RESEARCH ARTICLE

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

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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 regarded 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.
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, comorbidity 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 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         |

(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 | colorectal cancer | adjusted HROS | age, SES, stage and treatment | 7 |
| Bella, F. | 2013 | Italy | Prospective | 1039 | Hospital-based | 2003–2005 | — | 593446 | 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 | 310215 | 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 |

(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 |
|----------------|------|-------------------|---------------|-------------|-------------------|---------------------|-------------|----------------------|---------------------|-------------------|-----------------|----------|-------------------|-----------|
| 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 perineural 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 | 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 CSS | 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        |
| Author | Year | Region | Type of Study | Sample Size | Patients with DM (n) | Gender (male/female) | Age (Year) | Recruitment time | Study sample | Outcomes | Adjusted variable | Adjusted HR | NOS score |
|--------|------|--------|---------------|-------------|---------------------|---------------------|------------|-----------------|-------------|-----------|-------------------|-------------|-----------|
| Lai, C. C. | 2011 | Korea | Prospective | 2529 | 307 | 1315/1214 | — | 1995–2008 | Hospital-based | 5-year OS | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 7 |
| Sarfati, D. | 2011 | New Zealand | Prospective | 11524 | 5477/6047 | — | 1996–2003 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 7 |
| Lieffers, J. R. | 2011 | Canada | Retrospective | 574 | 335/239 | 72 | 2004–2006 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 8 |
| Chiao, E. Y. | 2010 | USA | Retrospective | 470 | 122 | 46/46 | 1999–2006 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 8 |
| Chen, C. Q. | 2010 | China | Prospective | 564 | 26 | 556/989 | 1994–2002 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 9 |
| Noh, G. Y. | 2010 | Korea | Retrospective | 67 | 67 | 335/239 | 2004–2006 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 7 |
| Jullumstro, E. | 2009 | Norway | Retrospective | 1194 | 97 | 628/666 | 1980–2004 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 9 |
| van de Poll-Franse, L. V. | 2007 | Netherlands | Prospective | 8328 | 913 | 4465/3863 | 1995–2002 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 5 |
| Shonka, N. A. | 2006 | USA | Retrospective | 1853 | 255 | 911/1962 | 1986–2003 | Hospital-based | — | adjusted HROS; HRDFS; 5-year OS and TNM stage | — | 5 |

The relationship between diabetes and colorectal cancer prognosis.
| 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      | 23936/613           | 287                 | Medical records   | colon cancer       | adjusted          | HROS, HRRFS and unadjusted HRDFS; 5-year at OS, 5-year DFS and 5-year RFS | 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.

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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.

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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) | I² (%) | 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.

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

| Region         | 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 |
| 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 | F | 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 | R | 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 | F | 2[8, 10] | F | 0.91 (0.56, 1.25) | 7.6 | 0.298 |
| Oceania        | 0 — — — — 1[31] | — | — | — | 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) | \( \hat{\text{I}}^2 \) | HR (95% CI) | \( \hat{\text{I}}^2 \) | HR (95% CI) | \( \hat{\text{I}}^2 \) |
|                   |              | \( p \)       |              |              | \( p \)       |              | \( p \)       |
| Hospital-based    | F            | 1.14 (1.02, 1.25) | 31.8         | 0.129        | R            | 1.18 (1.06, 1.30) | 80.7         | <0.001        |
|                   |              |               |              |              |              |              |              |              |
| DM ascertainment  |              |               |              |              |              |              |              |              |
| Medical records   | R            | 1.18 (1.11, 1.24) | 70.7         | <0.001       | R            | 1.20 (1.11, 1.28) | 89.0         | <0.001        |
|                   |              |               |              |              |              |              |              |              |
| Self-reported     | F            | 1.29 (1.08, 1.51) | 49.5         | 0.095        | F            | 1.02 (1.03, 1.15) | 0.0          | 0.504         |
|                   |              |               |              |              |              |              |              |              |
| Blood glucose test| F            | 0.95 (0.65, 1.25) | 27.2         | 0.249        | —            | 0.57 (0.22, 1.47) | —            | 0             |
|                   |              |               |              |              |              |              |              |              |
| Quality of studies|              |               |              |              |              |              |              |              |
| Moderate          | R            | 1.16 (1.03, 1.28) | 75.5         | 0.003        | —            | 1.00 (0.77, 1.30) | —            | 0             |
|                   |              |               |              |              |              |              |              |              |
| High              | R            | 1.19 (1.11, 1.27) | 47.4         | 0.014        | R            | 1.19 (1.11, 1.28) | 87.6         | <0.001        |
|                   |              |               |              |              |              |              |              |              |
| Adjusted variables|              |               |              |              |              |              |              |              |
| no                | F            | 1.03 (0.96, 1.10) | 0.0          | 0.823        | —            | 1.00 (0.77, 1.30) | —            | 0             |
|                   |              |               |              |              |              |              |              |              |
| yes               | R            | 1.20 (1.14, 1.26) | 57.8         | 0.001        | R            | 1.19 (1.11, 1.28) | 87.6         | <0.001        |

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.
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 ≥ 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 etiopathogenesis 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].

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

| Cancer Type    | 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.

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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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