

CHOLESTEROL, LIPOPROTEINS, AND BREAST CANCER RISK IN AFRICAN AMERICAN WOMEN

Background: Lipid levels, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides, have been reported to be associated with breast cancer risk.

Methods: We studied African American women (97 breast cancer cases and 102 controls) accrued through a population-based, case-control study in the Washington, DC metropolitan area during 1997 and 1998. Plasma lipid levels were measured using enzymatic methods. Logistic regressions (adjusted for age, age at menarche, parity, previous alcohol consumption, and education) were used to explore the associations between lipid levels and breast cancer.

Results: Through multivariable-adjusted regression, we observed a significant inverse association between breast cancer risk and increasing levels of total cholesterol (OR=.46, 95% CI=.25-.85) and LDL (OR=.41, 95% CI=.21-.81), whereas lower levels of HDL were associated with a significant increase in risk (OR=1.99, 95% CI=1.06-3.74).

Conclusions: Our data demonstrate significant reductions in breast cancer risk with high levels of total cholesterol and significant increase in risk when HDL levels are low. These data are in support of a protective effect of cholesterol which has been reported in other populations; further, these findings add to the literature in an understudied population, African American women. (*Ethn Dis.* 2012;22[3]:281-287)

Key Words: Breast Cancer, Cholesterol, HDL, LDL, Triglycerides, African Americans

Adana A. Llanos, PhD; Kephher H. Makambi, PhD;
Cynthia A. Tucker, PhD; Sherrie Flynt Wallington, PhD;
Peter G. Shields, MD; Lucile L. Adams-Campbell, PhD

INTRODUCTION

Diet and obesity are important factors that have been extensively shown to be related to breast cancer risk.¹⁻⁴ Obesity, as a result of unhealthy diet as well as physical inactivity, is plausibly related to unfavorable lipid profiles, which have also been linked to breast cancer. Several recent epidemiological studies⁵⁻¹³ have investigated lipid profiles in the context of breast cancer, and some have indicated possible associations between cholesterol and lipoprotein levels and breast cancer risk. However, data on these associations remain inconclusive.

Five recent case-control studies have investigated the association between cholesterol levels and breast cancer.^{6,8,9,11,13} A hospital-based case-control study in Italy⁶ demonstrated significantly higher total cholesterol and higher low density lipoprotein (LDL) among cases (226.4 vs 215.0; and 148.3 vs 138.7, respectively) and no difference in high density lipoprotein (HDL) or triglyceride levels (54.5 vs 52.9; and 112.7 vs 109.6, respectively). In contrast, another Italian study,⁹ demonstrated no significant differences in total cholesterol, HDL, LDL or triglyceride levels between breast cancer cases and controls.

In a case-control study of Korean women,¹³ it was demonstrated that among premenopausal women, high HDL levels were inversely associated with breast cancer (OR=.49, 95% CI=.35-.68), whereas no association between triglyceride levels and breast cancer was found in this group. Conversely, among postmenopausal women in this study, there was no association between HDL and breast cancer and a

positive association between triglyceride levels (OR= 1.96, 95% CI= 1.29-2.98). In a case-control study of Taiwanese women,¹¹ no associations were observed between total cholesterol, LDL, or triglyceride levels and breast cancer, whereas an inverse association was observed for HDL (OR= 2.59, 95% CI= 1.41-4.77). This is an indication, that lower HDL levels may significantly increase breast cancer risk by almost 3-fold.

A nested case-control study⁸ conducted in the United States, investigated the association between HDL and breast cancer risk by menopausal status. This study demonstrated no association between HDL and breast cancer in neither premenopausal nor postmenopausal women.

Additionally, four recent cohort studies^{5,7,10,12} have investigated the associations between cholesterol, lipoproteins and breast cancer. In a study of Danish women,⁵ it was shown that the relative risk of breast cancer was highest among women in the fourth quartile of total cholesterol (RR=1.0, 95% CI=.4-2.2) and lowest among those in the fourth quartile of HDL (RR=.3, 95% CI=.1-.8). Furthermore, this study demonstrated no association between LDL or triglyceride levels and breast cancer risk. In a study of Norwegian women,⁷ no association was found between total cholesterol, HDL, LDL, or triglycerides and breast cancer. Furberg et al¹⁰ demonstrated a significant inverse association between total cholesterol (RR=.63, 95% CI=.48-.82), HDL (RR=.75, 95% CI=.58-.97) and postmenopausal breast cancer in a Norwegian population. In the Atherosclerosis Risk in Communities (ARIC) cohort, no association

From Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC (AAL, KHM, SFW, PGS, LLA) and Department of Nutritional Sciences/Dietetics, Morgan State University, Baltimore (CT) and Howard University Cancer Center, Washington, DC (CT).

Address correspondence to Lucile L. Adams-Campbell, PhD; Lombardi Comprehensive Cancer Center; Georgetown University Medical Center; 3970 Reservoir Road, NW; Suite E501; Washington, DC 20057; LLA9@georgetown.edu

between HDL and incident breast cancer was found. However, when the sample was limited to premenopausal women, low HDL was shown to increase breast cancer risk (HR=1.67, 95% CI=1.06–2.63).¹²

Breast cancer is one example of an emotional event that may cause sustained emotional arousal and thus elevated plasma lipid levels. Based on Leventhal's Self-Regulation Theory,¹⁴ we sought to describe possible associations between lipoprotein levels and breast cancer risk. This knowledge is necessary to help women manage modifiable factors such as HDL and LDL to potentially reduce their breast cancer risk. Self-Regulation Theory asserts that cognitive and psychological representations (ie, mental images) affect personal anticipatory reactions to a pending experience.^{14,15} As such, a breast cancer diagnosis or perceived breast cancer risk may have a cognitive effect on women, causing potential elevated lipid levels.

It is clear that the currently available data regarding the associations between cholesterol, lipoproteins, and breast cancer are inconsistent. Furthermore, the majority of previous studies have investigated non-US populations. Of the nine previous studies investigating lipid profiles in relation to breast cancer risk, only two^{8,12} included American women, and one study included African American participants.¹² Thus, in our study we investigated the associations between plasma levels of total cholesterol,

HDL, LDL and triglycerides, and breast cancer risk in African Americans.

METHODS

To investigate the association between lipid profiles and breast cancer risk in an understudied population, we conducted a population-based, case-control study in the Washington, DC metropolitan area during 1997 and 1998. All cases and controls included in the study were African American women who were aged ≥ 21 years at time of enrollment. Approval for this study was obtained from the Institutional Review Boards of Howard and Georgetown Universities.

Selection of the Study Population

Cases

All incident breast cancer cases recruited into this study were African American women, born in the United States, residing in the Washington, DC metropolitan area. The cases were enrolled within 6 months of diagnosis at Howard University Hospital (HUH). Inclusion criteria for cases were that they must self identify as African American, have been diagnosed with breast cancer (including DCIS) within the previous 6 months, were born in the United States, reside in Washington, DC, have a working residential telephone inside their home, speak English well enough to be interviewed, be physically and mentally capable of being interviewed, and never have been interviewed as a control for this study. Exclusion criteria were having had a breast cancer diagnosis more than 6 months prior to study enrollment, residence in an institution (ie, prison, nursing home or shelter), severe illness, and inability to give informed consent, known diagnosis of HIV or chronic hepatitis, and having suffered from drug abuse. After initial identification of cases

from pathology reports, consent was obtained from the surgeon to contact potential participants. Potential participants were sent an introductory letter mailed to their home address and followed-up by a telephone call to discuss their willingness to participate in the study and schedule an appointment. On the day of interview, the consent form was signed, anthropometric measurements were taken, phlebotomy was performed, and an interview-administered survey questionnaire was completed.

Controls

The population-based controls for this study were randomly selected from the Washington, DC Voter's Election Board. Inclusion criteria for controls were the same as those for cases, except that controls must have had no personal history of breast cancer. Exclusion criteria for controls were having a history of cancer other than non-melanotic skin cancer or in situ cervical cancer, known diagnosis of HIV or chronic hepatitis, residence in an institution, and severe illness. Women who suffered from drug abuse or who were unable to give formal consent were also excluded. The controls were contacted via an introductory letter mailed to their home address, followed by a telephone call to discuss the study and determine their willingness to participate and schedule an appointment. On the day of the interview, informed consent was signed, anthropometric measurements were taken, phlebotomy was performed, and an interview-administered survey questionnaire was completed.

Overall, the study population comprised 97 incident breast cancer and 102 controls. The overall participation rate was 70%.

Questionnaire

An interview-administered questionnaire for each eligible study participant was obtained by trained research staff to collect extensive epidemiological data. This questionnaire addressed personal

...in our study we investigated the associations between plasma levels of total cholesterol, HDL, LDL and triglycerides, and breast cancer risk in African Americans.

and family medical history (specifically of cancer), occupation, reproductive history (ie, parity and estrogen use), previous smoking and alcohol use, and socioeconomic status (based on education, income and insurance coverage).

Anthropometric Measurements

Height and weight were measured on all participants in light indoor clothing without shoes. Height measurements were conducted using a stadiometer. The individual stood straight with her head positioned such that the Frankfort Plane was horizontal, with the heels of the feet together, and knees straight. The back of the head, heels, buttocks and shoulder blades were in contact with the vertical surface of the stadiometer. Weight was measured using a computerized scale. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The categories were defined as: BMI < 25 kg/m^2 , normal; BMI 25–29, overweight; and BMI ≥ 30 , obese. Waist circumference was measured at the minimal circumference (approximately at the umbilicus) and the hips were measured at the maximum circumference over the buttocks. Waist and hip circumference were measured to assess body fat distribution and calculate waist-to-hip ratio (WHR), which was used as a continuous variable in all analyses.

Biospecimen Collection

Approximately 75 mL of fasting blood was drawn from each case and control on the day of the interview by trained personnel at HUH. Plasma samples were collected in green top heparinized blood tubes, separated, and then aliquoted and stored at -80°C . Pathology reports were reviewed to confirm case status and to collect pathological data.

Plasma Lipid and Lipoprotein Assays

Plasma levels of cholesterol, including high-density lipoprotein cholesterol

(HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol and triglycerides were measured through enzymatic colorimetric methods utilizing an in vitro diagnostic reagent system for the Cobas Integra 700/700 Autoanalyzer.

Statistical Analysis

Means (and standard deviations) and frequencies were used to assess the distribution of selected baseline characteristics among the study participants. The Student's *t* test and chi-square test were used to evaluate differences in selected characteristics as well as plasma lipid levels by case-control status. To estimate the odds ratios (ORs) and 95% confidence intervals (95% CI) for breast cancer risk associated with total cholesterol, HDL, LDL, and triglycerides in plasma, unconditional logistic regression modeling was used. In the models, clinically significant cut-off values (high and low) of plasma total cholesterol, HDL, LDL, and triglycerides were used to compare the odds ratios by plasma lipid levels. Variables included as covariates in the regression models represent potential risk factors for breast cancer: age, age at menarche, parity (number of children), previous alcohol consumption (ever vs. never drinker), and education. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), and all *P* were from two-sided tests in which values less than .05 were considered statistically significant.

RESULTS

Characteristics of the study population by breast cancer status are shown in Table 1. The mean ages at enrollment of cases and controls were 57.6 and 52.4 years, respectively. Although there was no significant difference in BMI by breast cancer status, women in the control group had significantly higher WHR. Controls were also more likely to have ever consumed alcohol than

cases (45.1% vs 30.9%). Total cholesterol and LDL levels in plasma were significantly lower among cases than controls (189.3 mg/dL vs. 206.8 mg/dL and 119.0 mg/dL vs 134.6 mg/dL, respectively). Total cholesterol was positively correlated with plasma LDL ($r=.63$, $P<.0001$) and triglycerides ($r=.26$, $P=.0002$), whereas HDL was inversely correlated with triglycerides ($r=-0.32$, $P<.0001$), waist circumference ($r=-.20$, $P=.005$) and BMI ($r=-.24$, $P=.001$). Triglyceride levels were positively associated with waist circumference, waist-to-hip ratio, and BMI ($r=.25$, $.21$, and $.19$, respectively; $P<.01$).

There was an inverse association between breast cancer risk and increasing levels of total cholesterol (OR=.46, 95% CI=.25–.85) (Table 2). A significant increase in breast cancer risk among women who had clinically low levels of HDL was observed (OR=1.99, 95% CI=1.06–3.74), whereas a reduced risk was found among those who had clinically high levels of LDL (OR=.41, 95% CI=.21–.81). Additional analyses were conducted to determine the associations between the ratios of total cholesterol and HDL (TC/HDL) and LDL and HDL (LDL/HDL) with breast cancer, although neither of the two ratios were significantly associated with breast cancer (OR=.59, 95% CI=.28–1.24 and OR=1.03, 95% CI=.21–4.99, respectively)(data not shown). However, we observed a potential, though not statistically significant, increase in breast cancer risk associated with a combination of low HDL and low LDL levels (OR=2.41, 95% CI=.74–7.85) (Table 3).

DISCUSSION

Several previous studies have investigated the association between cholesterol levels and breast cancer risk; however these studies have not included the investigation of minority women in

Table 1. Baseline characteristics of study participants

Characteristic	Cases (n= 97)		Controls (n= 102)		P
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Age at enrollment, years		57.6 (13.2)		52.4 (9.9)	.002
Education					
<High school	10 (10.3)		15 (14.7)		.49
High school	20 (20.6)		16 (15.7)		
>High school	67 (69.1)		71 (69.6)		
Income					.39
<\$10,000	12 (12.8)		16 (16.0)		
\$10,000-\$30,000	26 (27.7)		30 (30.0)		
\$30,000-\$60,000	22 (23.4)		29 (29.0)		
≥\$60,000	34 (36.2)		25 (25.0)		
Body mass index, kg/m ²		32.0 (6.8)		31.3 (6.8)	.48
Waist-to-hip ratio		.86 (.07)		.87 (.12)	<.001
Age at menarche, years					
≤11	23 (23.7)		27 (26.5)		.86
12	23 (23.7)		25 (24.5)		
>12	51 (52.6)		50 (49.0)		
Parity					
Nulliparous	10 (10.3)		15 (14.7)		.61
1-2 children	29 (29.9)		31 (30.4)		
≥3 children	58 (59.8)		56 (54.9)		
History of alcohol consumption					.04
Never	67 (69.1)		56 (54.9)		
Ever	30 (30.9)		46 (45.1)		
Total cholesterol, mg/dL		189.3 (52.3)		206.8 (57.5)	.03
HDL, mg/dL		54.7 (13.9)		58.1 (17.6)	.14
LDL, mg/dL		119.0 (36.2)		134.6 (46.1)	.01
Triglycerides, mg/dL		115.4 (64.8)		120.8 (94.8)	.65

SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein.

general, and African American women specifically. Thus, virtually nothing is known about the association between cholesterol and breast cancer risk among African Americans. Prior epidemiological studies have suggested that African Americans are more likely to consume energy-dense foods and less likely to consume recommended amounts of fruits and vegetables, which increases the risk of obesity, cancer, and other conditions,^{1,16-18} including dyslipidemia. In our study, we demonstrated a statistically significant reduction in breast cancer risk among African American women with high levels of total cholesterol. Furthermore, a significant increase in breast cancer risk among women with low HDL levels was observed. These data support an inverse association between

cholesterol levels, which has been previously reported.^{5,8-10,12,13}

In a Danish study by Hoyer and Engholm,⁵ they demonstrated a relative risk of .30 (95% CI=.10-.80) for breast cancer among those in the highest quartile of plasma HDL. The study by

...we demonstrated a statistically significant reduction in breast cancer risk among African American women with high levels of total cholesterol.

Moorman et al⁸ reported mean HDL levels among cases and controls of 32.8 ± 10.2 mg/dL and 33.3 ± 12.2 mg/dL, respectively, with a reduction in breast cancer risk by 4% with each 1 mg/dL increase in HDL among premenopausal women (not statistically significant). It was suggested that the findings did not reach significance due to the degradation of HDL during storage, although the trend was towards an inverse association. In the ARIC study,¹² the mean reported HDL level among women was 57.9 ± 16.3 mg/dL. In addition, 4.7% of the total cohort population developed breast cancer during the follow-up period, and a significant increase in risk of breast cancer in relation to low HDL levels (OR= 1.67, 95% CI=1.06-2.63) was observed among premenopausal women only. Kim et al,¹³ through a study of Korean women, also demonstrated an inverse association between HDL and breast cancer among premenopausal women, especially those with BMI < 23 kg/m² (OR=.34, 95% CI=.22-.53 for the highest category of HDL vs the lowest category). Conversely, Furberg et al,¹⁰ through a large cohort of Norwegian women, reported a relative risk of .43 (95% CI=.28-.67) for breast cancer among postmenopausal women in the highest quartile of HDL, specifically among women with BMI ≥25 kg/m².

The Italian study by Fiorenza et al⁹ reported significant differences in mean levels of total cholesterol (181.4 ± 48.0 vs 204.7 ± 35.2 mg/dL), HDL (49.9 ± 18.9 vs 57.6 ± 15.5 mg/dL), and LDL (107.0 ± 39.7 vs 124.4 ± 29.8 mg/dL) among breast cancer cases and controls, which were similar to our findings. Additionally, and maybe more importantly, they indicated that HDL levels were even lower among patients with metastatic disease.

Our observation that low HDL levels may be associated with an increased risk of breast cancer is in line with the hypothesis that high HDL

Table 2. Odds ratios of breast cancer in relation to plasma levels of total cholesterol, HDL, LDL and triglycerides

	<i>n</i>	Odds Ratio (95% CI) ^a	Odds Ratio (95% CI) ^b
Total cholesterol, mg/dL			
Low, <200.0 mg/dL	103	1.00 (reference)	1.00 (reference)
High, ≥200.0 mg/dL	96	.49 (.27, .87)	.46 (.25, .85)
HDL, mg/dL			
High, ≥60.0 mg/dL	74	1.00 (reference)	1.00 (reference)
Low, <60.0 mg/dL	125	2.03 (1.11, 3.71)	1.99 (1.06, 3.74)
LDL, mg/dL			
Low, <130.0 mg/dL	56	1.00 (reference)	1.00 (reference)
High, ≥130.0 mg/dL	143	.48 (.25, .91)	.41 (.21, .81)
Triglycerides, mg/dL			
Low, <150.0 mg/dL	159	1.00 (reference)	1.00 (reference)
High, ≥150.0 mg/dL	40	.67 (.33, 1.37)	.67 (.32, 1.41)

HDL, high density lipoprotein; LDL, low density lipoprotein.

^a Adjusted for age.

^b Adjusted for age, age at menarche, parity (number of children), history of alcohol consumption (ever vs never), and education.

levels may elicit a protective effect. HDL transports circulating cholesterol within the arteries back to the liver for excretion and/or re-utilization. It is therefore plausible that as total cholesterol levels increase, potentially stimulating increases in HDL levels, breast cancer risk subsequently decreases (and vice versa). However, our finding of an inverse association between LDL and breast cancer cannot be as easily explained. Fiorenza et al⁹ also demonstrated a significant inverse association between LDL, and breast cancer risk and suggested this association might be due to increased activity of the LDL receptor, which promotes the removal of LDL from circulation, thereby reducing breast cancer risk. Two additional studies^{5,7} also suggested an inverse

association although the confidence intervals included unity. Gaard et al⁷ indicated that this association may be an indication that LDL levels are affected by the presence of the disease, rather than by influencing its development.

Although more data are needed to determine the biological mechanisms for the effect of plasma cholesterol and the HDL and LDL lipoproteins on breast cancer, several reasons as to why there may be an inverse association have been proposed. A biologically plausible explanation for the association between cholesterol and breast cancer is through the production of cholesterol epoxides, which are present in breast nipple fluid aspirates.¹⁹⁻²¹ This is important because cholesterol epoxides are mutagenic and when exposure to epithelial cells occurs,

this may promote breast carcinogenesis.^{22,23} Additionally, there are several other biomarkers that have been shown to associate with cholesterol levels, including sex hormones,²⁴ which influence the levels of circulating HDL through the regulation of hepatic lipase activity.²⁵ Levels of HDL are also significantly associated with levels of free, biologically active estradiol,²⁴ which have long been an established risk factor for breast cancer.²⁶ Moreover, Furberg et al²⁴ hypothesized that the aromatization of androgens to estrogens within adipose tissues is the causal mechanism for an inverse association between HDL and breast cancer. Another potential mechanism involves the insulin-like growth factor (IGF) pathway.²⁷⁻²⁹ Congruent with this hypothesis, epidemiological studies have pointed towards a positive association between IGF-1 levels and both breast cancer risk^{27,30-37} and poor prognosis.^{38,39} Yet another potential mechanism is related to inflammation.⁴⁰⁻⁴² Decreased levels of HDL have been reported to be associated with increased levels of cytokines,^{43,44} which have been shown to be related to both obesity and breast cancer. Our finding of a significant increase in breast cancer risk when both HDL and LDL levels are low would support all of those observations, and implies that cholesterol may be an important factor in the pathogenesis of breast cancer.

There are limitations that should be noted in our study. One limitation was the lack of detailed information on menopausal status. It is unknown whether there are significant differences in the breast cancer-cholesterol link due to menopausal status. Medication information on the use of cholesterol-lowering drugs among study participants was not available. Therefore, it is not known if our estimates of risk are biased. We also recognize that our study is based on a small sample size and limited power. Yet, we have shown some interesting and significant findings

Table 3. Odds ratios of breast cancer in relation to combinations of LDL and HDL

HDL (mg/dL) - LDL (mg/dL)	<i>n</i>	Odds Ratio (95% CI) ^a	Odds Ratio (95% CI) ^b
High-low	18	1.00 (reference)	1.00 (reference)
High-high	56	.59 (.20, 1.78)	.47 (.15, 1.49)
Low-high	87	1.08 (.38, 3.07)	.87 (.29, 2.59)
Low-low	38	2.41 (.74, 7.85)	2.15 (.64, 7.28)

HDL, high density lipoprotein; LDL, low density lipoprotein.

^a Adjusted for age.

^b Adjusted for age, age at menarche, parity (number of children), history of alcohol consumption (ever vs never), and education.

that warrant further investigation in a larger study population of African Americans.

Our data provide possible insight into an understudied relationship between important biomarkers that are related to cholesterol and breast cancer risk among African American women. We have shown that high cholesterol levels, especially high levels of HDL as well as LDL, are inversely associated with breast cancer in this group. This adds to the current literature, and expands information available on an understudied population. Future epidemiology studies should investigate the relationship between cholesterol biomarkers and breast cancer risk to better understand cancer disparities. Also, a more in-depth study of dietary factors and obesity as potential mediators for the cholesterol-breast cancer link should be studied.

ACKNOWLEDGMENTS

This work was supported by the US Department of Defense (DAMD17-98-1-8110) awarded to Dr. Adams-Campbell.

REFERENCES

- Agurs-Collins T, Rosenberg L, Makambi K, Palmer JR, Adams-Campbell L. Dietary patterns and breast cancer risk in women participating in the Black Women's Health Study. *Am J Clin Nutr*. 2009;90:621-628.
- Khan N, Afaq F, Mukhtar H. Lifestyle as risk factor for cancer: evidence from human studies. *Cancer Lett*. 2010;293:133-143.
- Duncan AM. The role of nutrition in the prevention of breast cancer. *AACN Clin Issues*. 2004;15:119-135.
- Gonzalez CA, Riboli E. Diet and cancer prevention: contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Cancer*. 2010;46:2555-2562.
- Hoyer AP, Engholm G. Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. *Cancer Causes Control*. 1992;3:403-408.
- Ferraroni M, Gerber M, Decarli A, et al. HDL-cholesterol and breast cancer: a joint study in northern Italy and southern France. *Int J Epidemiol*. 1993;22:772-780.
- Gaard M, Tretli S, Urdal P. Risk of breast cancer in relation to blood lipids: a prospective study of 31,209 Norwegian women. *Cancer Causes Control*. 1994;5:501-509.
- Moorman PG, Hulka BS, Hiatt RA, et al. Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status. *Cancer Epidemiol Biomarkers Prev*. 1998;7:483-488.
- Fiorenza AM, Branchi A, Sommariva D. Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. *Int J Clin Lab Res*. 2000;30:141-145.
- Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst*. 2004;96:1152-1160.
- Chang SJ, Hou MF, Tsai SM, et al. The association between lipid profiles and breast cancer among Taiwanese women. *Clin Chem Lab Med*. 2007;45:1219-1223.
- Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. *Ann Epidemiol*. 2008;18:671-677.
- Kim Y, Park SK, Han W, et al. Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in Korea. *Cancer Epidemiol Biomarkers Prev*. 2009;18:508-515.
- Leventhal H, Nerenz D, Steele A. Self-regulation and the mechanisms for symptom appraisal. In: Mechanic D, ed. *Symptoms, Illness Behavior and Help-seeking*. New York, NY: Neale Watson Academic Publishers; 1984:55-86.
- Myers RE. Self-regulation and decision-making about cancer screening. In: Cameron L, Leventhal H, eds. *The Self-regulation of Health and Illness Behavior*. New York, NY: Routledge; 2003:298-313.
- Howarth NC, Murphy SP, Wilkens LR, Hankin JH, Kolonel LN. Dietary energy density is associated with overweight status among 5 ethnic groups in the multiethnic cohort study. *J Nutr*. 2006;136:2243-2248.
- Kant AK, Graubard BI, Kumanyika SK. Trends in Black-White differentials in dietary intakes of U.S. adults, 1971-2002. *Am J Prev Med*. 2007;32:264-272.
- Wang Y, Jahns L, Tussing-Humphreys L, et al. Dietary intake patterns of low-income urban African American adolescents. *J Am Diet Assoc*. 2010;110:1340-1345.
- Petrakis NL, Gruenke LD, Craig JC. Cholesterol and cholesterol epoxides in nipple aspirates of human breast fluid. *Cancer Res*. 1981;41:2563-2565.
- Gruenke LD, Wrensch MR, Petrakis NL, Miike R, Ernster VL, Craig JC. Breast fluid cholesterol and cholesterol epoxides: relationship to breast cancer risk factors and other characteristics. *Cancer Res*. 1987;47:5483-5487.
- Wrensch MR, Petrakis NL, Gruenke LD, et al. Breast fluid cholesterol and cholesterol beta-epoxide concentrations in women with benign breast disease. *Cancer Res*. 1989;49:2168-2174.
- Petrakis NL, Maack CA, Lee RE, Lyon M. Mutagenic activity in nipple aspirates of human breast fluid. *Cancer Res*. 1980;40:188-189.
- Sevanian A, Peterson AR. Cholesterol epoxide is a direct-acting mutagen. *Proc Natl Acad Sci U S A*. 1984;81:4198-4202.
- Furberg AS, Jasienska G, Bjurstam N, et al. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. *Cancer Epidemiol Biomarkers Prev*. 2005;14:33-40.
- Tikkanen MJ, Nikkila EA, Kuusi T, Sipinen SU. High density lipoprotein-2 and hepatic lipase: reciprocal changes produced by estrogen and norgestrel. *J Clin Endocrinol Metab*. 1982;54:1113-1117.
- Hankinson SE. Endogenous hormones and risk of breast cancer in postmenopausal women. *Breast Dis*. 2005;24:3-15.
- Schernhammer ES, Holly JM, Pollak MN, Hankinson SE. Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2005;14:699-704.
- Kawachi S, Takeda N, Sasaki A, et al. Circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 are associated with early carotid atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2005;25:617-621.
- Colao A, Di SC, Spiezia S, et al. The natural history of partial growth hormone deficiency in adults: a prospective study on the cardiovascular risk and atherosclerosis. *J Clin Endocrinol Metab*. 2006;91:2191-2200.
- Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*. 2004;363:1346-1353.
- Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*. 2000;92:1472-1489.
- Johansson H, Baglietto L, Guerrieri-Gonzaga A, et al. Factors associated with circulating levels of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in 740 women at risk for breast cancer. *Breast Cancer Res Treat*. 2004;88:63-73.
- Agurs-Collins T, Adams-Campbell LL, Kim KS, Cullen KJ. Insulin-like growth factor-1 and breast cancer risk in postmenopausal

- African American women. *Cancer Detect Prev.* 2000;24:199–206.
34. Kahan Z, Gardi J, Nyari T, et al. Elevated levels of circulating insulin-like growth factor-I, IGF-binding globulin-3 and testosterone predict hormone-dependent breast cancer in postmenopausal women: a case-control study. *Int J Oncol.* 2006;29:193–200.
 35. Baglietto L, English DR, Hopper JL, Morris HA, Tilley WD, Giles GG. Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16:763–768.
 36. Li BD, Khosravi MJ, Berkel HJ, et al. Free insulin-like growth factor-I and breast cancer risk. *Int J Cancer.* 2001;91:736–739.
 37. Shi R, Yu H, McLarty J, Glass J. IGF-I and breast cancer: a meta-analysis. *Int J Cancer.* 2004;111:418–423.
 38. Goodwin PJ, Ennis M, Pritchard KI, et al. Insulin-like growth factor binding proteins 1 and 3 and breast cancer outcomes. *Breast Cancer Res Treat.* 2002;74:65–76.
 39. Yu H, Levesque MA, Khosravi MJ, Papanastasiou-Diamandi A, Clark GM, Diamandis EP. Insulin-like growth factor-binding protein-3 and breast cancer survival. *Int J Cancer.* 1998;79:624–628.
 40. Ferretti G, Bacchetti T, Negre-Salvayre A, Salvayre R, Dousset N, Curatola G. Structural modifications of HDL and functional consequences. *Atherosclerosis.* 2006;184:1–7.
 41. Haddy N, Sass C, Droesch S, et al. IL-6, TNF-alpha and atherosclerosis risk indicators in a healthy family population: the STANISLAS cohort. *Atherosclerosis.* 2003;170:277–283.
 42. Burger D, Dayer JM. High-density lipoprotein-associated apolipoprotein A-I: the missing link between infection and chronic inflammation? *Autoimmun Rev.* 2002;1:111–117.
 43. Navab M, Ananthramiah GM, Reddy ST, et al. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. *J Lipid Res.* 2004;45:993–1007.
 44. Peng YS, Chiu YL, Chen HY, et al. Decreased high-density lipoprotein cholesterol is associated with inflammation and insulin resistance in non-diabetic haemodialysis patients. *Nephrology (Carlton).* 2010;15:692–699.

AUTHOR CONTRIBUTIONS

Design and concept of study: Adams-Campbell
Acquisition of data: Tucker, Adams-Campbell
Data analysis and interpretation: Llanos, Makambi
Manuscript draft: Llanos, Makambi, Tucker, Flynt Wallington, Shields
Statistical expertise: Makambi
Acquisition of funding: Adams-Campbell
Administrative: Llanos, Tucker
Supervision: Tucker, Adams-Campbell