CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Controlling Risk Factors Reduces Cancer Risk in Patients with Atherosclerotic Cardiovascular Disease: A Cohort Study

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ABSTRACT

BACKGROUND: The association of atherosclerotic cardiovascular disease (ASCVD) with cancer occurrence is not well examined, and the impact of common risk factors on the risk of cancer in ASCVD patients is not known. This study aimed to explore the effect and possible causes of ASCVD on cancer risk through a cohort study.

METHODS: A total of 14,665 age- and sex-matched pairs of participants were recruited from the Kailuan cohort (ASCVD vs non-ASCVD). A competing risk model was used to calculate the risk of cancer after ASCVD.

RESULTS: A total of 1124 cancers occurred after 5.80 (3.05-9.44) years of follow-up. The ASCVD group had a reduced risk of cancer (hazard ratio 0.74; 95% confidence interval, 0.65-0.85). Also, the risk of cancer in the digestive system, respiratory system, urinary system, and reproductive system was reduced by 17%, 16%, 14%, and 52%, respectively. According to the status of systolic and diastolic blood pressure, fasting blood glucose, high-sensitivity C-reactive protein and body mass index after ASCVD, the risk of overall cancer and digestive system cancer decreased with the increase in the number of ideal indicators (P for trend $< .01$). With the increase of follow-up time, the risk of cancer and the 5 site-specific cancers gradually decreased.

CONCLUSIONS: Cancer risk can be reduced by controlling for common risk factors after ASCVD event. This risk reduction is site-specific-, time-, and the number of ideal indicator-dependent.

 • The American Journal of Medicine (2024) 137:341−349

KEYWORDS: Atherosclerotic cardiovascular disease; Cancer; Competing risk model; Kailuan cohort; Risk factors

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality worldwide, accounting for 17.6 million deaths annually.[1] Cancer has also become a major public health problem globally and ranks as the first or second leading cause of death in 112/183 countries.[2] The 2 diseases share many similarities in risk factors and pathogenesis. Accumulating recent evidence supports "reverse cardio-oncology," in which cardiovascular disease influences cancer development.[3] Several studies have reported the association among stroke, atrial fibrillation, myocardial infarction (MI), heart failure (HF), and percutaneous

Funding: None.

Conflicts of Interest: These authors declare that they have no conflicts of interests.

Authorship: Conceptualization: QY, LY, TL, GW, and SW; Data curation: QY, ZW, and HZ; Formal analysis: QY, ZS, and HZ; Methodology: QY, LY, ZW, ZS, and SW; Project Administration: QY, BF, LY, TL, and SW; Writing − Original Draft: QY, BF, LY, TL, and SW; Writing − Review & Editing: QY, TL, BF, GW, and SW.

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0002-9343/© 2024 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjmed.2023.12.003

coronary intervention (PCI) and cancer.[4-11] However, most of the evidence has been obtained from retrospective analyses or cross-sectional studies and does not demonstrate a causal correlation. Furthermore, studies on the effect of ASCVD on cancer risk have been inconsistent and have not considered the competing risk of death.[10,12] Whether ASCVD itself or shared risk factors underlie the increased ASCVD-associated cancer risk is unclear, especially whether controlling risk factors can reduce the risk of cancer in patients with ASCVD.

The current study aimed to clarify the impact of ASCVD on cancer using complete Kailuan cohort data and to explore whether controlling the risk factors can reduce the risk of cancer in ASCVD patients.

CLINICAL SIGNIFICANCE

- Controlling the common risk factors of atherosclerotic cardiovascular disease (ASCVD) and cancer can reduce the risk of cancer in ASCVD patients.
- Our data suggest that clinical treatment should control common risk factors for ASCVD and cancer to achieve a common optimal outcome for both cardiovascular disease and cancer.

MATERIALS AND METHODS

Participants

The Kailuan study is an ongoing prospective cohort study in the Kailuan community in Tangshan. The study design and procedures have been described elsewhere.[13,14] All participants in Kailuan Study are employees and retirees of the Kailuan Group, which is a coal mining company in Tangshan. During the first survey from June 2006 to October 2007, 101,510 adult participants were enrolled in the Kailuan study, where all participants completed questionnaire assessments and health checkups. Following surveys were conducted every 2 years thereafter. During the follow-up period from 2006 to 2020, among the 15,645 patients with the first occurrence of ASCVD (including ischemic stroke, HF, MI, and coronary revascularization), excluding those with cancer at baseline (n = 360) and those who did not participate in biennial examination (n = 619), 14,666 people met the inclusion criteria. The baseline data used the most recent examination results prior to the onset of ASCVD; these cases were matched 1:1 for age (±1 year) and sex with those without ASCVD during the follow-up period and participated in the follow-up in the same year. A total of 14,665 case-control pairs of participants were matched. The follow-up period started from the date of diagnosis for the subjects with ASCVD and from the time of the examination for the non-ASCVD group.[15]

While analyzing whether controlling the risk factors could affect the cancer risk in ASCVD patients, we excluded 6775 patients who did not participate in the follow-up after the first occurrence of ASCVD. A total of 1475 people participated in the follow-up but missed data on systolic blood pressure (SBP) and diastolic blood pressure (DBP), fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), and height and weight. Finally, 6415 people were included and grouped according to SBP and DBP, FBG, hs-CRP, and body mass index (BMI) (these 4 indicators used the same examination data with the shortest interval after the onset of ASCVD). The flowchart is shown in the Supplementary Figure (available online).

The Kailuan study was approved by the ethics committee of the Kailuan General Hospital and complies with the Declaration of Helsinki (trial registration number ChiCTR-TNRC-11001489). All participants signed written informed consent forms.

Ascertainment of ASCVD

The detailed definition for individual components of the ASCVD events in Kailuan study has been described and listed in the Supplementary Materials (available online). We used the International Classification of Diseases, Tenth Revision (ICD-10) codes to identify cases of ischemic stroke (I63), HF (I50.9), and MI (I21); coronary revascularization refers to PCI and coronary artery bypass grafting surgery. Every year, trained medical staff review the inpatient diagnosis of the observation objects in the hospitals affiliated with the Kailuan Group and the city's designated hospitals for medical insurance, and record the end-point events.

Follow-Up

Cancer events were ascertained from the Municipal Social Insurance Institution that covered all study participants, the discharge registers of all 11 Kailuan hospitals, and a questionnaire survey (biennially since 2006). The cancer information was then confirmed by imaging, blood biomarkers, and pathological diagnoses in medical records. We coded cancers according to ICD-10 and ICD-O-3, see Supplementary Table 1 (available online). The confirmation of death was based on information from the local government vital statistics office. The follow-up ended at the date of cancer diagnosis, death, or termination of the study (December 31, 2020).

Definition of Blood Pressure, Blood Glucose, hs-CRP, and BMI Attainment

SBP, FBG, hs-CRP, and BMI are the 4 risk factors according to the results of cancer risk in the ASCVD group (Supplementary Table 2, available online). Ideal indicator of blood pressure: SBP <140 mm Hg and DBP <90 mm Hg; ideal indicator of blood glucose: FBG <7.0 mmol/L; ideal indicator of hs-CRP: hs-CRP <3.0 mmol/L; ideal indicator of body mass index: BMI <28.0 kg/m^2.

Data Collection

Biochemical indicators include FBG, triacylglycerol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hs-CRP. The above analyses were performed on a Hitachi automated analyzer (7600 Automatic Analyzer; Tokyo, Japan).

BMI = weight (kg)/height^2 (m^2). Blood pressure measurement: The blood pressure of the right brachial artery was measured by a uniformly trained and qualified medical staff member using a calibrated table-top mercury sphygmomanometer according to the standard. Since 2014, blood pressure has been measured with the HEM-8102A electronic sphygmomanometer produced by Omron (Dalian) Co., Ltd (Liaoning, China).

Definitions of smoking, alcohol consumption, physical activity, education level, and salt status were given in the previous definitions for the Kailuan cohort.[16] Family history of cancer was defined as having at least one parent or sibling with cancer.[17]

Statistical Analysis

Analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided, and differences were considered statistically significant when $P < .05$. Continuous variables are reported as mean ± SD, and categorical variables as the percentage. The baseline characteristics of the case subjects with new-onset ASCVD and the matched control subjects were compared using a *t* test or Wilcoxon signed-rank test for continuous variables and the

Table 1 Baseline Characteristics of Non-ASCVD and ASCVD Populations

Variables	Non-ASCVD (n = 14,665)	ASCVD (n = 14,665)	*P* Value
Age, years	62.93 ± 10.02	62.93 ± 10.02	—
Men, %	13,028 (88.84)	13,028 (88.84)	1.00
High school education or above, %	2393 (16.32)	2044 (13.94)	< .001
Smoking status, %			< .001
No	10,243 (69.85)	9823 (66.98)	
Yes	4422 (30.15)	4842 (33.02)	
Drinking status, %			< .001
No	9819 (66.96)	10,266 (70.00)	
Yes	4846 (33.04)	4399 (30.00)	
Salt intake, %			.002
≤10 g/d	13,390 (91.31)	13,233 (90.24)	
>10 g/d	1275 (8.69)	1432 (9.76)	
Physical activity, %			.13
Low	3860 (26.32)	3951 (26.94)	
Medium	8427 (57.46)	8454 (57.65)	
High	2378 (16.22)	2260 (15.41)	
BMI, kg/m^2	24.95 ± 3.25	25.59 ± 3.42	< .001
hs-CRP, mg/L	1.44 (0.64-3.40)	1.81 (0.80-4.20)	< .001
TG, mmol/L	1.25 (0.89-1.85)	1.39 (0.99-2.09)	< .001
LDL-C, mmol/L	2.66 (2.11-3.22)	2.77 (2.20-3.37)	< .001
HDL-C, mmol/L	1.40 (1.19-1.69)	1.37 (1.14-1.65)	< .001
SBP, mm Hg	138.58 ± 20.50	145.96 ± 22.11	< .001
DBP, mm Hg	84.09 ± 10.92	87.49 ± 12.41	< .001
FBG, mmol/L	5.42 (4.92-6.10)	5.62 (5.01-6.80)	< .001
Hypertension, %	8321 (56.74)	10,597 (72.26)	< .001
Diabetes mellitus, %	2156 (14.70)	3794 (25.87)	< .001
Hyperlipidemia, %	4483 (30.57)	6015 (41.02)	< .001
Antihypertensive drugs use,* %	2110 (14.39)	3744 (25.53)	< .001
Antidiabetic drugs use,* %	755 (5.15)	1344 (9.16)	< .001
Lipid-lowering drugs use,* %	252 (1.72)	666 (4.54)	< .001
Family history of cancer, %	86 (0.59)	45 (0.31)	< .001
Antihypertensive drugs use,† %	5030 (34.30)	8749 (59.66)	< .001
Antidiabetic drugs use,† %	3081 (21.01)	4565 (34.13)	< .001
Lipid-lowering drugs use,† %	1115 (7.60)	5715 (38.97)	< .001

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; DBP = diastolic blood pressure; FBG = fasting blood glucose; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hs-CRP = High-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TG = triglycerides.

*Data of the last examination prior to the occurrence of ASCVD.

†Data of the last examination after the occurrence of ASCVD.

χ^2 test for categorical variables. We calculated cancer incidence densities (per 1000 person-years) in ASCVD patients and non-ASCVD group. Because the number of deaths in each group exceeded the number of new cancers, a competing risk model was used to calculate the risk of cancer in the ASCVD group using death as a competing event.

When analyzing whether the control of risk factors can affect the risk of cancer in ASCVD patients, according to the common risk factors of ASCVD and cancer:[18] blood pressure, blood glucose, hs-CRP, and BMI, the number of 4 indicators reached the ideal standard, and the patients who participated in the examination after the occurrence of ASCVD participated in the examination. The participants were divided into 3 groups (ideal indicator ≤1, ideal indicators = 2, ideal indicators ≥3), using a competing risk model, with the non-ASCVD group as the reference, to calculate the risk of cancer and site-specific cancers.

For primary study, models were adjusted for education level, smoking status, drinking status, high salt intake, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, SBP, FBG, hs-CRP, family history of cancer, taking antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs at baseline. Participants with new-onset cancer within 4 years of developing ASCVD and those with a difference of more than 2 years between onset and examination were excluded from the sensitivity analysis. We also calculated E-values to quantify the effect of unmeasured confounders on the results. Our results were further validated by analyzing time effects, calculating the risk of developing cancer after 1-14 years of follow-up. For the second study, age and sex were included in the model-adjusted variables, and SBP, DBP, hs-CRP, and BMI were excluded. To exclude the possibility of causal inversion and to maintain sample size, we excluded patients who developed cancer within 3 years of ASCVD disease.

RESULT

As shown in Table 1, of the 14,665 ASCVD patients and 14,665 non-ASCVD participants, 88.8% were male. After 5.80 (3.05-9.44) years of follow-up, a total of 1124 (3.83%)

Table 2 Baseline Characteristics of Each Group According to the Number of Ideal Indicators After the Onset of ASCVD

Variables	Total (n = 6415)	Group 1 (n = 788)	Group 2 (n = 1859)	Group 3 (n = 3768)	*P* Value
Age, years	62.89 ± 9.62	61.83 ± 8.65	63.27 ± 8.94	62.93 ± 10.11	.002
Men, %	5623 (87.7)	644 (81.7)	1653 (88.9)	3326 (88.3)	< .001
High school education or above, %	945 (14.7)	109 (13.8)	271 (14.6)	565 (15.0)	.69
Smoking status, %					.22
No	4802 (74.9)	598 (75.9)	1413 (76.0)	2791 (74.1)	
Yes	1613 (25.1)	190 (24.1)	446 (24.0)	977 (25.9)	
Drinking status, %					.18
No	5013 (78.1)	629 (79.8)	1428 (76.8)	2956 (78.5)	
Yes	1402 (21.9)	159 (20.2)	431 (23.2)	812 (21.5)	
Salt intake, %					.09
≤10 g/d	5975 (93.1)	739 (93.8)	1748 (94.0)	3488 (92.6)	
>10 g/d	440 (6.86)	49 (6.22)	111 (5.97)	280 (7.43)	
Physical activity, %					.12
Low	2056 (32.0)	277 (35.2)	596 (32.1)	1183 (31.4)	
Medium	3498 (54.5)	399 (50.6)	1031 (55.5)	2068 (54.9)	
High	861 (13.4)	112 (14.2)	232 (12.5)	517 (13.7)	
BMI, kg/m^2	25.67 ± 3.29	28.91 ± 3.39	26.44 ± 3.31	24.61 ± 2.65	< .001
hs-CRP, mg/L	1.53 (0.70-3.52)	4.24 (3.10-6.90)	2.60 (1.00-4.70)	1.10 (0.56-2.00)	< .001
TG, mmol/L	1.33 (0.95-1.90)	1.65 (1.17-2.38)	1.37 (1.00-2.02)	1.24 (0.90-1.73)	< .001
LDL-C, mmol/L	2.60 (2.01-3.23)	2.78 (2.13-3.49)	2.65 (2.01-3.27)	2.56 (1.99-3.16)	< .001
HDL-C, mmol/L	1.28 (1.08-1.54)	1.25 (1.04-1.48)	1.25 (105-1.50)	1.30 (1.11-1.57)	< .001
SBP, mm Hg	143.25 ± 21.19	156.32 ± 18.41	151.73 ± 19.20	136.33 ± 19.82	< .001
DBP, mm Hg	84.52 ± 11.78	89.93 ± 12.24	87.56 ± 11.71	81.89 ± 10.94	< .001
FBG, mmol/L	5.62 (5.05-6.73)	7.77 (6.11-9.63)	6.06 (5.23-7.97)	5.40 (4.91-5.92)	< .001
Hypertension, %	5147 (80.2)	781 (99.1)	1751 (94.2)	2615 (69.4)	< .001
Diabetes mellitus, %	1665 (26.0)	544 (69.0)	722 (38.8)	399 (10.6)	< .001
Hyperlipidemia, %	4058 (63.3)	570 (72.3)	1253 (67.4)	2235 (59.3)	< .001
Antihypertensive drugs use, %	3600 (56.1)	538 (68.3)	1152 (62.0)	1910 (50.7)	< .001
Antidiabetic drugs use, %	810 (12.6)	239 (30.3)	331 (17.8)	240 (6.37)	< .001
Lipid-lowering drugs use, %	3000 (46.8)	388 (49.2)	925 (49.8)	1687 (44.8)	< .001
Family history of cancer, %	27 (0.42)	4 (0.51)	6 (0.32)	17 (0.45)	.72

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

cancers and 5526 (18.84%) deaths occurred in the participants. The proportion of ASCVD patients taking antihypertensive, hypoglycemic, and lipid-lowering drugs after onset increased to 59.7%, 15.8%, and 39.0%, respectively. According to the number of ideal indicators, 6415 participants after the onset of ASCVD were finally divided into Group 1 (ideal indicator ≤1), 788 people, Group 2 (ideal indicators = 2), 1859 people, and Group 3 (ideal indicators ≥3) 3768 people. Among them, 5623 were male (87.7%). The compliance of the 4 indicators in each group is shown in Supplementary Table 3 (available online), Table 2.

The incidence density and 95% confidence interval (CI) of cancer in the non-ASCVD group and ASCVD group were 6.25 (5.80-6.73)/1000 person-years and 5.83 (5.30-6.41)/1000 person-years, respectively. The incidence densities of digestive, respiratory, and urinary systems are shown in Table 3. After adjustment, the risk of cancer in the ASCVD group was lower than that in the non-ASCVD group (hazard ratio [HR] 0.74; 95% CI, 0.65-0.85). The risk of digestive, respiratory, urinary, and genital system cancer also decreased (Table 4). Similar results were observed in sensitivity analyses, see Supplementary Tables 6-8 (available online). After adjusting for covariates, the HR for cancer and the E-value for the upper limit of the confidence interval were 2.04 and 1.63, respectively (Supplementary Table 9, available online).

The incidence density of each group is shown in Supplementary Table 4 (available online). After adjustment, it was found that after the occurrence of ASCVD, with the increase of the number of indicators reaching the target, the risk of cancer will gradually decrease: Group 1 (ideal indicator ≤1), Group 2 (ideal indicator = 2) and Group 3 (ideal indicators ≥3) developed cancer. HR (95% CI) were 0.90 (0.60-1.35), 0.81 (0.60-1.10), and 0.77 (0.62-0.97), respectively (*P* for trend = .02). The risk of digestive system cancer and its downward trend were similar to that of overall cancer (*P* for trend = 0.01). Similar results have not been found for respiratory and urinary system cancers (Table 5 and Supplementary Table 5). We calculated the risk of developing cancer in the ASCVD group from the 1st to 14th years during follow-up, which decreased from HR 1.18 (95% CI, 0.89-1.57) to HR 0.59 (95% CI, 0.51-0.67). The risk of developing cancer gradually decreased with increasing follow-up time. Results were similar in digestive, respiratory, urinary, germinal, and blood systems, see the Figure. The specific HR and 95% CI is shown in the Supplementary Table 10 (available online).

DISCUSSION

The key finding was that patients with ASCVD had a reduced risk of developing cancer and that this risk reduction is site-specific-, time-, and the number of ideal indicator-dependent. Compared with participants without ASCVD, patients with ASCVD had a decreased risk of developing cancer. However, this risk reduction was only reflected in the digestive, respiratory, urinary, and germinal systems. The risk of developing cancer in patients with ASCVD decreases with prolonged survival. The risk of developing cancer in patients with ASCVD was inversely

Table 3 Incidence Density of Cancer and its Site-Specific in Both Groups

Cancer	Non-ASCVD	ASCVD
Total system		
Case/participants, n/n	705/14,665	419/14,665
Incidence (/1000 person-years)	6.25 (5.80-6.73)	5.83 (5.30-6.41)
Digestive system		
Case/participants, n/n	271/14665	158/14665
Incidence (/1000 person-years)	2.37 (2.11-2.68)	2.18 (1.86-2.55)
Respiratory system		
Case/participants, n/n	225/14665	140/14665
Incidence (/1000 person-years)	1.97 (1.73-2.24)	1.93 (1.64-2.28)
Urinary system		
Case/participants, n/n	56/14665	42/14665
Incidence (/1000 person-years)	0.49 (0.38-0.64)	0.58 (0.43-0.78)
Germinal system		
Case/participants, n/n	47/14665	21/14665
Incidence (/1000 person-years)	0.41 (0.31-0.55)	0.29 (0.19-0.44)
Blood system		
Case/participants, n/n	36/14665	17/14665
Incidence (/1000 person-years)	0.31 (0.23-0.44)	0.23 (0.15-0.38)
Endocrine system		
Case/participants, n/n	12/14665	12/14665
Incidence (/1000 person-years)	0.10 (0.06-0.18)	0.16 (0.09-0.29)
Other system		
Case/participants, n/n	59/14665	31/14665
Incidence (/1000 person-years)	0.51 (0.40-0.66)	0.43 (0.30-0.61)

ASCVD = atherosclerotic cardiovascular disease.

Table 4 HR and 95% CI for Cancer and Site-Specific in ASCVD Group

Cancer	Model 1	Model 2	Model 3	Model 4	Model 5	Sensitivity
Non-ASCVD	1.00	1.00	1.00	1.00	1.00	1.00
Total system	0.73 (0.64-0.83)	0.75 (0.66-0.85)	0.73 (0.65-0.83)	0.74 (0.65-0.84)	0.74 (0.65-0.85)	0.69 (0.55-0.86)
Digestive system	0.81 (0.72-0.92)	0.84 (0.74-0.96)	0.82 (0.72-0.93)	0.82 (0.72-0.94)	0.83 (0.73-0.95)	0.77 (0.61-0.96)
Respiratory system	0.82 (0.73-0.93)	0.85 (0.75-0.97)	0.82 (0.73-0.93)	0.83 (0.73-0.95)	0.84 (0.73-0.96)	0.78 (0.62-0.97)
Urinary system	0.85 (0.75-0.96)	0.88 (0.77-1.00)	0.85 (0.75-0.96)	0.85 (0.75-0.97)	0.86 (0.76-0.99)	0.80 (0.64-0.99)
Germinal system	0.50 (0.30-0.85)	0.49 (0.29-0.83)	0.51 (0.30-0.85)	0.47 (0.269-0.82)	0.48 (0.28-0.83)	0.27 (0.10-0.76)
Blood system	0.55 (0.30-1.00)	0.58 (0.31-1.06)	0.55 (0.30-1.00)	0.62 (0.34-1.15)	0.62 (0.34-1.15)	0.73 (0.26-2.00)
Endocrine system	1.59 (0.73-3.44)	1.76 (0.78-3.98)	1.58 (0.73-3.44)	2.09 (0.95-4.58)	2.10 (0.95-4.53)	1.73 (0.55-5.50)
Other system	0.66 (0.42-1.04)	0.69 (0.44-1.08)	0.66 (0.42-1.04)	0.62 (0.37-1.01)	0.62 (0.38-1.02)	0.88 (0.40-1.93)

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

Model 1 was adjusted for education level, smoking status, drinking status, high salt intake, physical activity, LDL-C, HDL-C, SBP, FBG, hs-CRP, and family history of cancer at baseline; model 2 was further adjusted for antihypertensive drugs; model 3 was adjusted for hypoglycemic drugs on the basis of model 1; model 4 was adjusted for lipid-lowering drugs on the basis of model 1; model 5 was adjusted for antihypertensive, hypoglycemic, and lipid-lowering drugs on the basis of model 1. Sensitivity: 10,493 patients developed cancer within 4 years of ASCVD, leaving 18,837 patients on the basis of Model 5.

Note: The use of antihypertensive, hypoglycemic, and lipid-lowering drugs is the sum of the drug use prior to and after the onset of ASCVD.

Table 5 HR and 95% CI for the Cancer in Each Group According to the Number of Ideal Indicators After the Onset of ASCVD

Cancer	Non-ASCVD	Group 1 (Ideal Indicator ≤ 1)	Group 2 (Ideal Indicators = 2)	Group 3 (Ideal Indicators ≥ 3)	*P* for Trend
Total system					.018
Model 1	1.00	0.84 (0.57-1.23)	0.76 (0.59-1.00)	0.74 (0.61-0.90)	
Model 2	1.00	0.88 (0.60-1.30)	0.79 (0.61-1.03)	0.74 (0.61-0.90)	
Model 3	1.00	0.92 (0.62-1.36)	0.82 (0.62-1.08)	0.76 (0.62-0.93)	
Model 4	1.00	0.85 (0.58-1.26)	0.78 (0.59-1.02)	0.74 (0.61-0.92)	
Model 5	1.00	0.91 (0.61-1.36)	0.81 (0.60-1.09)	0.76 (0.61-0.95)	
Model 6	1.00	0.90 (0.60-1.35)	0.81 (0.60-1.10)	0.77 (0.62-0.97)	
Sensitivity	1.00	1.04 (0.62-1.76)	0.94 (0.63-1.40)	0.88 (0.66-1.17)	
Digestive system					.008
Model 1	1.00	0.90 (061-1.33)	0.85 (0.65-1.11)	0.82 (0.68-1.00)	
Model 2	1.00	0.92 (0.62-1.35)	0.86 (0.66-1.12)	0.82 (0.67-1.00)	
Model 3	1.00	0.97 (0.65-1.43)	0.90 (0.78-1.19)	0.85 (0.69-1.04)	
Model 4	1.00	0.90 (0.61-1.33)	0.85 (0.65-1.11)	0.82 (0.67-1.00)	
Model 5	1.00	0.93 (0.62-1.39)	0.87 (0.64-1.17)	0.83 (0.66-1.04)	
Model 6	1.00	0.93 (0.62-1.41)	0.88 (0.65-1.19)	0.84 (0.67-1.05)	
Sensitivity	1.00	1.06 (0.63-1.79)	1.00 (0.67-1.50)	0.96 (0.72-1.27)	
Respiratory system					.17
Model 1	1.00	0.92 (0.62-1.35)	0.86 (0.66-1.12)	0.84 (0.69-1.02)	
Model 2	1.00	0.93 (0.63-1.37)	0.86 (0.66-1.13)	0.83 (0.68-1.00)	
Model 3	1.00	0.98 (0.66-1.45)	0.91 (0.68-1.20)	0.86 (0.70-1.01)	
Model 4	1.00	0.91 (0.62-1.35)	0.86 (0.65-1.12)	0.83 (0.68-1.01)	
Model 5	1.00	0.94 (0.62-1.41)	0.87 (0.65-1.18)	0.83 (0.67-1.04)	
Model 6	1.00	0.95 (0.63-1.42)	0.89 (0.65-1.20)	0.85 (0.68-1.06)	
Sensitivity	1.00	1.08 (0.65-1.82)	1.02 (0.68-1.52)	0.97 (0.73-1.29)	
Urinary system					.46
Model 1	1.00	0.94 (0.64-1.38)	0.88 (0.68-1.15)	0.86 (0.71-1.05)	
Model 2	1.00	0.94 (0.64-1.39)	0.88 (0.67-1.15)	0.85 (0.69-1.03)	
Model 3	1.00	0.99 (0.67-1.48)	0.92 (0.70-1.22)	0.88 (0.72-1.08)	
Model 4	1.00	0.93 (0.63-1.37)	0.87 (0.67-1.14)	0.85 (0.69-1.03)	
Model 5	1.00	0.94 (0.63-1.42)	0.88 (0.65-1.19)	0.85 (0.68-1.06)	
Model 6	1.00	0.96 (0.64-1.44)	0.90 (0.66-1.21)	0.86 (0.69-1.08)	
Sensitivity	1.00	1.09 (0.65-1.83)	1.03 (0.69-1.54)	0.98 (0.74-1.31)	

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.

Model 1 was adjusted for age and sex; model 2 was further adjusted education level, smoking status, drinking status, high salt intake, physical activity, LDL-c, HDL-c, family history of cancer; model 3 was adjusted for antihypertensive drugs on the basis of model 2; model 4 was adjusted for hypoglycemic drugs on the basis of model 2; model 5 was adjusted for lipid-lowering drugs on the basis of model 2; model 6 was adjusted for antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs on the basis of model 2. Sensitivity: 2,832 patients developed cancers within 3 years of ASCVD, leaving 21, 076 patients on the basis of model 6.

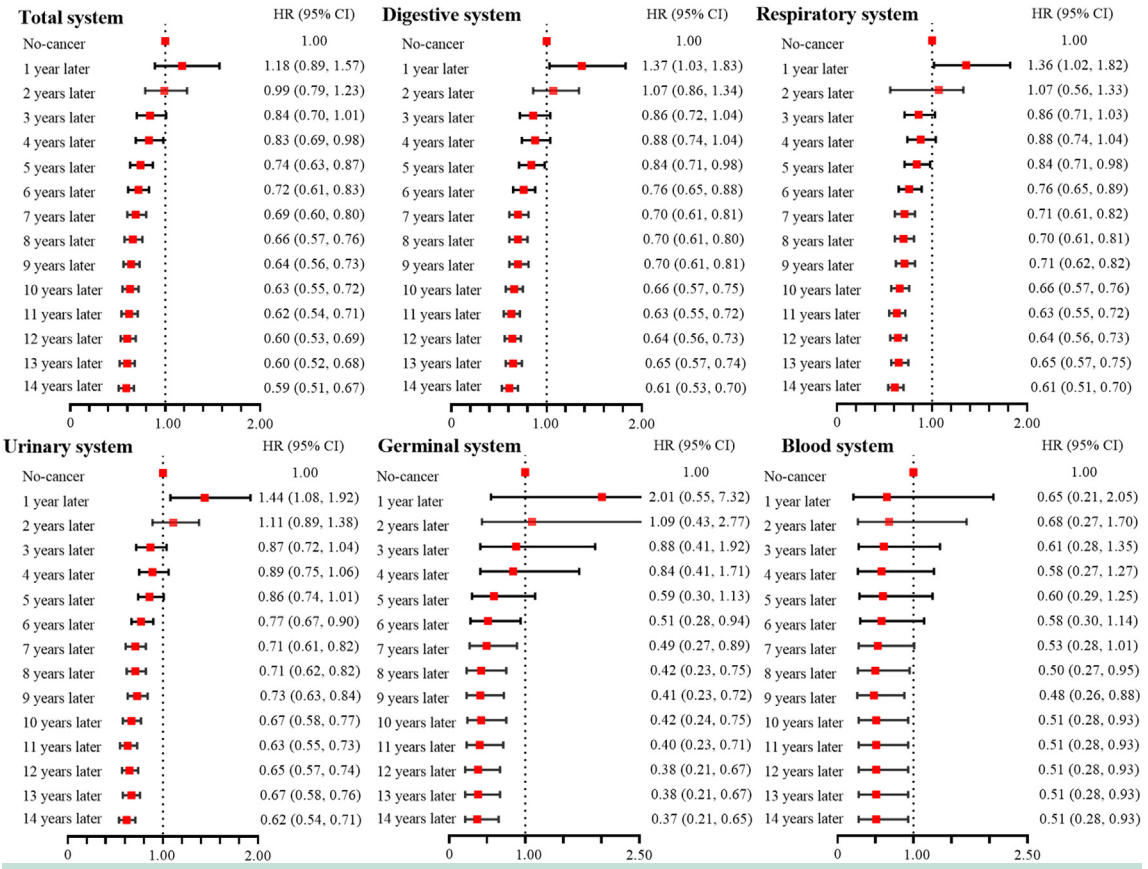

Figure Risk of atherosclerotic cardiovascular disease by time from cancer diagnosis. CI = confidence interval; HR = hazard ratio.

correlated to the number of ideal indicators (Graphical Abstract).

Previous studies have evaluated the impact of ASCVD events on cancer risk. The Study of Health in Pomerania (SHIP) cohort study demonstrated that ASCVD patients had a 37% increased risk of developing cancer.[10] An analysis based on National Health Interview Survey (NHIS) data in Korea found that patients undergoing PCI had a 6% increased risk of new malignancies.[12] Although both the SHIP and NHIS were cohort studies, measures to control the common risk factors (such as antihypertensive, hypoglycemic, and lipid-lowering drugs) and inflammation in co-pathogenesis (hs-CRP) were lacking in adjusted covariates factors; also, data from the Framingham Heart Study and the Prevention of Renal and Vascular Endstage Disease (PREVEND) study did not show any increased cancer risk in individuals with ASCVD.[19]

Contrary to the previous findings, we found that, after adjustment for possible confounders, ASCVD patients had a 30% reduction in the risk of developing cancer and a 17%, 16%, 14%, and 52% reduction in the risk of cancers of the digestive, respiratory, urological, and germinal systems, respectively. Compared with previous studies, our follow-up time was longer (median follow-up time was 5.8 years; SHIP study follow-up time was 2.80 years, NHIS study follow-up time was 4.56 years). Cancer diagnosis and medication information were obtained through the linked health insurance system, which is relatively complete and accurate, and corrected for inflammatory indicators (hs-CRP). The statistical methods used a competing risk model to reduce the effect of mortality, and the introduction of E-values reduced the interference of unmeasured confounding factors. In addition, our observation was terminated in 2020. Compared with previous cohorts, currently, there are more effective means of controlling the risk factors, such as sodium-sugar co-transporter 2 inhibitors, which might also be one of the reasons for the decreased cancer risk in ASCVD patients.

We found a reduction in the risk of developing cancer with ASCVD; however, this reduction was the number-of-ideal-indicator-dependent. The results showed no statistically significant difference in the risk of cancer in the 2 groups with the number of ideal indicators ≤ 1 and ideal indicators = 2, while the group with the number of ideal indicators ≥ 3 showed a 23% reduction in cancer risk. The risk of developing cancer in ASCVD patients was inversely correlated with the number of ideal indicators. This finding is consistent with the consensus that ASCVD and cancer share common risk factors. A prospective study showed that each 1-point increase in the American Heart Association health score was associated with a 5% reduced risk of developing cancer.[19] The Atherosclerosis Risk in Communities (ARIC) study found that participants who achieved a goal of 6-7 desirable health markers had a 51% lower risk

of developing cancer compared with those who achieved a goal of 0 desirable health markers.[20] The CANTOS clinical study found that the anti-inflammatory drug canakinumab in patients with MI reduced the future risk of adverse cardiovascular outcomes, lung cancer morbidity, and lung cancer-related mortality in a dose−response manner. The results of these studies indirectly substantiated our conclusions.

In addition to the dependence of the number of ideal indicators, we also performed a time-dependent analysis to separately calculate the risk of new cancer with a follow-up of 1-14 years during developing ASCVD development, which was missing from previous studies. The current results showed a 17% reduction in cancer risk from the 4th year of follow-up, a 41% reduction after 14 years of follow-up, and a gradual decline. A similar trend was observed in the risk of digestive, respiratory, and urinary system cancers. A Danish study found an increased risk of colorectal cancer in the first year after stroke diagnosis, but the risk of developing colorectal cancer was not statistically different from the second year onwards.[21] In the NHIS cohort, after excluding patients who developed cancer within 1 year, no association was detected between PCI and cancer.[12] These results suggested a time-dependent reduction in the risk of developing cancer, possibly by the additive effect of treatment and the control of risk factors that reduce the risk of developing cancer after ASCVD. In addition, the drugs commonly used to treat ASCVD, such as aspirin, statins, or metformin, can potentially reduce cancer development through other mechanisms. One study found that patients taking aspirin, statins, or metformin simultaneously had a 17% lower risk of developing lung cancer and a 51% lower risk of developing lung cancer after taking the drugs for >1.5 years.[22] In our ASCVD patients, the proportion of antihypertensive, hypoglycemic, and lipid-lowering drugs increased to 59.7%, 15.8% and 39.0%, respectively, after the disease.

Taken together, our findings have critical public health and clinical implications. First, with the improvement of diagnosis and treatment technology, the life expectancy of ASCVD patients is prolonged; how to prevent and reduce other adverse outcomes of ASCVD patients remains a huge challenge. The current findings confirmed that comprehensive control of risk factors in ASCVD patients reduced the risk of developing cancer. Second, this study confirmed that the shared risk factor hypothesis could be translated into clinical interventions because the risk of developing cancer in ASCVD patients is inversely related to the control of risk factors. Therefore, doctors and ASCVD patients should work together to control the common risk factors, such as blood pressure, blood glucose, body weight, and inflammation, through individualized rational drug use and increased compliance according to the guidelines, thereby preventing ASCVD recurrence and reducing the risk of cancer. Future work in cardio-oncology should aim to elucidate the underlying pathophysiological mechanisms that affect cancer risk in patients with ASCVD and develop canakinumab-like treatments for the dual treatment of ASCVD and cancer.

STUDY LIMITATIONS

Although our cohort has a prolonged follow-up and complete disease diagnosis and medication information, the inherent limitations based on the Kailuan cohort cannot be ignored. First, all the participants were employees with medical insurance, and the proportion of males was 88%. Hence, the subgroup analysis of sex-specific tumors was not possible, and the promotion of the results may be limited. Second, we did not have information on tumor histology, and we attempted to attenuate the influence of these confounding factors by performing subtype analysis and E-value analysis. Third, the latent period of most cancers is >10 years; our follow-up time was insufficient, and the number of cancer events was limited.

CONCLUSION

The current findings suggested a reduction in the risk of cancer after ASCVD by controlling the common risk factors. This risk reduction is site-specific-, time-, and the number of ideal indicator-dependent. The findings underscore the importance of post-onset control of ASCVD in reducing the risk of cancer, and controlling the common risk factors for both diseases can achieve a co-optimal outcome for both ASCVD and cancer.

DECLARATIONS

Ethics in publishing

The study was performed according to the guidelines of the Helsinki Declaration (trial registration number ChiCTR-TNRC-11001489) and was approved by the Ethics Committee of Kailuan General Hospital (approval number: 2006-05). All participants agreed to take part in the study and provided informed written consent.

ACKNOWLEDGMENT

The authors thanks all the staff members of the Kailuan Study Team and the participants for their contribution.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2023.12.003.

DETAILED DEFINITION OF ASCVD IN THE KAILUAN STUDY

Myocardial infarction was determined by the patient's clinical symptoms, electrocardiogram, and dynamic changes of myocardial enzyme following the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease criteria.[1]

The diagnosis of stroke was based on neurological signs, clinical symptoms, and neuroimaging tests, including computed tomographic or magnetic resonance imaging, in line with the World Health Organization criteria.[2]

Heart failure was defined in accordance with the criteria of the European Society of Cardiology, based on clinical symptoms, echocardiography, chest X-ray, and electrocardiography.[3]

Because the ASCVD group took the onset time as the starting time and the control group took the same period of examination time as the starting time, the enrollment time of the two groups was different, and because the ASCVD group used the pre-onset examination data, the admission time of the non-ASCVD group was earlier than that of the case group. In order to mitigate this effect, we excluded those who had more than two years of difference between the time of ASCVD and the time of examination, and rematched 1:1 according to age (±1) and gender, and finally excluded 6, 119 people, successfully matching 8, 546 pairs for a total of 17, 092 people. The basic information is provided in Supplementary Table 6. The incidence density is shown in Supplementary Table 7. After adjusted, the HR and 95% CI of the cancer site-specific are shown in Supplementary Table 8.

To explain the effects of unmeasured confounding factors, we performed an additional sensitivity analysis by computational E-value methods. The method estimated the minimum strength of association required between unmeasured confounding factors and ASCVD onset and cancer risk to overcome the significant effects of residual confounding observed in studies. This calculation is based on the HR value obtained from the adjusted model in this study. In the fully tuned model, the HR of cancer developed in patients with ASCVD was 0.74, with a confidence interval of 0.65-0.85 for 95% (Table 3 of the main article). The point has an estimated E-value of 2.04 and an upper confidence interval of 1.63. We found that the observed HR value of 0.74 had an unmeasured confounding factor that correlated with both exposure (with ASCVD) and outcome (diagnosed with cancer) that could mask the effect of ASCVD on outcomes when the risk of cancer developing

Supplementary Table 1 Coding of ICD-10 and ICD-O-3 in each system

Cancer	ICD-10 and ICD-O-3
Digestive system	ICD-10.C00-C25
Respiratory system	ICD-10.C30-C34, C37-C39
Urinary system	ICD-10.C64-C68
Germinal system	ICD-10.C51-C58, C60-C63
Blood system	ICD-10.C81-C85, C90-C95, D46.9, D47.7; ICD-O-3.C42.0
Endocrine system	ICD-10.C73-C75
Other system	Cancer in other sites than the above

Supplementary Table 2 The association between baseline risk factors and risk of cancer in the overall cohort

Variables	HR	95% CI
Baseline FBG for every 1 mmol/L increase	1.17	(1.02-1.34)
Baseline SBP for every 1 mmHg increase	1.01	(1.00-1.01)
Baseline hs-CRP for every 1 mg/L increase	1.01	(1.01-1.02)
Baseline BMI ≥28.0 kg/m2	1.12	(1.00-1.25)
Baseline LDL-C for every 1 mmol/L increase	0.91	(0.85-0.98)
Bassline HDL-C for every 1 mmol/L increase	1.04	(0.94-1.16)
Salt intake > 10, g/day	1.08	(0.93-1.25)
Smoking history	1.15	(0.98-1.41)
Drinking history	1.03	(0.90-1.18)
High school education or above	0.91	(0.76-1.08)
Family history of CVD	1.29	(0.58-2.87)
Physical exercise		
Low	1.00 (ref)	1.00 (ref)
Medium	1.07	(0.92-1.24)
High	1.13	(0.94-1.36)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; FBG = fasting blood glucose; HDL-C = HDL cholesterol; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; LDL-C = LDL cholesterol; SBP = systolic blood pressure.

Supplementary Table 3 The distribution of different number of ideal indicators in each group after the occurrence of ASCVD

Ideal indicators	Total	Group1 (Ideal indicator ≤ 1)	Group2 (Ideal indicators = 2)	Group3 (Ideal indicators ≥ 3)
Participants, n	6415	788	1859	3768
Blood pressure, n (%)	2523 (39.33)	22 (2.79)	280 (15.06)	2221 (58.94)
Blood sugar, n (%)	4969 (77.46)	250 (31.73)	1183 (63.64)	3536 (93.84)
hs-CRP, n (%)	4500 (70.15)	162 (20.56)	991 (53.31)	3347 (88.83)
BMI, n (%)	5036 (78.50)	218 (27.66)	1264 (67.99)	3554 (94.32)

was greater than 1.63 times. In the current study, it seems unlikely that there would be such a large unmeasured confusion with exposure and outcomes, especially given that it is at much greater risk than known common risk factors for ASCVD and cancer, such as hypertension, diabetes mellitus, obesity, smoking, alcohol abuse, use of other tobacco products, and hyperlipidemia (Supplementary Table 9).

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Supplementary Table 4 The incidence density of cancer and its site-specific in each group according to the number of ideal indicators after the onset of ASCVD

Cancer	Non-ASCVD	Group1 (Ideal indicator ≤ 1)	Group2 (Ideal indicators = 2)	Group3 (Ideal indicators ≥ 3)
Total system				
Case/Participants, n/n	705/14665	27/788	60/1859	119/3768
Incidence (/1,000 person years)	6.25 (5.80-6.73)	5.45 (3.74-7.95)	5.13 (3.98-6.60)	4.88 (4.08-5.84)
Digestive system				
Case/Participants, n/n	271/14665	13/788	26/1859	40/3768
Incidence (/1,000 person years)	2.37 (2.11-2.68)	2.60 (1.51-4.47)	2.20 (1.50-3.23)	1.63 (1.19-2.22)
Respiratory system				
Case/Participants, n/n	228/14665	5/788	21/1859	35/3768
Incidence (/1,000 person years)	1.97 (1.73-2.24)	1.00 (0.42-2.40)	1.78 (1.16-2.73)	1.42 (1.02-1.98)
Urinary system				
Case/Participants, n/n	56/14665	5/788	5/1859	12/3768
Incidence (/1,000 person years)	0.49 (0.38-0.64)	1.00 (0.42-2.40)	0.42 (0.18-1.02)	0.49 (0.28-0.86)
Germinal system				
Case/Participants, n/n	47 /14665	0/788	0/1859	8 /3768
Incidence (/1,000 person years)	0.41 (0.31-0.55)	—	—	0.32 (0.16-0.65)
Blood system				
Case/Participants, n/n	36/14665	0/788	1/1859	8/3768
Incidence (/1,000 person years)	0.31 (0.23-0.44)	—	0.08 (0.01-0.60)	0.32 (0.16-0.65)
Endocrine system				
Case/Participants, n/n	12/14665	0/788	2/1859	5/3768
Incidence (/1,000 person years)	0.10 (0.06-0.18)	—	0.17 (0.04-0.6 8)	0.20 (0.08-0.49)
Urinary system				
Case/Participants, n/n	59/14665	4/788	5/1859	11/3768
Incidence (/1,000 person years)	0.51 (0.40-0.65)	0.80 (0.30-2.13)	0.42 (0.18-1.02)	0.45 (0.25-0.81)

Supplementary Table 5 HR and 95% CI of cancer occurred in each group according to the number of ideal indicators after the onset of ASCVD

Cancer	Non-ASCVD	Group1 (Ideal indicator ≤ 1)	Group2 (Ideal indicators = 2)	Group3 (Ideal indicators ≥ 3)	*P* for trend
Germinal system					0.28
Model 1	1.00	—	—	0.70 (0.31-1.58)	
Model 2	1.00	—	—	0.66 (0.29-1.50)	
Model 3	1.00	—	—	0.69 (0.32-1.48)	
Model 4	1.00	—	—	0.66 (0.29-1.51)	
Model 5	1.00	—	—	0.73 (0.30-1.76)	
Model 6	1.00	—	—	0.77 (0.33-1.78)	
Sensitivity	1.00	—	—	0.72 (0.28-1.85)	
Blood system					0.97
Model 1	1.00	—	0.24 (0.03-1.77)	0.95 (0.44-2.05)	
Model 2	1.00	—	0.24 (0.03-1.71)	0.91 (0.41-2.03)	
Model 3	1.00	—	0.24 (0.03-1.98)	0.91 (0.38-2.19)	
Model 4	1.00	—	0.20 (0.03-1.53)	0.90 (0.40-2.02)	
Model 5	1.00	—	0.28 (0.03-2.43)	1.05 (0.46-2.42)	
Model 6	1.00	—	0.26 (0.03-2.33)	1.11 (0.48-2.56)	
Sensitivity	1.00	—	0.75 (0.07-8.34)	1.51 (0.50-4.50)	
Endocrine system					0.13
Model 1	1.00	—	1.58 (0.36-7.02)	1.79 (0.63-5.04)	
Model 2	1.00	—	1.54 (0.36-6.52)	1.76 (0.63-4.89)	
Model 3	1.00	—	1.65 (0.31-8.89)	1.85 (0.58-5.91)	
Model 4	1.00	—	1.79 (0.42-7.63)	1.81 (0.65-5.02)	
Model 5	1.00	—	2.11 (0.37-11.92)	2.30 (0.83-6.39)	
Model 6	1.00	—	2.14 (0.38-12.21)	2.21 (0.76-6.42)	
Sensitivity	1.00	—	0.84 (0.07-9.81)	1.23 (0.31-4.91)	
Other system					0.79
Model 1	1.00	1.29 (0.47-3.52)	0.77 (0.31-1.92)	0.82 (0.43-1.57)	
Model 2	1.00	1.36 (0.50-3.71)	0.80 (0.32-1.97)	0.83 (0.43-1.59)	
Model 3	1.00	1.71 (0.57-5.12)	0.96 (0.36-2.53)	0.95 (0.47-1.95)	
Model 4	1.00	1.29 (0.50-3.37)	0.78 (0.31-1.93)	0.83 (0.43-1.59)	
Model 5	1.00	1.48 (0.49-4.44)	0.86 (0.31-2.37)	0.89 (0.39-2.02)	
Model 6	1.00	1.57 (0.52-4.78)	0.91 (0.32-2.56)	0.94 (0.42-2.13)	
Sensitivity	1.00	2.58 (0.60-11.12)	1.16 (0.28-4.85)	1.25 (0.43-3.62)	

Model 1 was adjusted for age and sex ; model 2 was further adjusted education level, smoking status, drinking status, high salt intake, physical activity, HDL-c, family history of cancer; model 3 was adjusted for antihypertensive drugs on the basis of model 2; model 4 was adjusted for hypoglycemic drugs on the basis of model 2; model 5 was adjusted for lipid-lowering drugs on the basis of model 2; model 6 was adjusted for antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs on the basis of model 2. Sensitivity: 2,832 patients developed cancers within three years of ASCVD, leaving 21,076 patients on the basis of model 6.

Supplementary Table 6 Baseline characteristics of the non-ASCVD group versus the ASCVD group

Variables	Non-ASCVD (N=8546)	ASCVD (N=8546)	*P* Value
Age, years	63.05±9.95	63.05±9.95	0.99
Men, %	7553 (88.4)	7553 (88.4)	1.00
High school education or above, %	1445 (16.9)	1301 (15.2)	<0.001
Smoking status, %			<0.001
No	6069 (71.0)	5784 (67.7)	
Yes	2477 (29.0)	2762 (32.3)	
Drinking status, %			<0.001
No	5810 (68.0)	6078 (71.1)	
Yes	2736 (32.0)	2468 (28.9)	
Salt intake, %			0.19
≤ 10, g/day	7813 (91.4)	7764 (90.8)	
> 10, g/day	733 (8.58)	782 (9.15)	
Physical activity, %			0.35
Low	2476 (29.0)	2530 (29.6)	
Medium	4761 (55.7)	4769 (55.8)	
High	1309 (15.3)	1247 (14.6)	
BMI, kg/m^2	24.97±3.21	25.70±3.45	<0.001
eGFR, $ml/min/1.73m^2$	84.31±19.02	82.56±21.17	<0.001
hs-CRP, mg/L	1.48 (0.63-3.40)	1.90 (0.80-4.26)	<0.001
TG, mmol/L	1.25 (0.89-1.85)	1.40 (1.00-2.09)	<0.001
LDL-C, mmol/L	2.70 (2.17-3.27)	2.82 (2.24-3.43)	<0.001
HDL-C, mmol/L	1.41 (1.19-1.68)	1.36 (1.13-1.63)	<0.001
SBP, mmHg	138.93±20.33	146.55±22.08	<0.001
DBP, mmHg	83.79±10.99	87.25±12.39	<0.001
FBG, mmol/L	5.45 (4.94-6.10)	5.66 (5.01-6.83)	<0.001
Hypertension, %	4873 (57.0)	6271 (73.4)	<0.001
Diabetes mellitus, %	1306 (15.3)	2261 (26.5)	<0.001
Hyperlipemia, %	2611 (30.6)	3587 (42.0)	<0.001
Antihypertensive agent use, %	1217 (14.2)	2296 (26.9)	<0.001
Antidiabetic medication use, %	452 (5.29)	843 (9.86)	<0.001
Lipid-lowering medication use, %	153 (1.79)	471 (5.51)	<0.001
Family history, %	52 (0.61)	34 (0.40)	0.05

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; hs-CRP = High-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TG = Triglycerides.

Supplementary Table 7 Incidence density of cancer and its site-specific in both groups

Cancer	Non-ASCVD	ASCVD
Total system		
Case/Participants, n/n	366/8546	270/8546
Incidence (/1,000 person years)	6.07 (5.48-6.72)	5.70 (5.06-6.43)
Digestive system		
Case/Participants, n/n	144/8546	103/8546
Incidence (/1,000 person years)	2.36 (2.00-2.78)	2.15 (1.78-2.61)
Respiratory system		
Case/Participants, n/n	123/8546	85/8546
Incidence (/1,000 person years)	2.01 (1.69-2.40)	1.78 (1.44-2.20)
Urinary system		
Case/Participants, n/n	28/8546	31/8546
Incidence (/1,000 person years)	0.46 (0.32-0.66)	0.65 (0.46-0.92)
Germinal system		
Case/Participants, n/n	23/8546	11/8546
Incidence (/1,000 person years)	0.37 (0.25-0.56)	0.23 (0.13-0.41)
Blood system		
Case/Participants, n/n	17/8546	11/8546
Incidence (/1,000 person years)	0.28 (0.17-0.45)	0.23 (0.13-0.41)
Endocrine system		
Case/Participants, n/n	6/8546	10/8546
Incidence (/1,000 person years)	0.10 (0.04-0.22)	0.21 (0.11-0.39)
Other system		
Case/Participants, n/n	25/8546	21/8546
Incidence (/1,000 person years)	0.41 (0.28-0.60)	0.44 (0.29-0.67)

Supplementary Table 8 Cancer occurred in the ASCVD group and its site-specific of HR and 95% CI

Cancer	Model 1	Model 2	Model 3	Model 4	Model 5
Control	1.00	1.00	1.00	1.00	1.00
Total system	0.79 (0.67-0.93)	0.78 (0.66-0.92)	0.79 (0.67-0.92)	0.79 (0.67-0.93)	0.78 (0.66-0.92)
Digestive system	0.84 (0.72-0.99)	0.84 (0.71-0.99)	0.84 (0.71-0.99)	0.84 (0.71-0.99)	0.83 (0.70-0.98)
Respiratory system	0.86 (0.73-1.01)	0.85 (0.72-1.00)	0.85 (0.72-1.00)	0.85 (0.72-1.00)	0.84 (0.71-1.00)
Urinary system	0.87 (0.74-1.02)	0.86 (0.73-1.02)	0.86 (0.73-1.02)	0.86 (0.73-1.01)	0.86 (0.72-1.01)
Germinal system	0.87 (0.74-1.03)	0.87 (0.73-1.02)	0.87 (0.73-1.02)	0.86 (0.73-1.02)	0.86 (0.72-1.02)
Blood system	0.87 (0.74-1.03)	0.87 (0.74-1.03)	0.87 (0.74-1.03)	0.87 (0.74-1.02)	0.86 (0.73-1.02)
Endocrine system	0.88 (0.74-1.03)	0.87 (0.74-1.03)	0.87 (0.74-1.03)	0.87 (0.74-1.02)	0.87 (0.73-1.02)
Other system	0.87 (0.73-1.02)	0.86 (0.73-1.01)	0.86 (0.73-1.01)	0.86 (0.73-1.01)	0.85 (0.72-1.01)

Model 1 was adjusted for education level, smoking status, drinking status, high salt intake, physical activity, LDL-C, HDL-C, and family history of cancer at baseline; model 2 was further adjusted for antihypertensive drugs; model 3 was adjusted for hypoglycemic drugs on the basis of model 1; model 4 was adjusted for lipid-lowering drugs on the basis of model 1; model 5 was adjusted for antihypertensive, hypoglycemic, and lipid-lowering drugs on the basis of model 1.

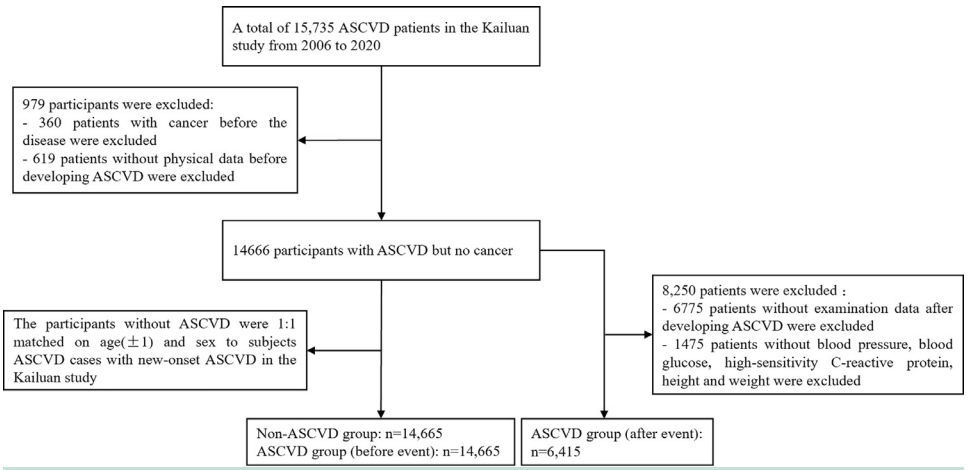
Supplementary Table 9 HR and 95% CI of each variable in the competitive risk model

Variables	HR	95% CI	*P* Value
Group			< 0.001
Group 0	1 (ref)	1 (ref)	
Group 1	0.71	(0.63-0.81)	
Age, years	1.02	(1.01-1.02)	< 0.001
Gender			0.21
Women	1 (ref)	1 (ref)	
Men	1.15	(0.93-1.43)	
High school education or above			0.52
No	1 (ref)	1 (ref)	
Yes	0.94	(0.79-1.12)	
Drinking			0.34
No	1 (ref)	1 (ref)	
Yes	1.07	(0.93-1.23)	
Smoking			< 0.001
No	1 (ref)	1 (ref)	
Yes	1.23	(1.07-1.41)	
Salt intake			0.29
≤ 10, g/day	1 (ref)	1 (ref)	
> 10, g/day	1.11	(0.92-1.34)	
Physical activity			0.32
Low	1 (ref)	1 (ref)	
Medium	1.08	(0.93-1.26)	
High	1.10	(0.92-1.33)	
BMI			0.12
< 28.0 kg/m2	1 (ref)	1 (ref)	
≥ 28.0 kg/m2	1.13	(0.97-1.31)	
hs-CRP			0.021
< 3.0 mg/L	1 (ref)	1 (ref)	
≥ 3.0 mg/L	1.17	(1.03-1.32)	
Hyperlipemia			< 0.001
No	1 (ref)	1 (ref)	
Yes	0.81	(0.73-0.923)	
Diabetes mellitus			0.71
No	1 (ref)	1 (ref)	
Yes	1.04	(0.86-1.25)	
Hypertension			0.08
No	1 (ref)	1 (ref)	
Yes	1.13	(0.97-1.30)	
Family history of cancer			0.43
No	1 (ref)	1 (ref)	
Yes	1.38	(0.62-3.08)	
Antihypertensive drugs use			0.47
No	1 (ref)	1 (ref)	
Yes	0.94	(0.80-1.11)	
Antidiabetic drugs use			0.95
No	1 (ref)	1 (ref)	
Yes	0.99	(0.75-1.31)	
Lipid-lowering drugs use			0.24
No	1 (ref)	1 (ref)	
Yes	1.27	(0.85-1.89)	

Supplementary Table 10 Follow-up of HR and 95% CI of cancer in the ASCVD group during 1-14 years

Years of follow up	Non-ASCVD	Total	Digestive system	Respiratory system	Urinary system
1 year later	1.00	1.18 (0.89-1.57)	1.37 (1.03-1.83)	1.36 (1.02-1.82)	1.44 (1.08-1.92)
2 years later	1.00	0.99 (0.79-1.23)	1.07 (0.86-1.34)	1.07 (0.56-1.33)	1.11 (0.89-1.38)
3 years later	1.00	0.84 (0.70-1.01)	0.86 (0.72-1.04)	0.86 (0.71-1.03)	0.87 (0.72-1.04)
4 years later	1.00	0.83 (0.69-0.98)	0.88 (0.74-1.04)	0.88 (0.74-1.04)	0.89 (0.75-1.06)
5 years later	1.00	0.74 (0.63-0.87)	0.84 (0.71-0.98)	0.84 (0.71-0.98)	0.86 (0.74-,1.01)
6 years later	1.00	0.72 (0.61-0.83)	0.76 (0.65-0.88)	0.76 (0.65-0.89)	0.77 (0.67-0.90)
7 years later	1.00	0.69 (0.60-0.80)	0.70 (0.61-0.81)	0.71 (0.61-0.82)	0.71 (0.61-0.82)
8 years later	1.00	0.66 (0.57-0.76)	0.70 (0.61-0.80)	0.70 (0.61-0.81)	0.71 (0.62-0.82)
9 years later	1.00	0.64 (0.56-0.73)	0.70 (0.61-0.81)	0.71 (0.62-0.82)	0.73 (0.63-0.84)
10 years later	1.00	0.63 (0.55-0.72)	0.66 (0.57-0.75)	0.66 (0.57-0.76)	0.67 (0.58-0.77)
11 years later	1.00	0.62 (0.54-0.71)	0.63 (0.55-0.72)	0.63 (0.55-0.72)	0.63 (0.55-0.73)
12 years later	1.00	0.60 (0.53-0.69)	0.64 (0.56-0.73)	0.64 (0.56-0.73)	0.65 (0.57-0.74)
13 years later	1.00	0.60 (0.52-0.68)	0.65 (0.57-0.74)	0.65 (0.57-0.75)	0.67 (0.58-0.76)
14 years later	1.00	0.59 (0.51-0.67)	0.61 (0.53-0.70)	0.61 (0.54-0.70)	0.62 (0.54-0.71)
Years of follow up	Non-ASCVD	Germinal system	Blood system	Endocrine system	Other system
1 year later	1.00	2.01 (0.55-7.32)	0.65 (0.21-2.05)	3.83 (0.56-26.22)	0.55 (0.22-1.40)
2 years later	1.00	1.09 (0.43-2.77)	0.68 (0.27-1.70)	9.26 (1.46-58.74)	0.39 (0.15-0.99)
3 years later	1.00	0.88 (0.41-1.92)	0.61 (0.28-1.35)	3.39 (1.03-11.18)	0.42 (0.21-0.85)
4 years later	1.00	0.84 (0.41-1.71)	0.58 (0.27-1.27)	2.62 (0.85-8.12)	0.52 (0.28-0.98)
5 years later	1.00	0.59 (0.30-1.13)	0.60 (0.29-1.25)	2.19 (0.71-5.89)	0.47 (0.25-0.88)
6 years later	1.00	0.51 (0.28-0.94)	0.58 (0.30-1.14)	1.91 (0.73-4.97)	0.53 (0.30-0.93)
7 years later	1.00	0.49 (0.27-0.89)	0.53 (0.28-1.01)	2.11 (0.86-5.16)	0.63 (0.37-1.10)
8 years later	1.00	0.42 (0.23-0.75)	0.50 (0.27-0.95)	2.06 (0.85-4.96)	0.56 (0.33-0.97)
9 years later	1.00	0.41 (0.23-0.72)	0.48 (0.26-0.88)	1.80 (0.80-4.06)	0.55 (0.32-0.92)
10 years later	1.00	0.42 (0.24-0.75)	0.51 (0.28-0.93)	1.64 (0.74-3.65)	0.49 (0.30-0.82)
11 years later	1.00	0.40 (0.23-0.71)	0.51 (0.28-0.93)	1.64 (0.74-3.65)	0.49 (0.30-0.81)
12 years later	1.00	0.38 (0.21-0.67)	0.51 (0.28-0.93)	1.64 (0.74-3.65)	0.50 (0.30-0.81)
13 years later	1.00	0.38 (0.21-0.67)	0.51 (0.28-0.93)	1.64 (0.74-3.65)	0.50 (0.30-0.81)
14 years later	1.00	0.37 (0.21-0.65)	0.51 (0.28-0.93)	1.64 (0.74-3.65)	0.49 (0.30-0.80)

Adjusted for education level, smoking status, drinking status, high salt intake, physical activity, BMI, hs-CRP, LDL-c, HDL-c, FBG, SBP, family history of cancer, antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs.



Supplementary Figure 1 Flowchart of this study.
ASCVD = atherosclerotic cardiovascular disease