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Bioavailable Insulin-Like Growth Factor-I as Mediator of Racial Disparity in Obesity-Relevant Breast and Colorectal Cancer Risk among Postmenopausal Women

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Abstract

Objectives—Bioavailable insulin-like growth factor (IGF)-I interacts with obesity and exogenous estrogen in a racial disparity in obesity-related cancer risk, yet their interconnected pathways are not fully characterized. We investigated whether circulating bioavailable IGF-I acted as a mediator of the racial disparity in obesity-related cancers such as breast and colorectal (CR) cancers and how obesity and estrogen use regulate this relationship.

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Methods—A total of 2,425 white and 164 African American (AA) postmenopausal women from the Women's Health Initiative Observational Study were followed from October 1, 1993, through August 29, 2014. To assess bioactive IGF-I as a mediator of race–cancer relationship, we used the Baron-Kenny method and quantitative estimation of the mediation effect.

Results—Compared with white women, AA women had higher IGF-I levels; their higher risk of CR cancer, after accounting for IGF-I, was no longer significant. IGF-I was associated with breast and CR cancers even after controlling for race. Among viscerally obese (waist/hip ratio >0.85) and overall non-obese women (body mass index <30), IGF-I was a strong mediator, reducing the racial disparity in both cancers by 30% and 60%, respectively. In estrogen-only users and nonusers, IGF-I explained the racial disparity in CR cancer only modestly.

Conclusions—Bioavailable IGF-I is potentially important in racial disparities in obesity-related breast and CR cancer risk between postmenopausal AA and white women. Body fat distribution and estrogen use may be part of the interconnected hormonal pathways related to racial difference in IGF-I levels and obesity-related cancer risk.

Keywords

insulin-like growth factor-I; obesity; exogenous estrogen; mediation; postmenopausal women

Introduction

A racial disparity between African American (AA) and white postmenopausal women in the risk of obesity-relevant cancer types is well documented for both reproductive cancers, such as breast cancer, and non-reproductive cancers, including colorectal (CR) cancer.(1,2) For example, during 2008–2012, overall breast cancer incidence rates increased among AA but were stable among whites. In addition, among younger women (< 50 years), the incidence increased slightly in whites (0.4% per year) and was stable in AA women, whereas among older women (i.e., postmenopausal age), an increasing trend was observed only in AA women.(3) CR cancer incidence is also disparate; during 2006-2010, its incidence in AA was about 25% higher than it was in white women.(4)

Previous epidemiologic and clinical studies have suggested that free bioavailable insulin-like growth factor-I (IGF-I) is an important mediator of obesity-associated tumorigenesis (i.e., it is a cancer-relevant biomarker) and that greater bioavailable IGF-I is associated with greater risk of obesity-related cancers, including breast and CR cancers.(5-11) Previous studies also showed that these circulating IGF-I levels are higher in AA than in white postmenopausal women (10,12); thus, this variation is plausibly related to the racial disparity in those cancers. However, studies evaluating the role of IGF-I in the racial disparity in risk of those cancers have not shown enough evidence to confirm this relationship. The findings are inconsistent, mainly because of small samples sizes, different measures of IGF-I concentration (e.g., total versus bioavailable IGF-I), and lack of consideration of interactions with effect modifiers such as obesity and sex hormones.

As a crucial modifiable factor, obesity has been postulated to be a driver of IGF-I production, given its association with the growth hormone (GH)–IGF axis.(13) However, the

obesity–IGF-I association is not simple, and it differs by race: it is nonlinear, rather closer to an L shape, and in AA women, obesity is inversely related to the level of bioavailable IGF-I.(9,10,12) The association between obesity and IGF-I may also differ by body fat distribution, such as overall obesity (measured by body mass index [BMI]) or abdominal adiposity (measured by waist circumference and waist/hip ratio [W/H]).(8,14,15)

Additionally, in postmenopausal women, IGF and endogenous estrogen (E)receptors interact in a synergistic cross-talk mechanism, inducing both receptors' signaling pathways and resulting in the enhanced anabolic state necessary for tumor growth and development.(16-19) Likewise, exogenous E in this population has been postulated to interact with circulating IGF-I proteins to affect cancer risk. However, unopposed E (i.e., E only) has a different effect than opposed E (i.e., E + progestin [P]) has on IGF-I production. Because of first-pass effect induced by oral E resulting in suppressing hepatic production of IGF-I, E-only users have lower IGF-I levels and lower risk of breast and CR cancers than nonusers have.(20-22) Due to non–progesterone-like effects, contrasting with the hepatocellular effects of oral E on IGF-I production, E+P users, (compared with E-only users) have different IGF-I levels and cancer risk (22-25), although the precise mechanisms are unknown. There are few studies evaluating the role of exogenous E in the racial disparity in IGF-I levels and obesity-related cancer risk. Furthermore, to our knowledge, no study to date has combined obesity and exogenous E as effect modifiers to evaluate the role of IGF-I in the racial disparity in risk of obesity-related cancers (breast and CR).

In this retrospective analysis, using secondary data from postmenopausal women in the Women's Health Initiative Observation Study (WHI-OS), we therefore evaluated statistically the role of free bioavailable IGF-I as a mediator in the racial disparity in the risk of obesity-related breast and CR cancers and determined how modifiable factors, such as obesity and the use of exogenous E, regulate this relationship. We hypothesized that AA women, compared with white women, have a greater risk of such cancers and that their higher IGF-I levels mediate this racial disparity. In AA women, obesity and the use of exogenous E may act as strong predictors of bioavailable IGF-I and obesity-related breast and CR cancers.

Most studies evaluating cancer disparity in relation to IGF-I in different racial groups conducted subset analyses of one racial group or the other. This approach reduces the statistical power with which to evaluate the main association, especially after accounting for multiple other covariates in the models, owing to the decreased sample size resulting from dividing the sample by race. To address this methodologic challenge, in this study, we examined the mediation effect of IGF-I in relationship with the racial cancer disparity by using two complementary statistical methods: a Baron-Kenny approach (26) and quantitative estimation of a mediation effect.(26-28) Our findings may thus contribute to better understanding of the role of IGF-I as a mediator of the racial disparity in risk of obesity-related cancers and emphasize the role of obesity and exogenous E in reducing this racial disparity among postmenopausal women.

Methods

Study population

The study included 2,589 postmenopausal women enrolled in the WHI-OS, a longitudinal cohort of postmenopausal women, 50–79 years old, who had been recruited at 40 clinical centers across the United States between October 1, 1993, and December 31, 1998. Details on the WHI's rationale and design have been described elsewhere.(29) For the purposes of our study, of the 93,676 women enrolled in the WHI-OS, we included only European-American and AA women (n = 85,651) (Figure S1). Among these, 3,585 women who had free bioavailable IGF-I concentrations (obtained after at least 8 hours' fasting) available at baseline (i.e., screening or first annual visit) were included. After excluding women (n = 659) who had been followed up for less than 1 year or those diagnosed with any cancer at enrollment, we had 2,926 participants. We excluded another 337 women for whom information regarding covariates was not available, leaving a final total of 2,589 women (89% of the 2,926). The participants had been followed up through August 29, 2014 (758 [29% of white and 32% of AA women] breast cancer patients, and 365 [14% of white and 23% of AA women] CR cancer patients). This study was approved by the institutional review boards at the University of California, Los Angeles.

Data collection and outcome variables

Standardized written protocols were used to ensure uniform data collection. At baseline, participants completed self-administered questionnaires on demographic (age, race, education, marital status, and family history of cancer) and lifestyle factors (physical activity, smoking status, alcohol intake, and diet) and their medical (cardiovascular disease [CVD], diabetes, hypertension, and hypercholesterolemia) and reproductive (oral contraceptive and exogenous E use, history of hysterectomy or oophorectomy, and ages at menarche and menopause) histories. Anthropometric measurements, including height, weight, and waist and hip circumferences were measured at baseline by trained staff. Of 32 variables initially selected from a literature review for their associations with race, IGF-I, and obesity-related cancers including breast and CR cancers, after multicollinearity testing and univariate and stepwise regression analyses, we finally selected 24 variables for this study.

Cancer outcomes were formally determined through a centralized review of medical charts and cancer cases were coded according to the National Cancer Institute's Surveillance, Epidemiology, and End-Results guidelines.(30) The outcome variables were the specific cancer type (obesity-relevant, breast, and CR) and the time to develop such cancer. Obesity-relevant cancers included any of nine cancer types (reproductive cancers: breast, endometrial, and ovarian; and non-reproductive cancers: CR, kidney, esophageal, gastric, pancreatic, and hepatic).(1,2) The time in days from enrollment to cancer development, censoring, death, or study end point were recorded and converted into years.

Laboratory methods

Fasting blood samples were collected from each participant at baseline by trained phlebotomists and immediately centrifuged and stored at –70°C. Serum IGF binding protein

(BP)-3 and both total and free bioavailable IGF-I concentrations were determined using an enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories, Webster, TX), with coefficients of variation of 2.2% for IGFBP-3, 3.5% for total IGF-I, and 16.4% for free IGF-I. The correlation coefficients of values were high (IGFBP-3, $R^2 = 0.98$; total IGF-I, $R^2 = 0.98$; free IGF-I, $R^2 = 0.91$). For our analysis, we used the level of free bioavailable IGF-I and replaced missing data with the molar ratios of total IGF-I/IGFBP-3.(31)

Statistical analysis

Differences in baseline characteristics between the white and AA women were assessed using unpaired two-sample *t* test for continuous variables and chi-square test for categorical variables. If continuous variables were skewed or had outliers, Wilcoxon's rank-sum test was implemented. Multicollinearity was evaluated by using the coefficient of multiple determination, tolerance, and variance-inflation factors for each covariate, using the remaining covariates as its predictors; no significant multicollinearity was identified.

Multiple linear regression with the regression assumptions to be met was conducted to produce the effect sizes of race (AA versus white women) and potential effect modifiers (obesity and exogenous E use) for bioavailable IGF-I. Cox proportional hazards regression model was performed to yield hazard ratios (HRs) and 95% confidence intervals (CIs) for race, IGF-I, and effect modifiers on obesity-relevant, breast, and CR cancers. The proportional hazard assumption was tested via a Schoenfeld residual plot and rho.

To assess bioavailable IGF-I as a mediator of the race–cancer risk relationship, we applied two approaches: 1) Baron-Kenny approach (26,32) and 2) computation of the mediation effect (i.e, indirect effect) directly from a delta method using Structural Equation Modeling (SEM) (28), along with the percentage change in the HRs.(26,27) According to the Baron-Kenny approach, the formal analysis to detect a mediation effect, follows from the definition of a mediator: Variable M is considered a mediator if 1) X (the independent variable, i.e., race in this study) significantly predicts Y (the outcome of interest, i.e., cancer risk in this study), 2) X significantly predicts M (potential mediator, i.e., IGF-I in this study), and 3) M significantly predicts Y, controlling for X.(26,32-34) These criteria are assessed by estimating the following system of equations:

$$\mathrm{Y}=\acute{\imath}_1+\mathrm{cX} \quad (1)$$

$$\mathrm{M}=\acute{\imath}_2+\mathrm{aX} \quad (2)$$

$$\mathrm{Y}=\acute{\imath}_3+\mathrm{c}'\mathrm{X}+\mathrm{bM} \quad (3)$$

where ί is an intercept coefficient.(32,34)

In our study, the first step (path c) of the Baron-Kenny approach was to test the hypothesis that AA women have higher risk of cancers than white women; the second step (path a) was to evaluate the association between AA (compared with whites) women and IGF-I. The third and final step (path b) was to assess whether IGF-I levels were significantly associated with cancer risk after accounting for race.

However, those steps can be affected by type II errors and cannot estimate the amount or test the significance of the mediation effect.(26) Thus, to estimate and test for the significance of the pathway of racial disparity in cancer risk through IGF-I (28), we performed a delta method, which is very conservative when it falsely presumes a symmetric distribution, via SEM using Mplus software. Additionally, we calculated the proportional change in the HRs for the race–cancer risk relationship by comparing a model that includes all covariates with a model that includes all covariates and IGF-I.(26,27) A two-tailed P value < 0.05 was considered statistically significant. R (v 2.15.1) was used.

Results

Baseline characteristics of participants between white and AA women are presented in Table 1. Compared with white women, AA women were younger, less educated, less likely to be married and to have a family history of cancer, and they were more likely to have comorbid conditions (CVD, diabetes, and hypertension ever), a history of hysterectomy or oophorectomy, and later menopausal transition. AA women were less likely to use exogenous estrogen and to meet the physical activity and dietary guidelines, and they were more likely to be obese (overall [BMI] and viscerally [waist circumference and W/H]) and to have higher bioavailable IGF-I levels.

Breast cancer: mediation effect of bioavailable IGF-I in racial disparity, stratified by obesity status (BMI; waist; W/H) and exogenous E usage (nonusers; E only; E+P)

We first examined the overall mediation effect of IGF-I on the racial disparity of breast cancer risk between AA and white women using the three-step Baron and Kenny approach. The racial disparity in breast cancer risk (step 1 = path c) was not significant (HR = 1.25, 95%CI, 0.92–1.68), and AA women had higher IGF-I levels than white women (step 2 = path a; effect size = 0.12, 95%CI, 0.07–0.17); women who had higher IGF-I levels were 50% more likely to have breast cancer (step 3 = path b; HR = 1.49, 95%CI, 1.20–1.85). Comparing the step-1 model, the introduction of IGF-I into the model (i.e., step-3 model) reduced the racial disparity by 29% ($HR_{\text{without IGF-I}} = 1.25$ vs. $HR_{\text{with IGF-I}} = 1.18$; $P < 0.05$ using the bootstrapping method), indicating that IGF-I mediates the racial disparity in breast cancer risk to a modest degree (Figure S2).

We next explored obesity status with different types of adiposity measures (i.e., BMI, waist, and W/H) for its contribution as an effect modifier on the racial disparity in breast cancer risk, which could have been mediated by IGF-I (Table 2). Even though the racial disparity in breast cancer was not significant (paths c and c′), AA women tended to have higher breast cancer risk across obesity status. Notably, the racial difference in IGF-I levels (path a) in the overall non-obese group (BMI <30) was greater than it was in the overall obese group (BMI ≥30). This pattern was reversed when stratified by W/H: in the non-obese group (W/H

≤0.85), the racial difference in IGF-I levels was smaller than it was in the obese group (W/H >0.85). We also evaluated the association between obesity status and IGF-I, stratified by race (Table S1), and found that IGF-I levels in white women increased as BMI and W/H increased. However, in AA women, IGF-I levels decreased as BMI increased, but increased as W/H increased. This may explain the smaller racial difference in IGF-I levels in the overall obese group (BMI ≥30) than in the overall non-obese group (BMI <30) and the larger racial difference in IGF-I levels in the viscerally obese group (W/H >0.85) compared with those in the viscerally non-obese group (W/H ≤0.85).

Additionally, higher IGF-I levels were associated with breast cancer risk (path b). In path c′, introduction of IGF-I in the model evaluating the association between race and breast cancer (indirect, mediation effect = a*b) produced a greater reduction of racial disparity (i.e., reduction of the HR of IGF-I level on breast cancer) in the overall non-obese group (a*b = 0.07; Proportion explained = 59%) than it did in the overall obese groups (a*b = 0.03; Proportion explained = 6%), but in the W/H-stratified groups, the effect of IGF-I on racial disparity were not apparently different.

We then explored IGF-I's role in the race–breast cancer relationship by exogenous E usage (nonusers; E only; E+P) (Table 3). The racial disparity in IGF-I levels was smallest in the nonusers and largest in the E+P users because the AA women who used E+P had higher IGF-I levels than the nonusers had, whereas the white women who used E+P had lower IGF-I levels than the nonusers had (Table S1). This also contributed to a lesser mediation effect (a*b = 0.05; 17%) of IGF-I on racial disparity in breast cancer risk in nonusers than in E+P users. Next, in path c, among nonusers, AA women were more likely than white women to have higher breast cancer risk, whereas among E+P users, AA women were less likely to have breast cancer risk, although those differences were not significant. Among the E+P users, although the higher IGF-I levels in AA women reduced the breast cancer risk disparity ($HR_{\text{without IGF-I}} = 0.83$ vs. $OR_{\text{with IGF-I}} = 0.76$), this cannot explain the higher breast cancer risk in white women. This opposite pattern of racial risk (higher breast cancer risk in white than in AA women) in E+P users may be due to a confounding effect of E+P, suggesting that AA women are less likely than white women to use E+P (Table S2) and that E+P users are more likely than nonusers to develop breast cancer (Table S3).

CR cancer: mediation effect of bioavailable IGF-I on racial disparity, stratified by obesity status (BMI; waist; W/H) and exogenous E usage (nonusers; E only; E+P)

In contrast to our findings relative to breast cancer, the racial disparity in CR cancer risk was significant (HR = 1.47, 95% CI, 1.02–2.12). AA women had higher IGF-I levels (effect size = 0.12, 95% CI, 0.07–0.17), but after adjusting for IGF-I, the disparity in CR cancer risk was no longer significant (HR = 1.30, 95% CI, 0.90–1.88), with the risk reduced by 37% (P = 0.002, using the bootstrapping method).

When we assessed the role of IGF-I in the racial disparity in CR cancer risk, stratified by obesity status with different types of adiposity measures, we observed results similar to those we found for breast cancer risk (Table 4): introduction of IGF-I into the association between race and CR cancer produced a greater reduction in racial disparity (i.e., reduction of the HR of IGF-I level on CR cancer) in the overall non-obese group (a*b = 0.15; 61%)

than it did in the overall obese groups (a*b = 0.04; 20%). However, in the W/H-stratified groups, the effect of IGF-I on racial disparity in risk of CR cancer among obese group (W/H >0.85) was greater than it was among non-obese group (W/H ≤0.85).

When compared with our results in breast cancer, we found that the role of IGF-I in the racial disparity in CR cancer differed among exogenous E users (Table 5): a greater mediating effect of IGF-I on the racial disparity in CR cancer was found in nonusers or E-only users (a*b, 0.10 in nonusers; 0.11 in E-only users) than in E+P users (a*b = 0.02). In path c, racial disparity in CR cancer risk was observed in nonusers; thus, IGF-I may act as a mediator of that racial disparity in those women. Additionally, given that among E+P users, AA women had higher IGF-I levels and CR cancer risk than white women had (even if the results were not significant), the racial disparity in CR cancer risk was not affected by E+P's confounding effect on the associations among race, E+P usage, and CR cancer risk (Table S4).

Finally, we analyzed the racial disparity in the risk of any of nine types of obesity-related cancer that could be mediated by IGF-I; the results were similar to those we found for CR cancer (Tables 6 and S5). In addition, for each cancer, when obesity status was stratified by usage of exogenous E, the results were not significantly different.

Discussion

In this retrospective study of a large cohort of postmenopausal women, we found that compared with white women, AA women had higher bioavailable IGF-I levels and their higher risk of CR cancer, after accounting for IGF-I, was no longer significant. IGF-I levels were associated with breast and CR cancers even after controlling for race. Further, when stratified by obesity status, bioavailable IGF-I among viscerally obese and overall non-obese groups was a statistically strong mediator, reducing the racial disparity in obesity-relevant breast cancer risk by 30% and CR cancer risk by 60%. In addition, when stratified by exogenous E use status, among E+P users, the higher IGF-I levels in AA women mediated the racial disparity in breast cancer risk, whereas among nonusers and E-only users, the racial differences in IGF-I accounted for the racial disparity in CR cancer risk. To our knowledge, this is the first study to combine obesity and exogenous E usage as effect modifiers to evaluate the role of IGF-I in mediating the racial disparity in the risk of obesity-relevant cancers, including breast and CR cancers. We used two complementary statistical methods together to assess the effect of IGF-I as a mediator; this approach enabled us not only to use our entire study population in the analysis but also to estimate directly the mediation effect of IGF-I.

Obesity, specifically visceral obesity, is a central driver of bioavailable IGF-I through the GH–IGF pathway and systemic effects such as hyperglycemia and insulin resistance.(8,11,14,15,35) However, the obesity–IGF-I relationship is not linear. For example, a decreased IGF-I level was observed in obesity, possibly due to the negative feedback loop of lower GH.(12) In addition, this relationship differs by race (12), probably depending on body-fat distribution. Consistent with previous studies (9,12,36), our study showed that obese white women had increased IGF-I levels regardless of fat-distribution pattern but that

AA women had increased IGF-I levels in only visceral obesity, as measured via W/H; these results suggest an important role of visceral adiposity, with its local (i.e., paracrine secretions of pro-inflammatory factors) and systemic effect (14) on racial differences in IGF-I levels. Further, in this study, the higher IGF-I levels in abdominally obese AA women than their white counter parts strongly act as a mediator of the racial disparity in obesity-related breast and CR cancer risk. This concurred with our hypothesis, indicating that the association between IGF-I and racial cancer disparity interacts with obesity status with different types of adiposity measures.

In addition, the interplay between IGF-I and estrogen acts synergistically in postmenopausal women, up-regulating both receptors' downstream cellular cascades, thereby resulting in the enhanced anabolic state necessary for tumor growth and development.(16-19) Similarly, exogenous estrogen interacts with IGF-I to affect cancer risk, and the extent of this influence may depend on the type of estrogen usage. E-only users than nonusers, have lower IGF-I levels, owing to the first-pass metabolic effect of suppressed hepatic IGF-I production. Users of E+P, however, have different levels of IGF-I and cancer risk due to non–progesterone-like effects (i.e., different effect from natural progesterone) contrasting with the hepatocellular effect of oral estrogen (20-25), but the mechanism is unclear. In this study, decreased IGF-I levels in E-only users were observed in both AA and white women, but in E+P users, a different pattern was shown; among AA women, users had higher IGF-I levels than nonusers had, while among white women, users had lower levels than nonusers had. This difference explains the highest racial difference in IGF-I levels in E+P users in relation to obesity-related breast and CR cancer risk, and the higher IGF-I levels in AA than in white women in this group explain the significant racial disparity in breast cancer risk. Interestingly, we found that the white women in the E+P group—despite their lower IGF-I levels—had a higher risk of breast cancer than their AA counterparts had; this may be due to genetic (37) and environmental factors such as diet (4,38,39) in addition to the confounding factor such as E+P users that are associated with white women and higher risk of breast cancer. Overall, these findings support our hypothesis that the association between IGF-I and racial disparity in obesity-related cancer is modified by exogenous E use status.

This study has limitations. We measured serum IGF-I levels only at baseline, which prevented us from evaluating possible changes over time in circulating levels. We acknowledge that long freezer storage of biological specimens might potentially lead to degradation which could affect the measurements of the IGF-I. We could not substratify women by transdermal vs. oral estrogen usage, but the small proportion (6%) of transdermal users may not have affected the overall analytic results. This study evaluated the hypothesis-driven questions retrospectively (i.e., non-randomized study) among postmenopausal women; thus, the results could be prone to selection and information bias and limit the generalizability to other populations. AA women made up only 6% of our study population, which may lead to an increased risk of type II errors. In addition, the self-reported basis of race information may affect the biologic accuracy of race. About 80% of IGF-I proteins are bound to IGFBP-3, and 19% of IGF-I is bound to other binding proteins, resulting in less than 1% of IGF-I being free, which speaks to the bioactivity of IGF-I. We used the level of free bioavailable IGF-I and replaced missing data with the molar ratios of total IGF-I/IGFBP-3, which roughly represents bioavailable IGF-I.(31)

Conclusions

In conclusion, our findings suggest that in postmenopausal women, bioavailable IGF-I accounts for a substantial amount of the racial disparity in risk of obesity-related cancers such as breast and CR cancers. Body-fat distribution and exogenous estrogen usage may contribute to the connected hormonal pathways associated with the racial disparities in IGF-I levels and obesity-related cancer risk, and further studies are needed to explore these complicated mechanisms. Our findings may provide improved understanding of the role of bioavailable IGF-I in explaining the racial disparity directly or indirectly in obesity-related cancer risk and emphasize the potentially important roles of obesity and exogenous estrogen usage in reducing the racial disparity in cancer risk among postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of participants, stratified by race, in the Women's Health Initiative Observational Study

	White Women (n = 2,425)		African American Women (n = 164)	
Variable	**n**	**(%)**	**n**	**(%)**
Age in years, median (range)	66	(50-79)	62	(50-79) *
Education				
≤ High school	707	(29.2)	61	(37.2) *
> High school	1,718	(70.8)	103	(62.8)
Marital status				
Not married	908	(37.4)	99	(60.4) *
Married	1,517	(62.6)	65	(39.6)
Family history of cancer				
No	859	(35.4)	77	(47.0) *
Yes	1,566	(64.6)	87	(53.0)
Family history of breast cancer				
No	1,947	(80.3)	139	(84.8)
Yes	478	(19.7)	25	(15.2)
Family history of colorectal cancer				
No	2,064	(85.1)	134	(81.7)
Yes	361	(14.9)	30	(18.3)
Cardiovascular disease ever				
No	1,954	(80.6)	123	(75.0) *
Yes	471	(19.4)	41	(25.0)
Diabetes ever ¥				
No	2,308	(95.2)	131	(79.9) *
Yes	117	(4.8)	33	(20.1)
Hypertension ever				
No	1,643	(67.8)	59	(36.0) *
Yes	782	(32.2)	105	(64.0)
High cholesterol requiring pills ever				
No	2,097	(86.5)	134	(81.7)
Yes	328	(13.5)	30	(18.3)
Oral contraceptive use				
Never	1,532	(63.2)	104	(63.4)
Ever	893	(36.8)	60	(36.6)
Exogenous estrogen use				
No	1,026	(42.3)	95	(57.9) *
Yes	1,399	(57.7)	69	(42.1)

	White Women (n = 2,425)		African American Women (n = 164)	
Variable	**n**	**(%)**	**n**	**(%)**
Exogenous estrogen (E-only) use				
No	1,611	(66.4)	114	(69.5)
Yes	814	(33.6)	50	(30.5)
Exogenous estrogen (E+P) use				
No	1,672	(68.9)	143	(87.2) *
Yes	753	(31.1)	21	(12.8)
History of hysterectomy or oophorectomy				
No	1,633	(67.3)	86	(52.4) *
Yes	792	(32.7)	78	(47.6)
Age at menarche in years, median (range)	13	(≤ 9 - ≥ 17)	13	(≤ 9 - ≥ 17)
Age at menopause in years, median (range)	50	(20 - 60)	50	(30 -60) *
METs·hour·week^{-1} ¶				
<10	1,156	(47.7)	115	(70.1) *
≥10	1,269	(52.3)	49	(29.9)
Smoking status				
Never	1,194	(49.2)	71	(43.3)
Past	1,096	(45.2)	83	(50.6)
Current	135	(5.6)	10	(6.1)
Total HEI-2005 score, median (range) ‡	71.0	(32.2 - 91.8)	67.7	(34.1 - 87.4) *
Dietary alcohol per day in g, median (range)	1.015	(0.0 - 243.3)	0.017	(0.0 - 70.3) *
BMI in kg/m^2, median (range)	26.1	(14.4 - 65.5)	30.5	(18.6 - 61.2) *
Waist circumference in cm, median (range)	83.0	(39.0 - 177.0)	91.0	(70.5 - 133.5) *
Waist/hip ratio, median (range)	0.800	(0.366 - 1.893)	0.823	(0.642 - 1.005) *
Free IGF-I in ng/ml, median (range)	0.234	(0.015 - 2.643)	0.332	(0.017 - 2.505) *

E, estrogen; E+P, estrogen + progestin; MET, metabolic equivalent; HEI-2005, Healthy Eating Index-2005; BMI, body mass index; IGF-I, insulin-like growth factor-I.

* P <0.05, chi-square test or Wilcoxon's rank-sum test.

¥ A participant was considered to have diabetes if a doctor had ever said that she had diabetes when she was not pregnant.

¶ Physical activity was estimated via MET from recreational physical activity combining walking and mild, moderate, and strenuous physical activity; each activity was assigned a MET value corresponding to intensity, and the total MET·hours·week^{-1} was calculated by multiplying the MET level for the activity by the hours exercised per week and summing the values for all activities. The total MET was stratified into two groups, with 10 METs as the cutoff.(40,41)

‡ HEI-2005 is a measure of diet quality that assesses adherence to the U.S. Department of Agriculture's Dietary Guidelines for Americans. The total HEI score ranges from 0 to 100, with higher scores indicating higher diet quality.

Table 2

Mediation effect of free insulin-like growth factor-I on the relationship between race and breast cancer risk, stratified by obesity status

	Non-Obese Group					Obese Group				
	Path a	**Path b**	**Path c**	**Path c′**	**(a*b)**	**Path a**	**Path b**	**Path c**	**Path c′**	**(a*b)**
Effect modifier	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on breast cancer risk**	**HR† of race on breast cancer risk**	**HR† of race on breast cancer risk adjusted by *free IGF-I***	**Indirect effect¥**	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on breast cancer risk**	**HR† of race on breast cancer risk**	**HR† of race on breast cancer risk adjusted by *free IGF-I***	**Indirect effect¥**
BMI	**BMI <30.0 (n = 1,888)**					**BMI ≥30.0 (n = 701)**				
Effect size	**0.19**	**1.47**	1.19	1.08	**0.07**	0.06	**1.66**	1.36	1.34	0.03
95% CI	**0.12–0.25**	**1.12–1.92**	0.76–1.85	0.69–1.69	**0.01–0.13***	-0.02–0.13	**1.13–2.45**	0.89–2.08	0.88–2.05	-0.02–0.08*
P value	**<0.05**	**0.01**	0.46	0.75	**0.02***	0.13	**0.01**	0.15	0.18	0.22*
Waist	**Waist ≤88 cm (n = 1,636)**					**Waist >88 cm (n = 953)**				
Effect size	**0.17**	**1.46**	1.32	1.22	**0.06**	**0.08**	**1.56**	1.25	1.20	0.04
95% CI	**0.10–0.24**	**1.08–1.96**	0.85–2.07	0.78–1.92	**0.002–0.13***	**0.01–0.15**	**1.12–2.17**	0.83–1.89	0.79–1.81	-0.01–0.08*
P value	**<0.05**	**0.01**	0.22	0.39	**0.04***	**0.02**	**0.01**	0.29	0.39	0.09*
w/h Ratio	**w/h Ratio ≤0.85 (n = 1,897)**					**w/h Ratio >0.85 (n = 692)**				
Effect size	**0.10**	**1.51**	1.23	1.16	**0.04**	**0.16**	**1.48**	1.38	1.28	0.06
95% CI	**0.04–0.16**	**1.16–1.97**	0.86–1.76	0.81–1.67	**0.002–0.08***	**0.06–0.25**	**1.00–2.20**	0.79–2.42	0.73–2.27	-0.01–0.13*
P value	**<0.05**	**<0.05**	0.27	0.42	**0.04***	**<0.05**	**0.05**	0.26	0.39	0.10*

IGF-I, insulin-like growth factor I; HR, hazard ratio; BMI, body mass index; CI, confidence interval; w/h ratio, waist-to-hip ratio.

Note: Proportions explained by free IGF-I for racial disparity in breast cancer risk = 58.9%, 32.2% and 29.1% among non-obese group (BMI <30.0, waist ≤88 cm, and waist/hip ratio [W/H] ≤0.85, respectively) and = 6.4%, 21.3%, and 25.4% among obese-group (BMI ≥30.0, waist >88 cm, and W/H >0.85, respectively). Numbers in bold face are statistically significant.

† Multivariate regression was adjusted by covariates (age, education, marital status, family history of breast cancer, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, total Healthy Eating Index-2005 score, dietary alcohol, smoking status, physical activity, oral contraceptive use, history of hysterectomy or oophorectomy, age at menarche, and age at menopause); effect-modifier variables (obesity and exogenous estrogen use), when not evaluated as effect modifier variables, were adjusted as a covariate; waist circumference and waist/hip ratio were exclusively adjusted, as were E-only and E+P use.

¥ Indirect effect indicates the effect of free IGF-I that mediates the relationship between race and breast cancer risk.

* 95% CIs and P values were estimated by using a delta method to test for a mediation effect of free IGF-I on the relationship between race and breast cancer risk.

Table 3

Mediation effect of free insulin-like growth factor-I on the relationship between race and breast cancer risk, stratified by exogenous estrogen usage status

		Exogenous Estrogen Usage Status								
		Nonusers (n = 1,121)			E-only users (n = 694)			E+P users (n = 604)		
Path	**Description**	**Effect size**	**95% CI**	**P value**	**Effect size**	**95% CI**	**P value**	**Effect size**	**95% CI**	**P value**
Path a	Effect size[†] of race on free IGF-I	**0.10**	**0.04–0.17**	**<0.05**	**0.13**	**0.05–0.21**	**<0.05**	**0.22**	**0.08–0.37**	**<0.05**
Path b	HR[†] of free IGF-I on breast cancer risk	**1.68**	**1.19–2.37**	**<0.05**	1.34	0.85–2.12	0.21	**1.50**	**1.00–2.25**	**0.05**
Path c	HR[†] of race on breast cancer risk	**1.59**	**1.01–2.48**	**0.04**	1.06	0.62–1.80	0.85	0.83	0.36–1.88	0.65
Path c′	HR[†] of race on breast cancer risk adjusted by free IGF-I	1.49	0.95–2.34	0.09	1.02	0.60–1.74	0.95	0.76	0.34–1.73	0.52
a*b	Indirect effect of free IGF-I that mediates relationship between race and breast cancer risk	0.05	-0.001–0.11[*]	0.06[*]	0.04	-0.03–0.10[*]	0.25[*]	0.09	-0.05–0.23[*]	0.19[*]

E, estrogen; E+P, estrogen + progestin; CI, confidence interval; IGF-I, insulin-like growth factor-I; HR, hazard ratio.

Note: Proportions explained by free IGF-I for racial disparity in breast cancer risk = 16.7% among nonusers, 66.2% among E-only users, and 27.0% among E+P users. Numbers in bold face are statistically significant.

[†]Multivariate regression was adjusted by covariates (age, education, marital status, family history of breast cancer, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, total Healthy Eating Index-2005 score, dietary alcohol, smoking status, physical activity, oral contraceptive use, history of hysterectomy or oophorectomy, age at menarche, and age at menopause); effect-modifier variables (obesity and exogenous estrogen use), when not evaluated as effect modifier variables, were adjusted as a covariate; waist circumference and waist/hip ratio were exclusively adjusted, as were E-only and E+P use.

[*]95% CIs and P values were estimated by using a delta method to test for a mediation effect of free IGF-I on the relationship between race and breast cancer risk.

Table 4

Mediation effect of free insulin-like growth factor-I on the relationship between race and colorectal cancer risk, stratified by obesity status

	Non-Obese Group					Obese Group				
Path a	**Path b**	**Path c**	**Path c′**	**(a*b)**	**Path a**	**Path b**	**Path c**	**Path c′**	**(a*b)**	
Effect modifier	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on colorectal cancer risk**	**HR† of race on colorectal cancer risk**	**HR† of race on colorectal cancer risk adjusted by *free IGF-I***	**Indirect effect¥**	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on colorectal cancer risk**	**HR† of race on colorectal cancer risk**	**HR† of race on colorectal cancer risk adjusted by *free IGF-I***	**Indirect effect¥**
BMI	**BMI <30.0 (n = 1,888)**					**BMI ≥30.0 (n = 701)**				
Effect size	**0.19**	**2.21**	1.34	1.13	**0.15**	0.06	**2.12**	1.54	1.43	0.04
95% CI	**0.12–0.25**	**1.53–3.17**	0.77–2.34	0.64–2.00	**0.04–0.26***	-0.02–0.13	**1.37–3.28**	0.94–2.52	0.86–2.37	-0.02–0.11*
P value	**<0.05**	**<0.05**	0.31	0.67	**0.01***	0.14	**<0.05**	0.09	0.17	0.21*
Waist	**waist ≤88 cm (n = 1,636)**					**waist >88 cm (n = 953)**				
Effect size	**0.17**	**1.88**	1.67	1.50	**0.11**	**0.08**	**2.41**	1.29	1.15	0.07
95% CI	**0.10–0.24**	**1.22–2.90**	0.89–3.11	0.80–2.82	**0.01–0.20***	**0.01–0.15**	**1.66–3.50**	0.82–2.03	0.72–1.83	-0.01–0.15*
P value	**<0.05**	**<0.05**	0.11	0.20	**0.03***	**0.02**	**<0.05**	0.27	0.56	0.07*
w/h Ratio	**w/h Ratio ≤0.85 (n = 1,897)**					**w/h Ratio >0.85 (n = 692)**				
Effect size	**0.10**	**2.14**	1.29	1.19	**0.08**	**0.15**	**2.13**	1.64	1.39	0.12
95% CI	**0.04–0.16**	**1.51–3.04**	0.79–2.10	0.73–1.95	**0.01–0.14***	**0.06–0.25**	**1.34–3.37**	0.93–2.87	0.78–2.50	-0.01–0.24*
P value	**<0.05**	**<0.05**	0.31	0.49	**0.02***	**<0.05**	**<0.05**	0.09	0.27	0.07*

IGF-I, insulin-like growth factor I; HR, hazard ratio; BMI, body mass index; CI, confidence interval; w/h ratio, waist-to-hip ratio.

Note: Proportions explained by free IGF-I for racial disparity in colorectal cancer risk = 60.9%, 24.2% and 34.7% among non-obese group (BMI <30.0, waist ≤88 cm, and waist/hip ratio [W/H] ≤0.85, respectively) and = 20.2%, 48.8%, and 38.3% among obese-group (BMI ≥30.0, waist >88 cm, and W/H >0.85, respectively). Numbers in bold face are statistically significant.

† Multivariate regression was adjusted by covariates (age, education, marital status, family history of colorectal cancer, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, total Healthy Eating Index-2005 score, dietary alcohol, smoking status, physical activity, oral contraceptive use, history of hysterectomy or oophorectomy, age at menarche, and age at menopause); effect-modifier variables (obesity and exogenous estrogen use), when not evaluated as effect modifier variables, were adjusted as a covariate; waist circumference and waist/hip ratio were exclusively adjusted, as were E-only and E+P use.

¥ Indirect effect indicates the effect of free IGF-I that mediates the relationship between race and colorectal cancer risk.

* 95% CIs and P values were estimated by using a delta method to test for a mediation effect of free IGF-I on the relationship between race and colorectal cancer risk.

Table 5

Mediation effect of free insulin-like growth factor-I on the relationship between race and colorectal cancer risk, stratified by exogenous estrogen usage status

		Exogenous Estrogen Usage Status								
		Nonusers (n = 1,121)			E-only users (n = 694)			E+P users (n = 604)		
Path	**Description**	**Effect size**	**95% CI**	**P value**	**Effect size**	**95% CI**	**P value**	**Effect size**	**95% CI**	**P value**
Path a	Effect size[†] of race on free IGF-I	**0.10**	**0.04–0.17**	**<0.05**	**0.13**	**0.05–0.21**	**<0.05**	**0.22**	**0.07–0.36**	**<0.05**
Path b	HR[†] of free IGF-I on colorectal cancer risk	**2.57**	**1.80–3.66**	**<0.05**	**2.40**	**1.29–4.46**	**0.01**	1.09	0.51–2.33	0.82
Path c	HR[†] of race on colorectal cancer risk	**1.86**	**1.17–2.96**	**0.01**	0.98	0.47–2.05	0.95	1.16	0.33–4.04	0.82
Path c′	HR[†] of race on colorectal cancer risk adjusted by free IGF-I	**1.66**	**1.03–2.67**	**0.04**	0.82	0.38–1.75	0.60	1.12	0.31–4.04	0.86
a*b	Indirect effect of free IGF-I that mediates relationship between race and colorectal cancer risk	**0.10**	**-0.001–0.20**[*]	**0.05**[*]	**0.11**	**0.003–0.22**[*]	**0.04**[*]	0.02	-0.14–0.18[*]	0.81[*]

E, estrogen; E+P, estrogen + progestin; CI, confidence interval; IGF-I, insulin-like growth factor-I; HR, hazard ratio.

Note: Proportions explained by free IGF-I for racial disparity in colorectal cancer risk = 23.7% among nonusers, 86.9% among E-only users, and 22.9% among E+P users. Numbers in bold face are statistically significant.

[†]Multivariate regression was adjusted by covariates (age, education, marital status, family history of colorectal cancer, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, total Healthy Eating Index-2005 score, dietary alcohol, smoking status, physical activity, oral contraceptive use, history of hysterectomy or oophorectomy, age at menarche, and age at menopause); effect-modifier variables (obesity and exogenous estrogen use), when not evaluated as effect modifier variables, were adjusted as a covariate; waist circumference and waist/hip ratio were exclusively adjusted, as were E-only and E+P use.

[*]95% CIs and P values were estimated by using a delta method to test for a mediation effect of free IGF-I on the relationship between race and colorectal cancer risk.

Table 6

Mediation effect of free insulin-like growth factor-I on the relationship between race and obesity-related cancer risk, stratified by obesity status

	Non-Obese Group					Obese Group				
	Path a	**Path b**	**Path c**	**Path c′**	**(a*b)**	**Path a**	**Path b**	**Path c**	**Path c′**	**(a*b)**
Effect modifier	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on obesity-related cancer risk**	**HR† of race on obesity-related cancer risk**	**HR† of race on obesity-related cancer risk adjusted by *free IGF-I***	**Indirect effect¥**	**Effect size† of race on free IGF-I**	**HR† of free IGF-I on obesity-related cancer risk**	**HR† of race on obesity-related cancer risk**	**HR† of race on obesity-related cancer risk adjusted by *free IGF-I***	**Indirect effect¥**
BMI	**BMI <30.0 (n = 1,888)**					**BMI ≥30.0 (n = 701)**				
Effect size	**0.19**	**1.35**	1.15	1.07	**0.06**	0.05	**1.56**	**1.41**	**1.37**	0.02
95% CI	**0.12–0.26**	**1.10–1.65**	0.83–1.59	0.77–1.49	**0.01–0.11***	-0.02–0.13	**1.18–2.05**	**1.05–1.90**	**1.02–1.85**	-0.02–0.06*
P value	**<0.05**	**<0.05**	0.40	0.69	**0.03***	0.17	**<0.05**	**0.02**	**0.04**	0.25*
Waist	**waist ≤88 cm (n = 1,636)**					**waist >88 cm (n = 953)**				
Effect size	**0.17**	1.26	1.32	1.25	0.04	**0.08**	**1.65**	1.20	1.13	0.04
95% CI	**0.10–0.24**	1.00–1.59	0.93–1.86	0.88–1.78	-0.01–0.09*	**0.01–0.15**	**1.30–2.09**	0.91–1.58	0.85–1.49	-0.01–0.08*
P value	**<0.05**	0.06	0.12	0.21	0.11*	**0.03**	**<0.05**	0.20	0.41	0.08*
w/h Ratio	**w/h Ratio ≤0.85 (n = 1,897)**					**w/h Ratio >0.85 (n = 692)**				
Effect size	**0.10**	**1.34**	1.28	1.23	**0.03**	**0.15**	**1.55**	1.23	1.12	0.07
95% CI	**0.05–0.16**	**1.09–1.64**	0.98–1.67	0.94–1.61	**0.00–0.06***	**0.06–0.24**	**1.16–2.06**	0.85–1.79	0.76–1.63	-0.01–0.14*
P value	**<0.05**	**0.01**	0.07	0.13	**0.05***	**<0.05**	**<0.05**	0.27	0.57	0.07*

IGF-I, insulin-like growth factor I; HR, hazard ratio; BMI, body mass index; CI, confidence interval; w/h ratio, waist-to-hip ratio.

Note: Proportions explained by free IGF-I for racial disparity in obesity-related cancer risk = 52.9%, 20.2% and 18.7% among non-obese group (BMI <30.0, waist ≤88 cm, and waist/hip ratio [W/H] ≤0.85, respectively) and = 9.5%, 37.2%, and 49.8% among obese-group (BMI ≥30.0, waist >88 cm, and w/h >0.85, respectively). Numbers in bold face are statistically significant.

† Multivariate regression was adjusted by covariates (age, education, marital status, family history of cancer, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, total Healthy Eating Index-2005 score, dietary alcohol, smoking status, physical activity, oral contraceptive use, history of hysterectomy or oophorectomy, age at menarche, and age at menopause); effect-modifier variables (obesity and exogenous estrogen use), when not evaluated as effect modifier variables, were adjusted as a covariate; waist circumference and waist/hip ratio were exclusively adjusted, as were E-only and E+P use.

¥ Indirect effect indicates the effect of free IGF-I that mediates the relationship between race and obesity-related cancer risk.

* 95% CIs and P values were estimated by using a delta method to test for a mediation effect of free IGF-I on the relationship between race and obesity-related cancer risk.