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Research

Is the number of ideal cardiovascular health metrics in midlife associated with lower risk of cancer? Evidence from 3 European prospective cohorts

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Abstract

Background: Primordial prevention may be a relevant strategy for the prevention of cancer. Given the commonality of risk factors and mechanisms between cancer and cardiovascular disease, we examined the associations between the number of ideal cardiovascular health metrics in midlife and incident cancer.

Methods: In 3 European cohorts (NutriNet-Santé and GAZEL, France; Whitehall II, United Kingdom), the number of ideal cardiovascular health metrics was determined at baseline (range 0–7). Follow-up for cancer events was until October 2020 (NutriNet-Santé), March 2017 (Whitehall II) and December 2015 (GAZEL). Cox regression was conducted in each cohort, and results were thereafter pooled using a random-effects model.

Results: Data were available on 39 718 participants. A total of 16 237 were from NutriNet-Santé (mean age 51.3 yr; 28% men), 9418 were from Whitehall II (mean age 44.8 yr; 68% men) and 14 063 were from GAZEL (mean age 45.2 yr; 75% men). The median follow-up was 8.1 years in NutriNet-Santé, 29.6 years in Whitehall II and 24.8 years in GAZEL, and yielded a total of 4889 cancer events. A greater number of ideal cardiovascular health metrics was associated with a lower overall cancer risk in each cohort, with an aggregate hazard ratio (HR) per 1 increment in number of ideal metrics of 0.91 (95% confidence interval [CI] 0.88–0.93). This association remained after removal of the smoking metric (aggregate HR per unit increment in number of ideal metrics: 0.94, 95% CI 0.90–0.97), and site-specific analysis demonstrated a significant association with lung cancer.

Interpretation: A greater number of ideal cardiovascular health metrics in midlife was associated with lower cancer risk, notably lung cancer. Primordial prevention of cardiovascular risk factors in midlife may be a complementary strategy to prevent the onset of cancer.

Primordial prevention (i.e., the prevention of risk factor onset) is increasingly recognized as a complementary strategy for preventing cardiovascular disease. The American Heart Association (AHA) developed the cardiovascular health score, a 7-item tool (nonsmoking, and ideal levels of body weight, physical activity, healthy diet, untreated blood pressure, fasting blood glucose and total cholesterol) for promoting ideal cardiovascular health.[1] Better cardiovascular health is associated with a lower risk of cardiovascular disease.[2] In addition, there is emerging evidence of an association between better cardiovascular health and noncardiovascular outcomes, such as dementia[3] and type 2 diabetes.[4,5]

Primordial prevention may also be a complementary strategy for the prevention of cancer. Cancer and cardiovascular disease can coexist in the same individuals,[6,7] and share common modifiable risk factors, including smoking, obesity, physical inactivity and unhealthy diet, and common pathophysiological mechanisms, including inflammation and oxidative stress.[6] For example, the recent CANTOS (Canakinumab

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Anti-inflammatory Thrombosis Outcome Study) found that anti-inflammatory therapy reduces the risk of both cardiovascular events[8] and lung cancer.[9] Taken together, these results suggest that combined cardiovascular and oncological preventive efforts might have synergistic public health benefits.

To date, a significant and inverse association between greater cardiovascular health and cancer risk was reported in 3[10–13] out of 4 previous existing studies,[14] all from the United States. However, such evidence is currently missing in non-US populations. In addition, it remains unclear whether the association between cardiovascular health and cancer is attributable solely to the smoking metric of the cardiovascular health score. If a significant risk reduction of cancer is observed beyond the smoking metric, this may provide important evidence for use of the composite cardiovascular health score in cancer prevention at the population level. Also, the association between cardiovascular health and site-specific cancer is largely unknown.

Using data from 3 large prospective cohort studies from France and the United Kingdom, our main objective was to examine the associations of midlife cardiovascular health with incident cancer. Secondary objectives were to evaluate whether any such association was independent of the smoking metric and existed for the most common site-specific cancer types, including lung, breast, prostate and colon cancer.

Methods

We used data from individuals free of cancer and cardiovascular disease at baseline enrolled in 3 cohort studies: NutriNet-Santé, Whitehall II and GAZEL (for details, see Appendix 1, available at www.cmajopen.ca/content/11/4/E774/suppl/DC1).

NutriNet-Santé is an ongoing Web-based cohort aiming to examine the relation between nutrition and health.[15] A total of 170 770 adults (37 789 men and 132 981 women aged 18–75 yr) from across France with Internet access have been recruited since 2009. Between 2011 and 2014, blood samples were obtained and physical examinations were done in a subsample of 19 473 participants. This subsample was included in the current analysis. Whitehall II is an ongoing prospective cohort study of adults originally employed by the British civil service in London-based offices.[16] A total of 10 308 adults (6895 men and 3413 women aged 35–55 yr) were recruited at baseline between 1985 and 1988, during which they underwent a clinical examination. GAZEL is a prospective cohort study aiming to address the determinants of several chronic noncommunicable diseases.[17] A total of 20 625 adults (15 011 men and 5614 women aged 35–50 yr) originally employed by the French national gas and electric company were enrolled between 1989 and 1990.

Cardiovascular health metrics

The 7 metrics of cardiovascular health were each dichotomized as ideal versus nonideal so that the number of ideal metrics — the primary exposure — ranged from 0 to 7. The AHA criteria (Table 1) were used to define the ideal level for each metric in each cohort. We considered nonsmoking, and ideal levels of body weight, physical activity and healthy diet, together with ideal levels of untreated blood pressure, fasting blood glucose and total cholesterol.

Outcomes

The primary outcome was incident cancer of any site (nonfatal cancer and cancer-related mortality combined), as defined by *International Classification of Diseases, 9th Revision*

Table 1: Definition of ideal cardiovascular health metrics in NutriNet-Santé, Whitehall II and GAZEL

Metric	Recommended ideal level
Smoking	All cohorts: Never or quit ≥ 12 mo
Body mass index	All cohorts: < 25
Physical activity	NutriNet-Santé and Whitehall II: ≥ 75 min/wk of vigorous activity, ≥ 150 min/wk of moderate activity or a combination of the two GAZEL: any sports activity in a competition context
Healthy diet	NutriNet-Santé: ≥ 4 optimal diet items out of the following 5 items: the equivalent of 5 servings per day of fruits and vegetables or 400 g/d, ≥ 2 times/wk fish consumption or average consumption of ≥ 100 g/d, average salt consumption < 1.5 g/d, average fibre intake ≥ 25 g/d, sugar-sweetened beverages ≤ 155 g/d Whitehall II: 3 optimal out of the following 3 items: 2 servings of a fruit and vegetable portion per day and fish consumption ≥ 3 times/wk GAZEL: 3 optimal out of the following 3 items: fruit portion every day or almost every day, vegetables portion every day or almost every day, and fish consumption ≥ 3 times/wk
Blood pressure	NutriNet-Santé and Whitehall II: < 120/80 mm Hg, untreated GAZEL: No diagnosis of hypertension and untreated
Fasting plasma glucose*	NutriNet-Santé and Whitehall II: < 100 mg/dL, untreated GAZEL: No diagnosis of diabetes and untreated
Total cholesterol†	NutriNet-Santé and Whitehall II: < 200 mg/dL, untreated GAZEL: No diagnosis of dyslipidemia and untreated

*SI conversion factor: to convert glucose to millimoles per litre, multiply by 0.0555.
†SI conversion factor: to convert cholesterol to millimoles per liter, multiply by 0.0259.

(ICD-9) codes 140–208 or *International Classification of Diseases, 10th Revision* [ICD-10] codes C00–C97. The secondary outcomes were the most common site-specific cancers: female breast (further referred to as breast, ICD-9 174; ICD-10 C50), prostate (ICD-9 185; ICD-10 C61), lung (ICD-9 162–163; ICD-10 C34, C39) and colon cancer (ICD-9 153; ICD-10 C18). Skin basal cell carcinoma was not considered as cancer. Method of ascertainment of the outcomes are provided in Appendix 1. Cancer follow-up was until Oct. 15, 2020 (NutriNet-Santé), Mar. 31, 2017 (Whitehall II) and Dec. 31, 2015 (GAZEL).

Statistical analysis

Analyses were undertaken in each study, and the individual study results were thereafter pooled to obtain combined effect measures. In all analyses, we excluded individuals with missing data on the cardiovascular health metrics or covariates, or with missing follow-up data (Appendix 1, Figures S1–S3).

In each study, the cumulative incidence function by number of ideal cardiovascular health metrics using time-in-study as the timescale is reported. The hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cancer (any type) and site-specific cancer per 1 increment in the number of ideal metrics were estimated in Cox proportional-hazards models. All models used age as the timescale, were stratified by year of birth (5-yr intervals) to account for birth cohort effects, and were adjusted for baseline covariates sex, education, marital/cohabitation status, occupation, alcohol use (in NutriNet-Santé and Whitehall II only), race/ethnicity (in Whitehall II only) and family history of cancer (in NutriNet-Santé only). To evaluate the impact of the smoking metric, analyses were repeated after omitting smoking from the number of ideal cardiovascular health metrics (which now ranged from 0 to 6) but keeping adjustment for smoking status. The proportional hazards assumption was assessed for the main exposure by visual inspection of the survival curves, the Kolmogorov test and the Schoenfeld residuals test. The linearity assumption for the relation between cardiovascular health score (i.e., number of ideal metrics) and incident cancer was evaluated using Martingale residuals plots. Follow-up time was from baseline to first incident cancer, non-cancer-related death or end of follow-up, whichever occurred first.

The HRs and 95% CIs per study were aggregated using a meta-analysis random-effects model to estimate a combined effect. Heterogeneity was assessed with the I^2 statistic (< 30% representing low, 30%–60% moderate, and 50%–90% substantial heterogeneity).

Additional analysis

To explore reverse causation due to potential undetected cancer, the analyses were repeated after excluding participants who had a diagnosis of cancer early during the first 2.5 years (in NutriNet-Santé) or 4 years (in Whitehall II and GAZEL) of follow-up. Competing risk by death was addressed using Fine and Gray method.[18] To contextualize our findings, the association between baseline cardiovascular health and incident cardiovascular disease events was reported. Incident coronary heart disease and stroke were adjudicated following procedures previously reported.[19–21] All statistical tests had an α threshold of 0.05 unless stated otherwise. Analysis was conducted using SAS 9.4 (SAS Institute Inc.) and Stata 17.0 (StataCorp).

Ethics approval

All studies were approved by local ethical committees (Appendix 1).

Results

In total, 39 718 participants were enrolled, including 16 237 from NutriNet-Santé (mean age 51.3 yr; 27.6% men), 9418 from Whitehall II (mean age 44.8 yr; 68.1% men) and 14 063 from GAZEL (mean age 45.2 yr; 75.0% men). The baseline characteristics of the individual cohorts are given in Table 2, and the study flow charts are provided in Appendix 1, Figures S1–S3. The characteristics of participants from each cohort according to incident cancer are shown in Appendix 1, Tables S1–S3. The rates of cancer in participants with and without missing data in each cohort are reported in Appendix 1, Table S4.

The median follow-up was 8.1 (interquartile range [IQR] 6.4–9.3) years in NutriNet-Santé, during which 948 participants were diagnosed with incident cancer and 38 died of a non-cancer-related cause. In Whitehall II, after a median follow-up of 29.6 (IQR 28.0–30.5) years, 1916 participants were diagnosed with incident cancer and 800 died of a non-cancer-related cause. In GAZEL, after a median follow-up of 24.8 (IQR 19.6–24.9) years, 2025 participants were diagnosed with incident cancer and 507 died of a non-cancer-related cause. The follow-up of the 3 studies combined yielded a total of 4889 cancer events, including 313 lung, 724 breast, 1226 prostate and 341 colon cancers. The number of site-specific cancer cases per cohort is given in the study flow charts (Appendix 1, Figures S1–S3). Mean age at cancer diagnosis was 64.8 (standard deviation [SD] 10.1) years in NutriNet-Santé, 66.3 (SD 8.7) years in Whitehall II and 61.3 (SD 7.0) years in GAZEL.

As shown on the survival curves, cumulative incidence of cancer (any type) progressively decreased with the number of ideal cardiovascular health metrics at baseline in each cohort (Appendix 1, Figure S4). Better cardiovascular health was related to a lower risk of cancer (any type) in each cohort, yielding an aggregate HR of 0.91 (95% CI 0.88–0.93) per 1 increment in the number of ideal cardiovascular health metrics (Figure 1). Analyses by site-specific cancer show that 1 increment in the number of ideal cardiovascular health metrics was associated with lower risk of lung cancer, but not breast, prostate or colon cancer in each cohort and in the aggregate analysis (Figure 2). When we excluded the smoking metric and additionally adjusted for smoking status, better cardiovascular health remained associated with a lower cancer risk (any type), with an aggregate HR of 0.94 (95% CI 0.90–0.97) per 1 increment in the number of ideal

Table 2: Baseline characteristics and incidence rates of cancer in the individual cohort studies

Characteristic	No. (%)*		
	NutriNet-Santé Study *n* = 16 237	Whitehall II Study *n* = 9418	GAZEL Cohort Study *n* = 14 063
Age, yr, mean ± SD	51.3 ± 13.5	44.8 ± 6.0	45.2 ± 3.5
Men	4488 (27.6)	6413 (68.1)	10 550 (75.0)
Education level*			
High	5778 (35.6)	2486 (26.4)	3599 (25.6)
Intermediate	7853 (48.4)	2535 (26.9)	9709 (69.0)
Low	2606 (16.0)	4397 (46.7)	755 (5.4)
Occupational position†			
High	7329 (45.1)	2828 (30.0)	3628 (25.8)
Intermediate	3880 (23.9)	4595 (48.8)	9487 (67.5)
Low	5028 (31.0)	1995 (21.2)	948 (6.7)
Marital/cohabitation status			
Married/cohabiting	11 664 (71.8)	7006 (74.4)	12 623 (89.8)
Single	2312 (14.2)	1538 (16.3)	483 (3.4)
Divorced	1760 (10.8)	761 (8.1)	804 (5.7)
Widowed	501 (3.1)	113 (1.2)	153 (1.1)
Race/ethnicity: White	NA	8522 (90.5)	NA
Family history of cancer	7285 (44.9)	NA	NA
Alcohol, units/wk			
0	NA	1679 (17.8)	1561 (16.6)§
1–13	NA	5202 (55.2)	4942 (52.4)§
≥ 14	NA	2537 (26.9)	2927 (31.0)§
Alcohol, g/d	8.82 (11.6)	NA	NA
No. of ideal cardiovascular health metrics, median (IQR)	3 (2–4)	4 (3–4)	5 (4–6)
Cardiovascular health score categories‡			
Low, 0–2 ideal metrics	4389 (27.0)	1657 (17.6)	762 (5.4)
Moderate, 3–4 ideal metrics	8491 (52.3)	5772 (61.3)	7921 (56.3)
High, 5–7 ideal metrics	2760 (17.0)	1989 (21.1)	5380 (38.3)
No. of incident cancer	948 (5.8)	1916 (20.3)	2025 (14.4)
Incidence rate of cancer per 1000 person years, 95% CI	6.3 (5.9–6.7)	7.5 (7.2–7.8)	6.8 (6.5–7.1)

Note: CI = confidence interval, IQR = interquartile range, NA = not available, SD = standard deviation.
*Unless stated otherwise.
*Education categories in NutriNet-Santé were 1) less than high school (low), 2) less than 2 years after high school (intermediate) and 3) more than or equal to 2 years after high school (high); in Whitehall, 1) lower secondary school (low), 2) higher secondary school (intermediate) and 3) university or higher university degree (high); and in GAZEL, 1) primary school (low), 2) lower secondary school (intermediate) and 3) university or higher university degree (high).
†Occupation categories in NutriNet-Santé were 1) employee/worker/farmer (low), 2) intermediary profession (intermediate) and 3) craftsperson, merchant, company director, specialized personnel, intellectual profession (high); in Whitehall II, 1) administrative (low), 2) professional/executive (intermediate) and 3) clerical/support (high); and in GAZEL, 1) watchman, worker (low), 2) commercial and technical agent, internship agent and others (intermediate) and 3) administrative and technical executives, teachers (high).
‡The cardiovascular health metrics included nonsmoking, and ideal levels of body weight, physical activity, diet, blood pressure, fasting blood glucose and total cholesterol. For definitions of the metrics, see Table 1.
§Data on alcohol use available in GAZEL cohort in *n* = 9430.

cardiovascular health metrics (Figure 3). Better cardiovascular health remained associated with lung cancer, but not with any of the other site-specific cancer types (Appendix 1, Figure S5).

Additional analysis

In each cohort, associations were similar after exclusion of individuals who had a cancer in the first years of follow-up (Appendix 1, Figure S6). Overall, there were 1375 deaths

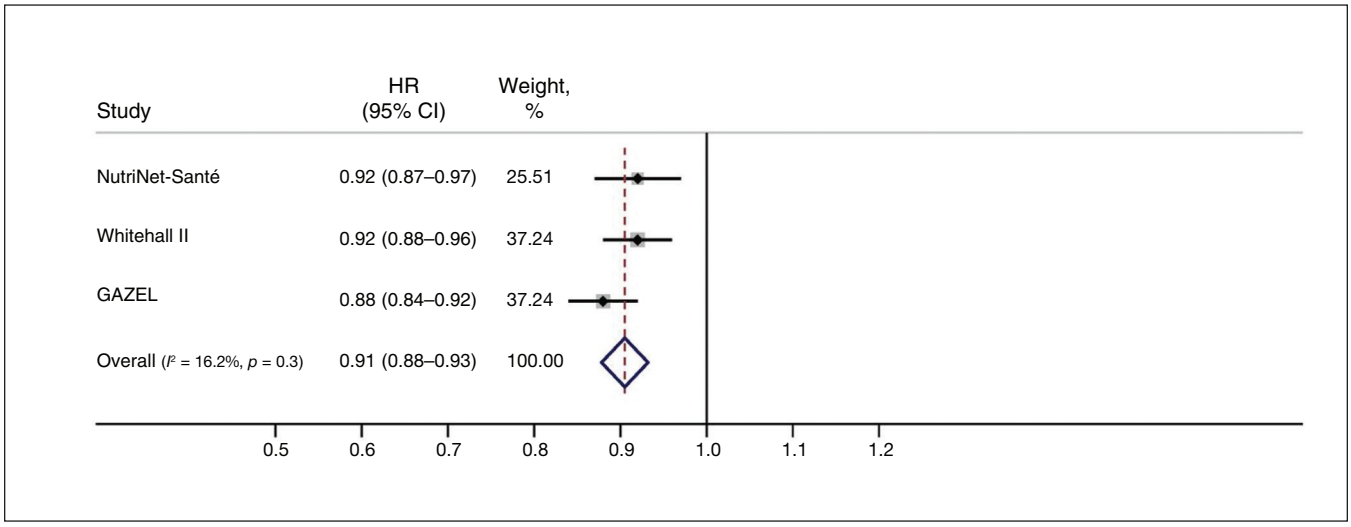

Figure 1: Hazard ratios (HRs) for incident cancer per 1 increment in ideal cardiovascular health metric. Hazard ratios and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models stratified by year of birth (5-yr intervals) and using age as the timescale. Hazard ratios were adjusted for sex, marital/cohabitation status, education and occupation at baseline. In NutriNet-Santé, results were additionally adjusted for alcohol use and family history of cancer. In Whitehall II, results were additionally adjusted for alcohol use and race/ethnicity. The overall HR and CI was estimated using random-effects meta-analysis.

before cancer in the 3 cohorts, and associations remained virtually unchanged after we accounted for competing risk by death (Appendix 1, Figure S7). For comparison, better cardiovascular health was related to lower risk of incident cardiovascular disease events in each cohort, with an aggregate HR per 1 increment in the number of ideal cardiovascular health metrics of 0.78 (95% CI 0.76–0.81) (Appendix 1, Figure S8).

Interpretation

We found a 9% risk reduction of cancer per number of ideal cardiovascular health metrics and a persistence of this effect even after the omission of the smoking metric from the cardiovascular health score. Risk reductions associated with greater cardiovascular health score were twice stronger for incident cardiovascular disease than for cancer owing to the primary focus of primordial prevention of cardiovascular disease. However, as in any observational study, we cannot exclude the possibility that at least some part of the observed associations may be due to residual confounding factors such as air pollution, second-hand smoke, the amount a person has smoked over a period of time, climactic or local geographic environment, and health care availability. There may also be genetic factors that connect some ethnic and cultural groups to both cardiovascular health status and cancer risk.

We found that the association between cardiovascular health and incident cancer was consistent across the 3 studies, despite heterogeneity between the studies regarding their study populations and design. For example, study recruitment took place in the 1980s in Whitehall II and GAZEL, and took place in 2009 in NutriNet-Santé, and women were overrepresented in NutriNet-Santé, whereas men were overrepresented in GAZEL. Also, duration of follow-up was more than 20 years in Whitehall II and GAZEL, but less than 10 years in NutriNet-Santé. The biological items of the cardiovascular health score were objectively measured in Whitehall II and NutriNet-Santé, but were self-reported by the participants in GAZEL, preventing use of the full 0–14 point score in a homogenous manner in the 3 cohorts. Furthermore, availability of data on potential confounders (i.e., family history of cancer, ethnicity and alcohol consumption), and definition of some covariates (i.e., education, cohabiting and alcohol consumption) differed according to the study. However, the consistency of the results across the 3 studies and with prior existing US studies[10–13] supports the validity of the study findings.

Better cardiovascular health was related to lower risk of cancer in the Atherosclerosis Risk in Communities (ARIC) study[13] and Framingham Heart Study,[11] whereby a 51% risk reduction existed between those achieving 6–7 versus 0 ideal metrics in the ARIC study and a 5% risk reduction existed per 1 point increase in the 0–14 points cardiovascular health score in the Framingham Heart Study. Associations with cancer-related mortality were reported in the Multi-Ethnic Study of Atherosclerosis (MESA)[12] and Women's Health Initiative (WHI) study, with a 20% decreased risk among those with an optimal cardiovascular health score (11–14 points) compared with those with an inadequate score (0–8) in the MESA and an 52% greater risk between postmenopausal women with 0–1 versus 6–7 ideal metrics in the WHI study.[10] However, the Aerobics Center Longitudinal Study[14] did not find an association between cardiovascular health and cancer-related mortality. Consistent with our study findings, in the ARIC study, the association between better cardiovascular health and lower cancer risk remained after exclusion of smoking from the cardiovascular health metrics. Similarly, the significant association between cardiovascular health and lung cancer was also found in the ARIC study[13] and the WHI study.[10]

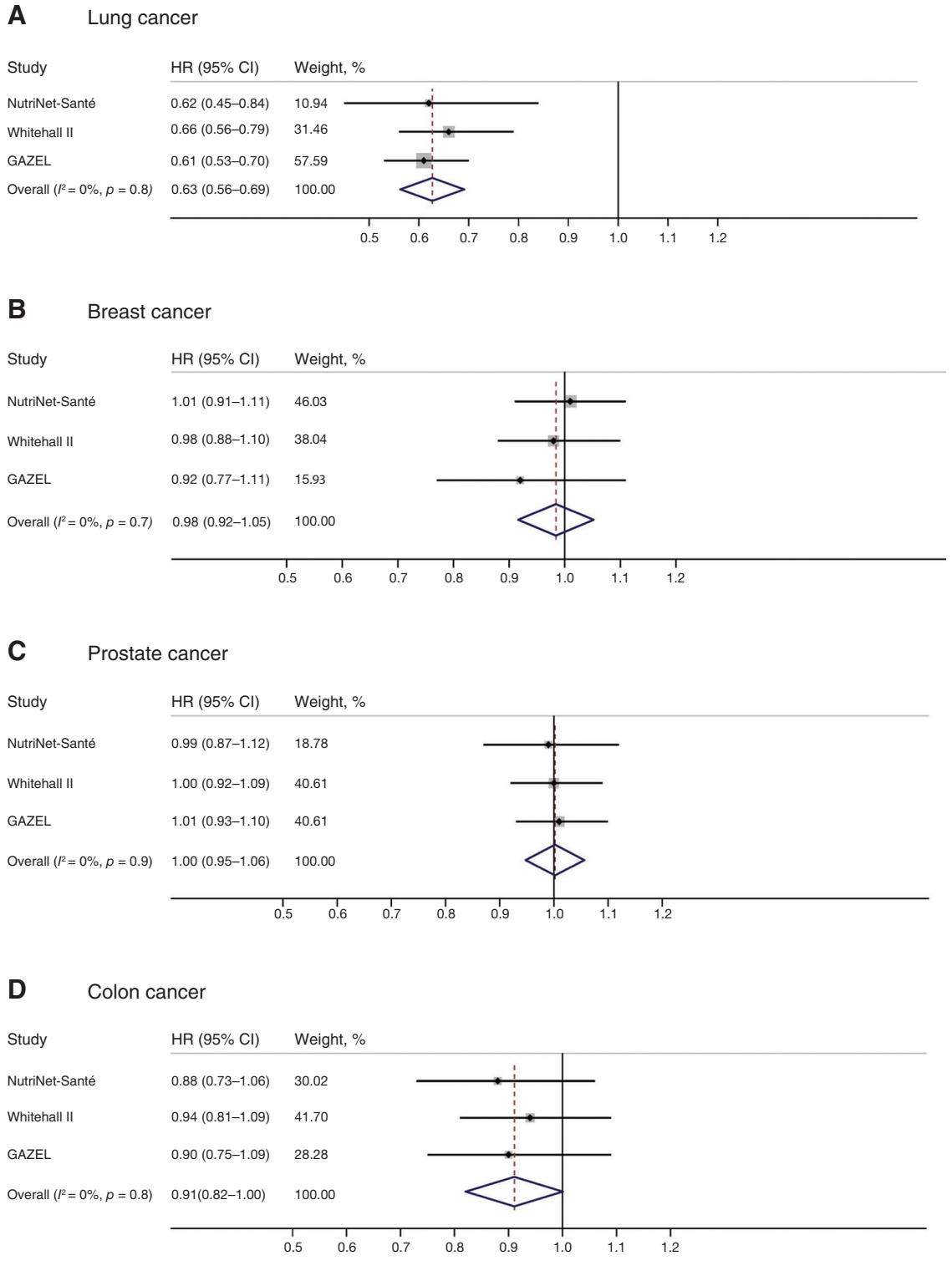

Figure 2: Hazard ratios (HRs) per 1 increment in ideal cardiovascular health metric for site-specific cancer — A) lung cancer, B) breast cancer, C) prostate cancer, D) colon cancer. Hazard ratios and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models stratified by year of birth (5-yr intervals) and using age as the timescale. Hazards ratios were adjusted for sex, marital/cohabitation status, education and occupation at baseline. In NutriNet-Santé, results were additionally adjusted for alcohol use and family history of cancer. In Whitehall II, results were additionally adjusted for alcohol use and race/ethnicity. The overall HR and CI was estimated using random-effects meta-analysis.

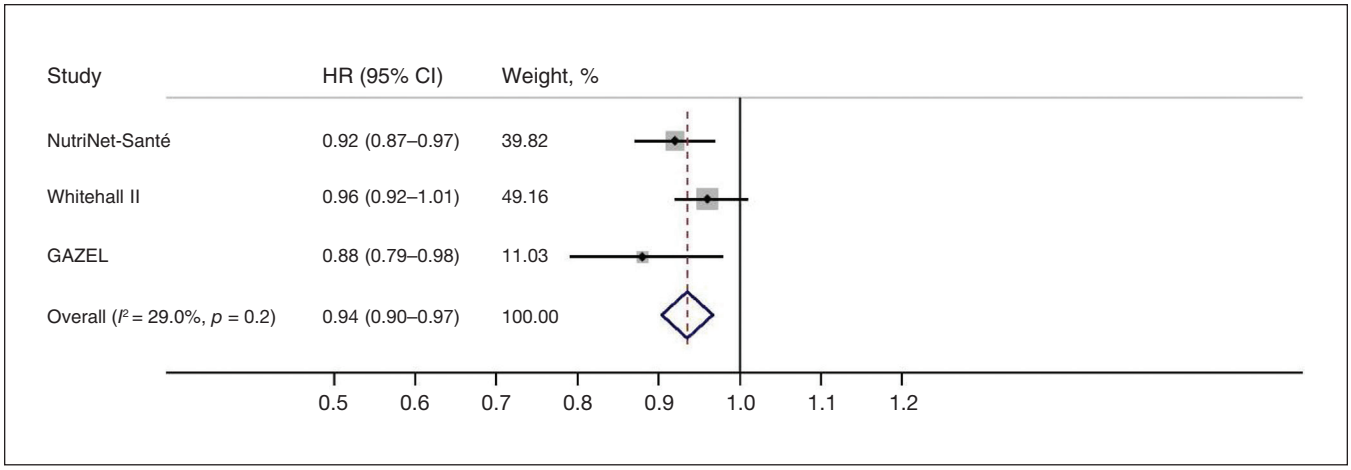

Figure 3: Hazard ratios (HRs) for incident cancer per 1 increment in ideal cardiovascular health metric excluding the smoking metric and adjusted for smoking status. Hazard ratios and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models stratified by year of birth (5-yr intervals) and using age as the timescale. Hazards ratios were adjusted for sex, marital/cohabitation status, education, occupation at baseline and smoking metric. In NutriNet-Santé, results were additionally adjusted for alcohol use and family history of cancer. In Whitehall II, results were additionally adjusted for alcohol use and race/ethnicity. The overall HR and CI was estimated using random-effects meta-analysis.

The strongest association for lung cancer versus other site-specific cancer types is consistent with previous studies showing a strong link between cardiovascular disease and cardiovascular risk factors (notably smoking and obesity) and lung cancer,[6] and of shared mechanisms underlying cardiovascular disease and lung cancer (e.g., inflammation).[6,8,9]

Future studies should refine cancer diagnosis and consider the staging of the disease, and dissociate primary cancer and metastasis. Contextual factors mentioned above should also be accounted for. Finally, future studies should evaluate how change in cardiovascular health score relates to subsequent risk of cancer.

Limitations

Our study has several limitations. The observational design precludes causal conclusions. Repeated evaluations of cardiovascular health were not available in all 3 cohorts, precluding an assessment of whether change in cardiovascular health over time is associated with cancer risk. Recent evidence suggests that change in cardiovascular health over time correlates with incident cardiovascular disease events, and this may apply to cancer as well.[22,23] Nearly one-third of the GAZEL participants were excluded. This may have affected the statistical power of the analyses, especially the site-specific analyses. Still, selection bias seemed unlikely given the characteristics of those excluded and not excluded together with the rates of cancer between these 2 groups. Sex distribution and length of follow-up differed between the 3 studies, and whether these differences explained part of the heterogeneity observed in some secondary analyses was not examined. Incomplete definitions were used for the diet metric (Whitehall II and GAZEL) and the physical activity metric (GAZEL), which may attenuate the associations between cardiovascular health and incident cancer. Whitehall II and GAZEL are based on government employees, which raises the issue of the healthy worker effect. This may affect the prevalence of cardiovascular health in these studies but not the association of cardiovascular health with study outcomes. Confounding by economic position, earnings or overall wealth was not addressed. The studies were mainly composed of White and middle-aged participants; therefore, the findings may not apply to other age groups or more ethnically diverse populations. Similar weight was allocated to each metric, whereas effects on the risk of cancer may be different for each metric. Lastly, in GAZEL, the biological cardiovascular health metrics were determined by self-reported data. Nevertheless, results were consistent with the results from NutriNet-Santé and Whitehall II, in which objectively measured data were available.

Conclusion

Better cardiovascular health in midlife was associated with lower risk of cancer, notably lung cancer, in addition to a lower risk of cardiovascular disease. This double effect may be useful for physicians and policy-makers in health promotion aimed at patients and the general population.

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