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Mediating Effects of Cancer Risk Factors on the Association between Race and Cancer Incidence; Analysis of the NIH-AARP Diet and Health Study

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Abstract

INTRODUCTION—Racial disparities exist in both the prevalence of cancer-related risk factors and incidence of cancer. The objective of this study is to determine if cancer-related risk factors mediate the association between race and cancer incidence.

METHODS—We performed a prospective cohort analysis using data National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, years 1995 through 2011. We compared differences in baseline characteristics between Black and White participants using Chi-Square tests and Wilcoxon tests, as appropriate. We determined risk of any cancer and the most common cancer types (i.e., breast, prostate, and colorectal) using Cox Proportional hazards models, adjusted for age, sex, marital status, education, health status, region, and adherence to guidelines on cancer-related risk factors (i.e., BMI, smoking status, physical activity, nutrition, and alcohol consumption). We examined the mediation effect of cancer-related risk factors on the association between race and cancer incidence.

RESULTS—Among 425,152 participants, 16,110 (3.79%) were Black, and 409,042 (96.21%) were White. White participants were more likely to be aged 65 and older (35.33% vs. 25.93%), male (60.88% vs. 42.67%), married (70.37% vs. 48.26%), reside in the West (30.14% vs. 23.88%), be physically active (46.72% vs. 41.94%), and have higher adherence scores (3.14 vs. 3.04). Blacks had reduced risk of breast cancer (adjusted HR: 0.82, 95% CI: 0.74 – 0.90), but higher risk of prostate (adjusted HR: 1.86, 95% CI: 1.75 – 1.98) and colorectal (adjusted HR: 1.17, 95% CI: 1.05 – 1.31) compared with Whites. Nutrition mediated the association between race and breast cancer (6.35% mediated, $p < 0.01$), while BMI mediated the association between race and colorectal cancer (7.99% mediated, $p < 0.01$).

CONCLUSIONS—Blacks were at reduced risk of breast cancer but increased risks for prostate and colorectal cancer incidence. Nutrition and BMI exerted small, but significant mediating effects on the racial disparity in risk of breast and colorectal cancer, respectively.

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Conflict of Interest:None

Keywords

cancer incidence; risk factors; mediation; racial disparities

INTRODUCTION

Modifiable risk factors, including diet, physical activity, body mass index (BMI), and smoking have consistently been associated with cancer risk[1–4]. The American Institute for Cancer Research/ World Cancer Research Fund provides specific guidelines on the appropriate levels for each of these modifiable risk factors, and greater adherence to these guidelines has been associated with reduced risk of cancer among adults [5–8]. However, multiple studies show significantly poor adherence [9–11], increasing prevalence of obesity [12–14] as well as consistently low levels of physical activity among US adults [15]. Racial disparities in the incidence of the major cancers have persisted among US adults for many decades [16]. Blacks are more likely to develop prostate, colorectal and ovarian cancers, while White women are more likely to develop breast cancer. Racial disparities also exist in the prevalence of modifiable cancer risk factors; although overall adherence to the American Institute of Cancer Research/ World Cancer Research Fund guidelines is low in all racial groups, Blacks are more likely to be obese and less physically active compared with other races [17]. Disparities in cancer-related risk factors may contribute to the observed disparities in cancer incidence; however, efforts to estimate the extent to which these modifiable cancer risk factors mediate the association between race and cancer incidence have been limited by the lack of high-quality prospective data with adequate Black sample sizes. The purpose of this paper is to estimate the direct, indirect and total effect of race (Black vs. White) on cancer incidence, accounting for the mediating effects of diet, physical activity, smoking, overweight/obesity and excess alcohol use as well as a composite measure of overall adherence to American Institute of Cancer Research/ World Cancer Research Fund guidelines.

METHODS**Study Participants**

Data for this study was obtained from the prospective National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. The cohort consists of 566,398 adults AARP members aged 50–71 years recruited in 1995–1996. At enrollment, participants completed a baseline questionnaire assessing lifestyle and behavioral risk factors such as smoking, alcohol, physical activity and dietary patterns. Participants with self-reported cancer at baseline (n=49,318), proxy respondents (n=15,760), death record data only (n=4,255) or who had missing data on behavioral risk factors (62,347) and race (9,566) were excluded from analysis. The final analysis included 425,152 adults; 16,110 Blacks and 409,042 Whites with no prior history of any cancer before completing the baseline questionnaire (Figure 1).

Cancer Incidence

Incident cancer cases were identified through a linkage with cancer registries through December 31, 2011. Detailed information for each cancer diagnosis was obtained on diagnosis date, stage, grade, and first course of treatment within the first year of diagnosis. Incident cancer ascertainment has been estimated to be about 90% complete [18]. In this study, data on any cancer, breast, colorectal, and prostate cancer cases were utilized for analysis.

Primary Exposure Variable

The primary exposure of interest in this study is self-reported race/ethnicity at baseline. Participants were defined as either Black/African American or White.

Cancer-Related Risk Factors

The American Cancer Society (ACS) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) developed specific guidelines regarding body weight, physical activity, diet, smoking and alcohol consumption to guide cancer prevention efforts [19, 20]. Here, we assessed adherence to the WCRF/AICR guidelines on five cancer-related risk factors; physical activity, body mass index (BMI in kg/m²), alcohol use, smoking and nutrition (fruit and vegetable intake). We used self-reported measures obtained during the 12-month period prior to enrollment. For analysis, we dichotomized physical activity as greater than or equal to three times per week within past 12 months that caused increased breathing, heart rate, or sweat. Smoking was dichotomized as current smoker or current/former smoker. Alcohol use was categorized as high/low based on gender specific consumption: 7 (females) or 14 (males) alcoholic drinks per week. Nutritional adherence was defined based on the total number of fruit and vegetable servings per day. BMI and nutritional adherence were defined as continuous variables in all models. We additionally calculated an adherence score for each participant based on the five cancer-related risk factors. Each participant was assigned a score for each risk factor; 1 if fully adherent, 0.5 if partially adherent, and 0 if not adherent (Appendix 1). Each risk factor was weighted equally and adherence scores were summed up to create a total adherence score ranging from 0–5.

Participant Characteristics

Participant characteristics examined in this study were self-reported age, gender, marital status, education, health status, and residence. Age were categorized into five groups; less than 55 years, 55 – 59, 60 – 64, 65 – 69, and greater than equal to 70 years. Marital status was categorized as married, widowed, divorced, separated, and never married. Education was categorized as less than high school, high school completion, post-high school training, some college education, and college and post-graduate education. Health status was categorized as excellent, very good, good, fair, and poor based on participants general health condition at baseline. We defined residence based on participant's state of residence at baseline and categorized according to the US Census definition (i.e., Midwest, Northeast, South, and West) [21].

Mediation Analysis

Mediators are variables that are on the causal pathway between an exposure and outcome variable, and explain in part the effect of exposure on outcome [22–28]. In this study we employed the counterfactual approach to mediation analysis proposed by Valeri & VanderWeele (2013) as this method allows for the decomposition of the total effect into a direct effect (main effect of exposure on outcome not through the mediator) and the indirect effect (the effect of the exposure on the outcome through the mediator) while accounting for exposure-mediator interactions and non-linearities [27–29]. Further, the counterfactual mediation approach allows for valid inferences of longitudinal data under the assumptions that there are measured covariates controlling for confounding of the relationships between the 1) exposure and outcome, 2) mediator and outcome, 3) exposure and mediator, and 4) that none of the mediator-outcome confounders are affected by the exposure [27, 28].

Two common mediation practices are the difference and product methods. The difference method consists of regressing two models on the outcome given the primary exposure, mediator and confounders (Model A) and on the outcome given the exposure and confounders (Model B). The mediation effect can be estimated from the difference method by taking the difference between the coefficients for the exposure estimated from these two regression models (Model C) [27, 28]. The mediation effect estimated from model C is interpreted as the reduction in the independent effect of exposure on the outcome while controlling for the mediator. In the following models, let a , c , and m , be the variables for the exposure, confounder, and mediator, respectively.

$$\text{Model A} = E[Y|a, m, c] = \theta_{A0} + \theta_{A1} a + \theta_{A2} m + \theta'_{A3} c$$

$$\text{Model B} = E[Y|a, c] = \theta_{B0} + \theta_{B1} a + \theta'_{B3} c$$

$$\text{Model C} = \text{Difference Method Indirect Effect} = \theta_{B1} - \theta_{A1}$$

In contrast, to estimate the indirect effect using product method introduced by Baron and Kenny (1986) [30], the mediator is regressed on the exposure and confounders (Model D), and the outcome is regressed on the exposure, mediator, and confounders (Model A). Lastly, the indirect effect (Model E) is estimated by taking the product of the coefficient of the exposure in model D times the coefficient for the mediator in model E.

$$\text{Model D} = E[M|a, c] = \theta_{D0} + \theta_{D1} a + \theta'_{D3} c$$

$$\text{Model E} = \text{Product Method Indirect Effect} = \theta_{D1} \times \theta_{A2}$$

However, while these mediation statistical approaches have been commonly used there are two important limitations when performing these methods. First, there remains unmeasured confounding of the mediator and outcome relationship even when controlling for exposure and outcome confounding. Second, there is possibility for biased indirect and direct effect estimates if the interactions between the effects of the exposure and mediator are present [28]. As a result, we adopted the causal mediation analysis methods to determine the indirect (mediation) and direct effects on the relationship between exposure, mediator, and outcome. As explained by Valeri and VanderWeele (2013), we accounted for the exposure and mediator interaction while modeling on the outcome (Model F) [28].

$$\text{Model F} = [Y|a, m, c] = \theta_{F0} + \theta_{F1} a + \theta_{F2} m + \theta_{F3} am + \theta'_{A4} c$$

Given the aforementioned assumptions for the counterfactual mediation approach the natural direct effect (NDE) and the natural indirect effect (NIE) are estimated by the following equations, where we compare exposure present (a) and absent (a^*):

$$\text{NDE}(a, a^*; a^*) = (\theta_{F1} + \theta_{F3} (\theta_{D0} + \theta_{D1} a^* + \theta'_{D3} E[C])) (a - a^*)$$

$$\text{NIE}(a, a^*; a) = (\theta_{F2} \theta_{D1} + \theta_{F3} \theta_{D1} a) (a - a^*)$$

Using these models, we examined the mediating effects of cancer-related risk factors (i.e., physical activity, obesity, alcohol use, smoking, and nutrition as well as overall adherence) on racial disparities in any, breast, colorectal, and prostate cancer incidence. We determined the mediating effects of cancer-related risk factors on the association between race and cancer incidence using methodology for mediation analysis with survival data developed by Valeri and VanderWeele (2015) [27, 28, 31]. We presented results from mediation analysis as the 1) natural direct effects (NDE) (i.e., the effect of Black race on cancer outcome not through the mediator), 2) natural indirect effect (NIE) (i.e., the effect of race on cancer outcome through the mediator), 3) total effects (i.e., total association between race and cancer outcome), 4) and proportions mediated (i.e., the percent of the total association (on the log hazard scale) that was mediated by cancer-related risk factors) [31]. We present the direct, indirect, total effect as the hazard ratios (HRs) and associated 95% confidence intervals, determined using the delta method [27, 28]. The natural direct effect can be interpreted as the hazard ratio for cancer among Black participants versus White participants if the mediator were set to what it would have been for White participants, while controlling for all known confounding. The natural indirect effects can be interpreted as the hazard ratio for cancer among individuals with both the exposure and mediator present compared to those with exposure present but absence of the mediator, while accounting for all known confounding. We computed the proportion mediated on the log hazard scale using the formula $1 - (\ln HR_{nde} / \ln HR_{total})$ where nde represents the natural direct effect and $total$ represents total effect [27, 28, 31]. We examined whether there was a statistically significant interaction between race and potential mediators by including an interaction term and using the Wald test to assess the significance.

Statistical Analysis

We compared differences in baseline characteristics between Blacks and White participants using Chi-Square (χ^2) test for categorical variables and Wilcoxon tests for continuous variables. We reported categorical variables as proportions, normal continuous variables as the mean and standard deviation (i.e., BMI), and non-normal continuous variables as median with interquartile range (IQR). To estimate the relative risk of any incident cancer between Black and White participants, we fit a series of Cox proportional hazards models with incident cancer as the endpoint. We examined the risk of cancer overall, breast, prostate, and colorectal cancer. We adjusted the estimates for participant age, sex, marital status, education, health status, and region. To account for differences in BMI due to premenopausal cases, we performed secondary analysis excluding participants less than 55 years at baseline. The results of all models were expressed as adjusted hazard ratios (HR) and the corresponding 95% confidence intervals (CI). Individuals were censored at the time of death, loss to follow-up, or the end of cancer mortality ascertainment (December 31, 2011). SAS version 9.4 and STATA version 13 were used for all statistical analysis. We considered two-sided p values <0.05 as statistically significant.

Ethics Statement

The Institutional Review Board of the University of Alabama at Birmingham approved this study.

RESULTS

Among 425,152 eligible study participants, 16,110 were Black (3.8%) and 409,042 were White (96.2%). A flowchart depicting the exclusion of participants from baseline are presented in Figure 1. At baseline, White participants were more likely to be aged 65 and older (Table 1; 35.33% vs. 25.92%, $p < 0.01$), male (60.88% vs. 42.67%, $p < 0.01$), married (70.37% vs. 48.26%, $p < 0.01$), and more physically active (46.72% vs. 41.94%, $p < 0.01$) compared with Blacks. Black participants were more likely to have lower education (27.79% vs. 25.62% high school graduates, $p < 0.01$), reside in the Midwest (11.02% vs. 4.95%, $p < 0.01$), be current smokers (15.55% vs. 12.23%, $p < 0.01$), have higher BMI (28.93 vs. 27.04 kg/m², $p < 0.01$), and higher nutritional adherence (4.01 vs. 3.51 fruit and vegetable servings per day, $p < 0.01$) compared with Whites. Overall, White participants had higher adherence scores when compared with Black participants (3.14 vs. 3.04, $p < 0.01$).

Over the follow-up period, Blacks had a reduced risk of *any* cancer incidence (HR: 0.91, 95% CI: 0.88 – 0.94, Table 2) when compared with White participants. However after adjustments for age, sex, marital status, education, health status, region, and adherence score, this association became attenuated (adjusted HR: 1.01, 95% CI: 0.97 – 1.05). In unadjusted analysis, Blacks had a 19% increased risk of *breast* cancer incidence (HR: 1.19, 95% CI: 1.09 – 1.30), but after adjustment for confounders this association reversed and Blacks were at a 18% reduced risk of breast cancer incidence (adjusted HR: 0.83, 95% CI: 0.74 – 0.90). Blacks had a 15% increased risk of *prostate* cancer before adjustment (HR: 1.15, 95% CI: 1.08 – 1.21), an association that strengthened after adjustment for confounders, and increased to an 85% higher risk of prostate cancer (adjusted HR: 1.86, 95% CI: 1.75 – 1.98).

when compared with White participants. Although there were no associations between race and risk of colorectal cancer in crude analysis, Blacks had a 17% increased risk of *colorectal* cancer (adjusted HR: 1.17, 95% CI: 1.05 – 1.31) after adjustment for confounders.

We examined if cancer-related risk factors mediated the associations between race and cancer incidence. Nutrition (6.35%, $p < 0.01$) and physical activity (0.63%, $p = 0.01$) each weakly mediated the effect of race on breast cancer incidence (Table 3). Thus, a standard deviation increase in nutrition adherence is associated with a 6.35% reduction in the hazard ratio for breast cancer incidence between Black women compared to White women. Black race was positively associated with nutrition adherence ($\beta_a = 0.432$, $p < 0.01$), while nutrition adherence reduced the risk of breast cancer incidence ($\beta_b = -0.027$, $p < 0.01$). We observed no evidence of mediation by any cancer-related risk factor on the association between race and prostate cancer incidence, however BMI significantly mediated the association between race and colorectal cancer incidence (7.99%, $p < 0.01$). Black participants were more likely to have higher BMI ($\beta_a = 0.279$, $p < 0.01$) and BMI was positively associated with the risk of colorectal cancer incidence ($\beta_b = 0.080$, $p < 0.01$). A pathway diagram illustrating the association between race and cancer incidence mediated through BMI and nutrition is outlined in Figure 2. In additional analysis excluding participants less than 55 years at baseline, we observed very similar results for all associations (Appendices 2 & 3). Moreover, the mediating effect of BMI on the association between race and colorectal cancer increased from 7.99% to 16.04% when excluding premenopausal aged participants.

DISCUSSION

In the large, prospective NIH-AARP cohort, we examined the association between race and any cancer, breast, colorectal, and prostate cancer incidence and assessed whether adherence to cancer-related risk factor guidelines mediated this relationship. Blacks were at a non-significantly increased risk of any cancer, but experienced 85% increased risk of prostate cancer, 16% increased risk of colorectal cancer and 17% reduced risk of breast cancer compared with Whites. Adjustment for adherence to cancer-related risk factor guidelines further strengthened these associations. In mediation analysis, the only cancer-related risk factors that mediated the association between race and breast cancer incidence were nutrition and physical activity, while BMI mediated the association between race and colorectal cancer incidence. None of the other cancer related risk factors were significant mediators of the race-cancer incidence association.

To our knowledge, this is the largest study to date to formally evaluate whether adherence to specific cancer risk factor guidelines mediate the association between race and cancer incidence. As in our study, prior studies have reported an almost doubled risk of prostate cancer among Black men compared with White men, and almost 20% higher risk of colorectal cancer among Blacks compared with Whites. For instance, the incidence rate of prostate cancer was 198 per 100,000 among Blacks compared with 114 per 100,000 among Whites in 2009–2013, while for colorectal cancer the incidence rate was 43 per 100,000 and 35 per 100,000 in females, and 58 per 100,000 and 46 per 100,000 in males among Blacks and Whites, respectively [16]. These racial differences have persisted for many decades, despite numerous attempts to identify the causal factor(s) that are either differentially

distributed by race, or predispose Blacks to develop cancer at a higher rate compared with Whites. Epidemiologic causal inference, for instance using mediation analysis, is one approach that can be used to validly delineate the causal effect of 'race', by identifying variables on the causal pathway between race and health outcomes that may be amenable to interventions. As discussed by VanderWeele and Robinson (2014)[32], under a set of assumptions, the 8% mediation effect observed in the association between race and colorectal cancer incidence through BMI can be interpreted as the proportion of the racial difference in colorectal cancer incidence that would be eliminated if BMI values were equalized between races. For breast cancer, there was a 6% mediation effect due to nutrition further meaning that for every standard deviation increase in nutrition among Black women there would be about a 6% reduction in the hazard ratio for breast cancer incidence between Black and White women.

Although modest, these mediation effect estimates suggest that interventions focused on improving adherence to nutrition and BMI may directly eliminate the persistent racial disparities in incidence of certain major cancers. As breast and colorectal cancer are two of the top cancers among US adults, 6–8% reductions in the racial difference in incidence may go a long way in reducing the burden of cancer and deserve further study. Other studies have reported that increasing adherence is associated with about a 10% reduction in all-cancer incidence, and 25% reduction in total cancer mortality in the NIH-AARP dataset [33], as well as in European prospective cohort studies [6]. Very few studies have examined these associations among Blacks. In studies conducted in the Black Women's Health Study only 8.5% of women met at least 4 of the guidelines, and although no association was observed between increased adherence and colorectal cancer incidence [10], increasing adherence was also associated with reduced breast cancer incidence [7]. Another study reported that BMI mediated nearly 18% of the association between Black race and breast cancer mortality, though non-significant [34]. Further studies of large, prospective cohorts with diverse study populations and objective measures of pre- and post- diagnostic data on cancer-related risk factors will be required to better identify other causal mechanisms underlying persistent disparities in cancer risk, and to provide more definitive evidence for whether racial disparities in cancer are due to differential distribution of cancer risk factors, or etiological mechanisms that differ by race. Furthermore, larger studies will be needed to have adequate power to examine specific subtypes of cancer, for instance, examining if nutrition and BMI explain racial differences in the incidence of the aggressive, triple negative breast cancer subtype among Blacks compared with Whites. However, there is some research that suggests that tumor characteristics (i.e., triple negative, HER2, and luminal A and B) and stage at diagnosis mediate up to 23.8% and 34.2% of the association between race and breast cancer mortality, respectively [34]. Furthermore, interventions focused on improving diet quality and reducing the rates of obesity are urgently needed especially among Blacks. The health impact of such programs would extend well beyond cancer prevention, and also have measurable impacts on other chronic diseases such as diabetes and cardiovascular diseases, also with significantly higher rates among Blacks compared with Whites.

There are several limitations relevant to our study. Data on cancer-related risk factors were only assessed at one time point at baseline; therefore we were unable to examine changes over time. However, participants who developed cancer within two years of enrollment were

excluded from analysis to reduce the potential for reverse causation due to lifestyle related changes following cancer diagnosis. Data on cancer-related risk factors were also based on participant self-reports, which may be subject to measurement error and may not be representative of long-term behavior. However, the prospective design of the study reduces the possibility of selection bias, and differential measurement error by cancer status is minimized. The NIH-AARP cohort included adults ages 50 to 71 years at enrollment, therefore results may not be generalizable to the entire US population. In addition, the cohort consisted of less than 4% Black participants, limiting the sample sizes for the analysis of racial differences. Nevertheless, the large cohort sample size and prospective design makes this one of the largest studies to directly examine mediation of racial differences in cancer incidence by established cancer-related modifiable risk factors.

CONCLUSION

Blacks had higher incidence of prostate and colorectal cancers compared with Whites, and adherence to nutrition and BMI guidelines explained 6–8% of this racial difference.

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Appendix 1

Cancer-related risk factors adherence criteria

Risk Factor	Adherence Guideline	Adherence Score
Physical Activity (# of 20 minute activities)	5 per week	1
	1 per month – <5 per week	0.5
	< 1 per month	0
Obesity (BMI)	18.5 – 25 kg/m ²	1
	>25 – 30 kg/m ²	0.5
	<18.5 or >30 kg/m ²	0
Alcohol Use (# drinks/week)	Women 7, Men 14	1
	Women >7 – 14, Men >14 – 28	0.5
	Women >14, Men >28	0
Smoking	Non-smoker	1
	Former smoker	0.5
	Current smoker	0
Nutrition (Fruit And Vegetables Servings per day)	5	1
	3 – <5	0.5
	<3	0

Appendix 2

Hazard Ratios (HRs) and associated 95 % Confidence Intervals (CIs) for cancer incidence and mortality by race. Among 365,679 participants from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. Excluding participants aged 55 and younger at baseline.

Incident Cancer			
	White (Referent) (N = 352,277)	Black / AA ^I (N = 13,402)	p value
Any Cancer			
# Events (%)	90,582 (25.71)	3,163 (23.60)	<0.01
Crude HR (95% CI)	-	0.91 (0.87 – 0.94)	<0.01
Adjusted HR ² (95% CI)	-	1.00 (0.97 – 1.04)	0.99
Adherence Adjusted HR ³ (95% CI)	-	1.00 (0.96 – 1.04)	0.96
Breast Cancer			
# Events (%)	9,613 (2.73)	446 (3.33)	<0.01
Crude HR (95% CI)	-	1.20 (1.10 – 1.32)	<0.01
Adjusted HR ² (95% CI)	-	0.83 (0.75 – 0.91)	<0.01
Adherence Adjusted HR ³ (95% CI)	-	0.82 (0.74 – 0.91)	<0.01
Prostate Cancer			

Incident Cancer			
	White (Referent) (N = 352,277)	Black / AA ¹ (N = 13,402)	p value
# Events (%)	24,472 (6.95)	1,056 (7.88)	<0.01
Crude HR (95% CI)	-	1.12 (1.05 – 1.19)	<0.01
Adjusted HR ² (95% CI)	-	1.79 (1.68 – 1.91)	<0.01
Adherence Adjusted HR ³ (95% CI)	-	1.80 (1.69 – 1.93)	<0.01
Colorectal Cancer			
# Events (%)	8,162 (2.32)	330 (2.46)	0.27
Crude HR (95% CI)	-	1.05 (0.94 – 1.17)	0.38
Adjusted HR ² (95% CI)	-	1.14 (1.02 – 1.28)	0.02
Adherence Adjusted HR ³ (95% CI)	-	1.17 (1.04 – 1.32)	0.01

% - Denotes column percentage - proportion with cancer by race/ethnicity.

¹ Black.

² Adjusted for age, sex, marital status, education, health status, and region.

³ Further adjusted for adherence score.

Bold indicates significance.

Appendix 3

Mediating analysis¹ of cancer-related risk factors on the associations between race and incidence of most common cancer subtypes, modeling interaction between race and mediators. Excluding participants aged 55 and younger at baseline.

	p value for Interaction ²	NDE ³ HR (95% CI)	NIE ⁴ HR (95% CI)	Total Effect HR (95% CI)	Percent Mediated ⁵ (%)
Race and Breast Cancer Association					
Mediators					
BMI (kg/m ²) Per SD ⁶	0.94	0.81 (0.75, 0.86)	1.02 (1.01, 1.02)	0.82 (0.76, 0.88)	Not Mediated
Current Smoker ⁷	0.36	0.83 (0.77, 0.89)	1.00 (0.99, 1.00)	0.83 (0.77, 0.89)	0.09
Physical Activity ⁸	0.37	0.83 (0.77, 0.89)	0.99 (0.99, 1.00)	0.83 (0.77, 0.89)	0.68
Alcohol Use ⁹	0.60	0.83 (0.76, 0.89)	1.00 (0.99, 1.00)	0.83 (0.77, 0.89)	Not Mediated
Nutrition Per SD ¹⁰	0.88	0.84 (0.78, 0.90)	0.99 (0.98, 1.00)	0.83 (0.77, 0.89)	6.39
Adherence Score ¹¹	0.37	0.84 (0.76, 0.91)	0.99 (0.99, 1.00)	0.84 (0.76, 0.91)	0.32
Race and Prostate Cancer Association					
Mediators					
BMI (kg/m ²) Per SD ⁶	0.53	1.81 (1.73, 1.90)	0.98 (0.98, 0.98)	1.77 (1.69, 1.87)	Not Mediated
Current Smoker ⁷	0.42	1.80 (1.72, 1.89)	1.00 (0.99, 1.00)	1.80 (1.72, 1.89)	0.03
Physical Activity ⁸	0.45	1.80 (1.72, 1.89)	1.00 (0.99, 1.00)	1.80 (1.72, 1.89)	0.04
Alcohol Use ⁹	0.65	1.80 (1.72, 1.89)	1.00 (0.99, 1.00)	1.80 (1.72, 1.89)	0.00
Nutrition Per SD ¹⁰	0.93	1.81 (1.73, 1.90)	0.99 (0.99, 1.00)	1.79 (1.71, 1.88)	Not Mediated

	<i>p</i> value for Interaction ²	NDE ³ HR (95% CI)	NIE ⁴ HR (95% CI)	Total Effect HR (95% CI)	Percent Mediated ⁵ (%)
Adherence Score ¹¹	0.87	1.81 (1.73, 1.90)	1.00 (0.99, 1.00)	1.81 (1.73, 1.90)	0.04
Race and Colorectal Cancer Association					
Mediators					
BMI (kg/m ²) Per SD ⁶	0.13	1.12 (1.03, 1.26)	1.02 (1.02, 1.03)	1.14 (1.05, 1.29)	16.04
Current Smoker ⁷	0.77	1.14 (1.05, 1.29)	0.99 (0.99, 1.00)	1.14 (1.05, 1.28)	Not Mediated
Physical Activity ⁸	0.06	1.16 (1.07, 1.29)	1.00 (0.99, 1.01)	1.16 (1.08, 1.29)	0.90
Alcohol Use ⁹	0.12	1.14 (1.05, 1.29)	1.00 (0.99, 1.00)	1.14 (1.05, 1.29)	0.10
Nutrition Per SD ¹⁰	0.41	1.16 (1.07, 1.30)	0.99 (0.98, 0.99)	1.14 (1.05, 1.28)	Not Mediated
Adherence Score ¹¹	0.52	1.17 (1.05, 1.32)	0.99 (0.99, 1.00)	1.17 (1.05, 1.32)	Not Mediated

¹ Models adjusted for age, sex, marital status, education, health status, and region.

² Estimated using Wald test.

³ NDE = Natural Direct Effect (i.e., the effect of the race on cancer incidence *NOT through* mediator)

⁴ NIE = Natural Indirect Effect (i.e., the effect of the race on cancer incidence *through* the mediator)

⁵ Percent Mediated = Percent of the total association between the race and cancer incidence that was mediated on the log hazard scale.

⁶ BMI: continuous, per standard deviation increase.

⁷ Smoking: dichotomous, current smoking vs. past or never smoking

⁸ Physical activity: dichotomous, 3 times per week – within past 12 months that caused increased breathing, heart rate, or sweat.

⁹ Alcohol use: dichotomous, 7 (females) or 14 (males) alcoholic drinks per week.

¹⁰ Nutritional adherence – Number of fruit and vegetable servings per day: continuous, per standard deviation increase.

¹¹ Adherence score ranges from 0–5, summed from cancer-related risk factors: smoking status, physical activity, alcohol use, BMI, and nutritional adherence

¹² - Percent mediated calculated to be <0%

References

1. Tamimi RM, et al. Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. *Am J Epidemiol.* 2016; 184(12):884–893. [PubMed: 27923781]
2. Masala G, et al. Up to one-third of breast cancer cases in post-menopausal Mediterranean women might be avoided by modifying lifestyle habits: the EPIC Italy study. *Breast Cancer Res Treat.* 2017; 161(2):311–320. [PubMed: 27832394]
3. McKenzie F, et al. Healthy Lifestyle and Risk of Cancer in the European Prospective Investigation Into Cancer and Nutrition Cohort Study. *Medicine (Baltimore).* 2016; 95(16):e2850. [PubMed: 27100409]
4. Emaus MJ, et al. Vegetable and fruit consumption and the risk of hormone receptor-defined breast cancer in the EPIC cohort. *Am J Clin Nutr.* 2016; 103(1):168–77. [PubMed: 26607934]
5. Tabung FK, et al. Associations between adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations and biomarkers of inflammation, hormonal, and insulin response. *Int J Cancer.* 2017; 140(4):764–776. [PubMed: 27798951]
6. Jankovic N, et al. Adherence to the WCRF/AICR Dietary Recommendations for Cancer Prevention and Risk of Cancer in Elderly from Europe and the United States: A Meta-Analysis within the CHANCES Project. *Cancer Epidemiol Biomarkers Prev.* 2017; 26(1):136–144. [PubMed: 27793797]

7. Nomura SJ, et al. Adherence to diet, physical activity and body weight recommendations and breast cancer incidence in the Black Women's Health Study. *Int J Cancer*. 2016; 139(12):2738–2752. [PubMed: 27578546]
8. Lucas AL, et al. Adherence to World Cancer Research Fund/American Institute for Cancer Research recommendations and pancreatic cancer risk. *Cancer Epidemiol*. 2016; 40:15–21. [PubMed: 26605429]
9. Hastert TA, White E. Association between meeting the WCRF/AICR cancer prevention recommendations and colorectal cancer incidence: results from the VITAL cohort. *Cancer Causes Control*. 2016; 27(11):1347–1359. [PubMed: 27752849]
10. Nomura SJ, et al. Is adherence to diet, physical activity, and body weight cancer prevention recommendations associated with colorectal cancer incidence in African American women? *Cancer Causes Control*. 2016; 27(7):869–79. [PubMed: 27220873]
11. Smith WA, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. *Cancer*. 2014; 120(17):2742–50. [PubMed: 25070001]
12. Greenlee H, et al. Trends in Obesity Prevalence in Adults With a History of Cancer: Results From the US National Health Interview Survey, 1997 to 2014. *J Clin Oncol*. 2016; 34(26):3133–40. [PubMed: 27458295]
13. Thomas DM, et al. Dynamic model predicting overweight, obesity, and extreme obesity prevalence trends. *Obesity (Silver Spring)*. 2014; 22(2):590–7. [PubMed: 23804487]
14. Flegal KM, et al. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002; 288(14):1723–7. [PubMed: 12365955]
15. Keadle SK, et al. Prevalence and trends in physical activity among older adults in the United States: A comparison across three national surveys. *Prev Med*. 2016; 89:37–43. [PubMed: 27196146]
16. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017; 67(1):7–30. [PubMed: 28055103]
17. Byrd DA, et al. Racial and Ethnic Differences in Dietary Intake, Physical Activity, and Body Mass Index (BMI) Among Cancer Survivors: 2005 and 2010 National Health Interview Surveys (NHIS). *J Racial Ethn Health Disparities*. 2017
18. Michaud DS, et al. Dietary patterns and pancreatic cancer risk in men and women. *J Natl Cancer Inst*. 2005; 97(7):518–24. [PubMed: 15812077]
19. Kushi LH, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012; 62(1):30–67. [PubMed: 22237782]
20. World Cancer Research Fund, Food, nutrition, physical activity, and the prevention of cancer: a global perspective. World Cancer Research Fund/American Institute of Cancer Research; Washington, DC: 2007.
21. Census. [cited 2016 May 15] Geographic Terms and Concepts - Census Divisions and Census Regions. 2016. Available from: https://www.census.gov/geo/reference/gtc/gtc_census_divreg.html
22. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*. 1986; 51(6):1173–1182. [PubMed: 3806354]
23. Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: Does method really matter? *Psychological Science*. 2013; 24(10):1918–1927. [PubMed: 23955356]
24. Hayes, AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York: Guilford Press; 2013.
25. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. *Br J Math Stat Psychol*. 2014; 67(3):451–70. [PubMed: 24188158]
26. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010; 172(12):1339–48. [PubMed: 21036955]
27. Valeri L, VanderWeele TJ. SAS macro for causal mediation analysis with survival data. *Epidemiology*. 2015; 26(2):e23–4. [PubMed: 25643116]

28. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013; 18(2):137–50. [PubMed: 23379553]
29. VanderWeele TJ, et al. Genetic variants on 15q25.1, smoking, and lung cancer: an assessment of mediation and interaction. *Am J Epidemiol*. 2012; 175(10):1013–20. [PubMed: 22306564]
30. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986; 51(6): 1173–82. [PubMed: 3806354]
31. Rice MS, et al. Mammographic density and breast cancer risk: a mediation analysis. *Breast Cancer Res*. 2016; 18(1):94. [PubMed: 27654859]
32. VanderWeele TJ, Robinson WR. On the causal interpretation of race in regressions adjusting for confounding and mediating variables. *Epidemiology*. 2014; 25(4):473–84. [PubMed: 24887159]
33. Kabat GC, et al. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. *Am J Clin Nutr*. 2015; 101(3):558–69. [PubMed: 25733641]
34. Warner ET, et al. Racial and Ethnic Differences in Breast Cancer Survival: Mediating Effect of Tumor Characteristics and Sociodemographic and Treatment Factors. *J Clin Oncol*. 2015; 33(20): 2254–61. [PubMed: 25964252]

Figure 1.
National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study population flowchart and cancer incidence. AA = Black.

Figure 2.

These models represent the component effects of significant mediation effects on the association between Black race and breast cancer (top - A) and colorectal cancer (bottom - B) incidence. The mediator on the association between Black race and breast cancer is nutrition per SD (SD = 2.50). The mediator on the association between Black race and colorectal cancer is BMI per SD (SD = 5.07).

β_a = represents the effect of race on the mediator, calculated from linear regression (mediators are continuous).

β_b = represents the effect of the mediator on outcome, calculated from Cox regression and on the log hazard scale.

β_c = the controlled direct effect of the exposure (race) on the outcome, calculated from Cox regression and on the log hazard scale.

Table 1

Characteristics of National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study population by race. Among 425,152 participants.

	Race / Ethnicity		<i>p</i> value
	Black / AA ¹ (<i>N</i> = 16,110)	White (<i>N</i> = 409,042)	
	Presented as Column %, Mean (S.D), or Median (IQR)		
Age Category			
< 55 years	16.81	13.88	<0.01
55–59 years	27.70	22.78	
60–64 years	29.58	28.01	
65–69 years	23.83	31.86	
70 years	2.09	3.47	
Male Gender	42.67	60.88	<0.01
Marital Status			
Married	48.26	70.37	<0.01
Widowed	16.49	10.52	
Divorced	23.70	13.36	
Separated	5.24	0.98	
Never Married	6.32	4.78	
< High School Education	27.79	25.62	<0.01
Poor Health Status	2.43	1.53	<0.01
Region of Residence			
West	23.88	30.14	<0.01
South	35.38	36.55	
Northeast	29.72	28.36	
Midwest	11.02	4.95	
Current Smoker	15.55	12.23	<0.01
Physical Activity ²	41.94	46.72	<0.01
Alcohol Use Adherence ³	98.76	98.84	0.53
BMI (kg/m²)	28.93 (6.09)	27.04 (5.01)	<0.01
Nutritional Adherence ⁴	4.01 (2.54 – 6.17)	3.51 (2.43 – 4.92)	<0.01
Adherence Score ⁵	3.04 (0.80)	3.14 (0.79)	<0.01

¹ Black

² Physical activity 3 times per week, within past 12 months that caused increased breathing, heart rate, or sweat.

³ 7 (females) or 14 (males) alcoholic drinks per week.

⁴ Number of fruit and vegetable servings per day.

Significance determined using χ^2 or Wilcoxon tests.

⁵ Adherence score ranges from 0–5, summed from cancer-related risk factors: smoking status, physical activity, alcohol use, BMI, and nutritional adherence.

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Table 2

Hazard Ratios (HRs) and associated 95 % Confidence Intervals (CIs) for cancer incidence by race. Among 425,152 participants from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study.

Incident Cancer			
	White (Referent) (<i>N</i> = 409,042)	Black / AA ¹ (<i>N</i> = 16,110)	<i>p</i> value
Any Cancer			
# Events (%)	99,891 (24.42)	3,624 (22.50)	<0.01
Crude HR (95% CI)	-	0.91 (0.88 – 0.94)	<0.01
Adjusted HR ² (95% CI)	-	1.01 (0.97 – 1.04)	0.73
Adherence Adjusted HR ³ (95% CI)	-	1.01 (0.97 – 1.05)	0.68
Breast Cancer			
# Events (%)	11,089 (2.71)	528 (3.28)	<0.01
Crude HR (95% CI)	-	1.19 (1.09 – 1.30)	<0.01
Adjusted HR ² (95% CI)	-	0.83 (0.76 – 0.90)	<0.01
Adherence Adjusted HR ³ (95% CI)	-	0.82 (0.74 – 0.90)	<0.01
Prostate Cancer			
# Events (%)	26,879 (6.57)	1,230 (7.64)	<0.01
Crude HR (95% CI)	-	1.15 (1.08 – 1.21)	<0.01
Adjusted HR ² (95% CI)	-	1.85 (1.74 – 1.96)	<0.01
Adherence Adjusted HR ³ (95% CI)	-	1.86 (1.75 – 1.98)	<0.01
Colorectal Cancer			
# Events (%)	8,837 (2.16)	371 (2.30)	0.22
Crude HR (95% CI)	-	1.05 (0.95 – 1.17)	0.33
Adjusted HR ² (95% CI)	-	1.16 (1.04 – 1.28)	<0.01
Adherence Adjusted HR ³ (95% CI)	-	1.17 (1.05 – 1.31)	<0.01

% - Denotes column percentage - proportion with cancer by race/ethnicity.

¹ Black.

² Adjusted for age, sex, marital status, education, health status, and region.

³ Further adjusted for adherence score.

Bold indicates significance.

Mediating analysis¹ of cancer-related risk factors on the associations between race and incidence of most common cancer subtypes, modeling interaction between race and mediators.

Table 3

	<i>p</i> value for Interaction ²	NDE ³ HR (95% CI)	NIE ⁴ HR (95% CI)	Total Effect HR (95% CI)	Percent Mediated ⁵ (%)	<i>p</i> value for NIE ⁶
Race and Breast Cancer Association						
Mediators						
BMI (kg/m ²) Per SD ⁷	0.09	0.81 (0.74, 0.89)	1.01 (1.01, 1.02)	0.82 (0.75, 0.90)	Not Mediated ¹³	-
Current Smoker ⁸	0.40	0.83 (0.76, 0.91)	1.00 (1.00, 1.00)	0.83 (0.76, 0.91)	0.12	0.18
Physical Activity ⁹	0.32	0.83 (0.76, 0.91)	0.998 (0.997, 0.999)	0.83 (0.76, 0.91)	0.63	0.01
Alcohol Use ¹⁰	0.28	0.83 (0.76, 0.91)	1.00 (1.00, 1.00)	0.83 (0.76, 0.91)	Not Mediated	-
Nutrition Per SD ¹¹	0.80	0.84 (0.77, 0.92)	0.988 (0.979, 0.996)	0.83 (0.76, 0.91)	6.35	<0.01
Adherence Score ¹²	0.23	0.82 (0.75, 0.91)	0.998 (0.997, 1.000)	0.82 (0.75, 0.91)	0.61	0.06
Race and Prostate Cancer Association						
Mediators						
BMI (kg/m ²) Per SD ⁷	0.24	1.88 (1.78, 1.99)	0.979 (0.975, 0.984)	1.84 (1.74, 1.95)	Not Mediated	-
Current Smoker ⁸	0.46	1.87 (1.77, 1.98)	1.00 (1.00, 1.00)	1.87 (1.77, 1.98)	0.05	0.09
Physical Activity ⁹	0.30	1.87 (1.76, 1.98)	1.00 (0.99, 1.00)	1.87 (1.76, 1.98)	0.05	0.27
Alcohol Use ¹⁰	0.68	1.87 (1.76, 1.98)	1.00 (0.99, 1.00)	1.87 (1.76, 1.98)	Not Mediated	0.70
Nutrition Per SD ¹¹	0.91	1.88 (1.77, 1.99)	0.99 (0.987, 0.997)	1.86 (1.76, 1.97)	Not Mediated	-
Adherence Score ¹²	0.49	1.88 (1.77, 2.01)	1.00 (0.99, 1.00)	1.89 (1.77, 2.00)	0.10	0.07
Race and Colorectal Cancer Association						
Mediators						
BMI (kg/m ²) Per SD ⁷	0.30	1.11 (1.00, 1.24)	1.022 (1.017, 1.027)	1.14 (1.02, 1.26)	7.99	<0.01
Current Smoker ⁸	0.88	1.14 (1.02, 1.26)	0.99 (0.99, 1.00)	1.14 (1.02, 1.26)	Not Mediated	-
Physical Activity ⁹	0.04	1.15 (1.03, 1.28)	1.00 (0.99, 1.01)	1.15 (1.03, 1.28)	0.96	0.56

	<i>p</i> value for Interaction ²	NDE ³ HR (95% CI)	NIE ⁴ HR (95% CI)	Total Effect HR (95% CI)	Percent Mediated ⁵ (%)	<i>p</i> value for NIE ⁶
Alcohol Use ¹⁰	0.17	1.14 (1.02, 1.26)	1.00 (0.99, 1.00)	1.14 (1.02, 1.26)	0.31	0.40
Nutrition Per SD ¹¹	0.45	1.15 (1.04, 1.28)	0.98 (0.97, 0.99)	1.14 (1.02, 1.26)	Not Mediated	-
Adherence Score ¹²	0.53	1.16 (1.03, 1.30)	1.00 (1.00, 1.00)	1.15 (1.03, 1.29)	Not Mediated	-

¹ Models adjusted for age, sex, marital status, education, health status, and region.

² Estimated using Wald test.

³ NDE = Natural Direct Effect (i.e., the effect of the race on cancer incidence *NOT through* mediator)

⁴ NIE = Natural Indirect Effect (i.e., the effect of the race on cancer incidence *through* the mediator)

⁵ Percent Mediated = Percent of the total association between the race and cancer incidence that was mediated on the log hazard scale.

⁶ Estimated using delta method.

⁷ BMI: continuous, per standard deviation increase.

⁸ Smoking: dichotomous, current smoking vs. past or never smoking

⁹ Physical activity: dichotomous, 3 times per week – within past 12 months that caused increased breathing, heart rate, or sweat.

¹⁰ Alcohol use: dichotomous, 7 (females) or 14 (males) alcoholic drinks per week.

¹¹ Nutritional adherence – Number of fruit and vegetable servings per day: continuous, per standard deviation increase.

¹² Adherence score ranges from 0-5, summed from cancer-related risk factors: smoking status, physical activity, alcohol use, BMI, and nutritional adherence

¹³ - Percent mediated calculated to be <0%