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Cardiovascular disease risk in cancer survivors: a population-based cohort study from the UK Biobank, and meta-analysis of cohort studies

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ABSTRACT

Introduction In addition to the well-recognised cardiotoxicity of cancer treatment, possible aetiological links between cancer diagnosis and cardiovascular disease (CVD) have gained growing research interests. We aimed to estimate the CVD burden among cancer survivors and illustrate population-level associations between these two conditions.

Methods We first conducted a prospective cohort study in the UK Biobank and a meta-analysis of previous population-based cohorts. HRs were estimated in the cohort study to evaluate the effect of cancer diagnosis on the subsequent risk of CVD compared with that of non-cancer individuals. We then systematically searched Pubmed, Embase and Cochrane Library to retrieve previous cohorts. Random-effect meta-analysis was performed to pool relative risk estimates. A combination of multiple statistical metrics was employed to appraise the evidence.

Results A total of 39 755 811 participants (5 898 597 cancer survivors vs 33 857 214 cancer-free controls) were identified in our study. In the cohort study, a 51% higher hazard of CVD risk was found among cancer survivors (95% CI 1.48 to 1.55, p<0.001). The hazard decreased to 29% after adjusting competing risk. The meta-analysis identified 104 published cohorts. We found a 1.34-fold increased CVD risk among patients with cancer (95% CI 1.22 to 1.47, p<0.001). The association remains significant among multiple cancer sites and multiple CVD subtypes. This association was consistent, irrespective of chemo or radiotherapy use. Evidence appraisal identified one convincing association between hematologic/lymphatic malignancies and ischaemic heart disease, along with 29 highly suggestive associations.

Conclusions Our study provided comprehensive estimates of CVD incidence in cancer survivors and identified a significantly elevated CVD risk among patients with cancer, regardless of chemotherapy or radiotherapy. These findings underscore the need for routine assessment of CVD risk factors at cancer diagnosis to enhance the well-being and survival of patients with cancer.

PROSPERO registration number CRD42022307056

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Shared aetiology of cancer and cardiovascular disease (CVD) has been revealed, but the existing evidence remains inconclusive.
⇒ No comprehensive meta-analyses assessing the risk of CVD among cancer survivors have been performed in recent years.
⇒ Evidence classification is warranted considering the evidence base of multiple subtypes of CVDs and cancers.

WHAT THIS STUDY ADDS

⇒ Population-based estimates of CVD incidence were provided for patients of various cancers.
⇒ Cancer survivors are subjected to a significantly increased CVD risk.
⇒ Strong evidence was identified for the association between hematologic/lymphatic cancer and higher CVD risk with a sufficient amount of evidence and no hints of biases.

HOW THIS THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Oncologists and cardiologists should collaborate closely in monitoring CVD risk for cancer survivors at their cancer diagnosis. Cardioprotective strategies should be considered for patients receiving systemic or radiotherapy to balance therapeutic effects and increased CVD risk.

INTRODUCTION

Cancer and cardiovascular disease (CVD) remain two of the leading causes of death worldwide, accounting for an estimated 18 and 10 million deaths, respectively, and have been imposing a heavy burden on human well-being and healthcare systems.[1 2] Historically, these two conditions have been treated as separate entities. With the advance of cancer treatment, cardiotoxicity of common treatment modalities such as chemo and

radiotherapy has been widely recognised, and cardio-oncology, as an emerging interdisciplinary field, gained more and more interest among oncologists and cardiologists.[3 4] In addition, biological evidence has shed light on the shared risk factors, such as obesity,[5] dyslipidaemia[6] and lifestyle,[7] which may play key roles in the complex interplay between cancer and CVD.

Despite the wealth of mechanistic evidence, the epidemiologic association composed of both treatment effect and etiological link has not been well studied, resulting in inclusive population-level evidence thus far. Previous studies observed an elevated CVD risk among individuals after cancer diagnosis,[8 9] while other investigations reported a decreased CVD risk.[10–12] These seemingly contradictory findings could be attributed to limited sample sizes and varied sources of biases, for example, biased estimates of CVD risk in hospital-based selection of patients with cancer.[13 14] There has been a dearth of systematic summaries and critical appraisal of published evidence.

Herein, we first reported a prospective population-based cohort study, which estimated the absolute CVD risk among cancer survivors and the relative risk compared with the general population. We then conducted a systematic review with evidence triangulation in pursuit of a comprehensive assessment on CVD risk among cancer survivors.

MATERIALS AND METHODS

Study population for the cohort

UK Biobank is a large-scale prospective study that recruited over 500 000 participants from 40 to 69 years of age during 2006–2010. It received ethics approval from the North West-Haydock Research Ethics Committee (21/NW/0157) and obtained written informed consent from all participants prior to the study. This study was conducted under UK Biobank Research Application ID 73759. The detailed description can be found in the online supplemental methods.

We identified patients with cancer incidence using the International Classification of Diseases (ICD) 10th edition (ICD-10) codes C00 to C97 and ICD-9 codes 1400 to 2089 recorded in cancer registries and hospital inpatient data. Follow-up information was retrieved through linkage to hospitalisation records and death registries up to 1 July 2021. The primary outcome was defined as an incident CVD event or CVD-related death (any ischaemic heart disease, cerebrovascular disease, emboli/thrombosis, heart failure, arrhythmia/conduction disorder or a composite of these endpoints) based on the corresponding ICD-10 codes (online supplemental table 1). Patients with missing cancer diagnosis date or with CVD history before cancer diagnosis were excluded. In order to control possible selection bias, we only included incident CVD events documented after the index date. Other essential characteristics such as sociodemographic, lifestyle, anthropometric factors, comorbidities and drug intake data were also obtained as covariates (online supplemental methods).

Meta-analysis

The meta-analysis was performed and reported adhering to the Cochrane Handbook for Systematic Reviews, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline and the Meta-analysis of Observational Studies in Epidemiology guideline.[15–17] The study was registered on PROSPERO (CRD42022307056).

We searched Pubmed, EMBASE and Cochrane Library databases without language limitations from inception to 1 July 2022 by using a structured search strategy including key words of ‘cancer’, ‘cardiovascular’ and ‘population-based studies’ (online supplemental table 2).

Two reviewers (CS and BY) examined the retrieved records of titles and abstracts based on the inclusion criteria below: (1) population-based cohort studies with prospective or retrospective study design that compared CVD risk in patients with cancer with risk in cancer-free individuals; (2) studies reporting relative effect estimates including risk ratio (RR), HR, OR or standardised incidence rate (SIR) with their 95% CIs or with numbers of events where the RRs can be calculated. We excluded hospital-based studies, cohorts conducted using the same database with overlapped time spans (the latest study was included); studies with participants reporting CVD event prior to cancer diagnosis; studies focusing on childhood cancers or studies with inadequate data. Any discrepancies regarding study selection or data abstraction were resolved by discussion with another senior investigator (YH). Characteristics of each included study were extracted independently using a standardised form by two reviewers (CS and XW) (online supplemental methods).

Statistical analysis

For the cohort study, we compared the distributions of essential characteristics between the cancer and cancer-free groups. The absolute CVD event rate was estimated by person-years among survivors of various cancers. We fitted Cox proportional hazard models to estimate the association between cancer diagnosis and subsequent CVD risk rate adjusting for three sets of covariates (online supplemental methods). The effect estimates were expressed using HRs with 95% CIs, and the proportional hazard assumption was tested using Schoenfeld residuals.[18] When the assumption was violated, a stratification analysis was conducted.[19] Given that patients with cancer were subjected to non-CVD-related deaths prior to CVD occurrence, which incurred competing risk biases, we also conducted a survival analysis by modelling subdistributions of cumulative incident rates of competing risk events using a Fine-Gray model.[20] We analysed the associations in subgroups of age, sex, cancer sites, CVD subtypes, study design and treatment regimen. An interaction test provided by Altman was performed to evaluate the difference of effect estimates between the

two subgroups.[21] Cancer types with over 1000 cases from the UK Biobank were investigated to ensure adequate statistical power. Sensitivity analysis was performed by investigating only incident cancer cases—patients diagnosed after the index date—to control possible 'healthy volunteer' effects.[22] Mediation analyses were performed to examine whether the association between cancer and CVD was mediated by social connection factors,[23] with technical details presented in online supplemental methods.

We performed a DerSimonian-Laird random-effect meta-analysis to generate pooled estimates of relative risks in consideration of the inherent heterogeneity across different studies.[24] HRs, RRs, ORs and SIRs were extracted as study metrics. Given the relatively low prevalence of case, evidence demonstrated that RRs could be acceptably approximated by these metrics.[25 26] Fully adjusted effect estimates were employed for each included study and the pooled estimates were presented with RRs. Heterogeneity across studies was examined using Cochran's Q and I^2 statistic (>50% was deemed as large heterogeneity).[27] Funnel plot symmetry combined with an Egger's test was used to assess possible small study effects when over 10 studies were included in the meta-analysis.[28 29] Subgroup meta-analyses were also performed based on age, cancer sites, CVD subtypes, treatment regimen and study metrics. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were conducted using Stata (V.16.0; Stata Corp LP, College Station) and R (V.4.2.1; R Foundation for Statistical Computing).

Critical appraisal and evidence triangulation

We assessed the risk of bias for each study included in the meta-analysis using the Newcastle–Ottawa scale (NOS) tool. Nine scores were assigned to three domains, with the NOS scores of 8 to 9, 6 to 8 and ≤5 for low, moderate and high risk of bias, respectively. We performed sensitivity analysis by only including studies with a low risk of bias. For the meta-analysis results, we appraised the evidence using our previously published criteria comprised of multiple statistical metrics including the amount of evidence, statistical significance, heterogeneity, small-study effect, excess significance and 95% prediction interval[30] (details in online supplemental methods). Based on that, we graded the evidence into four categories, namely convincing (class I), highly suggestive (class II), suggestive (class III) and weak (class IV) evidence.

Patient and public involvement

The analyses were based on a population-based cohort, UK Biobank and a meta-analysis of previously published studies. Since we did not participate in the participant recruitment of the UK Biobank cohort, and the meta-analysis used secondary data, patients and the public were not involved in the planning, design and implementation of the study. No patients were asked to advise on interpretation or writing up of the manuscript.

RESULTS

Cohort study in the UK Biobank

Among the 447 338 patients included in our study (Diagram of patient selection in figure 1A), 64 578 (14.4%) CVD events were observed within a median of 12.06 years of follow-up, and 13 549 of non-CVD deaths were documented. Distributions of essential characteristics between patients with cancer and cancer-free individuals are presented in table 1, while the crude incidence rate (per 1000 person-years) of CVD subtypes among multiple cancer sites is found in online supplemental table 3.

We observed a higher CVD incidence among cancer survivors compared with cancer-free individuals (20.08 vs 11.72 per 1000 person-years). Effect estimates from multivariable Cox and competing risk models adjusting

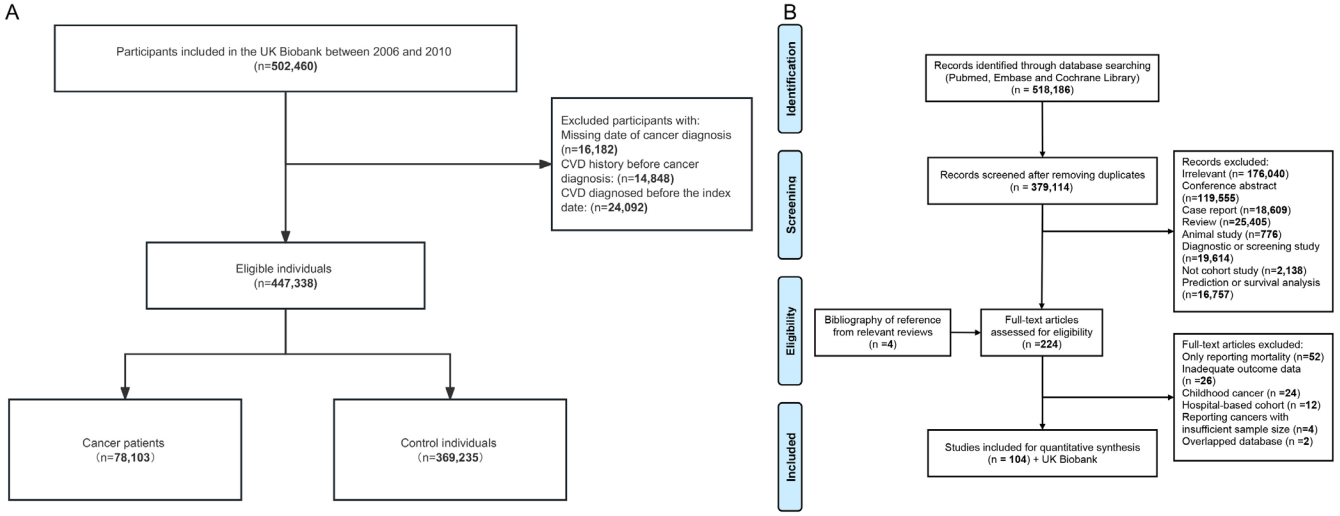

Figure 1 (A) Diagram for participant selection in the UK Biobank. (B) Diagram for study selection of the systematic review and meta-analysis. CVD, cardiovascular disease.

Table 1 Baseline characteristics of participants included from the UK Biobank stratified by the status of cancer diagnosis

Characteristics	Cancer patients (N=78 103)	Non-cancer individuals (N=369 235)
Follow-up time, mean (SD), years	9.18 (8.36)	11.60 (2.52)
Age at the index date, mean (SD), years	59.59 (7.04)	55.24 (8.10)
Sex, number (%)		
Female	34 750 (44.49%)	208 043 (56.34%)
Male	43 353 (55.51%)	161 192 (43.66%)
Race, number (%)		
British	70 978 (90.88%)	322 013 (87.21%)
Others	7032 (9.00%)	46 527 (12.6%)
Unknown	93 (0.12%)	695 (0.19%)
Townsend deprivation index, mean (SD)	−1.48 (3.01)	−1.28 (3.09)
Body mass index, mean (SD), kg/m^2	27.34 (4.68)	27.30 (4.77)
Aspirin intake, number (%)		
Yes	9529 (12.20%)	36 934 (10.00%)
No	66 941 (85.71%)	324 475 (87.88%)
Unknown	1633 (2.09%)	7826 (2.12%)
Smoking status, number (%)		
Never	39 842 (51.01%)	209 091 (56.63%)
Ever	37 823 (48.43%)	158 072 (42.81%)
Unknown	438 (0.56%)	2072 (0.56%)
Alcohol status, number (%)		
Never	3036 (3.89%)	16 664 (4.51%)
Ever	74 865 (95.85%)	351 328 (95.15%)
Unknown	202 (0.26%)	1243 (0.34%)
Hypertension, number (%)		
Yes	46 613 (59.68%)	165 544 (44.83%)
No	31 490 (40.32%)	203 691 (55.17%)
Diabetes, number (%)		
Yes	4111 (5.26%)	16 403 (4.44%)
No	73 992 (94.74%)	352 832 (95.56%)
Dyslipidaemia, number (%)		
Yes	52 410 (67.10%)	235 377 (63.75%)
No	25 693 (32.90%)	133 858 (36.25%)
CVD incidence, number (%)		
Yes	14 391 (18.43%)	50 187 (13.59%)
No	63 712 (81.57%)	319 048 (86.41%)

CVD, cardiovascular disease; SD, standard deviation.

for different sets of covariates are summarised in online supplemental table 4. With the fully adjusted Cox model, we observed a 51% increased CVD risk (HR 1.51, 95% CI 1.48 to 1.55) for all patients with cancer compared with the cancer-free individuals. In particular, increased CVD risk was identified among patients with prostate, colorectal, lung, hematologic/lymphatic, bladder, head and neck, renal, ovary and uterus cancer, with the largest 6.85-fold increased hazard in lung cancer (95% CI 6.33 to 7.41). No significantly elevated CVD risk was found among patients with breast cancer or melanoma. As for specific CVD events, an increased risk was consistently observed in most studied cancers except for breast cancer. Effect estimates on CVD risk from competing risk models tended to be smaller in size compared with estimates from Cox models, with a 29% higher CVD risk observed in cancer survivors (HR 1.29, 95% CI 1.26 to 1.32). The effect estimates from multivariable models with different sets of covariates are presented in online supplemental table 5. By testing Schoenfeld residuals, we found that the proportional hazard assumption might be violated for variables including sex, smoking status, hypertension, dyslipidaemia and aspirin intake. Stratification analyses for these variables observed similar effects of cancer diagnosis on CVD risk (details in online supplemental table 6).

The findings of subgroup analyses are also presented in online supplemental table 6. We found significantly larger effects of increased CVD risk in male patients, patients with age <65 years, patients with no history of aspirin intake, and patients without diabetes or hypertension. A smaller HR was observed among patients with cancer without chemo or radiotherapy compared with those who received therapy (p for interaction <0.001), although they were still subjected to an increased CVD risk in comparison to cancer-free individuals (HR 1.22, 95% CI 1.19 to 1.25). In sensitivity analysis, we only included patients with cancer diagnosed after the index date, and a similar increased risk of CVD was observed (HR 2.74, 95% CI 2.69 to 2.81) among them.

Mediation analysis showed that social connection factors, including the absence of leisure/social activities and lower frequencies of ability to confide, were identified as possible mediators between cancer and CVD risk, but the proportions of effects mediated were small (0.297% for leisure/social activities and 0.578% for the ability to confide, details in online supplemental table 7.

Meta-analysis

The literature search identified a total of 379 114 eligible hits and after reviewing their titles and abstracts, 224 potentially relevant studies were retained for full-text review (diagram in figure 1B). At last, our meta-analysis included 104 studies and the UK Biobank, which involved a total of 39 755 811 participants (5 898 597 cancer survivors and 33 857 214 cancer-free individuals). Moreover, 5 046 993 CVD events were documented, with 610 429

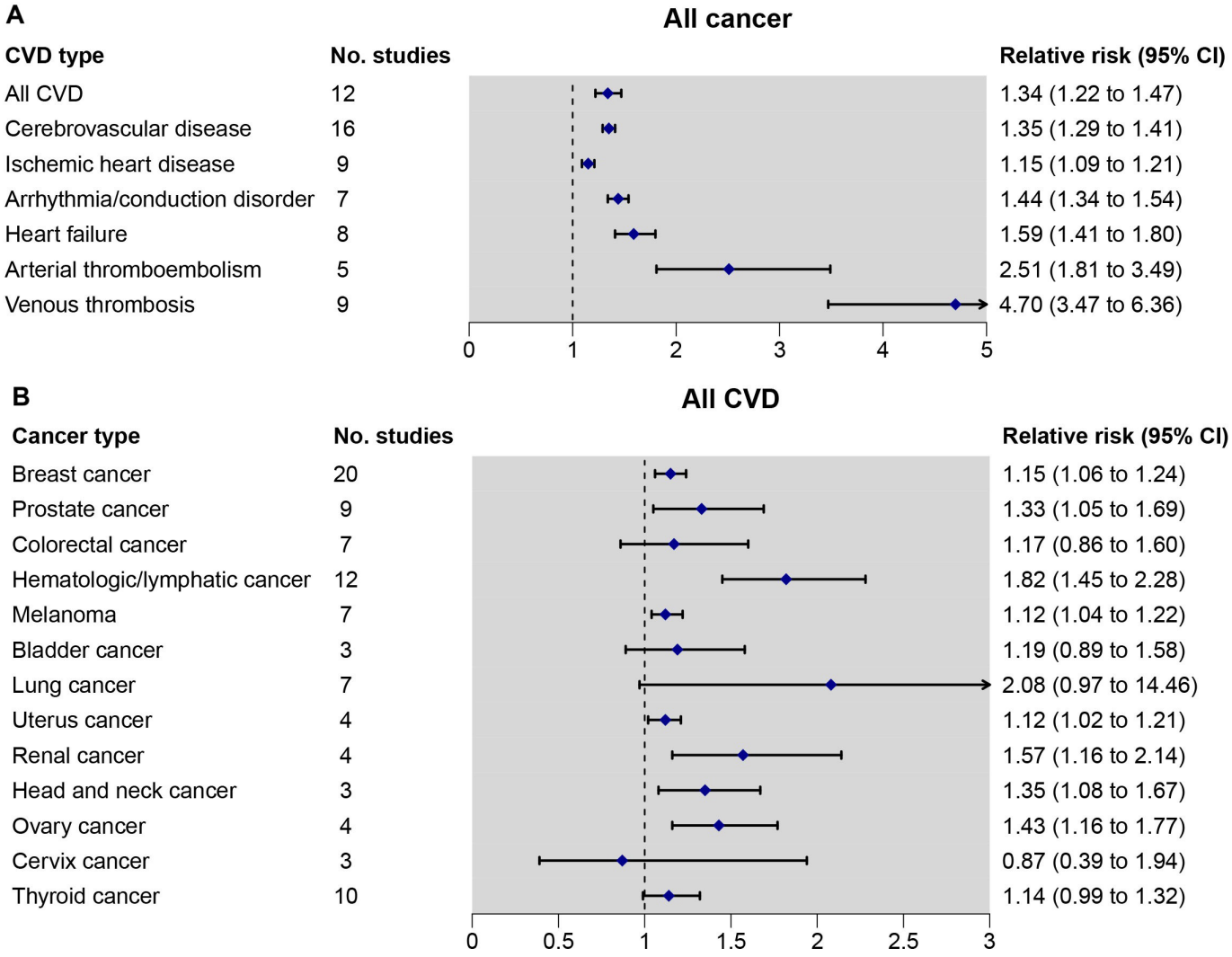

Figure 2 (A) The summary of relative risk and forest plots for associations between overall cancer and CVD subtypes risk. (B) The summary of relative risk and forest plots for association between different cancer sites and CVD risk. CVD, cardiovascular disease.

among cancer survivors and 4 436 564 among cancer-free individuals.

The baseline characteristics of 104 included studies are shown in online supplemental table 8. Published from 2005 to 2022, a total of 48 studies originated from Europe, 31 from Asia and 21 from the USA. Eighty-four studies were retrospective cohorts and 20 were prospectively designed. A median sample size of 41 077 along with a median follow-up of 1–18.4 years was reported. Sixty-two (59.6%) of the included studies were at low risk of bias based on an NOS score ≥8.

Essential characteristics of the 104 included studies and the UK Biobank for meta-analysis are presented in online supplemental table 9, with the details of NOS score presented in online supplemental table 10. The random-effect meta-analysis yielded a significantly higher overall CVD risk for cancer survivors (RR 1.34, 95% CI 1.22 to 1.47), meanwhile a relatively large amount of heterogeneity was revealed (I^2=97%). Stratified by cancer sites or CVD event subtypes, we identified overall consistent effects of cancer diagnosis on increased subsequent CVD risk (figure 2A,B). Detailed effect estimates for associations between cancer sites and specific CVD subtype events are found in online supplemental table 11 and forest plots are shown in online supplemental figures 1–16. Funnel plots for each meta-analysis showed no evident asymmetry, together with findings from Egger's tests (p=0.09 for all cancer sites on all CVD events), indicating no potential evidence of small study effects (funnel plots in online supplemental figure 17).

Due to the data availability of included studies, subgroup meta-analyses were only performed based on sex (online supplemental table 12), where an increased risk of CVD was statistically significant in both female and male patients with cancer, although interaction test showed no significant difference between the effects in these two groups (p for interaction=0.605).

We performed sensitivity analysis by including studies with prospective design, studies with NOS ≥8 and studies reporting HRs as the primary metric (online supplemental

table 13). Consistent elevated CVD risk in cancer survivors was observed in all the sensitivity analyses.

Critical appraisal and evidence triangulation

We conducted 81 unique meta-analyses for the effects of cancer diagnosis at various sites on different CVD events. Effects with nominal statistical significance (p<0.05) were observed in 62 (76.5%) meta-analyses (online supplemental table 14).

Among the 62 nominal significant associations, 57 (91.9%) of them documented more than 1000 CVD events, and 10 (16.4%) meta-analyses showed small amount of between-study heterogeneity (I^2<50%). Fifty-seven (91.9%) associations were subjected to no hints of biases. Based on these criteria, only one outcome was graded as convincing (class I) evidence, namely the observed increased ischaemic heart disease risk in hematologic/lymphatic cancer survivors (RR 1.36, 95% CI 1.30 to 1.42). Twenty-nine outcomes presented highly suggestive (class II) evidence (table 2).

DISCUSSION

Principal findings

We reported a large population-based prospective cohort study, along with, to our best knowledge, the first systematic review and meta-analysis to estimate absolute and relative CVD risk in cancer survivors. An increased overall CVD risk, as well as a spectrum of particular CVD events, was observed in patients diagnosed with any cancer and cancers at specific sites. The relative risk was prominent in patients with cancer regardless of chemo or radiotherapy.

Potential mechanisms and interpretation

Our findings indicated larger effects on CVD in patients with cancer with chemo or radiotherapy, which have been well-recognised as cardiotoxic and have been listed in recent cardio-oncology guidelines.[3 31–33] As a common anthracycline agent, doxorubicin can lead to cardiomyopathy characterised by both systolic and diastolic dysfunctions.[34–36] Cisplatin causes drug-related endothelial dysfunction, leading to delayed cardiovascular toxicity, including acute myocardial infarction and other cardiovascular events.[37 38] Targeted therapeutic agents such as bevacizumab can elicit endothelial dysfunction and vascular stiffness, resulting in systemic vasoconstriction and increased blood pressure.[39 40] Radiotherapy can promote inflammation where cytokines and adhesion molecules are upregulated in endothelial cells,[32 41] increasing the risk for multiple CVD events.[13 42]

We also observed that patients with cancer without chemo or radiotherapy were still subjected to a higher CVD risk, indicating a possible aetiological link between cancer and CVD. The hypercoagulation state established with cancer progression elevates the risk for pulmonary embolism and stroke.[43] Cancer-related inflammation also contributes to atrial remodelling,[44] where conduction disorders such as atrial fibrillation can be induced.[45 46] Although our study confirmed the association between cancer and subsequent CVD risk, shared risk factors, including obesity, smoking, stress and unhealthy lifestyle,[47–50] may have confounded these findings, impeding further causal inference in the association. Therefore, advanced approaches such as Mendelian randomisations are merited in the future to overcome potential confounding effects.

We observed that effect estimates reduced in size using competing risk model compared with estimates from conventional Cox models. This indicates possible influence by the presence of competing events, which might bias the estimates. Noah *et al* reported that ignoring competing events resulted in overestimating the cumulative incidence of outcomes.[51] Given that cancer survivors are disposed to high risk of non-CVD deaths (incidence of non-CVD deaths 14.13 per 1000 person-years), overestimation of CVD relative risk might have occurred in Cox models. Therefore, estimates from competing risk models should be interpreted as primary findings in our study. Note that this model was not widely used by previous publications. Therefore, more competing risk-adjusted estimates are expected for future research.[52]

In our cohort study, after adjusting multiple covariates, male cancer survivors suffered higher CVD risk than females (p for interaction <0.001), and consistent results, although non-significant interaction, were obtained by our meta-analysis. There has been evidence that men are predisposed to higher CVD risk than women in the general population.[53] As for cancer survivors, the predicted heart age, proxied by a weighted risk score, tended to be higher among male patients with cancer,[54] resonating with our findings on the sex disparities. A reverse direction of effect estimates was observed in aspirin intake strata analysis, as multiple studies have revealed that aspirin intake can reduce the risk of CVD.[55 56]

There have been similar cohort studies using UK Biobank.[57 58] Our study covered a wider spectrum of cancer sites and CVD subtypes than a previous study by Raisi-Estabragh *et al*[57] (six cancer types investigated). In addition, we have adjusted the competing risk of non-CVD deaths, which was not considered by previous studies,[58] and provided more robust estimates.

Previous studies reported the association between social capital and cancer/cardiovascular mortality,[59–63] suggesting a potential mediating role of social capital in the cancer/CVD nexus. We performed mediation analysis and found that social connection factors might mediate only a small proportion of the observed effects. Given that social capital is an umbrella term with components not captured by social connection measures,[61] population-based cohorts with more inclusive social capital variables are needed.

Using predefined criteria, we identified one piece of evidence with high credibility (class I), where sufficient data had been accumulated with no hints of biases. The association between hematologic/lymphatic cancer and elevated ischaemic heart disease risk might be attributed

Table 2 Credibility assessment criteria for meta-analyses of observational studies and main result of evidence assessment (for association with at least nominal significance at p<0.05)

Evidence classification	Detailed criteria	Outcome
Convincing (class I)	Associations with p<0.000001; >1000 cases having the event of interest; the largest component study reporting a nominal statistically significant result (p<0.05); a 95% PI that excluded the null; no large heterogeneity (I^2<50%); no evidence of small-study effect (p>0.10); and no excess significance bias (p>0.10).	Hematologic/lymphatic cancer-ischaemic heart disease.
Highly suggestive (class II)	Associations with p<0.000001; >1000 cases having the event of interest; and the largest component study reporting a statistically significant result (p<0.05).	All cancer—CVD, all cancer—arrhythmia, all cancer—cerebrovascular disease, all cancer—ischaemic heart disease, all cancer—ATE, all cancer—VTE, all cancer—arrhythmia/conduction disorder, breast cancer—VTE, prostate cancer—VTE, lung cancer—arrhythmia/conduction disorder, lung cancer—VTE, hematologic/lymphatic cancer—arrhythmia/conduction disorder, haematologic/lymphatic cancer—cerebrovascular disease, hematologic/lymphatic cancer—heart failure, haematologic/lymphatic cancer—ATE, haematologic/ lymphatic cancer—VTE, prostate cancer—VTE, colorectal cancer—VTE, melanoma—VTE, bladder cancer—ischaemic heart disease, bladder cancer—arrhythmia/conduction disorder, bladder cancer—VTE, head and neck cancer—cerebrovascular disease, renal cancer—ischaemic heart disease, renal cancer—arrhythmia/conduction disorder, renal cancer—VTE, ovary cancer—VTE, uterus cancer—VTE, cervix cancer—VTE.
Suggestive (class III)	Associations with p<0.001 and >1000 cases having the event of interest.	Breast cancer—CVD, breast cancer—arrhythmia/conduction disorder, breast cancer—heart failure, prostate cancer—ischaemic heart disease, colorectal cancer—arrhythmia/conduction disorder, lung cancer—cerebrovascular disease, thyroid cancer—cerebrovascular disease, melanoma—arrhythmia/conduction disorder, bladder cancer—cerebrovascular disease, head and neck cancer—VTE, uterus cancer—cerebrovascular disease.
Weak (class IV)	Remaining statistically significant associations with p<0.05.	Breast cancer—ATE, breast cancer—ischaemic heart disease, prostate cancer—CVD, prostate cancer—arrhythmia/conduction disorder, prostate cancer—heart failure, prostate cancer—ATE, colorectal cancer—ATE, colorectal cancer—ischaemic heart disease, lung cancer—ischaemic heart disease, lung cancer—heart failure, lung cancer—ATE, thyroid cancer—arrhythmia/conduction disorder, thyroid cancer—VTE, bladder cancer—ATE, head and neck cancer—CVD, head and neck cancer—arrhythmia/conduction disorder, melanoma—CVD, renal cancer—CVD, ovary cancer—CVD, ovary cancer—cerebrovascular disease, uterus cancer—CVD.

ATE, arterial thromboembolism; CVD, cardiovascular disease; PI, prediction interval; VTE, venous thrombosis.

to specific treatments such as hematopoietic cell transplantation, which could confer markedly higher CVD risk including ischaemic heart disease.[64] Further research is needed to explore the aetiological link from a molecular perspective for these two conditions. However, it should be noted that the associations identified in our meta-analysis were mostly with low to modest credibility (class II to IV), including a reverse association between breast cancer and the risk of ischaemic heart disease. Tamoxifen, a drug commonly used in patients with breast cancer, has been identified with possible cardioprotective effects.[65 66] However, due to the data availability, we could not evaluate any drug-specific associations. In summary, these findings with low credibility should be interpreted with caution, and more well-designed investigations with larger sample sizes are needed in the future.

Clinical implications

The observed significantly elevated CVD risk among cancer survivors calls for a holistic approach to patient care, requiring close collaboration between oncologists and cardiologists. Cardiovascular risk should be profiled and monitored to identify patients at high risk of CVD events, where cardioprotective strategies could be timely initiated. Preventative lifestyle modifications, such as smoking cessation, should also be promoted among cancer survivors. During cancer treatment, cardiotoxicity ought to be closely followed up, and the treatment regimen may be amended if necessary to balance the elevated CVD risk and treatment effects.

Strengths and limitations

To our best knowledge, this is the largest comprehensive analysis estimating the absolute and relative risk of CVD in cancer survivors. We also conducted a critical appraisal and recommended evidence with high credibility to inform clinical and public health practice.

Several limitations should be noted. First, a substantial amount of between-study heterogeneity was observed in a sizeable proportion of meta-analyses. The heterogeneity had been expected due to the mixed population of patients with cancer and CVD events, this also impeded further exploration in the sources of heterogeneity by conducting subgroup analysis due to limited data. However, we performed multiple types of sensitivity analysis and obtained consistent results, pointing to the robustness of our findings. High-quality studies for specific CVD events among various cancers are still warranted in the future. Second, considering the nature of observational cohort studies, the associations found might be attributed to causality, reverse causation or confounding factors. Third, due to data availability, we could not perform further subgroup analysis based on different cancer treatment regimens. Finally, our cohort study identified smaller effect sizes in competing risk models than Cox models, but most previous published studies did not report competing risk estimates, thus meta-analysis could not be performed.

CONCLUSION

This study provides population-level evidence on CVD risk among cancer survivors, including those without chemotherapy or radiotherapy. Credibility assessment identified convincing evidence for the association between hematologic/lymphatic cancer and risk of ischaemic heart disease. Our findings underline the necessity for continuous research to gain a deeper understanding in the aetiological link cancer and CVD. They also spotlight the clinical importance of early assessment on CVD risk for patients with cancer from their diagnosis, so as to further enhance the survival rate and overall well-being of cancer survivors.

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