The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies

Bo Zhu[1]*, Xiaomei Wu[2], Bo Wu[3], Dan Pei[4], Lu Zhang[1], Lixuan Wei[1]

1 Department of Cancer Prevention and Treatment, Cancer Hospital of China Medical University/ Liaoning Cancer Hospital & Institute, Dadong District, Shenyang, People's Republic of China, 2 Department of Clinical Epidemiology and Evidence Medicine, The First Hospital of China Medical University, Heping District, Shenyang, People's Republic of China, 3 Department of Anus and Intestine Surgery, The First Hospital of China Medical University, Heping District, Shenyang, People's Republic of China, 4 Department of Occupational health, Liaohe Petrochemical Company of China National Petroleum Corporation, Xinglongtai District, Panjin, People's Republic of China

* 15998896991@163.com

Abstract

Introduction

Though a meta-analysis reported the effect of diabetes on colorectal prognosis in 2013, a series of large-scale long-term cohort studies has comprehensively reported the outcome effect estimates on the relationship between diabetes and colorectal prognosis, and their results were still consistent.

Methods

We carried out an extensive search strategy in multiple databases and conducted a meta-analysis on the effect of diabetes on colorectal prognosis, based on the included 36 cohort studies, which contained 2,299,012 subjects. In order to collect more data, besides conventional methods, we used the professional software to extract survival data from the Kaplan-Meier curves, and analyzed both the 5-year survival rate and survival risk in overall survival, cancer-specific survival, cardiovascular disease—specific survival, disease-free survival, and recurrence-free survival, to comprehensively reflect the effect of diabetes on colorectal prognosis.

Results

The results found that compared to patients without diabetes, patients with diabetes will have a 5-year shorter survival in colorectal, colon and rectal cancer, with a 18%, 19% and 16% decreased in overall survival respectively. We also found similar results in cancer-specific survival, cardiovascular disease—specific survival, disease-free survival, and recurrence-free survival, but not all these results were significant. We performed the subgroup analysis and sensitivity analysis to find the source of heterogeneity. Their results were similar to the overall results.

Conclusions

Our meta-analysis suggested that diabetes had a negative effect on colorectal cancer in overall survival. More studies are still needed to confirm the relationship between diabetes and colorectal prognosis in cancer-specific survival, cardiovascular disease—specific survival, disease-free survival, and recurrence-free survival.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in global incidence and the fourth in mortality all over the world, and the incidence and mortality are higher in men than in women in most parts of the world [1]. In recent years, diagnosis and treatment had made a certain degree of progress, but CRC is still a very important public health problem in the world. Thus, early diagnosis, effective treatment and analysis prognosis were of great significance to reducing the CRC mortality. To guide decision-making for therapeutic strategies for CRC patients and improve their prognosis, a better understanding of the relevant factors affecting CRC prognosis is urgently needed.

Diabetes mellitus (DM) is one of the most common chronic and metabolism diseases. The number of people with DM worldwide has increased by two times in the past three decades[2]. An estimated 285 million people worldwide had diabetes mellitus in 2010, and the number of DM sufferers will rise to 439 million by 2030, represents 7.7% of the total adult population of the world aged 20–79 years[3]. The concurrence of DM pandemics with the growing burden of cancer globally has generated interest in defining the epidemiological and biological relationships between these medical conditions[3, 4].

DM can seriously affect quality of life. DM can not only cause neurological and vascular complications, but is also closely related to the occurrence, development and prognosis of cancer. Currently, more and more clinicians are considering whether patients have suffered from diabetes during the treatment of cancer, and diabetologists often have to manage diabetes in patients who are being treated for cancer[4]. Insulin resistance or compensatory hyperinsulinemia leads to hormonal and metabolic alterations, and is involved in the formation of the microenvironment for tumorigenesis and tumor progression. Diabetes mellitus might influence survival of CRC patients due to insulin-stimulated growth of colorectal cancer cells or inadequate treatment of persons with concomitant disease. However, it is unclear whether colorectal cancer patients with DM are more likely to receive a worse colorectal cancer prognosis compared to patients without DM. A meta-analysis has reported the effect of DM on CRC prognosis[5], but since 2013, a series of large-scale long-term cohort studies had comprehensively reported the outcome effect estimates on the relationship between DM and CRC prognosis, and their results were still consistent[6–20]. For example, in overall survival (OS) of CRC, several studies found that DM showed a significant decreased risk in OS[6, 7, 12–14, 17], and others found no link[8–11, 15, 16, 18–20]. The data from these studies has also allowed us to evaluate the relationship between DM and CRC prognosis more accurately. Thus we want to perform a meta-analysis to determine the relationship between DM and CRC prognosis, and provide a theoretical basis for clinical research. Our meta-analysis first reported the 5-year survival estimates on the effect of DM on CRC prognosis, and respectively analyzed the effects of DM on the colorectal, colon and rectal cancer from OS, cancer-specific survival (CSS), cardiovascular disease—specific survival (CVDS), disease-free survival (DFS), or recurrence-free survival (RFS).

Methods

Literature search

A systematic literature review was independently carried out by two groups (Bo Zhu, Bo Wu as a group, and Lu Zhang, Lixuan Wei as another group) in multiple databases (Pubmed, Web of Science, Embase and Google Scholar) up to March 19, 2017. In order to collect as many relevant studies as possible, we set the following search terms: (diabetes OR hyperglycemia OR glucose intolerance) AND (colorectal cancer OR colorectal neoplasms OR colon cancer OR colonic neoplasms OR rectal cancer OR rectal neoplasms) AND (prognosis OR survival analysis OR survival OR survival rate OR mortality). The reviewed reference lists from all the relevant original research and reviews were also searched to identify additional potentially eligible studies. There were no language or other restrictions. All retrieved studies were initially selected by reading the title and abstract. S1 File showed the detailed methods used for searching all the databases.

Inclusion and exclusion criteria

The final included studies were identified by reading the full text, according to the inclusion and exclusion criteria. Three authors (Bo Zhu, Xiaomei Wu and Bo Wu) participated in this process, and any disagreements were solved by discussion.

The included studies in our meta-analysis should meet the following criteria: the study should (1) investigate the relationship between DM and CRC prognosis; (2) be cohort study; (3) provide the hazard ration (HR) or rate, which reflected overall survival (OS), cancer-specific survival (CSS), cardiovascular disease—specific survival (CVDS), disease-free survival (DFS), or recurrence-free survival (RFS); (4) provide the relevant data to calculate the corresponding outcome effect estimates.

The diagnostic criterion for DM and hyperglycemia was used by the World Health Organization (WHO) 1999 criteria or American Diabetes Association (ADA) 2010 guidelines. OS was defined as the time from the date of surgery to death from any cause. CSS was defined as the time from the date of surgery to death from colorectal cancer-specific cause of death. CVDS defined as the time from the date of surgery to death from cardiovascular disease -specific cause of death. DFS was defined as time from the date of surgery to tumor recurrence or occurrence of a new primary colorectal tumor or death from any cause. RFS was defined as the time from the surgery to tumor recurrence or occurrence of a new primary colon tumor[8, 21].

The exclusion criteria of our meta-analysis are: (1) the study did not investigate the relationship between the relationship between DM and CRC prognosis; (2) the study did not provide the relevant data to calculate outcome effect estimates (including HR and/or rate), which reflected OS, CSS, CVDS, DFS, or RFS; (3) the type of study excluded animal experiment, chemistry and cell-line research, letters to the editor, meetings abstracts, communications or review.

Data extraction and conversion

The data from the final included studies were extracted independently by two authors (Bo Zhu and Xiaomei Wu). These authors used the standard table to extract the information, which included author, year of publication, country, type of study, sample size, population source, recruitment time, age, gender, patients with DM, DM ascertainment, type of cancer, outcomes, and adjusted variables. If the study provided more than two outcome effect estimates adjusted for different numbers of potential confounders, we extracted the estimate that adjusted for the

highest number of potential confounders for analysis. If more than two studies provided the outcome effect estimates from the same population, we extracted the latest or highest-quality outcome effect estimates.

Quality assessment

Two authors (Bo Zhu and Xiaomei Wu) independently conducted the quality assessment of the final studies included by using the Newcastle-Ottawa Quality Assessment Scale (NOS)[22]. The NOS is a semi quantitative method for assessing the quality of studies, and consisted of three main parts: selection (4 points), comparability (2 points) and outcome (3 points). Thus, the quality of study was determined on a scale from zero to nine points. Studies with seven or more points were regarded as "high quality", studies with the points from four to six were regard as "moderate quality", and otherwise, the study was regarded as "low quality"[23].

Statistical analysis

The Stata v.12.0 software was used to conduct our meta-analysis and used the pooled outcome effect estimates and corresponding 95% confidence interval (CI) for OS, CSS, CVDS, DFS or RFS to analyze the relationship between DM and CRC prognosis. If the study did not provide the corresponding results, we used the Engauge Digitizer v.4.1 software (http://digitizer. sourceforge.net/) to extract survival rates from the Kaplan-Meier curves [24–26], the survival rates were entered in the spreadsheet by the method in Tierney's article[24]. The process of extracting survival rates was performed by two independent authors (Dan Pei and Lixuan Wei) to make the extracted data more accurate. The heterogeneity in the included studies was evaluated by the Chi-square-based Q-test and I^2 (I^2 = 0% to 25%, no heterogeneity; I^2 = 25% to 50%, moderate heterogeneity; I^2 = 50% to 75%, high heterogeneity; I^2 = 75% to 100%, extreme heterogeneity). When I^2 was larger than 50%, a random effects model was used; otherwise, the fixed effects model was used.

We used subgroup analysis by region, type of study, sample size, population source and DM ascertainment to find the potential heterogeneity among the included studies. If the number of study was less than or equal to 1, we did not carry out the subgroup analysis. We used the sensitivity analysis to evaluate the robustness of the results by excluding each study in turn and obtaining the pooled estimates from the remaining studies. The purpose of sensitivity analysis was to evaluate the effect of a single study on the overall pooled estimates. If the number of study was less than or equal to 1, we did not carry out the subgroup analysis and sensitivity analysis.The possibility of publication bias was assessed using Begger's and Egger's test. Where publication bias existed, we also performed the Duval and Tweedie nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis. If the number of study was less than or equal to 2, we did not carry out the sensitivity analysis and publication bias test. A two-sided P value <0.05 in statistical process was considered significantly different.

Results

Search results

Originally, we retrieved 19166 potential studies from four electronic databases. By reading the title and abstract, we found that 1014 studies were repetitive and 18010 studies did not report the relationship between DM and CRC Prognosis. By reading the full text, 101 studies were excluded for different reasons, and 5 studies did not provide sufficient data to calculate the

outcome effect estimates. Finally, 36 studies were included in our meta-analysis[6–20, 27–47]. The study selection process for inclusion in our meta-analysis was shown in Fig 1.

Study characteristics and quality

In our meta-analysis, year of publication ranged from 2003 to 2016, and the regions included 2 American countries[7, 13–15, 18, 19, 27, 30, 33, 37, 41, 42, 45, 46], 6 European countries[6, 11, 17, 28, 32, 39, 40, 44], 2 Asian countries[8, 9, 12, 16, 20, 29, 34–36, 38, 43, 47] and 1 Oceania country[31]; the included studies contained 15 retrospective[9, 10, 14, 16–20, 27, 33, 36, 37, 39, 41, 47] and 21 prospective[6–8, 11–13, 15, 28–32, 34, 35, 38, 40, 42–46] cohort studies; the sample size ranged from 391 to 1056243, and the mean age of study ranged from 46.4 to 72.07. In DM ascertainment, 25 studies[6, 8, 9, 11–15, 18, 19, 28, 29, 31, 33–37, 39–42, 44–46] used the method of medical records, 5 studies[16, 20, 38, 43, 47] used the method of blood sugar test, and 6 studies[7, 10, 17, 27, 30, 32] used the method of self-reported. To avoid the effects of confounders, we preferred to extract the adjusted outcome effect estimates, but we still found that the outcome effect estimates of 4 studies were not adjusted.

The quality score ranged from 5 to 9. 11 studies were evaluated as 9 scores, 7 studies were evaluated as 8 scores, 12 studies were evaluated as 7 scores, 4 studies were evaluated as 6 scores, and 2 studies were evaluated as 5 scores. All the included studies were regarded as moderate and high quality.

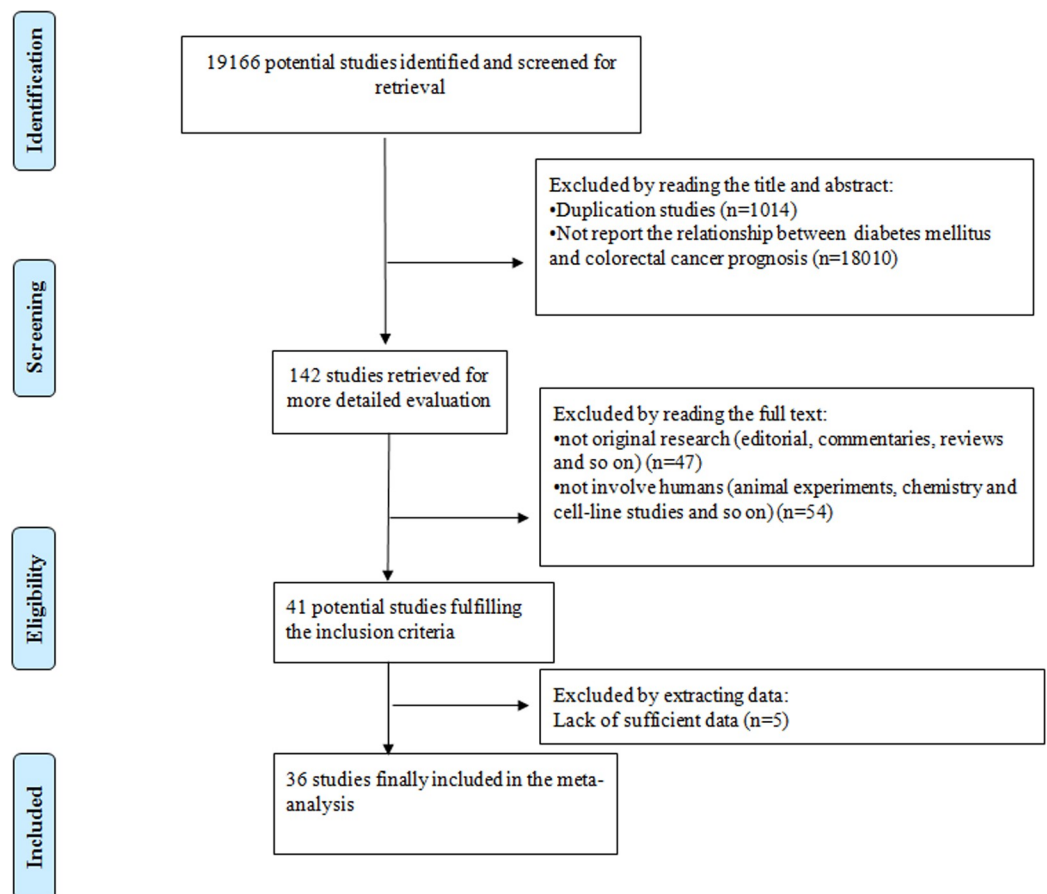The characteristic and quality of the included studies is shown in Table 1.

Fig 1. The study selection process for inclusion in our meta-analysis

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Table 1. The characteristic and quality of the included studies.

Author	Year	Region	Type of Study	Sample Size	Population source	Recruitment time	Age (Year)	Gender (male/female)	Patients with DM (n)	DM ascertainment	Type of cancer	Outcomes	Adjusted variable	NOS score
Lee, S. J.	2016	Korea	retrospective	741	Hospital-based	1999–2010	65.20	440/301	634	Blood glucose test	colon cancer	adjusted HROS; 5-year OS	age and sex, WBC, CRP, total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides	9
Paulus, J. K.	2016	USA	retrospective	21292	population-based	2001–2008	69.16	20866/426	4983	Medical records	colorectal cancer	adjusted HROS; 5-year OS	age, race, AJCC stage, BMI, co-morbidity index, CRC treatment, smoking status	8
Fransgaard, T.	2016	Denmark	retrospective	29353	Hospital-based	2003–2012	70.05	15495/13858	3250	Self-reported	colorectal cancer	adjusted HROS	age, gender, ASA score, BMI, blood transfusions, smoking, alcohol consumption, elective or emergency surgery, AL, type of cancer (colon or rectal) and year of operation	9
Yang, I. P.	2016	Chinese Taiwan	retrospective	520	Hospital-based	2005–2011	64.56	310/210	135	Blood glucose test	colorectal cancer	adjusted HROS and DFS	age, gender, stage, tumor size, location, invasive depth, vascular invasion, perineural invasion and serum blood sugar of CRC patients	9
Ramjeesingh, R.	2016	Canada	retrospective	1304	Hospital-based	2005–2011	71.09	764/540	277	Medical records	colorectal cancer	adjusted HROS; 5-year OS	age, gender, co-morbidities (cardiac, diabetic, renal,and respiratory), diabetes treatments (metformin or not), BMI, smoking history, alcohol history, family history of CRC, location of cancer (rectal vs. colon), stage at diagnosis and differentiation	9
Cui, G.	2015	China	retrospective	391	Hospital-based	2008–2013	—	222/169	58	Blood glucose test	colorectal cancer	unadjusted HROS; 5-year OS	—	5
Chen, K. H.	2014	Chinese Taiwan	Prospective	6937	Population-based	2004–2008	67.3	3946/2991	1371	Medical records	colon cancer	adjusted HROS and HRCSS; 5-year OS and 5-year CSS	age, gender, tumor stage, treatment, cirrhosis, and all other co-morbidities	8

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Table 1. (Continued)

Author	Year	Region	Type of Study	Sample Size	Population source	Recruitment time	Age (Year)	Gender (male/female)	Patients with DM (n)	DM ascertainment	Type of cancer	Outcomes	Adjusted variable	NOS score
Luo, J.	2014	USA	Prospective	46400	Population-based	2003–2009	>65	20638/25762	14813	Medical records	colorectal cancer; colon and rectal cancer	adjusted HROS, HRCSS, and HRCVDS; 5-year OS and 5-year CSS	age at diagnosis, gender, race, marital status, grade, census tract median income and co-morbidity	8
Waheed, S.	2014	USA	Prospective	16977	Population-based	2000–2005	>67	7094/9883	4414	Medical records	colorectal cancer	unadjusted HROS, HRCSS and HRCVDS; 5-year OS, 5-year CSS and 5-year CVDS	—	6
Tong, L.	2014	USA	retrospective	375462	Population-based	1975–2009	—	190189/185273	—	Medical records	colorectal cancer	adjusted HROS	age, gender, race, and regions	6
Walker, J. J.	2013	Scotland	Prospective	19505	Population-based	2000–2007	—	10417/9088	2387	Medical records	colon and rectal cancer	adjusted HROS	age, SES, stage and treatment	7
Bella, F.	2013	Italy	Prospective	1039	Hospital-based	2003–2005	—	593/446	373	Medical records	colorectal cancer; colon and rectal cancer	adjusted HROS and HRCSS; 5-year OS and 5-year CSS	age, gender, stage, type of treatment, morphology and grade	7
Jeon, J. Y.	2013	Korea	Prospective	4131	Hospital-based	1995–2007	59	2479/1652	517	Medical records	colorectal cancer; colon and rectal cancer	adjusted HROS, HRRFS, HRDFS and HRCSS; 5-year DFS	age, gender, BMI, family history of CRC, TNM stage, adjuvant therapy and the year of surgery.	9
Morrison, D. S.	2013	Asia Pacific region	retrospective	600427	Population-based	1961–1999	46.4	216154/384273	182569	Self-reported	Colorectal cancer, rectal and colon cancer	adjusted HROS	age, BMI, physical activity, height, drink, smoke, cholesterol, diabetes and education	9
Liu, D.	2013	China	retrospective	525	Hospital-based	2004–2011	63.2	310/215	86	Medical records	colorectal cancer	unadjusted HROS and HRDFS; 5-year OS and 5-year DFS	—	6
Cossor, F. I.	2013	USA	Prospective	2066	Population-based	1993–1998	71.92	0/2066	212	Self-reported	colorectal cancer	adjusted HROS and HRCSS; 5-year OS and 5-year CSS	age and stage at diagnosis	7

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Table 1. (Continued)

Author	Year	Region	Type of Study	Sample Size	Population source	Recruitment time	Age (Year)	Gender (male/female)	Patients with DM (n)	DM ascertainment	Type of cancer	Outcomes	Adjusted variable	NOS score
Huang, C. W.	2012	Chinese Taiwan	Prospective	1197	Hospital-based	2002–2008	64.18	673/524	283	Medical records	colorectal cancer	adjusted HROS and HRCSS; 5-year OS and 5-year CSS	age, gender, location, tumor size, BMI, albumin, histology, AJCC stage, Pre-op CEA, Post-op CEA, vascular invasion and perineurial invasion	8
Dehal, A. N.	2012	USA	Prospective	2278	Population-based	1992–1993	—	—	393	Self-reported	colorectal cancer	adjusted HROS, HRCVDS and HRCSS; 5-year OS, 5-year CSS and 5-year CVDS	gender, age at CRC diagnosis, BMI, smoking status, physical activity, red meat intake, and surveillance, epidemiology, and end results summary stage	6
van de Poll-Franse, L. V.	2012	Netherlands	Prospective	10862	Hospital-based	1997–2007	68.34	5806/5056	1224	Medical records	colon cancer	adjusted HROS, HRCSS; 5-year OS and 5-year CVDS	age at diagnosis, gender, stage, number of examined lymph nodes, adjuvant therapy, SES, year of diagnosis, hypertension, CVD, cerebrovascular disease, previous cancer and lung disease	9
Yeh, H. C.	2012	USA	retrospective	18240	Population-based	1989	51.8	7795/10445	599	Self-reported	colorectal cancer	adjusted HROS	age, the square of age, gender, BMI, smoking, education level, hypertension treatment, and high cholesterol treatment	9
Morrison, D. S.	2011	UK	Prospective	17949	Population-based	1967–1970	—	17949/0	236	Self-reported	colon and rectal cancer	adjusted HROS	age at risk, height, BMI, plasma cholesterol, diastolic blood pressure, systolic blood pressure, physical activity, socioeconomic position and smoking	7
Huang, Y. C.	2011	Chinese Taiwan	Prospective	2762	Hospital-based	1998.1–2008.1	—	1756/1006	469	Medical records	colon cancer	adjusted HROS and HRCSS; 5-year OS and 5-year CSS	age, gender, stage, bowel perforation at diagnosis, bowel obstruction at diagnosis, poorly differentiated or undifferentiated histology	7

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Table 1. (Continued)

Author	Year	Region	Type of Study	Sample Size	Population source	Recruitment time	Age (Year)	Gender (male/female)	Patients with DM (n)	DM ascertainment	Type of cancer	Outcomes	Adjusted variable	NOS score
Lai, C. C.	2011	Korea	Prospective	2529	Hospital-based	1995–2008	—	1315/1214	307	Medical records	colon cancer	adjusted HROS; 5-year OS	age, gender, hypertension, cardiac disease, old CVA, liver cirrhosis, other disease, CEA level, albumin level, morbidity, tumorphology, histologic type, histologic grade and TNM stage	7
Sarfati, D.	2011	New Zealand	Prospective	11524	Hospital-based	1996–2003	—	5477/6047	1107	Medical records	colon cancer	adjusted HROS	age, gender, ethnicity, NZ deprivation quintiles and extent of disease;	7
Lieffers, J. R.	2011	Canada	retrospective	574	Population-based	2004–2006	64	335/239	72	Medical records	colorectal cancer	adjusted HROS	age, gender, stage, and all co-morbidities	8
Chiao, E. Y.	2010	USA	retrospective	470	Hospital-based	1999–2006	67.7	464/6	122	Medical records	colorectal cancer	adjusted HROS; 5-year OS	age, race, BMI, stage, treatment received and Deyo co-morbidity score	9
Chen, C. Q.	2010	China	Prospective	945	Hospital-based	1994–2002	62.3	556/389	26	Blood glucose test	colorectal cancer	adjusted HROS and HRDFS; 5-year OS and 5-year DFS	gender, surgery type, chemotherapy, TNM, gross type, differentiation, intestinal obstruction and location	8
Noh, G. Y.	2010	Korea	retrospective	657	Hospital-based	1997–2004	57.97	374/283	67	Medical records	colorectal cancer	adjusted HROS and HRRFS; 5-year OS and 5-year RFS	age, gender, BMI, stage, grade	7
Jullumstro, E.	2009	Norway	retrospective	1194	Hospital-based	1980–2004	72.07	628/566	97	Medical records	colorectal cancer	adjusted HROS and unadjusted HRCSS; 5-year OS and 5-year CSS	age, gender, cardiac disease, pulmonary disease, ASA, bowel obstruction, bowel perforation, location, stage, poor differentiation, mean percentage positive nodes after resection and adjuvant chemotherapy	9
van de Poll-Franse, L. V.	2007	Netherlands	Prospective	8328	Hospital-based	1995–2002	68.15	4465/3863	913	Medical records	colon and rectal cancer	adjusted HROS; 5-year OS	age, gender, stage, treatment and CVD	7
Shonka, N. A.	2006	USA	retrospective	1853	Hospital-based	1986–2003	—	891/962	255	Medical records	colon cancer	unadjusted HROS; 5-year OS	—	5

(Continued)

Table 1. (*Continued*)

Author	Year	Region	Type of Study	Sample Size	Population source	Recruitment time	Age (Year)	Gender (male/female)	Patients with DM (n)	DM ascertainment	Type of cancer	Outcomes	Adjusted variable	NOS score
Polednak, A. P.	2006	USA	Prospective	9395	Population-based	1994–1999	—	4487/4908	1014	Medical records	colorectal cancer	adjusted HROS	age at diagnosis, gender, race, extent of disease at diagnosis, lymph-node status and poverty-rate category	7
Park, S. M.	2006	Korea	Prospective	14578	Population-based	1996–2004	50.8	14578/0	1223	Blood glucose test	colorectal cancer	adjusted HROS	age, alcohol consumption, BMI, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other co-morbidities (heart disease, liver disease, and cerebrovascular disease	8
Lemmens, V. E.	2005	Netherlands	Prospective	6931	Population-based	1995–2001	—	3660/3271	—	Medical records	colon and rectal cancer	adjusted HROS	age, gender, tumor stage, treatment and number of co-morbid conditions or single concomitant diseases	7
Coughlin, S. S.	2004	USA	Prospective	1056243	Population-based	1982	—	467922/588321	52803	Medical records	colon and rectal cancer	adjusted HROS	age, race, years of education, BMI, cigarette smoking history, alcohol consumption, total red meat consumption, consumption of citrus fruits and juices, consumption of vegetables, physical activity	7
Meyerhardt, J. A.	2003	USA	Prospective	3549	Hospital-based	1988–1992	61.92	2936/613	287	Medical records	colon cancer	adjusted HROS, HRRFS and unadjusted HRDFS; 5-year at OS, 5-year DFS and 5-year RFS	age, BMI, gender, race, baseline performance status, bowel obstruction, bowel perforation, stage of disease, presence of peritoneal implants, and completion of chemotherapy	9

DM: diabetes mellitus; HROS: HR on overall survival; HRCSS: HR on cancer-specific survival; HRCVDS: HR on cardiovascular disease specific survival; HRDFS: HR on disease-free survival; HRRFS: HR on recurrence-free survival; 5-year at OS: the 5-year overall survival rate; 5-year at CSS: the 5-year cancer-specific survival rate; 5-year at CVDS: the 5-year cardiovascular disease specific survival rate; 5-year at DFS: the 5-year disease-free survival rate; RFS: the 5-year recurrence-free survival rate; BMI: body mass index; AJCC stage: the American Joint Committee on Cancer; CRC: colorectal cancer; ASA score: American Society of Anesthesiologists Score; AL: anastomotic leakage; SES: the socioeconomic status; TNM: tumor-node-metastasis; CVD: cardiovascular disease; CVA: old cardiovascular accident; CEA: carcinoembryonic antigen; WBC: white blood cell; CRP: C-reactive protein.

The pooled survival rate for the effect of DM on CRC prognosis

In colorectal cancer, the pooled 5-year OS rate in patients with DM was 49.8%, and that in patients without DM was 53.6%; the pooled 5-year CVDS rate in patients with DM was 90.5%, and that in patients without DM was 94.3%; the pooled 5-year CSS rate in patients with DM was 65.6%, and that in patients without DM was 69.0%; the pooled 5-year DFS rate in patients with DM was 60.9%, and that in patients without DM was 70.0%; the pooled 5-year RFS rate in patients with DM was 63.4%, and that in patients without DM was 68.5%. Similar results were also found in colon and rectal cancer. The detailed results on the pooled survival rate for the effect of DM on CRC Prognosis were shown in Table 2.

The overall pooled HRs for the effect of DM on CRC prognosis

In our meta-analysis, the number of studies on the colorectal cancer data provided was 23[6–10, 13–20, 27, 29, 30, 33, 36–39, 42, 43], the pooled HRs on OS and CVDS were statistically significant (HR on OS: 1.18, 95%CI: 1.12–1.24; HR on CVDS: 1.40, 95%CI: 1.29–1.52), the pooled HRs indicated that there were no significant difference on CSS, DFS and RFS. No publication bias was found in OS, CVDS, CSS and DFS.

The number of studies on the colon cancer data provided was 18[6, 8, 10–13, 28, 31, 40, 41, 44–47]. There was only one study on CVDS, and the pooled HR on CVDS was not analyzed. The pooled HRs on OS and DFS were statistically significant (HR on OS: 1.19, 95%CI: 1.10–1.27; HR on DFS: 1.35, 95%CI: 1.12–1.58), the pooled HRs indicated that there were no significant difference on CSS and RFS. Publication bias might exist in OS and CSS (OS: P for Begger test = 0.049, P for Egger test = 0.115; CSS: P for Begger test = 0.260, P for Egger test = 0.012), we used "trim and fill" analysis to deduce the potential unpublished studies, the results of OS and CSS(HR on OS: 1.19, 95%CI: 1.11–1.28; HR on CSS: 1.06, 95%CI: 0.98–1.14) were similar to the overall results, respectively.

The number of studies on the rectal cancer data provided was 10[6, 8, 10, 11, 13, 28, 40, 44, 45], there was only one study on CVDS, DFS and RFS, the pooled HRs on CVDS, DFS or RFS

Table 2. The pooled survival rate for the effect of DM on CRC Prognosis.

	Colorectal cancer (%)	Colon cancer (%)	Rectal cancer (%)
OS			
Patients with DM	49.8 (45.9, 53.6)	49.9 (21.5, 78.2)	50.9 (46.0, 55.8)
Patients without DM	58.1 (53.5, 62.6)	56.5 (44.1, 68.9)	64.1 (62.0, 66.3)
CVDS			
Patients with DM	90.5 (85.9, 95.1)	—	—
Patients without DM	94.3 (89.1, 99.5)	—	—
CSS			
Patients with DM	65.6 (61.3, 69.8)	71.7 (55.1, 88.3)	67.0 (64.8, 69.2)
Patients without DM	69.0 (63.3, 74.7)	75.4 (59.4, 91.3)	74.8 (74.0, 75.7)
DFS			
Patients with DM	60.9 (46.2, 75.5)	59.3 (37.2, 81.5)	65.9 (63.0, 68.8)
Patients without DM	70.0 (56.8, 83.3)	69.5 (48.9, 90.1)	68.2 (67.2, 69.2)
RFS			
Patients with DM	63.4 (51.9, 74.9)	57.0 (51.3, 62.7)	—
Patients without DM	68.5 (64.8, 72.3)	65.0 (63.4, 66.6)	—

DM: diabetes mellitus; OS: overall survival; CSS: cancer-specific survival; CVDS: cardiovascular disease—specific survival; DFS: disease-free survival; RFS: recurrence-free survival.

were not analyzed. The pooled HR on OS was statistically significant (HR on OS: 1.16, 95%CI: 1.04–1.29), the pooled HR indicated that there were no significant difference on CSS. No publication bias was found in OS and CSS.

The detailed results on the relationship between DM and CRC Prognosis are shown in Table 3.

Subgroup analysis

Because of fewer studies on CVDS, CSS, DFS, and RFS, we used subgroup analysis on OS by the potential confounding factors, including region, type of study, sample size, population source, DM ascertainment, quality of studies and adjusted variables. In colorectal cancer, we found that the relationship between DM and CRC prognosis was significant in all groups, but not in Asian or blood glucose test groups. We found similar results in colon and rectal cancer. The detailed results on the subgroup analysis on OS for the effect of DM on CRC Prognosis were shown in Table 4.

Sensitivity analysis

The pooled HRs and their 95%CIs of sensitivity analysis were calculated by excluding one study at a time in colorectal cancer, colon cancer and rectal cancer, and the results indicated that the overall result was dependable. The results of sensitivity analysis were shown in Table 5.

Discussion

Our meta-analysis first analyzed both the 5-year survival rate and survival risk, which reflected the effect of DM on CRC prognosis. The results indicated that compared to patients without

Table 3. The overall pooled HR on the effect of DM on CRC Prognosis.

	Number of study	Model for meta-analysis	HR (95%CI)	I^2 (%)	P for heterogeneity	P for Begger's test	P for Egger's test
Colorectal cancer							
OS	23[6–10, 13–20, 27, 29, 30, 33, 36–39, 42, 43]	R	**1.18(1.12, 1.24)**	64.8	<0.001	0.492	0.740
CVDS	3[13, 15, 30]	F	**1.40(1.29, 1.52)**	31.6	0.232	0.296	0.193
CSS	8[6–8, 13, 15, 29, 30, 39]	R	1.03(0.93, 1.12)	63.3	0.008	0.711	0.225
DFS	4[8, 9, 20, 38]	R	1.14(0.71, 1.58)	80.0	0.002	0.734	0.893
RFS	2[8, 36]	F	1.08(0.84, 1.23)	0.0	0.771	—	—
Colon cancer							
OS	18[6, 8, 10–13, 28, 31, 32, 34, 35, 40, 41, 44–47]	R	**1.19(1.10, 1.27)**	86.9	<0.001	0.049	0.115
CVDS	1[13]	—	1.35(1.26, 1.45)	—	—	—	—
CSS	6[6, 8, 12, 13, 28, 35]	F	1.07(0.98, 1.16)	38.9	0.146	0.260	0.012
DFS	2[8, 46]	F	**1.35(1.12, 1.58)**	0	0.447	—	—
RFS	2[8, 46]	F	**1.24(1.04, 1.44)**	0	0.634	—	—
Rectal cancer							
OS	10[6, 8, 10, 11, 13, 28, 40, 44, 45]	R	**1.16(1.04, 1.29)**	61.9	0.005	0.474	0.529
CVDS	1[13]	—	1.48(1.04, 1.29)	—	—	—	—
CSS	4[6, 8, 13, 28]	R	1.12(0.91, 1.32)	55.2	0.082	0.308	0.389
DFS	1[8]	—	0.98(0.76, 1.25)	—	—	—	—
RFS	1[8]	—	0.96(0.72, 1.28)	—	—	—	—

R: the random effects model; F: the fixed effects model; DM: diabetes mellitus; OS: overall survival; CSS: cancer-specific survival; CVDS: cardiovascular disease—specific survival; DFS: disease-free survival; RFS: recurrence-free survival.

Table 4. The subgroup analysis on OS for the effect of DM on CRC Prognosis.

	Colorectal cancer					Colon cancer					Rectal cancer				
	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity
Region															
America	11[7, 13–15, 18, 19, 27, 30, 33, 37, 42]	R	1.19 (1.11, 1.27)	78.0	<0.001	5[13, 41, 45, 46]	F	1.21 (1.14, 1.29)	33.5	0.198	3[13, 45]	F	1.16 (1.01, 1.32)	24.1	0.268
Europe	4[6, 16, 17, 39]	F	1.25 (1.12, 1.37)	5.3	0.366	6[6, 11, 28, 32, 40, 44]	F	1.16 (1.09, 1.24)	1.7	0.406	5[6, 11, 28, 40, 44]	R	1.26 (1.03, 1.49)	74.8	0.003
Asia	8[8–10, 20, 29, 36, 38, 43]	F	1.06 (0.91, 1.22)	26.1	0.220	6[8, 10, 12, 34, 35, 47]	F	1.25 (1.12, 1.39)	31.7	0.198	2[8, 10]	F	0.91 (0.56, 1.25)	7.6	0.298
Oceania	0	—	—	—	—	1[31]	—	1.00 (0.98, 1.02)	—	—	0	—	—	—	—
Type of study															
Retrospective	12[9, 10, 14, 16–20, 33, 36, 37, 39]	F	1.14 (1.09, 1.19)	2.5	0.420	3[10, 41, 47]	F	0.98 (0.72, 1.18)	0.0	0.416	1[10]	—	0.32 (0.04, 2.39)	—	—
Prospective	11[6–8, 13, 15, 27, 29, 30, 38, 42, 43]	R	1.22 (1.12, 1.33)	78.6	<0.001	15[6, 8, 11–13, 28, 31, 32, 34, 35, 40, 44–46]	R	1.21 (1.12, 1.29)	89.0	<0.001	9[6, 8, 11, 13, 28, 40, 44, 45]	R	1.17 (1.05, 1.30)	62.9	<0.001
Sample size															
≥10000	8[10, 13–15, 17, 18, 27, 43]	R	1.14 (1.07, 1.20)	70.0	0.001	7[10, 11, 13, 31, 32, 45]	R	1.14 (1.01, 1.26)	93.3	<0.001	4[10, 13, 45]	F	1.10 (0.89, 1.32)	37.7	0.186
<10000	15[6–9, 16, 19, 20, 29, 30, 33, 36–39, 42]	R	1.21 (1.08, 1.33)	55.6	0.005	11[6, 8, 12, 28, 34, 35, 40, 41, 44, 46, 47]	F	1.22 (1.13, 1.31)	45.2	0.051	6[6, 8, 11, 28, 40, 44]	R	1.21 (1.01, 1.41)	72.5	0.003
Population source															
Population-based	10[7, 13–15, 18, 27, 30, 33, 42, 43]	R	1.20 (1.12, 1.28)	79.8	<0.001	8[10–13, 32, 44, 45]	F	1.20 (1.17, 1.23)	0.0	0.456	6[10, 11, 13, 44, 45]	F	1.09 (0.95, 1.23)	49.1	<0.001

(Continued)

Table 4. (Continued)

	Colorectal cancer					Colon cancer					Rectal cancer				
	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity	Number of study	Model for meta-analysis	HR (95% CI)	I² (%)	P for heterogeneity
Hospital-based	13[6, 8–10, 16, 17, 19, 20, 29, 36–39]	F	**1.14 (1.02, 1.25)**	31.8	0.129	10[6, 8, 28, 31, 34, 35, 40, 41, 46, 47]	R	**1.18 (1.06, 1.30)**	80.7	<0.001	4[6, 8, 28, 40]	R	**1.30 (1.02, 1.58)**	75.2	0.007
DM ascertainment															
Medical records	14[6, 8, 9, 13–15, 18, 19, 29, 33, 36, 37, 39, 42]	R	**1.18 (1.11, 1.24)**	70.7	<0.001	15[6, 8, 11–13, 28, 31, 34, 35, 40, 41, 44–46]	R	**1.20 (1.11, 1.28)**	89.0	<0.001	9[6, 8, 11, 13, 28, 40, 44, 45]	R	**1.17 (1.05, 1.30)**	62.9	0.006
Self-reported	5[7, 10, 17, 27, 30]	F	**1.29 (1.08, 1.51)**	49.5	0.095	2[10, 32]	F	1.02 (0.30, 1.73)	0.0	0.504	1[10]	—	0.32 (0.04, 2.39)	—	—
Blood glucose test	4[16, 20, 38, 43]	F	0.95 (0.65, 1.25)	27.2	0.249	1[47]	—	0.57 (0.22, 1.47)	—	—	0	—	—	—	—
Quality of studies															
Moderate	5[9, 14–16, 30]	R	**1.16 (1.03, 1.28)**	75.5	0.003	1[41]	—	1.00 (0.77, 1.30)	—	—	0	—	—	—	—
High	18[6–8, 10, 13, 17–20, 27, 29, 33, 36–39, 42, 43]	R	**1.19 (1.11, 1.27)**	47.4	0.014	17[6, 8, 10–13, 28, 31, 32, 34, 35, 40, 44–47]	R	**1.19 (1.11, 1.28)**	87.6	<0.001	10[6, 8, 10, 11, 13, 28, 40, 44, 45]	R	**1.16 (1.04, 1.29)**	61.9	0.005
Adjusted variables															
no	3[9, 15, 16]	F	1.03 (0.96, .10)	0.0	0.823	1[41]	—	1.00 (0.77, 1.30)	—	—	0	—	—	—	—
yes	20[6–8, 10, 13, 14, 17–20, 27, 29, 30, 33, 36–39, 42, 43]	R	**1.20 (1.14, 1.26)**	57.8	0.001	17[6, 8, 10–13, 28, 31, 32, 34, 35, 40, 44–47]	R	**1.19 (1.11, 1.28)**	87.6	<0.001	10[6, 8, 10, 11, 13, 28, 40, 44, 45]	R	**1.16 (1.04, 1.29)**	61.9	61.9

R: the random effects model; F: the fixed effects model; DM: diabetes mellitus; OS: overall survival; CSS: cancer-specific survival; CVDS: cardiovascular disease—specific survival; DFS: disease-free survival; RFS: recurrence-free survival.

Table 5. The sensitivity analysis of the overall pooled HR on the effect of DM on CRC Prognosis.

	The lowest HR (95%CI)	The highest HR (95%CI)
Colorectal cancer		
OS	1.18(1.12, 1.24)	1.38(1.31, 1.46)
CVDS	1.38(1.31, 1.46)	1.66(1.11, 2.51)
CSS	1.00(0.92, 1.09)	1.11(0.97, 1.27)
DFS	1.03(0.68, 1.58)	1.37(1.03, 1.83)
Colon cancer		
OS	1.18(1.10, 1.27)	1.22(1.17, 1.26)
CSS	1.03(0.97, 1.11)	1.13(1.04, 1.23)
Rectal cancer		
OS	1.15(1.02, 1.28)	1.22(1.09, 1.38)
CSS	1.08(0.91, 1.29)	1.24(0.93, 1.67)

DM: diabetes mellitus; OS: overall survival; CSS: cancer-specific survival; CVDS: cardiovascular disease—specific survival; DFS: disease-free survival; RFS: recurrence-free survival.

DM, patients with DM will have a 5-year shorter survival rate in colorectal, colon and rectal cancer, showed 18%, 19% and 16% decreased in OS, respectively. We also found similar results in CVDS, CSS, DFS and RFS. Due to the heterogeneity, we performed the subgroup analysis and sensitivity analysis to find the source of heterogeneity and make our results robust and credible. In subgroup analysis, though few results showed no statistical significance, we found that the results of subgroup analysis were generally similar to the overall results. When we carried out subgroup analysis by region, in Europe, patients with DM significantly have shorter OS in colorectal cancer, colon cancer and rectal cancer. In Asia, patients with DM significantly have shorter OS in colon cancer; there was no significance in colorectal cancer and rectal cancer, this may be the small sample size due to subgroup analysis. When we carried out subgroup analysis by type of study, there were significant differences in the results, except for that in prospective studies of colon cancer. When we carried out subgroup analysis by sample size and population source, the subgroup results were consistent with the overall results in colorectal and colon cancer, the results in size $\geq$ 10000 and population-based group did not show statistical significant in rectal cancer. When we carried out subgroup analysis by DM ascertainment, the results were consistent with the overall results in the group of medical records, except for that in the group of self-reported and blood glucose test. The sensitivity analysis also showed that the results of our meta-analysis were robust and credible.

Currently, the biological mechanism linkage between DM and CRC prognosis is still uncertain. This association may be mainly based on the effect of hyperinsulinemia, insulin resistance and cancer pathogenesis on the insulin/ insulin-like growth factor (IGF) system, which plays a critical role in the pathogenesis, progression, and prognosis of CRC. On the one hand, the insulin-like effects of IGF-1 interacting with associated receptors, such as IGF-1R, IR or hybrid receptors, play an important role in the maintenance of normal glucose homeostasis and etio-pathogenesis of DM[48]. In DM patients, insulin resistance leads to a compensatory increase in insulin secretion, and by inhibition of IGF binding proteins, this hyperinsulinemia may increase the biological activity of IGF-1, which is an antiapoptotic and mitogenic factor[49]. On the other hand, insulin-like growth factors activate the IGF-1R, make it over expressed in cancer cells, and then trigger a number of intracellular signaling cascades that enhance cell cycle progression and inhibit apoptosis. Zhang et al indicated that IGF-1 and its receptor promoted both the growth and malignant transformation of adenomatous polyps[50]. Over

expression of IGF-1, IGF-1R and IR were found in CRC group with DM than that in without DM[51]. The activation of insulin/IGF-dependent pathways has been also identified as a critical step contributing to several mechanisms of CRC resistance to both conventional and targeted therapeutic agents, leading to increased PI3K/Akt signaling that hinders the apoptotic signals triggered by chemotherapeutic drugs and desensitizes CRC cells to the effect of anti-EGFR antibodies[52]. Scartozzi et al. had reported that high IGF-1 expression correlated with poor clinical outcome in wild-type KRAS metastatic CRC patients treated with cetuximab and irinotecan. Their results indicated that engaging the IGF-1/IGF-1R system might enable tumor cells to escape anti-EGFR-mediated treatment as a consequence of IGF-1-driven stimulation of the PI3K–Akt pathway[53]. In recent years, some evidence suggested that IGF-1/IGF-1R polymorphisms are potential predictive/prognostic markers for cetuximab efficacy in metastatic CRC patients presenting wild- type KRAS[54].

In order to make our results more robust and credible, we made efforts in several ways. First of all, we not only searched the relevant studies in the four commonly used electronic databases, but also searched in Google Scholar, and tried our best not to miss the relevant studies. We also extracted the data on OS, CSS, CVDS, DFS and RFS, and used these indicators to evaluate the effect of DM on CRC prognosis. So far, our meta-analysis is the most comprehensive study of collecting indicators on the effect of DM on CRC prognosis. Second, we performed the quality assessment by NOS, which was widely used in meta-analysis and systematic reviews, and all the included studies were evaluated as high quality, which made our extracted data reliable. Third, we found that only one result in CSS of colon cancer existed publication bias, there were no publication bias in all other results. We used the "trim and fill" analysis to assess the possible effect of publication bias, but there was no significant change in the CSS result of colon cancer. The results of subgroup analysis and sensitivity analysis has also shown that our results were robust and credible. Finally, and most importantly, compared to previous studies[5], we not only routinely performed the pooled analysis on HR of OS, CSS, CVDS, DFS and RFS, which comprehensively reflect the difference of CRC prognosis between diabetic patients and nondiabetic patients; but also first extracted the 5-year survival rate from the included studies, and made the pooled analysis. Meanwhile, for collecting more useful data, we used the professional software to extract survival rate from the Kaplan-Meier curves[24, 25]. This would make the results stable, and give the researchers more intuitive impression on the effect of DM on prognosis in the fifth year.

There were several limitations in our meta-analysis. First, in order to collect the literatures more extensively, we searched the relevant articles in Google Scholar. If we found the relevant articles in Google Scholar, we purchased the article or sought help online[55].Second, in the included studies, we found that more studies focused on OS, compared to CSS, CVDS, DFS and RFS. In OS, the number of studies on colorectal, colon and rectal cancer was twenty-three, seventeen and ten. In CSS, CVDS, DFS and RFS, the maximum number of relevant studies was only eight. This might make the results unstable. In our meta-analysis, we analyzed both the 5-year survival rate and survival risk, and found their results were consistent. This indicated that our results were stable. Third, the results of our meta-analysis had a certain degree of heterogeneity. We performed subgroup analysis by the confounding factors, which might be the potential source of heterogeneity, and the results of subgroup analysis were similar to the overall results. We also performed the analysis of the effect of each study on the overall results sensitively, and did not find significant changes in the overall results.

In conclusion, our meta-analysis showed that DM could significantly decrease OS in CRC patients, but not CSS, CVDS, DFS and RFS. In future, to provide more evidence of clinical treatment, more high quality prospective cohort studies are needed to comprehensively analyze the effect of DM on CRC prognosis by CSS, CVDS, DFS and RFS.

Supporting information

S1 PRISMA Checklist.
(DOCX)

S1 File. The detailed methods used for searching all the databases.
(DOCX)

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Author Contributions

Conceptualization: BZ XMW.

Data curation: BZ BW LZ LXW.

Formal analysis: BZ XMW DP LXW.

Funding acquisition: XMW.

Investigation: BZ XMW DP LXW.

Methodology: BZ.

Project administration: BZ.

Software: BZ XMW.

Supervision: DP LXW.

Visualization: BZ.

Writing – original draft: BZ XMW.

Writing – review & editing: BZ XMW BW DP LZ LXW.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65(2):87–108. Epub 2015/02/06.

2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010; 87(1):4–14. Epub 2009/11/10. https://doi.org/10.1016/j.diabres.2009.10.007 PMID: 19896746

3. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews Endocrinology. 2011; 8(4):228–36. Epub 2011/11/09. https://doi.org/10.1038/nrendo.2011.183 PMID: 22064493

4. Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? Nature reviews Clinical oncology. 2016. Epub 2016/10/26.

5. Mills KT, Bellows CF, Hoffman AE, Kelly TN, Gagliardi G. Diabetes mellitus and colorectal cancer prognosis: a meta-analysis. Diseases of the colon and rectum. 2013; 56(11):1304–19. Epub 2013/10/10. PubMed Central PMCID: PMCPMC3800045. https://doi.org/10.1097/DCR.0b013e3182a479f9 PMID: 24105007

6. Bella F, Minicozzi P, Giacomin A, Crocetti E, Federico M, Ponz de Leon M, et al. Impact of diabetes on overall and cancer-specific mortality in colorectal cancer patients. Journal of cancer research and clinical oncology. 2013; 139(8):1303–10. Epub 2013/05/02. https://doi.org/10.1007/s00432-013-1439-8 PMID: 23633003

7. Cossor FI, Adams-Campbell LL, Chlebowski RT, Gunter MJ, Johnson K, Martell RE, et al. Diabetes, metformin use, and colorectal cancer survival in postmenopausal women. Cancer epidemiology. 2013; 37(5):742–9. Epub 2013/06/19. PubMed Central PMCID: PMCPMC3769471. https://doi.org/10.1016/j. canep.2013.04.015 PMID: 23773299

8. Jeon JY, Jeong DH, Park MG, Lee JW, Chu SH, Park JH, et al. Impact of diabetes on oncologic outcome of colorectal cancer patients: colon vs. rectal cancer. PloS one. 2013; 8(2):e55196. Epub 2013/02/14. PubMed Central PMCID: PMCPMC3566217. https://doi.org/10.1371/journal.pone.0055196 PMID: 23405123

9. Liu D, Li Q, Yang Z, Hu X, Qian W, Du Y, et al. Association of body mass index and smoking on outcome of Chinese patients with colorectal cancer. World journal of surgical oncology. 2013; 11:271. Epub 2013/10/15. PubMed Central PMCID: PMCPMC3853928. https://doi.org/10.1186/1477-7819-11-271 PMID: 24119458

10. Morrison DS, Parr CL, Lam TH, Ueshima H, Kim HC, Jee SH, et al. Behavioural and metabolic risk factors for mortality from colon and rectum cancer: analysis of data from the Asia-Pacific Cohort Studies Collaboration. Asian Pacific journal of cancer prevention: APJCP. 2013; 14(2):1083–7. Epub 2013/04/30. PMID: 23621191

11. Walker JJ, Brewster DH, Colhoun HM, Fischbacher CM, Lindsay RS, Wild SH. Cause-specific mortality in Scottish patients with colorectal cancer with and without type 2 diabetes (2000–2007). Diabetologia. 2013; 56(7):1531–41. Epub 2013/04/30. https://doi.org/10.1007/s00125-013-2917-x PMID: 23624531

12. Chen KH, Shao YY, Lin ZZ, Yeh YC, Shau WY, Kuo RN, et al. Type 2 diabetes mellitus is associated with increased mortality in Chinese patients receiving curative surgery for colon cancer. The oncologist. 2014; 19(9):951–8. Epub 2014/07/26. PubMed Central PMCID: PMCPMC4153450. https://doi.org/10. 1634/theoncologist.2013-0423 PMID: 25061090

13. Luo J, Lin HC, He K, Hendryx M. Diabetes and prognosis in older persons with colorectal cancer. British journal of cancer. 2014; 110(7):1847–54. Epub 2014/02/27. PubMed Central PMCID: PMCPMC3974085. https://doi.org/10.1038/bjc.2014.68 PMID: 24569466

14. Tong L, Ahn C, Symanski E, Lai D, Du XL. Temporal trends in the leading causes of death among a large national cohort of patients with colorectal cancer from 1975 to 2009 in the United States. Annals of epidemiology. 2014; 24(6):411–7. Epub 2014/02/18. https://doi.org/10.1016/j.annepidem.2014.01.005 PMID: 24529646

15. Waheed S, Azad N, Waheed S, Yeh HC. Racial disparities and colorectal cancer survival in older adults with and without diabetes mellitus. Journal of gastroenterology and hepatology. 2014; 29(12):1963–8. Epub 2014/06/10. PubMed Central PMCID: PMCPMC4612638. https://doi.org/10.1111/jgh.12637 PMID: 24909501

16. Cui G, Zhang T, Ren F, Feng WM, Yao Y, Cui J, et al. High Blood Glucose Levels Correlate with Tumor Malignancy in Colorectal Cancer Patients. Medical science monitor: international medical journal of experimental and clinical research. 2015; 21:3825–33. Epub 2015/12/09. PubMed Central PMCID: PMCPMC4677694.

17. Fransgaard T, Thygesen LC, Gogenur I. Increased 30-day mortality in patients with diabetes undergoing surgery for colorectal cancer. Colorectal disease: the official journal of the Association of Coloproctology of Great Britain and Ireland. 2016; 18(1):O22–9. Epub 2015/10/16.

18. Paulus JK, Williams CD, Cossor FI, Kelley MJ, Martell RE. Metformin, Diabetes, and Survival among U. S. Veterans with Colorectal Cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2016; 25(10):1418–25. Epub 2016/08/09. PubMed Central PMCID: PMCPMC5050110.

19. Ramjeesingh R, Orr C, Bricks CS, Hopman WM, Hammad N. A retrospective study on the role of diabetes and metformin in colorectal cancer disease survival. Current oncology (Toronto, Ont). 2016; 23(2): e116–22. Epub 2016/04/29. PubMed Central PMCID: PMCPMC4835004.

20. Yang IP, Tsai HL, Huang CW, Lu CY, Miao ZF, Chang SF, et al. High blood sugar levels significantly impact the prognosis of colorectal cancer patients through down-regulation of microRNA-16 by targeting Myb and VEGFR2. Oncotarget. 2016; 7(14):18837–50. Epub 2016/03/05. PubMed Central PMCID: PMCPMC4951333. https://doi.org/10.18632/oncotarget.7719 PMID: 26934556

21. Zhu L, Dong C, Cao Y, Fang X, Zhong C, Li D, et al. Prognostic Role of BRAF Mutation in Stage II/III Colorectal Cancer Receiving Curative Resection and Adjuvant Chemotherapy: A Meta-Analysis Based on Randomized Clinical Trials. PloS one. 2016; 11(5):e0154795. Epub 2016/05/04. PubMed Central PMCID: PMCPMC4854379. https://doi.org/10.1371/journal.pone.0154795 PMID: 27138801

22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010; 25(9):603–5. Epub 2010/07/24. https://doi.org/10.1007/s10654-010-9491-z PMID: 20652370

23. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ (Clinical research ed). 2016; 355: i5953. Epub 2016/11/25. PubMed Central PMCID: PMCPMC5121106.

24. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16. Epub 2007/06/09. PubMed Central PMCID: PMCPMC1920534. https://doi.org/10.1186/1745-6215-8-16 PMID: 17555582

25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in medicine. 1998; 17(24):2815–34. Epub 1999/01/28. PMID: 9921604

26. Liu JL, Gao W, Kang QM, Zhang XJ, Yang SG. Prognostic value of survivin in patients with gastric cancer: a systematic review with meta-analysis. PloS one. 2013; 8(8):e71930. Epub 2013/08/13. PubMed Central PMCID: PMCPMC3732238. https://doi.org/10.1371/journal.pone.0071930 PMID: 23936532

27. 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 care. 2012; 35(1):113–8. Epub 2011/11/22. PubMed Central PMCID: PMCPMC3241297. https://doi.org/10.2337/dc11-0255 PMID: 22100961

28. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012; 55(8):2163–72. Epub 2012/04/25. PubMed Central PMCID: PMCPMC3390707. https://doi.org/10.1007/s00125-012-2555-8 PMID: 22526616

29. Huang CW, Sun LC, Shih YL, Tsai HL, Chen CW, Yeh YS, et al. The impact on clinical outcome of high prevalence of diabetes mellitus in Taiwanese patients with colorectal cancer. World journal of surgical oncology. 2012; 10:76. Epub 2012/05/05. PubMed Central PMCID: PMCPMC3533895. https://doi.org/10.1186/1477-7819-10-76 PMID: 22553992

30. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30(1):53–9. Epub 2011/11/30.

31. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. The New Zealand medical journal. 2011; 124(1338):76–88. Epub 2011/09/29. PMID: 21946965

32. Morrison DS, Batty GD, Kivimaki M, Davey Smith G, Marmot M, Shipley M. Risk factors for colonic and rectal cancer mortality: evidence from 40 years' follow-up in the Whitehall I study. Journal of epidemiology and community health. 2011; 65(11):1053–8. Epub 2011/03/11. https://doi.org/10.1136/jech.2010.127555 PMID: 21389009

33. 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 (9):1957–65. Epub 2011/04/22. https://doi.org/10.1002/cncr.25653 PMID: 21509773

34. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. International journal of colorectal disease. 2011; 26(4):473–81. Epub 2010/12/31. https://doi.org/10.1007/s00384-010-1113-4 PMID: 21190025

35. Huang YC, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, et al. Diabetes mellitus negatively impacts survival of patients with colon cancer, particularly in stage II disease. Journal of cancer research and clinical oncology. 2011; 137(2):211–20. Epub 2010/04/14. https://doi.org/10.1007/s00432-010-0879-7 PMID: 20387072

36. Noh GY, Hwang DY, Choi YH, Lee YY. Effect of diabetes mellitus on outcomes of colorectal cancer. Journal of the Korean Society of Coloproctology. 2010; 26(6):424–8. Epub 2011/01/12. PubMed Central PMCID: PMCPMC3017979. https://doi.org/10.3393/jksc.2010.26.6.424 PMID: 21221244

37. 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. Journal of cancer survivorship: research and practice. 2010; 4(4):381–7. Epub 2010/08/20. PubMed Central PMCID: PMCPMC3175493.

38. Chen CQ, Fang LK, Cai SR, Ma JP, Yang GX, Yang W, et al. Effects of diabetes mellitus on prognosis of the patients with colorectal cancer undergoing resection: a cohort study with 945 patients. Chinese medical journal. 2010; 123(21):3084–8. Epub 2010/12/18. PMID: 21162960

39. Jullumstro E, Kollind M, Lydersen S, Edna TH. Diabetes mellitus and outcomes of colorectal cancer. Acta oncologica (Stockholm, Sweden). 2009; 48(3):361–7. Epub 2008/12/23.

40. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. International journal of cancer. 2007; 120(9):1986–92. Epub 2007/01/19. https://doi.org/10.1002/ijc.22532 PMID: 17230509

41. Shonka NA, Anderson JR, Panwalkar AW, Reed EC, Steen PD, Ganti AK. Effect of diabetes mellitus on the epidemiology and outcomes of colon cancer. Medical oncology (Northwood, London, England). 2006; 23(4):515–9. Epub 2007/02/17.

42. Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer detection and prevention. 2006; 30(5):466–72. Epub 2006/10/31. https://doi.org/10.1016/j.cdp.2006.07.003 PMID: 17069990

43. 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. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2006; 24(31):5017–24. Epub 2006/11/01.

44. 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. The British journal of surgery. 2005; 92(5):615–23. Epub 2005/03/22. https://doi.org/10.1002/bjs.4913 PMID: 15779071

45. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. American journal of epidemiology. 2004; 159(12):1160–7. Epub 2004/06/12. https://doi.org/10.1093/aje/kwh161 PMID: 15191933

46. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2003; 21(3):433–40. Epub 2003/02/01.

47. Lee SJ, Kim JH, Park SJ, Ock SY, Kwon SK, Choi YS, et al. Optimal glycemic target level for colon cancer patients with diabetes. Diabetes research and clinical practice. 2016; 124:66–71. Epub 2017/01/21. https://doi.org/10.1016/j.diabres.2016.12.009 PMID: 28107755

48. Rajpathak SN, Gunter MJ, Wylie-Rosett J, Ho GY, Kaplan RC, Muzumdar R, et al. The role of insulin-like growth factor-I and its binding proteins in glucose homeostasis and type 2 diabetes. Diabetes/metabolism research and reviews. 2009; 25(1):3–12. Epub 2009/01/16. PubMed Central PMCID: PMCPMC4153414. https://doi.org/10.1002/dmrr.919 PMID: 19145587

49. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2002; 11(4):385–91. Epub 2002/04/03.

50. Zhang R, Xu GL, Li Y, He LJ, Chen LM, Wang GB, et al. The role of insulin-like growth factor 1 and its receptor in the formation and development of colorectal carcinoma. The Journal of international medical research. 2013; 41(4):1228–35. Epub 2013/06/27. https://doi.org/10.1177/0300060513487631 PMID: 23801064

51. Ding J, Li C, Tang J, Yi C, Liu JY, Qiu M. Higher Expression of Proteins in IGF/IR Axes in Colorectal Cancer is Associated with Type 2 Diabetes Mellitus. Pathology oncology research: POR. 2016; 22(4):773–9. Epub 2016/05/04. https://doi.org/10.1007/s12253-016-0065-6 PMID: 27138191

52. Dallas NA, Xia L, Fan F, Gray MJ, Gaur P, van Buren G 2nd, et al. Chemoresistant colorectal cancer cells, the cancer stem cell phenotype, and increased sensitivity to insulin-like growth factor-I receptor inhibition. Cancer research. 2009; 69(5):1951–7. Epub 2009/02/27. PubMed Central PMCID: PMCPMC3198868. https://doi.org/10.1158/0008-5472.CAN-08-2023 PMID: 19244128

53. Scartozzi M, Mandolesi A, Giampieri R, Pierantoni C, Loupakis F, Zaniboni A, et al. Insulin-like growth factor 1 expression correlates with clinical outcome in K-RAS wild type colorectal cancer patients treated with cetuximab and irinotecan. International journal of cancer. 2010; 127(8):1941–7. Epub 2010/01/26. https://doi.org/10.1002/ijc.25193 PMID: 20099280

54. Winder T, Zhang W, Yang D, Ning Y, Bohanes P, Gerger A, et al. Germline polymorphisms in genes involved in the IGF1 pathway predict efficacy of cetuximab in wild-type KRAS mCRC patients. Clinical cancer research: an official journal of the American Association for Cancer Research. 2010; 16(22):5591–602. Epub 2010/10/12. PubMed Central PMCID: PMCPMC2982939.

55. Zhu B, Wu X, Bi Y, Yang Y. Effect of bilirubin concentration on the risk of diabetic complications: A meta-analysis of epidemiologic studies. Scientific reports. 2017; 7:41681. Epub 2017/01/31. PubMed Central PMCID: PMCPMC5278382. https://doi.org/10.1038/srep41681 PMID: 28134328