Risk of cardiovascular disease among cancer survivors: systematic review and meta-analysis

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Summary

Background There have been conflicting studies on the associations between cancer and cardiovascular disease (CVD) risk. The hypothesis of this meta-analysis was to investigate whether cancer survivors had an increased risk of CVD compared to those without cancer based on population-based cohort studies.

Methods We did a systematic review and meta-analysis of prospective and retrospective cohort studies. We searched PubMed, Embase, Web of Science, and Scopus published in any language from January 1, 1990 to February 24, 2025. We included cancer survivors and non-cancer controls. The primary outcome was the risk of CVD. The secondary outcomes included 17 CVD subtypes (e.g., ischemic heart, cerebrovascular, and peripheral vascular disease). Effect estimates (hazards ratios, HRs) with 95% CIs were pooled. Subgroup analyses, sensitivity analyses and meta-regression were performed to explore the stability of the results and the sources of heterogeneity. The protocol of this review was registered in PROSPERO: CRD42024559349.

Findings A total of 160 population-based cohort studies involving 49,395,865 participants (9,092,869 cancer survivors vs. 40,302,996 non-cancer controls) were identified. Overall, the HR for CVD in cancer survivors was 1.47 [95% CI, 1.33–1.62] compared with that in non-cancer controls. Cancer increased the risk of all 17 CVD subtypes, with cancer having the greatest effect on venous embolism, thrombosis or thrombophlebitis (HR, 3.07 [2.03–4.65]) and the least on ischemic heart disease (HR, 1.13 [1.03–1.24]). The increased risk of CVD was consistently shown in cancer survivors of brain, hematological, respiratory, male genital, and breast cancers, whereas no significant higher CVD risk was observed for other cancer types. Elevated risk of CVD was consistently shown in subgroup analyses of study design, age at cancer diagnosis, sex, location, follow-up duration, control, disease diagnosis, and therapy. Male and younger cancer survivors had elevated risk of CVD than female and older cancer survivors.

Interpretation This meta-analysis provides an up-to-date comprehensive global overview that cancer survivors had increased risk of CVD and 17 CVD subtypes than non-cancer controls. CVD risk evaluation and management need to be prioritized in cancer survivors, particularly among male, younger, and specific cancer survivors (brain, hematological, respiratory, male genital, and breast). This study provides supporting evidence that may inform future updates to guidelines for CVD prevention in cancer survivors, highlighting its public health relevance.

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Research in context

Evidence before this study

Previous systematic review and meta-analysis had reported that cancer survivors had higher risk of stroke than non-cancer controls. Another systematic review and meta-analysis observed that breast cancer survivors had higher risk of heart failure, atrial fibrillation, but not other cardiovascular disease (CVD) subtypes than non-cancer populations. To date, there has been no meta-analysis exploring the associations between cancer and CVD risk, and studies on cancer and CVD subtypes have shown inconsistent results. Therefore, this meta-analysis study searched for papers published in PubMed, Embase, Web of Science, and Scopus published in any language from January 1, 1990 to February 24, 2025, including 49,395,865 participants (9,092,869 cancer survivors vs. 40,302,996 non-cancer controls), to explore whether cancer survivors have an increased risk of CVD and 17 CVD subtypes compared with non-cancer populations.

Added value of this study

This systematic review and meta-analysis provides the most comprehensive and contemporary review to date. First, cancer increased the risk of CVD and all 17 CVD subtypes, with cancer having the greatest effect on venous embolism, thrombosis or thrombophlebitis and the least on ischemic heart disease. Second, the increased risk of CVD was consistent shown in cancer survivors of brain, hematological, respiratory, male genital, and breast cancers, whereas no significant higher CVD risk was observed for other cancer types. Third, elevated risk of CVD was consistent shown in subgroup analyses of study design, age at cancer diagnosis, sex, location, follow-up duration, control, disease diagnosis, and therapy. Fourth, stratified analyses found male and younger cancer survivors had elevated risk of CVD than female and older cancer survivors.

Implications of all the available evidence

This meta-analysis provides an up-to-date comprehensive global overview that cancer survivors had increased risk of CVD and 17 CVD subtypes than non-cancer controls. CVD risk evaluation and management need to be prioritized in cancer survivors, particularly among males, younger and specific cancer survivors (brain, hematological, respiratory, male genital, and breast). This study provides supporting evidence that may inform future updates to guidelines for CVD prevention in cancer survivors, highlighting its public health relevance.

Introduction

Cardiovascular disease (CVD), including ischemic heart, cerebrovascular, and peripheral vascular disease et al., has a high burden worldwide, and it has become the leading cause of death globally.[1–4] According to the report by the Global Burden of Disease Study in 2022, the prevalence of age-standardized CVD mortality ranged from 73.6/100,000 in Asia Pacific to 432.3/100,000 in Eastern Europe.[5] Due to the improvement in the level of diagnosis and treatment in recent years, CVD mortality decreased by 34.9% from 1990 to 2022 globally, but the high prevalence of CVD still has placed a heavy global burden.[5] Preventing CVD is of great significance to global public health.[1–4]

As shown in the systematic analysis for the Global Burden of Disease Study 2019, global burden of cancer is substantial and growing. From 2010 to 2019, there had increase in new cancer cases (26.3%, [95% uncertainty interval (UIs), 20.3%–32.3%]), in deaths (20.9%, [95% UI, 14.2%–27.6%]), and in DALYs (16.0%, [95% UI, 9.3%–22.8%]).[6] Cancer was second only to CVD for the number of deaths globally.[6] As the top two causes of death worldwide, cancer and CVD have been the focus of research for long years. It is generally considered plausible that cancer survivors have a higher risk of CVD since they share common risk factors (e.g., age, diabetes, hypertension, dyslipidaemia, obesity, unhealthy lifestyle, smoking, and treatment),[7] and molecular pathways of disease development, but results of previous studies are inconsistent, and there is insufficient evidence to confirm the relationships between cancer and CVD risk.

To date, studied of 13 countries had investigated the associations of cancer and CVD risk, and most of the studies found an increased risk of CVD in the cancer group compared with the non-cancer group (19 studies, including eight from Europe[8–15]), some studies did not find a significant association between cancer and CVD risk (seven studies,[16–22] five from the United States[16–20]), and three studies found that cancer survivors had a reduced risk of CVD compared with the non-cancer group (two from China[23,24] and one from the United States[25]). Previous studies had mostly been conducted in survivors with breast cancer[8,16,18,19,22,25,26] and hematologic

malignancies,[15,27,28] and the conclusions were inconsistent. Most of the previous studies were conducted in older participants (age at cancer diagnosis >50 y), and some studies were performed in children,[9,11,13,15,29] adolescents, and adults,[10,30,31] but the conclusions were not completely consistent. Regarding sex, some studies had found that cancer survivors had an increased risk of CVD in both males and females.[9–11,21,32,33] The associations between cancer and CVD risk may also vary depending on the follow-up time. For example, Yoon et al. found that, compared with the non-cancer group, lung cancer survivors had an increased risk of CVD and coronary heart disease one and three years after diagnosis, but no significant associations of lung cancer and CVD and coronary heart disease were found five years after cancer diagnosis.[34]

In addition to CVD, there had some studies on CVD subtypes, mainly on stroke, myocardial infarction, and venous thromboembolism (VTE). Zhang et al. conducted a meta-analysis of cohort studies, and found that cancer survivors had an increased risk of stroke and ischemic stroke compared with those without cancer, but did not find an increased risk of haemorrhagic stroke.[35] Meta-analysis by Galimzhanov et al. observed that breast cancer survivors had higher risk of heart failure, atrial fibrillation, but not myocardial infarction, coronary artery disease, or ischemic stroke than non-cancer populations.[36] There was no meta-analysis of VTE risk in cancer survivors and non-cancer populations, but Di Nisio et al. counted the incidence of VTE in cancer patients receiving neoadjuvant therapy, and found that the incidence of VTE was significantly increased in patients with bladder and esophageal cancer.[37] Hau et al. found that survivors with acute lymphoblastic leukemia who received chemotherapy of anthracyclines, no radiation therapy, and high-dose radiation therapy were at higher risk of CVD than their siblings, and did not have an increased risk of CVD in survivors treated with other chemotherapeutic agents and low-dose radiation therapy.[15]

Considering the inconsistencies of the above studies and the absence of meta-analyses of cancer and CVD risk, therefore, the aim of this study intends to conduct a meta-analysis to investigate the links of cancer and risk of CVD (primary outcome) and 17 CVD subtypes (secondary outcomes), taking into account the effects of study design, age at cancer diagnosis, sex, location, follow-up duration, control, disease diagnosis, therapy, and cancer type on their associations.

Methods

Standard protocol approvals, registrations, and patient consents

This systematic review was conducted according to a predefined protocol and in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[38] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations.[39] The protocol of this review was registered in International Prospective Register of Systematic Reviews (PROSPERO) (no. CRD42024559349, https://www.crd.york.ac.uk/prospero/).

Search strategy and selection criteria

Databases of PubMed, Embase, Web of Science, and Scopus were systematically searched by two independent investigators (QL and MY). The searching codes (updated on February 24, 2025) were described detailly in the Supplemental Material (Appendix S1, pp 5–7).

Eligibility criteria

Studies would be included in this analysis if they satisfied the following inclusion criteria: (1) prospective/retrospective population-based cohort; (2) participants: people previously diagnosed with cancer at the time of enrollment; (3) controls: participants without cancer in the past and at the time of enrollment; (4) outcome: cardiovascular disease (including CVD and 17 subtypes); (5) the measure of association: hazard ratio (HR), relative risk (RR), odds ratio (OR), incidence rate ratio (IRR) or standardized incidence ratio (SIR), and corresponding 95% confidence intervals (CIs), or the risk estimates could be calculated by the method recommended by Morris and Gardner.[40]

Study selection, data collection, and data extraction

Studies published from January 1, 1990 to February 24, 2025 in PubMed, Embase, Web of Science, and Scopus underwent a title, abstract, and full-text review by two independent investigators (QL and MY). If there were any discrepancies, the third investigator (LVT) would be consulted until a consensus was reached. Information including authors, publication year, location, study design, age at cancer diagnosis, number of females, population and control population, outcomes, diagnostic method for cancer and outcomes, follow-up duration, risk estimates and covariates adjusted were abstracted, and filled in the pre-designed data extraction excel forms. Manual reference check of relevant articles, meta-analyses, and reviews was also performed. “Cancer survivor” was defined as any individual who had been diagnosed with cancer.

Quality assessment

The methodological quality was evaluated using the Newcastle–Ottawa scale (NOS) tool[41] regarding representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis controlled for confounders, assessment of outcome, was follow-up long enough for

outcomes to occur, and adequacy of follow-up of cohorts. The total score ranged from 0 to 9 points, and a score of 7∼9 was defined as high quality.

Statistical analysis

The primary outcome (CVD) and the secondary outcomes (17 CVD subtypes) were the pooled HR in cancer survivors compared with the HR of the non-cancer populations. Heterogeneity between studies was calculated using I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to be low, moderate, and high degrees of heterogeneity. The DerSimonian and Laird random effects ($I^2 \geq 50\%$) and fixed effects meta-analysis ($I^2 < 50\%$) were used to calculate the pool HRs and the corresponding 95% CIs. If HR was not reported, RR, OR, IRR or SIR was used to compare the risk of outcomes in cancer and non-cancer population. If the risk estimates were not reported in the article, we use methods recommended by Morris and Gardner to calculate RR and 95% CIs.[40] To further explore the sources of heterogeneity, the following stratified analyses were performed, including: study design (prospective, retrospective), age at diagnosis (<20 y, 20–49 y, ≥50 y), sex (male, female), location (Europe, North America, and Asia and Oceania), follow-up duration (<5 y, 5–9 y, ≥10 y), control (matched or sibling, non-cancer), disease diagnosis (ICD, others), therapy (radiotherapy, chemotherapy), and 10 cancer types (brain/hematological/respiratory/male genital/urinary tract/breast/gynecologic/skin/thyroid/gastrointestinal). Sensitivity analyses were conducted by omitting one study at a time, among studies with high quality, among studies with HRs, among studies after 2017, with adjustment, age-adjusted and sex-adjusted. Associations of cancer and CVD subtypes were stratified by age and treatment modality. To enhance result reliability, pooled estimates were calculated only from strata with ≥4 studies, and we did not report pooled risk estimates with too few studies. Publication bias was evaluated using Egger's test. The analyses in this study were performed with Stata statistical software (version 18.0; Stata Corporation, College Station, TX, USA) and R (version 4.2.1). All tests in this study were 2-sided, with a $P < 0.05$ to be considered significant.

Role of funding source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Literature search

The flow diagram of this study is shown in Fig. 1. A total of 446,105 articles from the PubMed (n = 76,345), Embase (n = 122,688), Web of Science (n = 50,710), and Scopus (n = 196,362) published from January 1, 1990 to February 24, 2025 were identified. After removing the duplicate 363,585 articles, 85,520 articles underwent title and abstract review, excluding 69,627 no relevant exposure or outcome, 5771 meta or review or case report or comment or reply, 2789 randomized controlled trial (RCT) or case-control, the remaining 4333 articles were checked for full text, excluding 3430 no control group or were not cohort, 166 no exposure of interest, 515 no outcome of interest, 82 without risk estimates, and 140 articles remained. After adding 20 articles from handcheck, finally 160 articles were included in this meta-analysis (36 focused on the primary outcome of CVD, 142 focused on the secondary outcomes of 17 CVD subtypes) (full reference lists see Appendix S16, pp 119–136).

Study characteristics

Tables S1–S3 depicts the baseline characteristics of the 160, 36, and 142 included studies, respectively. The 160 studies included 49,395,865 participants (9,092,869 cancer survivors vs. 40,302,996 non-cancer controls). The studies were published in the year since 2001 to 2024. As shown in Fig. 2, more than half of the studies (56.3%, 90/160) were published in the last eight years (2017–2024). There were 46 in the North America, 65 studies conducting in Europe, 46 from Asia, and three from Oceania (two from Australia,[42] one from New Zealand[33]). Studies with larger datasets began to emerge in 2012, mainly in European countries, and studies with larger datasets in Asia were mainly concentrated from 2018 to 2022. More than two-thirds (110/160, 68.8%) were prospective studies, 75% (120/160) of participants were older than 50 years when diagnosed with cancer, 71.3% of studies (114/160) used International Classification of Disease (ICD) as a criterion for cancer and outcome diagnosis, and 85.0% of studies (136/160) had high quality (NOS ≥ 7) (Table S4). Ninty-two studies used matched participants, 59 used general population, and nine used siblings as controls. The duration of follow-up time ranged from 271.5 days to more than 30 years. The vast majority of studies used HR as risk assessment, nineteen used SIR, fourteen used RR, eight used IRR, seven used OR, and the remaining two used original data to calculate the risk estimates.[42,43]

Associations of cancer and CVD

When we meta-analyzed the 36 studies on CVD, the results showed that the pooled HR of CVD was 1.47 [95% CI, 1.33–1.62] in cancer survivors compared with non-cancer controls. The heterogeneity among studies was high ($I^2 = 99.0\%$; $P < 0.0001$) (Fig. 3). There was no evidence of publication bias according to Egger's test ($P = 0.33$). The Funnel plot is shown in Figure S1.

Associations of cancer and 17 CVD subtypes

As shown in Table 1, the pooled HRs for 17 CVD subtypes associated with cancer were all significant (all

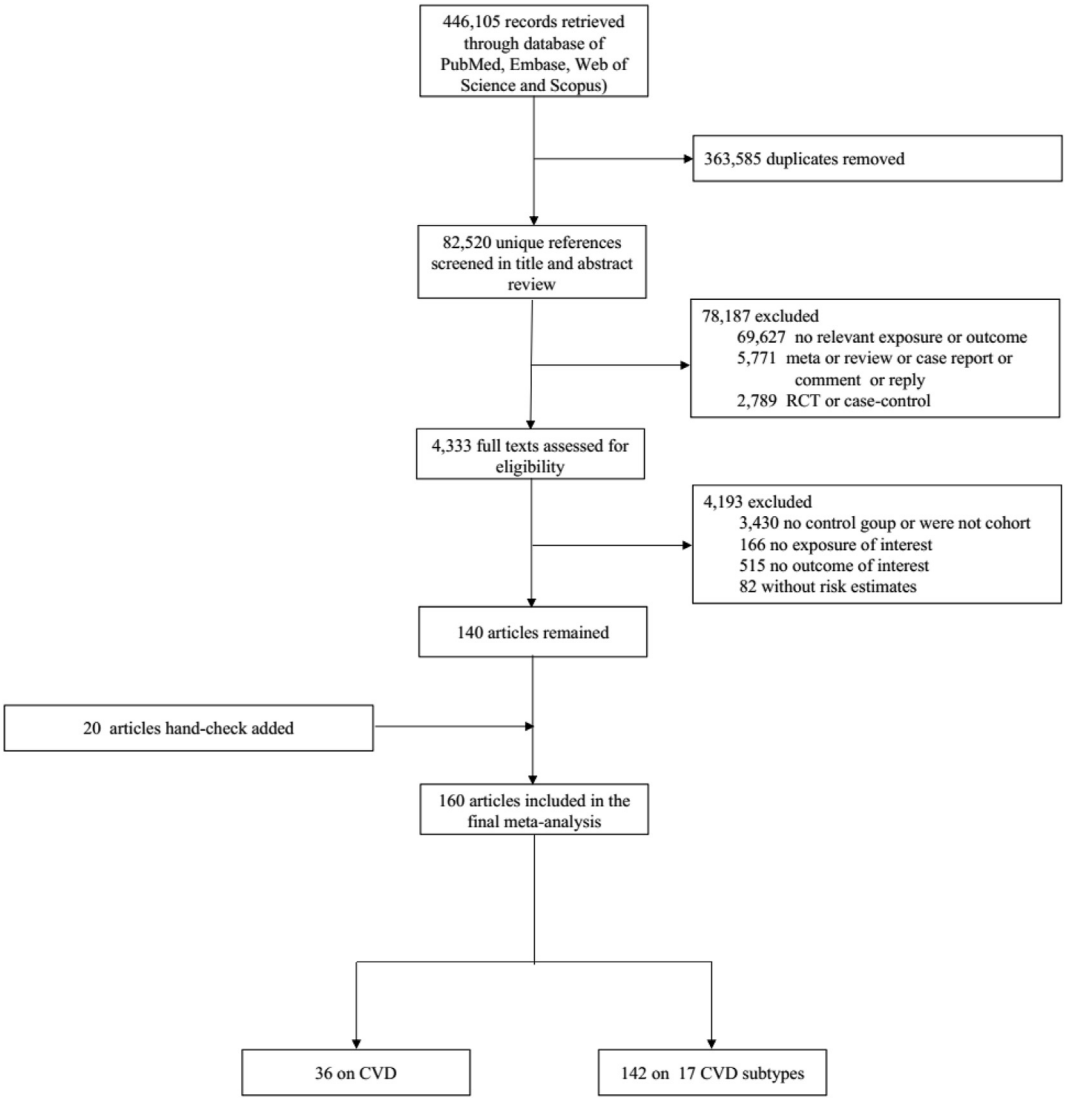

***Fig. 1:* Flow diagram of this study.** CVD: cardiovascular disease; RCT: randomized controlled trial.

HR > 1), and with high heterogeneity except for the outcomes of other and undefined circulatory disease (I^2 = 71.4%, medium heterogeneity), conduction disorder (I^2 = 62.9%, medium heterogeneity), and venous- and lymphatic disease (I^2 = 59.2%, medium heterogeneity). Of all the secondary outcomes, cancer had the greatest effect on the risk of venous embolism, thrombosis or thrombophlebitis (HR, 3.07 [2.03–4.65]), and had the least on the risk of ischemic heart disease (HR, 1.13 [1.03–1.24]).

Subgroup analysis

This meta-analysis conducted subgroup analyses on the associations of cancer and CVD (Fig. 4). Subgroup analyses showed that the increased risk of CVD was evident in all subgroups of study design (prospective, retrospective), age at diagnosis (<20 y, 20–49 y, ≥50 y), sex (male, female), location (North America, Europe, Asia, and Oceania), follow-up duration (<5 y, 5–9 y, ≥10 y), control (matched or sibling, non-cancer), disease diagnosis (ICD, others), and therapy (radiotherapy, chemotherapy). The study found that males had a higher risk of CVD than female cancer survivors (P = 0.0040), and there were significant differences in the risk of developing CVD among cancer survivors of different ages (P < 0.0001).

This study analyzed the effect of age on the associations of cancer and CVD subtypes. Subgroup analysis by age found that younger cancer survivors had a significantly increased risk of almost all CVD subtypes,

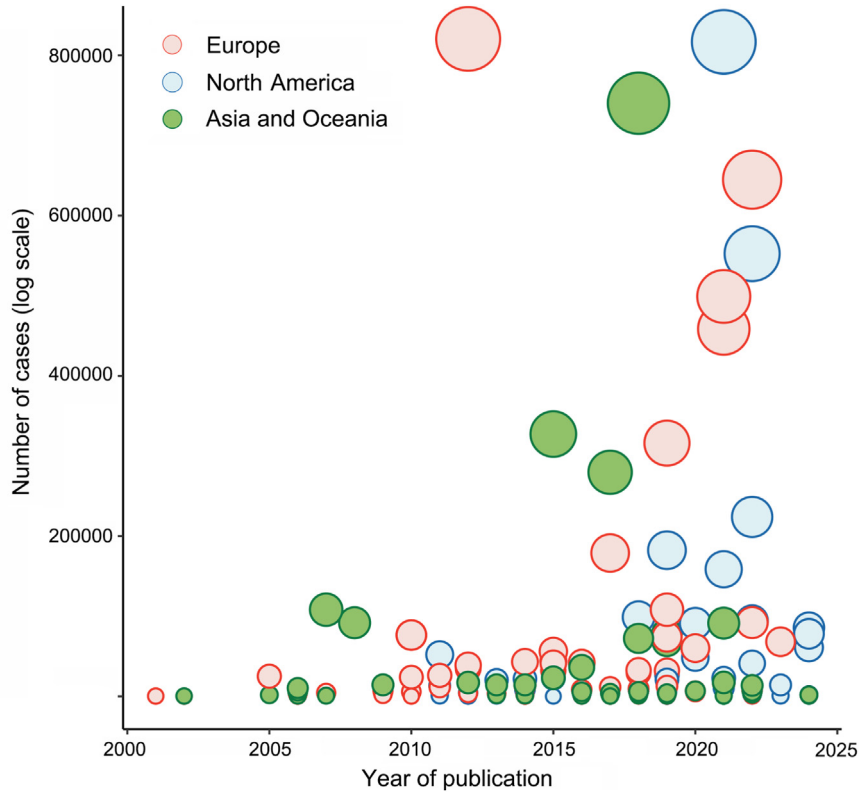

***Fig. 2:* Datasets by year and population group.** Size of circle is proportional to sample size.

but in older cancer survivors, seven CVD subtypes were found to have an increased risk, and some CVD subtypes were not found to have an increased risk of disease (Table S5).

Stratification by therapy to explore the association between cancer and CVD subtype risk found that cancer survivors with radiotherapy and chemotherapy had significantly increased risk of myocardial infarction (Table S6).

As illustrated in Fig. 5, stratified analyses of cancer type presented that significant associations of cancer and CVD were found in brain (HR, 2.54 [1.36–4.77]), hematological (HR, 2.20 [1.47–3.28]), respiratory (HR, 1.48 [1.28–1.71]), male genital (HR, 1.45 [1.02–2.00]), and breast cancer (HR, 1.16 [1.02–1.31]). Urinary tract, gynecologic, skin, thyroid, and gastrointestinal cancer survivors were not found to have higher risk of CVD than non-cancer controls.

Meta-regression

Meta-regression analysis was utilized to quantify the heterogeneity among studies. In the meta-regression model, the details are as follows: 1) Response variable: The response variable is the log-transformed effect size (log(HR)) to ensure normality and linearity in the model. 2) Predictors: the predictors include study design (prospective, retrospective), age at diagnosis (<20 y, 20–49 y, ≥50 y), sex (male, female), location (North America, Europe, Asia, and Oceania), follow-up duration (<5 y, 5–9 y, ≥10 y), control (matched or sibling, non-cancer), disease diagnosis (ICD, others), and therapy (radiotherapy, chemotherapy). 3) Random error distribution: The random error term is assumed to follow a normal distribution with mean 0 and variance σ^2. 4) Link function: this study used an identity link function because the response variable (log-transformed effect size) is already on a linear scale. 5) Random-effect term: To account for between-study heterogeneity, we included a random-effect term, which is assumed to follow a normal distribution with mean 0 and variance τ^2. 6) Model assumptions: linear relationship between predictors and log-transformed effect size. Independence of random effects and errors across studies.

Normality of random effects and errors. Heterogeneity captured by the random-effect variance (τ^2). Results of meta regression found that the heterogeneity could ascribe to age at cancer diagnosis (univariate, $\beta = -0.36$, $P = 0.0002$; multivariate, $\beta = -0.38$, $P = 0.0070$). In exploring sources of heterogeneity using univariate meta regression, sex demonstrated a borderline significant effect ($\beta = 0.27$, $P = 0.05$), suggesting it may partially account for variation across studies. Study

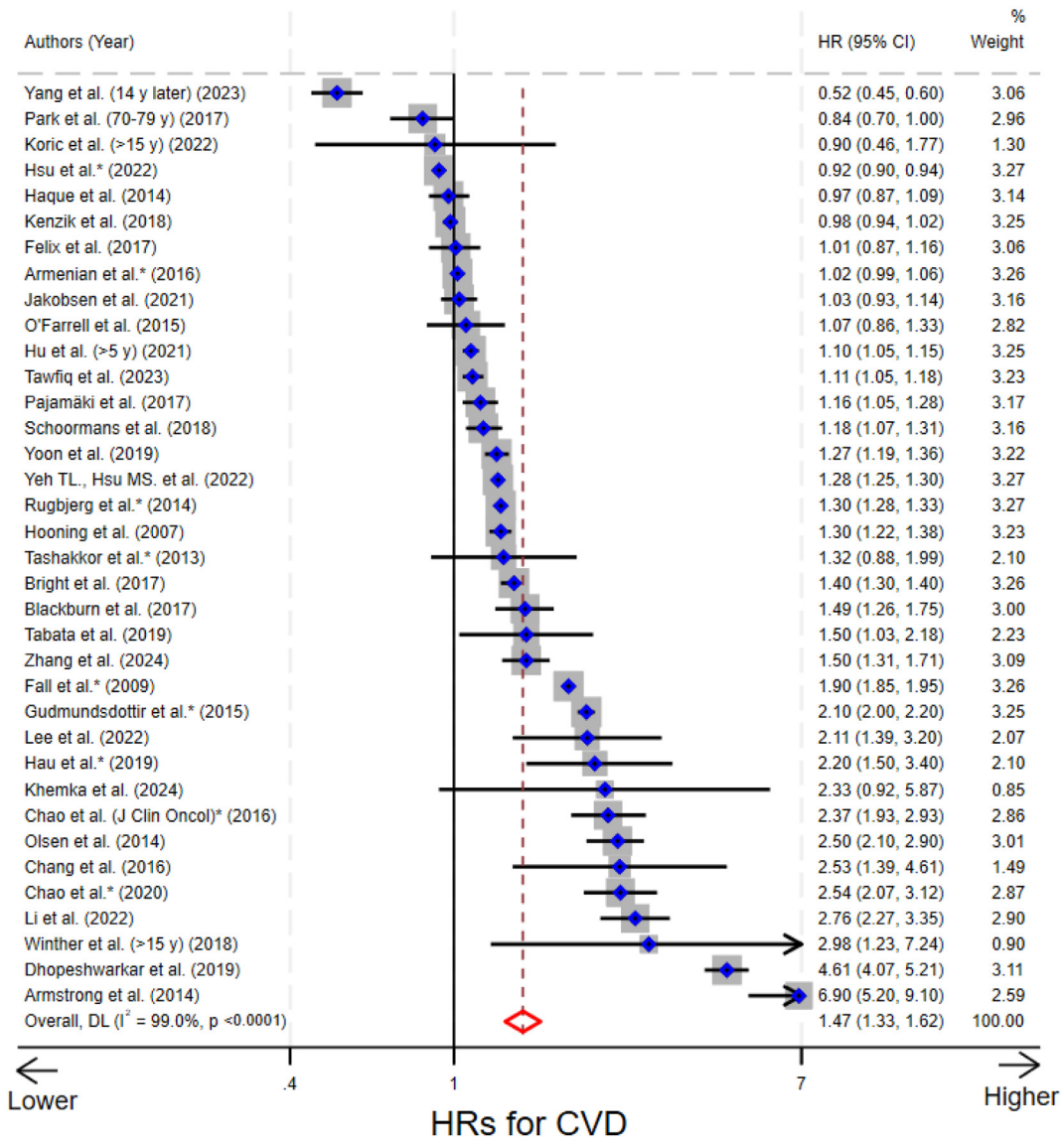

***Fig. 3:* Forest plots for the associations of cancer with CVD.** *Study used effect estimates other than HR. CVD: cardiovascular disease; HR: hazard ratio.

design, location, follow-up duration, control, disease diagnosis, and therapy were not found to be the main source of heterogeneity in univariate and multivariate meta regression analyses.

Sensitivity analyses

To examine the stability of the result, sensitivity analyses were performed with the leave-one-out method (Figure S2). No individual study was found to significantly alter the summary HRs (lowest HR 1.41, [95% CI, 1.28–1.56]; highest HR 1.52, [95% CI, 1.38–1.68]). Sensitivity analysis was carried out among studies with high quality, finding an increased summary estimate of 1.54 [95% CI, 1.39–1.70] (Figure S3). Sensitivity analysis was conducted among studies using time-to-event risk estimates (HRs) to pool the estimates. HRs were pooled, yielding a similar summary estimate of 1.42 [95% CI, 1.27–1.58] (Figure S4). Sensitivity analysis was also launched among studies published after 2017. HRs showed a summary estimate of 1.35 [95% CI, 1.21–1.51], which was consistent with the primary result (Figure S5). We performed sensitivity analyses in adjusted, age-adjusted and sex-adjusted studies, and found conclusions were consistent with those of the main study, with HRs of 1.51 [95% CI, 1.35–1.68] (n = 34, Figure S6), 1.54 [95% CI, 1.37–1.73] (n = 25,

Category of cardiovascular disease and diagnostic entity (ICD-10)	No. of Ref. included	I^2 (%)	HR (95% CI)
Hypertension I10–I15	15	97.4	1.27 (1.11–1.44)
Ischemic heart disease I20–I25	20	92.6	1.13 (1.03–1.24)
Myocardial infarction (I21–I22)	35	91.5	1.15 (1.01–1.32)
Else Ischemic heart disease (I20, I23–I25)	23	97.5	1.23 (1.09–1.39)
Pulmonary heart disease I26–I28	10	97.4	2.42 (1.77–3.31)
Peri-, myo-, and endocardial disease I30–I33, I38–I41, I51.4	8	95.1	1.57 (1.12–2.18)
Valvular disease (nonrheumatic) I34–I37	15	97.1	1.48 (1.34–1.63)
Heart failure I42–I43, I50, I51.5, I51.7	36	96.8	1.44 (1.25–1.66)
Conduction disorder I44–I49	5	62.9	1.45 (1.29–1.62)
Cerebrovascular disease I60–I69, G45	17	97.5	1.29 (1.03–1.60)
Cerebral infarction (I63)	37	98.4	1.31 (1.14–1.50)
Cerebral hemorrhage (I61–I62)	13	95.0	1.37 (1.08–1.75)
Stroke, unspecified (I64)	45	98.3	1.54 (1.38–1.73)
Arterial disease I70–I79	27	98.3	1.38 (1.21–1.58)
Venous- and lymphatic disease (I80–I89)	6	59.2	1.35 (1.25–1.47)
Venous embolism, thrombosis or thrombophlebitis I80–I82	31	99.8	3.07 (2.03–4.65)
Other and undefined circulatory disease (I01, I05–I09, I51, I52, I95–I99 excluding I97.2)	6	71.4	1.80 (1.54–2.10)

CVD: cardiovascular disease; HR: hazard ratio.

Table 1: **Risk of 17 CVD subtypes among cancer survivors.**

Figure S7), and 1.88 [95% CI, 1.61–2.20] (n = 16, Figure S8), respectively.

Discussion

This meta-analysis study found that cancer survivors had increased risk of CVD and 17 CVD subtypes (especially venous embolism, thrombosis or thrombophlebitis) compared with the non-cancer population. The increased risk of CVD in cancer survivors occurs mainly in those with brain, hematological, respiratory, male genital, and breast cancers. Subgroup analyses found that an elevated risk of CVD was consistently shown in the stratification of study design, age at cancer diagnosis, sex, location, follow-up duration, control, disease diagnosis, and therapy. Male and younger cancer survivors had elevated risk of CVD than female and older cancer survivors.

This study identified high-risk populations (e.g., male, younger, and specific cancer survivors), enabling the development of targeted monitoring and intervention strategies for cancer. For these high-risk populations, personalized treatment plans should be implemented to more intensively manage CVD risk factors. This study highlights the need for multidisciplinary collaboration between oncology and cardiology to optimize long-term health outcomes in cancer survivors.

The results of this study are similar to those of most previous studies that have found that cancer increases the risk of CVD and CVD subtypes. The results of the previous studies that found a negative association between cancer and CVD, mostly in breast cancer survivors,[16,18,19,22] found that the risk estimates for breast cancer and CVD were around 1, which was similar to the results of this meta-analysis (breast cancer, HR, 1.16, [1.02–1.31]). Park et al.'s study found a borderline association between cancer and CVD risk in breast cancer survivors (HR, 0.84 [0.70–1.00]).[25]

Previous meta-analyses of cancer and CVD subtypes had only been conducted on cancer and stroke,[35] which were similar to ours in that they found that cancer increased the risk of stroke and ischemic stroke, but that study did not find that cancer increased the risk of haemorrhagic stroke. We speculate that the main reason why their study was different from ours was that it did not include six published studies,[42,44–47] three of which found a positive association of cancer with haemorrhagic stroke risk[42,45,48] and three of which were not significantly linked.[44,46,47] Among them, the risk of hemorrhagic stroke in cancer survivors compared with non-cancers was up to 2.97 times (HR, 2.97 [1.00–8.60]). More studies are needed to verify the associations of cancer and stroke and its subtypes. Another meta-analysis of cancer and CVD subtypes was conducted only in breast cancer survivors. The study by Galimzhanov et al. found that breast cancer survivors had an increased risk of some CVD subtypes (e.g., heart failure, atrial fibrillation) and some CVD subtypes did not (e.g., myocardial infarction, coronary artery disease, or ischemic stroke).[36] Unfortunately, in this study, we did not analyze the risk of CVD subtypes in survivors with specific types of cancer, and future studies should further explore the associations. This study is the first meta-analysis to explore the associations of cancer and 17 CVD subtypes at the same time, and the associations of cancer with other CVD subtypes except stroke needs to be verified by more studies in the future.

Different from ours, two studies from China found that cancer survivors had a reduced risk of developing CVD. Yang et al. found that cancer survivors and non-cancer populations in China Tianjin had a similar risk of CVD and subtypes (myocardial infarction, heart failure, ischemic stroke, and revascularization) in the first few years after cancer diagnosis, and that the risk of CVD and subtypes was significantly lower in cancer survivors in later years than in non-cancer populations.[24] According to the authors, the main reason why the results of their study differed from other studies might be that the participants took part in the Kailuan cohort, which provided the participants with free health check-ups, professional disease prevention and treatment services every 2 years.[36] For example, if a participant has high blood pressure, the cohort will provide him or her with free regular blood pressure monitoring, free antihypertensive medications, and free personalized medical guidance. As a result, participants in that cohort might have better cardiovascular health and better

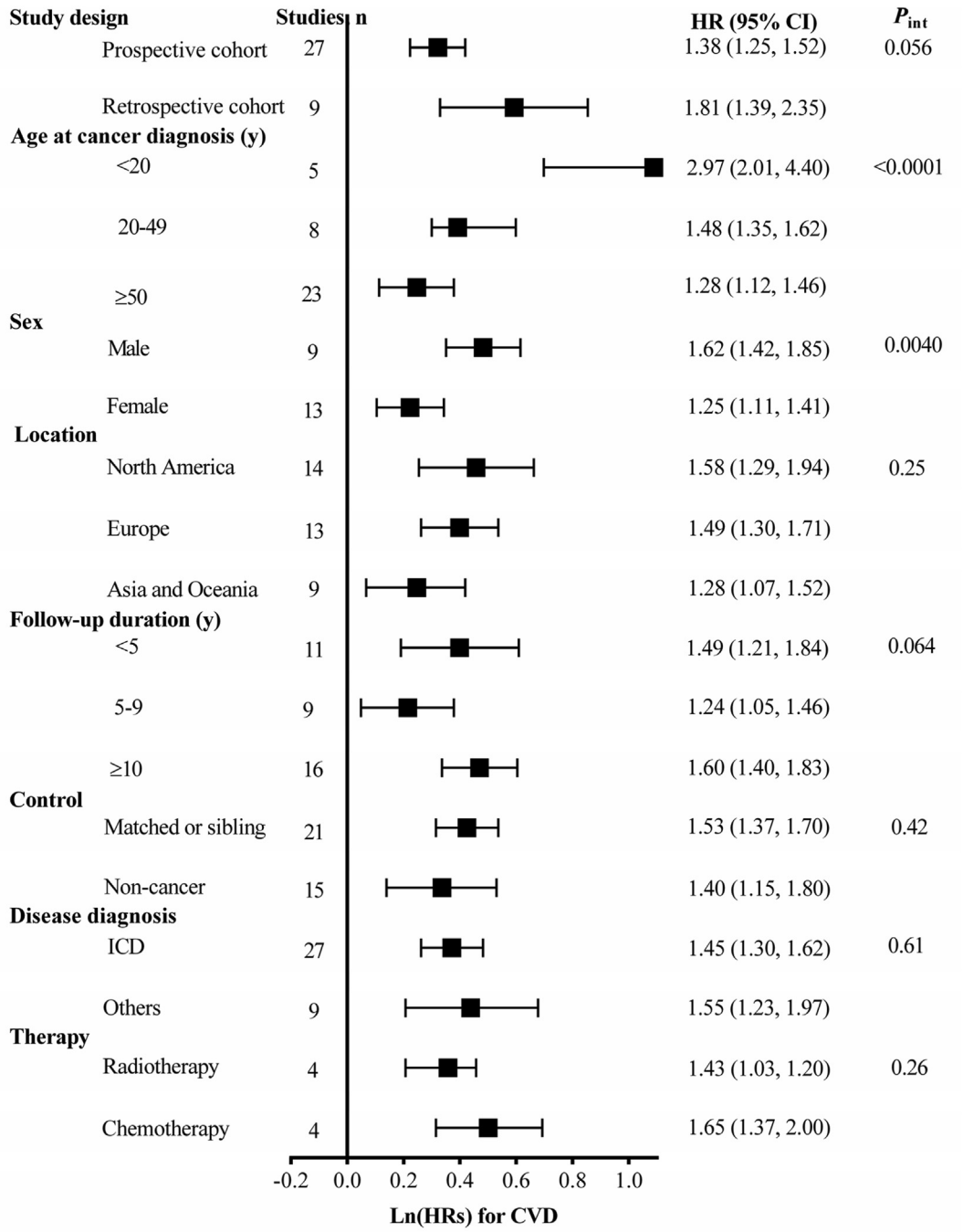

Fig. 4: **Subgroup analyses on the associations of cancer with CVD.** CVD: cardiovascular disease; HR: hazard ratio; ICD: International Classification of Disease.

prevention of CVD. Hsu et al. followed participants in China Taiwan for a median of 4.4 years, and found a slight and significant reduction in the risk of CVD in survivors with colorectal cancer compared with the general population (SIR, 0.92 [0.90–0.94]).[23] In that study, the risk of CVD in colorectal cancer survivors was higher than that of the general population in the first three years, and the risk of CVD in colorectal cancer survivors decreased over time, which was close to or lower than that of the general population.[13] The authors also speculate that the low risk of CVD in cancer survivors may be attributed to intensive integrated medical

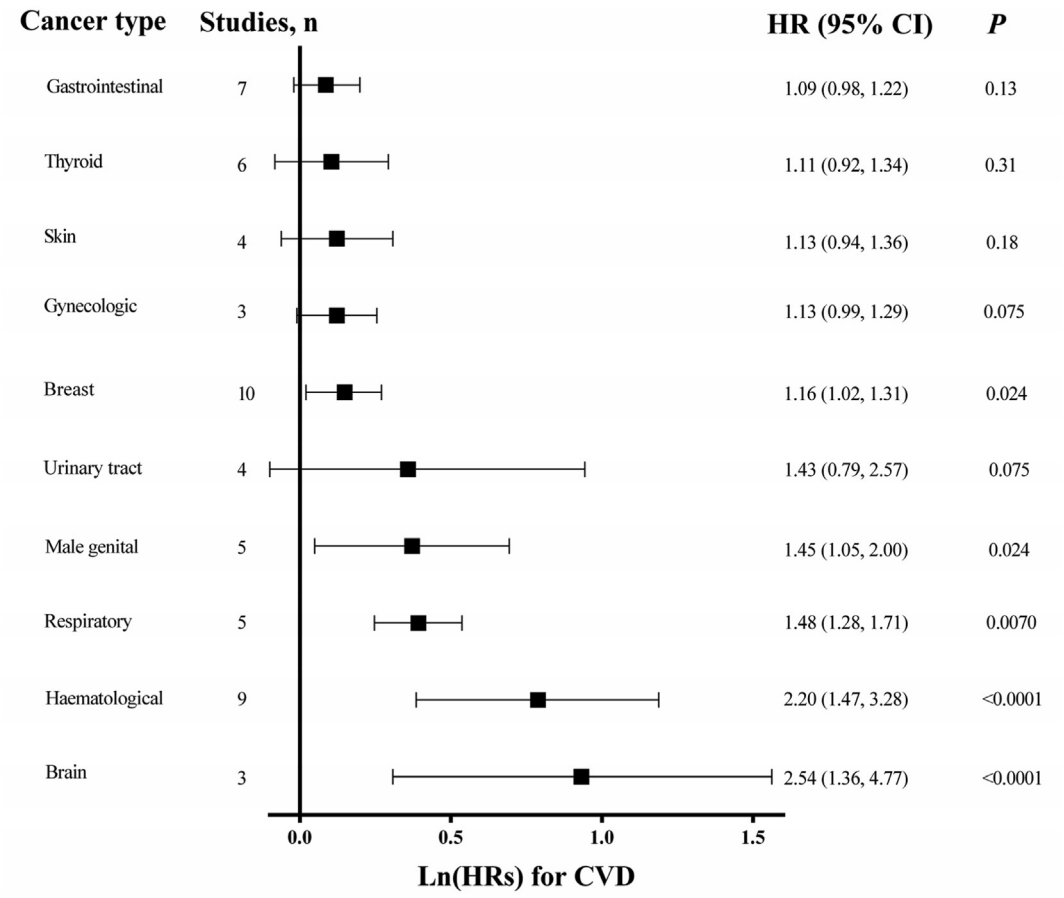

***Fig. 5:* Associations of cancer with CVD by cancer type.** CVD: cardiovascular disease; HR: hazard ratio.

services, which are better at preventing CVD to some extent.[15]

This meta-analysis observed that the association of cancer and higher CVD risk was more pronounced among younger cancer survivors. All previous studies in children,[9,11,13,15,29] adolescents and young adults[10,30,31] had found that cancer was significantly associated with an increased risk of CVD, while about half of studies in older cancer survivors (age ≥ 50 y) found that cancer increased the risk of CVD. Results of this meta-analysis were consistent with the study by Yeh et al., it found age and cancer had interactive effect on CVD.[49] Our results were also similar to Gudmundsdottir et al.'s.[11] They reported that the RR of CVD associated with cancer diminished significantly with age, from an increased RR of 18.7 in cancer survivors aged 1–9 years to 1.3 in those with age ≥60 years.[11] They speculated that the relative risk reduction by age was primarily due to an age-dependent increase in CVD in the general population, rather than alterations in the devastating effects associated with childhood cancer treatment.[11] For example, in the study conducted by Olsen et al. with the longest follow-up time (median 27 y), most participants were still younger than 50 years at the time of outcome assessment. Additionally, older participants may have more multiple risk factors for CVD, such as advanced age and other comorbidities (e.g., diabetes, hypertension, dyslipidaemia), this may partly explain why the effect of cancer on CVD is more pronounced in younger participants. The main source of heterogeneity in this study was the age of the participants. There may exist differences in immune function, metabolic status, treatment differences (such as drug dose), baseline diseases, and lifestyles of different age groups, and what specific impact these factors have on the occurrence of CVD, and follow-up studies should continue to carry out in-depth mechanistic studies.

This study found that cancer increased the risk of CVD significantly in both males and females. This is similar to the results of most previous studies.[9–11,33,49] Unlike the study by O'Farrell et al.,[21] it found an increased risk of CVD in men with prostate cancer treated with GnRH agonists + flare protection and surgical orchiectomy, but a reduced risk of CVD in those

with antiandrogens (HR, 0.87 [0.82–0.91]). Our study was similar to the study by Yeh et al. which found an increased risk of CVD in both male and female cancer survivors, with no significant difference in sexual risk between male and female.[49] That study found that the interaction between sex and age differed across different cancer types. They speculated that sex and age differences may alter the association between cancer and CVD by influencing visceral obesity, hyperinsulinemia, modifiable common risk factors, and clonal hematopoiesis of indeterminate potential.[50–52]

This study found an increased risk of CVD among cancer survivors in subgroups of North America, Europe and Asia and Oceania. Of the 36 studies included in the CVD analysis, Asia and Oceania had a smaller number (9 (6 in China) compared with 27 in Europe and the United States). There may be a relationship with genetic differences in different ethnic populations.[53] Drug metabolizing enzymes and drug transporters differ in different ethnicity populations, and drug toxicity may vary in cancer treatment.[53] There are significant differences in the incidence of overweight and obesity (which is closely related to cardiovascular events)[54,55] between Chinese and Western populations. Therefore, It is important to be cautious whether our findings can be extrapolated to other studies, more studies are needed to verify whether there are differences in CVD disease among cancer survivors of different races, and to explore the potential mechanisms.

Consistent with Zhang et al.'s,[35] it also found that the association of follow-up time with cancer and CVD was U-shaped, with the lowest risk of CVD when follow-up was 5–10 years after cancer diagnosis. None of the eight retrospective cohort studies were followed up 5–10 years after cancer diagnosis, but one-third (7/21) of the articles included in prospective cohort studies were followed up 5–10 years after cancer diagnosis (with the lowest risk of CVD). There were studies speculating, due to cancer-mediated hypercoagulability, the CVD risk peak rose immediately, followed by a decrease in risk, and then gradually increased due to the long-term effects of cancer treatment.[49] It is still unclear why 5–10 years after cancer diagnosis is the lowest risk period for CVD, and more studies with longer follow-up time are needed to explore it.

This study found that the increased risk of CVD with cancer was only present in survivors with specific cancers. In previous studies, an elevated risk of CVD was found in almost all survivors with brain,[10,11,33] respiratory,[14,20,33,34] and hematologic cancers.[10,11,14,15,20,27,28,30,33] Of all the published studies, breast cancer survivors were the most studied, with risk estimates for breast cancer and CVD association overwhelmingly in the range of 0.8[25]–1.4[10] (no association or mildly related). We do not know whether the increased risk of CVD in participants with specific cancers was related to the treatment modality. In this study, cancer survivors who received radiotherapy and chemotherapy were found to have a higher risk of CVD than the control population. The conclusion of this study is consistent with the results of most current studies on the therapy of cancer, and further confirms the influence of chemoradiotherapy on cardiovascular toxicity. However, there were only four studies of radiotherapy and chemotherapy for CVD, and we were unable to classify the specific dose, duration, and drug of treatment (e.g., immune checkpoint inhibitors, anthracyclines) for a more in-depth analysis. We analyzed four CVD subtypes with a larger number of articles (>4) and found that cancer survivors undergoing chemoradiotherapy had a significantly increased risk of myocardial infarction. Due to the small number of literatures, the reliability of the findings in this study remains to be investigated, and subsequent studies with larger sample sizes need to be further explored.

The mechanisms of cancer in increasing the risk of CVD are not well understood, and we speculate that the following explanations may be possible. First, cancer and CVD share common risk factors and molecular pathways for disease development (e.g., older age, overweight or obesity, sedentary lifestyle, and smoking).[51] Second, several types of anti-cancer therapies (e.g., radiotherapy, chemotherapy drugs, targeted therapy, and immune checkpoint inhibitors) had also been shown to accelerate the development of CVD.[56–58] Third, It may be related to arterial stenosis[59] and increased plaque deposits.[60] Fourth, cancer survivors tend to be in a hypercoagulable state, leading to an increased risk of VTE.[61] Fifth, it may be related to systemic inflammatory responses, including chronic inflammation and immune activation.[62] Accumulating evidence suggest that oxidative stress-induced lipid peroxidase is associated with cancer, CVD, and inflammation.[62] Finally, it may be related to other factors such as hormones, cytokines, metabolic enzymes, autonomic dysfunction, psychological stress, and lifestyle changes et al.[63]

Compared with single-country studies, this meta-analysis enhanced generalizability by combining findings from 160 studies across four continents. Strengths of this meta-analysis include the large sample size, diverse populations, the rigorous study design, and the robust results. A large number of participants (49,395,865 participants (9,092,869 cancer survivors vs. 40,302,996 non-cancer controls)) were included in this meta-analysis, and only prospective or retrospective cohort studies were included to minimize recall bias of studies. Sensitivity analyses were performed in high-quality literature, with HRs, articles published after 2017, with adjustment, age-adjusted and sex-adjusted, and the conclusions of the studies remained consistent. We searched four online databases (PubMed, Embase, Web of Science, and Scopus) with a comprehensive and clear search strategy so that we could search for as many relevant articles as possible from around the world, avoid the impact of publication bias on the pooled

results, and improve the reproducibility of results. Publication bias analysis was also performed in this study and no significant publication bias was found. This study not only examined CVD, but also included 17 CVD subtypes, and found an increased risk in both CVD and 17 CVD subtypes, indicating that the conclusions of the study are relatively reliable. Overall, this study is the first large-scale meta-analysis to explore the risk of cancer and CVD and its subtypes, providing up-to-date evidence for revealing the association between cancer and CVD risk.

However, some limitations should also be noted. First, the number of articles related to chemo-radiotherapy was limited, whether the conclusions of this meta-analysis can be extrapolated to other populations remains to be discussed, and follow-up articles should pay special attention to the relationships between cancer and CVD risk when cancer survivors undergo therapies at different frequencies, doses, and drug use (e.g., immune checkpoint inhibitors, anthracyclines).[64,65] Second, some studies did not adjust for important confounding factors, such as sociodemographic characteristics, baseline health status (e.g., level of cholesterol, HbA1c, history of CVD), complications (e.g., diabetes, hypertension, dyslipidaemia), smoking, alcohol consumption, exercise and so on, which are closely related to the occurrences of CVD, and follow-up studies should include these confounding factors. Third, this study did not consider the effect of body mass index, and the latest studies found that weight loss in cancer survivors will reduce life expectancy,[66] whether overweight and obesity have an impact on the occurrence of CVD in cancer survivors, and whether cancer survivors need to lose weight to prevent CVD, these should be confirmed in more subsequent studies to provide more scientific basis for the disease prevention guidelines among cancer survivors. Fourth, this study had potential selection bias, differences in follow-up duration, and the lack of individual patient data, which limits the ability to adjust for comorbidities and risk factors. CVD is dependent to the cancer type, which was evaluated, but also affected by stage at diagnosis and metastasis. Fifth, due to the limited number of included articles, the outcomes including CVD and 17 subtypes, we are unable to perform a more detailed analysis based on the stage of the cancer and whether it has metastasized, and these important topics should continue to be explored in subsequent studies. Sixth, the assessment of heterogeneity in our meta-analysis was based on HRs, which is a multiplicative scale. It is important to note that heterogeneity assessment can be scale-dependent. For example, if we had used risk differences (RDs) instead of HRs, the results might have been different.

Seventh, this study may exist the potential selection bias associated with HRs, particularly in the presence of time-dependent confounding or competing risks.

Eighth, this study may exist inaccurate estimation of the between-study heterogeneity due to small number of included studies in some meta-analyses. Lastly, this study may exist the potential for bias due to the use of different effect measures across studies (HR/SIR/RR/OR/IRR), though we restricted the analyses among studies reporting HRs and achived the consistent results. Future studies should aim to report consistent effect measures to facilitate more robust meta-analyses.

This meta-analysis and systematic review provide an up-to-date comprehensive global overview that cancer survivors had increased risk of CVD. This study demonstrates that CVD risk evaluation and management need to be prioritized in cancer survivors, particularly among male, younger, and specific cancer survivors (brain, hematological, respiratory, male genital, and breast). It provides a foundation for future mechanistic studies to explore the long-term cardiovascular effects of cancer treatments. This study provides valuable insights into the increased CVD risk among specific subgroups of cancer survivors and offers a framework for clinical, public health, and research strategies to address this issue.

Contributors

YH, LVT, QL, and MY designed this study. QL, MY, and LVT conducted literature search, selection, and data extraction. QL, MY, LVT, YH, GFZ, XTL, SZX, HFW, JD, ZPC, FJF, and SC analyzed the data. QL drafted the original manuscript. All authors had full access to the data, and verified the results in this study. All authors revised the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

All data generated or analyzed during this study are included in this published article [and its Supplementary Information files].

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103274.

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