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Cancer, genetic susceptibility and risk of coronary artery disease: A prospective study

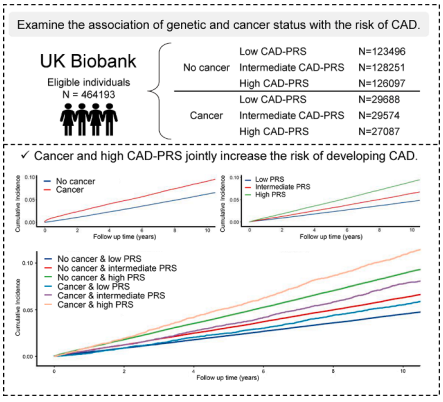
Yidan Wang [a,b], Shan Zhong [a], Na Sun [a], Yunfei Wu [a], Jun Lyu [c], Minghui Piao [a], Wenbo Qu [a], Xueyu Wang [a], Wenjun Ni [a], Xia Gu [a], Tianshu Han [d,**], Jinwei Tian [a,b,*]

[a] Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Harbin 150081, China
[b] Key Laboratory of Myocardial Ischemia, Ministry of Education, Harbin Medical University, Harbin 150001, PR China
[c] Department of Clinical Research, The First Affiliated Hospital of Jinan University, 613 West Huangpu Avenue, Guangzhou 510630, China
[d] Department of Nutrition and Food Hygiene, National Key Discipline, School of Public Health, Harbin Medical University, 157 Baojian Road, Harbin 150081, China

HIGHLIGHTS

- Cancer survivors have a significantly higher risk of CAD events compared to those without cancer. Positive joint effects suggest that high genetic susceptibility can further elevate the risk of CAD.
- Cancer survivors with high CAD genetic susceptibility may have higher risk of fatal CAD outcomes.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: Cancer survivors have an increased risk of developing coronary artery disease (CAD). We introduce CAD polygenic risk scores (PRS) and examine associations with cancer status on CAD outcomes.
Methods: From the UK Biobank, we identified cancer survivors and CAD outcomes among 464,193 CAD-free participants using linked cancer registries, hospitalizations, and death records. CAD-PRS was categorized as low (lowest tertile), intermediate (tertile 2), and high (highest tertile). Adjusted Cox models assessed the joint and interaction effects of cancer status and CAD-PRS on CAD outcomes.
Results: Over the follow-up (median 11.7 years), 36,332 participants developed CAD. Compared to low CAD-PRS, the hazard ratios (HRs) and 95% confidence intervals (CIs) for CAD was 1.35 (1.31–1.38) for intermediate and 1.86 (1.81–1.91) for high CAD-PRS. The HR (95% CI) for CAD in cancer survivors was 1.16 (1.13–1.19) compared to those without cancer. In the joint effect analysis, compared to participants with low CAD-PRS and

* Corresponding author at: Department of Cardiology, The second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Harbin 150081, China.
** Corresponding author at: Department of Nutrition and Food Hygiene, National Key Discipline, School of Public Health, Harbin Medical University, 157 Baojian Road, Harbin 150081, China.
E-mail addresses: shirlly_cool@163.com (N. Sun), 102403@hrbmu.edu.cn (T. Han), tianjinwei@hrbmu.edu.cn (J. Tian).

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no cancer, the HRs (95% CIs) for CAD were 1.37 (1.32–1.41) and 1.90 (1.84–1.96) for intermediate and high CAD-PRS without cancer, respectively. For those with cancer, the HRs (95% CIs) were 1.26 (1.19–1.33), 1.59 (1.51–1.67), and 2.13 (2.03–2.23) for low, intermediate, and high CAD-PRS, respectively. A significant multiplicative interaction (HR: 0.94, 95% CI: 0.91–0.98) was observed between CAD-PRS and cancer status on CAD. Additionally, a significant additive interaction between cancer and high CAD-PRS was found for fatal CAD.
Conclusion: Cancer was associated with a higher risk of CAD and may further increase the risk of CAD related to genetic factors.

1. Introduction

Cancer and cardiovascular diseases (CVD) account for approximately 50% of all deaths worldwide [1]. Owing to the explosion of novel cancer therapies, cancer survivors are expected to be 28.4 million in 2040 [2]. CVD remains the leading cause of non-cancer related mortality among cancer survivors, with coronary artery disease (CAD) being a significant contributor [3,4]. While cancer and CAD are traditionally viewed as distinct disease entities, there is growing evidence that they may interact on both genetic and non-genetic levels to influence disease progression [5]. The first guideline on cardio-oncology highlights the remarkable efficacy of cancer therapies while potential adverse effects, which may contribute to increased cardiovascular burden [6]. Despite sharing common risk factors and pathogenesis[7–9], the interplay between genetic factors and cancer in the development of CAD remains poorly understood.

Polygenic risk score (PRS) can provide a personalized assessment of an individual's susceptibility to disease by analyzing genetic variants, which can inform early intervention strategies. The US health organizations are considering integrating PRS into clinical practice [10]. The PRS for CAD risk was initially created and validated in the population of the UK Biobank, and has subsequently been validated in multiple populations, including French Canadian and South Asian descents [11,12]. Compared to the PRS for other types of CVD, PRS of CAD have stronger predictive effect. Therefore, it is particularly of interest to investigate the joint and interaction effects of cancer and CAD-PRSs on CAD outcomes for establishing more accurate intervention strategies for preventing the development of CAD among cancer survivors.

Therefore, to fill this evidence gap, this study aims to prospectively examine the joint and interaction effects of cancer and CAD-PRSs for CAD on the association between PRS for CAD and the occurrence of CAD outcomes, including total CAD, fatal and non-fatal CAD. By identifying individuals at higher risk of developing cancer-related CAD outcomes, our findings will contribute to the development of targeted and effective prevention strategies.

2. Materials and methods

2.1. Study design and participants

The study participants were recruited from the first survey of the UK Biobank study, which is an ongoing population-based prospective cohort study that recruited over 500,000 individuals aged 37–73 years between March 2006 and October 2010 from 22 assessment centers in England, Scotland, and Wales. Detailed information about the study design and recruitment has been previously described [13]. The data regarding this project were from Application No. 82,444. After excluding the participants in Fig. 1, 464,193 participant including 86, 349 cancer survivors and 377,844 no cancer controls were recruited in this study.

The North West Multi-center Research Ethics Committee in the United Kingdom, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland authorized the UK Biobank research. The UK Biobank received ethical approval from the North West Multicenter Research Ethics Committee (REC reference: 11/NW/03,820). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Assessment of cancer exposure

Information on cancers was obtained by linking hospital admission records and cancer registries with the UK Biobank [13]. Patients who had been diagnosed with cancer were identified by referring to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes. Specifically, the codes used to identify cancer cases were C00-C97. Further details of these specific cancer can be found in the **Supplemental Table 3**. In this study, individuals diagnosed with cancer before the occurrence of CAD were classified as cancer survivors, while those without any cancer diagnosis were assigned to the no cancer group.

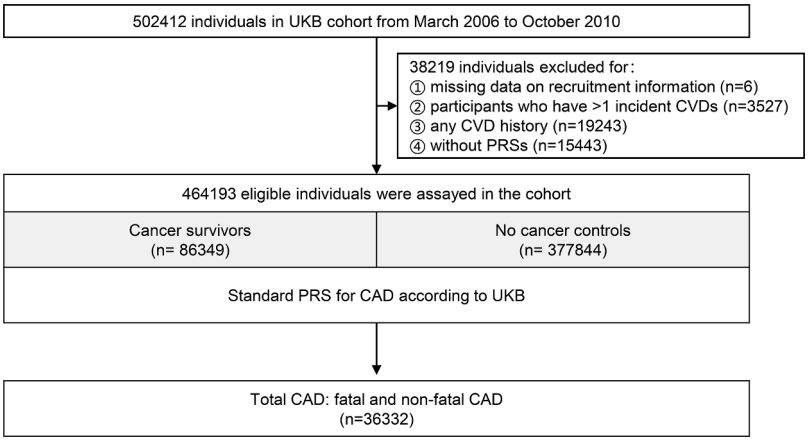

Fig. 1. Workflow.
Flowchart outlining eligible participants for this study in the UK Biobank. This flow diagram summarizes the number of participants available for each analysis. Abbreviations: Cardiovascular disease (CVD), coronary artery disease (CAD), polygenic risk score (PRS).

2.3. Polygenic risk score

PRS for CAD information for the genotyping and imputation in the UK Biobank has been described in detail elsewhere [14]. Genetic variants used to generate PRS weights were required to have an INFO score > 0.8 in both UKB and GWAS meta-analysis dataset. The odds ratio (OR_j) value of each SNP was extracted from the literature and the β_j (the log of the OR) value was calculated to represent the weight of each genetic variant. Then the SNP_j was recoded as 0, 1, and 2 according to the number of risk alleles (M). The PRS was calculated by the following formula [15]:

$$PRS = \sum_{j=1}^{M} \beta_j SNP_j.$$

2.4. Ascertainment of CAD outcomes

The UK Biobank (https://www.ukbiobank.ac.uk) primarily obtained information on total CAD, fatal and non-fatal CAD by referring to hospital admission records and death registries [13]. Information on CAD was obtained from medical records by utilizing the following ICD-10 codes: I20-I25 for CAD. Incident cases of all-cause death were identified by linking the dataset to national death registries. Additionally, we conducted a sensitivity analysis using myocardial infarction (MI) diagnosis (ICD 121) as a secondary outcome.

2.5. Assessment of covariates

In the present study, potential confounders including demographics and risk factors in CAD and cancer are as follows. The following covariates were included: age, sex, ethnicity, education, household income, physical activity, smoking status, drinking status, body mass index (BMI), Townsend Deprivation Index (TDI), diastolic blood pressure (DBP), systolic blood pressure (SBP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL), triglycerides (TG), total cholesterol (TC), glucose, use of antihypertensive drugs, use of lipid-lowering drugs, history of diabetes, and history of lipidaemias in accordance with prior knowledge [8,16,17]. Further details of these measurements can be found in the **Supplemental methods** and **Supplemental Table 1**.

2.6. Statistical analysis

All statistical analyses were performed by R 4.2.1, and two-sided $P < 0.05$ were considered to be statistically significant. Baseline demographic characteristics were reported and compared between the cancer survivors' group and the no cancer control group. Continuous variables were presented as the means ± standard deviations or medians (25th-75th percentiles) depending on their distributions that were examined by the Kolmogorov-Smirnov test. Categorical variables are presented as numbers (percentages). Differences in the baseline characteristics were compared between cancer survivors and cancer-free controls using Student's t-test for normally distributed continuous variables, and the Mann-Whitney U test for nonnormally distributed continuous variables and the $\chi 2$ test for categorical variables.

After testing the proportional hazards (PH) assumption using log-minus-log (LML) plots (**Supplemental Figure 1**), cox proportional hazards regression models were applied to estimate the hazard ratios (HRs) and 95% CIs of CAD outcomes in relation to CAD-PRS and cancer status. The survival time was defined as the number of years from recruitment to death and the occurrence of CAD or the census (1st February 2022), whichever came first. Models were adjusted for covariates, including age (years) (continuous), sex (male/female) (categorical), ethnicity (college degree/other) (categorical), education level (categorical), household income (< £31,000 / ≥ £31,000) (categorical), physical activity (high: ≥3000 MET-min/week, moderate: 600-<3000 MET-min/week, low: <600 MET-min/week) (categorical), smoking status (current/former/never) (categorical), drinking status (current/former/never) (categorical), BMI (<25 kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2) (categorical), TDI (continuous), DBP (mmHg) (continuous), SBP (mmHg) (continuous), HDL-C (mmol/L) (continuous), LDL (mmol/L) (continuous), TG (mmol/L) (continuous), TC (mmol/L) (continuous), glucose (mmol/L) (continuous), use of antihypertensive drugs (Yes/No) (categorical), use of lipid-lowering drugs (Yes/No) (categorical), history of diabetes (Yes/No) (categorical), and history of lipidaemias (Yes/No) (categorical). We assigned missing data as a separate indicator category for categorical variables (BMI, household income, ethnicity, education level, physical activity, smoking status, drinking status) and imputation was using mean values for continuous variables as DBP, SBP, HDL-C, LDL, TG, TC, glucose, detailed in **Supplemental Table 2**.

To analyze the joint effects of cancer exposure and genetic factors on total, non-fatal CAD, fatal CAD. The CAD-PRSs were categorized into tertiles (low, intermediate, and high). Therefore, the participants were cross-grouped into 6 groups based on cancer exposure and CAD-PRS tertiles. The group with no cancer and the lowest CAD-PRSs was set as the reference group. Additionally, we examined the multiplicative interaction between cancer and CAD-PRS by incorporating both variables and their cross-product term in the same model. [18] The relative excess risk due to interaction (RERI) was used to assess the additive interaction between cancer and PRS exposure for CAD outcomes. [19] RERI quantifies the increase in risk due to both exposures over the sum of the risks caused by each individual exposure factor. A positive RERI indicates a synergistic interaction, meaning the combined effect of two exposures are greater than the sum of their individual effects. Conversely, a negative RERI suggests an antagonistic interaction, where the combined effect is less than the sum of the individual effects, indicating that one exposure reduces the effect of the other. [20] Notably, RERI represents an absolute measure of excess risk due to interaction, despite being derived from relative measures.

Cox proportional hazard (CPH) models and the cumulative risks of CAD outcomes for cancer exposure and genetic risks were calculated using the R packages "survival". The cumulative risk curves were plotted using the R packages and "survminer" package, where no cancer exposure and the low genetic risk group were set as the reference group.

Several additional analyses were performed to assess the robustness of our study results. The analyses were conducted by stratifying the population by sex and median age to identify subgroups susceptible to CAD outcomes and to evaluate the joint PRS for CAD and cancer risk in different populations. In our sensitivity analyses, participants with a history of cancer at baseline were categorized into the cancer group, while those without a history of cancer were assigned to the no cancer group. Additionally, participants diagnosed with CAD within two years of their cancer diagnosis were excluded to reduce potential reverse causality. Furthermore, we excluded individuals undergoing cancer treatment to ensure the robustness of our findings. Besides, we analyze the joint effects of cancer exposure and genetic factors on MI as a secondary outcome to avoid bias in those undergoing cancer surveillance for the stable CAD diagnosis.

We also evaluated the joint effects of specific cancer types, including lung cancer, breast cancer, and colon cancer, with no such cancers and CAD-PRS on CAD outcomes. This analysis aimed to understand the interaction between these specific cancers and CAD-PRS in influencing CAD outcomes.

3. Results

3.1. Characteristics of the study population

During a median follow-up of 11.7 years (interquartile range 12.6–13.5 years), a total of 36,332 (7.8%) participants were diagnosed with CAD, including 32,741 (90.1%) with non-fatal CAD and 3591

(9.9%) with fatal CAD (Fig. 1). The characteristics of the study population were presented in Table 1, and differences in these characteristics were observed between cancer survivors and no cancer controls. The breakdown of cancer cases by site is shown in **Supplemental Table 3**. Specifically, cancer survivors were more likely to be older, female, white, and former smokers. They also had a higher prevalence of lipidaemias, diabetes, use of hypotensive and lipid-lowering drugs, higher TG, and higher SBP and DBP. They also had lower TDI scores, education levels, and household incomes (all $P < 0.001$) compared to participants without cancer.

Table 1
Baseline characteristics of study cohorts according to cancer status.

	Cancer survivors (N = 86,349)	No cancer controls (N = 377,844)	P -value
Age, years (mean ± SD)	59.8 ± 7.0	55.5 ± 8.1	<0.001
Sex, n (%)			<0.001
Female	45,928 (53.2)	210,960 (55.8)	
Male	40,421 (46.8)	166,884 (44.2)	
Body mass index, kg/m² (mean ± SD)	27.4 ± 4.7	27.3 ± 4.8	0.076
Household income, n (%)			<0.001
< £31,000	39,208 (45.4)	148,138 (39.2)	
≥ £31,000	33,556 (38.9)	176,080 (46.6)	
Missing	13,585 (15.7)	53,626 (14.2)	
Drinking status, n (%)			<0.001
Never	3192 (3.7)	16,885 (4.5)	
Former	3070 (3.6)	12,897 (3.4)	
Current	79,929 (92.6%)	347,074 (91.9)	
Missing	158 (0.2%)	998 (0.3%)	
Smoking status, n (%)			<0.001
Never	44,196 (51.2)	212,147 (46.0)	
Former	33,025 (38.2)	124,275 (32.9)	
Current	8684 (10.1)	39,595 (10.5)	
Missing	444 (0.5)	1827 (0.5)	
Physical activity, n (%)			0.003
High (≥3000 MET-min/week)	21,508 (24.9)	94,350 (25.0)	
Moderate (600-<3000 MET-min/week)	35,002 (40.5)	154,937 (41.0)	
Low (<600 MET-min/week)	12,944 (15.0)	56,537 (15.0)	
Missing	16,895 (19.6)	71,984 (19.1)	
Ethnicity, n (%)			<0.001
White	83,791 (97.0)	353,786 (93.6)	
Black	303 (0.4)	2445 (0.6)	
Asian	756 (0.9)	9396 (2.5)	
Mixed	738 (0.9)	6640 (1.8)	
Missing	761 (0.9)	5577 (1.5%)	
Education level, n (%)			<0.001
College degree or above	26,470 (30.7)	126,403 (33.5)	
High school or below	41,604 (48.2)	188,260 (49.8)	
Missing	18,275 (21.2)	63,181 (16.7)	
History of lipidaemias, n (%)	13,135 (15.2)	45,977 (12.2)	<0.001
History of diabetes, n (%)	2284 (2.6)	7663 (2.0)	<0.001
Hypotensive drug, n (%)	14,548 (16.8)	50,193 (13.3)	<0.001
Lipid-lowering drug, n (%)	17,582 (20.4)	60,139 (15.9)	<0.001
HDL-C, mmol/L (median, IQR)	1.5 (1.2, 1.6)	1.4 (1.2, 1.7)	0.641
LDL, mmol/L (median, IQR)	3.6 (3.0, 4.1)	3.5 (3.0, 4.1)	0.548
TG, mmol/L (median, IQR)	1.6 (1.1, 2.1)	1.5 (1.0, 2.1)	<0.001
TC, mmol/L (median, IQR)	5.7 (5.0, 6.4)	5.7 (5.0,6.4)	0.090
Glucose, mmol/L (mean ± SD)	82.5 ± 10.3	82.3 ± 10.3	0.702
SBP, mmHg (mean ± SD)	142.1 ± 19.3	139.1 ± 18.9	<0.001
DBP, mmHg (mean ± SD)	82.5 ± 10.6	82.3 ± 10.7	<0.001
Townsend Index (median, IQR)	−2.4 (−3.8, 0.1)	−2.1 (−3.6, 0.5)	<0.001

Abbreviations: Diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), interquartile range (IQR), low-density lipoprotein (LDL), standard deviation (SD), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG).

3.2. Cumulative risks of total CAD for cancer and CAD-PRS exposure

The cumulative risks of total CAD were markedly higher in cancer survivors versus no cancer controls (Fig. 2A). The 10-year cumulative CAD incidence was 9.1% versus 6.2%, respectively. Cumulative CAD risks also rose with increasing CAD-PRS (Fig. 2B). The 10-year CAD cumulative incidence was 4.6%, 6.4%, and 9.0% for low, intermediate, and high CAD-PRS tertiles. As illustrated in Fig. 2C, the highest 10-year cumulative CAD risk from cancer diagnosis occurred in cancer survivors with high CAD-PRS, followed by no cancer/high PRS, cancer/intermediate PRS, no cancer/intermediate PRS, cancer/low PRS, and finally no cancer/low PRS groups. The 10-year cumulative total CAD incidence was 10.9%, 8.9%, 7.8%, 6.3%, 5.5%, and 4.5% in each risk tertile, respectively. In summary, cumulative CAD risks were highest for those with joint cancer history and elevated genetic CAD predisposition.

3.3. Association between CAD outcomes and exposures of CAD-PRS and cancer status

Participants with cancer had a higher risk compared to those without cancer. Specifically, the HRs (95% CI) were 1.16 (1.13–1.19), 1.15 (1.12–1.19), and 1.22 (1.12–1.33) for total CAD, non-fatal CAD, and fatal CAD, respectively. When considering genetic predisposition, participants with high CAD-PRS had significantly higher risks across all outcomes. For total CAD, the HRs were 1.35 (1.31–1.38) for intermediate and 1.86 (1.81–1.91) for high CAD-PRS. For non-fatal CAD, the HRs were 1.32 (1.29–1.36) for intermediate and 1.79 (1.74–1.84) for high CAD-PRS. For fatal CAD, the HRs were 1.55 (1.41–1.71) for intermediate and 2.54 (2.32–2.78) for high CAD-PRS. Details were shown in **Supplemental Table 4**.

3.4. Joint effect of cancer status and genetic predisposition on CAD risk

Fig. 3 shows the association between CAD outcomes and the joint exposures of cancer status and level of CAD-PRS. For total CAD, compared to participants with low genetic predisposition and no cancer, the HRs (95% CIs) were 1.26 (1.19–1.33), 1.59 (1.51–1.67), and 2.13 (2.03–2.23) for low, intermediate, and high genetic predisposition and cancer, respectively, and 1.37 (1.32–1.41) and 1.90 (1.84–1.96) for those with intermediate and high genetic predisposition and no cancer. For non-fatal CAD, compared to participants with low genetic predisposition and no cancer, the HRs (95% CIs) were 1.35 (1.30–1.39) and 1.84 (1.78–1.89) for those with intermediate and high genetic predisposition, respectively, and 1.57 (1.49–1.65) and 2.02 (1.92–2.12) for those with cancer. For fatal CAD, compared to participants with low genetic predisposition and no cancer, the HRs (95% CIs) were 1.54 (1.39–1.72) and 2.48 (2.24–2.74) for those with intermediate and high genetic predisposition, respectively, and 1.81 (1.53–2.13) and 3.24 (2.82–3.72) for those with cancer. There were significant multiplicative interactions between cancer exposure and CAD-PRS tertiles (as a dummy variable) for total CAD with HRs (95% CI) being 0.94 (0.91–0.98), and the according $P = 0.001$. Additionally, there was significant additive synergistic interaction between exposures of cancer and high CAD-PRS for fatal CAD (RERI: 0.21, 95% CI: 0.09–0.32, $P < 0.001$) compared to participants with low CAD-PRS and no cancer (**Supplemental Figure 2**). Full results of interaction effects between cancer status and genetic disposition were shown in **Supplemental Table 5**.

3.5. Additional analyses

Similar results were obtained when we (1) analyzed the associations of CAD and cancer and CAD-PRS exposure stratified by sex and median age (**Supplemental Tables 6–7**), (2) categorizing participants with a history of cancer at baseline into the cancer group and those without a history of cancer into the control group. (**Supplemental Table 8**), (3) excluding individuals with CAD outcomes within 2 years of their cancer

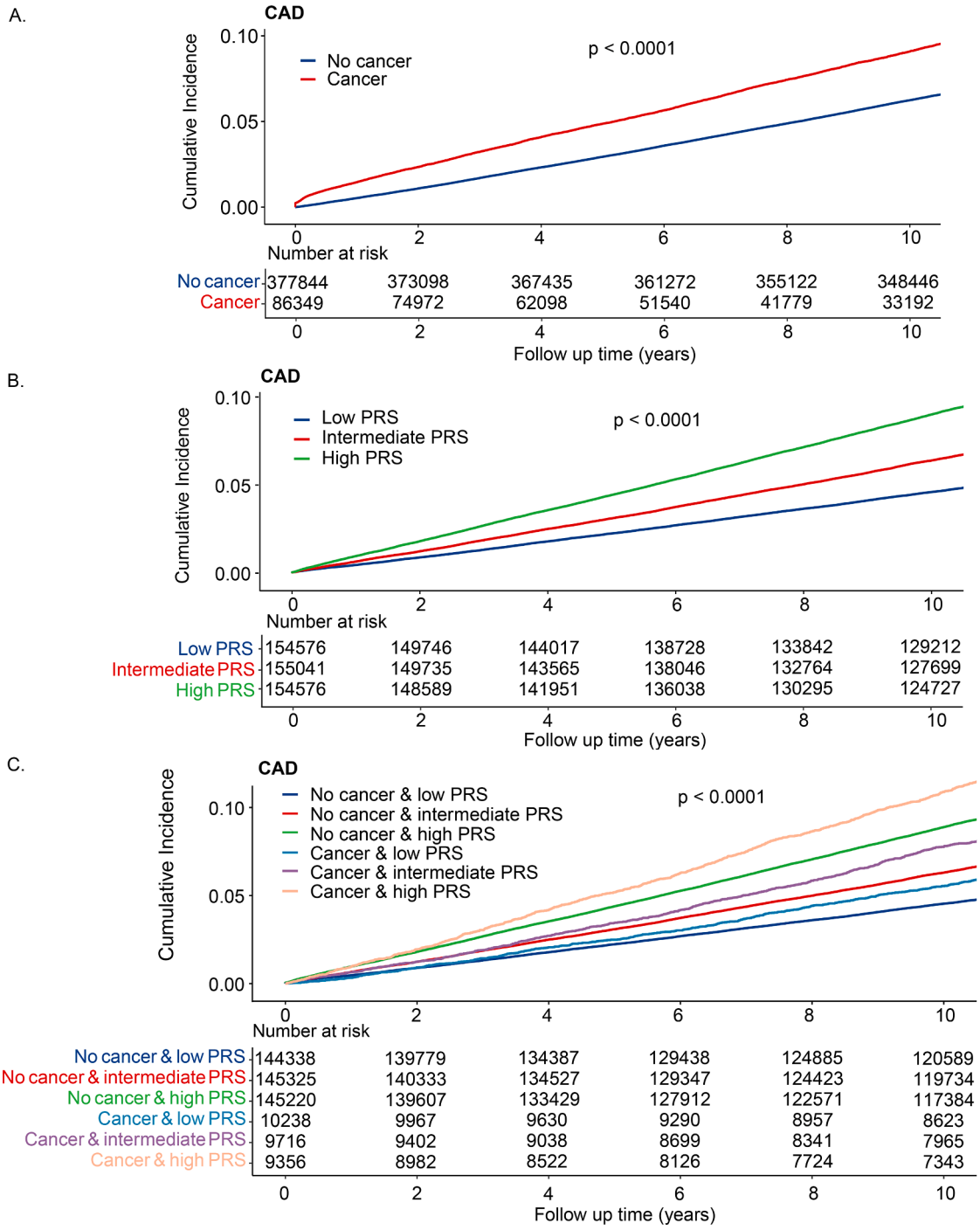

Fig. 2. The cumulative risks of total CAD by cancer status and tertiles of CAD-PRS.
High CAD-PRS (tertile1): ≥0.23, intermediate CAD-PRS (tertile2): −0.59 −0.23, low CAD-PRS (tertile3): < −0.59. Abbreviations: Coronary artery disease (CAD), polygenic risk score (PRS).

diagnosis (**Supplemental Table 9**), (4) excluding individuals undergoing cancer treatment (**Supplemental Table 10**). (5) considering MI as a secondary outcome (**Supplemental Table 11**), (6) analyzed the joint effects of specific cancer types, including lung cancer, breast cancer, and colon cancer, compared to no specific cancer types (**Supplemental Table 12**).

4. Discussion

Based on a large cohort of UK Biobank, this study found that (1) cancer is associated with an increased risk of CAD, (2) genetic factors are associated with a higher risk of CAD, (3) the risk of CAD is further elevated in individuals with cancer, particularly those with a high genetic predisposition, and (4) the association between cancer and fatal CAD is stronger in individuals with high genetic risk compared to those with low genetic predisposition.

Cancer survivors are at a higher risk of developing CAD, especially those with a high genetic risk for CAD. It is not surprising that cancer survivors are at an increased risk for CAD, as cancer treatments such as radiation therapy and chemotherapy can damage the cardiovascular

Outcomes		Exposures	Participants	Cases	HR (95% CI)	*P-value*
Fatal CAD	Cancer	High CAD-PRS	27087	339	3.24 (2.82,3.72)	<0.001
		Intermediate CAD-PRS	29574	195	1.81 (1.53,2.13)	<0.001
		Low CAD-PRS	29688	117	1.13 (0.92,1.38)	0.248
	No cancer	High CAD-PRS	126097	1494	2.48 (2.24,2.74)	<0.001
		Intermediate CAD-PRS	128251	913	1.54 (1.39,1.72)	<0.001
		Low CAD-PRS	123496	533	Reference	
Non-fatal CAD	Cancer	High CAD-PRS	27087	2300	2.02 (1.92,2.12)	<0.001
		Intermediate CAD-PRS	29574	1920	1.57 (1.49,1.65)	<0.001
		Low CAD-PRS	29688	1523	1.27 (1.20,1.35)	<0.001
	No cancer	High CAD-PRS	126097	12033	1.84 (1.78,1.89)	<0.001
		Intermediate CAD-PRS	128251	8842	1.35 (1.30,1.39)	<0.001
		Low CAD-PRS	123496	6123	Reference	
Total CAD	Cancer	High CAD-PRS	27087	2639	2.13 (2.03,2.23)	<0.001
		Intermediate CAD-PRS	29574	2115	1.59 (1.51,1.67)	<0.001
		Low CAD-PRS	29688	1640	1.26 (1.19,1.33)	<0.001
	No cancer	High CAD-PRS	126097	13527	1.90 (1.84,1.96)	<0.001
		Intermediate CAD-PRS	128251	9755	1.37 (1.32,1.41)	<0.001
		Low CAD-PRS	123496	6656	Reference	

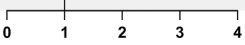

Fig. 3. Adjusted HRs and 95% CI of CAD outcomes by joint effect of cancer status and CAD-PRS tertiles: results from Cox regression models.
Significant RERI was observed for fatal CAD between high CAD-PRS with cancer and low CAD-PRS without cancer (HR: 0.21, 95% CI: 0.09–0.32). Model adjusted for age, sex, ethnicity, education level, household income, physical activity, smoking status, drinking status, BMI, TDI, DBP, SBP, HDL-C, LDL, TG, TC, glucose, use of antihypertensive drugs, use of lipid-lowering drugs, history of diabetes, and history of lipidaemias. High CAD-PRS (tertile1): ≥0.23, intermediate CAD-PRS (tertile2): −0.59 −0.23, low CAD-PRS (tertile3): < −0.59. Abbreviations: Body mass index (BMI), coronary artery disease (CAD), confidence interval (CI), Cox proportional hazard models (CPH), diastolic blood pressure (DBP), hazard ratios (HRs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL), polygenic risk score (PRS), systolic blood pressure (SBP), total cholesterol (TC), Townsend Deprivation Index (TDI), and triglycerides (TG).

system [21–23]. Existing research indicates that cancer and CAD share common predictive factors. Previous studies have demonstrated the utility of Coronary Artery Calcium (CAC) scoring in predicting cardiovascular events and cancer [24,25]. Similarly, the Pooled Cohort Equations (PCE) score, which is widely used to estimate the 10-year risk of atherosclerotic cardiovascular disease (ASCVD), has also been validated in cancer prediction [17]. These findings suggest that patients with cancer are more likely to develop CAD. The study also found that individuals with a high genetic risk for CAD had a significantly higher risk of developing CAD, regardless of whether they had cancer or not [26]. This suggests that genetic factors play a crucial role in the development of CAD and that individuals with a high genetic risk should be closely monitored for the development of CAD [15,26]. Identifying individuals with a high genetic risk for CAD is now possible due to the availability of genetic testing [27,28].

Previous research has mainly focused on the relationship between CAD-PRS and CAD [11,15,26] or cancer and CAD [16,22]. There is a lack of confirmation in the general population regarding the impact of cancer on the relationship between CAD-PRS and CAD. The findings in this study suggest that there is a significant joint effect between these two factors. Specifically, individuals with high CAD-PRS and cancer have a higher risk of developing CAD than those with no cancer and low CAD-PRS. Analysis of the secondary outcome MI also supports this view. These results are consistent with a previous study that childhood cancer survivors with high PRS scores may be at greater risk of CAD and would benefit from targeted screening and personalized preventive interventions [29]. Additionally, we found that the joint effect of high CAD-PRS in breast cancer patients significantly increased the risk of CAD outcomes. Further evidence can be found that a CAD-PRS can risk-stratify breast cancer survivors independently of other established cardiovascular risk factors [30]. Similar results were observed in lung and colon cancers. The study also identified significant modification effects between cancer and CAD-PRS, indicating that the effect of cancer on CAD risk may differ depending on an individual's genetic risk.

It is noteworthy that an additive interaction was found between cancer and high tertiles of CAD-PRS on the risk of fatal CAD. This indicates that the combined impact of cancer and genetic predisposition for CAD exceeds the sum of their individual risks, implying that cancer survivors with a high CAD-PRS may face a heightened risk of fatal CAD events compared to those without cancer. Thus, cancer survivors with a high CAD-PRS should pay more attention to prevention of fatal CAD.

Although the precise mechanisms underlying the interaction between cancer and high genetic CAD risk remain unclear, existing evidence suggests shared genetic susceptibility may contribute [31]. Recent studies demonstrate somatic mutations like clonal hematopoiesis of indeterminate potential (CHIP) may negatively impact cardiovascular health [32]. CHIP is associated with multiple cancers, especially hematological cancers and some solid tumors such as lung cancer, breast cancer, and colorectal cancer [33]. While somatic mutations are known to increase hematological cancer risk, experimental studies reveal TET2-deficient hematopoietic cells with somatic mutations exhibit larger atherosclerotic plaques [34,35]. Moreover, whole-exome sequencing has linked CHIP mutations to increased CAD risk [36]. Further research is needed to better understand the underlying mechanisms behind the joint and interaction effect of cancer and high CAD-PRS on CAD outcomes and to develop effective prevention and treatment strategies for high-risk individuals.

The strengths of our study include the large sample size and the comprehensive genetic data available in the UK Biobank. Firstly, it demonstrates that high genetic predisposition can further elevate CAD risk in cancer survivors, emphasizing the necessity of incorporating both factors in risk assessment. Secondly, interaction analysis indicates that genetic predisposition to CAD in cancer survivors is more predictive of fatal CAD implying that cancer survivors with high CAD-PRS should focus more on preventing fatal CAD. Thirdly, we adjusted all the variables included in the PCE in models to provide a comprehensive assessment of CAD risk. However, this study has some limitations. Firstly, the absence of CAC data in the UK Biobank is a limitation, as CAC scoring provides a direct assessment of CAD risk. Future research should aim to integrate CAC scoring with genetic risk scores and traditional risk factors to develop more robust CAD risk prediction models. Second, the UK Biobank cohort may limit generalizability to other populations. Third, the study design, including the selection of non-cancer controls, is a limitation. We have conducted a sensitivity analysis by categorizing

participants with a history of cancer before enrollment into the cancer group and those without a history of cancer into the control group. Fourth, the UKB database does not specifically collect detailed information on cancer staging and prognosis. Future studies should consider including detailed cancer staging and prognosis information to better understand their impact on CAD risk.

5. Conclusions

The study suggests that cancer survivors with a high genetic risk of CAD are particularly vulnerable to developing CAD outcomes. Cancer and high genetic predisposition for CAD jointly increased the risk of developing CAD. Furthermore, cancer survivors with high CAD-PRS may face a higher risk of fatal CAD. This study provides initial evidence warranting additional mechanistic research to better understand the observed joint and interaction effects between cancer status and genetic CAD risk on CAD outcomes. Besides, the findings underscore that cancer survivors with high CAD-PRS should pay more attention to prevent CAD, especially fatal-CAD.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 3.5 in order to improve readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data availability statement

Data are available in a public, open access repository. Data are available on reasonable request and with the permission of the UK Biobank.

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CRediT authorship contribution statement

Yidan Wang: Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Shan Zhong:** Methodology. **Na Sun:** Writing – review & editing. **Yunfei Wu:** Formal analysis. **Jun Lyu:** Resources. **Minghui Piao:** Methodology. **Wenbo Qu:** Investigation. **Xueyu Wang:** Investigation. **Wenjun Ni:** Investigation. **Xia Gu:** Funding acquisition. **Tianshu Han:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jinwei Tian:** Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100926.

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