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Cancer risk subsequent to cardiovascular disease: a prospective population-based study and meta-analysis

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Abstract

Background Previous preclinical studies have revealed the biological links between cardiovascular diseases (CVD) and cancer. However, population-based evidence remained inconclusive.

Methods We assessed cancer incidence among individuals with and without CVD condition in a prospective cohort from the UK Biobank (UKB). Multivariable Cox regression and competing risk models were fitted to estimate hazard ratios (HR). A systematic literature search was conducted in Medline, Embase and Cochrane Library databases to identify published population-based cohort studies (last updated on 1 October 2023) investigating the associations between CVD status and subsequent cancer risk. Random-effects meta-analysis was employed to pool relative effect estimates reported by eligible cohorts. Subgroup and sensitivity analyses were conducted to evaluate the associations across various CVD and cancer subtypes.

Results For the cohort study in the UKB, after a median follow-up of 11.58 years, a total of 18,471 and 66,891 cancer cases occurred among 94,845 CVD patients and 368,695 non-CVD individuals (Incidence rate: 25.62 vs. 15.41 per 1000 person-years). Individuals with prior CVD exhibited higher overall cancer risk (HR 1.14, 95% CI 1.12–1.17, $p < 0.001$), and we observed consistently higher cancer risk after adjusting for competing risk from non-cancer deaths. The effect size of CVD on cancer risk was greater among younger individuals (< 65 years) than those ≥ 65 years (p for interaction < 0.001). The meta-analysis included 47 population-based cohort studies where a total of 1.49 million cancer cases were documented among over 45 million participants (9.49 million CVD patients). A 13% higher risk of overall cancer was observed among individuals with prior CVD (pooled RR 1.13, 95% CI 1.11–1.15, $p < 0.001$). The associations remained significant between various CVD subtypes and cancer risk at multiple sites.

Conclusions Our study identified a significantly higher cancer risk among individuals with CVD conditions compared with the non-CVD population, underpinning the need for continued cancer surveillance among CVD patients and further exploration of the possible etiological relation between CVD and cancer.

Keywords Cardiovascular disease, Cancer, Population-based cohort, Meta-analysis

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Background

Cardiovascular disease (CVD) and cancer are two leading causes of mortality worldwide, resulting in an estimated 18 and 10 million deaths per year, respectively [1, 2]. Although historically recognised as distinct pathological entities, accumulating evidence has highlighted common risk factors shared by CVD and cancer, including obesity, hypertension, dyslipidaemia and lifestyle factors [3–5]. In addition, recent pre-clinical investigations have found that CVD-induced biological alterations might contribute to tumour formation, suggesting a potential etiological association between these two diseases [6–8].

With respect to population-level evidence, the high risk for CVD among cancer patients due to cardiotoxicity of anti-cancer treatment has been well-recognised in cardio-oncology. However, whether pre-existing CVD is linked to subsequent cancer, recently known as 'reverse cardio-oncology', remained relatively understudied [9]. Current epidemiological findings regarding this association have been inconsistent, with some investigations reporting a higher risk of cancer among CVD patients [10, 11], while others suggesting lower overall cancer risk [12]. These studies were generally limited by small sample sizes and biased selection of hospital-based CVD cases, and unfortunately, there has been a lack of comprehensive summary of the totality of existing evidence.

Herein, we aimed to analyse the association between CVD condition and cancer incidence using a large prospective, population-based cohort. We then performed a systematic review and meta-analysis of population-based studies to summarise current epidemiological evidence.

Methods

Study design

This study consists of a prospective cohort study in the UK Biobank (UKB) and a meta-analysis of population-based cohorts. The cohort study was reported adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [13]. The meta-analysis was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [14], with the protocol registered on PROSPERO (CRD42024506956). The graphic summary of our study design is presented in Fig. 1.

Cohort study in the UK Biobank

Study population

Our prospective cohort study used participants from the UKB, a large population-based study encompassing over half a million individuals aged between 40 and 69 years recruited from 2006 to 2010. Individuals diagnosed with cancer before or at study enrolment were excluded. The ethics approval was obtained from the North West-Haydock Research Ethics Committee (Reference: 21/NW/0157), with written informed consent obtained from each participant prior to enrolment.

Ascertainment of the exposures and outcomes

The exposure of the study, namely the CVD, included diagnoses of ischemic heart disease, cerebrovascular disease, emboli/thrombosis, heart failure, arrhythmia/conduction disorder, identified using the International Classification of Diseases 9th (ICD-9) and 10th edition (ICD-10) codes recorded in self-reported data, primary care or hospital inpatient data, including either primary or secondary diagnosis. The primary outcome was defined as any type of cancer diagnosis based on hospital inpatient data, cancer registry and death registry data. Detailed ICD codes to define CVD and cancer are presented in Additional file 1: Table S1. All participants were followed up from enrolment until the date for a first diagnosis of cancer, cancer-specific death, or the administrative censoring for cancer data (31 Dec 2020 for England data, 31 Dec 2016 for Wales, and 30 Nov 2021 for Scotland for individuals not developing cancer). All cancer types are included for the overall analysis on the association between CVD and cancer. To ensure adequate statistical power, only cancer types with more than 500 cases were investigated to analyse the effects of CVD on cancer subtypes.

Measurement of covariates

A panel of local epidemiologists and clinicians discussed and selected covariates with reported associations with CVD and cancer risk. The covariates included sociodemographic (sex, age, Townsend deprivation index (TDI), ethnicity, geographical location, income, employment, education), anthropometric (body mass index (BMI)), lifestyle and environment (physical activity, diet, smoking, alcohol, sun exposure) factors, comorbidities (hypertension, diabetes, dyslipidaemia) and cardiovascular medications (aspirin intake), with detailed definitions presented in Additional file 1: Table S2 [15–18].

Meta-analysis

Study design and search strategies

We systematically searched the Medline, Embase and Cochrane Library databases to identify population-based cohort studies from inception to 1 October 2023, using a structured search strategy featuring medical subject headings and keywords of 'cardiovascular', 'cancer' and 'cohort studies' (search strategy can be found in Additional file 1: Table S3).

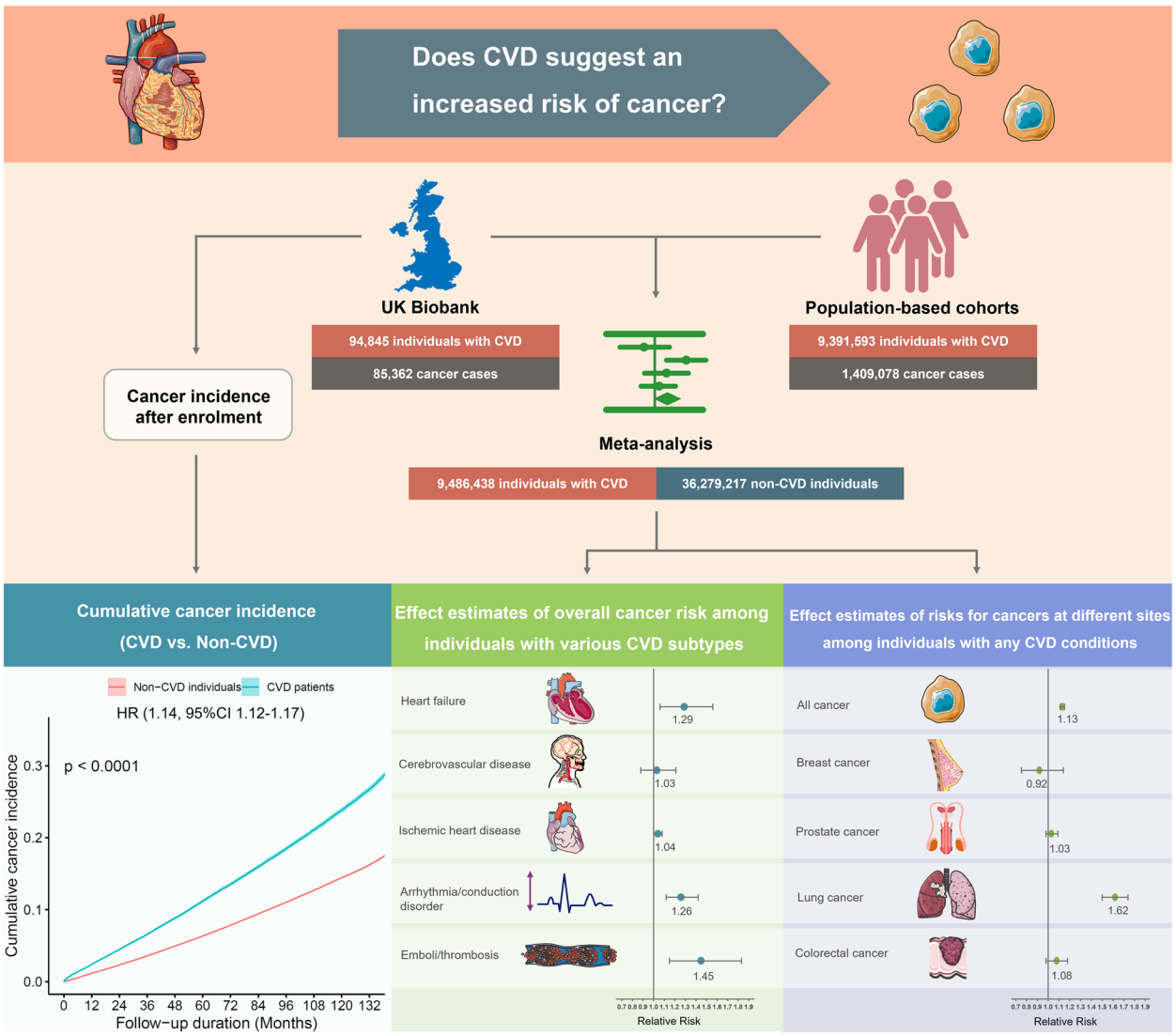

Fig. 1 The graphic summary of our study. In this study which included a prospective cohort in the UKB, and a meta-analysis of 46 population-based cohorts, CVD patients are subjected to a higher cancer risk in comparison to non-CVD individuals

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) population-based cohort studies comparing cancer risk between CVD patients and non-CVD population; (2) studies reporting relative effect estimates including relative risk (RR), hazard ratio (HR), odds ratio (OR) or standardised incidence rate (SIR) with 95% confidence intervals (CIs). We excluded hospital-based studies, studies investigating childhood or adolescent CVD patients, studies with participants reporting cancer events prior to CVD diagnosis or studies lacking adequate data for analysis. If multiple studies investigated the same outcome and CVD type using the same database, we only included the latest study. Two independent reviewers (CS and HH) screened the titles and abstracts and reviewed full texts for eligibility. Any discrepancies were resolved by discussion with another senior investigator (YH).

Data extraction and quality assessment

Basic characteristics (presented in Table 1) for each study were extracted using a standardised form independently by two reviewers (CS and LW). We extracted fully adjusted effect estimates along with confidence intervals (95% CI), including HRs, ORs, SIRs and RRs, from each eligible study. Previous evidence demonstrated that RRs could be acceptably approximated by HRs, ORs or SIRs provided a relatively low outcome event rate [19, 20]. Here given the low cancer incidence

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

Characteristics	CVD patients (*N* = 94,845)	Non-CVD individuals (*N* = 368,695)
Follow-up time, median (IQR), years	11.58 (10.64, 12.42)	11.58 (10.67, 12.39)
Age at the index date, median (IQR), years	62.00 (56.00, 66.00)	56.00 (48.00, 62.00)
Sex, no. (%)		
Female	38,921 (41.04%)	211,068 (57.25%)
Male	55,924 (58.96%)	157,627 (42.75%)
Ethnicity, no. (%)		
British	84,128 (88.70%)	322,856 (87.57%)
Non-British	10,502 (11.07%)	45,198 (12.26%)
Unknown	215 (0.23%)	641 (0.17%)
Geographical location, no. (%)		
England	84,144 (88.72%)	327,146 (88.73%)
Scotland	7190 (7.58%)	25,795 (7.00%)
Wales	3511 (3.70%)	15,754 (4.27%)
Townsend deprivation index, median (IQR)	−1.87 (−3.50, 1.13)	−2.17 (−3.67, 0.44)
Body mass index, median (IQR), kg/m^2	27.93 (25.18, 31.30)	26.46 (23.92, 29.53)
Diet, no. (%)		
Meat eater	91,055 (96.00%)	347,310 (94.20%)
Pescatarian	1441 (1.52%)	9101 (2.47%)
Vegetarian	1172 (1.24%)	7332 (1.99%)
Fish poultry	937 (0.99%)	4246 (1.15%)
Unknown	240 (0.25%)	706 (0.19%)
Smoking status, no. (%)		
Current	11,959 (12.62%)	37,511(10.17%)
Never	43,642 (46.01%)	209,949 (56.94%)
Previous	38,502 (40.59%)	119,261 (32.35%)
Unknown	742 (0.78%)	1,974 (0.54%)
Alcohol status, no. (%)		
Current	84,473 (89.06%)	340,336 (92.30%)
Never	5021 (5.29%)	15,666 (4.25%)
Previous	4957 (5.23%)	11,531 (3.13%)
Unknown	394 (0.42%)	1162 (0.32%)
Physical activity, IPAQ, no. (%)		
Low	15,818 (16.68%)	54,412 (14.76%)
Moderate	29,309 (30.90%)	121,916 (33.07%)
High	28,874 (30.44%)	121,436 (32.93%)
Unknown	20,844 (21.98%)	70,931 (19.24%)
Education, qualification no. (%)		
College or university degree	23,916 (25.22%)	125,768 (34.12%)
A levels/AS levels or equivalent	8722 (9.20%)	42,599 (11.55%)
O levels/GCSE or equivalent	18,487 (19.49%)	78,554 (21.31%)
CSE or equivalent	4147 (4.37%)	21,308 (5.78%)
NVQ or HND or HNC or equivalent	7431 (7.83%)	22,800 (6.18%)
Other professional qualifications	5549 (5.85%)	17,924 (4.86%)
None of the above	24,205 (25.52%)	52,813 (14.32%)
Unknown	2388 (2.52%)	6929 (1.88%)
Income, no. (%)		
Less than £18,000	25,643 (27.04%)	62,266 (16.89%)
18,000 to 30,999	21,489 (22.66%)	77,420 (21.01%)

Table 1 (continued)

Characteristics	CVD patients (*N* = 94,845)	Non-CVD individuals (*N* = 368,695)
31,000 to 51,999	17,116 (18.05%)	86,142 (23.36%)
52,000 to 100,000	11,114 (11.72%)	70,399 (19.09%)
Greater than 100,000	2777 (2.93%)	18,925 (5.13%)
Unknown	16,706 (17.60%)	53,543 (14.52%)
Employment		
In paid employment or self-employed	39,256 (41.39%)	232,305 (63.01%)
Retired	44,428 (46.84%)	102,647 (27.84%)
In paid employment or self-employed	1580 (1.67%)	11,472 (3.11%)
Unable to work because of sickness or disability	6317 (6.66%)	8812 (2.39%)
Unemployed	1606 (1.69%)	6290 (1.71%)
Doing unpaid or voluntary work	400 (0.42%)	1748 (0.47%)
Full or part-time student	124 (0.13%)	1177 (0.32%)
None of the above	532 (0.56%)	2076 (0.56%)
Unknown	602 (0.64%)	2168 (0.59%)
Sun exposure		
Time spend outdoors in summer, median (IQR), hours/day	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)
Time spend outdoors in winter, median (IQR), hours/day	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)
Hypertension, no.(%)		
Yes	64,593 (68.10%)	191,632 (51.98%)
No	30,252 (31.90%)	177,063 (48.02%)
Diabetes, no. (%)		
Yes	9304 (9.81%)	14,607 (3.96%)
No	85,541 (90.19%)	354,088 (96.04%)
Dyslipidaemia, no. (%)		
Yes	25,082 (26.44%)	22,631 (6.14%)
No	69,054 (72.81%)	344,498 (93.44%)
Unknown	709 (0.75%)	1566 (0.42%)
Aspirin intake		
Yes	32,407 (34.17%)	30,996 (8.41%)
No	60,158 (63.43%)	330,075 (89.53%)
Unknown	2280 (2.40%)	7624 (2.06%)
Cancer occurrence, no. (%)		
Yes	18,471 (19.47%)	66,891 (18.14%)
No	76,374 (80.53%)	301,804 (81.86%)
Survival, no. (%)		
Yes	81,181 (85.59%)	349,974 (94.92%)
No	13,664 (14.41%)	18,721 (5.08%)

CVD Cardiovascular disease, *IQR* Interquartile range, *IPAQ* International Physical Activity Questionnaire, *A* Advanced, *AS* Advanced subsidiary, *O* Ordinary, *GCSE* General Certificate of Secondary Education, *CSE* Certificate of Secondary Education, *NVQ* National Vocational Qualification, *HND* Higher national diploma, *HNC* Higher national certificate

for our study, we used RRs as the pooled estimates [19]. We assessed the risk of bias for each individual study using the Newcastle–Ottawa scale (NOS) tool [21]. Nine scores were assigned to three domains, with the NOS scores of 8–9, 6–8 and ≤ 5 standing for low, moderate and high risk of bias, respectively.

Statistical analysis

UKB cohort study

We calculated and compared the absolute cancer incidence rate in person-years. As the primary analysis, multivariable Cox proportional hazards models were fitted to estimate the CVD-cancer association (expressed as HRs

with 95% CIs) while adjusting for covariates. Considering that the outcome of cancer incidence is age-dependent, we used age as the time scale in the Cox model [22, 23]. Notably, the main exposure CVD status was adopted as a time-varying covariate—for incident CVD cases, the time periods from enrolment to CVD diagnosis and from CVD diagnosis to cancer incidence were modelled separately on a time-dependent basis [24].

We performed competing risk analysis by modelling sub-distributions of accumulated incident rates of competing risk events (non-cancer deaths) [25, 26]. Sensitivity analyses were conducted among incident CVD patients and CVD patients only defined by the primary diagnosis. We also performed sensitivity analyses by excluding sex-specific cancers (breast, prostate, gynaecological and genital system cancers) and by setting multiple lag times (cancer cases within 1, 2 and 3 years of follow-up were censored). Subgroup analyses based on age, sex, ethnicity, comorbidities and follow-up times (cancer incidence ≤ 3 vs > 3 years) were conducted.

Meta-analysis

We performed DerSimonian-Laird random-effect meta-analysis to generate pooled estimates of relative risk with 95% CI and *P*-values, in consideration of the inherent heterogeneity across different studies [27]. The between-study heterogeneity was evaluated using the I^2 statistic ($I^2 > 50\%$ was deemed as large heterogeneity) [28]. Possible small study effects were assessed using funnel plot symmetry and Egger's test for meta-analysis including over ten studies [29, 30]. We performed sensitivity analysis by only including studies with a low risk of bias, with a prospective design, reporting HRs as the primary metric and adjusting for the same set of confounding factors. Subgroup analyses were also performed based on sex, cancer and CVD subtypes and adjusted confounding factors. Studies reporting ≥ 3 CVD subtypes will be categorised as the 'All CVD' group, and who reported ≥ 3 cancer sites will be categorised as the 'All cancer' group. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using R (Version 4.2.1; R Foundation for Statistical Computing) software.

Results

Cohort study in the UKB

Among the 463,540 participants (94,845 CVD patients and 368,695 non-CVD individuals) included in the cohort study, 85,362 of them developed cancer with a median of 11.58 years of follow-up. A total of 50,031 CVD cases developed after enrolment. The detailed diagram of patient selection is presented in Additional file 1: Fig. S1A. The distributions of baseline characteristics between CVD patients and non-CVD individuals are shown in Table 1, with the crude incidence rate (per 1000 person-years) of different cancers among multiple CVD subtypes presented in Additional file 1: Table S4.

Overall, a higher cancer incidence was observed in CVD patients in comparison to non-CVD individuals (25.62 vs. 15.41 per 1000 person-years). In the multivariable Cox proportional hazards model, there was a significant association between CVD condition and a higher risk of any cancer (HR 1.14, 95% CI 1.12–1.17, $p < 0.001$). Similar significant results were observed among the five CVD subtypes, with the HRs ranging from 1.04 to 1.22. The associations were also significant at multiple cancer sites, except for prostate, head and neck cancer and melanoma. The full sets of effect estimates are presented in Additional file 1: Table S5. After adjusting for the potential competing effect, a similar 33% higher cancer risk was observed among patients with any CVD conditions (95% CI 1.30–1.36, $p < 0.001$). The detailed effect estimates from the Cox model are presented in Table 2 and Additional file 1: Fig. S2, with results from the competing risk model presented in Additional file 1: Table S6 and Fig. S3.

Consistent direction of effects of CVD on cancer risk was observed across subgroup (Additional file 1: Table S7) and sensitivity (Additional file 1: Table S8) analyses. The effect estimates observed in male CVD patients were similar to those in females (p for interaction 0.302). A larger effect size of HR was observed among CVD patients with age < 65 years old in comparison to those ≥ 65 years (p for interaction < 0.001). CVD patients diagnosed with cancer within 3 years of follow-up exhibited a larger effect on cancer risk in comparison to those > 3 years.

Meta-analysis

A total of 37,890 unique studies were identified through the literature search. After reviewing abstracts and full-texts, at last, 47 studies (The PRISMA flowchart presented in Additional file 1: Fig. S1B) including our UKB cohort study with 45,765,655 participants (9,486,438 CVD patients and 36,279,217 non-CVD individuals) included for our meta-analysis, with 1,494,440 cancer events occurring during follow-up. The basic characteristics of the included studies are presented in Additional file 1: Table S9 [10, 12, 24, 31–73].

Extracted adjusted effect estimates for each study are presented in Additional file 1: Table S10. Quality assessment identified an average NOS score of 7.5 out of 9 (Additional file 1: Table S11). Random-effect meta-analysis yielded a significantly higher overall cancer risk in patients with any CVDs (RR 1.13, 95% CI 1.11–1.15, $p < 0.001$), with significant heterogeneity shown ($I^2 = 52.5\%$). Stratified by CVD subtypes and cancer sites,

Table 2 Risk of cancer among CVD patients compared with non-CVD individuals in the UK Biobank

Cancer sites	All CVD (*N* = 94,845)		Ischemic heart disease (*N* = 41,681)		Cerebrovascular disease (*N* = 13,561)		Heart failure (*N* = 2636)		Arrhythmia/conduction disorder (*N* = 30,097)		Emboli/thrombosis (*N* = 6870)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
All cancer (*N* = 85,362)												
Cox model	1.14 (1.12, 1.17)	< 0.001	1.04 (1.01, 1.08)	0.007	1.13 (1.07, 1.19)	< 0.001	1.15 (1.02, 1.29)	0.028	1.18 (1.14, 1.22)	< 0.001	1.22 (1.14, 1.31)	< 0.001
Breast cancer (*N* = 10,571)[a]												
Cox model	1.02 (0.96, 1.05)	0.452	0.94 (0.83, 1.06)	0.325	1.08 (0.90, 1.30)	0.420	0.75 (0.44, 1.30)	0.278	0.91 (0.80, 1.04)	0.160	1.34 (1.10, 1.65)	0.004
Prostate cancer (*N* = 12,072)[a]												
Cox model	1.05 (0.99, 1.11)	0.121	0.97 (0.90, 1.06)	0.389	0.96 (0.85, 1.10)	0.574	0.90 (0.64, 1.25)	0.516	1.15 (1.05, 1.25)	0.001	0.89 (0.73, 1.08)	0.233
Colorectal cancer (*N* = 6721)												
Cox model	1.06 (0.98, 1.15)	0.168	0.93 (0.83, 1.05)	0.253	1.08 (0.89, 1.29)	0.440	1.01 (0.65, 1.58)	0.947	1.18 (1.08, 1.33)	0.007	1.09 (0.85, 1.39)	0.507
Haematologic/lymphatic cancer (*N* = 5134)												
Cox model	1.28 (1.17, 1.40)	< 0.001	1.06 (0.93, 1.21)	0.358	1.27 (1.05, 1.54)	< 0.001	1.72 (1.16, 2.56)	0.007	1.24 (1.08, 1.42)	0.002	1.55 (1.22, 1.98)	< 0.001
Melanoma (*N* = 2997)												
Cox model	1.04 (0.91, 1.18)	0.580	1.03 (0.85, 1.24)	0.776	0.93 (0.67, 1.29)	0.660	0.72 (0.30, 1.73)	0.464	1.21 (1.00, 1.45)	0.047	0.75 (0.53, 1.23)	0.235
Non-melanoma skin cancer (*N* = 25,481)												
Cox model	1.12 (1.08, 1.17)	< 0.001	1.02 (0.96, 1.08)	0.602	1.06 (0.97, 1.17)	0.205	1.08 (0.86, 1.37)	0.500	1.26 (1.13, 1.27)	< 0.001	1.17 (1.09, 1.33)	0.012
Bladder cancer (*N* = 2655)												
Cox model	1.22 (1.08, 1.37)	< 0.001	1.15 (0.98, 1.34)	0.078	1.33 (1.05, 1.70)	0.029	1.28 (0.72, 2.27)	0.399	1.24 (1.03, 1.48)	0.020	0.93 (0.77, 1.40)	0.736
Lung cancer (*N* = 4306)												
Cox model	1.65 (1.50, 1.81)	< 0.001	1.46 (1.29, 1.65)	< 0.001	1.46 (1.22, 1.76)	< 0.001	1.74 (1.15, 2.64)	0.008	1.56 (1.33, 1.79)	< 0.001	1.75 (1.37, 2.23)	< 0.001
Renal cancer (*N* = 1647)												
Cox model	1.40 (1.20, 1.64)	< 0.001	1.18 (0.96, 1.43)	0.112	1.44 (1.05, 1.96)	0.002	1.29 (0.61, 2.72)	0.504	1.35 (1.07, 1.71)	0.020	1.42 (0.93, 2.18)	0.107
Head and neck cancer (*N* = 1147)												
Cox model	1.06 (0.86, 1.30)	0.585	1.07 (0.81, 1.42)	0.628	0.89 (0.74, 1.46)	0.652	0.95 (0.31, 2.98)	0.936	1.19 (0.88, 1.62)	0.270	0.72 (0.34, 1.51)	0.383
Gynaecologic cancer (*N* = 3197)[a]												
Cox model	1.01 (0.90, 1.14)	0.873	0.93 (0.75, 1.15)	0.503	1.18 (0.87, 1.61)	0.296	1.09 (0.60, 2.24)	0.801	0.87 (0.69, 1.09)	0.230	1.37 (0.97, 1.94)	0.074
Gastroesophageal cancer (*N* = 1956)												
Cox model	1.19 (1.03, 1.37)	0.018	1.12 (0.93, 1.34)	0.249	1.31 (0.98, 1.74)	0.071	0.71 (0.71, 1.72)	0.451	1.21 (0.97, 1.50)	0.084	0.92 (0.58, 1.47)	0.735
Pancreatic cancer (*N* = 1388)												
Cox model	1.36 (1.15, 1.60)	< 0.001	1.12 (0.89, 1.41)	0.314	1.19 (0.83, 1.70)	0.347	1.90 (0.95, 3.55)	0.072	1.42 (1.11, 1.80)	0.004	1.74 (1.47, 2.64)	< 0.001
CNS tumour (*N* = 951)												
Cox model	1.31 (1.05, 1.62)	0.015	0.95 (0.69, 1.32)	0.766	2.75 (1.93, 3.93)	< 0.001	0.40 (0.06, 2.82)	0.365	0.92 (0.63, 1.34)	0.671	1.67 (0.96, 2.91)	0.069

Cox model: age, sex, ethnicity, geographical location, body mass index, Townsend deprivation index, diet, smoking, alcohol, physical activity, education, income, employment, sun exposure, hypertension, diabetes, dyslipidaemia and aspirin intake, *HR* Hazard ratio, *CI* Confidence interval, *CNS* Central nerve system

[a] For sex-specific (breast, prostate and gynaecologic) cancers, sex is not adjusted in the Cox models

we identified overall consistent effects of CVD diagnosis on higher subsequent cancer risk, with forest plots presented in Fig. 2 (details of effect estimates for specific CVD and cancer subtypes presented in Additional file 1: Table S12, with forest plots shown in Additional file 1: Fig. S4–S9). In particular, a significantly higher overall cancer risk was observed among individuals with heart failure (RR 1.29, 95% CI 1.06–1.56, $p=0.010$), arrhythmia/conduction disorder (RR 1.26, 95% CI 1.12–1.42, $p<0.001$) and emboli/thrombosis patients (RR 1.45, 95% CI 1.15–1.83, $p=0.002$). A lower risk of prostate cancer was observed among heart failure patients (RR 0.88, 95% CI 0.78–1.00, $p=0.053$). Funnel plots corresponding to meta-analysis with over ten studies revealed no evident asymmetry, and Egger's tests also suggested no small study effect bias (Additional file 1: Fig. S10).

Subgroup analyses were performed based on sex and adjusted confounding factors. As shown in Additional file 1: Table S13, all the subgroups presented a higher cancer risk among CVD patients, albeit no significant interaction was detected (p for interaction >0.05). We conducted further sensitivity analyses by only including prospective studies, studies with NOS ≥ 8, studies reporting HRs as the primary metric and studies adjusting for the same confounding factors. The results were consistent across all sensitivity analyses (Additional file 1: Table S14).

Discussion

As one of the largest cohort studies along with the first systematic review and meta-analysis, our findings underscored the higher cancer risk among individuals with prior CVD. Consistent results across various CVD and cancer subtypes together with multiple sensitivity analyses reinforced the robustness of our findings.

Shared biological risk factors could underlie the observed association between CVD and subsequent risk of cancer [3–5, 74–77]. For example, hypertension induces structural vascular and cardiac remodelling, and the angiogenic factors including VEGF secreted during hypertension could promote carcinogenesis [78, 79]. Diabetes mellitus, hyperlipidaemia, smoking and alcohol abuse are also associated with both CVD and cancer risk [80, 81]. Our results from multivariable analysis adjusting for these covariates remained significant. However, the effects of other unknown shared factors could not be precluded, which merits future exploration.

There has been growing interest in whether biological alterations in the context of CVD could cause tumorigenesis [6–8]. Biological evidence showed that hypoxia-inducible factor 1(HIF-1), produced in response to myocardial infarction, can stimulate tumour growth by promoting the expression of antiapoptotic factors and angiogenesis [82]. Other evidence included epigenetic alterations including DNA methylation, histone protein modification and RNA-based dysregulation in the context of ischemic CVD have also been associated with higher cancer risk [83, 84]. In addition, heart failure-induced microbial dysbiosis could contribute to colonic tumour formation in vivo [6]. On the basis of these animal studies, future efforts exploring relevant mechanisms using human samples are warranted. Although a recent study leveraged the Mendelian randomisation (MR) approach failed to identify a causal link between CVD and lung cancer risk at population-level [85], future collaborative efforts are expected to use this approach and comprehensively investigate possible causal effects of various CVD-related traits on cancer risk at different sites.

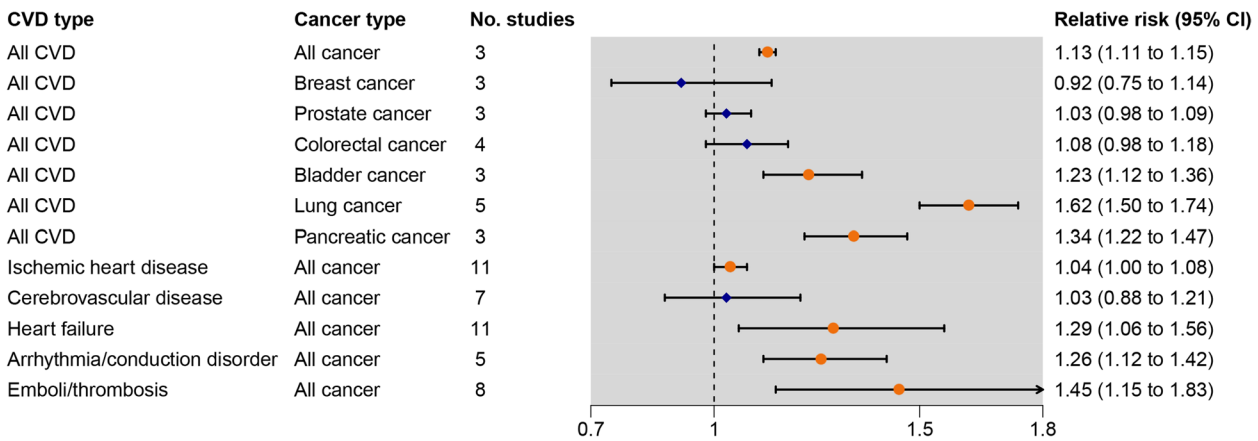

Fig. 2 Pooled effect estimates of relative risks for associations of CVD and subtypes with overall and site-specific cancer risk from meta-analysis. The blue squares showed that the effect estimate was insignificant, while the orange circle showed that the effect estimate was significant

Cardiovascular medications, such as Statin [86], Aspirin [87, 88], Metformin [89] and antihypertensive agents [90], have been widely linked to cancer risk, although evidence with high credibility remained sparse [86, 91]. However, their associations with cancer risk varied across different cancer types. For example, our UKB cohort study verified the widely reported association between aspirin intake and lower risk of colorectal cancer [87, 88]. Limited by data availability, we were unable to fully adjust these drug-specific effects. In addition to medications, exposure to radiation during cardiac imaging and intervention procedures might also contribute to higher risk, especially for cancer at lung and breast [92]. Given that this association is highly dependent on radiation dosage and site [93], these effects should be extensively adjusted by future efforts with more granular data being available.

In our cohort study, we employed both the standard Cox model and the competing risk model to estimate the effect. A previous study has claimed that subdistribution HRs cannot be interpreted as conventional HRs, because the subdistribution hazard model treats individuals who experienced competing risks as remaining in the numbers at-risk population rather than censoring [94, 95]. Non-cancer deaths have been widely investigated as a competing risk by previous studies [96, 97], although they would be censored in Cox regression. The fact that Cox and competing risk models yielded mostly consistent findings further underpinned the robustness of our findings. Notably, the Cox model identified a protective effect (HR < 1) of ischemic heart disease on breast cancer, which differed from the results of the competing risk model. A previous population-based cohort study reported a 30% lower risk of breast cancer among CVD patients [24]. Although mechanisms underlying this association are still unclear, there has been an increasing understanding of multiple shared pathways in sterol/oxysterol and hormone metabolism that influence plaque progression in atherosclerotic CVD and hormone-sensitive malignancies including breast cancer [98].

Our study analysed the association across various subgroups. Previous evidence suggested that the CVD-cancer association might be sex-specific [99, 100]. Our cohort study found no significant difference in the association among male and female individuals. Also, our findings remained consistent after excluding sex-specific cancers. In the meta-analysis, however, due to the limited number of included studies, we could not evaluate the potential interaction effect of sex. More large-scale cohort studies with sex subgroups investigating the association between CVD and different cancer risks are warranted in the future. Notably, our cohort study found that younger CVD patients (< 65 years) were subjected to significantly higher cancer risk in comparison to those ≥ 65 years, which resonated with previous evidence that cancer risk is higher among individuals diagnosed with congenital heart disease at younger age [101, 102]. The role of age in the CVD-cancer association merits further exploration in the future.

The prospective large-scale population-based cohort study design of UKB is the major strength of our study. We also performed, to our best knowledge, the first systematic review and meta-analysis on the association between pre-existing CVD and subsequent cancer risk. However, several limitations should be noted. Firstly, given the nature of observational cohort studies, although our observational study could not establish causality between prior CVD and subsequent cancer risk due to residual confounding effects, our findings support future causal investigation to further explore the association between CVD and cancer; Secondly, significant heterogeneity was observed among a sizable proportion of meta-analyses. Considering the limited data and diverse CVD and cancer subtypes among included studies, further exploration of the source of heterogeneity with more data on the associations between CVD and cancer subtypes is warranted. In addition, more data are needed for assessing overall cancer risk among patients with any CVD conditions; Thirdly, most previously published cohorts did not adopt competing risk models, and thus, meta-analysis could not be conducted. Lastly, the meta-analysis only evaluated observational studies published on peer-reviewed journals. Conference abstracts, grey literature and letters were therefore excluded.

Conclusions

Our findings support a higher risk of both overall and multiple types of cancer subsequent to various CVD conditions. After adjusting for common confounders, CVD patients are still subject to higher cancer risk, underscoring the rationale for deeper exploration of the potential causal mechanisms between CVD and cancer, and also highlighting the clinical significance of dynamic monitoring of cancer risk among CVD patients for the purpose of preventing malignancy and improving treatment strategies for both diseases.

Abbreviations

CVD	Cardiovascular disease
ICD	The International Classification of Diseases
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
HR	Hazard ratio
OR	Odds ratio
SIR	Standardised incidence ratio
CI	Confidence interval
NOS	Newcastle–Ottawa scale
RR	Relative risk

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04013-1.

Additional file 1: Table S1-[ICD codes for diagnoses]. Table S2-[Covariate characteristics (UKB)]. Table S3-[Literature search strategy]. Table S4-[Cancer incidence: CVD vs. non-CVD (UKB)]. Table S5-[Multivariable analysis for cancer risk in CVD patients (UKB)]. Table S6-[CVD-cancer risk via competing risk model (UKB)]. Table S7-[Subgroup analysis (UKB)]. Table S8-[Sensitivity analysis (UKB)]. Table S9-[Baseline characteristics of included studies (Meta-analysis)]. Table S10-[Outcome data summary (Meta-analysis)]. Table S11-[NOS scores (Meta-analysis)]. Table S12-[Specific CVD-cancer subtype associations (Meta-analysis)]. Table S13-[Subgroup analysis (meta-analysis)]. Table S14-[Sensitivity analysis(meta-analysis)]. Figure S1 to S10: FigS1-[Participant/study selection flowcharts (UK Biobank & meta-analysis)]. FigS2-[CVD-cancer hazard ratios (Cox model)]. FigS3-[CVD-cancer hazard ratios (competing risk model)]. FigS4 to S9-[CVD subtypes and cancer risk (All CVD, ischemic heart disease, cerebrovascular disease, heart failure, arrhythmia, embolism/thrombosis)]. FigS10-[Funnel plots (meta-analyses with >10 studies)].

Additional file 2. STROBE statement for UKB cohort study. PRISMA checklist for abstract (Meta-analysis). PRISMA checklist.

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Authors' contributions
Acquisition, analysis, or interpretation of data: C.S., H.H., H.L., L.W., H.W, C.L., X.X., B.Z., Z.L., X.C., J.Z. and Y.Z. Drafting of manuscript: C.S., H.H., Y.H. and C.X. Critical revision of the manuscript for important intellectual content: All co-authors. Statistical analysis: C.S., H.H., H.L., Z.L., X.C. and L.W. Study supervision: Y.H. and C.X. All authors read and approved the final manuscript.

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Data availability
All data supporting the UKB study are obtained from the UK Biobank. The usage of UK Biobank data has been approved by UK Biobank Research Team (Application ID:73759). Researchers who wish to access the data must follow the official procedure of data application from the UK Biobank (https://ams.ukbiobank.ac.uk/ams/). All data supporting the meta-analysis are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The UKB received ethical approval from the Research Ethics Committee (21/NW/0157).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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