Effect of Diabetes Mellitus on Survival in Patients with Gallbladder Cancer: A Systematic Review and Meta-analysis

Chen Jing
Nanfang College of Sun Yat-sen University
Zhengyi Wang
Nanfang College of Sun Yat-sen University
Xue Fu (fu1xue@163.com)
Nanfang College of Sun Yat-sen University

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Abstract

Background

Increasing evidences indicate that diabetes may increase the incidence of gallbladder cancer. However, no sufficient data clarify the effect of diabetes on survival in patients with gallbladder cancer.

Methods

We comprehensively search PubMed, Embase, and the Cochrane Library databases through July 2019 in order to find sufficient eligible researches. The pooled hazard risks (HRs) and relative risks (RRs) with 95% confidence intervals (CIs) were calculated with either fix-effects or random-effects model.

Results

Ten eligible studies were included in this meta-analysis. Analysis of eight cohorts found that diabetes was closely associated with the mortality of gallbladder cancer (HR=1.10; 95% CI: 1.06-1.14; P<0.00001). However, no significant differences were found between male and female diabetes patients (RR=1.08, 95%CI=0.57-2.04, P=0.80).

Conclusions

These findings indicate that diabetes patients have a higher mortality of gallbladder cancer compared with non-diabetes and general population.

Background

Gallbladder cancer is one of the most common biliary tract malignancies worldwide [1]. By and large, poor overall prognosis seriously affects the mortality of patients with gallbladder cancer[2]. Gallbladder cancer patients survive the mean survival rate of 6 months and a 5-year survival rate of 5%[3]. A growing number of putative risk factors are probably associated with the mortality of gallbladder cancer, including age, gender, smoking, ethnic, and menopause[4–8]. Generally, women are two to six times more likely to be attacked by gallbladder cancer[9]. Advancing age partly demonstrates the prevalence of gallbladder cancer[10].

Diabetes mellitus (DM) is one of the most prevalent globe diseases. Approximately 415 million people suffer from diabetes in 2015 with 5 million deaths ascribed to diabetes[11]. By 2040, the number of diabetes patients are predicted to ascend to 642 million. DM is always regarded as a pivotal risk factor linked to cancer at different sites, including lung[12], liver[13], esophagus[14], stomach[15], colorectum[16], kidney[17], breast[18], leukemia, non-Hodgkin lymphoma, myeloma[19], ovary[20], and prostate[21]. As several studies and meta-analyses have pointed out, DM is closely associated with the risk of gallbladder cancer[22, 23]. However, rare study has focused on the relationship between DM and gallbladder cancer.

Methods

Search strategy

A comprehensive search has been made on the PubMed, Embase and the Cochrane Library databases to find all the eligible studies up to July 24th 2019. The following text words were used in the PubMed: (“diabetes” OR “glucose intolerance” OR “insulin resistance” OR “hyperglycemia” OR “hyperinsulinemia” OR “metabolic syndrome”) AND (“gallbladder cancer” OR “gallbladder carcinoma”) AND (“cohort” OR “epidemiologic”). Correlative key words were used in the Embase and the Cochrane Library. To comprehensively search eligible studies, we simultaneously searched the reference lists of relevant reviews or included publications for further studies.

Inclusion and exclusion criteria

The included literatures met the following criteria: (1) cohort design; (2) investigated gallbladder cancer outcomes; (3) assessed the gallbladder cancer mortality with or without DM; (4) reported the information of odd ratios (ORs), hazard ratios (HRs), relative risks (RRs), or standard mortality ratios (SMRs). The exclusion criteria were as follows: (1) case-control or cross-sectional design; (2) unavailable data.

Data extraction

Two authors independently extracted all data from publications using the same criteria. The following data were included: the first author’s name, publication year, country, sample size, the number of male or female participants, mean age at baseline, average follow-up duration, diabetes assessment, and adjusted factors.

Statistical analysis

We used Reviewer Manager 5.3 in this meta-analysis to analyze the data. The pool HRs with 95% CIs were calculated with a random-effects or a fix-effects model as the effect estimates for the relationship between DM and gallbladder cancer mortality. The RRs, SMR were considered equivalent to the HRs on account of the low gallbladder cancer mortality in general population. Statistical heterogeneity among studies was assessed by the I^2 and Q statistics. Both $I^2 > 50\%$ and P value < 0.1 were regarded a measure of significant heterogeneity. We conducted subgroup analysis to evaluate the potential sources of heterogeneity from country, follow-up duration, diabetes assessment, and adjusted factors (including BMI, smoking, and education). A sensitivity analysis was performed by removing each study from the overall analysis to investigate the influence of a single study. We used funnel plots, Begg and Egger tests to assess publication bias, with P value < 0.05 was viewed as a significant level. The statistical analyses were performed with Stata software (version 12.0).

Results

Study selection

Detailed study selection process is described in Fig. 1. From the initial search, we screened and identified 382 records. 211 articles were discarded for the sake of duplication. 141 articles were excluded based on title or abstract. We further removed 9 studies that enrolled single-arm DM patients. 11 of the 21 remaining studies were subsequently removed due to lack of eligible data. Finally, a total of 10 studies were included in the meta-analysis[24–33].

Study characteristics

The baseline characteristics of the included studies were listed in Table 1. A total of 5522636 participants were included in all 10 studies. Two studies were conducted in the USA, two in the UK, three in the Asia, one in Australia, and two were international conducted studies. The average follow-up duration ranged from 2 to 18 years. Diabetes assessment methods included self-report, medical record, WHO diagnostic criteria, and read code classification. Eight studies reported the relationship between DM and gallbladder cancer mortality, while four studies assessed the different gallbladder cancer mortality in male and female DM patients.

Table 1

Baseline characteristics of included studies.

First author, publication year	Country	Sample size	Male/female	Mean age (year)	Average follow-up duration (year)	Diabetes assessment	Adjusted factors
Coughlin, 2004	USA	1056243	467922/588321	56.7	12.5	Self-report	Age, smoking, race, BMI, exercise, education
Yagyu, 2004	Japan	113394	47673/65721	40–89	9.7	Self-report	Age, gender, history of hepatic disease
Swerdlow, 2005	UK	28900	15688/13212	NA	18.0	Medical record	Age, region, duration
Tseng, 2009	Taiwan	244920	113347/131573	NA	12	Medical record	Age, gender
Lam, 2011	Asia, Australia	367361	216743/150618	48	4	Self-report or WHO diagnostic criteria	Age
Seshasai, 2011	Members of ERFC	820900	426868/394032	55	NA	Medical record	Age, gender, smoking, BMI
Campbell, 2012	USA	1053831	467143/586688	63.1	12.1	Self-report	Age, BMI, education, exercise, NSAIDs, alchhol
Currie, 2012	UK	112408	54086/58322	67.8	2	Read code classification	Age, gender, smoking, Charlson comorbidity index, year of diagnosis
Harding, 2015	Australia	953382	506312/447070	T1DM: 27.4 T2DM: 60.4	10	Medical record	Age
Chen, 2017	Asia	771297	391619/379678	53.9	12.7	Self-report	Age, gender, BMI, smoking, alcohol, education, region

DM and Gallbladder cancer mortality

Eight studies focused on the relationship between diabetes mellitus and gallbladder cancer mortality. We pooled the data of these studies and found that pre-existing diabetes had a high correlation with the mortality of gallbladder cancer compared with non-DM participants (HR = 1.10; 95% CI: 1.06–1.14; P < 0.00001; Fig. 2). A fix-effects model was applied owing to low heterogeneity (I^2 = 0%; P = 0.95). The sensitivity analysis results indicated that the summary HR ranged from 1.09 (95%CI: 1.06–1.13) when excluding study from Chen 2017 to 1.12 (95%CI: 1.07–1.17) when excluding study from Currie 2012[29, 31].

Subgroup analysis were conducted according to country, follow-up duration, diabetes assessment, and adjustment for confounding factors, including BMI, smoking, and education. The results were demonstrated in Table 2. Though positive associations existed in all subgroup analyses, no evidence indicated that there are differences between these subgroups.

Table 2
Subgroup analysis of relative risk for gallbladder cancer mortality in DM patients.

subgroup	No. of references	HR and 95% CI	P_a	I^2%	P_b
Country					
Western countries	4	1.09(1.05–1.13)	< 0.0001	0%	0.29
Eastern countries	2	1.10(1.06–1.13)	0.001	0%	
Follow-up duration					
≦10	4	1.03(0.89–1.20)	0.70	84%	0.27
>10	3	1.13(1.06–1.21)	0.0005	0%	
Diabetes assessment					
Self-report	3	1.14(1.06–1.22)	0.0003	0%	0.34
Medical record	3	1.01(0.81–1.27)	0.92	73%	
Adjusted BMI					
Yes	3	1.14(1.07–1.21)	< 0.0001	0%	0.30
No	5	1.04(0.90–1.21)	0.57	78%	
Adjusted smoking					
Yes	4	1.10(1.05–1.14)	< 0.0001	0%	0.63
No	4	1.05(0.87–1.26)	0.64	44%	
Adjusted education					
Yes	2	1.13(1.05–1.21)	0.0007	0%	0.43
No	6	1.06(0.93–1.21)	0.35	78%	
P_a= P value for heterogeneity within subgroup					
P_b= P value for heterogeneity between subgroups					

DM and gallbladder cancer mortality in men and women

A total of four studies estimated the difference of gallbladder cancer mortality between male and female DM patients. The pooled analysis results demonstrated that no significant differences had existed between DM men and women (RR = 1.08, 95%CI = 0.57–2.04, P = 0.80; Fig. 3.). A random-effect model was applied due to high heterogeneity (P = 0.0007, I^2 = 82%).

Publication bias

The symmetric funnel plots indicated a potential low publication bias(Fig. 4.). Moreover, Egger test (P = 0.371) and Begg test (P = 0.845) showed no significant evidence of publication bias.

Discussion

This meta-analysis of cohort studies provides comprehensive evidence on the effect of diabetes mellitus on survival in patients with gallbladder cancer. Our results suggest that diabetes patients have a high mortality rate of gallbladder cancer compared with non-diabetes patients or general population. The results are independent of country, follow-up duration, diabetes assessment, BMI, smoking, or education. Though previous analysis has indicated that DM women are more likely to develop gallbladder cancer than DM men due to sex hormones[34], we found no obvious differences between male and female diabetes patients in gallbladder cancer mortality. However, the results remain to be tested due to lack of eligible data.

Several physiological mechanisms may account for the increased gallbladder cancer mortality in DM patients. A growing number of studies have found that overweight, obesity, metabolic syndrome, and insulin resistance are closely related to the increase of gallbladder disease[35–37]. Hyperinsulinemia is also a phenomenon commonly existed in DM patients. Excess insulin directly or indirectly regulates the activity of insulin-like growth factor-1 (IGF-1), which is an important cytokine that influences the development and progression of cancer[38]. Both in vitro and in vivo researches have proved that up-regulation of IGF-1 contributes to the bile duct cancer cells proliferation and the inhibition of apoptosis[39, 40]. In addition, diabetes impairs the function of gallbladder emptying. The gallbladder smooth muscle cells of DM patients have reduced sensitivity to cholecystokinin. Meanwhile, the number of cholecystokinin receptors on the gallbladder wall in DM patients is also reduced[41]. The increase of these problems with gallbladder is consistent with the increase of the risk of biliary tract cancer[42].

To our knowledge, our meta-analysis is the first study focused on the effect of DM on survival in patients with gallbladder cancer mortality. Previous study has proved that diabetes may increase the risk of gallbladder cancer[43]. However, the meta-analyses combined cancer incidence and cancer mortality in DM patients and no subgroup analyses were performed based on this difference. Furthermore, the majority of the included cohort studies were focused on the gallbladder cancer incidence rather than mortality. Only three researches had eligible cancer mortality data, which might affect the accuracy of the results.

The present meta-analyses have some strengths, including prospective design of cohort studies, eligible data from large sample size, detailed subgroup analyses, and low heterogeneity. Our findings provide an important message for patients with comorbid DM and gallbladder cancer that preventing the progression of diabetes may increase the survival from gallbladder cancer.

There are several potential limitations in our study. First, residual confounding cannot be ignored. Because compared with non-DM participants, DM patients often have less healthy lifestyles, including higher rate of obesity, less physically activity, and more likely to smoke and drink. Though most of the included studies have adjusted these factors and our subgroup analysis showed no obvious heterogeneity between subgroups, we cannot completely exclude the influence of these factors. Second, most studies did not tell the differences between type 1 and type 2 DM, though the majority of individuals were type 2 survivals. Older individuals are more likely to develop type 2 DM, while type 1 DM is a more common form in younger individuals. As a result of incomplete initial data on distinguishing this difference, some degree of inaccuracy of results is inevitable. Third,

the number of eligible literatures remained low, which might have some influence on the final conclusion. The results of the difference of gallbladder cancer mortality between male and female patients remains open to question due to the lack of data and a high heterogeneity. Finally, the effect of medicine has not taken into account in the researches. Many studies have indicated that metformin, a commonly used diabetic medication, could retard the development of some cancers. None of the included researches have made adjustments for the use of diabetic medication.

Conclusion

In conclusion, this meta-analysis suggests that diabetes patients have a higher mortality of gallbladder cancer. More relevant studies are needed to certify this association and tell the difference between men and women.

Abbreviations

HRs:hazard risks; RRs:relative risks; CIs:confidence intervals; DM:Diabetes mellitus; ORs:odd ratios; SMRs:standard mortality ratios; BMI:body mass index; IGF-1:insulin-like growth factor-1; ERFC:Emerging Risk Factors Collaboration; T1DM:Type 1 Diabetes Mellitus; T2DM:Type 2 Diabetes Mellitus; WHO:World Health Organization; NSAIDs:Nonsteroidal Anti-inflammatory Drugs

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data materials

All data generated in this analysis are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

CJ and ZYW collected and analyzed all the included data. XF designed this study and drafted the manuscript. All of the authors approved the final manuscript.

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Author details

[1] Nanfang College of Sun Yat-sen University, School of Nursing and Health, Guangzhou, Guangdong Province, China

Disclosure

There is no conflict of interests.

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Figures

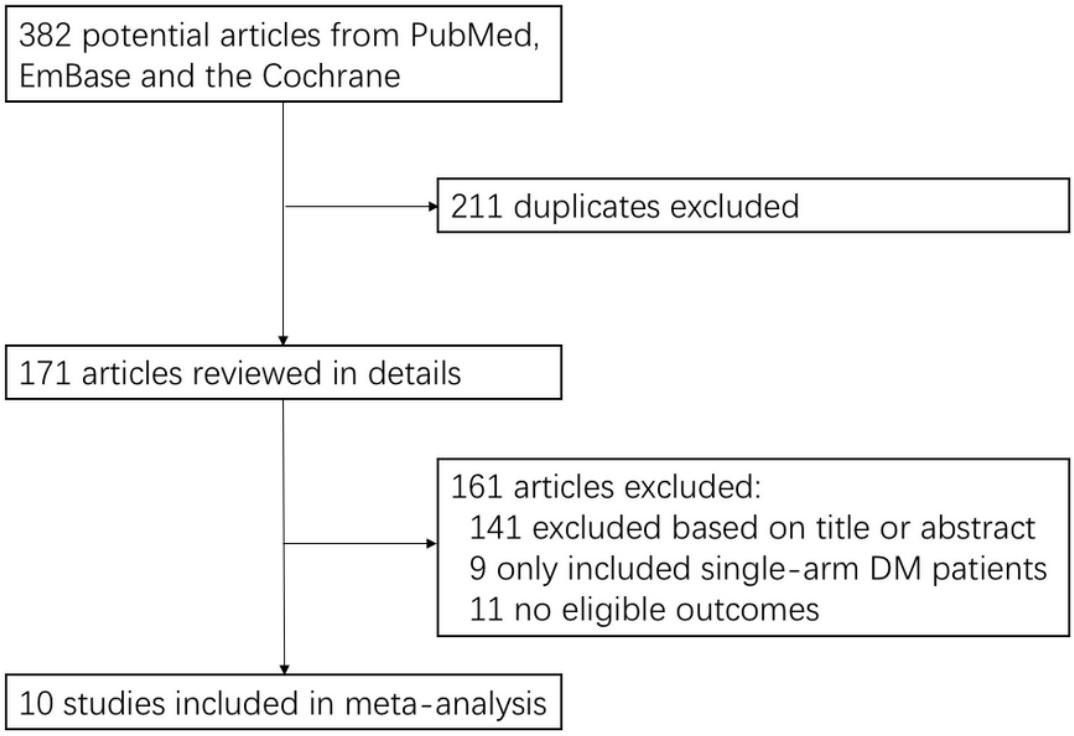

Figure 1

Flow-chart of study selection for the meta-analysis.

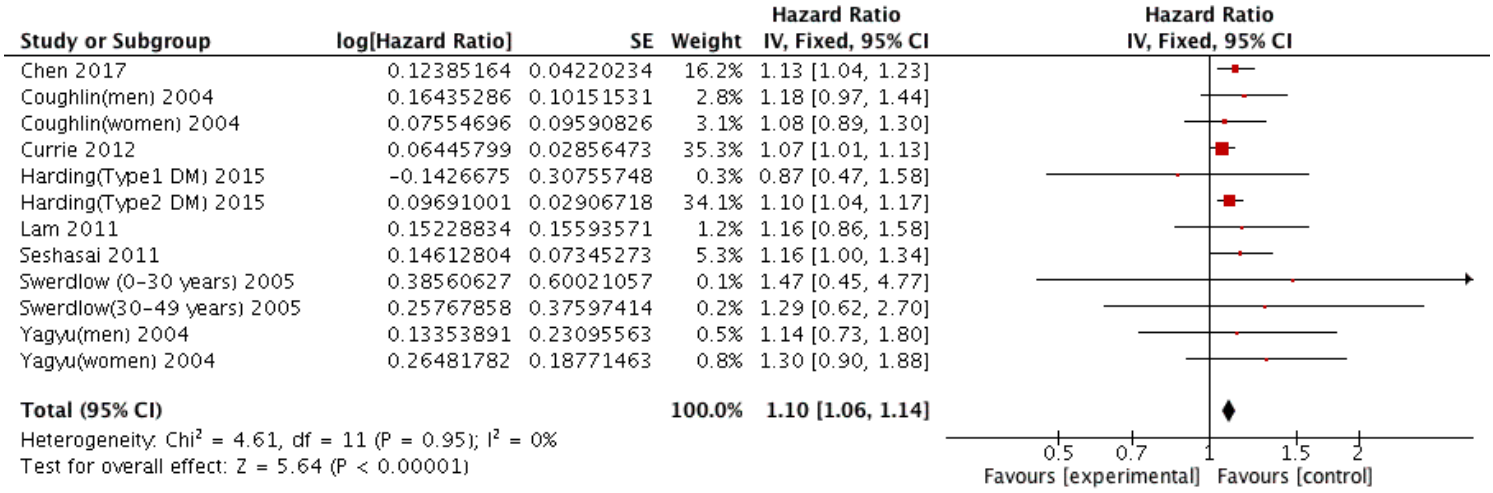

Figure 2

Association between diabetes mellitus and the mortality of gallbladder cancer.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Campbell 2012	21	26617	23	26186	26.0%	0.90 [0.50, 1.62]
Coughlin 2004	4	2974	6	2524	14.4%	0.57 [0.16, 2.00]
Tseng 2009	224	113347	126	131573	32.3%	2.06 [1.66, 2.57]
Yagyu 2004	26	26565	30	26090	27.3%	0.85 [0.50, 1.44]
Total (95% CI)		**169503**		**186373**	**100.0%**	**1.08 [0.57, 2.04]**
Total events	275		185			

Heterogeneity: Tau² = 0.31; Chi² = 16.97, df = 3 (P = 0.0007); I² = 82%
Test for overall effect: Z = 0.25 (P = 0.80)

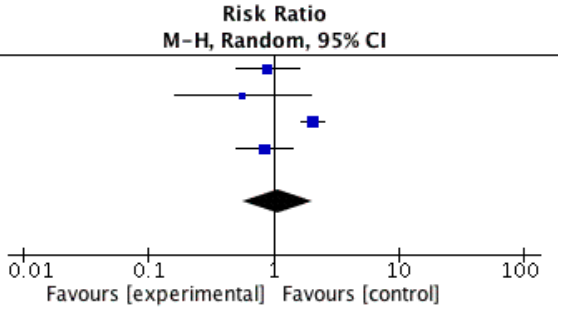

Figure 3

Different mortality of gallbladder cancer between male and female diabetes patients.

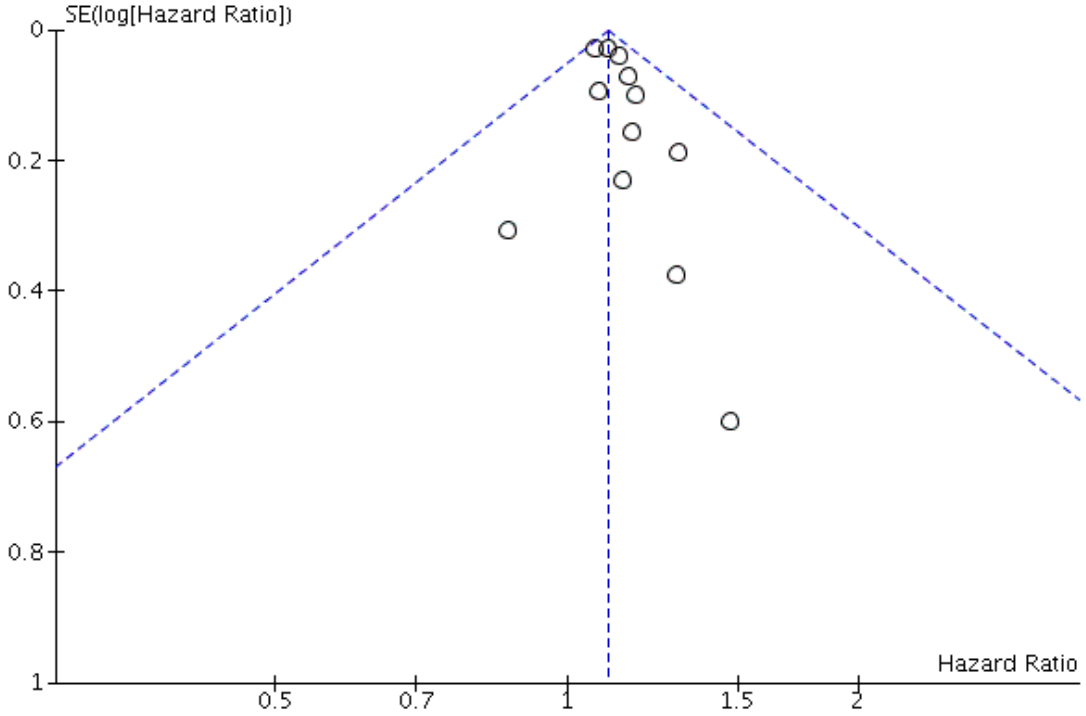

Figure 4

Funnel plot analysis of all the studies about the association between diabetes and gallbladder cancer.