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ORIGINAL RESEARCH

Association of Midlife Cardiovascular Health and Subsequent Change in Cardiovascular Health With Incident Cancer

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ABSTRACT

BACKGROUND The commonality of risk factors between cancer and cardiovascular disease suggests that primordial prevention (preventing the onset of risk factors) is a relevant strategy for cancer prevention.

OBJECTIVES This study sought to examine the association between baseline and change in the cardiovascular health (CVH) score and incident cancer.

METHODS Using serial examinations of the GAZEL (GAZ et ELECTRICITE de France) study in France, we examined the associations between the American Heart Association's Life's Simple 7 CVH score (range: 0-to 14 [poor, intermediate, and ideal level of smoking, physical activity, body mass index, diet, blood pressure, diabetes status, or lipids]) in 1989/1990, their change over 7 years, and incident cancer and cardiac events up to 2015.

RESULTS The study population included 13,933 participants (mean age: 45.3 ± 3.4 years, 24% women). After a median follow-up of 24.8 years (Q1-Q3: 19.4-24.9 years), 2,010 participants had an incident cancer and 899 a cardiac event. The risk of cancer (any site) decreased by 9% (HR: 0.91; 95% CI: 0.88-0.93) per 1-point increase in the CVH score in 1989/1990 compared with a 20% (HR: 0.80; 95% CI: 0.77-0.83) risk reduction for cardiac events. The risk of cancer decreased by 5% (HR: 0.95; 95% CI: 0.92-0.99) per unit of change in the CVH score between 1989/1990 and 1996/1997 compared with a 7% risk reduction for cardiac events (HR: 0.93; 95% CI: 0.88-0.98). These associations remained after omitting the smoking metric from the CVH score.

CONCLUSIONS Primordial prevention is a relevant strategy for the prevention of cancer in the population. (J Am Coll Cardiol CardioOnc 2023;5:39-52) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/igo/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVDs = cardiovascular diseases

CVH = cardiovascular health

ICD-9 = International Classification of Diseases-Ninth Revision

ICD-10 = International Classification of Diseases-Tenth Revision

Cardiovascular diseases (CVDs) and cancer represent the 2 leading causes of death worldwide.[1,2] Both conditions share common modifiable risk factors such as smoking; obesity; physical inactivity and unhealthy diet; and underlying mechanisms, including chronic inflammation and oxidative stress.[3-5] As a result, preventive strategies for CVD onset may also be effective for cancer onset.

Accumulating evidence indicates that primordial prevention, which aims to prevent risk factor onset, is an effective and complementary strategy for the prevention of CVD.[6] Accordingly, a higher cardiovascular health (CVH) score, as defined by the American Heart Association's Life's Simple 7 (nonsmoking and ideal levels of body weight, physical activity, diet, untreated blood pressure, untreated fasting blood glucose, and untreated total cholesterol), has been consistently associated with a lower risk of CVD. [7] Emerging evidence suggests that primordial prevention might also be a relevant strategy for preventing cancer onset. This is based on the results of 5 prior studies from the United States that report a significant association between a better CVH score and a lower risk of incident cancer or cancer-related mortality.[8-12] However, all 5 studies evaluated CVH at only 1 point in time. Therefore, it is unknown whether a change in CVH is related to the risk of cancer. Finally, the extent to which an association between CVH and cancer exists beyond the smoking metric is poorly known because this question was evaluated in 1 study addressing baseline CVH only.[8]

Using longitudinal data from a large community-based study, the main objective of this study was to examine the association between baseline and change in CVH and incident cancer. The secondary objectives were to explore these associations for the most common site-specific cancer, including lung, breast, prostate, and colon cancer, and to evaluate whether associations with cancer existed beyond the smoking metric. Given that primordial prevention has been primarily introduced to combat CVD, to contextualize our findings, the association of CVH with incident cardiac events and mortality was also examined.

METHODS

PARTICIPANTS. The GAZ et ELECTRICITE de France (GAZEL) cohort is a prospective cohort study that was set up in 1989 aiming to address the determinants of several chronic diseases in adults, with an emphasis on occupational factors.[13] It recruited employees of France's national electricity and gas company (Electricité de France-Gaz de France). At study recruitment, a total of 20,625 employees (15,011 men and 5,614 women aged 35-50 years) participated. Participants were mainly of Caucasian origin and lived in rural and urban areas of France. In January of each year between 1989 and 2015, participants completed a self-administrated questionnaire on their lifestyle, health, and occupational situation. In addition to the annual questionnaire, a comprehensive update includes data from the human resources department, the firm's medical insurance program, and the department of occupational medicine. In 2015, after 25 years of follow-up, 74% of the participants were still responding to the study questionnaires. The study was approved by the French authority for data confidentiality (Commission Nationale Informatique et Libertés) and the Ethics Evaluation Committee of the Institut National de la Santé et de la Recherche Médicale. All participants gave written informed consent to participate.

CVH METRICS. The 7 CVH metrics were defined according to the American Heart Association criteria using self-reported data as detailed in **Table 1**.[6] Each metric was assigned a score of 0, 1, or 2 to define poor, intermediate, or ideal level, respectively. The ideal

TABLE 1 Definition of the Metrics of the Cardiovascular Health Score

	Poor	Intermediate	Ideal
Smoking	Current smokers	Ex-smokers	Never smoked
BMI, kg/m^2	≥30	25-29.9	18.5-25
Diet	Fish less than twice per week and no fruits and vegetables every day	Fish twice per week or more or consume fruits and vegetables every day	Fish twice per week or more and consume fruits and vegetables every day
Physical activity	Never or occasionally	At least once a week	Sport in competition
Hypertension	Untreated hypertension[a]	Treated for hypertension[b]	No diagnosis of hypertension and untreated
Diabetes	Untreated diabetes[a]	Treated for diabetes[b]	No diagnosis of diabetes and untreated
Total cholesterol	Untreated dyslipidemia[a]	Treated for dyslipidemia[b]	No diagnosis of dyslipidemia and untreated

[a]Untreated participants are less likely to reach the recommended levels of blood pressure, glycemia, or total cholesterol and are therefore categorized as having a poor level for the considered metric.
[b]Treated participants may reach the recommended levels of blood pressure, glycemia, or total cholesterol and are therefore categorized as having an intermediate level for the considered metric.

level for the behavioral metrics corresponds to a body mass index (BMI) <25 kg/m^2, never smoked, engagement in sports in competition, fish twice a week or more, and consume vegetables and fruits every day (data on fibers, salt consumption, and sweetened beverages are unavailable). The ideal level for the biological metrics corresponds to the absence of any medication and diagnosis for high blood pressure, diabetes, or dyslipidemia. The CVH score (range: 0-14) and the categories of the CVH score 0 to 7, 8 to 11, and 12 to 14 to reflect a low, moderate, and high CVH score were calculated.[14]

The change in the CVH score was examined between 1990 (baseline) and 1997 in people with all 7 metrics available at both time points. Participants with a history of a cancer diagnosis and cardiac events in 1997 were excluded from the analysis.

COVARIATES. The sociodemographic variables included age, sex, occupational grade (low: manual and clerical or unskilled work, medium: technical or skilled work, and high: managers) and education (primary school, lower secondary school [up to age 16], and university or higher university degree). Occupational grade and education were obtained from the employer's human resources files at baseline.

OUTCOMES. The primary outcome was incident cancer of any site. The secondary outcomes were the most common site-specific cancers (ie, female breast [referred as breast cancer throughout the paper], prostate, lung, and colon cancer). To contextualize our findings, incident cardiac events and all-cause mortality were considered as additional outcomes. The follow-up for cancer, cardiac events, and mortality was until December 31, 2015. Incident cancer was defined as International Classification of Diseases-9th Revision (ICD-9) codes 140 to 208 or International Classification of Diseases-10th Revision (ICD-10) codes C00 to C97. Skin basal cell carcinoma cancer was not considered as cancer in this study. The following ICD codes were used to define breast (ICD-9 174 and ICD-10 C50), prostate (ICD09 185 and ICD-10 C61), lung (ICD-9 162-163 and ICD-10 C34 and C39), and colon (ICD-9 153 and ICD-10 C18) cancer. Incident cardiac events including those who died of cardiac events were defined as ICD-9 codes 410 to 414 (acute and old myocardial infarction, other acute and subacute forms of ischemic heart disease, and angina pectoris) or 428 (heart failure) and ICD-10 codes I20 to I25 (ischemic heart disease such as acute myocardial infarction including ST-segment and non-ST-segment elevation myocardial infarction, other acute ischemic heart disease, angina pectoris, chronic ischemic heart disease, and current complications within 28 days after ST-segment and non-ST-segment elevation myocardial infarction) or I50 (heart failure). Nonischemic CVD events including cardiac arrhythmias, thromboembolic events, or cardiac valvular disease were only self-reported but not clinically validated, explaining why they were not investigated in the present study.

The ascertainment of cancer, cardiac, and death in the GAZEL cohort has been described previously.[15-17] Briefly, before retirement, incident cancer events were ascertained from the employer's medical registry, which has been validated for accuracy and completeness.[15] After retirement, any self-reported cancer diagnoses were thereafter validated with the participant's physician.[16] Similarly, before retirement, incident cardiac events were ascertained using a dedicated ad hoc registry set up by the Electricité de France-Gaz de France medical department and a validation survey of self-reported events after retirement.[17] Vital status and date of death were obtained annually for all participants from the company and the national French registry for the cause of mortality (Centre d'Epidémiologie sur les Causes Médicales de Décès).

STATISTICAL ANALYSIS. In the descriptive analysis, continuous data are presented as mean ± SD, median with 25th and 75th percentiles (Q1-Q3) when appropriate, and categoric data as counts with percentages.

Baseline CVH and incident cancer. The follow-up time was from 1990 to the first cancer event, cardiac event, death, or the end of follow-up (December 31, 2015), whichever came first. The HRs per 1-point increase in the CVH score and for the moderate and high vs the low CVH category in 1990 were examined using Cox proportional hazard regression and presented with 95% CIs.

Change in CVH between 1990 and 1997 and subsequent cancer. Follow-up started with the 1997 follow-up questionnaire. The low, moderate, and high CVH score categories in 1990 and 1997 were cross-tabulated, and 7 categories of change with at least 15 cancers of any site per category were examined: low-low, low-moderate/high, moderate-moderate, moderate-low, moderate-high, high-moderate/low, and high-high, respectively. The HRs per unit of change in the CVH score were also computed in Cox models.

The previously described analyses (baseline and change in CVH score) were conducted for cancer of any site; for the most common sites including breast, prostate, lung, and colon cancer; and for other cancers. Because obesity decreased the risk of breast

cancer in premenopausal women but increased the risk in postmenopausal women, the association between CVH and incident breast cancer was further stratified on menopausal status. To evaluate the contribution of smoking in the association between CVH score and cancer risk, analyses were repeated 1) after omitting the smoking metric from the CVH score and (in the same analysis) adjusting alternatively for the smoking status (never, ex, or current smoker) or the pack-year status (never, <15 pack-years, and 15 pack-years or more); and 2) after stratifying the analysis by smoking status and the pack-year status.

Incidence rates per 1,000 person-years and their 95% CI were calculated using Poisson regression analysis. All Cox models used time in study as the time scale and were adjusted for baseline covariates of age, sex, education, and occupation. Additional adjustment for the baseline CVH score was made when examining the association with change in the CVH score as a discrete variable. The proportional hazard assumption was assessed by visual inspection of the survival curves and the Kolmogorov-type supremum test. The log-linearity assumption was verified by comparing the likelihood ratio of models with the CVH score as a discrete variable and models additionally including a quadratic term on the CVH score; the same approach was used when studying the change in CVH score.

Additional analyses. To address any residual confounding by alcohol consumption, the multivariable analysis was further adjusted for alcohol consumption at baseline, which was only available in a subsample of 9,551 of the 13,933 participants included in the main analysis. To evaluate competing risks by death, subdistribution HRs were estimated using the Fine and Gray method.[18] To explore reverse causation, participants who had a diagnosis of cancer during the first 3 years of follow-up were excluded, meaning that cancers diagnosed before 1993 were excluded for the baseline analysis, and cancers diagnosed before 2000 were excluded for the change analysis. To evaluate the effect of missing data on CVH metrics and covariates, multiple imputation using a fully conditional specification method under SAS multiple imputations (SAS Institute, Inc) procedure (n = 10 imputation data sets) was used. To evaluate the effect of sample attrition between 1990 and 1997 when examining the change in CVH, inverse probability of attrition weighting analysis was used.[19] To account for the change in the ascertainment of cancer and cardiac events before and after retirement, the analyses were conducted separately in the period before and the period after retirement. Furthermore, the associations between baseline and change in each individual metric with incident cancer were also examined. Lastly, the association between the average of the CVH score in 1990 and 1997 and the risk of cancer (all site and site specific) was calculated.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc), and a P value ≤ 0.05 indicates statistical significance in the main analyses.

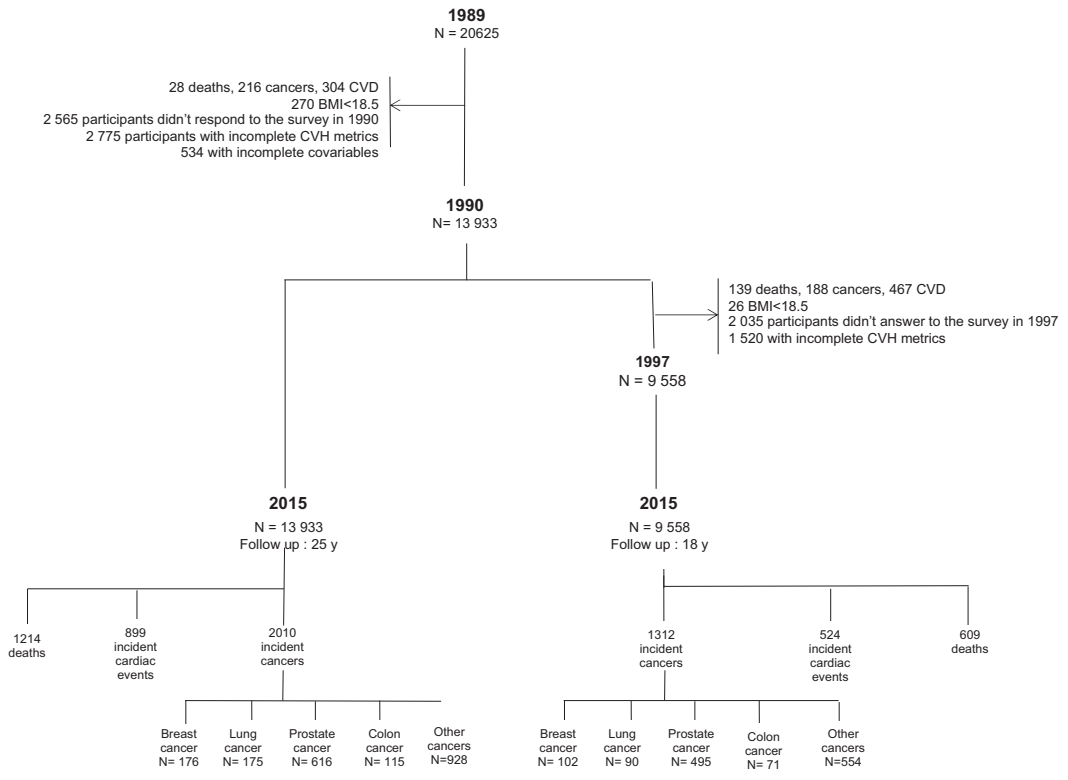
RESULTS

After excluding those with prevalent CVD or cancer (n = 520), those who died between 1989 and 1990 (n = 28), those with BMI <18.5 kg/m^2 (n = 270), those with missing CVH metrics (n = 2,775) or with missing covariates (n = 534), and those who did not answer the health questionnaire in 1990 (n = 2,565), the study population included 13,933 participants at baseline (ie, 1990) (**Figure 1**). The mean age was 45.3 ± 3.4 years; 24% were women; and 2,209 participants (15.8%) had a poor CVH score (range: 0-7), 1,1046 (79.3%) a moderate CVH score (range: 8-11), and 678 (4.9%) a high CVH score (range: 12-14) (**Table 2**). The baseline characteristics of the included participants compared with those excluded (n = 6,686) are reported in Supplemental Table 1.

BASELINE CVH AND INCIDENT CANCER. After a median follow-up of 24.8 years (Q1-Q3: 19.4-24.9 years) starting in 1990, 2,010 incident cancer cases were diagnosed, including 176 breast, 175 lung, 616 prostate, 115 colon, and 928 other cancers (most frequent phenotypes [ie, n >20], including renal cancer [n = 58], bladder cancer [n = 55], rectal cancer [n = 43], pancreatic cancer [n = 35], lymphoid chronic leukemia [n = 30], thyroid cancer [n = 30], liver cancer [n = 28], and cancer of an unspecified site [n = 25]). The mean ± SD age at cancer diagnosis was 61.3 ± 7.0 years. During follow-up, 899 participants had incident cardiac events, and 1,214 had died.

The incidence rates and adjusted HRs are reported in **Table 3**. There was a 9% (HR: 0.91; 95% CI: 0.88-0.93) risk reduction of cancer (any site) per additional point in the CVH score (range: 0-14). Significant associations were also found for moderate (range: 8-11) and high (range: 12-14) CVH score compared with low CVH score (range: 0-7). Analysis by site-specific cancer showed significant risk reduction for lung cancer and other cancers but not breast, prostate, or colon cancer (**Table 3**). The lack of association with breast cancer was not influenced by the menopausal status (P for interaction = 0.48, data not shown). For comparison, there was a 20% (HR: 0.80; 95%

FIGURE 1 Study Flowchart



BMI = body mass index; CVD = cardiovascular disease; CVH = cardiovascular health.

CI: 0.77-0.83) lower risk for cardiac events and an 18% (HR: 0.82; 95% CI: 0.79-0.84) lower risk of all-cause mortality per additional point in the CVH score (Supplemental Table 2).

CHANGE IN CVH BETWEEN 1990 AND 1997 AND INCIDENT CANCER. Change in CVH over a median of 6.9 years (range: 6.2-7.7 years) was conducted in 9,558 individuals (mean age: 52.3 ± 3.4 years, 22.7% women). The baseline characteristics of the included participants compared with those who had a cardiac event (n = 467), cancer (n = 188), BMI <18.5 kg/m^2 (n = 26), or died (n = 139) between 1990 and 1997; dropped out (n = 2,035); or had incomplete metrics (n = 1,520) are shown in Supplemental Table 3.

In total, 8% (n = 770) had an increase (ie, low to moderate/high score or moderate to high score), 76% (n = 7,259) did not change (low-low, moderate-moderate, high-high), and 16% (n = 1,529)

TABLE 2 Baseline Characteristics (1990) of the Total Study Population and by Categories of Cardiovascular Health Score

	Total Population (N = 13,933)	Low (0-7) (n = 2,209)	Moderate (8-11) n = 11,046	High (12-14) (n = 678)
Age, y	45.3 ± 3.4	45.9 ± 3.1	45.2 ± 3.5	45.0 ± (3.5
Women	3,362 (24)	241 (11)	2,922 (26)	199 (29)
Education level				
High	3,551 (26)	462 (21)	2,879 (26)	210 (31)
Intermediate	9,631 (69)	1,590 (72)	7,595 (69)	446 (66)
Low	751 (5)	157 (7)	572 (5)	22 (3)
Occupation				
High	3,614 (26)	549 (25)	2,866 (26)	199 (29)
Intermediate	9,366 (67)	1,458 (66)	7,462 (68)	446 (66)
Low	953 (7)	202 (9)	718 (7)	33 (5)

Values are mean ± SD or n (%). Low (0-7), moderate (8-11), and high (12-14) reflect the categories of the cardiovascular health score, and higher scores reflect better cardiovascular health. The cardiovascular health metrics include smoking, body weight, physical activity, diet, hypertension, diabetes, and dyslipidemia diagnosis. Each metric is assigned 0, 1, or 2 points to reflect poor, intermediate, or ideal level so that the cardiovascular health score ranges from 0 to 14.

JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:39–52

TABLE 3 Associations of Baseline CVH Score (1990) With Incident Cancer

CVH Score	n/N	Incidence Rate per 1,000 Person-Years (95% CI)[a]	Adjusted HR (95%CI)[b]
		Incident Cancer of Any Site (n/N = 2,010/13,933)	
CVH score categories			
0-7	383/2,209	8.61 (7.79-9.52)	1.00 (Ref.)
8-11	1,554/11,046	6.64 (6.32-6.98)	0.79 (0.71-0.89)
12-14	73/678	4.84 (3.85-6.09)	0.58 (0.45-0.74)
CVH score (0-14), per 1-point increase	2,010/13,933		0.91 (0.88-0.93)
		Breast cancer (n = 176)[c]	
CVH score categories			
0-7	13/241	2.78 (1.61-4.79)	1.00 (Ref.)
8-11	154/2,922	2.52 (2.15-2.95)	0.92 (0.52-1.62)
12-14	9/199	2.05 (1.07-3.95)	0.75 (0.32-1.75)
CVH score (0-14), per 1-point increase	176/3362		0.93 (0.84-1.02)
		Lung cancer (n = 175)	
CVH score categories			
0-7	59/2209	1.33 (1.03-1.71)	1.00 (Ref.)
8-11	112/11046	0.48 (0.40-0.58)	0.41 (0.30-0.56)
12-14	4/678	0.27 (0.10-0.71)	0.23 (0.09-0.65)
CVH score (0-14), per 1-point increase	175/13,933		0.69 (0.64-0.75)
		Prostate cancer (n = 616)[d]	
CVH score categories			
0-7	102/1,968	2.56 (2.11-3.11)	1.00 (Ref.)
8-11	491/8,124	2.84 (2.60-3.10)	1.07 (0.86-1.33)
12-14	23/479	2.15 (1.43-3.24)	0.79 (0.50-1.24)
CVH score (0-14), per 1-point increase	616/10,571		1.01 (0.96-1.06)
		Colon cancer (n = 115)	
CVH score categories			
0-7	22/2,209	0.50 (0.33-0.75)	1.00 (Ref.)
8-11	89/11,046	0.38 (0.31-0.47)	0.84 (0.53-1.35)
12-14	4/678	0.27 (0.10-0.71)	0.60 (0.21-1.74)
CVH score (0-14), per 1-point increase	115/13,933		0.94 (0.84-1.05)
		Other cancers (n = 924)[e]	
CVH score categories			
0-7	187/2,209	3.15 (2.73-3.64)	1.00 (Ref.)
8-11	705/11,046	2.95 (2.74-3.18)	0.74 (0.63-0.87)
12-14	32/678	2.80 (1.98-3.96)	0.52 (0.36-0.76)
CVH score (0-14), per 1-point increase	924/13,933		0.89 (0.86-0.92)

[a]Incident cancer events occurred over a median follow-up duration of 24.8 years (25th-75th percentiles: 19.4-24.9 years). [b]HRs and 95% CIs were estimated by Cox proportional hazard models using time in study as the time scale and were adjusted for age, sex, education, and occupation in 1990. [c]In women only. [d]In men only. [e]The sum of the site-specific and other cancers reached 2,006 instead of 2,010 because the 4 breast cancers in men were not considered in the analysis of the breast cancer that was exclusively conducted in women. The most frequent phenotypes (ie, n > 20) in "other cancers" include renal cancer (n = 58), bladder cancer (n = 55), rectal cancer (n = 43), pancreatic cancer (n = 35), lymphoid chronic leukemia (n = 30), thyroid cancer (n = 30), liver cancer (n = 28), or cancer of unspecified site (n = 25).

had a decrease (moderate to low or high to moderate/low) in the CVH score between 1990 and 1997. The baseline characteristics of the participants by category of change in the CVH score are shown in Supplemental Table 4.

After a median follow-up of 18.0 (IQR: 17.0-18.0) years starting in 1997, 1,312 participants were diagnosed with an incident cancer, including 102 breast, 90 lung, 495 prostate, 71 colon, and 554 other cancers (most frequent phenotypes [ie, n > 20], including bladder cancer [n = 40], renal cancer [n = 37], pancreatic cancer [n = 24], rectal cancer [n = 27], lymphoid chronic leukemia [n = 20], or thyroid cancer [n = 20]). In addition, 524 participants had a cardiac event, and 609 had died, respectively.

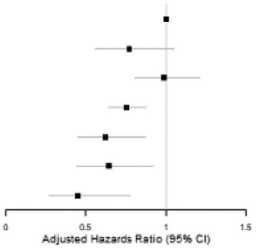
The incidence rates per categories of change in the CVH score and the corresponding adjusted HRs are reported in Supplemental Table 5 and **Figures 2A**

FIGURE 2 CVH Score in 1990 and 1997 and Cancer Risk of Any Site and Site Specific

A

All site cancers (1312/9558)

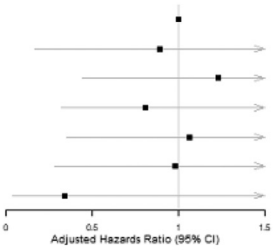
Change in the CVH score	n/N	HR [CI 95%]
Low->Low (ref)	175/1010	1 ref
Low->Moderate/High	51/372	0.77 [0.56 - 1.05]
Moderate->Low	209/1219	0.99 [0.81 - 1.21]
Moderate->Moderate	784/6061	0.75 [0.64 - 0.88]]
Moderate->High	43/398	0.62 [0.45 - 0.87]
High->Moderate/Low	35/310	0.64 [0.44 - 0.92]
High->High	15/188	0.45 [0.27 - 0.77]



B

Breast cancers* (102/2173)

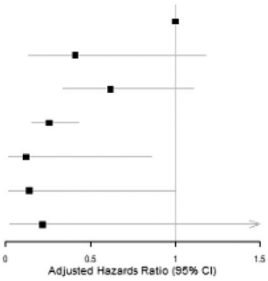
Change in the CVH score	n/N	HR [CI 95%]
Low->Low (ref)	5/96	1 ref
Low->Moderate/High	2/44	0.89 [0.17 - 4.62]
Moderate->Low	13/195	1.23 [0.44 - 3.47]
Moderate->Moderate	67/1538	0.81 [0.32 - 2.01]
Moderate->High	9/152	1.06 [0.35 - 3.17]
High->Moderate/Low	5/95	0.98 [0.28 - 3.41]
High->High	1/53	0.34 [0.04 - 2.93]



C

Lung cancers (90/9558)

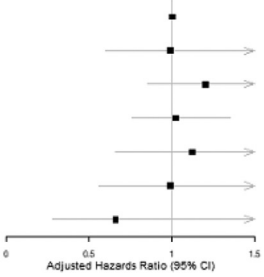
Change in the CVH score	n/N	HR [CI 95%]
Low->Low (ref)	26/1010	1 ref
Low->Moderate/High	4/372	0.41 [0.14 - 1.18]
Moderate->Low	19/1219	0.62 [0.34 - 1.11]
Moderate->Moderate	38/6061	0.26 [0.16 - 0.43]
Moderate->High	1/398	0.12 [0.02 - 0.86]
High->Moderate/Low	1/310	0.14 [0.02 - 1.00]
High->High	1/188	0.22 [0.03 - 1.62]



D

Prostate cancers † (495/7385)

Change in the CVH score	n/N	HR [CI 95%]
Low->Low (ref)	56/914	1 ref
Low->Moderate/High	21/328	0.99 [0.6 - 1.64]
Moderate->Low	78/1024	1.2 [0.85 - 1.69]
Moderate->Moderate	300/4523	1.02 [0.76 - 1.35]
Moderate->High	19/246	1.12 [0.66 - 1.88]
High->Moderate/Low	15/215	0.99 [0.56 - 1.76]
High->High	6/135	0.66 [0.28 - 1.53]



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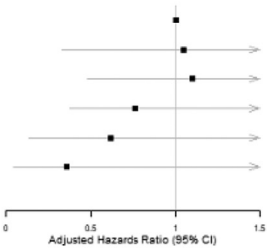
JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:39–52

FIGURE 2 Continued

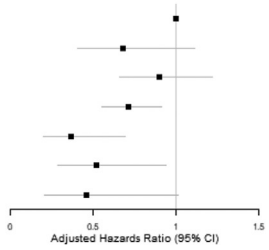
E
Colon cancers (71/9558)

	n/N	HR [CI 95%]
Change in the CVH score		
Low->Low (ref)	10/1010	1 ref
Low->Moderate/High	4/372	1.05 [0.33 - 3.35]
Moderate->Low	13/1219	1.10 [0.48 - 2.51]
Moderate->Moderate	41/6061	0.76 [0.38 - 1.51]
Moderate->High	2/398	0.62 [0.14 - 2.86]
High->Moderate/Low	1/310	0.36 [0.05 - 2.81]
High->High	0/188	-



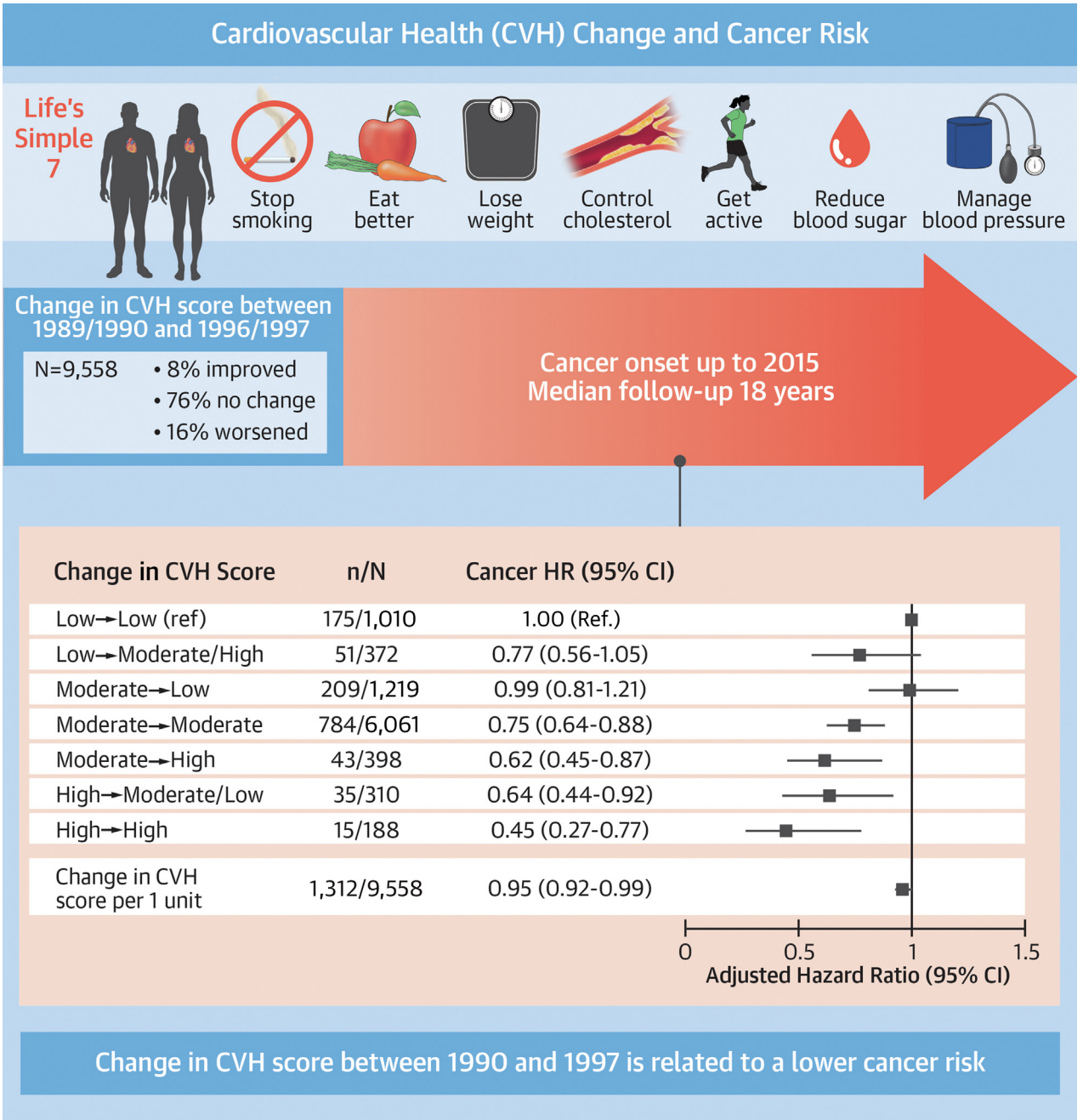
F
Other cancers ‡ (554/9558)

	n/N	HR [CI 95%]
Change in the CVH score		
Low->Low (ref)	78/1010	1 ref
Low->Moderate/High	20/372	0.68 [0.41 - 1.11]
Moderate->Low	85/1219	0.90 [0.66 - 1.22]
Moderate->Moderate	338/6061	0.71 [0.55 - 0.91]
Moderate->High	12/398	0.37 [0.20 - 0.69]
High->Moderate/Low	13/310	0.52 [0.29 - 0.94]
High->High	7/188	0.46 [0.21 - 1.01]



(A) The forest plot presents the HRs and 95% CIs for cancer of any site associated with the categories of change in the cardiovascular health (CVH) score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997. HRs were adjusted for sex, education, and occupation in 1990. **(B)** The CVH score in 1990 and 1997 and breast cancer. The forest plot presents the HRs and 95% CIs for breast cancer associated with the categories of change in the CVH score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997; the low-low category is the reference group. HRs were adjusted for sex, education, and occupation in 1990. *In women only. **(C)** The CVH score in 1990 and 1997 and lung cancer. The forest plot presents the HRs and 95% CIs for lung cancer associated with the categories of change in the CVH score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997; the low-low category is the reference group. HRs were adjusted for sex, education, and occupation in 1990. **(D)** The CVH score in 1990 and 1997 and prostate cancer. The forest plot presents the HRs and 95% CIs for prostate cancer associated with the categories of change in the CVH score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time-in-study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997; the low-low category is the reference group. HRs were adjusted for sex, education, and occupation in 1990. †In men only. **(E)** The CVH score in 1990 and 1997 and colon cancer. The forest plot presents the HRs and 95% CIs for colon cancer associated with the categories of change in the CVH score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997; the low-low category is the reference group. HRs were adjusted for sex, education, and occupation in 1990. **(F)** The CVH score in 1990 and 1997 and other cancer. The forest plot presents the HRs and 95% CIs for other cancer associated with the categories of change in the CVH score between 1990 and 1997 (low-low group as the reference category). Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997; the low-low category is the reference group. HRs were adjusted for sex, education, and occupation at baseline (ie, in 1990). ‡The sum of the site-specific and other cancers reached 1,311 instead of 1,312 because 1 breast cancer in 1 man was not considered in the analysis of the breast cancer that was exclusively conducted in women.

CENTRAL ILLUSTRATION **Cardiovascular Health Change Is Related to Lower Risk of Cancer**



Van Sloten T, et al. J Am Coll Cardiol CardioOnc. 2023;5(1):39–52.

The forest plot presents the HRs and 95% CIs for cancer of any site associated with the categories of change in the cardiovascular health (CVH) score between 1990 and 1997 (the low-low group as the reference category) and per 1 unit of change in the CVH score in separate models. Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years) starting in 1997. Analysis was adjusted for age, sex, education, and occupation in 1990 and for the CVH score in 1990 for the change analysis.

TABLE 4 Baseline and Change in Cardiovascular Health and Incident Cancer: Impact of the Smoking Metric

	Cardiovascular Health in 1990		Cardiovascular Health Change Between 1990 and 1997	
	n/N	Adjusted HR (95% CI)[a]	n/N	Adjusted HR (95% CI)[d]
Total cardiovascular health score (range: 0-14)	2,010/13,933	0.91 (0.88-0.93)	1,312/9,558	0.95 (0.92-0.99)
Cardiovascular health score without the smoking metric (range: 0-12)	2,010/13,933[b]	0.94 (0.91-0.97)	1,155/8,256[e]	0.95 (0.91-0.99)
Never smoker	752/5,946	1.00	414/3,387	1.00
Ex-smoker	646/4,498	1.09 (0.98-1.21)	486/3,261	1.15 (1.01-1.32)
Current smoker	612/3,489	1.49 (1.34-1.66)	255/1,608	1.32 (1.12-1.54)
Cardiovascular health score without the smoking metric (range: 0-12)	1,955/13,629[c]	0.95 (0.92-0.98)	1,067/7,775[f]	0.96 (0.92-1.00)
Never smoker	752/5,949	1.00	414/3,390	1.00
<15 pack-years	507/3,743	1.09 (0.97-1.22)	285/2,145	1.09 (0.93-1.26)
≥15 pack-years	696/3,937	1.41 (1.26-1.57)	368/2,240	1.26 (1.09-1.46)
Stratified analysis				
Never + ex-smokers	1398/10,444	0.92 (0.89-0.96)	900/6,648	0.94 (0.89-0.98)
Current smokers	612/3,489	0.97 (0.92-1.04)	255/1,608	0.96 (0.88-1.05)
		P for interaction = 0.30		*P* for interaction = 0.55
Stratified analysis				
Never smoker	752/5,949	0.93 (0.88-0.98)	414/3,390	0.94 (0.88-1.01)
<15 pack-years	507/3,743	0.97 (0.91-1.03)	285/2,145	0.93 (0.85-1.01)
≥15 pack-years	696/3,937	0.95 (0.90-1.00)	368/2,240	1.00 (0.93-1.08)
		P for interaction = 0.79		*P* for interaction = 0.25

[a]HRs and 95% CIs are calculated per 1-point increase in the cardiovascular health score in 1990; were estimated by Cox proportional hazard models using time in study as the time scale; and were adjusted for age, sex, education, and occupation in 1990. [b]Analysis of the baseline cardiovascular health score was further adjusted for the smoking status in 1990. [c]Analysis of the baseline cardiovascular health score in 1990 was further adjusted for the categories of pack-years in 1990, which was missing in 304 participants. [d]HRs and 95% CIs are calculated per 1 unit of change in the cardiovascular health score between 1990 and 1997. The analysis was adjusted for age, sex, education, and occupation in 1990 and further adjusted for the CVH score in 1990. [e]Analysis of the change in the cardiovascular health score between 1990 and 1997 was further adjusted for the smoking status in 1997, which was missing in 1,302 participants. [f]Analysis of change in the cardiovascular health score between 1990 and 1997 was further adjusted for the categories of pack-year status in 1997, which was missing in 1,783 participants.

to 2F. There was a 5% (HR: 0.95; 95% CI: 0.92-0.99) reduction in the risk of cancer (any site) per unit of change in the CVH score over time (**Figure 2A, Central Illustration**). Significant risk reductions were found for the moderate-moderate, moderate-high, high-moderate/low, and high-high categories of change in the CVH score compared with those who stayed with a low CVH score (low-low) (**Figure 2A, Central Illustration**). Significant risk reduction was also found with some categories of change in the CVH score for lung (**Figure 2C**) and other cancers (**Figure 2F**) but not breast (**Figure 2B**), prostate (**Figure 2D**), and colon cancer (**Figure 2E**). The lack of association with breast cancer was not influenced by the menopausal status (*P* for interaction = 0.76, data not shown). For comparison, each 1-U of change in the CVH score was associated with a significant 7% risk reduction of incident cardiac events (HR: 0.93; 95% CI: 0.88-0.98) and a nonsignificant 3% risk reduction for all-cause mortality (HR: 0.97; 95% CI: 0.92-1.02), respectively (Supplemental Table 6). Compared with the low-low group, all the categories of change in the CVH score were related to a significant lower risk of cardiac events, and all the categories of change in the CVH score except the moderate-low group were related to a significant lower risk of all-cause mortality (Supplemental Table 6).

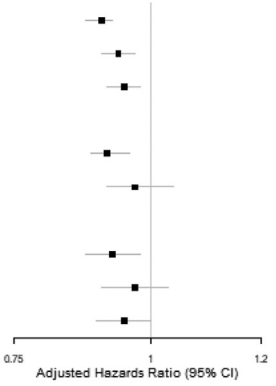
IMPACT OF THE SMOKING METRIC. The results of these analyses are reported in **Table 4** (baseline and change in the CVH score) and **Figures 3A** (baseline CVH score) and 3B (change in CVH score). After omitting the smoking metric from the CVH score while adjusting for smoking, the association of the baseline CVH score and the change in CVH score over time with cancer of any site remained statistically significant. The stratified analysis did not reveal any statistically significant interaction between CVH score, cancer risk, and smoking status.

ADDITIONAL ANALYSES. The results essentially remained unchanged after additional adjustment for alcohol consumption, competing risk analysis, exclusion of participants who had a diagnosis of cancer during the first 3 years of follow-up, multiple imputations, inverse probability weighted analysis, and analysis distinguishing outcomes validated

FIGURE 3 **Baseline CVH Score in 1990, Change in CVH Score Between 1990 and 1997 and Cancer Risk of Any Site: Impact of the Smoking Metric**

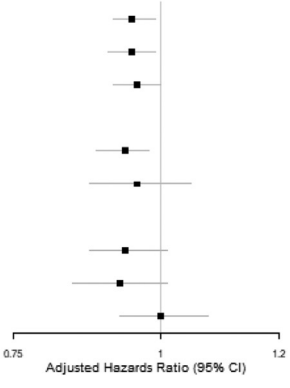
A

	n/N	HR [CI 95%]
Total CVH score	2010/13933	0.91 [0.88 - 0.93]
CVH score w/o smoking metric *	2010/13933	0.94 [0.91 - 0.97]
CVH score w/o smoking metric †	1955/13629	0.95 [0.92 - 0.98]
Stratified analysis ‡		
Never and ex smokers	1398/10444	0.92 [0.89 – 0.96]
Current smokers	612/3489	0.97 [0.92 – 1.04]
Stratified analysis §		
Never smoker	752/5949	0.93 [0.88 – 0.98]
<15 pack-years	507/3743	0.97 [0.91 - 1.03]
>= 15 pack-years	696/3937	0.95 [0.90 – 1.00]



B

	n/N	HR [CI 95%]
Total CVH score	1312/9558	0.95 [0.92 – 0.99]
CVH score w/o smoking metric *	1155/8256	0.95 [0.91 – 0.99]
CVH score w/o smoking metric †	1067/7775	0.96 [0.92 – 1.00]
Stratified analysis ‡		
Never and ex smokers	900/6648	0.94 [0.89 – 0.98]
Current smokers	255/1608	0.96 [0.88 – 1.05]
Stratified analysis §		
Never smoker	414/3390	0.94 [0.88 – 1.01]
<15 pack-years	285/2145	0.93 [0.85 – 1.01]
>= 15 pack-years	368/2240	1.00 [0.93 – 1.08]



(A) The forest plot presents the association between the CVH score in 1990 and cancer of any site after excluding the smoking metric from the score and after stratification on the smoking status. HRs are calculated per 1-point increase in the score. Cox proportional hazard models stratified by year of birth (5-year intervals) used time in study as the time scale with a subsequent median follow-up time of 24.8 years (25th-75th percentiles: 19.4-24.9 years). Analyses were adjusted for age, sex, education, and occupation in 1990. *Analysis is further adjusted for the smoking status in 1990. †Analysis is further adjusted for the categories of pack-years missing in 304 participants. ‡Analysis is stratified for the smoking status in 1990. §Analysis is stratified for the categories of pack-years in 1990 missing in 304 participants. **(B)** CVH change and cancer: impact of the smoking metric. The forest plot presents the association of the change in the CVH score between 1990 and 1997 with cancer of any site after excluding the smoking metric and after stratification on the smoking status. HRs are calculated per unit of change in the score. Cox proportional hazard model stratified by year of birth (5-year intervals) used time in study as the time scale with a median follow-up time of 18 years (25th-75th percentiles: 17.0-18.0 years). Analysis was adjusted for age, sex, education, and occupation in 1990 together with the CVH score in 1990. *Further adjustment for the smoking status in 1997, missing in 1,302 participants. †Further adjustment for the categories of pack-years in 1997, missing in 1,783 participants. ‡Stratified analysis on the smoking status in 1997, missing in 1,302 participants. §Stratified analysis on the categories of pack-years in 1997, missing in 1,783 participants.

before and after retirement (Supplemental Table 7). The results of the individual metrics analysis are reported in Supplemental Table 8 (baseline analysis) and Supplemental Table 9 (change analysis). The smoking metric and the physical activity metric were significantly associated with a lower risk of cancer of any site (baseline and change analysis). By comparison, all the metrics, except diet and physical activity, were related to incident cardiac events (baseline and change analysis). Regarding all-cause mortality, significant associations were seen with all the metrics except diet, total cholesterol, and diabetes for the baseline analysis and with all the metrics except total cholesterol and diabetes for the change analysis. Lastly, when considering the average CVH score over 1990 and 1997 (mean = 8; range: 2-14; IQR: 8-10),

JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:39–52

significant associations were found with cancer of any site, lung cancer, prostate cancer, colon cancer, and other cancers (Supplemental Table 10).

DISCUSSION

In this community-based longitudinal study with almost 25 years of follow-up, better CVH and an improvement in CVH in midlife were associated with a lower risk of cancer. These associations existed beyond the smoking metric.

PREVIOUS STUDIES ON BASELINE CARDIOVASCULAR HEALTH AND CANCER RISK. The association between better CVH at 1 time point and a lower risk of cancer in this European population complements the findings of 5 previous studies all conducted in U.S. populations. [8-12] Significant risk reductions were reported in the ARIC (Atherosclerosis Risk In Communities)[8] and Framingham study[9] for incident cancer and MESA (Multi-Ethnic Study of Atherosclerosis)[10] and the Women's Health Initiative study[11] for cancer-related mortality. In the Aerobics Center Longitudinal Study,[12] the association between higher baseline CVH and lower cancer-related mortality did not reach statistical significance.

PREVIOUS STUDIES ON CHANGE IN CVH AND CANCER RISK. Prior studies have examined the association between a change in 1 single risk factor such as weight, diet, or lifetime alcohol consumption and cancer risk,[20-22] but, to the best of our knowledge, this is the first study evaluating the association between a change in CVH per se and incident cancer. The lower risk of cancer associated with an improvement in CVH remained consistent upon multiple additional analyses, supporting the robustness of the findings. In a mutually adjusted analysis, higher CVH at baseline and an improvement in CVH over time were each independently related to a lower risk of cancer. This is a particularly encouraging finding for those at low-level CVH because it is never too late to improve CVH no matter how low the current score.

IMPACT OF THE SMOKING METRIC. The present findings further suggest that the lower risk of cancer associated with either higher CVH or an improvement in CVH over time is not entirely caused by smoking. Indeed, although attenuated, the association between higher CVH at baseline or an improvement in CVH over time with cancer remained significant even after omitting the smoking metric from the CVH score. Similar findings were reported in ARIC,[8] but in that study CVH at 1 single point only was examined on the one hand, and the analysis did not adjust for smoking status on the other hand, raising the issue of residual confounding. In addition, in the current study, an improvement in CVH was not only related to a lower risk of lung cancer but also to a lower risk of other cancers in the main analysis and a lower risk of colon and prostate cancer in sensitivity analysis when considering the averaged CVH score. Lastly, when analyzing the individual metrics, associations with cancer at any site (baseline and change analysis) were not only found for the smoking metric but also for the physical activity metric.

CANCER SITE-SPECIFIC ANALYSIS. In the present study, the association of CVH with cancer was mainly observed for lung cancer and other cancers in the main analysis. The association between CVH and incident breast cancer was in the expected direction but was not statistically significant. The relatively low number of cancer diagnoses may partly explain this finding. However, this finding is consistent with the study results from ARIC in which the inverse association between higher CVH at baseline and breast cancer risk was not statistically significant.[8] Also, it appears that the association between CVH and breast cancer, if any, is of a much lower magnitude than the association of CVH with lung or colon cancer in postmenopausal women from the Women's Health Initiative study.[11] In the present study, any lack of association between risk factors and prostate cancer incidence might be explained by the fact that prostate cancer diagnosis was driven by screening and that screening may lead to the identification of many prostate cancers that have a low likelihood of metastasis. It is unclear whether better CVH is associated with reduced prostate cancer mortality or a lower incidence of metastatic prostate cancer. Lastly, the nonsignificant association of CVH with colon cancer in the main analysis may partly be caused by the lack of data on fiber-rich whole grains in the diet metric because there is strong evidence for an inverse association between whole grains and colon cancer.[23]

IMPLICATIONS OF THE STUDY. The present study findings may have implications for the prevention of cancer in the population. The lower risk of cancer associated with higher CVH in prior studies and with a change in CVH, as newly shown in the present study, supports that primordial prevention may be a relevant strategy for the prevention of cancer. Although associations with cancer were of a lower

magnitude than with cardiac events (confirming the prominence of primordial prevention for CVD), the results of the present study further indicate that primordial prevention may be a unified preventative strategy for CVD and cancer. Only 8% of the participants improved their CVH score over 7 years, whereas 16% had a lower CVH over time. This observation further confirms that promoting primordial prevention is a challenging task that requires efforts from multiple health care stakeholders including patients, providers, policy makers, and politicians. In particular, these findings may be of help for clinicians when engaging discussions with their patients to find the best strategies to change their health behaviors and improve their CVH score.

The key strengths of this study include the assessment of change in CVH, a large sample size, a long follow-up for the incidence of events, and the robustness of the main findings after multiple additional analyses.

STUDY LIMITATIONS. First, the observational design precludes from causal conclusions. Second, there might be misclassification biases in the distribution of the biological CVH metrics, which were based on self-reported data only. A self-reported biological score has been shown to have excellent sensitivity (92%) but low specificity (30%) compared with its objectively measured counterpart.[24] Furthermore, self-reported CVH has been previously related to a lower risk of cancer mortality in postmenopausal women.[11] Third, the diet and the physical activity metrics had incomplete definitions, which are likely to attenuate the findings toward the null. Fourth, we cannot exclude the possibility of residual confounding (eg, family history of cancer was unavailable). Fifth, a change in CVH was based on 2 measures over 7 years, whereas trajectories of CVH over a longer period of follow-up at multiple time points are likely to be more precise. Sixth, in the site-specific analysis, there were few cancer events in some categories of change in the CVH score. Seventh, the incidence of prostate cancer was several-fold higher than the incidence of breast, colon, or lung cancer in the current study, likely reflecting advocacy for regular prostate cancer screening in the company. Eighth, the GAZEL cohort is based on government employees, which raises the issue of the healthy worker effect. Ninth, the study was mainly composed of White participants aged 30 to 50 years at baseline; therefore, the findings might not apply to other age groups or more ethnically diverse populations. Lastly, the American Heart Association has just defined the Life's Essential 8, which refines the definition of some metrics, including sleep duration as an additional metric, and calculates the score on a 100-point scale; however, this score was not available at the time of the analysis.[25]

CONCLUSIONS

Better CVH and the maintenance or improvement of CVH midlife were associated with a lower risk of cancer.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In adult men and women free of CVD and cancer, a higher CVH score as defined by the American Heart Association's Life's Simple 7 and a change in the CVH score over time are associated with a lower risk of cancer. Monitoring and promoting adherence to optimal CVH may be relevant to prevent cancer in this population.

TRANSLATIONAL OUTLOOK: The analysis on change in CVH with the risk of cancer should be replicated in more ethnically and socioeconomically diverse populations. Furthermore, future studies should use a lifetime approach to investigate how and if CVH and a change in CVH before midlife (ie, childhood) affect the risk of cancer in late life.

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KEY WORDS cancer, cohort, ideal cardiovascular health, prevention

APPENDIX For supplemental tables, please see the online version of this paper.