Metabolism Clinical and Experimental 94 (2019) 69–76

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Association between obesity and biomarkers of inflammation and metabolism with cancer mortality in a prospective cohort study

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ARTICLE INFO

Article history:
Received 9 October 2018
Accepted 16 January 2019

Keywords:
Inflammatory cytokines
Metabolic biomarkers
Cancer mortality
Obesity

ABSTRACT

Objective: To investigate the association between biomarkers of inflammation and metabolic dysregulation and cancer mortality by obesity status.
Methods: Data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort was used to examine the associations between baseline biomarkers of inflammation (IL-6, IL-8, IL-10, and CRP) and metabolism (adiponectin, resisting and lipoprotein (a)) with cancer mortality among 1822 participants cancer-free at baseline. Weighted Cox proportional hazard regression with the robust sandwich method was used to estimate the hazard ratios and 95% confidence intervals (CIs) adjusting for baseline covariates and stratified by BMI (normal, overweight/obese) given the significant interaction between biomarkers and BMI ($p < 0.1$).
Results: During a mean follow-up of 8 years, there were statistically significant associations between cancer mortality and being in the highest vs. lowest tertile of IL-6 (HR: 5.3; 95% CI: 1.6, 17.8), CRP (HR: 3.4; 95% CI: 1.0, 11.2) and resistin (HR: 3.7; 95% CI: 1.2, 11.2) among participants with normal BMI. IL-6 was also associated with a 3-fold (HR: 3.5; 95% CI: 1.5, 8.1) increased risk of cancer mortality among participants with overweight/obesity; however, neither CRP nor resistin was significantly associated with cancer mortality in this group.
Conclusions: Higher baseline inflammatory and metabolic biomarkers were associated with significantly increased risk of cancer mortality after adjusting for baseline risk factors and the associations varied by BMI. Cancer patients may benefit from interventions that modulate inflammatory and metabolic biomarkers.

1. Introduction

Established risk factors for cancer include obesity, physical inactivity, smoking, and alcohol use [1–4]. These risk factors are associated with chronic inflammation and metabolic dysregulation, and growing evidence links these mechanisms with development, progression and mortality of cancer [5–7]. Obesity, specifically, has long been associated with increased risk of cancer mortality [8], every 5 kg/m^2 increase in BMI has been shown to increase the risk of cancer mortality by about 10% [9]. Furthermore, obesity is associated with adipose tissue dysfunction and chronic low-grade inflammation that leads to worse prognosis in cancer patients. However, there is also evidence of adipose tissue inflammation and pro-tumorigenic consequences in some lean individuals [10]. Metabolism-related biomarkers [11–13] such as adiponectin, resistin, and lipoprotein (a) (Lp(a)), and inflammation-related cytokines [5,6] such as interleukin (IL)-6, IL-8, IL-10 and C-reactive protein (CRP) have also been shown to reflect a fertile, pro-tumorigenic inflammatory microenvironment that promotes tumor initiation, angiogenesis, and metastasis [14].

Recent studies, including by our group, suggests that metabolic health status may be more clinically and epidemiologically important for cancer risk and mortality than obesity alone [15,16]. Increased risk of cancer mortality has been observed in normal BMI individuals with

Abbreviations: BMI, body mass index; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; CRP, C-reactive protein; Lp(a), lipoprotein (a); REGARDS, Reasons for Geographic and Racial Disparities in Stroke; SSDI, Social Security Death Index; NDI, National Death Index; HR, hazard ratio; CI, confidence interval.

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https://doi.org/10.1016/j.metabol.2019.01.007
0026-0495/

metabolic dysregulation, an association not consistently observed among obese individuals who are metabolically healthy- a phenomenon termed 'metabolic healthy obesity' [15]. While the prevalence of obesity has increased significantly among US adults [17], it is important to better delineate the role of obesity, metabolic dysregulation and chronic inflammation in cancer risk. This helps to improve risk prediction and stratification, target appropriate clinical and interventions strategies based on precise biomarkers, and reduce reliance on the crude measure of BMI as a predictor of cancer mortality risk. The aim of the present study was to investigate the role of pre-diagnostic metabolic and inflammatory biomarkers in the risk of cancer mortality by obesity status, and to assess whether racial disparities exist in this association given the higher risk of cancer mortality, obesity, and associated conditions among Blacks.

2. Material and methods

2.1. Study participants

Data for this study was obtained from the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study. REGARDS is a prospective cohort study of Black and White participants recruited nationally in the United States between 2003 and 2007, with oversampling of Blacks and residents of the Stroke Belt (South Carolina, North Carolina, Tennessee, Georgia, Louisiana, Arkansas, Mississippi, and Alabama). Detailed data on demographics, health behaviors, and history of comorbid conditions were collected at baseline using a computer-assisted telephone interview. Blood sample collection after 10–12 hour of overnight fasting, echocardiography, and physical measurements including height and weight were conducted during initial in-home visits by trained staff following informed consent. Overall, 30,239 participants aged ≥45 years at baseline, 55% female, 42% Black, and 50% from the Stroke Belt region were recruited. The REGARDS study is ongoing and it is described in detail elsewhere [18,19]. In the present analysis, 1822 individuals who were cancer-free at baseline and selected into a sub-cohort with available inflammatory and metabolic biomarker data were included. The sub-cohort was selected as a stratified random sample defined by equal distribution by race (Black/White) and sex, age (20% from each 10-year interval from 45 to 64, 25% from each 10-year interval from 65 to 84, and 10% from those over 84 years old), and region (50% from Stroke Belt) using study weights created based on the inverse probability of being selected. REGARDS participants were followed-up every 6 months for deaths, hospitalizations ormedical events, and cause of death was ascertained using death certificates, medical records, and/or interviewed proxies. All participating institutional review boards approved the REGARDS study.

2.2. Exposure variables

Main exposure variables of interest in this study were inflammatory biomarkers – IL-6, IL-8, IL-10, and CRP, and metabolic biomarkers – adiponectin, resistin, and Lp(a). Biomarkers were analyzed from blood samples that were collected during the baseline in-home visit, centrifuged, separated and shipped overnight on gel ice packs to the central laboratory (Laboratory for Clinical Biochemistry Research at the University of Vermont). Ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems, Minneapolis, MN) was used to measure IL-6 (minimum detectable dose/sensitivity = 0.031 pg/ml and inter-assay coefficient of variation = 6.3%) and no significant cross-reactivity was observed. The Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc., St. Charles, MO) was used to measure IL-8 (sensitivity = 0.20 pg/ml, intra-assay coefficient of variation ranged from 1.4% to 7.9%, and inter-assay-coefficient of variation was <21%). Milliplex MAP Human Cardiovascular Disease Panel 3 (Millipore Corporation, Billerica, MA) run as a singleplex assay was used to measure IL-10 (sensitivity = 0.30 pg/ml, average analytical coefficient of variation = 8.09%). CRP was measured in batches utilizing a validated high-sensitivity particle-enhanced immunonephelometric assay on the BN II nephelometer (High Sensitivity CRP, Dade Behring Inc., Deerfield, IL), (sensitivity = 0.16 μg/ml, intra-assay-coefficient of variation ranged from 2.3% to 4.4%, and inter-assay coefficient of variation = 2.1% to 5.7%). Adiponectin and resistin were measured using the Human Serum Adipokine Panel A LINCOplex Kit (Linco Research, Inc., St. Charles, MO) (for adiponectin: sensitivity = 80.3 pg/ml, inter-assay coefficient of variation ranged from 5.68 to 8.20%, and for resistin: sensitivity = 4.5 pg/ml and inter-assay coefficient of variation ranged from 8.04% to 9.42%). Lp(a) was measured with the BN II nephelometer utilizing a particle-enhanced immunonephelometric assay (N Latex Lipoprotein-a, Siemens Healthcare Diagnostics, Deerfield, IL) (sensitivity = 0.002 g/Ll, inter-assay coefficient of variation ranged from 6.10% to 10.28%). For LP(a), no cross-reactivity with apolipoprotein B (<1%) and plasminogen (<5%) was observed.

2.3. Covariates

Study covariates included baseline demographic variables such as age (continuous), gender (male/female), education (college graduate, some college, high school graduate or less than high school), race (Black/White), and income (≥$75K, $35K–$74K, $20K–$34K, <$20K or refused). Additionally, analyses adjusted for baseline data on exercise (≥4 times/week, 1–3 times/week or none), BMI (kg/m^2), smoking (current, past, or never smoker), alcohol intake (heavy, moderate, or none), comorbidity score (number of comorbidities- score ranging from 0 to 7), regular aspirin use (yes/no), and statin use (yes/no).

2.4. Cancer mortality

Cancer mortality was identified through semi-annual telephone follow-up, death information from participants' proxies, linkages with the Social Security Death Index (SSDI) and the National Death Index (NDI). Date of death was confirmed using death certificates, SSDI and/or NDI. A committee of experts adjudicated the cause of death using all available information as recommended by national guidelines [20]. Follow-up data for this analysis was available through December 31, 2015.

2.5. Statistical analysis

Chi-squared tests were used to compare baseline categorical participants' characteristics by BMI category i.e. obese/overweight (BMI ≥ 25 kg/m^2) and normal BMI (BMI = 18.5–24.9 kg/m^2), and *t*-tests were used to compare continuous variables by BMI category. Weighted Cox proportional hazard regression analysis was used to compare the risk of cancer mortality by levels of metabolic and inflammatory biomarkers stratified by BMI category in models sequentially adjusted for potential confounding variables. Robust sandwich estimation method was used to estimate the confidence intervals around the hazard ratio. The crude model included each of the main exposure variable (i.e. IL-6, IL-8, IL-10, CRP, adiponectin, leptin, resistin or Lp(a)) and age. Model 1 further adjusted for sex, BMI, education, income, and race. Model 2 (the main analytical model) further adjusted for exercise. Model 3 additionally adjusted for alcohol, smoking, aspirin and statin use, and comorbidity score. Since the continuous exposure variables were not normally distributed, they were log-transformed. Statistical interactions between log-transformed biomarker levels and BMI were tested using the likelihood ratio test and interaction *p*-values ≤0.1 were considered statistically significant. In addition, participants were ranked into tertiles according to the levels of biomarkers and the highest tertiles were compared to the lowest for risk of cancer mortality. Associations between the exposure variables and mortality were considered statistically significant if the 95% confidence intervals (95% CIs) do not include the null value (1.0) or if the *p*-values are ≤0.05,

and for interaction terms, if the *p*-values are ≤0.1. The interactions between BMI and each biomarker in the non-stratified crude models were statistically significant at $\alpha = 0.1$, therefore results from BMI stratified models were presented. Participants were censored at the date of death, loss to follow-up or December 31, 2015, whichever happened first. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.)

3. Results

At baseline, compared with participants with normal BMI, those with overweight or obesity were younger, more likely to be male and Black, have less than high school education, and higher average comorbidity score (all *p*-values < 0.05, Table 1). Participants with normal BMI tended to have higher IL-8 and adiponectin levels, while those with overweight or obesity tended to have higher CRP, IL-6, and Lp(a) (*p*-value < 0.05). Distribution of IL-10 and resistin values were not significantly different between BMI categories (Table 2), however a higher proportion of participants with normal BMI were in the highest tertile of IL-6 and CRP compared with participants with overweight/obesity, Fig. 1. Participants with normal BMI also tended to be in the highest tertile of adiponectin compared with participants with overweight/obesity, while those with overweight/obesity tended to be in the highest tertile of leptin, Fig. 1.

The average follow-up time in the REGARDS sub-cohort was 8 years (SD = 3.3). Figs. 2 and 3 present the survival probabilities by tertiles of IL-6 and resistin, respectively. Tests of interaction between assessed biomarkers and BMI were statistically significant, p-values <0.05. Among participants with normal BMI, those in the highest vs. lowest tertile of IL-6 had a 5-fold (HR: 5.3, 95% CI: 1.6–17.8) increased risk of cancer mortality. Similar results were observed for log-transformed values of IL-6. In addition, those in the highest tertile of CRP had over a 3-fold (HR: 3.4; 95% CI: 1.0, 11.2) increased risk of cancer mortality (Table 3), while those in the highest tertile of resistin had a nearly 4-fold increased risk of cancer mortality (HR: 3.7; 95% CI: 1.2, 11.2) (Table 4). Among participants with overweight/obesity, highest tertile of IL-6 was associated with more than a 3-fold increased risk of cancer mortality (HR: 3.5; 95% CI: 1.5, 8.1), (Table 3). However, CRP and resistin were not significantly associated with cancer mortality in this group (Table 4).

In race-stratified analyses (Table 5), IL-6 was significantly associated with higher risk of cancer mortality among Black participants with normal BMI (HR: 4.7; 95% CI: 1.3, 16.9) and overweight/obesity (HR: 3.3; 95% CI: 1.6, 7.0), and among White participants with overweight/obesity (HR: 3.1; 95% CI: 1.3, 7.5). Furthermore, CRP was significantly associated with an increased risk of cancer mortality, but only among White participants with normal BMI (HR: 1.9; 95% CI: 1.0, 3.4). The interaction between BMI and the exposure variables remained among Black participants (*p*-values < 0.05) but disappeared among White participants (*p*-values > 0.1), Table 5. In sensitivity analysis excluding those who died of cancer within 6 months from baseline, the associations remained consistent for all biomarkers evaluated (data not shown).

Table 1
Baseline characteristics of REGARDS participants by BMI category.

	BMI categories		*p*-Value
	Normal (18.5–24.9 kg/m^2)	Overweight or obese (≥25 kg/m^2)	
Participants n	*454*	*1368*	
Weighted participants n	*6402*	*19,904*	
Age at baseline, mean (SE)[a]	70.3 (12.0)	66.4 (10.2)	<0.0001
Race (Blacks) %[b]	28.4	45.7	<0.0001
Male gender, %	42.4	46.9	0.0001
Education <high school, %	10.0	12.9	0.003
Income <$20,000, %	14.7	16.7	0.501
No exercise activity, %	34.0	32.5	0.740
BMI (kg/m^2), median (IQR)[c]	23.2 (2.3)	30 (6.4)	
Current smoking status, %	18.0	12.7	0.353
Heavy alcohol consumption, %	6.0	3.3	0.558
Medication use, %			
NSAIDs - Aspirin	43.9	45.1	0.836
Statins	28.6	35.9	0.243
Comorbid conditions, %			
Atrial fibrillation	12.2	8.0	0.030
Chronic lung disease	6.7	9.0	0.516
Coronary artery disease	16.5	16.6	0.551
Deep vein thrombosis	4.5	6.6	<0.0001
Diabetes	9.9	27.5	<0.0001
Dyslipidemia	50.6	63.6	<0.0001
Hypertension	44.7	63.8	<0.0001
Myocardial infarction	13.2	12.8	0.685
Peripheral artery disease	1.1	1.4	0.827
Stroke	7.6	4.6	0.081
Comorbidity score, mean (SE)	1.9 (1.4)	2.3 (1.4)	<0.0001

[a] Results are mean and standard deviation (SD).
[b] Results are percent.
[c] Results are median and interquartile ranges.

Table 2
Distribution of inflammatory and metabolic biomarkers among study participants.

	BMI category		*p*-Value
	Normal (18.5–24.9 kg/m^2)	Overweight or obese (≥25 kg/m^2)	
Inflammatory biomarkers (n = 1822)			
IL-6 (pg/ml)[a]	2.2 (1.9)	3.1 (2.4)	<0.0001
IL-8 (pg/ml)[a]	2.7 (1.8)	2.5 (1.8)	0.013
IL-10 (pg/ml)[a]	9.5 (7.1)	9.1 (7.1)	0.58
CRP (mg/l)[b]	3.5 (6.5)	4.8 (7.1)	<0.0005
Metabolic biomarkers (n = 1733)			
Adiponectin (ng/ml)[a]	14,568 (20,982.2)	10,072 (20,904.2)	<0.0001
Resistin (pg/ml)[a]	23.1 (20)	24.3 (12.1)	0.69
Lp(a) (mg/dl)[a]	0.13 (0.3)	0.20 (0.40)	0.045

Abbreviation: CRP, C-reactive protein; IQR, inter quartile range; IL, interleukin; Lp(a), lipoprotein (a); SD, standard deviation.
[a] Median (IQR).
[b] Results are mean and SD.

4. Discussion

In prospective REGARDS cohort, after adjusting for study covariates, higher baseline IL-6, CRP, and resistin were significantly associated with increased risk of cancer mortality among participants with normal BMI, while higher IL-6 was also associated with increased risk of cancer mortality among participants with overweight/obesity. When stratified by race, IL-6 remained significantly associated with higher risk of cancer mortality among Blacks regardless of BMI, but only among Whites with overweight/obesity. To our knowledge, this is the first study to simultaneously evaluate the independent associations of inflammatory and metabolic biomarkers with cancer mortality across levels of obesity.

Obesity has been well studied in relation to the risk of cancer mortality; however, estimates of the risk associated with higher BMI have been inconsistent due to the limitations in the validity of BMI as a measure of adiposity, and due to differences in the type and pattern of adiposity. This has led to a renewed interest in identifying biomarkers that may be less vulnerable to measurement error and thus more reliably predict cancer risk. Recent studies have also shown that independent of obesity, metabolic health status is a key risk factor for cancer. Significant associations have been observed between high blood pressure [21], dyslipidemia, and type 2 diabetes [22–25] with cancer risk and mortality. Furthermore, obesity is associated with low-grade chronic inflammation, which is independently associated with cancer risk [26,27]. Therefore, it is likely that obesity induces measurable changes in metabolism and inflammatory biomarkers associated with risk of cancer. It is also likely that non-obese individuals with higher levels of certain risk-associated biomarkers may be at higher risk of cancer. However, studies evaluating the impact of obesity in modifying the association between

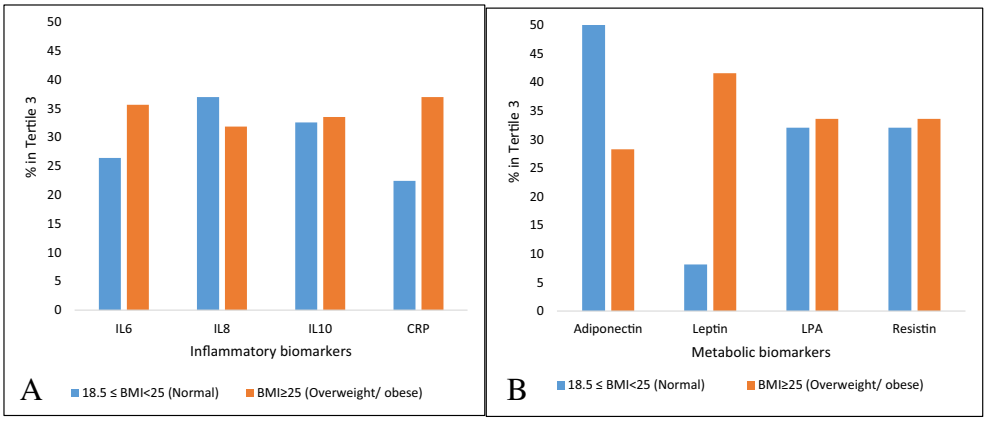

Fig. 1. Distribution of inflammatory (A) and metabolic (B) biomarkers by BMI in REGARDS BMI in kg/m^2.

biomarkers of inflammation and metabolic dysregulation are limited. In particular, given that obesity has been evaluated well as a risk factor for cancer incidence and mortality, the emphasis to date has been on identifying biomarkers of this association in obese individuals. Our finding suggests that chronic inflammation and metabolic dysregulation in normal BMI individuals may substantially increase their risk of cancer mortality.

We observed a robust association between IL-6 and cancer mortality in both obese and non-obese participants after adjusting for sociodemographics, physical activity, and comorbidities. The association became attenuated and non-significant, although remained a 2-fold increased risk, among normal BMI but not obese individuals when adjusted for behavioral risk factors (smoking, alcohol) and statin use. In contrast, estimates for overweight/obese participants became stronger after adjusting for the behavioral risk factors and statin use. We also observed significantly increased cancer mortality risk with higher CRP levels in normal BMI participants in the fully adjusted models. These findings suggest that regardless of BMI, certain markers of inflammation influence the risk of cancer mortality. In addition, the results suggest that behavioral factors may explain part of the increased risk associated with IL-6 in individuals with normal BMI but not overweight/obese, the robust association between CRP and cancer mortality risk in normal BMI individuals highlights an important role for chronic inflammation. Past studies have also observed independent and significant associations of high levels of IL-6 [28–30], CRP [31–34], and obesity [35–37] with cancer mortality. Our study adds to this body of work by showing that the association between inflammatory biomarkers and cancer mortality varies by BMI. Mechanistically, it has been suggested that a chronic inflammatory microenvironment promotes tumor cell motility, invasion, epithelial to mesenchymal transition and metastasis which in turn lead to poor prognosis [38]. IL-6 promotes tumorigenesis, angiogenesis, invasiveness, and metastasis, and inhibits apoptosis [29,39]. IL-6 also protects cancer cells from therapy-induced DNA damage and oxidative stress by facilitating the repair and induction of counter-signaling pathways, thus increasing cancer mortality [39].

We also found a consistent association between higher resistin, a metabolism biomarker, and increased risk of cancer mortality, but only among participants with normal BMI. This association remained statistically significant after adjusting for behavioral risk factors even though mean resistin was not significantly different by BMI. Thus, the differences in the association between resistin and cancer mortality by BMI may be due to the interaction between resistin and BMI rather than resistin alone. Resistin has been studied as a potential missing link between obesity, chronic inflammation, and cancer [40] due to its association with increased low-density lipoprotein production and inflammatory response. A previous study has found a direct association between resistin and cancer mortality [41], and studies have documented that resistin promotes insulin resistance [42], chronic low-grade inflammation [43], and tumor cells adhesion to endothelium-a critical step for metastasis [44,45]. The BMI differences BMI in the assocaition between resistin and risk of cancer mortality may be because obese individuals are more likely to already have chronic inflammation, while among individuals with normal BMI who might otherwise be without chronic inflammation, higher resistin levels induces chronic inflammation and thus worsen the prognosis of cancer. Lp(a), another metabolism-related biomarker, is involved in cholesterol transport, wound healing and tissue repair-pathways that are co-opted by cancer cells to enhance invasion and metastasis. We did not observe

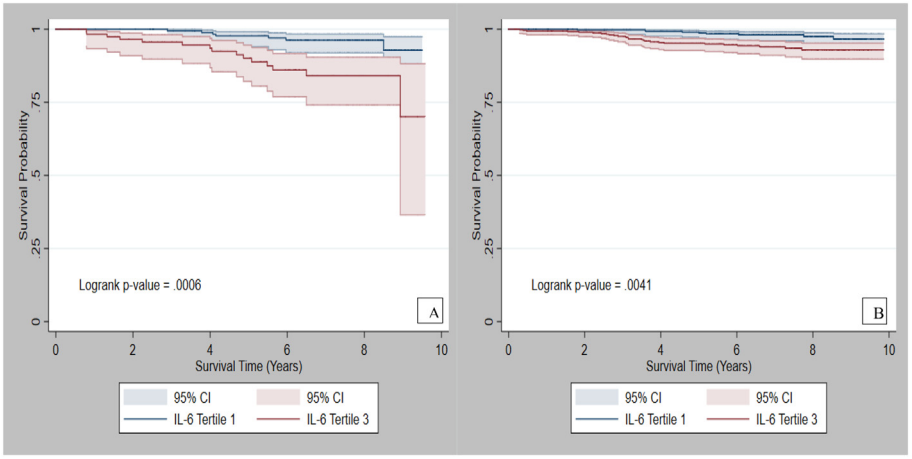

Fig. 2. Survival probability of cancer patients with A) normal BMI, and B) overweight/obesity by tertiles of IL-6.

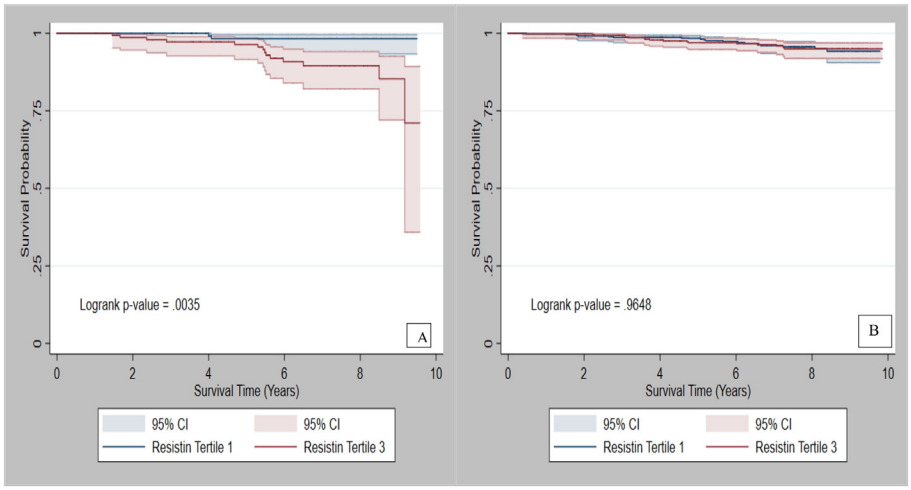

Fig. 3. Survival probability of cancer patients with A) normal BMI and B) overweight/obese by tertiles of resistin.

a significantly increased risk of cancer mortality associated with Lp(a) or adiponectin in the current study, although there was a suggestion of increased risk for adiponectin. Studies with larger sample sizes may be needed to definitively evaluate the role of adiponectin and Lp(a) in cancer mortality among obese and non-obese individuals; it is possible that these associations are easier to detect in lean individuals.

The associations between baseline biomarkers and risk of cancer mortality also varied by race. IL-6 was associated with an increased risk of cancer mortality among Blacks with normal BMI and overweight/obesity, but only among Whites with overweight/obesity. CRP was associated with increased risk of cancer mortality among Whites with normal BMI, but not among Blacks despite those with overweight/obesity having significantly higher mean CRP levels. This difference may be because obese/overweight participants have other risk factors that cumulatively increase the risk of cancer mortality, and inflammation due to CRP may not significantly further increase the risk in contrast with participants with normal BMI. A higher proportion of participants with normal BMI died of cancer in the REGARDS cohort

Table 3
Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by baseline inflammatory biomarkers.

	BMI categories				$p_{int\ with\ BMI}$
	Normal (18.5 ≤ BMI < 25 kg/m^2)		Overweight or obese (BMI ≥ 25 kg/m^2)		
	Log transformed	T3[a]	Log transformed	T3	
IL-6 (pg/ml), *N* (cases)	*454 (29)*	*120 (15)*	*1368 (54)*	*488 (27)*	
Weighted *N* (cases)	*6402 (371)*	*1136 (195)*	*19,904 (937)*	*6310 (492)*	
Crude	**3.3 (1.5, 6.7)****	**5.5 (1.8, 16.4)****	**2.8 (1.6, 4.7)****	**3.2 (1.5, 6.7)***	<0.0001
Model 1	**3.0 (1.4, 6.3)****	**4.2 (1.5, 11.9)****	**2.8 (1.6, 5.0)****	**3.4 (1.4, 7.0)****	0.007
Model 2	**3.2 (1.5, 7.0)****	**5.3 (1.6, 17.8)****	**3.0 (1.7, 5.4)****	**3.5 (1.5, 8.1)****	0.007
Model 3	2.1 (0.8, 5.4)	2.4 (0.6, 9.0)	**2.6 (1.4, 4.9)****	**2.9 (1.2, 6.6)***	0.716
IL-8 (pg/ml), *N* (cases)	*454 (29)*	*168 (12)*	*1368 (54)*	*436 (25)*	
Weighted *N* (cases)	*6402 (371)*	*2101 (187)*	*19,904 (937)*	*6228 (552)*	
Crude	1.1 (0.7, 1.8)	1.8 (0.6, 5.2)	**1.4 (1.0, 2.2)****	1.5 (0.8, 3.1)*	0.047
Model 1	0.9 (0.5, 1.7)	1.5 (0.5, 4.2)	1.4 (0.9, 2.3)	1.4 (0.7, 2.8)	0.049
Model 2	0.9 (0.5, 1.7)	1.5 (0.5, 4.1)	1.4 (0.9, 2.3)	1.4 (0.7, 2.9)	0.043
Model 3	0.9 (0.4, 1.9)	1.1 (0.3, 4.4)	1.2 (0.7, 2.2)	1.3 (0.6, 2.8)	0.710
IL-10 (pg/ml), *N* (cases)	*454 (29)*	*148 (9)*	*1368 (54)*	*459 (22)*	
Weighted *N* (cases)	*6402 (371)*	*2307 (148)*	*19,904 (937)*	*6230 (367)*	
Crude	0.7 (0.5, 1.1)	0.7 (0.3, 1.7)	1.0 (0.6, 1.5)	1.2 (0.6, 2.2)	0.006
Model 1	0.8 (0.5, 1.2)	0.7 (0.3, 1.9)	0.9 (0.6, 1.6)	1.0 (0.5, 2.0)	0.021
Model 2	0.7 (0.5, 1.2)	0.7 (0.2, 2.1)	0.9 (0.6, 1.5)	1.0 (0.5, 2.0)	0.016
Model 3	0.6 (0.4, 1.1)	0.6 (0.2, 2.6)	0.9 (0.5, 1.6)	0.8 (0.4, 1.7)	0.636
CRP (mg/l), *N* (cases)	*678 (31)*	*102 (8)*	*1368 (54)*	*506 (20)*	
Weighted *N* (cases)	*6402 (371)*	*1217 (92)*	*19,904 (937)*	*6987 (364)*	
Crude	**1.7 (1.2, 2.4)****	**3.6 (1.2, 10.4)****	1.1 (0.8, 1.4)	1.1 (0.6, 2.2)	0.0003
Model 1	**1.6 (1.1, 2.2)****	**3.5(1.1, 11.4)***	1.1 (0.8, 1.4)	1.2 (0.6, 2.4)	0.009
Model 2	**1.6 (1.1, 2.2)****	**3.4 (1.0, 11.2)***	1.1 (0.8, 1.5)	1.3 (0.6, 2.8)	0.008
Model 3	**1.6 (1.1, 2.2)***	**4.2 (1.1, 16.4)***	1.2 (0.9, 1.6)	1.6 (0.7, 3.5)	0.412

Crude model included the exposure and age.
Model 1: Adjusted for age, gender, education, race, and income.
Model 2: Additionally adjusted for exercise.
Model 3: Additionally adjusted for smoking status, alcohol use, aspirin use, statin, and comorbidity score.
Bold indicates significance at 0.05 alpha level.
*p*int, *p* for the interaction of the log form with BMI. The *p*-values are from type 3 tests. *p* for the interaction is considered significant at alpha = 0.1.
[a] T1: 1st tertile, was the reference category; T3: 3rd tertile.
** *p*-Values were ≤0.01.
* *p*-Values were ≤0.05 while the rest of *p*-values were >0.05.

Table 4
Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by baseline metabolic biomarkers.

	BMI categories				$p_{int\ with\ BMI}$
	Normal (18.5 ≤ BMI < 25 kg/m^2)		Overweight or obese (BMI ≥ 25 kg/m^2)		
	Log-transformed	T3[a]	Log transformed	T3	
Adiponectin (pg/ml), *N* (cases)	*418 (31)*	*207 (19)*	*1315 (55)*	*178 (214)*	
Weighted *N* (cases)	*5664 (322)*	*2713 (191)*	*18,694 (938)*	*2563 (102)*	
Crude	1.0 (0.7, 1.5)	0.9 (0.4, 2.3)	0.9 (0.6, 1.3)	0.9 (0.5, 1.6)	0.029
Model 1	1.2 (0.8, 1.8)	1.7 (0.6, 4.9)	1.1 (0.8, 1.7)	1.3 (0.6, 2.6)	0.025
Model 2	1.3 (0.9, 1.9)	2.1 (0.7, 6.0)	1.1 (0.7, 1.6)	1.3 (0.6, 2.7)	0.014
Model 3	1.4 (0.9, 2.2)	2.3 (0.5, 9.4)	1.1 (0.7, 1.7)	1.3 (0.6, 2.9)	0.141
Lipoprotein a (mg/dl), *N* (cases)	*418 (31)*	*134 (10)*	*1315 (55)*	*220 (9)*	
Weighted *N* (cases)	*5664 (322)*	*1467 (99)*	*18,694 (938)*	*3339 (170)*	
Crude	0.8 (0.5, 1.3)	1.2 (0.5, 2.8)	0.9 (0.7, 1.2)	0.8 (0.5, 1.7)	0.008
Model 1	0.7 (0.4, 1.1)	0.8 (0.3, 2.2)	0.9 (0.6, 1.2)	0.8 (0.4, 1.7)	0.082
Model 2	0.7 (0.4, 1.2)	0.9 (0.3, 2.6)	0.9 (0.6, 1.2)	0.8 (0.4, 1.8)	0.066
Model 3	1.0 (0.5, 1.9)	1.7 (0.5, 6.3)	0.9 (0.7, 1.3)	1.0 (0.4, 2.3)	0.712
Resistin (pg/ml), *N* (cases)	*418 (31)*	*134 (15)*	*1315 (55)*	*224 (8)*	
Weighted *N* (cases)	*5664 (322)*	*1528 (112)*	*18,694 (938)*	*3025 (148)*	
Crude	**2.5 (1.1, 5.7)**[*]	**3.7 (1.3, 11.0)**[*]	0.8 (0.5, 1.5)	0.7 (0.4, 1.5)	0.001
Model 1	**2.4 (1.1, 5.3)**[*]	**4.0 (1.3, 11.7)**[*]	1.0 (0.5, 1.8)	0.8 (0.4, 1.6)	0.012
Model 2	**2.3 (1.0, 5.0)**[*]	**3.7 (1.2, 11.2)**[*]	1.0 (0.5, 1.8)	0.7 (0.3, 1.5)	0.008
Model 3	2.5 (0.9, 7.0)	**8.7 (1.9, 39.9)**[**]	1.0 (0.5, 2.0)	0.9 (0.4, 1.8)	0.001

Crude model included the exposure and age.
Model 1 adjusted for age, gender, education, race, and income.
Model 2 additionally adjusted for exercise.
Model 3 additionally adjusted for smoking status, alcohol use, aspirin use, statin, and comorbidity score.
Bold indicates significance at 0.05 alpha level.
*p*int, *p* for the interaction of the log form with BMI. The *p*-values are from type 3 tests. *p* for the interaction is considered significant at alpha = 0.1.
[a] T1: 1st tertile was the reference category; T3: 3rd tertile.
[**] *p*-Values were ≤0.01.
[*] *p*-Values were ≤0.05 while the rest of p-values were >0.05.

Table 5
Hazard ratios (HR) and 95% confidence intervals (CI) for cancer mortality by inflammatory and metabolic biomarkers by race.

	BMI categories		$p_{int\ with\ BMI}$
	Normal BMI (18.5 ≤ BMI < 25 kg/m^2)	Overweight or obese (BMI ≥ 25 kg/m^2)	
	Log-transformed[a]	Log transformed[a]	
Black participants (N = 798, cancer death = 40)			
IL-6			
Model 1	**3.6(1.2, 10.6)**[*]	**3.4 (1.6, 7.0)**[**]	0.008
Model 2	**4.7 (1.3, 16.9)**[*]	**3.3 (1.6, 7.0)**[*]	0.021
Model 3	**5.9 (1.5, 23.1)**[*]	**3.0 (1.3, 6.9)**[*]	0.156
CRP			
Model 1	1.4 (0.9, 2.0)	1.3 (0.9, 2.0)	0.039
Model 2	1.4 (0.9, 1.9)	1.3 (0.9, 2.0)	0.043
Model 3	1.3 (0.7, 2.2)	1.3 (0.9, 2.0)	0.396
Resistin			
Model 1	4.4 (0.6, 31.4)	1.3 (0.7, 2.3)	0.007
Model 2	4.2 (0.7, 26.9)	1.3 (0.7, 2.3)	0.013
Model 3	**8.5 (2.0, 35.8)**[**]	1.3 (0.7, 2.5)	0.008
White participants (N = 1024, cancer death = 46)			
IL-6			
Model 1	2.6 (0.8, 9.1)	**2.4 (1.0, 5.7)**[*]	0.269
Model 2	3.0 (0.8, 12.0)	**3.1 (1.3, 7.5)**[*]	0.278
Model 3	1.0 (0.20, 4.6)	**2.7 (1.1, 6.4)**[*]	0.649
CRP			
Model 1	**1.8(1.1, 3.1)**[*]	0.9 (0.6, 1.3)	0.115
Model 2	**1.9 (1.0, 3.4)**[*]	0.9 (0.6, 1.4)	0.131
Model 3	**1.7 (1.2, 2.5)**[**]	1.0 (0.6, 1.5)	0.571
Resistin			
Model 1	1.3 (0.3, 5.5)	0.4 (0.1, 1.6)	0.625
Model 2	1.3 (0.3, 6.0)	0.4 (0.1, 1.8)	0.454
Model 3	3.6 (0.5, 24.2)	0.4 (0.1, 2.5)	<0.0001

Crude model included the exposure and age.
Model 1 adjusted for age, gender, education, and income.
Model 2 additionally adjusted for exercise.
Model 3 further adjusted for comorbidity scores, smoking, alcohol, aspirin, and statin use.
Bold indicates significance at 0.05 alpha level.
*p*int, *p* for the interaction of the log form with BMI. The *p*-values are from type 3 tests. *p* for the interaction is considered significant at alpha = 0.1.
[a] Biomarkers (except CRP) were log-transformed due to non-normal distributions.
[**] *p*-Values were ≤0.01.
[*] *p*-Values were ≤0.05 while the rest of p-values were >0.05.

compared with overweight/obes participants; however, excluding participants that died within 6 months of entry into the cohort did not materially change the results. In a previous study, IL-6 was found to be associated with increased risk of cancer mortality in both Blacks and White participants, consistent with current findings [46]. However, our analysis was underpowered given the limited sample sizes to detect racial differences in cancer mortality risk across BMI categories. Future studies with larger, racially diverse prospective cohorts, or including a larger subset of this cohort, are needed to definitively evaluate racial differences in the independent and potentially synergistic associations of inflammatory and metabolic biomarkers with cancer mortality risk. The finding from this study improves our understanding of the role of metabolic health status and obesity in cancer outcomes and adds to the limited but growing literature that will inform race-specific cancer prevention interventions.

The strengths of the study include sensitivity analysis that excluded those who died of cancer within six months from baseline, the large biracial prospective cohort, and detailed baseline measures of the biomarkers of interest and covariates. REGARDS participants were recruited nationally across the US, although residents of the stroke belt were over-sampled, thus improving the generalizability of the study results. This study also has some limitations relevant to the interpretation of the results. First, the mean follow-up period was 8 years, this also resulted in a limited number of events especially in stratified analysis, leading to reduced power to detect significant associations especially in the race-stratified analyses. Second, since REGARDS was originally designed to evaluate stroke outcomes, there is currently no data available on cancer incidence. While cost-effective and convenient, the methods used to determine the assay levels in this study such as the BN II nephelometer, Milliplex MAP Human Cardiovascular Disease Panel 3, and Human Serum Adipokine Panel B LINCOplex Kit may have low sensitivity, especially for LP(a); however, in this study, there was satisfactory sensitivity with MDD well below 1% for each biomarker except for LP(a), and the methods have been used previously and had similar coefficients of variations as in our study [47,48]. Larger cohorts of racially diverse participants using other assay measurement methods may help to confirm these findings and potentially identify other relevant biomarkers that may vary by BMI and race.

In conclusion, biomarkers of inflammation (IL-6 and CRP) and metabolism (resistin) were significantly associated with increased risk of cancer mortality independent of obesity, suggesting that both pathways may play a synergistic role in creating a favorable microenvironment for tumorigenesis and prognosis. This study supports the need for improved risk stratification based on metabolic health and/or inflammatory biomarkers regardless of BMI or obesity status in predicting cancer outcomes. Interventions targeting the inflammatory and metabolic biomarkers may improve cancer survival.

Author contributions

TA led the design, analysis, interpretation of data and writing of the manuscript. DD conducted the statistical analysis and drafted the manuscript. DD, SJ, SG, MC, MP, and MS contributed to the interpretation of data, writing and reviewing the manuscript. All authors have read and approved the final version of the manuscript.

Funding

The REGARDS study was supported by cooperative agreement U01-NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org. This analysis was supported by award R01-NR012726 from the National Institute of Nursing Research, UL1-RR025777 from the National Center for Research Resources, K08HL096841 and R01HL080477 from the National Heart, Lung, and Blood Institute, and by grants from the Center for Clinical and Translational Science and the Lister Hill Center for Health Policy of the University of Alabama at Birmingham. Dr. Akinyemiju was supported by grant K01TW010271 from the NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies. Representatives of the funding agencies have been involved in the review of the manuscript but not directly involved in the collection, management, analysis or interpretation of the data.

Conflict of interest

The authors declare no conflict of interest.

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