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MINI-FOCUS ISSUE: EPIDEMIOLOGIC AND BIOLOGIC LINKS BETWEEN CANCER AND CV DISEASE

ORIGINAL RESEARCH

Association of Cardiometabolic Disease With Cancer in the Community

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ABSTRACT

BACKGROUND Obesity and cardiometabolic dysfunction have been associated with cancer risk and severity. Underlying mechanisms remain unclear.

OBJECTIVES The aim of this study was to examine associations of obesity and related cardiometabolic traits with incident cancer.

METHODS FHS (Framingham Heart Study) and PREVEND (Prevention of Renal and Vascular End-Stage Disease) study participants without prevalent cancer were studied, examining associations of obesity, body mass index (BMI), waist circumference, visceral adipose tissue (VAT) and subcutaneous adipose tissue depots, and C-reactive protein (CRP) with future cancer in Cox models.

RESULTS Among 20,667 participants (mean age 50 years, 53% women), 2,619 cancer events were observed over a median follow-up duration of 15 years. Obesity was associated with increased risk for future gastrointestinal (HR: 1.30; 95% CI: 1.05-1.60), gynecologic (HR: 1.62; 95% CI: 1.08-2.45), and breast (HR: 1.32; 95% CI: 1.05-1.66) cancer and lower risk for lung cancer (HR: 0.62; 95% CI: 0.44-0.87). Similarly, waist circumference was associated with increased risk for overall, gastrointestinal, and gynecologic but not lung cancer. VAT but not subcutaneous adipose tissue was associated with risk for overall cancer (HR: 1.22; 95% CI: 1.05-1.43), lung cancer (HR: 1.92; 95% CI: 1.01-3.66), and melanoma (HR: 1.56; 95% CI: 1.02-2.38) independent of BMI. Last, higher CRP levels were associated with higher risk for overall, colorectal, and lung cancer ($P < 0.05$ for all).

CONCLUSIONS Obesity and abdominal adiposity are associated with future risk for specific cancers (eg, gastrointestinal, gynecologic). Although obesity was associated with lower risk for lung cancer, greater VAT and CRP were associated with higher lung cancer risk after adjusting for BMI. (J Am Coll Cardiol CardioOnc 2022;4:69–81)
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**ABBREVIATIONS
AND ACRONYMS**

BMI = body mass index

CRP = C-reactive protein

CT = computed tomographic

CVD = cardiovascular disease

HOMA-IR = homeostatic model
assessment of insulin
resistance

PAI = plasminogen activator
inhibitor

SAT = subcutaneous adipose
tissue

VAT = visceral adipose tissue

WC = waist circumference

Cardiometabolic risk factors, in particular obesity, are known risk factors for many highly burdensome diseases, including diabetes, cardiovascular disease (CVD), cancer, and death.[1,2] Obesity is increasing globally, with more than 40% of adults and 20% of children in the United States currently categorized as obese (body mass index [BMI] ≥30 kg/m^2) and 6.9% of incident cancers attributed to excess body weight.[3-5] Increased adiposity creates a chronic proinflammatory state, which may be a shared mechanism underlying the development of many comorbidities, including cancer.[6-8] Additionally, obesity may alter the tumor microenvironment and promote tumor progression via complex immunologic mechanisms.[9] Other putative mechanisms for obesity and cancer risk include adipose production of excess estrogen, hyperinsulinemia or insulin resistance, increased production of adipokines, and direct or indirect effects on cell growth regulators.[6,10] Epidemiologic studies have long shown an association between obesity and incident cancer, and there is consensus among the National Cancer Institute and World Health Organization that 13 cancer types are associated with excess body weight, including breast, female reproductive, and colon cancers.[11-14]

Retrospective electronic health record–based and registry-based studies, however, may introduce selection and ascertainment bias. Furthermore, there is broad agreement that although BMI is a widely available measurement used to categorize obesity, it may not accurately reflect adiposity across age, sex, race, and muscle composition.[15] For example, abdominal adiposity measured by waist circumference (WC) has been more closely associated with CVD risk factors[16] and may impart additional valuable information compared with BMI alone in understanding the association between obesity and cancer.[17] In this context, we sought to leverage 2 large prospective longitudinal community-based inception cohorts to examine the association of obesity with future development of histologically confirmed cancer. Moreover, we sought to examine detailed phenotyping of obesity-related traits, including anthropometrics, advanced imaging to quantify adipose tissue depots including visceral adiposity as a known source of inflammatory mediators, and circulating biomarker evidence of putative mechanisms linking obesity to cancer risk.

METHODS

STUDY SAMPLE. We studied participants in the FHS (Framingham Heart Study) and the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study, 2 prospective community-based cohorts.[18-21] We included FHS participants who attended Original Cohort examination 16 (1979-1982) or 24 (1995-1998), Offspring Cohort examination 2 (1979-1983) or 6 (1995-1998), and Third Generation Cohort examination 1 (2002-2005) and PREVEND participants who attended the first examination (1997-1998). We excluded individuals with prevalent cancer (except for nonmelanoma skin cancer; n = 934), prevalent heart failure (n = 185), prevalent myocardial infarction (n = 800), end-stage renal disease (n = 52), missing covariates (n = 625), and missing follow-up data (n = 1), leaving a final sample of 20,667 partici-

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pants (see Supplemental Figure 1 for details). The study was approved by the appropriate Institutional Review Boards, and all participants provided written informed consent.

STUDY PROCEDURES. At baseline examination, study participants underwent medical history review, physical examination, anthropometry, and collection of fasting blood as described previously.[18-21] BMI was calculated as weight (kilograms) divided by height (meters) squared. Obesity is defined as BMI ≥30 kg/m². Current smoking was defined as smoking 1 or more cigarettes per day over the past year. Fasting circulating inflammatory biomarkers, glucose, and insulin were ascertained among FHS participants at Offspring Cohort examination 6 and PREVEND (N = 10,995) (details are provided in the Supplemental Appendix).

A subset of FHS participants attending Offspring Cohort examination 7 (1998-2001) and Third Generation Cohort examination 1 (N = 3,077) underwent multidetector computed tomographic (CT) assessment of various adipose depots as previously described (LightSpeed Ultra, GE Medical Systems; details are provided in the Supplemental Appendix).[22,23] Intrareader and interreader reproducibility were excellent (intrareader intraclass correlation coefficients: visceral adipose tissue [VAT], 0.99; subcutaneous adipose tissue [SAT], 0.99; intrathoracic fat, 0.99; and pericardial fat, 0.97; interreader intraclass correlation coefficients: VAT, 0.992; SAT, 0.997; intrathoracic fat, 0.98; and pericardial fat, 0.95).[23,24]

ASCERTAINMENT OF CANCER OUTCOMES. Participants were followed prospectively for the occurrence of incident cancer. In FHS, cancer cases were identified through surveillance of routine examinations, health updates, hospital admissions, or death records through December 31, 2016. We reviewed medical records and pathology reports, and cancer cases were adjudicated and coded on the basis of topology and morphology and graded by 2 independent physicians using International Classification of Diseases codes.[25] In PREVEND, cancer cases were identified through linkage with the Dutch nationwide network and registry of histopathology and cytopathology in the Netherlands, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief Foundation (https://www.palga.nl/).[26] All malignancies except nonmelanoma skin cancers were included for analysis. Site-specific cancers included gastrointestinal, colorectal (a subset of gastrointestinal cancers), lung cancer, melanoma, hematologic, bladder, prostate, breast, and gynecologic cancers (additional details are provided in the Supplemental Appendix).

STATISTICAL ANALYSIS. Baseline characteristics are reported as mean ± SD, median (IQR), or percentages as appropriate. The primary outcome was incident cancer, and secondary analyses examined time to incident site-specific cancers. Gynecologic and breast cancer analyses were restricted to women, and prostate cancer analyses were restricted to men. We plotted cumulative cancer incidence by BMI and sex-specific WC quartiles using the Fine and Gray method. To highlight parallel associations with incident CVD (defined as myocardial infarction, stroke, or heart failure), we similarly plotted cumulative CVD incidence across BMI and WC quartiles. Using multivariable cause-specific Cox models to examine potential etiology of disease, we examined associations of BMI and WC with incident cancer, and effect estimates were presented per 1-SD difference. Cox models were adjusted for age, sex, diabetes mellitus, systolic blood pressure, hypertension treatment, smoking status (current, former, or never), and ratio of total cholesterol to high-density lipoprotein. These covariates were chosen a priori on the basis of prior associations with cancer or cancer subtypes.[2] There was no evidence of multicollinearity in our models, and restricted cubic splines revealed no evidence of a nonlinear association of BMI and cancer. Additional sensitivity analyses was performed using the Fine and Gray method to derive the subdistribution hazards.

In secondary analyses, we examined the association of adipose depots, C-reactive protein (CRP), plasminogen activator inhibitor (PAI)-1, and homeostatic model assessment of insulin resistance (HOMA-IR) with cancer incidence in multivariable Cox models with and without the addition of BMI. Biomarkers were natural log transformed because of right-skewed distributions and effect sizes expressed per 1-SD change in log unit. Exploratory analyses including sex interactions, stratified analyses by smoking status, and lag time analyses are detailed in the Supplemental Appendix.

Follow-up was censored at the time of first cancer event, death, or 15 years of follow-up. For site-specific cancer analyses, participants who developed 1 subtype of cancer distinct from the outcome of interest were still considered at risk for subsequent development of the cancer subtype of interest. Analyses accounted for cohort as a strata variable. A 2-sided *P* value <0.05 was considered to indicate statistical significance. Cox models met proportional

TABLE 1 Baseline Characteristics by Obesity Status			
	Overall (n = 20,667)	Obese[a] (n = 3,924 [19%])	Nonobese (n = 16,743 [81%])
Age, y	50 ± 14	53 ± 13	50 ± 14
Women	11,024 (53)	2,023 (52)	9,001 (54)
Body mass index, kg/m²	26.5 ± 4.8	33.9 ± 4.0	24.7 ± 2.9
Systolic BP, mm Hg	126 ± 19	133 ± 19	125 ± 19
Diastolic BP, mm Hg	75 ± 10	79 ± 10	75 ± 10
Total cholesterol, mg/dL	209 ± 42	214 ± 41	208 ± 43
HDL cholesterol, mg/dL	52 ± 16	45 ± 13	53 ± 16
Triglycerides, mg/dL	104 (74-153)	137 (98-197)	97 (70-142)
Diabetes	894 (4)	407 (10)	487 (3)
Hypertension	6,572 (32)	1,969 (50)	4,603 (27)
Current smoking	5,876 (28)	951 (24)	4,925 (29)
Former smoking	6,918 (33)	1,435 (37)	5,483 (33)

Values are mean ± SD, n (%), or median (IQR). [a]Obesity is defined as body mass index ≥ 30 kg/m².

BP = blood pressure; HDL = high-density lipoprotein.

hazards assumption. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

We studied 20,667 participants from the FHS and PREVEND cohorts (mean age 50.3 ± 14.2 years, 53% women) who were free from cancer at baseline examination. Prevalent comorbidities included 4% with diabetes, 32% with hypertension, 19% with obesity (BMI ≥30 kg/m²), and 28% with current and 33% with former smoking. Clinical characteristics are displayed by obesity status in **Table 1**, with greater comorbid burden among obese compared with nonobese individuals. For stratification by cohort, CT imaging, and biomarker availability, see Supplemental Tables 1 to 3.

ASSOCIATION OF BMI AND WC WITH INCIDENT CANCER. We observed 2,619 incident cancers over a median follow-up period of 15 years (IQR: 13-15 years), including 165 melanomas, 534 gastrointestinal (338 of which were colorectal), 295 lung, 194 hematologic, 176 bladder, 408 prostate, 455 breast, and 128 gynecologic cancers. Over that same time period, there were 1,966 CVD events. In cumulative incidence plots, we observed increasing risk for future cancer across higher BMI quartiles and similar trends across higher WC quartiles over 15 years of follow-up. In parallel, we observed increasing cumulative incidence of CVD across higher BMI and WC quartiles (**Central Illustration**) (*P* < 0.001 for both, Gray's test). The incidence rate of overall cancer was 9.5 per 1,000 person-years, and that of CVD was 7.1 per 1,000 person-years.

In multivariable Cox models, BMI as a continuous variable and obesity status were both associated with gastrointestinal, gynecologic, and lung cancers but not overall cancer (**Tables 2 and 3, Figure 1**). Specifically, a 1-SD higher BMI was associated with 14% increased risk for gastrointestinal and colorectal cancers (HR: 1.14 [95% CI: 1.03-1.25; *P* = 0.008] for gastrointestinal cancer; HR: 1.14 [95% CI: 1.01-1.28; *P* = 0.040] for colorectal cancer) and 34% increased risk for gynecologic cancer (HR: 1.34; 95% CI: 1.16-1.55; *P* < 0.001). In contrast, a 1-SD higher BMI was associated with 23% lower risk for lung cancer (HR: 0.77; 95% CI: 0.67-0.89; *P* < 0.001), an association that appeared linear across the BMI range when examining a restricted cubic spline. Obesity status, defined as BMI ≥30 kg/m², was associated with increased risk for incident gastrointestinal (HR: 1.30; 95% CI: 1.05-1.60), gynecologic (HR: 1.62; 95% CI: 1.08-2.45), and breast (HR: 1.32; 95% CI: 1.05-1.66) cancer, and lower risk for lung cancer (HR: 0.62; 95% CI: 0.44-0.87) (**Table 3**).

We found that higher WC was associated with increased risk for future overall cancer (HR: 1.07; 95% CI: 1.01-1.13; *P* = 0.020) (**Table 2, Figure 1**). With respect to site-specific cancer, a 1-SD higher WC was associated with an increased risk for future gastrointestinal cancer, including colorectal cancer (HR: 1.22; 95% CI: 1.07-1.40; *P* = 0.003), and 32% increased risk for gynecologic cancer (HR: 1.32; 95% CI: 1.07-1.63; *P* = 0.010). In contrast, WC was not associated with incident lung cancer. Sensitivity analyses using the Fine and Gray method to determine the subdistribution HRs yielded similar associations between cancer type and BMI and WC.

ASSOCIATION OF CT MEASURES OF ADIPOSITY WITH INCIDENT CANCER. In secondary analyses, we examined the association of various adipose depots with future incident cancer (**Table 4**). In multivariable analyses adjusting for BMI in addition to covariates in main analyses, we observed that VAT was associated with overall cancer (HR: 1.22; 95% CI: 1.05-1.43; *P* = 0.011) as well as certain site-specific cancers. Specifically, 1-SD higher VAT was associated with an almost 2-fold increased risk for lung cancer (HR: 1.92; 95% CI: 1.01-3.65; *P* = 0.045) and 56% increased risk for melanoma (HR: 1.56; 95% CI: 1.02-2.37; *P* = 0.038). We found no significant associations with other site-specific cancers.

We found similar associations of pericardial adipose tissue with overall cancer (HR: 1.14; 95% CI: 1.02-1.27; *P* = 0.018), melanoma (HR: 1.40; 95% CI: 1.07-1.82; *P* = 0.013), and lung cancer (HR: 1.51; 95%

CI: 1.01-2.26; $P = 0.044$). In contrast, we found no associations of subcutaneous or intrathoracic adipose depots or indexes of liver adiposity with overall cancer or site-specific cancers.

ASSOCIATION OF INFLAMMATORY BIOMARKERS AND HOMA-IR WITH INCIDENT CANCER. In multivariable analyses without accounting for BMI, we observed that circulating CRP level was associated with increased risk for overall cancer and gastrointestinal, colorectal, lung, and gynecologic cancers (Supplemental Table 4). Specifically, a 1-SD increase in CRP was associated with a 13% increase in risk for overall cancer (HR: 1.13; 95% CI: 1.07-1.19; $P < 0.001$). The association of CRP with overall cancer, colorectal cancer, and lung cancer remained significant after further adjusting for BMI, whereas the associations with gynecologic and gastrointestinal cancers were attenuated.

For PAI-1 and HOMA-IR, models with and without BMI showed inconsistent associations with specific cancer outcomes (Supplemental Table 4).

SENSITIVITY AND EXPLORATORY ANALYSES. To minimize the potential contribution of undiagnosed cancer cases at baseline, we excluded 129 cancer cases that were diagnosed within 1 year of baseline examination in sensitivity analyses. The results for association of BMI and WC were similar to those of our main analyses (Supplemental Table 5). In exploratory analyses with further adjustment for heavy alcohol use in the multivariable model, results were similar to those of the main analyses (Supplemental Table 6).

In sex-stratified analyses, there was no significant sex × BMI interaction for overall or site-specific cancer. There was, however, a significant sex × WC interaction ($P_{interaction} = 0.03$) for overall cancer (HR: 1.11 [95% CI: 1.02-1.21; $P = 0.021$] for men; HR: 1.06 [95% CI: 0.98-1.15; $P = 0.12$] for women) but not site-specific cancers.

To examine the finding of an association of higher BMI with lower lung cancer risk, we stratified analyses by smoking status (current, 166 events per 5,876 participants; former, 107 events per 6,918 participants; never, 22 events per 7,873 participants). We found no significant associations between BMI and lung cancer among never and former smoking groups, though directionality of effect was similar to overall analyses (never smoking: HR: 0.81 [95% CI: 0.49-1.36; $P = 0.44$]; former smoking: HR: 0.84 [95% CI: 0.66-1.08; $P = 0.17$]). Higher BMI was associated with lower risk for lung cancer among individuals with current smoking (HR: 0.74; 95% CI: 0.61-0.90; $P = 0.003$).
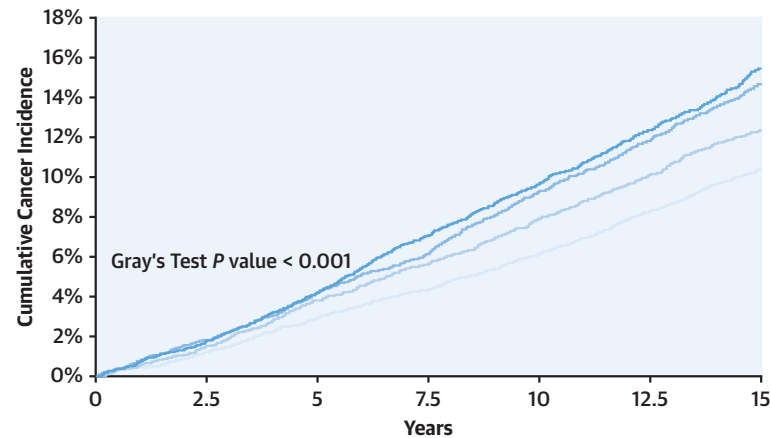
Last, to address potential surveillance bias, we examined survival after cancer diagnosis stratified by obese and nonobese individuals. In both Kaplan-Meier survival curves (P for log rank = 0.11) as well as time-to-event analyses (Cox model adjusted for age; HR: 1.02 [95% CI: 0.83-1.25; $P = 0.87$] comparing obese vs nonobese individuals), we found no differences in postcancer diagnosis survival on the basis of obesity status.
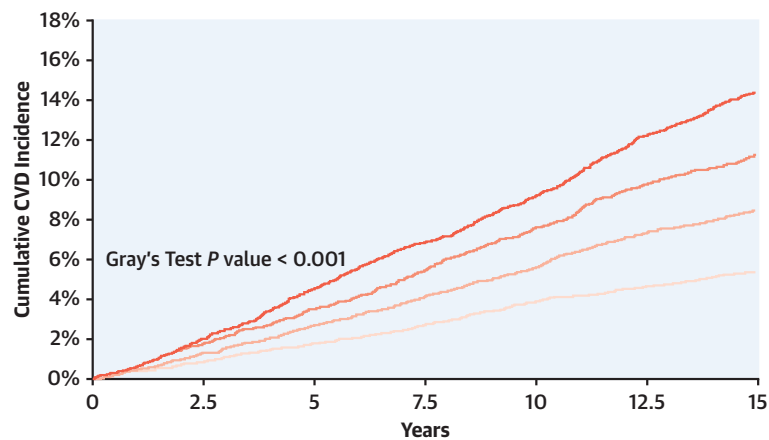
DISCUSSION

We leveraged 2 large longitudinal community-based inception cohorts with histologically confirmed incident cancer cases to examine associations of obesity and related traits with risk for future cancer. First, we found that obesity, defined as BMI ≥30 kg/m², was associated with future risk for specific cancer subtypes, including approximately 30% greater risk for gastrointestinal and breast cancers and approximately 60% increased risk for gynecologic cancers. Conversely, obesity was associated with approximately 38% lower risk for lung cancer. Second, abdominal adiposity (WC) was associated with gastrointestinal, breast, and overall cancer but not lung cancer. The importance of abdominal adiposity independent of BMI was substantiated in secondary analyses demonstrating that greater VAT but not SAT was associated with overall and lung cancer, as well as melanoma. Last, on interrogation of potential obesity-associated pathways using biomarkers, we found that baseline inflammation (CRP) was associated with greater risk for overall cancer, colorectal, and lung cancer, whereas no such association was observed for insulin resistance (HOMA-IR). Our findings suggest that abdominal adiposity and systemic inflammation are associated with specific cancer subtypes and underscore the need for future studies to elucidate underlying mechanisms contributing to cancer risk among obese individuals. Last, although obesity-related traits portend both increased risk for cancer and CVD in parallel, incidence rates of cancer are higher compared with those of CVD.

In prospective observational studies, BMI has been associated with incident cancers including gastrointestinal, colorectal, lung, gynecologic, and melanoma across broad populations.[10,27-29] Furthermore, limiting weight gain in murine models,[14] weight loss in patients with breast cancer,[30] and weight loss after

CENTRAL ILLUSTRATION Cumulative Incidence of Cancer and Cardiovascular Disease by Body Mass Index and Waist Circumference Quartiles


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The cumulative incidence of all-cause cancer over 15 years of follow-up is displayed by body mass index (BMI) quartiles **(A)** and by sex-specific waist circumference (WC) quartiles **(C)**. The cumulative incidence of cardiovascular disease over 15 years of follow-up is displayed by BMI quartiles **(B)** and by WC quartiles **(D)**. BMI quartile cutpoints were as follows: 25th percentile, 23.2 kg/m^2; 50th percentile, 25.8 kg/m^2; and 75th percentile, 28.9 kg/m^2. WC quartile cutpoints for women were as follows: 25th percentile, 76 cm; 50th percentile, 84.2 cm; and 75th percentile, 94.9 cm. WC quartile cutpoints for men were as follows: 25th percentile, 88.3 cm; 50th percentile, 95.3 cm; and 75th percentile, 103.5 cm. BMI = Body Mass Index; CVD = Cardiovascular Disease; Q1 = Quartile 1; Q2 = Quartile 2; Q3 = Quartile 3; Q4 = Quartile 4; WC = Waist Circumference.
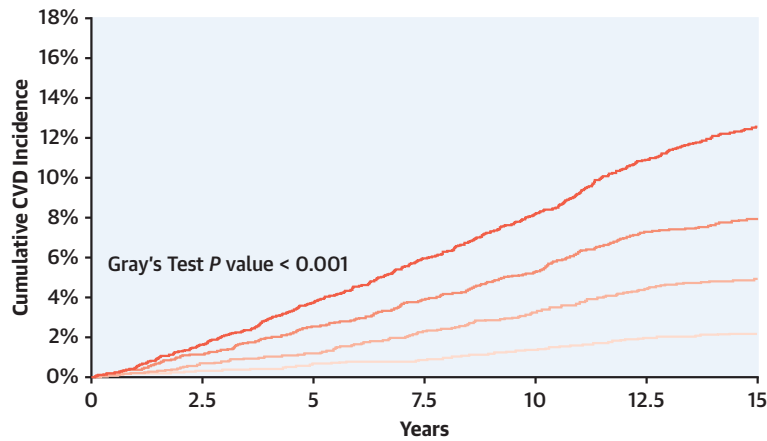
CENTRAL ILLUSTRATION Continued

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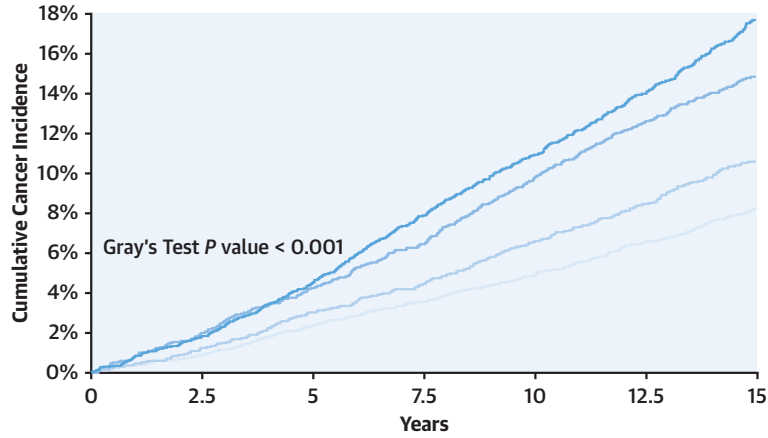
No. at risk for cancer:

WC Q1	3,688	3,594	3,469	2,519
WC Q2	3,594	3,474	3,308	2,274
WC Q3	3,669	3,494	3,232	2,164
WC Q4	3,672	3,475	3,144	1,875

— WC Quartile 1 — WC Quartile 2 — WC Quartile 3 — WC Quartile 4

D

No. at risk for CVD:

WC Q1	3,688	3,652	3,586	2,671
WC Q2	3,589	3,529	3,407	2,407
WC Q3	3,655	3,531	3,366	2,346
WC Q4	3,646	3,478	3,199	1,976

— WC Quartile 1 — WC Quartile 2 — WC Quartile 3 — WC Quartile 4

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TABLE 2   BMI and WC Multivariable Associations With Cancer Incidence

	BMI (No. at Risk = 20,667)			WC (No. at Risk = 14,623)		
	Events	HR (95% CI)	P Value	Events	HR (95% CI)	P Value
Overall cancer	2,619	1.03 (0.98-1.07)	0.25	1,789	1.07 (1.01-1.13)	0.020
GI cancer	534	1.14 (1.03-1.25)	0.008	328	1.22 (1.07-1.40)	0.003
Colorectal cancer	338	1.14 (1.01-1.28)	0.040	206	1.21 (1.02-1.43)	0.027
Lung cancer	295	0.77 (0.67-0.89)	<0.001	182	0.85 (0.70-1.02)	0.084
Melanoma	165	1.05 (0.89-1.24)	0.53	132	1.04 (0.85-1.29)	0.68
Hematologic cancer	194	0.97 (0.83-1.14)	0.75	142	0.92 (0.74-1.13)	0.41
Bladder cancer	176	0.98 (0.82-1.18)	0.84	129	1.07 (0.84-1.33)	0.65
Prostate cancer	408	1.02 (0.89-1.16)	0.80	283	1.13 (0.96-1.32)	0.15
Breast cancer	455	1.04 (0.95-1.14)	0.39	320	1.08 (0.95-1.22)	0.23
Gynecologic cancer	128	1.34 (1.16-1.55)	<0.001	93	1.32 (1.07-1.63)	0.010

BMI and WC are standardized. Multivariable model is adjusted for age, sex, diabetes mellitus, systolic blood pressure, hypertension treatment, smoking status, and cholesterol ratio. Effect sizes for BMI and WC were expressed per 1-SD change. *P* values <0.05 were considered to indicate statistical significance. SDs for BMI and WC are 4.8 kg/m^2 and 14.3 cm, respectively.

BMI = body mass index; GI = gastrointestinal; WC = waist circumference.

bariatric surgery in morbidly obese patients[31] were associated with decreased tumor progression, recurrence, and cancer risk. Additionally, prior work from the FHS showed that abdominal adiposity as measured by WC was associated with obesity-related cancer including colorectal, breast, and female reproductive cancers.[32,33] We now extend this prior work with additional follow-up across a larger sample. Although BMI was not associated with overall cancer, we observed higher risk for future gastrointestinal, colorectal, and gynecologic cancers and lower risk for future lung cancer, highlighting the importance of examining site-specific cancers. Our findings mirror those of a Swedish hospital registry-based prospective study that demonstrated significantly increased burden of overall cancer and site-specific cancer, including gastrointestinal and gynecologic, in obese compared with nonobese individuals[13] and extend implications of obesity on cancer risk to a large community-based sample. Furthermore, we observed that greater abdominal adiposity (WC) was associated with increased risk for overall cancer, gastrointestinal, colorectal, and gynecologic cancers, which supports prior prospective epidemiologic studies.[34,35]

Notably, we found that greater BMI was associated with decreased risk for future lung cancer after adjustment for confounders including smoking status. This "obesity paradox" contrasts with other cancers in which greater BMI has been associated higher risk. This discrepancy has been demonstrated in numerous studies that suggest that higher BMI is associated with decreased risk for incident lung cancer and improved survival in patients with lung cancer.[36,37] We explored this inverse association by stratifying lung cancer analyses by smoking status, as smoking is a known risk factor for lung cancer and is associated with lower average BMI.[38] Our findings support a previous prospective cohort study of about 450,000 individuals,[39] demonstrating reduced risk among current smoking but no association among former and never smoking. Although this might suggest that the "obesity paradox" may be explained by smoking, analyses of never smoking were likely underpowered, with other studies supporting an association across all smoking statuses including never smoking.[28] We performed lag-time analyses starting 1 year after baseline examination to account for potentially undiagnosed cancers and found similar results. In contrast to the inverse association of BMI with lung cancer, both visceral and pericardial adipose tissue depots were associated with greater risk for lung cancer, as was inflammation assessed by CRP. This extends prior findings that abdominal adiposity appears to be associated with higher risk for lung cancer.[36] Our findings highlight the importance of examining obesity-related phenotypes to better appreciate adiposity-associated cancer risk.

To provide insight into potential mechanisms linking obesity to increased predisposition to specific cancers, we further investigated the association of regional adipose depots with future cancer after accounting for BMI. We show that both visceral and pericardial adipose depots were associated with greater risk for overall cancer, lung cancer, and melanoma. In contrast, subcutaneous adipose depots

TABLE 3 Obesity Multivariable Associations With Cancer Incidence

	Events	HR (95% CI)	P Value
Overall cancer	2,619	1.04 (0.95-1.15)	0.41
Gastrointestinal cancer	534	1.30 (1.05-1.60)	0.014
Colorectal cancer	338	1.31 (1.01-1.71)	0.043
Lung cancer	295	0.62 (0.44-0.87)	0.006
Melanoma	165	1.01 (0.68-1.50)	0.97
Hematologic cancer	194	0.87 (0.61-1.24)	0.44
Bladder cancer	176	0.99 (0.68-1.45)	0.96
Prostate cancer	408	0.87 (0.68-1.13)	0.30
Breast cancer	455	1.32 (1.05-1.66)	0.017
Gynecologic cancer	128	1.62 (1.08-2.45)	0.021

Obesity status is dichotomous, and HRs are presented for obesity (defined as body mass index ≥30 kg/m²). Multivariable model is adjusted for age, sex, diabetes mellitus, systolic blood pressure, hypertension treatment, smoking status, and cholesterol ratio. Values of P <0.05 were considered to indicate statistical significance.

were not associated with greater risk for future cancer. These findings are notable, as prior studies of VAT and cancer present conflicting findings.[40-43] The present study expands upon previous findings by assessing site-specific cancers in addition to overall cancer. In contrast to the "obesity paradox," we show importantly and conversely that higher VAT was associated with increased risk for lung cancer, suggesting that BMI and obesity may not fully capture adiposity-associated risk. We also report that VAT was associated with melanoma, which builds upon previous studies showing an association of obesity with risk for melanoma and its progression.[29,44] Previous retrospective studies have reported inverse associations of SAT with cancer mortality and progression of some cancer subtypes.[45,46] Although we did not observe an association between SAT and

FIGURE 1 Multivariable-Adjusted Associations of Obesity, BMI, and WC With Incident Cancer
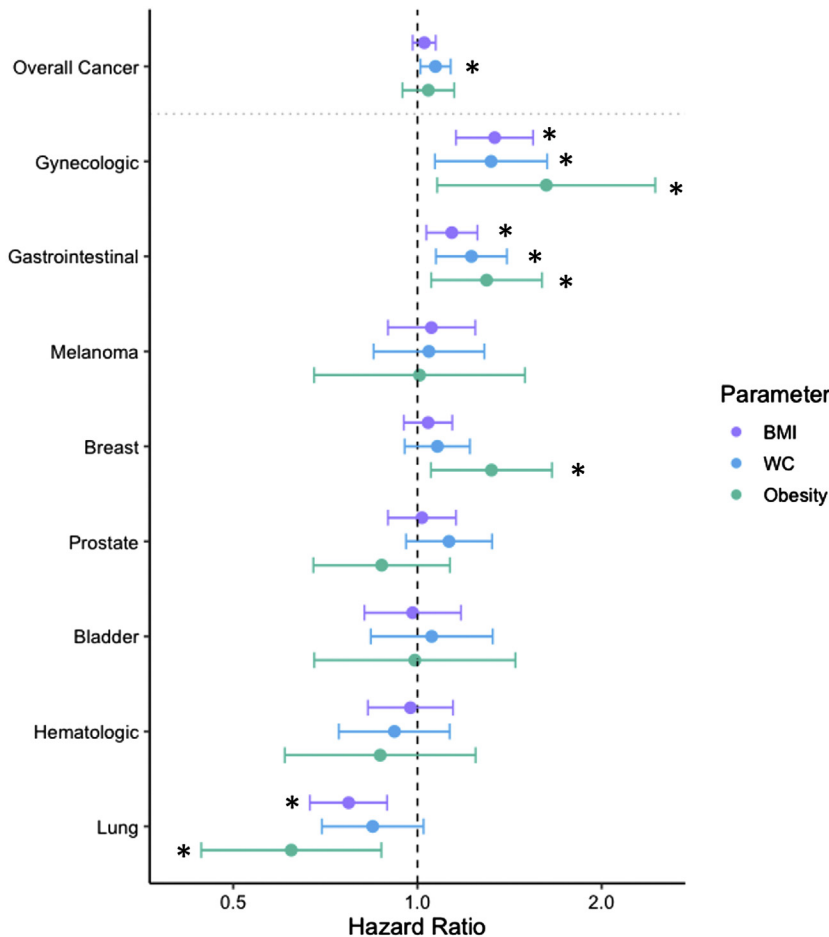
The multivariable Cox model was adjusted for age, sex, diabetes, systolic blood pressure, hypertension treatment, smoking status (current, former, or never), and ratio of total cholesterol to high-density lipoprotein. Gynecologic and breast cancer analyses were performed only in women, and prostate cancer analyses were performed only in men. Effect sizes for body mass index (BMI) and waist circumference (WC) were expressed per 1-SD change. *P < 0.05.

TABLE 4 Computed Tomographic Adipose Depot Multivariable Model Associations With Cancer Incidence

	Visceral Adipose Tissue		Pericardial Adipose Tissue		Intrathoracic Adipose Tissue		Subcutaneous Adipose Tissue		Liver Phantom Ratio	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Overall cancer (n/N = 394/3,077)	1.22 (1.05-1.43)	0.011	1.14 (1.02-1.27)	0.018	1.11 (0.97-1.27)	0.12	0.95 (0.79-1.14)	0.56	1.02 (0.92-1.14)	0.70
Gastrointestinal cancer (n/N = 49/3,077)	1.11 (0.73-1.68)	0.62	1.08 (0.79-1.47)	0.62	1.33 (0.97-1.83)	0.078	1.47 (0.88-2.43)	0.14	1.07 (0.78-1.46)	0.67
Colorectal cancer (n/N = 28/3,077)	1.55 (0.90-2.67)	0.11	1.03 (0.67-1.57)	0.91	1.32 (0.85-2.05)	0.21	1.70 (0.89-3.24)	0.11	0.97 (0.66-1.43)	0.90
Lung cancer (n/N = 21/3,077)	1.92 (1.01-3.65)	0.045	1.51 (1.01-2.26)	0.044	1.51 (0.87-2.62)	0.15	1.53 (0.67-3.51)	0.31	0.85 (0.58-1.26)	0.43
Melanoma (n/N = 54/3,077)	1.56 (1.02-2.37)	0.038	1.40 (1.07-1.82)	0.013	1.38 (1.00-1.91)	0.047	1.09 (0.65-1.83)	0.75	0.92 (0.68-1.23)	0.56
Hematologic cancer (n/N = 43/3,077)	0.96 (0.60-1.54)	0.88	0.76 (0.51-1.12)	0.17	0.70 (0.44-1.11)	0.13	0.91 (0.50-1.64)	0.74	1.31 (0.89-1.93)	0.18
Bladder cancer (n/N = 30/3,077)	1.16 (0.71-1.91)	0.55	1.18 (0.84-1.67)	0.34	0.84 (0.52-1.34)	0.46	1.07 (0.50-2.28)	0.86	1.05 (0.71-1.54)	0.80
Prostate cancer (n/N = 81/1,595)	1.29 (0.95-1.76)	0.10	1.11 (0.89-1.39)	0.34	1.07 (0.82-1.40)	0.63	1.05 (0.67-1.63)	0.84	0.93 (0.75-1.17)	0.54
Breast cancer (n/N = 84/1,482)	1.29 (0.86-1.93)	0.22	1.22 (0.93-1.61)	0.15	1.03 (0.68-1.57)	0.88	0.94 (0.64-1.38)	0.77	0.92 (0.72-1.19)	0.53
Gynecologic cancer (n/N = 21/1,482)	1.03 (0.48-2.21)	0.94	0.61 (0.31-1.23)	0.17	1.46 (0.70-3.02)	0.31	0.39 (0.19-0.79)	0.009	1.15 (0.68-1.94)	0.60

Adiposity measures are standardized. Decreasing liver phantom ratio corresponds to a greater amount of liver fat. Multivariable model includes variables from main analyses (age, sex, diabetes mellitus, systolic blood pressure, hypertension treatment, smoking status, and cholesterol ratio) and body mass index. Displayed events (n/N) are those of visceral adipose tissue analyses. Event numerator and denominator vary slightly for other adipose depots analyses. Effect sizes were expressed per 1-SD change. Values of $P < 0.05$ were considered to indicate statistical significance. SDs for adiposity measures are 1,011.4 cm^3 (visceral), 1,390.9 cm^3 (subcutaneous), 42.9 cm^3 (pericardial), 61.6 cm^3 (intrathoracic), and 9.7 (liver phantom ratio).

overall cancer, we found that higher SAT was associated with protection against gynecologic cancer. To our knowledge, SAT has not previously been associated with cancer risk in a prospective inception cohort, though some studies have shown that increased SAT may portend better outcomes in patients with cancer.[45,47]

The biological mechanisms underlying greater cancer risk in obesity remain incompletely understood, but research has been focused on inflammation and immune cell dysfunction.[7,48,49] It is known that VAT specifically appears to contribute to proinflammatory states,[50,51] and our findings of associations of both WC and VAT with cancer risk support this hypothesis. In line with this, we examined circulating markers of systemic inflammation (CRP and PAI-1) previously associated with cancer[52,53] and indeed found that CRP was significantly associated with overall cancer, colorectal, and lung cancer. These findings are in keeping with those of the recent CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), in which baseline CRP was significantly higher in patients later diagnosed with lung cancer than those who did not develop lung cancer.[54] Additionally, treatment with anti-interleukin-1β immunotherapy compared with placebo in CANTOS was associated with decreased lung cancer mortality and lung cancer incidence, further supporting the importance of inflammatory pathways as underlying mechanisms. In contrast, we did not find associations of PAI-1 with cancer risk.

STUDY LIMITATIONS. First, this was an observational study, and we could not draw causal inferences or eliminate residual confounding. For example,

surveillance bias may have led to greater cancer screening in obese vs nonobese individuals. This effect was likely limited given that survival after cancer diagnosis was not different between obese and nonobese individuals.

Second, our study may not be generalizable to the general population, as our sample was overwhelmingly White. Third, specific cancer subtype-stratified and sex-stratified analyses were exploratory, and results will need to be confirmed.

Finally, there were relatively small event numbers for specific cancer subtypes, which may have limited power to detect potentially modest but significant associations for secondary outcomes. For example, although some studies have shown differential sex patterns in obesity-associated cancers, including colorectal,[55,56] our study did not reveal significant sex × BMI interactions for future cancers, as it may have been underpowered to detect such associations.

Our study's strength, however, is the rigorous ascertainment of obesity and related adipose phenotypes across a harmonized dataset of 2 large inception cohorts with histologically confirmed cancer events, which offered the unprecedented opportunity to longitudinally examine the association of antecedent clinical factors with cancer risk in the community.

CONCLUSIONS

We report that obesity and abdominal adiposity (WC) were associated with increased future risk for cancer, including gastrointestinal, colorectal, and gynecologic cancers. Of note, although we found that obesity status and higher BMI were associated with lower risk

for lung cancer, we further shed light onto these associations by specifically demonstrating that greater visceral and pericardial adipose tissue depots and circulating CRP were associated with greater risk overall cancer and site-specific cancers, including lung and melanoma. These findings highlight the importance of examining obesity-related phenotypes, including adipose tissue depots, to better understand the association between obesity and cancers. Although the association of obesity-related traits with CVD has been firmly established,[57,58] our data now further support the notion that obesity is a shared risk factor between CVD and cancer.[59] A novel aspect of this study is the examination of incident CVD and cancer side by side within the same cohort, with greater risk for both outcomes with higher body weight. In this context, it is notable that incidence rates of cancer outnumber CVD events, highlighting the importance of understanding long-term consequences of cardiometabolic disease with respect to both outcomes. Although initial studies suggest benefits of weight loss with respect to cancer-related outcomes, we acknowledge the multifaceted effects of weight loss and how it is achieved, which may vary. Future studies are needed to better understand mechanisms underlying obesity, abdominal adiposity, and cancer.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Obesity and abdominal adiposity as measured by WC are associated with increased risk for several specific cancers, including gastrointestinal and gynecologic cancer. Although BMI is conversely associated with lower risk for lung cancer, visceral adiposity confers higher lung cancer risk, highlighting the importance of examining obesity-related phenotypes.

TRANSLATIONAL OUTLOOK: Future studies are needed to elucidate the mechanisms underlying the association of obesity and obesity-related phenotypes with cancer.

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APPENDIX For supplemental methods, tables, a figure, and references, please see the online version of this paper.