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Cholesterol, lipoproteins, and breast cancer risk in African-American women

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Abstract

Background—Cholesterol 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= 0.46, 95% CI= 0.25-0.85) and LDL (OR=0.41, 95% CI= 0.21-0.81), whereas lower levels of HDL were associated with a significant increase in risk (OR= 1.99, 95% CI= 1.06-3.74).

Conclusions—These 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.

Keywords

Breast cancer; cholesterol; HDL; LDL; triglycerides; African-Americans

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 studies[5-13] have investigated lipid profiles in the context of breast cancer, and some have indicated possible associations between cholesterol and

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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 Italy[6] 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 inversely associated with breast cancer (OR= 0.49, 95% CI= 0.35-0.68), whereas no association between triglyceride levels and breast cancer were 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, 955 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 study[8] conducted in the U.S., 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= 0.4-2.2) and lowest among those in the fourth quartile of HDL (RR= 0.3, 95% CI= 0.1-0.8). 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 al.[10] demonstrated a significant inverse association between total cholesterol (RR= 0.63, 95% CI= 0.48-0.82), HDL (RR= 0.75, 95% CI= 0.58-0.97) and postmenopausal breast cancer in a Norwegian population. In the Atherosclerosis Risk in Communities (ARIC) cohort, no association 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 risks. 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 (i.e., mental images) affect personal anticipatory reactions to a pending experience.[14,15] As such, a breast cancer diagnosis or a 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-U.S. 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 the present 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 at least 21 years of age 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. 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 U.S., 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 (i.e. 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 phone calls 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 was comprised of 97 incident breast cancer and 102 controls. The overall participation rate was 70%.

Questionnaire

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

addressed personal and family medical history (specifically of cancer), occupation, reproductive history (i.e., 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 subjects 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 follows: BMI < 25 kg/m^2, normal; BMI 25-29 kg/m^2, overweight; and BMI ≥ 30 kg/m^2, 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 a 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 serum 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* values were from two-sided tests in which values less than 0.05 were considered statistically significant.

Results

Characteristics of the study population by breast cancer status are shown in Table 1. The mean age 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= 0.63, p-value <0.0001) and triglycerides (r= 0.26, p-value = 0.0002), whereas HDL was inversely correlated with triglycerides (r= −0.32, p-value <0.0001), waist circumference (r= −0.20, p-value= 0.005) and BMI (r= −0.24, p-value= 0.001). Triglyceride levels were positively associated with waist circumference, waist-to-hip ratio, and BMI (r = 0.25, 0.21, and 0.19, respectively; p-values <0.01).

There was an inverse association between breast cancer risk and increasing levels of total cholesterol (OR= 0.46, 95% CI= 0.25-0.85) (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= 0.41, 95% CI= 0.21-0.81). 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= 0.59, 95% CI= 0.28-1.24 and OR=1.03, 95% CI= 0.21-4.99, respectively)(data not shown). However, a potential increase in breast cancer risk associated with a combination of low HDL and low LDL levels (OR= 2.41, 95% CI= 0.74-7.85), although not statistically significant (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 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 the present 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 0.30 (95% CI= 0.10-0.80) for breast cancer among those in the highest quartile of plasma HDL. The study by Moorman and colleagues[8] 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 (HR= 1.67, 95% CI= 1.06-2.63) was observed among premenopausal women only. Kim and colleagues,[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/m^2 (OR= 0.34, 95% CI= 0.22-0.53 for the highest category of HDL vs. the lowest category). Conversely, Furberg and colleagues,[10] through a large cohort of Norwegian women, reported a relative risk of 0.43 (95% CI= 0.28-0.67) for breast cancer among

postmenopausal women in the highest quartile of HDL, specifically among women with BMI ≥25 kg/m^2.

The Italian study by Fiorenza and colleagues[9] 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 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 al.[9] 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 al.[7] 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 which 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] HDL levels 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 al.[24] 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 infers that cholesterol may be an important factor in the pathogenesis of breast cancer.

There are limitations that should be noted in the present 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 the present study is based on a small sample size and limited power. Yet, we have

shown some interesting and significant findings 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.

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Table 1

Baseline characteristics of study participants

	Cases (N= 97)		Controls (N= 102)		
Characteristic	**n (%)**	**Mean (SD)**	**n (%)**	**Mean (SD)**	**P-value**
Age at enrollment (years)		57.6 (13.2)		52.4 (9.9)	**0.002**
Education					
<High school	10 (10.3)		15 (14.7)		0.49
High school	20 (20.6)		16 (15.7)		
>High school	67 (69.1)		71 (69.6)		
Income					0.39
<$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-$90,000	34 (36.2)		25 (25.0)		
Body mass index (kg/m^2)		32.0 (6.8)		31.3 (6.8)	0.48
Waist-to-hip ratio		0.86 (0.07)		0.87 (0.12)	**<0.001**
Age at menarche (years)					
≤11	23 (23.7)		27 (26.5)		0.86
12	23 (23.7)		25 (24.5)		
>12	51 (52.6)		50 (49.0)		
Parity					
Nulliparous	10 (10.3)		15 (14.7)		0.61
1-2 children	29 (29.9)		31 (30.4)		
≥3 children	58 (59.8)		56 (54.9)		
History of alcohol consumption					**0.04**
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)	**0.03**
HDL (mg/dL)		54.7 (13.9)		58.1 (17.6)	0.14
LDL (mg/dL)		119.0 (36.2)		134.6 (46.1)	**0.01**
Triglycerides (mg/dL)		115.4 (64.8)		120.8 (94.8)	0.65

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

Table 2

Age- and multivariable-adjusted odds ratios of breast cancer in relation to plasma levels of total cholesterol, HDL, LDL and triglycerides

	N	Odds Ratio (95% CI)*	Odds Ratio (95% CI)†
Total cholesterol (mg/dL)			
Low, <200.0 mg/dL	103	1.00 (reference)	1.00 (reference)
High, ≥200.0 mg/dL	96	**0.49 (0.27, 0.87)**	**0.46 (0.25, 0.85)**
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	**0.48 (0.25, 0.91)**	**0.41 (0.21, 0.81)**
Triglycerides (mg/dL)			
Low, <150.0 mg/dL	159	1.00 (reference)	1.00 (reference)
High, ≥150.0 mg/dL	40	0.67 (0.33, 1.37)	0.67 (0.32, 1.41)

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

*Adjusted for age.

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

Table 3

Age- and multivariable-adjusted odds ratios of breast cancer in relation to combinations of LDL and HDL

	N	Odds Ratio (95% CI)*	Odds Ratio (95% CI)†
HDL (mg/dL) - LDL (mg/dL)			
High-low	18	1.00 (reference)	1.00 (reference)
High-high	56	0.59 (0.20, 1.78)	0.47 (0.15, 1.49)
Low-high	87	1.08 (0.38, 3.07)	0.87 (0.29, 2.59)
Low-low	38	2.41 (0.74, 7.85)	2.15 (0.64, 7.28)

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

*Adjusted for age.

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