoplasms; diabetes mellitus; colorectal neoplasms metabolism; colorectal neoplasms prognosis; meta-analysis

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast, with an estimated 1.24 million new cases diagnosed in 2008.[1] There is now ample evidence that diabetes mellitus is an independent risk factor for the development of CRC.[2-4] However, it is unclear if the presence of diabetes in patients with CRC is associated with prognosis after cancer diagnosis. Improved understanding of these associations could have important public health implications given the increasing incidence of diabetes worldwide,[5] particularly among those 65 years and older who are at highest risk for CRC.[6]

Conflicting results have been observed in previous studies of colorectal cancer patients for both all-cause [7-10] and cancer-specific mortality [11-14]. A prior meta-analysis of six studies published before October 2008 revealed a 32% increase in all-cause mortality associated with diabetes, but reported no pooled estimate for cancer-specific mortality.[15] Since diabetes is the third highest non-cancer cause of death among CRC patients and is strongly associated with cardiovascular disease, the leading cause of non-cancer death in CRC patients, only limited conclusions about the effects of diabetes on cancer-related prognosis can be drawn from overall survival data.[9, 16-18] Thus, cancer-specific mortality, disease-free survival and recurrence should also be considered when determining the role of diabetes in CRC prognosis.

Since 2008, several large studies have reported estimates of the association between diabetes and both cancer-specific and all-cause mortality.[13,16,19,20] These data provide an excellent opportunity to obtain more precise estimates of the association between diabetes and all-cause mortality and conduct the first meta-analysis examining the relationship between diabetes and cancer-specific mortality. Therefore, the goal of the current meta-analysis is to determine whether patients with CRC and diabetes have a higher risk for all-cause and cancer-specific mortality relative to patients without diabetes. In addition, we examine the association between diabetes and both disease-free survival and cancer recurrence among those with CRC.

METHODS

Eligibility criteria

We included observational studies that identified patients with CRC and evaluated survival, cancer recurrence and disease progression after CRC diagnosis according to diabetes status. Studies reporting only post-surgical or in-hospital mortality were excluded. For inclusion, studies had to report hazard ratios or other relative risk estimates and variance (or data to calculate these) of all-cause or cancer specific mortality, disease-free survival or recurrence associated with diabetes. No language exclusions were made.

Search strategy

Medline (through OVID) and Embase were searched from inception to August 22, 2012. The complete search strategy used for the OVID database is shown in Appendix 1. Titles and abstracts of all retrieved studies were then independently examined by two authors (GG and KM) to select potentially eligible studies for full text review. Full text review was also conducted in duplicate. References of relevant studies and review articles were searched to identify any additional papers.

Data extraction

Data extraction was carried out independently by two authors (GG and KM). Disagreements in data extraction were resolved by consensus. Abstracted data included study population characteristics, CRC location, cancer stage, cancer treatment, duration of follow-up, adjustment variables and relative risks and variance (or data to calculate these) of all-cause and cancer specific mortality, disease-free survival and recurrence associated with diabetes. Outcome effect estimates were abstracted overall and by type of cancer (colon or rectal). When multiple effect estimates were reported, the most fully adjusted estimate was used. Corresponding authors were contacted for clarifications and to obtain additional information when data of interest was not initially reported.

To judge quality, information was abstracted using elements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[21]

Effect estimates, both within and among publications, were checked for overlapping patient populations. When one study had the same patients or was a subgroup of another study, the study with the most complete outcome information or the larger number of patients was included, respectively. When effect estimates had some overlapping and some non-overlapping patients, due to use of the same cancer registry but with different inclusion criteria, for example, the largest study was included in the meta-analysis. A sensitivity analysis including all overlapping studies was done to assess the impact of excluding non-overlapping individuals from overlapping studies in the pooled analyses.

Statistical analysis

Relative risks (RR) were used to examine the association between diabetes and both survival and recurrence in CRC patients. When estimates of the RR were not reported, the unadjusted relative risk and accompanying standard error were calculated from the five-year survival rates reported by diabetes status. RRs and standard errors were logarithmically transformed to stabilize the variance and normalize their distribution. We pooled RRs using both fixed effects and DerSimonian and Laird random effects models. [22] We used inverse variance weighting to calculate fixed- and random-effects summary estimates. Formal statistical tests for heterogeneity were performed using the DerSimonian and Laird Q test and by examining the I^2 quantity. Because some evidence of heterogeneity was found, we present the more conservative results from the random-effects models. Results are presented both overall and

by cancer-type subgroup. An influence analysis was conducted by excluding each study individually to test whether the removal of any study would influence the pooled summary estimates. Additional sensitivity analyses were performed by restricting studies to those that included non-metastatic patients only, to those with a minimum, mean, or median follow-up time of at least three years, to those that presented appropriately adjusted effect estimates (at least age and cancer stage adjustment), and by including all studies with overlapping participants. Publication bias was assessed using Begg and Egger tests. We conducted all analyses using Stata software, version 10.1 (Stata Corp, College Station, Texas).

RESULTS

The study selection process for inclusion in the meta-analysis is illustrated in Figure 1. Of the 1,238 non-duplicate abstracts reviewed, 91 were included in the full text review, and 26 of those met our inclusion criteria. Two articles were excluded because the patient population was a subgroup of a larger study.[23,24] Three studies were excluded because they had partially overlapping patient populations with larger studies due to use of the same tumor registry or hospital population.[25-27] In order to avoid including participants in the analyses more than once, the smaller studies were excluded from the primary analyses, but were included in a sensitivity analysis. An additional overlapping study was not included in the main analyses, but was included in a priori sensitivity analyses that did not include the larger overlapping study.[28] One study reported estimates for diabetes with complications and diabetes without complications both compared to the same non-diabetic group.[29] In this case the estimate with the largest sample size (diabetes without complications) was used in the main analysis and both estimates were included in the sensitivity analysis. Overall, 26 articles met the inclusion criteria and were included in the meta-analysis.

Description and quality of studies

Characteristics of the 26 included studies are summarized in Table 1. All studies except one were published in the last 10 years.[11] There were seven prospective cohort studies, including 3 nationwide prospective mortality studies [10,11,16] and one follow-up of a chemotherapy trial.[8] All the other studies were retrospective cohort studies, including an age and sex matched cohort study.[39] All studies were limited to patients with invasive colorectal adenocarcinoma, except for one that included 124 out of 1853 patients with non-invasive colon cancer.[38] Ten of the 26 studies reported results restricted to those without metastatic disease.[8,9,16,19,20,28,35,40,41] Eleven studies included only patients undergoing surgery,[7,8,16,19,28,32-34,36,41] and in ten studies treatment was not reported.[9-14,37,38,40,42] The quality analysis of the studies is presented in Table 2. Ten of the studies were population-based,[9-12,14,16,20,37,40,42] one was a cohort based on a multicenter trial, [8] and all others were from single institutions. There were twelve studies where outcomes were not adjusted for age of the patient or for tumor stage.[7,10,11,14,28,32,33,36,39-42]

All-cause and cancer-specific mortality

Figure 2 shows the RR of all-cause mortality (2A), cancer-specific mortality (2B), disease-free survival (2C), and recurrence (2D) associated with diabetes for individual studies and overall pooled estimates. CRC patients with diabetes are at significantly increased risk of all-cause mortality (RR = 1.17, 95% CI: 1.09, 1.25), cancer-specific mortality (RR = 1.12, 95% CI: 1.01, 1.24), and have worse disease-free survival (RR for cancer recurrence or death = 1.54, 95% CI: 1.08, 2.18) compared to CRC patients without diabetes. A similar trend was observed for cancer recurrence, but this association did not reach statistical significance (RR = 1.24, 95% CI: 0.99, 1.55).

The results from the subgroup analysis by cancer type are presented in Figure 3. Diabetes was associated with all-cause mortality in both colon (RR = 1.17, 95% CI: 1.07, 1.29) and rectal (RR = 1.18, 95% CI: 1.08, 1.29) cancer patients with similar results obtained for the two cancer types (Figure 3A). Diabetes was also associated with cancer-specific mortality in both colon (RR = 1.22, 95% CI: 1.08, 1.39) and rectal (RR = 1.23, 95% CI: 1.13, 1.33) cancer patients (Figure 3B).

There was some evidence of publication bias for the all-cause mortality analysis (Egger p-value = 0.05; Begg p-value = 0.3). Using the trim and fill method to obtain an adjusted estimate in the presence of publication bias attenuated the association (RR = 1.03, 95% CI: 0.96-1.11) suggesting that the observed diabetes and all-cause mortality association could be due to publication bias. There was no evidence of publication bias for cancer-specific mortality (Egger p-value = 0.1; Begg p-value = 0.7), with no difference in the adjusted RR estimated using the trim and fill method (RR = 1.12, 95% CI: 1.02-1.24). Because the meta-analyses of disease-free survival and recurrence included only three studies each, analyses of publication bias would be severely underpowered and were not conducted.

Sensitivity Analysis

Table 3 shows results of the three sensitivity analyses. Because prognosis after CRC diagnosis is very different for those with metastatic and non-metastatic cancer, we conducted a sensitivity analysis restricted to non-metastatic cancers and observed stronger associations between diabetes and both all-cause (RR = 1.32, 95% CI: 1.21, 1.44) and cancer-specific (RR=1.27, 95% CI: 1.06, 1.52) mortality. Restricting the analyses to studies that had at least three years of follow-up also resulted in a stronger association with all-cause (RR=1.25, 95% CI: 1.15, 1.36) and cancer-specific mortality (RR=1.27, 95%CI: 1.14, 1.40). In addition, restricting the analyses to estimates that were appropriately adjusted for age and stage at diagnosis did not substantially change the magnitude of the effect estimates. In addition, including all overlapping studies did not meaningfully change the all-cause mortality pooled estimate. The cause-specific mortality, disease-free survival and recurrence endpoints did not have any overlapping studies. Furthermore, the removal of any individual study from each of the four meta-analyses did not have a substantial impact on the pooled effect estimates (data not shown).

DISCUSSION

Our meta-analysis of 21 studies reporting overall mortality, including 216,981 participants, showed that diabetes is associated with a 17% increased risk of all-cause mortality in patients with CRC. The reason for this association has previously been attributed to the general effects of diabetes on mortality including increased death from cardiovascular disease [9,16-18] and increased perioperative mortality.[15] However, our meta-analysis of cancer-specific outcomes suggests that the increased risk of all-cause mortality is at least in part due to an increase in deaths from CRC and to an increased recurrence rate in diabetic patients. A higher risk of cancer-specific mortality for those with diabetes could be attributed to several factors. First, diabetic patients may present with more advanced CRC due to underuse of screening.[43] However, of the studies included in this meta-analysis, only one reported advanced tumor stage in diabetics compared to non-diabetics.[32] In addition, three studies found a lower incidence of malignant bowel obstruction in patients with diabetes compared to those without diabetes.[8,13,30] Therefore, the difference in prognosis cannot be readily explained by more advanced stage at diagnosis in those with diabetes.

A second possible explanation is that the difference in cancer-related mortality in diabetic patients may be due to less aggressive cancer treatment, a finding reported by three of the studies included in the current meta-analysis.[9,20,31] Treatment differences could be related to

underlying diabetes-related co-morbidities that influence clinical decision making or to higher treatment-related toxicities in diabetic patients.[44,45] Moreover, a recent study reported a lower response rate to chemoradiotherapy in rectal cancer patients with diabetes compared to those without diabetes.[46] These data suggest not only that diabetic patients are receiving less aggressive treatment but that they are not responding as well to the treatment as those without diabetes.

A third possibility is that hyperinsulinemia or increased levels of insulin-like growth factors (IGF) may influence tumor aggressiveness.[2] In hyperinsulinemia, insulin binds to the IGF-1 receptor and works in competition with IGFBP to increase free IGF-1 levels in the blood.[47] IGF has been shown to promote tumor cell proliferation and angiogenesis.[48] Moreover, IGFBP levels have been inversely correlated with CRC mortality.[49,50] Insulin resistance is also considered to be an underlying cause for the correlation between obesity and CRC incidence.[2,51] However, the association between hyperinsulinemia and CRC mortality is unclear. While one study showed an increase in overall and CRC-specific mortality in diabetic patients with high HbA1c,[39] a recent large study found no influence of insulin use on CRC-specific mortality in type 2 diabetic patients.[18]

Recent observational studies showed that the use of the anti-hyperglycemic agent metformin is associated with a decreased incidence of CRC [52,53] and reduction in CRC-related deaths,[54,55] suggesting that metformin may have a potential use in CRC prevention and treatment. Interestingly, metformin not only decreases insulin resistance and lowers IGF-1 levels, but also inhibits the mammalian target of rapamycin (mTOR)-controlled synthesis of key proteins responsible for the malignant phenotypes of cancer cells, as well as angiogenesis.[56] A recent trial of metformin given to breast cancer patients 4 weeks before surgery failed to show a significant decrease of the Ki-67 levels in the tumor specimen compared to placebo.[57] However, there was a significant decrease of Ki-67 levels in patients with high homeostasis model assessment (HOMA) index (the ratio of fasting blood glucose to insulin) compared to patients with low HOMA index, and similar Ki-67 trends in patients with higher BMI, waist-hip ratio and C-reactive protein levels. These results suggest that the anti-tumoral effect of metformin may be limited to patients with insulin resistance and metabolic syndrome. At this time, several phase II-III trials are testing the effects of metformin, alone or in combination with other drugs, on decreasing the risk of recurrence in both diabetic and non-diabetic breast, pancreatic and prostate cancer patients.[58] The results of our meta-analysis suggest the need for adjuvant trials of metformin in CRC as well as the need to assess different therapeutic and lifestyle interventions, since low dietary glycemic load and physical exercise have been shown to be associated with improved survival after CRC diagnosis.[59,60] In addition, screening guidelines for diabetes in CRC patients should be implemented to diagnose insulin resistance early with the use of reliable indicators such as the HOMA index, and metformin should be regarded as the anti-diabetic drug of choice in CRC patients with diabetes or glucose intolerance, as has been advocated for breast cancer patients.[61]

Our sensitivity analyses show that if patients with metastatic disease at presentation are eliminated from the analysis, the associations between diabetes and both all-cause and cancer-specific mortality become stronger. Given the unanimous fatal outcome of patients with metastatic CRC, limiting the analysis to patients with a chance for long-term survival gives us an opportunity to better estimate the association between diabetes and CRC outcomes. This is also reflected in the stronger association found between diabetes and both all-cause and cancer-specific mortality after eliminating studies with insufficient follow-up. It is possible that the risk of recurrence increases with a longer exposure to diabetes, as has been shown for the risk of developing new cancer.[62]

The main strength of this meta-analysis is our comprehensive search strategy and the number of recent relevant publications identified. This allowed us to pool results for not only all-cause mortality but also cancer-specific mortality, disease-free survival, and recurrence. In addition, the number of included studies allowed us to conduct some sensitivity analyses to assess the quality of the included studies and to explore additional *a priori* hypotheses.

There are also several limitations of our study. First, our meta-analysis included some studies that did not adjust for age and cancer stage, which are important confounding variables that should be considered in these analyses. However, after restricting our analyses to only those studies with age and stage adjustment, the magnitude of the associations for all-cause and cancer-specific mortality were similar to those when all studies are included, suggesting that lack of adjustment for age and stage did not substantially impact our results. Moreover, several studies included in this meta-analysis fail to adjust for one or more confounding variables frequent in diabetic patients such as presence of cardiovascular disease, neurovascular disease and inadequacy of adjuvant therapy. Second, some studies have short follow-up or do not report mean or median follow-up. However, after eliminating studies with insufficient follow-up, the association between diabetes and poor prognosis persisted and became stronger. Third, many studies did not limit their patient population to those with non-metastatic disease. Our sensitivity analysis showed that if studies had been restricted to non-metastatic patients, stronger associations would likely be observed. Fourth, the included studies were somewhat heterogeneous in study population composition, diabetes diagnostic criteria, outcome ascertainment, and primary intent of the study. Lastly, evidence of publication bias was seen for the all-cause mortality outcome, which could explain the positive findings observed for this outcome. However, sensitivity analyses limited to non-metastatic patients, even after adjustment for potential publication bias (data not shown), strongly support an association between diabetes and all-cause mortality in CRC patients.

In conclusion, our meta-analysis found that CRC patients who have diabetes have a significantly increased risk of all-cause mortality and cancer-specific mortality, and significantly reduced disease-free survival. Further research is needed to assess the effect of different treatments on this adverse prognostic.

Acknowledgments

The authors are grateful to Christina C Newton, Peter T Campbell, Elizabeth Y Chiao, Annette Walder, Lonneke V van de Poll-Franse and Maryska LG Janssen-Heijnen for providing additional data.

SOURCE OF FUNDING

This work was supported by the National Institutes of Health (P20GM103518 to AEH).

Appendix 1. Literary Search Strategy Used for Searching Medline through the Ovid Database

1. diabetes mellitus [MESH exp] OR diabetes mellitus [mp and tw] OR diabetes [mp and tw] OR glucose intolerance [mp and tw] OR glucose intolerance[MESH exp] OR imp and twaired glucose tolerance [mp and tw] OR insulin resistance [MESH exp] OR insulin resistance [mp and tw] OR hyperinsulinemia [mp and tw] OR hyperinsulinism [MESH exp] OR metabolic syndrome X [MESH exp] or metabolic syndrome [mp and tw]

2. survival analysis [MESH exp] OR survival [MESH exp] OR survival rate [MESH exp] OR survival [mp and tw] OR mortality [mp and tw] OR mortality [MESH exp] OR recurrence [MESH exp] OR neoplasm recurrence, local [MESH exp] or recurrence [mp and tw] OR prognosis [mp and tw] or prognosis [MESH exp] OR metastasis [mp and tw] OR neoplasm metastasis [MESH exp]
3. colorectal cancer [mp and tw] OR colorectal neoplasms [MESH exp] OR colon cancer [mp and tw] or rectal cancer [mp and tw] OR colonic cancer [mp and tw] OR ((colon [mp and tw] OR colon [MESH exp] OR rectal [mp and tw] OR rectum [mp and tw] OR rectum [MESH exp] OR colorectal [mp and tw] OR colonic [mp and tw]) AND (neoplasm[mp and tw and tw] OR neoplasms [MESH exp] OR tumor [mp and tw and tw]))
4. #1 AND #2 AND #3

REFERENCES

1. Ferlay, J.; Shin, HR.; Bray, F.; Forman, D.; Mathers, C.; Parkin, DM. [Accessed December 17 2012] GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Available from: http://globocan.iarc.fr
2. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr. 2007; 86:s836–842. [PubMed: 18265477]
3. Berster JM, Göke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. Arch Physiol Biochem. 2008; 114:84–98. [PubMed: 18465362]
4. Aleksandrova K, Boeing H, Jenab M, et al. Metabolic syndrome and risks of colon and rectal cancer: the European prospective investigation into cancer and nutrition study. *Cancer Prev Res* (Phila). 2011; 4:1873–1883. [PubMed: 21697276]
5. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet. 2011; 378:31–40. [PubMed: 21705069]
6. National Cancer Institute. [Accessed December 17, 2012] SEER Stat Fact Sheets: Colon and Rectum. Available at: http://seer.cancer.gov/statfacts/html/colorect.html
7. Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg. 2002; 6:88–94. [PubMed: 11986023]
8. Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003; 21:433–440. [PubMed: 12560431]
9. Gross CP, Guo Z, McAcay GJ, Allore HG, Young M, Tinetti ME. Multimorbidity and survival in older persons with colorectal cancer. J Am Geriatr Soc. 2006; 54:1898–1904. [PubMed: 17198496]
10. Park SM, Lim Mk, Shin SA, Yun YH. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. J Clin Oncol. 2006; 24:5017–5024. [PubMed: 17075121]
11. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol. 1998; 147:816–825. [PubMed: 9583711]
12. Polendak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer Detect Prev. 2006; 30:466–472. [PubMed: 17069990]
13. Huang YC, Lin JK, Chen WS, et al. Diabetes mellitus negatively impacts survival of patients with colon cancer, particularly in stage II disease. J Cancer Res Clin Oncol. 2011; 137:211–220. [PubMed: 20387072]
14. Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. Cancer. 2012; 118:1353–1361. [PubMed: 21800292]

15. Stein KB, Snyder CF, Barone BB, et al. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. Dig Dis Sci. 2010; 55:1839–1851. [PubMed: 19731028]
16. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cacner diagnosis: the cancer Prevention Study-II Nutrition Study. J Clin Oncol. 2012; 30:53–59. [PubMed: 22124092]
17. Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: Implications for screening. Ann Intern Med. 2006; 145:646–653. [PubMed: 17088577]
18. Payne JE, Meyer HJ. The influence of other diseases upon the outcome of colorectal cancer patients. ANZ J Surg. 1995; 65:398–402.
19. Lai C-C, You J-F, Yeh C-Y, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis. 2011; 26:473–481. [PubMed: 21190025]
20. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colrectal cancer patients with diabetes: A large population-based analysis. Diabetologia. 2012; 55:2163–2172. [PubMed: 22526616]
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61:344–349. [PubMed: 18313558]
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–188. [PubMed: 3802833]
23. Sarfati D, Hill S, Blakely T, et al. The effect of comorbidity on the use of adjuvant chemotherpay and survival from colon cancer: a retrospective cohort study. BMC Cancer. 2009; 9:116. [PubMed: 19379520]
24. Lemmens VE, Janssen-Heijnen ML, Verheij CD, Houterman S, Repelaer van Driel OJ, Coebergh JW. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg. 2005; 92:615–623. [PubMed: 15779071]
25. Janssen-Heijnen ML, Maas HA, Houterman S, Lemmens VE, Rutten HJ, Coebergh JW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. Eur J Cancer. 2007; 43:2179–2193. [PubMed: 17681780]
26. Maas HA, Lemmens VE, Cox S, et al. The effects of age and comorbidity on treatment patterns of radiotherapy and survival in patients with mobile rectal cancer: a population-based study. European Geriatric Medicine. 2011; 2:273–279.
27. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less agreessive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007; 120:1986–1992. [PubMed: 17230509]
28. Zhou ZG, Pan ZZ, Wan DS, et al. Prognostic analysis of 443 cases of stage II colorectal cancer and the value of adjuvant chemotherapy. Ai Zheng. 2009; 28:908–912. [PubMed: 19728905]
29. Lieffers JR, Baracos VE, Winget M, Fassbender K. A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer. 2011; 117:1957–1965. [PubMed: 21509773]
30. Chen CQ, Fang LK, Cai SR, et al. Effects of diabetes mellitus on prognosis of the patients with colorectal cancer undergoing resection: a cohort study with 945 patients. *Chin Med J* (Engl).. 2010; 123:3084–3088. [PubMed: 21162960]
31. Chiao EY, Nambi PV, Naik AD. The impact of diabetes process and outcome quality measures on overall survival in patients with co-morbid colorectal cancer. J Cancer Surviv. 2010; 4:381–387. [PubMed: 20721633]
32. Feng JF, Zhou XM, Mao WM. Prognostic analysis of colorectal cancer patients with diabetes mellitus in China – the experience of a single institution. Adv Clin Exp Med. 2011; 20:473–480.
33. Gao RZ, Gu J, Du CZ, Li M. Impact of diabetes mellitus on clinicopathological factors and prognosis of patients with colorectal cancer. Chin J Surg. 2010; 48:88–92. [PubMed: 20302723]

34. Huang CW, Sun LC, Shih YL, et al. The impact on clinical outcome of high prevalence of diabetes mellitus in taiwanese patients with colorectal cancer. World J Surg Oncol. 2012; 10:76. [PubMed: 22553992]
35. Jullumstro E, Kollind M, Lydersen S, Edna TH. Diabetes mellitus and outcomes of colorectal cancer. Acta Oncol. 2009; 48:361–367. [PubMed: 19101848]
36. Noh GY, Hwang DY, Choi YH, Lee YY. Effect of diabetes mellius on outcomes of colorectal cancer. J Korean Soc Coloproctol. 2010; 26:424–428. [PubMed: 21221244]
37. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. N Z Med J. 2011; 124:76–88. [PubMed: 21946965]
38. Shonka NA, Anderson JR, Panwalkar AW, Reed EC, Steen PD, Ganti AK. Effect of diabetes mellitus on the epidemiology and outcomes of colon cancer. Med Oncol. 2006; 23:515–519. [PubMed: 17303910]
39. Siddiqui AA, Spechler SJ, Huerta S, Dredar S, Little BB, Cryer B. Elevated HbA1c is an independent predictor of aggressive clinical behavior in patients with colorectal cancer: a case-control study. Dig Dis Sci. 2008; 53:2486–2494. [PubMed: 18409001]
40. Tiwana J, Ortman S, Davies T, et al. Long-standing diabetes and its effects on outcomes in colon cancer. J Clin Oncol. 2011; 29:e14019.
41. Zhou ZG, Wu XJ, Li LR, et al. A multivariate analysis of prognostic determinants for stages II and III colorectal cancer in 141 patients. *Chin Med J* (Engl).. 2011; 124:2132–2135. [PubMed: 21933615]
42. Yeh HC, Platz EA, Wang NY, Visvanathan K, Helzlsouer KJ, Brancati FL. A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Car. 2012; 35:113–118.
43. McBean AM, Yu X. The underuse of screening services among elderly women with diabetes. Diabetes Care. 2007; 30:1466–1472. [PubMed: 17351285]
44. Gross, Cp; McAvay, GJ.; Guo, Z.; Tinetti, ME. The impact of chornic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer. 2007; 109:2410–2419. [PubMed: 17510973]
45. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H, for the Diabetes and Cancer Reseach Consortium. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012; 55:1619–1632. [PubMed: 22476948]
46. Caudle AS, Kim HJ, Tepper JE, et al. Diabetes mellitus afftects response to neoadjuvant chemoradiotherapy in the management of rectal cancer. Ann Surg Oncol. 2008; 15:1931–196. [PubMed: 18418656]
47. Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. Gut. 2006; 55:285–291. [PubMed: 16239255]
48. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol. 2005; 2:48–53. [PubMed: 16264856]
49. Wolpin BM, Meyerhardt JA, Chan AT, et al. Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. J Clin Oncol. 2009; 27:176–185. [PubMed: 19064975]
50. Fuchs CS, Goldberg RM, Sargent DJ, et al. Plasma insulin-like growth factors, insulin-like binding protein-3, and outcome in metastatic colorectal cancer: results from intergroup trial N9741. Clin Cancer Res. 2008; 14:8263–8269. [PubMed: 19073970]
51. Haydon AM, Macinnis RJ, English DR, Morris H, Giles GG. Physical activity, insulin-like growth factor 1, insulin-like growth factor binding protein 3, and survival from colorectal cancer. Gut. 2006; 55:689–694. [PubMed: 16299029]
52. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Car. 2009; 32:1620–1625.
53. DeCensi A, Puntoni M, Goodwin P, et al. Metformin and Cancer Risk in Diabetic Patients: A Systematic Review and Meta-analysis. Cancer Prev Res. 2010; 3:1451–1461.
54. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2012; 131:752–759. [PubMed: 21913184]

55. Garrett CR, Hassabo HM, Bhadkamkar NA, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012; 106:1374–1378. [PubMed: 22421948]

56. Shaw RJ, Lamia KA, Vasquez D, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005; 310:1642–1646. [PubMed: 16308421]

57. Bonanni B, Puntoni M, Cazzaniga M, et al. Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. J Clin Oncol. 2012; 30:2593–2600. [PubMed: 22564993]

58. Rattan R, Ali Fehmi R, Munkarah A. Metformin: an emerging new therapeutic option for targeting cancer stem cells and metastasis. J Oncol. 2012:928127. [PubMed: 22701483]

59. Meyerhardt JA, Sato K, Niedzwiecki D, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Natl Cancer Inst. 2012; 104:1702–1711. [PubMed: 23136358]

60. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol. 2013; 31:876–885. [PubMed: 23341510]

61. De Censi A, Gennari A. Insulin Breast Cancer Connection: Confirmatory Data Set the Stage for Better Care. J Clin Oncol. 2011; 29:7–10. [PubMed: 21115871]

62. Li C, Zhao G, Okoro CA, Wen XJ, Ford ES, Balluz LS. Prevalence of Diagnosed Cancer According to Duration of Diagnosed Diabetes and Current Insulin Use Among U.S. Adults With Diagnosed Diabetes: Findings from the 2009 Behavioral Risk Factor Surveillance System. Diabetes Care. 2013; 36:1569–1576. [PubMed: 23300288]

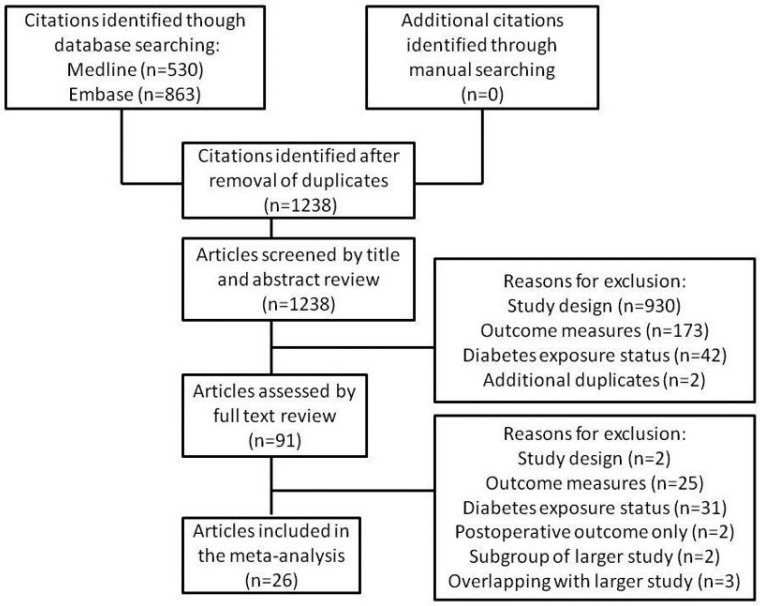
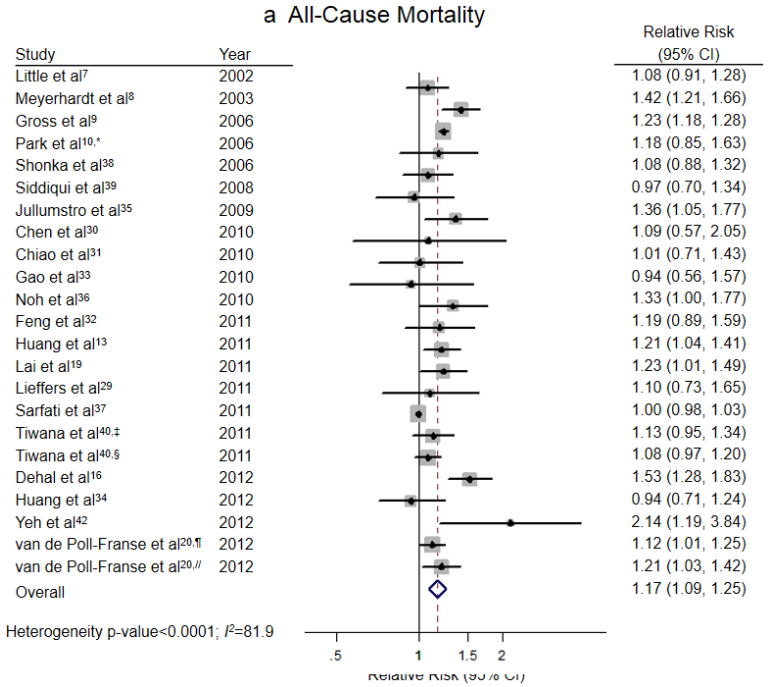
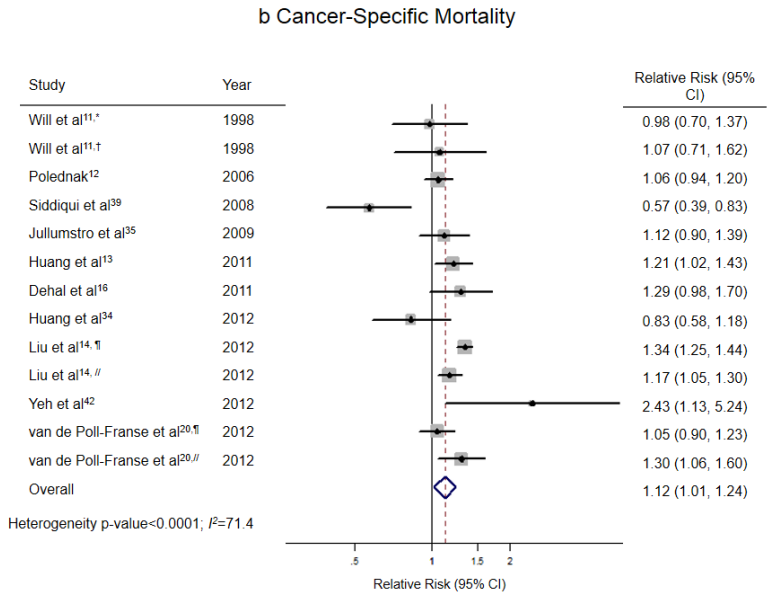


Figure 1.
Flowchart of study selection





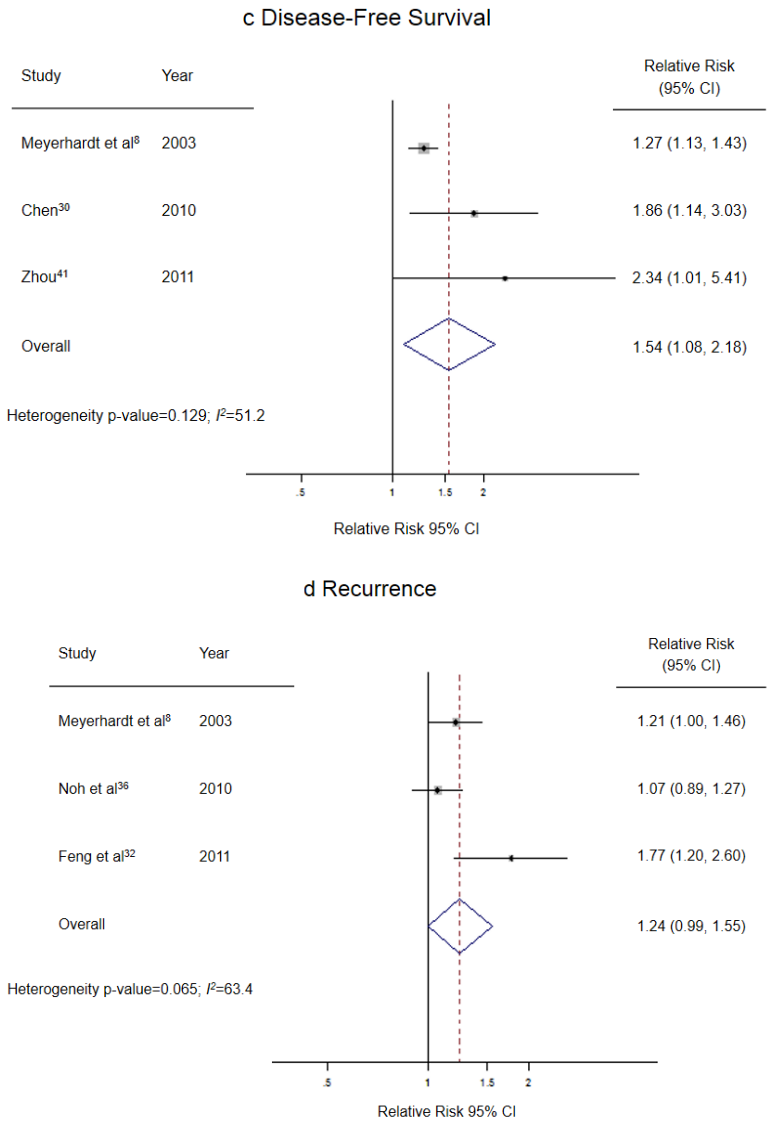


Figure 2.

Meta-analysis of the effect of pre-existing diabetes on all-cause mortality (a), cancer-specific mortality (b), disease-free survival (risk of recurrence or death) (c) and recurrence rate (d). * Males Only; † Females Only; ‡ Stage 3 Cancer; § Stage 4 Cancer; ¶ Colon Cancer; // Rectal Cancer

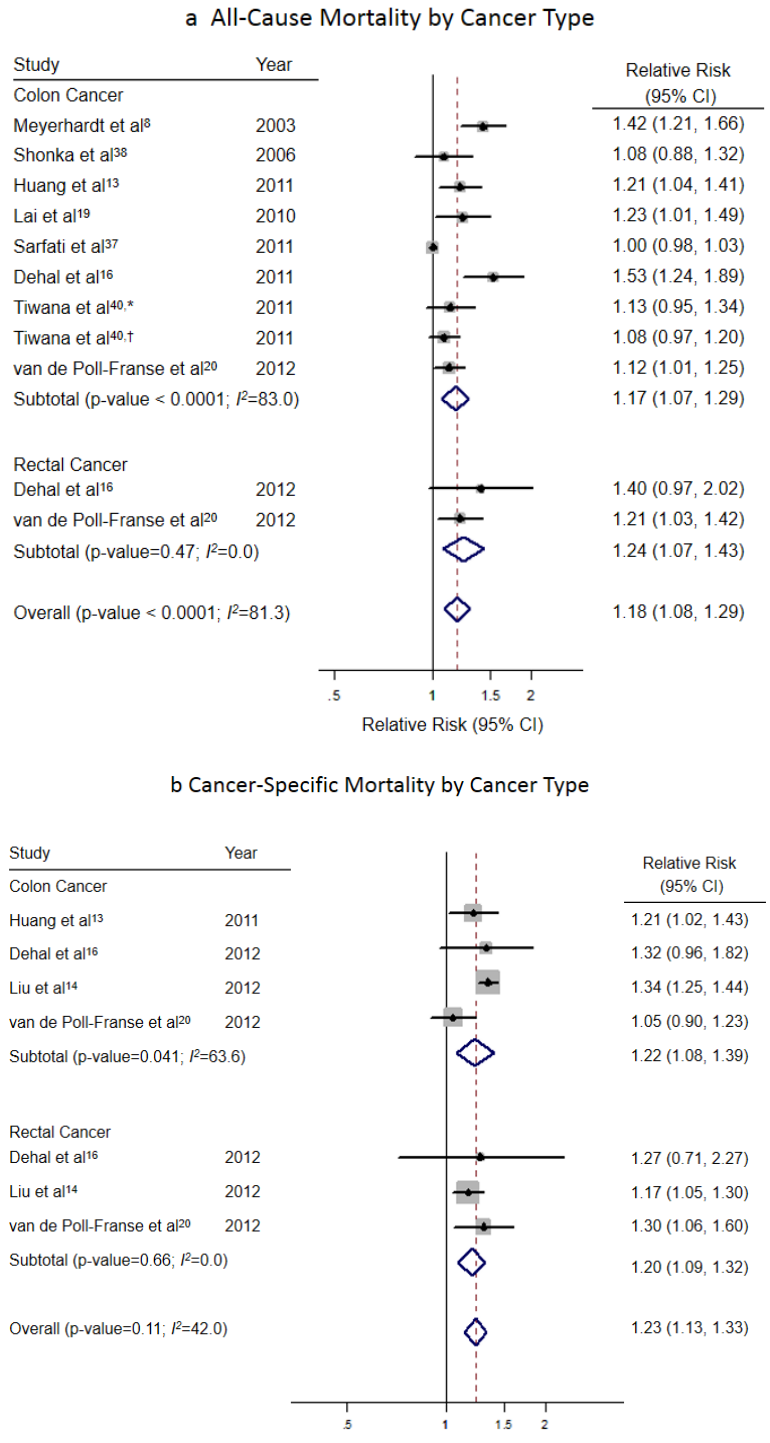


Figure 3.

Meta-analysis of the effect of pre-existing diabetes on all-cause mortality (a) and cancer-specific mortality (b) stratified by cancer type. * Stage 3 Cancer; † Stage 4 Cancer

Table 1

Study Characteristics

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
Chen et al.[30]	2010, China	Prospective cohort	Colon and rectal	945	26 (3)	Mean: 45.8 months	57.1	58.8	Stage 1: 8.9%; Stage 2: 44.9%; Stage 3: 31.5%; Stage 4: 14.7%	All patients undergoing surgical resection between 1994 and 2002 in one hospital	Tumor stage, intestinal obstruction, gross type	Unadjusted ACM, Adjusted DFS
Chiao et al.[31]	2010, USA	Retrospective cohort	Colon and rectal	470	122 (26)	Median: 35.2 months	67.7	98.7	Stage 0-1: 29.1%; Stage 2-3: 38.1%; Stage 4: 32.8%	Patients diagnosed between 1999 and 2006 in one veteran hospital, including 146 (31%) not undergoing surgery	Age, sex, tumor stage, year of diagnosis, treatment, BMI, Deyo comorbidity score	Adjusted ACM
Feng et al.[32]	2011, China	Retrospective cohort	Colon and rectal	773	75 (10)	Mean: 4.5 years	57.4	58.7	Stage 1: 12.9%; Stage 2: 57.1%; Stage 3: 25.2%; Stage 4: 4.8%	All patients undergoing surgical resection between 2000 and 2005 in one hospital	None	Unadjusted 5-year ACM, Unadjusted RR
Gao et al.[33]	2010, China	Retrospective cohort	Colon and rectal	599	58 (8)	NA	59.6	54.6	Stage 1:15.2%; Stage 2: 33.9%; Stage 3: 35.7%; Stage 4: 15.2%	All patients undergoing surgery	None	Unadjusted 5-year ACM
Gross et al.[9]	2006, USA	Retrospective cohort	Colon and rectal	29733	5292 (18)	Median: 4.1; Range: 3-10 yrs	77.2	45.0	Stage 1: 29.5%; Stage 2: 38%; Stage 3: 27.6%	Patients age 67 and older at time of diagnosis between 1993 and 1999 in Medicare database	Cancer stage, histological grade, and location, demographic characteristics, comorbid conditions	Adjusted ACM

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
Huang et al.[13]	2011, Taiwan	Prospective cohort	Colon	2762	469 (17)	NA	NA	63.6	Stage 1: 12.9%; Stage 2: 30.3%; Stage 3: 26.7%; Stage 4: 30.2%	All patients between 1999 and 2008 at one veteran hospital	Age, sex, tumor stage, differentiation and histology, bowel perforation	Adjusted ACM, Adjusted CSM
Huang et al.[34]	2012, Taiwan	Retrospective cohort	Colon and rectal	1197	283 (24)	Median: 32 months; Range 1-96 months	64.2	56.2	Stage 1: 17.3%; Stage 2: 35.5%; Stage 3: 30.5%; Stage 4: 16.7%	Patients receiving surgical treatment from a single hospital between 2002 and 2008	Age, sex, location, tumor size, BMI, albumin, histology, AJCC stage, pre- and post-op CEA, vascular invasion, perineurial invasion	Adjusted ACM, Adjusted CSM
Jullumstro et al.[35]	2009, Norway	Retrospective cohort	Colon and rectal	1194	97 (8)	NA	DM median: 76.2; NDM median: 71.7	52.6	Stage 1: 13.5%; Stage 2: 35.1%; Stage 3: 23.4%; Stage 4: 22.1%; Unknown: 5.9%	Patients treated between 1980 and 2004 in one hospital including 74 (6%) not undergoing surgery and 283 (24%) undergoing non-curative surgery	Age, Tumor stage, cardiac, pulmonary and other diseases	Adjusted ACM, Unadjusted 5-year CSM
Lai et al.[19]	2011, Taiwan	Retrospective cohort	Colon	2529	307 (12)	NA	62.5	52.0	Stage 1: 12.7%; Stage 2: 47.7%; Stage 3: 39.6%	Patients undergoing potentially curative surgery between 1995 and 2008 at one hospital	Age, sex, tumor stage, hypertension, cardiac disease, old cardiovascular accident, cirrhosis, other diseases, CEA level, albumin level, histology, morphology and differentiation	Adjusted ACM
Lieffers et al.[29]	2011, Canada	Retrospective cohort	Colon and rectal	574	72 (6)	Minimum: 3 yrs	64.0	58.4	Stage 2: 27.7%; Stage 3: 33.3%;	Patients seen between 2004 and 2006 in a	Age, sex, stage, MI, CHF, cerebrovascular	Adjusted ACM

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
									Stage 4: 39.0%	single oncology clinic including 59 (9%) not undergoing surgery	disease, dementia, chronic pulmonary disease, peptic ulcer disease, mild liver disease	
Little et al.[7]	2002, USA	Retrospective cohort	Liver metastasis	727	61 (8)	Median: 24 months; Range: 1-112	Median: 62.0	57.4	NA	Patients undergoing potentially curative resection of colorectal liver metastasis between 1990 and 1999 at a cancer center	none	Unadjusted ACM
Liu et al.[14]	2012, Sweden	Retrospective cohort	Colon and rectal	118,450	2247 (2)	Mean: 8 years	Colon Cancer: 69.9, Rectal Cancer: 68.9	NA	NA	Cancer patients hospitalized from 1961 to 2008 from national Swedish registries	age, sex, period, obesity, alcohol, smoking, SES, diagnosis region	Adjusted CSM
Meyerhardt et al.[8]	2003, USA	Prospective cohort	Colon	3549	287 (4)	Median: 9.4 years	61.9	54.6	Stage 2: 19.4%; stage 3: 80.6%	Patients undergoing curative resection from a chemotherapy trial from 1988 to 1992	Age, sex, race, BMI, baseline performance status, bowel obstruction, bowel perforation, stage of disease, presence of peritoneal implants, completion of chemotherapy	Adjusted ACM, Adjusted RR, Unadjusted DFS
Noh et al.[36]	2010, Korea	Retrospective cohort	Colon and rectal	657	67 (10)	Median: 4.7 years	58.0	56.9	Stage 1: 14.0%; Stage 2: 42.9%; Stage 3: 37.4%; Stage 4: 5.6%	Patients undergoing surgery between 1997 and 2004 by a single surgeon	Age, BMI	Adjusted ACM, Adjusted RR

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
Park et al.[10]	2010, Korea	Prospective cohort	Colon and rectal	1882	91 (8)	Median: 3.78 years	50.8	100.0	NA	Male government employees from a prospective cohort study who developed colorectal cancer	Age, BMI, alcohol consumption, fasting serum glucose, cholesterol level, physical activity, food preference, blood pressure, other comorbidities (heart, liver, cerebrovascular)	Adjusted ACM
Polednak[12]	2006, USA	Retrospective cohort	Colon and rectal	9395	1014 (11)	NA	NA	47.8	Stage 1: 15.8%; Stage 2-3: 60.1%; Stage 4: 17.4%; Unstaged: 6.7%	All patients diagnosed with colorectal cancer between 1994 and 1999 from state registry	Age, race, sex, tumor stage, lymph node status, poverty rate	Adjusted ACM, Adjusted CSM
Sarfati et al.[37]	2011, New Zealand	Retrospective cohort	Colon and rectal	11524	1107 (10)	NA	25-60: N=2035, 61-70: N=3209, 71-80: N=4028, >80: N=2252	47.5	NA	All patients diagnosed with colorectal cancer between 1996 and 2003 from national cancer registry	Age, sex, tumor stage, ethnicity, deprivation quintiles	Adjusted ACM
Shonka et al.[38]	2006, USA	Retrospective cohort	Colon	1853	255 (14)	NA	49-60: N=234, 50-69: N= 218, 60-69: N= 504, 70-79: N=600, >79: N=395	48.1	Stage 0: 7.3%; Stage 1: 17.7%; Stage 2: 26.8%; Stage 3: 29.1%; Stage 4: 19.1%	Patients diagnosed with colon cancer between 1986 and 2003 at one hospital including 124 (7%) intramucosal	Age, sex, tumor stage, smoking, family history, year of diagnosis	Adjusted ACM
Siddiqui et al.[39]	2008, USA	Matched retrospective cohort	Colon and rectal	269	155 (57)	NA	69.2	NA	Stage 1-2: 58.0%; Stage 3-4: 42.0%	Age and sex matched patients	none	Unadjusted ACM, Unadjusted CSM

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
										with colorectal cancer with and without T2DM at single veteran hospital between 1997 and 2001		
Tiwana et al.[40]	2011, USA	Retrospective cohort	Colon	6265	1173 (19)	Median: Diabetics 7.7. years, Non-diabetics - 7.0 years *	NA	NA	Stage 3: 45.5%; Stage 4: 54.5%	Patients diagnosed with colon cancer between 1995 and 2008 in the Veterans Affairs Central Cancer Registry	Age, Charlson Comorbidity Index, grade tobacco use, number of lymph nodes, chemotherapy,	Adjusted ACM
van de Poll-Franse et al.[20]	2012, Netherlands	Retrospective cohort	Colon and rectal	10862	1224 (11)	NA	Colon Cancer: 69.3, Rectal Cancer: 66.6	53.5	Stage 1: 25.4%; Stage 2: 41.9%; Stage 3: 32.7%	Patients diagnosed with colorectal cancer between 1997 and 2007 from a regional cancer registry	age, stage, sex, number of examined lymph nodes, adjuvant therapy, socioeconomic status, year of diagnosis, hypertension, cardiovascular disease, cerebrovascular accident, previous cancer, lung disease	Adjusted ACM, Adjusted CSM
Will et al.[11]	1998, USA	Prospective cohort	Colon and rectal	7224	160 (2)	NA	57.0	44.5	NA	Patients with a diagnosis of colorectal cancer from the 1959-1972 Cancer prevention Study I	Age, race, BMI, education, family history, smoking, type of food consumption, alcohol, aspirin use, exercise, pregnancy	Adjusted CSM

Study	Year, Country	Study design	Type of cancer	N	Patients with diabetes, N (%)	Follow-up	Mean age, years	Sex, % Male	Cancer Stage, %	Patient population	Adjustment variables	Outcomes reported
Yeh et al.[42]	2012, USA	Prospective cohort	Colon and rectal	286	17 (6)	NA	NA	NA	NA	Residents of a Maryland county included in a cohort study starting in 1989 who developed colorectal cancer before the end of 2006	age, sex, bmi, smoking, education level, hypertension treatment, high cholesterol treatment	Adjusted ACM, Adjusted CSM
Zhou et al.[28]	2009, China	Retrospective cohort	Colon and rectal	443	47 (11)	Median: 59 months	Median: 59.0	59.8	Stage 2: 100%	Patients undergoing curative surgery between 2000 and 2005 at one cancer center	Total number of lymph nodes, obstruction, positive margins, chemotherapy	Adjusted ACM
Zhou et al.[41]	2011, China	Retrospective cohort	Colon and rectal	141	13 (9)	Median: 59 months	Median: 59.0	57.4	Stage 2: 51.8%; Stage 3: n=48.2%	Patients undergoing potentially curative surgery between May and November 2003 at one cancer center	lymph node status,COX-2, MMP-2 and VEGF immunohistochemistry	Adjusted DFS

Abbreviations: DM diabetes mellitus; ACM all-cause mortality; CSM cancer-specific mortality; DFS disease free survival; RR recurrence rate; CHF congestive heart failure; CVD cerebrovascular disease; BMI body mass index; CEA carcinoembryonic antigen; COX cyclo-oxygenase; MMP matrix metalloproteinase; VEGF vascular endothelial growth factor; XRT radiotherapy

*Follow-up times reported for patients with all cancer stages, while outcomes of interest are only reported for stages 3 and 4

Dis Colon Rectum. Author manuscript; available in PMC 2014 November 01.

Table 2

Study Quality

Study	Population source		Diabetes ascertainment				Outcome ascertainment					Focus on diabetes		Statistical analysis	
	Population based	Hospital based	Medical records	Self reported	Blood glucose	Other	Death registry	Medical record	Follow-up	Tumor registry	Other	Primary exposure	Multiple prognostic factors	Adjusted models	Age and stage adjusted
Chen et al.[30]		x	x		x			x				x		x	x
Chiao et al.[31]		x	x					x				x		x	x
Dehal et al.[16]	x			x			x					x		x	x
Feng et al.[32]		x			x			x				x			
Gaoet al.[33]		x			x			x				x			
Gross et al.[9]	x					‡					†		x	x	x
Huang et al. 2011[13]		x	x					x				x		x	x
Huang et al. 2012[34]		x	x					x				x		x	x
Jullumstro et al.[35]		x	x					x				x		x	x
Lai et al.[19]		x	x							x			x	x	x
Lieffers et al.[29]		x	x							x			x	x	x
Little et al.[7]		x	x					x				x			
Liu et al.[14]	x		x				x					x		x	
Meyerhardt et al.[8]		x	x						x			x		x	x
Noh et al.[36]		x	x					x				x		x	
Park et al.[10]	x				x		x						x	x	
Polednak[12]	x		x				x					x		x	x
Sarfati et al.[37]	x		x				x						x	x	x
Shonka et al.[38]		x	x				x					x		x	x
Siddiqui et al.[39]		x	x				x					x		x	
Tiwana et al[40]	x		x							x		x		x	
van de Poll-	x		x							x		x		x	x

Study	Population source		Diabetes ascertainment				Outcome ascertainment					Focus on diabetes		Statistical analysis	
	Population based	Hospital based	Medical records	Self reported	Blood glucose	Other	Death registry	Medical record	Follow-up	Tumor registry	Other	Primary exposure	Multiple prognostic factors	Adjusted models	Age and stage adjusted
Franse et al.[20]															
Will et al.[11]	x			x			x						x	x	
Yeh et al.[42]	x			x			x					x		x	
Zhou et al. 2009[28]		x	x				x						x	x	
Zhou et al. 2011[41]		x	x				x						x	x	

Abbreviations: x=present in study; ‡ Medicare claims; † Medicare enrollment files

Table 3

Sensitivity analyses for the association between diabetes and survival in those with colorectal cancer.

	N	RR (95% CI)
All-Cause Mortality		
Non-Metastatic	10	1.32 (1.21, 1.44)
≥3 Years Follow-up *	11	1.25 (1.15, 1.36)
Appropriate Adjustment †	13	1.20 (1.08, 1.33)
Inclusion of Overlapping Studies ‡	31	1.21 (1.14, 1.30)
Cancer-Specific Mortality		
Non-Metastatic	5	1.27 (1.06, 1.52)
≥3 Years Follow-up	3	1.27 (1.14, 1.40)
Appropriate Adjustment	5	1.10 (0.98, 1.24)
Disease-Free Survival		
Non-Metastatic	2	1.49 (0.88, 2.52)

* Defined as mean, median, or minimum survival of at least three years

† Defined as multivariate adjustment for age and cancer stage

‡ All comparisons with overlapping participants were included