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ORIGINAL RESEARCH

Increased risk of diabetes in cancer survivors: a pooled analysis of 13 population-based cohort studies

Y. Xiao[1], H. Wang[2], Y. Tang[1], J. Yan[3], L. Cao[4], Z. Chen[4], Z. Shao[5*], Z. Mei[6,7*] & Z. Jiang[4*]

[1]National Clinical Research Center for Metabolic Diseases, Key Laboratory of Diabetes Immunology, Ministry of Education, and Department of Metabolism and Endocrinology, The Second Xiangya Hospital of Central South University, Changsha, Hunan; [2]Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai; [3]Department of Endocrinology, The First People's Hospital of Pingjiang, Yueyang City, Hunan Province; [4]Department of Perioperative Research Center of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou; [5]Department of General Surgery, Changhai Hospital, Naval Medical University, Shanghai; [6]Department of Anorectal Surgery, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai; [7]Anorectal Disease Institute of Shuguang Hospital, Shanghai, China

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Background: Diabetes is considered as an established risk factor for cancer development. However, the link between diabetes among cancer survivors remains inconclusive. The hypothesis of this study was to assess the hazard ratio (HR) of incidence of diabetes in cancer survivors compared with the HR in the general population.

Patients and Methods: A comprehensive literature search was performed in PubMed, Embase, and the Cochrane Library from database inception to 15 December 2020 for population-based cohort studies. Summary effect estimates were combined using random-effects models. We also performed subgroup analyses to test sources of heterogeneity and the stability of the results stratified by various study and participant characteristics.

Results: Thirteen population-based cohort studies involving 1 686 595 participants were analyzed. The HR for the development of diabetes in cancer survivors was 1.39 [95% confidence interval (CI) 1.29-1.50; $I^2 = 82.3\%$; $P < 0.001$] compared with that in noncancer controls, among which survivors of hematological, gynecologic, breast, colorectal and urinary tract cancer (all $P < 0.05$) showed consistent significant results, whereas no significant increased risk was observed for other cancer types. The effects were more prominent in populations of shorter cancer survival duration (<1 year) (HR 2.09, 95% CI 1.32-3.32; $P = 0.009$). Moreover, cancer survivors with a longer follow-up period (>10 years) had a relatively higher risk of diabetes (HR 1.54, 95% CI 1.34-1.77) than those with a shorter follow-up period.

Conclusions: In this large pooled analysis of population-based cohorts, evidence supports the hypothesis that the risk of developing diabetes is increased in cancer survivors compared with the general population. We should interpret the results with caution for considerable interstudy heterogeneity. However, health policy makers should take this as a challenge for the early prevention and effective intervention of diabetes.

Key words: cancer, diabetes, population-based cohort study, pooled analysis

INTRODUCTION

Cancer and diabetes are two global public health problems, which are also considered as the major lethal and disabling diseases worldwide.[1,2] They share a variety of common predisposing risk factors (such as hypertension, obesity, hyperlipidemia, and other metabolic disorders) and have similar etiological mechanisms.[3,4] There is growing evidence that cancer survivors suffer from metabolic diseases (including diabetes, obesity, and metabolic syndrome) more frequently than healthy populations.[5-8]

In the past two to three decades, amazing progress has been made in the diagnosis and treatment of cancer along with treatment-related complications resulting from comorbidities.[9-14] A considerable number of patients with cancer survived for a long period with early screening,

*Correspondence to: Dr Zubing Mei, Department of Anorectal Surgery, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Anorectal Disease Institute of Shuguang Hospital, 528 Zhangheng Road, Shanghai 201203, China. Tel: +86-21-20256187

E-mails: herrmayor@126.com or herrmayor@shutcm.edu.cn (Z. Mei).

*Dr Zhuo Shao, Department of General Surgery, Changhai Hospital, Navy Medical University, 200433 Shanghai, China. Tel: +86-2131161628

E-mail: szlaugh@163.com (Z. Shao).

*Dr Zhi Jiang, Department of Perioperative Research Center of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Number 111 Dade Road, Yuexiu District, Guangzhou 510120, China. Tel: +86-20-81887233

E-mail: 2000jiangzhi@163.com (Z. Jiang).

diagnosis, and effective treatment. However, compared with the noncancer population, cancer survivors also had a significantly increased risk of developing cardiovascular diseases, diabetes, and subsequent death.[15,16] This increase may be due to their shared risk factors or comorbid conditions, including obesity, excessive drinking, inactivity, and other metabolic disorders, or complications of adjuvant cancer therapy (chemotherapy or radiotherapy).[6,17-20]

Currently, there is no solid evidence from large-scale cohort studies on the risk of developing diabetes among cancer survivors. Although a number of small studies have reported these significant associations among patients with colorectal cancer, endometrial cancer, breast cancer, Hodgkin lymphoma, and uterine cancer, the results of other studies found no correlations between cancer and subsequent development of diabetes.[21-25] Therefore it is necessary to synthesize the updated evidence through a systematic review to comprehensively assess the relationship between cancer and the subsequent risk of diabetes. In addition, another purpose of this study is to investigate potential adjusted variables, including cancer survival duration, diabetes type, geographic regions, sex, age at diagnosis, methodologic quality, follow-up period, and adjuvant therapy.

METHODS

This study was conducted and reported according to a predefined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[26] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations.[27] The study protocol was registered in PROSPERO (registration number CRD CRD42021233151).

Data sources and searches

We searched PubMed, Embase, and the Cochrane Library using the terms diabetes, cancer/oncology/tumor/neoplasm/malignancy, and cohort/longitudinal/follow-up/prospective/retrospective studies from database inception to 15 December 2020. In addition, we performed hand searches of the reference lists of articles and other published reviews and meta-analyses identified in the primary search. Only articles published in English language journals were included.

The complete search strategy is detailed in Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2021.100218. Three reviewers (YX, ZM, and ZJ) independently screened the identified titles and abstracts, and resolved discrepancies by consensus through reappraisal of the original articles. The full text of each potentially eligible article was then further reviewed based on the prespecified inclusion criteria.

Eligibility criteria

Studies meeting the following criteria were included: (i) use of a population-based cohort study design; (ii) individuals were diagnosed with cancer without a history of diabetes at the time of study enrollment and reported outcomes of new occurrence of diabetes during the subsequent follow-up; (iii) provided the measurement of association using hazard ratio (HR) with 95% confidence intervals (CIs) from the original articles. Non-population-based cohort studies including hospital- or community-based observational studies and those having inadequate data to yield risk estimate for the association between cancer and risk of diabetes were excluded. Studies using other measurements of association including relative risk, odds ratio, incidence rate ratio, or standardized incidence ratio were also excluded.

Data extraction and quality assessment

Study-level participant characteristics were abstracted by two independent investigators (YX and ZM) using the predesigned data extraction forms. Discrepancies between investigators were settled by a senior investigator (ZJ) or through discussion until a consensus was reached. For each study, the data abstracted included first author of the study, year of publication, study design, geographical region, observation period, population characteristics and age at cancer diagnosis, control population, method of diagnosis for cancer and diabetes, main results, and estimates of the association of diabetes with cancer.

Internal validity of each article was assessed independently by two investigators (YX and ZM) and cross-checked using the Newcastle Ottawa Quality Assessment Scale (NOS) for cohort studies,[28] where selected items regarding the representativeness of the patients, ascertainment of exposure and outcomes, and adequacy of follow-up were assessed individually. We presented the overall study quality with a score ranging from 0 to 9 points for each study. We defined a study with a score of 8 or 9 as high-quality study.[20]

Statistical analysis

We conducted all statistical analyses using Stata statistical software (version 15.0; Stata Corporation, College Station, TX). To meta-analyze the effect estimates (HRs) of the study results, we applied random-effects models (the DerSimonian—Laird method), accounting for heterogeneity among studies.[29] The risk estimates (HRs) were transformed into their natural logarithm (log HR), along with their corresponding 95% CIs, and were used to calculate the standard errors for each log HR.[30] Heterogeneity across risk estimates was quantified using the I^2 statistic Cochran's Q test.[31]

Prespecified subgroup analyses were undertaken to investigate the potential sources of heterogeneity stratified by type of diabetes (type 1, type 2, or mixed type), cancer survival duration ($<$1 year, 1-5 years, 5-10 years, or $\geq$10 years), sex (male or female), geographical regions (North America, Europe, Asia, and Australia), patient age at cancer diagnosis ($<$20 years, 20-50 years, or $\geq$50 years), cancer site, follow-up period ($<$5 years, 5-10 years, or $\geq$10 years), matched for age and sex, methodological quality (moderate or high), and adjuvant therapy. In addition, tests for subgroup differences based on random-effects models were performed as recommended by the Cochrane

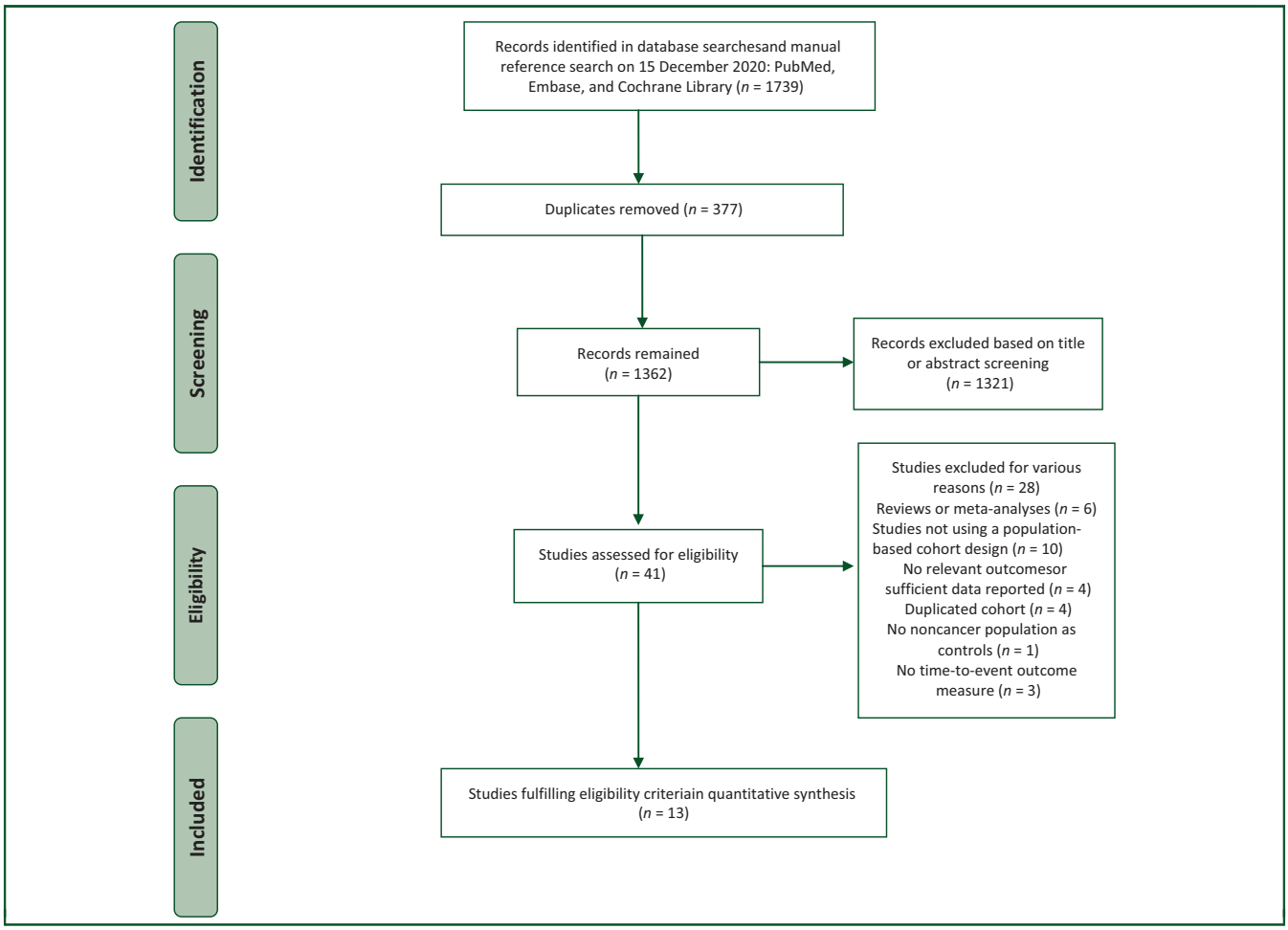

Figure 1. Flow diagram of study selection.

Collaboration.[32] We further tested the possibility of publication bias using visual inspection of funnel plots combined with Begg' and Egger's tests, with a P value <0.1 representing the presence of publication bias.[33] The impact of publication bias on the pooled effect estimates was evaluated using the trim and fill analyses.[34] We carried out a sensitivity analysis by individually omitting each study from the main analyses and rerunning the analyses of other data sets.

RESULTS

Identified studies from literature search

Our preliminary database searches yielded 1739 potentially relevant articles; of these, 377 records were excluded for duplication. Then 1321 irrelevant studies were ruled out during title and abstract screen, resulting in 41 studies for the full-text evaluation (Supplementary Material S2, available at https://doi.org/10.1016/j.esmoop.2021.100218). We finally identified 13 studies involving 1 686 595 participants (621 749 cancer survivors versus 1 064 846 noncancer controls) for quantitative synthesis after further review and removed another 28 studies due to various reasons demonstrated in Figure 1.[21,22,24,25,35-43] Three studies were excluded because they used other measurements of association including relative risk, incidence rate ratio, and odds ratio rather than HR.[23,44,45]

Study characteristics

Baseline characteristics of the 13 included studies are presented in Tables 1 and 2. In summary, 13 studies containing 15 sets of data published between 2011 and 2020 were included for meta-analysis, with 6 studies performed in North America, 2 in Europe, 3 in Asia, and 2 in Australia. All of the included studies had a retrospective design, and 62% (8/13) were of high quality with an NOS score of 8 or 9, whereas 38% (5/13) were of moderate quality (NOS score of 6 or 7). The median sample size of the included studies was 33 093 (range 2264-973 248). Eight of 13 studies enrolled patients with cancer and noncancer individuals matched for important factors such as age and sex. The diagnosis of cancer or diabetes was mostly identified by International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 codes. In addition, six studies used competing risk methodology and the others did not.

METHODOLOGICAL QUALITY ASSESSMENT

In terms of study quality, in general, the NOS scores of all enrolled studies were moderate to high (NOS

Table 1. Characteristics of studies included in the meta-analysis of associations of cancer with subsequent diabetes risk

Authors	Year of publication	Study design	Geographical region	Observation period	Population; age at cancer diagnosis (years)
Wang et al.[35]	2020	A nationwide population-based retrospective cohort study	China, Taiwan	2001-2015	4607 women with primary breast cancer and 23 035 age-matched controls without breast cancer; 58.6
Kim et al.[36]	2020	A population-based cohort study	USA	1996-2012	1520 patients with ovarian cancer and 5709 women from the general population; NR
Kim et al.[22]	2020	A population-based cohort study	USA	1997-2012	2314 endometrial cancer survivors and 8583 women from the general population; 60.5
Hawkins et al.[21]	2020	A population-based cohort study	USA	1997-2013	7114 CRC survivors and 25 979 matched individuals from the general population; 63.7
Ng et al.[38]	2018	A retrospective population-based cohort study	Australia	2003-2014	4278 women with hormone-dependent breast cancer who received endocrine therapy were matched 1 : 10 by age and sex with a control group of women without cancer; ≥55
Ng et al.[39]	2018	A retrospective population-based cohort study	Australia	2003-2014	3689 men with prostate cancer matched by age and sex with comparisons without any dispensing of antineoplastic agents during the study period and without the individual comorbidity of interest evaluated at baseline at a 1 : 10 ratio; ≥65
Lega et al.[40]	2018	A retrospective population-based cohort study	Canada	1990-2010	10 438 1-year childhood cancer survivors. Survivors were matched 1 : 5 by year of birth and sex with individuals in the general population from the Registered Persons Database who did not have a diagnosis of cancer before the index date; <21
Hwangbo et al.[41]	2018	A retrospective population-based retrospective cohort study	Korea	2002-2013	15 130 incident cancer survivors and 479 059 noncancer individuals from the general population; 20-70
Singh et al.[42]	2016	A population-based retrospective cohort study	Canada	2002-2010	39 707 incident CRC cases and 198 535 age- and sex-matched controls (1:5); 69
Chang et al.[43]	2016	A nationwide population-based retrospective cohort study	China, Taiwan	2000-2008	3356 patients with AML and 4400 age-, sex-, and index year-matched controls; 29.9 and 52.7
Van Nimwegen et al.[25]	2014	A population-based cohort study	The Netherlands	2004-2013	2264 5-year Hodgkin's lymphoma survivors in five Dutch University hospitals and cancer centers and controls from Dutch population; 27
Lipscombe et al.[24]	2012	A population-based retrospective cohort study	Canada	1996-2008	24 976 women with newly diagnosed breast cancer and 124 880 women; 68.5
Khan et al.[37]	2011	A population-based retrospective cohort study	UK	1 September 2003 to 31 August 2006	Breast cohort, 16 938 long-term breast cancer survivors and a matched control population of 67 649 from GPRD; 66.9. Prostate cohort, 4207 long-term prostate cancer survivors and a matched control population of 16 709 from GPRD; 74.1. Colorectal cohort, 5068 long-term colorectal cancer survivors and a matched control population of 20 128 from GPRD; 76.1

AML, acute myeloid leukemia; CRC, colorectal cancer; GPRD, UK General Practice Research Database; NR, not reported.

score >5), which indicated a moderately satisfactory quality or low risk of bias. The risk of bias mostly originated from domains regarding the reports of adequacy of follow-up, length of follow-up followed by comparability of cohorts. Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100218 provides a summary of methodological quality assessment and overall risk of bias among the included studies.

Risk of diabetes among cancer survivors

In this meta-analysis assessing a total of 1 686 595 individuals, the pooled HR for the incidence of diabetes was almost 1.4 times higher in cancer survivors than in cancer-free controls (HR 1.39, 95% CI 1.29-1.50; $P < 0.001$). Interstudy heterogeneity was found to be high ($I^2 = 82.3\%$; $P < 0.001$). Every included study revealed that the risk for diabetes was greater in individuals with cancer than in controls (Figure 2).

Table 2. Characteristics of included studies of cancer in relation to risk of diabetes: exposure and outcome assessment, results, and measure of associations

Study	Method of diagnosis; age at onset (years)		Results	Measure of associations; Application of competing risk methodology (yes/no)
	Cancer	Diabetes		
Wang et al.[35]	ICD-9, Clinical Modification coding scheme; 58.6	ICD-9, Clinical Modification code 250; NR	Postmenopausal women with breast cancer were at increased risk of developing diabetes mellitus, independent of receiving hormone therapy.	HR; yes
Kim et al.[36]	SEER International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes; NR	ICD-9 codes; NR	Ovarian cancer survivors had an increased risk of type II diabetes compared with women in the general population.	HR; no
Kim et al.[22]	SEER International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes; 60.5	ICD-9 diagnosis code and date; NR	Endometrial cancer survivors had increased risks of developing both type I and II diabetes in the first year after cancer diagnosis in the general population.	HR; no
Hawkins et al.[21]	The Utah Population Database; 63.7	ICD-9 diagnosis code and date; NR	CRC survivors had a higher risk of experiencing diabetes compared with the general population	HR; no
Ng et al.[38]	The World Health Organization Anatomical Therapeutic Chemical code and PBS schedule item codes; most $\geq$55	The RxRisk-V model; NR	Comorbid conditions including diabetes were more likely to develop in women who had been diagnosed with hormone-dependent breast cancer than in women without cancer.	HR; no
Ng et al.[39]	The World Health Organization Anatomical Therapeutic Chemical code and PBS schedule item codes; most $\geq$65	The RxRisk-V model; NR	Men with prostate cancer treated with androgen-deprivation therapy had a higher likelihood of developing new comorbidities including diabetes than general populations who did not receive androgen-deprivation therapy.	HR; no
Lega et al.[40]	Ontario Cancer Registry; International Classification of Childhood Cancer; <21	ICD-9 and ICD-10 diagnosis code combinations of physician billing claims and hospitalizations over various periods; NR	Cancer survivors had a 55% increased rate of developing diabetes compared with matched controls.	HR; yes
Hwangbo et al.[41]	ICD-10 and the Korean Drug and Anatomical Therapeutic Chemical Codes; 20-70	ICD-10 codes; ICD-10 codes at least two times, or a diabetes drug code plus an ICD-10 code; NR	Cancer survivors had an increased risk of developing diabetes.	HR; yes
Singh et al.[42]	Ontario Cancer Registry; 69	ICD9 250.x and ICD8 250.x; "2-claim" (one HDA or two PSCs within 2 years showing diabetes); NR	Patients with CRC were statistically significantly more likely to develop subsequent diabetes than persons without CRC for up to 5 years after the diagnosis.	HR; yes
Chang et al.[43]	ICD-9, Clinical Modification; 52.7	ICD-9-CM code 250; NR	Compared with the normal population, acute myeloid leukemia survivors had higher rates of diabetes	HR; no
Van Nimwegen et al.[25]	The hospital tumor registries in five Dutch University hospitals and cancer centers; 27	From medical records and by contacting general practitioners of all patients; NR	HL survivors who were treated with $\geq$36 Gy to the PAO fields had a 2.58-fold increased risk of developing diabetes compared with the general population	HR; yes
Lipscombe et al.[24]	The Ontario Cancer Registry; 68.49	Based on the diabetes status from the Ontario Diabetes Database, a validated registry of Ontarians with diabetes; NR	A modest increase in the incidence of diabetes among postmenopausal breast cancer survivors was found that varied over time.	HR; yes
Khan et al.[37]	The longitudinal primary care records of cancer survivors from the UK General Practice Research Database; 66.9, 74.1, and 76.1	The longitudinal primary care records from the UK General Practice Research Database; OXMIS codes; NR	The study confirms the occurrence of increased incidence of chronic illnesses including diabetes in long-term cancer survivors attributable to underlying lifestyle and/or cancer treatments.	HR; no

CRC, colorectal cancer; HDAs, hospital discharge abstracts; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; NR, not reported; PAO, para-aortic; PBS, the Pharmaceutical Benefits Scheme; PSCs, physician service claims; SEER, Surveillance, Epidemiology, and End Results Program.

Subgroup analysis

Given the significant heterogeneity in the meta-analysis of all the included studies, we performed preplanned exploratory subgroup analyses to better account for the potential heterogeneity. When stratified by diabetes types, cancer survivors appeared to have an increased risk for both type 2 diabetes (HR 1.60, 95% CI 1.16-2.20) and mixed type

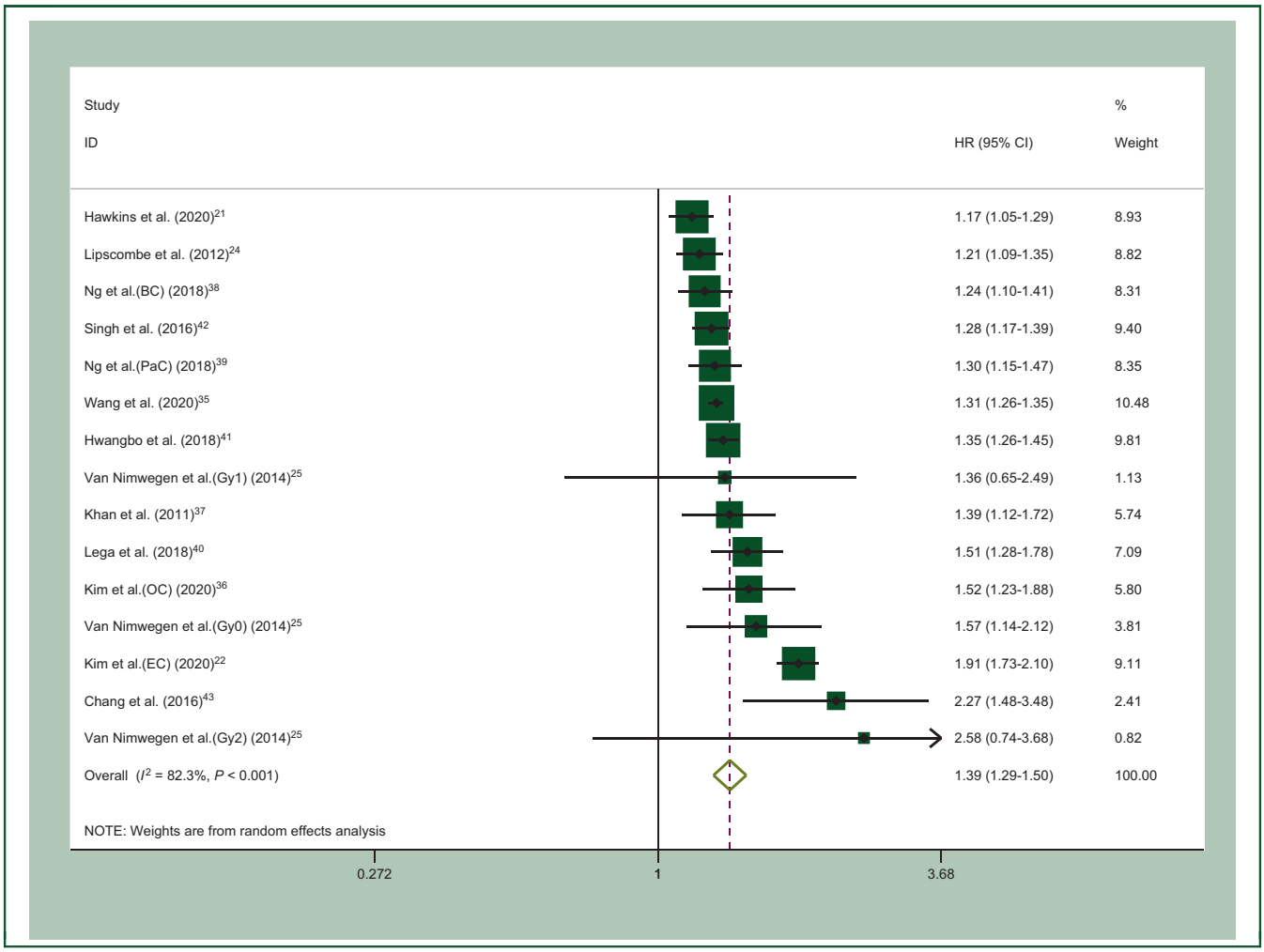

Figure 2. Hazard ratio (HR) for association of developing diabetes with cancer.

(HR 1.32, 95% CI 1.24-1.40) compared with noncancer individuals. For cancer types, the HRs were significantly increased for individuals diagnosed with breast cancer (1.29, 95% CI 1.21-1.38), hematological cancer (HR 1.83, 95% CI 1.57-2.14), gynecologic cancer (HR 1.54, 95% CI 1.21-1.97), colorectal cancer (HR 1.22, 95% CI 1.11-1.34), and urinary tract cancer (HR 1.83, 95% CI 1.37-2.44), but not with central nervous system cancer (HR 1.23 95% CI 0.80-1.88) or prostate cancer (HR 1.07, 0.67-1.68) compared with cancer-free controls. Data were available from less than two data sets for HRs of other cancer types, providing insufficient statistical power to draw strong conclusions within these caner types.

The increased risk remained constant among other subgroups stratified by cancer survival duration, geographic regions, matched for important variables, sex, age at cancer diagnosis, methodologic quality, follow-up period, and adjuvant therapy (Table 3 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100218). Moreover, the results of subgroup analyses showed significant between-group differences by cancer survival duration (P for between-group difference = 0.009). No significant between-group difference was found for diabetes type, age at cancer diagnosis, geographic regions, follow-up period, matched for age and sex, sex, methodologic quality, adjuvant therapy, or effect estimate (all P >0.05).

In addition, heterogeneity was high in the analysis of subgroups with cancer survival duration <1 year (I^2 = 96%) and 1-5 years (I^2 = 79.6%), but was not detected in the 5-10 years (I^2 = 0.0%) or ≥10 years study group (I^2 = 0.0%). Similarly, heterogeneity was also high in the subgroups of North America (I^2 = 92.2%) and Asia (I^2 = 70.4%), age at diagnosis ≥50 years (I^2 = 88.8%), follow-up period 5-10 years (I^2 = 35.7%), and no adjuvant therapy (I^2 =94.3%), but was not detected in the subgroups of Europe (I^2 = 0.0%) and Australia (I^2 = 0.0%), age at diagnosis ranging from 20 to 50 years (I^2 = 9%), and follow-up period <5 years (I^2 = 0.0%) or >10 years (I^2 = 0.0%).The subgroup analysis indicated that cancer survival duration, geographic region, age at diagnosis, follow-up period, and adjuvant therapy contributed to such heterogeneity and could be regarded as the potential sources of heterogeneity.

Table 3. Subgroup analyses for the effect of diagnosed cancer on risk of subsequent diabetes

Variables	HR	95% CI	I^2 (%)	Number of studies	*P* value for subgroup differences (random-effects model)
Overall	1.39	1.29-1.50	82.3	13	NA
Cancer survival duration, years					0.009
<1	2.09	1.32-3.32	96	4	
1-5	1.25	1.18-1.33	79.6	6	
5-10	1.26	1.20-1.32	0	3	
≥10	1.25	1.19-1.31	0	3	
Diabetes type					0.144
Type 1	1.93	1.03-14.97	—	1	
Type 2	1.60	1.16-2.20	96.1	3	
Mixed	1.32	1.24-1.40	49.7	10	
Geographic regions					0.366
North America	1.41	1.19-1.67	92.2	6	
Europe	1.48	1.25-1.75	0	2	
Asia	1.36	1.24-1.49	70.4	3	
Australia	1.27	1.16-1.39	0	2	
Matched for age and sex					0.408
Yes	1.34	1.23-1.46	58.6	8	
No	1.44	1.24-1.67	92.7	5	
Sex					0.707
Male	1.28	1.06-1.55	72.8	4	
Female	1.33	1.20-1.48	79.5	8	
Age at diagnosis, years					0.586
<20	1.51	1.28-1.78	—	1	
20-50	1.39	1.24-1.56	9.0	2	
≥50	1.36	1.23-1.51	88.8	9	
Methodologic quality (NOS)					0.446
Moderate (6-7)	1.44	1.20-1.72	93.4	5	
High (≥8)	1.34	1.25-1.43	47.3	8	
Follow-up period, years					0.077
<5	1.31	1.27-1.35	0	3	
5-10	1.30	1.20-1.41	35.7	3	
>10	1.54	1.34-1.77	0	2	
Adjuvant therapy					0.649
Yes	1.22	1.16-1.28	14.2	3	
No	1.25	1.11-1.42	94.3	2	

CI, confidence interval; HR, hazard ratio; NA, not available; NOS, Newcastle—Ottawa Scale.

Sensitivity analyses and publication bias

To assess the stability of our results, we also performed sensitivity analyses by omitting each study at a time and reanalyzing the others. The pooled HRs all remained similar across these analyses (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100218). The contour-enhanced funnel plot revealed that some studies were located in both significant and nonsignificant regions (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100218), indicating that the asymmetry of funnels might originate more from heterogeneity than publication bias. Although Begg's test ($P = 0.067$) indicated a slight publication bias, the trim-and-fill method applied to adjust for potential publication bias revealed five theoretical missing study (data were almost unchanged for the main analysis; adjusted HR 1.30, 95% CI 1.19-1.42), indicating that small-study effects, such as publication bias or study selection bias, did not substantially influence the main result.

DISCUSSION

Principal findings

The results of this meta-analysis by pooling data from 13 population-based cohort studies suggest that cancer survivors were associated with a relatively higher risk of subsequent diabetes. Our findings show that the pooled HR for diabetes among cancer survivors was 1.4 times higher than that of the general population. This risk remains elevated for most of the investigated cancer types. These effects were more prominent in cancer survivors with a shorter cancer survival duration (<1 year). Moreover, cancer survivors with a longer follow-up period (>10 years) had a relatively higher risk of diabetes than those with a shorter follow-up period.

Comparison with other studies

Our findings are similar to the result from a recent published conference abstract, suggesting a higher prevalence of type 2 diabetes among childhood cancer survivors compared with that of the cancer-free controls.[46]

However, our study was relatively weaker than this pooled analysis of 40 observational studies, which suggested 4.5 times higher risk of type 2 diabetes. The weaker association found in our study might be due to the inclusion of large-power cohort studies involving the general populations for analysis.

We included 12 cohort studies with adult populations, which yielded weaker associations. We also found the risk

was more obvious in the first period of cancer survivorship (<1 year), showing a 109% increased risk of cancer (Table 3). The findings are mostly consistent with the study by Lipscombe and colleges,[24] who had also put forward a point of view that adjuvant therapy could play a pivotal role in the incidence of diabetes, especially during the first 1-2 years after cancer diagnosis.

Potential mechanisms

The underlying mechanism for a significantly increased risk of developing diabetes among cancer survivors remains unclear. It has been reported that metabolic disorders, including insulin resistance, hyperinsulinemia, oxidative stress, inflammation, and changes in hormones, may be present more than 10 years earlier than the onset of diabetes.[47] This may explain one of the potential mechanisms for the increased incidence of diabetes after the diagnosis of many types of cancer. As a result, cancer survivors may be a special group in the early stages of metabolic disorders, and thus their risk of developing diabetes may be significantly increased. Furthermore, a large number of cancer survivors have hypercholesterolemia and are treated with statins, which can increase their risk of hyperglycemia or even new-onset diabetes. The mechanism of statin-induced diabetes, by contrast, remains unknown.

The elevated risk of diabetes after diagnosis of cancer may be associated with therapeutic interventions for the treatment of cancer. Corticosteroids, a commonly used adjuvant medication for cancer chemotherapy, are reported to contribute to hyperglycemia, insulin resistance, and subsequent diabetes development mainly through the mediation effect of decreased insulin sensitivity.[48] Studies have shown that adjuvant therapy containing corticosteroids can lead to hyperglycemia or diabetes in patients with several hematological malignancies.[49,50] Moreover, the synergistic effect of chemotherapy agents and corticosteroids may have a great impact on the risk of diabetes.

However, the consequences of endocrine disruption associated with other chemotherapy agents have not been completely made clear, and further research is needed to demonstrate their effects on the risk of diabetes.[51] Based on the subgroup analyses of our study, the elevated risk of diabetes seemed to be highest in the first year after cancer diagnosis, which further suggested the impact of the treatment toxicity of chemotherapy on the development of subsequent diabetes.

The increased risk of diabetes can also be induced by the cancer itself. More than 50% of patients with advanced cancer may experience cancer cachexia, a syndrome characterized by loss of weight, appetite, and muscle, leading to increased risk of fatigue, functional disorders, treatment-related toxicity, poor clinical outcomes, and diabetes.[52] Moreover, patients with cancer are more susceptible to metabolic disorders induced by some cachectic-related cytokines such as interleukin 6 and tumor necrosis factor alpha.[53,54] Besides, acute events will occur more frequently in patients with cancer, including surgery, infection, bleeding, and acute illness, which may lead to stress hyperglycemia. Acute hyperglycemia or stress-induced hyperglycemia is reported to be one of the risk factors for subsequent development of diabetes later.[55]

We found the risk of diabetes appeared to peak during the first year after the diagnosis of cancer, as suggested by the summary risk estimates through stratified analyses by cancer survival duration (Table 3). We put forward a theoretical hypothesis accordingly: many tumors develop relatively more rapidly within 1 year after the initial diagnosis, and patients with cancer are more likely to receive adjuvant therapy during this period, which may frequently lead to adjuvant treatment—related endocrine disruption such as hyperglycemia, which may in turn increase the risk of developing diabetes. Although the risk decreases slightly after 1 year or even 10 years after the termination of cancer-related treatment, the risk of developing diabetes persists among these survivors. However, more robust clinical evidence should be provided before we confirm this hypothesis in the future. Nevertheless, our findings still suggest that a blood glucose level or HbA1c test should be performed earlier to detect the presence of diabetes in cancer survivors. Cooperation and working with multidisciplinary teams will be important for oncologists and endocrinologists in the future.

Implications

Our study also has some implications for future clinical practice, which estimates an approximate risk (HR 1.39, 95% CI 1.29-1.50) of developing subsequent diabetes in cancer survivors. Early assessment of the risk of metabolic abnormalities and effective interventions has important clinical significance for the prevention and treatment of metabolic disorders such as hyperglycemia, obesity, and metabolic syndrome. Furthermore, cancer-related metabolic disorders are frequently overlooked, despite being a significant clinical issue that must not be overlooked. Nevertheless, the optimal management strategies for cancer-related metabolic disorders for patients with cancer have not been established. Because high-quality evidence could not be provided for physicians, endocrinologists can simply think about taking specific preventive measures based on the history of adjuvant therapy for patients with cancer, the potential mechanisms for the specific endocrine disorders, and the mode of institutional practice. One of the most important findings of this analysis indicated that oncologists should not only focus on cancer treatment, but also on the likely onset of new diseases, such as diabetes mellitus and other related metabolic disorders.

Strengths and limitations

To the best of our knowledge, this study is the first quantitative synthesis of data from cohort studies with respect to the effect of cancer status on the risk of subsequent diabetes. As a matter of fact, the majority of the included studies were from high-quality databases with long-term follow-up periods, which were controlled for a wide range

of potential measured and unmeasured confounders to minimize the recall bias. We conducted multiple subgroup analyses using the largest sample size until now regarding this topic, and the effect of different patterns (such as cancer survival duration, diabetes type, sex, and age) of association between cancer and risk of diabetes had been thoroughly examined.

There are several other notable strengths for this study. First, this study involves all of the published population-based studies with the largest representative populations across the world regarding diabetes incidence in cancer survivors, most of which were from nationwide coverage of total population so that it can provide the most comprehensive and up-to-date evidence on the association between of cancer and subsequent diabetes risk. Second, we have developed sensitive search strategies of three major databases with no limit to search date, making it unlikely to miss important publications, thereby minimizing the potential effect of publication bias on the main findings. Third, we applied a critical methodological quality assessment tool to evaluate the quality of the included studies using the NOS checklist recommended by the Cochrane handbook. Fourth, several analytical approaches including subgroup analyses and leave-one-out sensitivity analyses have been used to explore the sources of heterogeneity based on the abstracted study characteristics. The results remained similar to that of the main analysis, and the trim-and-fill method revealed no potential for missing studies, confirming the robustness of the result.

We should still acknowledge the limitations when interpreting the results of our study. First, we observed high heterogeneity among the included studies, which is expectable and can be explained in several aspects in terms of the differences among population characteristics (age at cancer diagnosis, sex, geographic region, cancer site, etc.), treatment exposure (chemoradiotherapy or hormonal therapy), study design (data sources), and analytical methods (different adjustments for confounders), which were indicated by subgroup analysis. We have discussed that the potential mechanisms of these cancer-related metabolic disorders and the risk of subsequent diabetes as a consequence of specific treatments are varied in specific cancer types. Although we adjusted the results using several sensitivity analyses, significant heterogeneity remained similar. Nevertheless, we noted that the results of most subgroup analyses and sensitivity analyses are highly in line with those of the main analysis. Therefore we consider that the inherent heterogeneity has little effect on the overall results. Meanwhile, we applied the trim-and-fill method to adjust for potential publication bias and found that the adjusted estimate (HR 1.30, 95% CI 1.19-1.42) remains constant with the primary analysis (HR 1.39, 95% CI 1.29-1.50), indicating the robustness of the main result.

Second, because the individual patient data of all the included studies were not available, we could not conduct further subgroup analyses; for example, the effect of different chemotherapy treatment and radiation dose on the risk of diabetes development. Furthermore, treatment duration and intensity varied significantly across cancer stages and cancer types, potentially leading to varying degrees of treatment-induced toxicities and treatment duration time. We attempted to investigate this association. Nonetheless, no adequate data could be extracted for further analysis from the included studies. Another significant limitation for this study is the insufficient data collection regarding the cancer and diabetes diagnosis using the ICD-9 coding without including data on the target therapy and immune checkpoint inhibitor (ICI) therapy. The lack of ICI therapy information among studies published in the recent few years limits our analysis of the effect of this variable on the risk of diabetes. Because of the widespread use of target therapy and ICI, such as programmed cell death protein 1 inhibitors among cancer survivors, ICI-induced insulin-dependent diabetes is becoming one of the most common complications. Endocrinopathy, including diabetes (hyperglycemia), is expected to become a major issue for cancer survivors in the near future.

Third, for subgroup analyses based on cancer type, we found a nonsignificant result for patients with prostate cancer and central nervous system cancer, which may be due to a relatively small sample size (only two data sets pooled) with low statistical power. Therefore further large prospective cohort studies regarding the effect of cancer on subsequent diabetes risk are warranted. Finally, only published studies rather than unpublished gray literature were used in the analysis, which could have led to publication bias in that studies with positive findings were more likely to be published than those with negative results. However, the risk estimates of multiple subgroup analyses, sensitivity analyses, and the trim-and-fill method for the adjustment of the summary HR all remained similar, further confirming the robustness of the results; nevertheless, we should exercise caution when interpreting the findings.

Conclusions

In summary, this pooled analysis of population-based cohort studies showed that cancer survivors are more likely to have an increased risk of subsequent diabetes. Multiple subgroup analyses based on some baseline factors confirm that this association remained stable, which is also biologically plausible. However, we should still exercise caution when interpreting the results. We advocate for high-level evidence from large prospective cohort studies to further prove causality.

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DISCLOSURE

The authors have declared no conflicts of interest.

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