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ORIGINAL RESEARCH

Impact of diabetes mellitus on the survival of pancreatic cancer: a meta-analysis

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Background: Diabetes mellitus (DM) is a risk factor for pancreatic cancer (PC), but its prognostic value in PC is still unclear. To elucidate this issue, we systematically reviewed the evidence concerning the association between diabetes status and PC.

Methods: Medline and EMBASE databases were searched to identify the eligible studies. Overall and subgroup analyses were performed to detect the discrepancy of prognosis according to diabetes status. Hazard ratios (HRs) with 95% CI were used to estimate the effect size.

Results: Eighteen studies including 16,181 patients with sample size ranging from 113 to 4,658 were pooled in this meta-analysis. Results showed that patients with DM had worse survival (HR 1.19, 95% CI: 1.07–1.32). In view of the impact of diabetes duration and tumor stage on the outcomes, we classified the studies into different groups. The results indicated that DM was associated with survival in both long-standing diabetes (HR 1.26, 95% CI: 1.14–1.40) and recent-onset diabetes (HR 1.29, 95% CI: 1.09–1.51). Data regarding localized disease (HR 1.57, 95% CI: 1.00–2.46) and nonlocalized (locally advanced and metastatic) disease (HR 1.42, 95% CI: 1.16–1.73) verified that the prognostic value was independent of tumor stage.

Conclusion: Our results suggested that patients with DM were associated with worse survival than those without DM. Diabetes may be a predictive factor of survival in patients with PC. Surveillance of diabetes status and antidiabetes medication administration after the diagnosis of PC is of clinical importance.

Keywords: diabetes mellitus, pancreatic cancer, survival, meta-analysis

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death. It is estimated that 227,000 deaths per year are related to PC.[1] In western countries, >80% of patients with PC have distant metastatic diseases at initial presentation. Radical surgery is restricted to these patients as their best chance of a cure. Moreover, the efficacy of chemotherapy and radiotherapy is limited, and the overall 5-year survival rate among patients is <5%.[2] The prognosis of patients with PC is affected by numerous factors, such as the number of metastatic lymph nodes, the infiltration of peripancreatic blood vessels, histologic grade, and positive margins after surgery,[1,3] all of which can be evaluated only after resection. The ability to find an optimal prognostic indicator prior to treatment would greatly improve management.

Diabetes mellitus (DM) is a common endocrine disease worldwide. Epidemic data show that the incidence of DM is increasing among the population aged from 20 years to 79 years.[4] It is well established that DM is one of the significant risk factors for PC, besides alcohol consumption, tobacco smoking, and obesity.[5,6] This may contribute to hormonal and metabolic alterations brought by insulin resistance or compensatory hyperinsulinemia. Long-term existence of insulin resistance-related

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metabolic and inflammatory components can be involved in the formation of the microenvironment for tumorigenesis and tumor progression. Accumulating evidence has demonstrated that people with diabetes may develop PC in the long run.[7,8] Furthermore, diabetes may also affect the survival of patients with PC. Several clinical studies confirm that patients with diabetes tend to have worse overall survival compared to patients without diabetes and the use of preoperative insulin will reduce the survival time.[9–11] However, Beg et al[12] from the University of Texas Southwestern Medical Center investigated 4,658 patients from the Veterans Affairs Central Cancer Registry and found that DM had no effect on the overall survival of PC.

So far, the association between diabetes and increased risk of several common cancers has reached a consensus. Nevertheless, the role of diabetes in PC prognosis is still uncertain. A previous meta-analysis tried to review the prognostic value of preoperative diabetes on the survival of patients.[13] However, it only enrolled patients with curative resection, which accounted for a small part of the population diagnosed with PC, and did not consider the discrepancy of different durations of diabetes. In addition, several new prospective cohorts are published recently. These data provide an excellent opportunity for us to determine the role of diabetes in the progression of PC. Therefore, we conduct this meta-analysis and hope to transform the results into clinical application.

Materials and methods

Search strategies

Using Medline and EMBASE databases, we conducted a literature search of studies published before May 2015 that evaluated the prognostic value of DM in PC. We also manually searched bibliographic reviews and associated abstracts. There was no restriction of language. Our research strategy included keywords of "diabetes mellitus" (eg, "diabetes," "glucose intolerance," "hyperglycemia," and "hyperglycemia"), "pancreatic cancer" (eg, "pancreatic carcinoma" and "pancreatic adenocarcinoma"), and "survival" (eg, "prognosis" and "outcome"). The complete search strategy is shown in Supplementary Material. All included records were added to an EndNote (Version X6) library.

Study inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: 1) studies published as an original series that evaluated the survival or outcomes of patients according to diabetes status after PC diagnosis, information of diabetes status acquired from patients' self-report on questionnaires, blood glucose tests, or medical records, and studies reported before May 2015 and 2) studies providing hazard ratios (HRs) with corresponding 95% CIs of overall survival (OS) or having sufficient information to reconstruct them.

Exclusion criteria were as follows: 1) studies with no sufficient data or consistent data; 2) literature reporting only the mortality of patients in hospital or after surgery; and 3) studies without enough information to estimate HR and 95% CI associated with diabetes.

Data extraction and quality assessment

All potential studies were independently reviewed by two reviewers (HS and MZ). Results were compared and consensus was reached. The following variables were recorded: first author, year of publication, median age-to-sex ratio of included patients, geographical region, duration of follow-up, adjustment variables, tumor stage, and treatment. If the patients mainly received surgical treatment, the study was classified into surgical therapy group. If part or all of the patients cannot undergo surgery, it was divided into multiple therapy group. We used the TNM staging system or metastatic status to represent the tumor stage. When important data was not reported, we tried to contact the authors. The definitions of long-standing and recent-onset diabetes are not the same in different studies. The cutoff in study by Yuan et al[14] was 4 years. Study by Hwang et al[15] defined DM >5 years as long-standing diabetes. The cutoff was 2 years in the studies by Ben et al[16] and Chu et al.[17]

The meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[18] The study quality was scored by HS and MZ using the Newcastle-Ottawa Scale.[19] Of the 18 studies, 17 obtain scores of ≥6. The Newcastle-Ottawa Scale is frequently used for nonrandom studies (case–control and cohort studies), and scores of ≥6 are identified as high-quality studies.

Data synthesis and analysis

HRs with 95% CIs were directly obtained from included studies. When multivariate and univariate analyses were available to obtain, multivariate data were extracted. Study-specific HR estimates were combined using a random- or fixed-effects model.[20] I^2 values were adopted for the quantification of statistical inconsistency, described as the percentage of variation between studies due to heterogeneity.[21] Publication bias was assessed by Begg's funnel plot[22] and Egger's bias indicator test.[23] The trim-and-fill method by Duval and

Tweedie[24] was applied to estimate the influence of publication bias on the overall effect. The stability of the results was evaluated by sensitivity analysis. We used Stata 12.0 (StataCorp LP, College Station, TX, USA) commercial software with meta-analysis commands to perform all statistical analyses.

Results

Literature search and study characteristics

By searching the dataset, 18 studies were included initially. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram depicting the selection process is shown in Figure 1. After excluding the studies that did not meet requirements, 89 identified studies concerning the prognostic value of diabetes in PC were further evaluated. By further review, 30 studies were not relative to diabetes. Twenty-nine studies did not provide the survival time of patients with diabetes. Three studies had the overlapping patient cohorts with other larger studies.[25–27] Five studies were review of previous studies. Three studies focused on the impact of diabetes on the mortality of general populations, not patients with PC,[9,28,29] and one study provided HR for patients with fasting serum glucose ≥126 mg/dL compared to 0–109 mg/dL group.[30] All of the studies mentioned above were excluded. Finally, 18 studies including 16,181 patients with sample size ranging from 113 to 4,658 were pooled in this meta-analysis.[12,14–17,31–43]

The general characteristics of included studies are summarized in Table 1. The study by Yuan et al[14] included three cohorts, so we divided them into three groups, Yuan(NHS), Yuan(HPFS), and Yuan(DFCI). The study by Olson et al[39] was classified into two cohorts, resected group and nonresected group. There were 16 retrospective studies (17 cohorts) and two prospective studies (four cohorts) identified. There were ten studies (13 cohorts) from USA, two studies from the People's Republic of China and two from Italy, and one study from each of the UK, Germany, the Netherlands, and France. Nine of these studies (11 cohorts) enrolled <500 people, and nine studies enrolled >500. Five studies only enrolled pancreatic ductal adenocarcinoma,[16,17,33,34,41] and others included all the exocrine pancreas cancer. HRs in only two of the 18 studies (21 cohorts) were produced by univariate analysis.

DM and OS

There were 18 studies (21 cohorts) presenting the HRs for the OS. The pooled HR was 1.19 (95% CI: 1.07–1.32; Figure 2) with remarkable heterogeneity (I^2=75.0%, P<0.001). Results of the combined analysis showed that patients with diabetes may have shorter OS. Due to the presence of heterogeneity, subgroup analysis was performed based on the different study

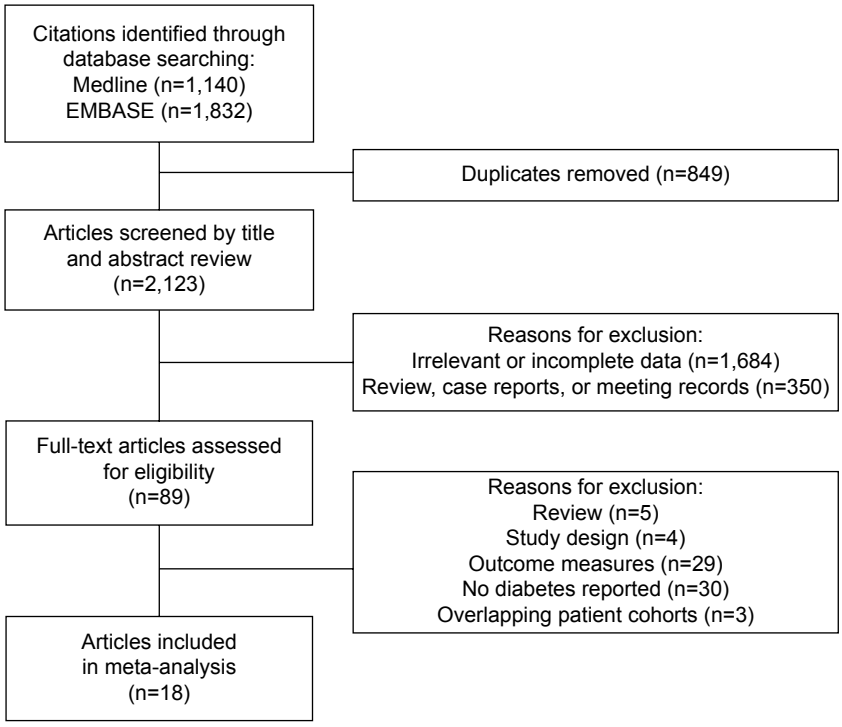

Figure 1 Search strategy of eligible studies.

Table 1 Data from studies included in this meta-analysis

Author	Year	Location	Study design	Study period	Follow-up (months)	Population source	Diabetes ascertainment	Adjustment variables	NOS score
Yuan et al[14]	2015	USA	Prospective	NHS/HPFS, 1986–2010; DFCI, 2004–2013	NR	NHS/HPFS: population based; DFCI: hospital based	Self-reported	Age, sex, race, smoking status, year of diagnosis, and cancer stage	7
Dong et al[34]	2014	People's Republic of China	Retrospective	2009–2011	15.2 (1.4–52.0)	Hospital based	Medical records/blood glucose test	Age, sex, jaundice, tumor location, treatment, tumor diameter, tumor stage, differentiation, surgical margins, and perineural invasion	6
Toriola et al[31]	2014	USA	Prospective	1993–2001	NR	Population based	Self-reported	Age, sex, BMI, race, smoking, and tumor stage	7
Pelucchi et al[32]	2014	Italy	Retrospective	1983–2008	NR	Hospital based	Self-reported	Age and calendar period at diagnosis, study center, and sex	6
Hart et al[33]	2014	USA	Retrospective	2000–2010	NR	Hospital based	Self-reported/ blood glucose test	Age, BMI, weight loss percentage, smoking status, family history of DM, DM treatment, tumor size, tumor grade, number of positive lymph nodes, margin status, adjuvant chemotherapy, and tumor stage	7
Beg et al[12]	2014	USA	Retrospective	1995–2008	3.6 (1.3–7.4)	Population based	Medical records	Age, sex, race, alcohol, tobacco, stage, tumor site, and treatment	7
Hwang et al[15]	2013	UK	Retrospective	2003–2010	NR	Population based	Medical records	Age, sex, history of pancreatic resection, pancreatitis, and Charlson index	7
Sahin et al[35]	2012	USA	Retrospective	1996–2011	NR	Hospital based	Self-reported	Perineural invasion, margin status, node status, and differentiation	6
Ben et al[16]	2012	People's Republic of China	Retrospective	2005–2010	20 (4–62)	Hospital based	Self-reported/ blood glucose test	Age, tumor stage, neural invasion, CA19-9 levels, and node involvement	7
Gong et al[42]	2012	USA	Retrospective	1995–2008	121.2	Hospital based	Self-reported	Age, sex, race, education, body mass index, smoking status, diabetes, stage, tumor grade, tumor site, and primary treatment	7
Barbas et al[36]	2012	USA	Retrospective	1996–2008	NR	Hospital based	Medical records	Age, sex, race, comorbidity, positive lymph node status, margin status, histological grade, vascular invasion, perineural invasion, and treatment	7
Hartwig et al[37]	2011	Germany	Retrospective	2001–2009	17 (1–92)	Hospital based	Medical records	Age, ASA score, CEA, CA19-9, histological grade, tumor stage, lymph node ratio, and margin status	7
Dandona et al[38]	2011	USA	Retrospective	1995–2009	NR	Hospital based	Self-reported	None	6
Dehayem et al[40]	2011	France	Retrospective	2002–2004	NR	Hospital based	Medical records/ blood glucose test	NR	7
Olson et al[39]	2010	USA	Retrospective	2004–2008	NR	Hospital based	Self-reported	None	6
van de Poll-Franse et al[43]	2007	the Netherlands	Retrospective	1995–2005	NR	Hospital based	Medical records	Age, sex, stage, treatment, and cardiovascular disease	7
Chu et al[17]	2010	USA	Retrospective	2000–2007	NR	Hospital based	Medical records	Age, sex, BMI, ethnicity, tumor location, and histopathologic variables	7
Sperti et al[41]	1996	Italy	Retrospective	1970–1992	NR	Hospital based	Medical records	NR	5

Abbreviations: ASA, American Society of Anesthesiologists; CEA, carcino-embryonic antigen; BMI, body mass index; DM, diabetes mellitus; NOS, Newcastle-Ottawa Scale; NR, not reported; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; DFCI, Dana-Farber Cancer Institute.

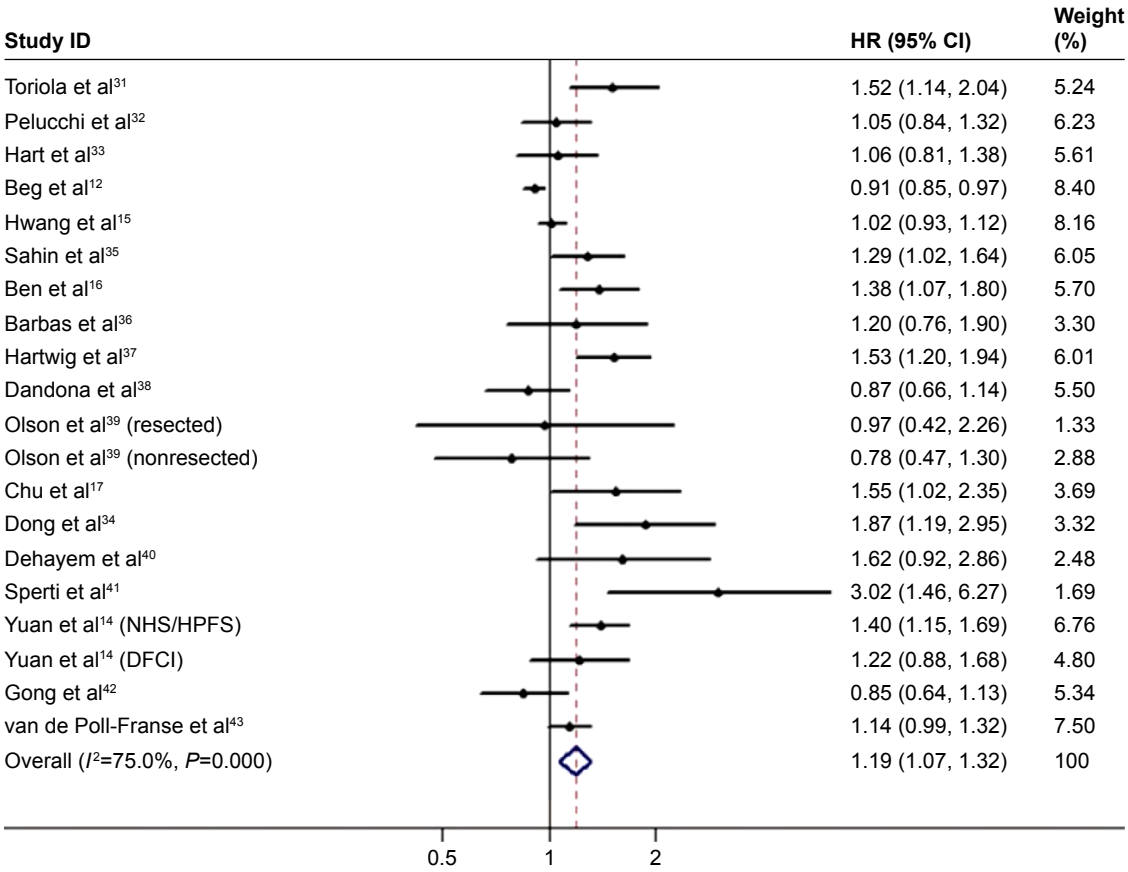

Figure 2 Meta-analysis of the effect of diabetes mellitus on overall survival.
Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; DFCI, Dana-Farber Cancer Institute.

types (prospective or retrospective), study regions (USA, Europe, or Asia), sample size (<500 or ≥500), and therapeutic interventions (curative resection or multiple treatment) (Table 2). Subgroup analysis by therapeutic interventions indicated that diabetes status was significantly associated with a poorer outcome in curative resection patients but not in multiple treatment patients. While the subgroup analysis failed to figure out the underlying source of heterogeneity, study types, study regions, sample size, and therapeutic interventions were not the main reasons for heterogeneity. Because tumor stage is one of the predominant factors for prognosis and knowledge about the role of tumor stage in the relationship between diabetes and PC is little, we pooled the results of two relevant studies.[14,31] Results showed that

Table 2 Subgroup analysis of the studies reporting the association between diabetes mellitus and overall survival

Stratified analysis	Number of cohorts	Pooled HRs (95% CI)		Heterogeneity	
		Fixed	Random	I^2 (%)	*P*-value
Study type					
Prospective	3	1.39 (1.20–1.60)	1.39 (1.20–1.60)	0	0.609
Retrospective	17	1.02 (0.98–1.07)	1.15 (1.03–1.28)	73	<0.001
Study region					
USA	11	1.00 (0.94–1.05)	1.12 (0.95–1.32)	75.5	<0.001
Europe	7	1.10 (1.03–1.18)	1.20 (1.03–1.40)	69.1	0.004
Asia	2	1.49 (1.19–1.87)	1.52 (1.16–1.99)	21.3	0.26
Sample size					
<500	11	1.21 (1.08–1.35)	1.26 (1.05–1.51)	55.9	0.012
>500	9	1.03 (0.98–1.08)	1.15 (1.01–1.31)	82.9	<0.001
Treatment					
Curative resection	9	1.33 (1.19–1.48)	1.37 (1.14–1.65)	57.9	0.015
Multiple treatment	11	1.01 (0.97–1.06)	1.09 (0.98–1.22)	72.9	<0.001

Abbreviation: HRs, hazard ratios.

diabetes was associated with survival in both localized disease (HR 1.57, 95% CI: 1.00–2.46; Figure 3) and nonlocalized (locally advanced and metastatic) disease (HR 1.42, 95% CI: 1.16–1.73).

In consideration of the impact of diabetes duration on the outcomes of PC, patients with DM were classified into long-standing and recent-onset groups. In the group of long-standing diabetes, the results of four studies (six cohorts) showed a pooled HR of 1.26 (95% CI: 1.14–1.40; Figure 4) with no heterogeneity (I^2=0.0%, P=0.582). There were three studies (five cohorts) providing data associated with recent-onset diabetes. The pooled estimate of HR was 1.29 (95% CI: 1.09–1.51; Figure 5) with no heterogeneity (I^2=19.3%, P=0.292), but data from three prospective cohorts showed an HR of 1.11 (95% CI: 0.89–1.39). The results indicated both long-standing and recent-onset diabetes tended to be related with poor survival of PC.

Publish bias and sensitivity analysis

In addition, Begg's funnel plot and Egger's test were used to evaluate the publication bias of included studies. The statistical results (Begg's test, P=0.49; Egger's test, P=0.003) showed evidence of publication bias, and the shape of the funnel plot was unsymmetrical (Figure 6). Then, trim-and-fill analysis was performed to deduce the potential unpublished studies. The results indicated that seven studies were missing. The filled analysis showed an HR of 2.79 (95% CI: 2.50–3.14), which was in accord with the previous result. Sensitivity analysis showed that the pooled results and heterogeneity could not be changed substantially by deleting a single study each time. All these analyses demonstrated the stable quality of our study.

Discussion

Although the guidelines for standardized treatment of PC are enacted, prognostication in advanced cancer relies heavily on the intuition and experience of clinicians. But the estimate by clinicians is often inaccurate according to previous studies.[44] The decision whether to give potent anticancer treatments with side effect (eg, chemotherapy) or not is often hard to make without the support of scientific assessment system. As a result, accurate prognostication is important, especially for patients nearing the end of life.

In this meta-analysis, we reported evidence from 18 studies (21 cohorts) about the effect of DM on the survival of PC investigated in a total of 16,181 patients. The results demonstrated the predictive value of diabetes on survival. It is known that some pancreatic tumors can secret excess insulin and lead to hyperglycemia.[45] Studies have shown that this PC-induced DM frequently happens within 3 years before PC

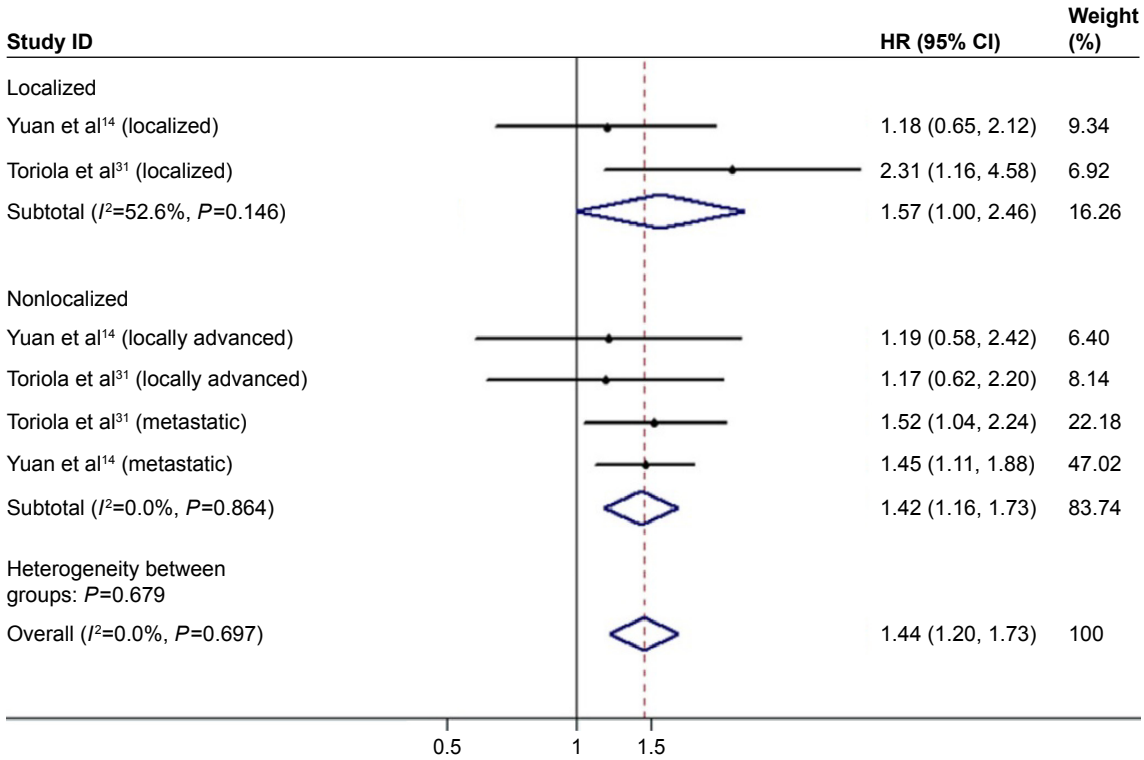

Figure 3 Meta-analysis of the pooled estimates stratified by different tumor stages.
Abbreviation: HR, hazard ratio.

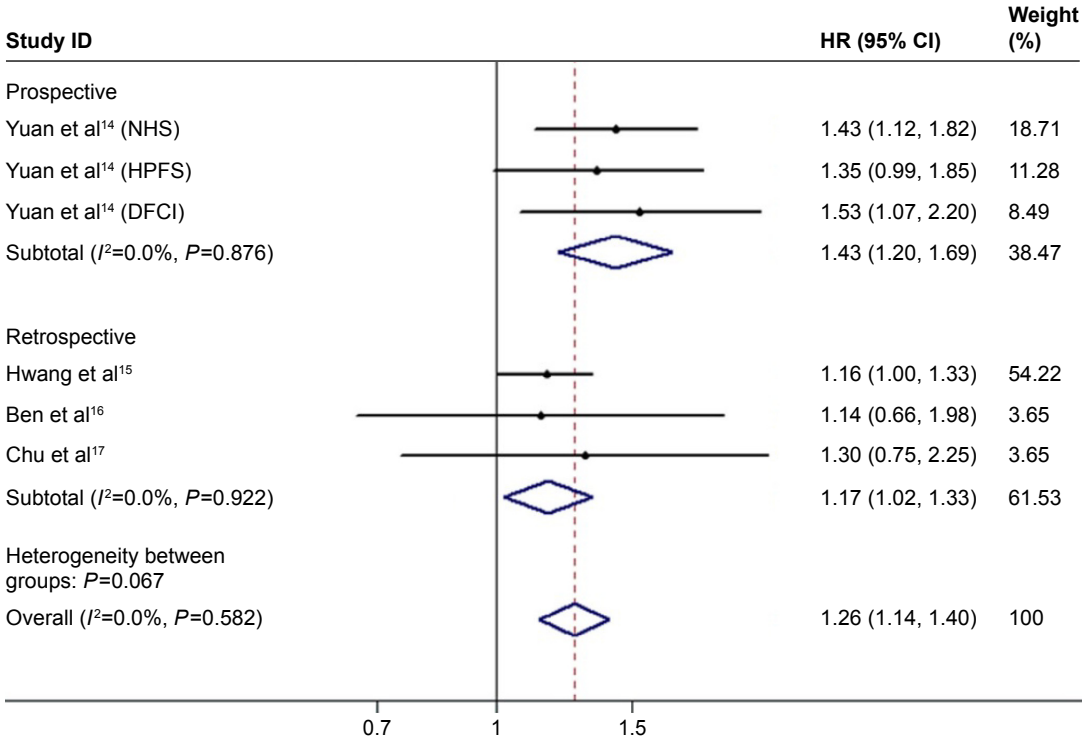

Figure 4 Meta-analysis of the effect of long-standing diabetes on overall survival.
Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; DFCI, Dana-Farber Cancer Institute.

diagnosis in 20%–30% of patients, and half of this new-onset DM will be cured after surgical resection of the tumors.[46] Therefore, we classified DM into long-standing and recent-onset groups according to the different duration. Further analysis verified that both long-standing and recent-onset diabetes were associated with shorter OS. But data from three prospective studies by Yuan et al[14] showed nonsignificant results for the recent-onset group.[14] The authors suggested

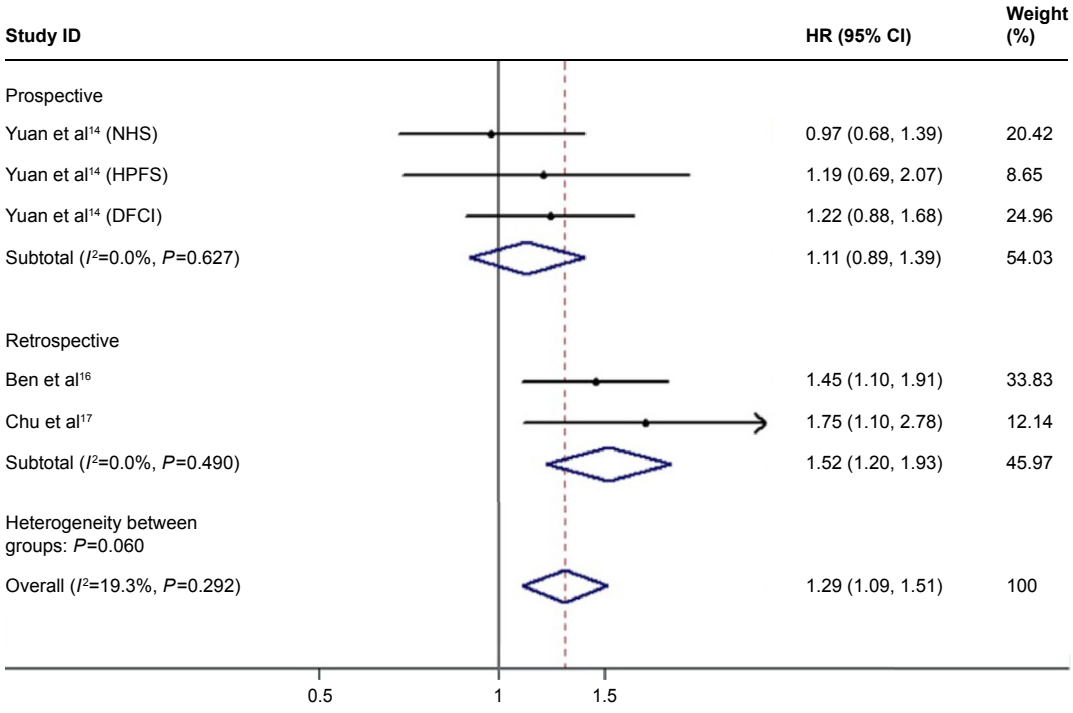

Figure 5 Meta-analysis of the effect of recent-onset diabetes on overall survival.
Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; DFCI, Dana-Farber Cancer Institute; HR, hazard ratio.

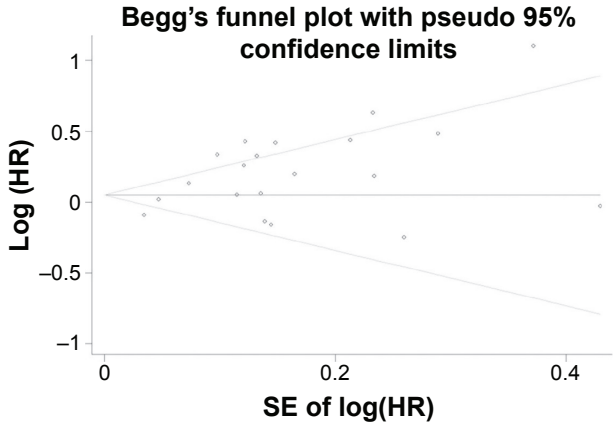

Figure 6 Begg's funnel plot of publication bias.
Abbreviations: SE, standard error; HR, hazard ratio.

that the chronic alterations in metabolic components brought by long-term glucose intolerance can lead to some genetic mutations, and the proto-oncogene mutation would make the tumor a more aggressive one.

The underlying mechanism is confusing and may be connected to the hormonal and metabolic alterations brought by diabetes. The compensatory hyperinsulinemia induced by reduced insulin sensitivity can increase the bioavailability of circulating insulin-like growth factors (IGFs).[47] Experimental studies have shown that both IGF-1 and IGF-1 receptor are highly expressed in PC. Once insulin or IGF-1 receptors interact with their ligands, multiple signaling pathways involved in proliferation, invasion, metastasis, angiogenesis, and antiapoptosis are activated. Increased oxidative stress and inflammatory responses also play an important role in this pathological process. Studies found that oxidative stress and inflammation state may be the first step of pathological process of insulin resistance, which can be suppressed by antioxidants.[4] Increased oxidative stress and inflammatory factors, such as nuclear factor-κB and signal transducer and activator of transcription protein, can activate the signaling pathway and then enhance the progression of cancer.[48] Metformin, the most commonly used medication in patients with diabetes, has been found to suppress cell proliferation and reduce cell cycle arrest by activation of adenosine 5′-monophosphate-activated protein kinase.[49] Experiments verified the antitumor effect of metformin on animals with high-energy diet.[50] The results suggest that treatment with metformin may reduce the mortality of cancer.

Heterogeneity within studies was observed, but subgroup analysis did not change the heterogeneity substantially. Study types, study regions, sample size, and therapeutic interventions had no contribution to the heterogeneity. The different forms of diabetes ascertainment in the recruited studies may be one of the reasons. Some studies acquired the information of diabetes status from patients' self-report on questionnaires. Others adopted the information from blood glucose tests or medical records. Patients' self-report can provide the whole history of diabetes status, but it is not so reliable, while the credible blood glucose tests or medical records only give the ongoing status. From another point of view, the potential publication bias may partially explain the source of heterogeneity, though trim-and-fill and sensitive analyses verified the reliability of the pooled results. It is recognized that studies with negative results are less likely to be published, and even though these results are reported, they are more frequently published in native languages.[51] As this meta-analysis only enrolled fully published studies in Medline or EMBASE, conference abstracts and studies with no sufficient data were excluded. Moreover, the study by Sperti et al[41] was conducted in the 20th century and involved only 113 patients. Because of the defective design and small sample size, it showed a result quite different from others. It decreased the heterogeneity in some degree by deleting the study.

To the best of our knowledge, this is the first study to discuss the impact of diabetes on the prognosis of PC in early or late stage. In this study, patients with surgical or nonsurgical cancer are all recruited. Two studies with four prospective cohorts published recently enhance the strength of the evidence. Moreover, in view of the bidirectional relationship between diabetes and PC, long-standing and recent-onset diabetes are analyzed separately with the help of pertinent studies. We also admitted some other limitations existing in this meta-analysis. First, with only two prospective studies (four cohorts), limitations are inherent to the biases brought by the retrospective studies included. Second, the studies in our review were done mainly in clinical centers from USA and population of white people. The differences in outcomes observed might reflect geographic differences among populations. Third, diabetes is often accompanied by cigarette smoking, obesity, and other unhealthy lifestyle habits, which were related to prognosis. The relevant confounding factors should be discussed. A study by Yuan et al[14] verified that sex, smoking status, and body mass index did not affect the association between diabetes status and PC. But the data of Toriola et al[31] suggested that the correlation may be more evident in the groups of male. Although the data adopted in our analysis excluded the interference of other multivariance, such as sex, smoking status, and body mass index, with the limit of stratified analysis, we cannot make a proper judgment.

Conclusion

In conclusion, this meta-analysis indicated that diabetes was associated with worse survival. DM may be a predictive factor for survival in patients with PC. Surveillance of diabetes status and antidiabetes medication administration after the diagnosis of PC is of clinical importance. Meanwhile, more prospective and large sample studies are still needed to confirm these results.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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