Association of Lipid Profile Biomarkers with Breast Cancer by Molecular Subtype: analysis of the Mechanisms for Established and Novel Risk Factors for Breast Cancer in Women of African Descent (MEND) study

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Abstract

Purpose: There is conflicting evidence on the role of lipid biomarkers in breast cancer (BC), and no study to our knowledge has examined this association among African women.

Methods: We estimated odds ratios (ORs) and 95% confidence intervals (95% CI) for the association of lipid biomarkers – total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides – with odds of BC overall and by subtype (Luminal A, Luminal B, HER2-enriched and triple-negative or TNBC) for 296 newly diagnosed BC cases and 116 healthy controls in Nigeria.

Results: Cases were slightly older than controls (48.5 vs. 46.0) and had a lower BMI (25.4 vs. 26.5). Each unit SD increase in triglycerides was associated with 39% increased odds of BC in fully adjusted models (aOR: 1.39; 95% CI: 1.03, 1.86). However, there were no significant associations of total cholesterol, LDL and HDL with odds of breast cancer in fully adjusted models. In analysis of molecular subtypes, each unit SD increase in LDL was associated with 64% increased odds of Luminal B BC (aOR 1.64; 95% CI: 1.06, 2.55). Each unit SD decrease in HDL was associated with 49% increased odds of TNBC (aOR: 1.49, 95% CI: 0.94, 2.34), and clinically low HDL was associated with 2.7 times increased odds of TNBC (aOR 2.67; 95% CI: 1.10, 6.49).

Conclusions: Low HDL and high LDL appear to significantly increase the odds of TN and Luminal B BC, among African women. Future prospective studies can characterize this association and inform clinical approaches targeting HDL as a BC prevention strategy.

Introduction

Breast cancer (BC) in Nigeria, like in other West African countries and among Blacks in the United States, is characterized by disproportionately high rates of the triple-negative (TN) molecular subtype [1,2]. TNBCs are aggressive cancers, described by estrogen (ER), progesterone (PR), and human epidermal growth factor-2 (HER2) receptor negativity and associated with poor clinical outcomes [3,4]. Africa suffers from the highest age-standardized BC mortality rate globally [5], and the past few decades have observed increasing BC incidence on the African continent [6]. An understanding of the risk factors contributing to the higher prevalence of TNBCs among women of African descent is crucial to the development of preventive interventions that may reduce the BC burden within this population. In addition to increasing BC incidence, the African continent has also experienced significantly increasing rates of obesity, diabetes, and dyslipidemia (abnormally elevated blood cholesterol or lipid levels), so called “diseases of affluence” due to globalization and the epidemiologic transition [7,8]. Prior studies have documented a positive association between measures of excess adiposity and BC incidence [9,10], but none to our knowledge has examined specific biomarkers associated with dyslipidemia with BC risk by molecular subtype on the African continent.

Prior studies in the US, Europe and parts of Asia evaluating the relationship between serum lipids and risk of BC have been inconclusive, and several review papers have summarized published results on this

topic. A recent systematic review of prospective studies reported an inverse association between biomarkers of total cholesterol and high-density lipoprotein (HDL) cholesterol and risk of breast cancer, but no significant associations with low-density lipoprotein (LDL) cholesterol [11]. This study noted significant heterogeneity among included studies for total cholesterol based on geographical location. The inverse association for HDL cholesterol was replicated in a separate systematic review which also reported a positive association for LDL cholesterol [12]. A third meta-analysis found that higher triglyceride levels, but not total cholesterol, HDL cholesterol or LDL cholesterol levels was inversely associated with BC risk [13]. It is worth noting that the majority of studies on this topic have been conducted among White populations in the United States and Europe. Studies among African American populations are limited and conflicting. While one study among African Americans in the United States found a statistically significant reduction in BC risk with high levels of total cholesterol and a significant increase in risk associated with low HDL cholesterol [14]; another study reported no significant association with total cholesterol [15]. Research on this topic deserves further study to more clearly elucidate the association between lipid biomarkers and BC risk. To our knowledge, studies on this topic have not been conducted in Nigeria or West Africa.

Importantly, few epidemiological studies have examined the association between lipids and BC molecular subtype. One study in Korea noted that low HDL cholesterol and high levels of triglycerides were associated with an increased risk of developing hormone receptor negative tumors [16]. Another study in Spain found that the risk of postmenopausal Luminal A BC significantly increased with higher circulating levels of triglycerides [17]. However, no study to our knowledge has examined this association among African women or in African American women, despite the higher risk of TNBC in these populations. To our knowledge, ours is the first study to evaluate the association between total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides with BC molecular subtypes among Nigerian women. Blood lipids are easily measurable markers that are routinely assessed in clinical practice. Thus, further insight on this relationship by molecular subtype may enable the development of preventative strategies that are well-suited to the Nigerian and African context.

Materials And Methods

Study design

The Mechanisms for Established and Novel Risk Factors for Breast Cancer in Women of African Descent (MEND) study has been previously described in detail [18]. Briefly, MEND enrolled newly diagnosed BC patients from four hospitals in southwestern Nigeria. At each hospital site, a trained nurse explained the study requirements to BC patients during their clinical visits. Interested participants were evaluated for eligibility. Reasons for exclusion included an inability to communicate in English to complete the required baseline survey, prior diagnosis and/or treatment for cancer, and other medical conditions that may have interfered with participation in the study. All study participants gave written and verbal informed consent, and then completed a questionnaire that covered information on sociodemographic characteristics, reproductive history, and past personal and family history of cancer. Anthropomorphic measurements

were taken, and blood samples and tumor biopsy samples were collected for all participants prior to receipt of any surgery, chemotherapy, or radiation treatment. After collection and processing, tissue and blood samples were stored in -80°C freezers until shipment to the United States for assays and further analysis. For their participation in this study, participants received an N500 telephone recharge card (valued at US $1.50) in addition to the supplies necessary for their biopsy. Healthy controls were selected from a cohort of 4,000 healthy, community-based women recruited as part of the Human Heredity and Health (H3) Africa Chronic Kidney Disease (CKD) Case-Control study [19]. The CKD study recruited from Nigeria and Ghana between 2015 and 2017, overlapping with case recruitment. The present analysis was restricted to controls recruited from Nigeria; recruitment occurred in the South-Western region of the country, also overlapping with case recruitment region. Extensive socio-demographic, clinical, family history and behavioral risk factor data was collected, and blood samples were collected and processed at clinical labs following a standardized protocol. Serum samples for cases and controls were assayed for lipid biomarkers at the Duke Molecular Pathology Institute at the same time, and the laboratory technician was blinded to case status. These procedures were approved by the Institutional Review Boards at Duke University and the participating hospitals.

Breast cancer cases and subtyping

BC diagnosis was ascertained either through pathology reports of clinical biopsy samples evaluated by a trained pathologist from the diagnosing hospital in Nigeria, or from samples that were shipped to the US for review by a trained US pathologist. If either indicated a cancer diagnosis, the sample was considered a confirmed case. Confirmed samples underwent immunohistochemistry in Nigeria as part of regular standard of care procedures, or at the Duke University BioRepository and Precision Pathology Center. If results from both were available, US typing was used as it constituted most of the available immunohistochemistry information on cases. Estrogen receptor (ER) and progesterone receptor (PR) status was scored using the Allred method [20,21]. The intensity of staining was categorized as 0 (none), 1 (mild), 2 (moderate), or 3 (strong), and the proportion of nuclear positivity was scored into 0 (0%), 1 (<1%), 2 (1-10%), 3 (11-33%), 4 (33-66%) or 5 (67-100%). The numbers from these two scores were summed to positive (3-8) or negative (0-2). HER2 status was categorized as negative (scores = 0-1), equivocal (score = 2), or positive (score = 3) [22]. In the determination of subtype, equivocal was classified as negative. Based into these categorizations, cancer subtype was determined: Luminal A (ER+ and/or PR+ / HER2-), Luminal B (ER+ and/or PR+ / HER2+), TN (ER-/PR-/HER2-), or HER2 (ER-/PR-/HER2+). In all, there were 124 cases with available data on ER/PR/HER2 status for classification into a molecular subtype.

Measures

Measurements of total cholesterol, HDL, LDL, and triglycerides for cases and controls were performed using a Beckman DxC 600 clinical analyzer with assays that utilized standard reagents also from Beckman (Brea, CA). Following the joint harmonized criteria for metabolic syndrome and guidelines set by the National Cholesterol Education Program, high total cholesterol was defined as >200 mg/dL [23];

low HDL was defined as <50 mg/dL [24]; high LDL was defined as >100 mg/dL [23]; and high triglycerides was defined as >150 mg/dL [24]. In addition, lipid measures were specified as standard deviation (SD) change by subtracting the sample mean from individual measurements and dividing by the sample standard deviation. Other covariates included in analysis were staff assessed height, weight, blood pressure; participants self-reported reproductive and clinical history, including age at menarche, number of pregnancies, number of births, and menopausal status. Participants who self-reported a history of cancer and those missing this information were excluded from the present analysis, in addition to participants who were missing information on their menopausal status. Missing values for variables with <10% missing for both cases and controls were replaced with the median (for continuous variables) or modal (for categorical variables) value of their respective group. For variables with more than >10% missing, a separate “missing” category was included (age at menarche).

Analytical approach

The sample was characterized via descriptive statistics, and results were reported as frequencies and proportions for categorical variables and medians (first quartile, third quartile) for continuous variables. Differences in associations by case/control status were tested using chi-square (χ^2) tests or Fisher exact tests for categorical variables and Kruskal-Wallis nonparametric tests for continuous variables. We estimated the association between each lipid biomarker (total cholesterol, HDL, LDL, and triglycerides) and odds of BC using logistic regression models. Each measure was analyzed separately in the following three models: unadjusted, adjusted for age only, and adjusted for age, body mass index (BMI), age at menarche, number of pregnancies, number of births, hypertension at enrollment, and menopausal status. In a final model, we mutually adjusted for all lipid measures in addition to all previous covariates. In each model, we specified each lipid biomarker as a categorical variable (high vs. low for total cholesterol, LDL, and triglycerides; and low vs. high for HDL), and also evaluated continuous measures of total cholesterol, HDL, LDL, and triglycerides based on one-unit standard deviation increase (for total cholesterol, LDL, and triglycerides) or decrease (for HDL). We further analyzed the subset of cases with cancer subtyping data available via multinomial logistic regression models. Control status was specified as the outcome reference group, and the fully adjusted model was repeated here to predict the odds of having Luminal A, Luminal B, TN, HER2 cancer subtypes. SAS v9.4 (SAS Institute, Cary, NC) was used for all analyses and significance was set at α=0.05.

Results

The present analysis includes 296 BC cases and 116 healthy controls (**Figure 1**). Cases were slightly older than controls—the median age at diagnosis for cases was 48.5 years, and the median age at enrollment for controls was 46 years (p = 0.0328; **Table 1**). There were no significant differences in reproductive characteristics among cases vs. controls; number of pregnancies (p = 0.7457), number of births (p = 0.7457), or menopausal status (p = 0.8799) among cases and controls. However, cases were more likely than controls to have high diastolic blood pressure (p = 0.0056), while controls were more likely to have higher BMI (p = 0.0451). Across total cholesterol quartiles (**Table 2**), those in the highest cholesterol group

were older (p = 0.0003), and more likely to be a higher weight (p = 0.0593), have a higher blood pressure (systolic: p = 0.0067; diastolic: p = 0.0202) and be post-menopausal (p = 0.0003). A higher proportion of controls relative to cases were within the lowest total cholesterol quartiles among participants who were 60 years or older and among those who were post-menopausal (**Figure 2**).

In fully adjusted multivariable logistic regression models (**Table 3**), one-unit SD increase in triglycerides was associated with 39% increased odds of BC (aOR: 1.39; 95% CI: 1.03, 1.86). High total cholesterol (aOR: 1.24; 95% CI: 0.94, 1.65) and LDL (aOR: 1.29; 95% CI: 0.97, 1.72) were associated with increased odds of BC, while low HDL (aOR: 0.89; 95% CI: 0.69, 1.14) was associated with reduced odds of BC but none of these estimates were statistically significant. In mutually adjusted models including all four lipid profile measures, each SD increase in triglycerides remained significantly associated with odds of BC (aOR 1.47; 95% CI 1.06, 2.03). No significant associations were noted for total cholesterol, HDL cholesterol, and LDL cholesterol in mutually adjusted models. Similar results were observed when examining categorical cut-points. In multinomial logistic regression models predicting the odds of each molecular subtype relative to controls (**Table 4; Figure 3**), clinically low HDL was associated with 2.7 times the odds of TNBC (aOR: 2.67; 95% CI: 1.10, 6.49). Additionally, each unit SD decrease in HDL was associated with 49% increased odds of TNBC (aOR 1.49; 95% CI: 0.94, 2.34), and each unit SD increase in LDL was associated with 64% increased odds of Luminal B BC (aOR: 1.64; 95% CI: 1.06, 2.55).

Discussion

For the first time, we describe the results of a case-control analysis of lipid biomarkers (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) and odds of BC and molecular subtypes among African women. Among cases and controls, those who were older, had high BMI and high blood pressure at enrollment were more likely to have high cholesterol. High triglycerides was the only lipid biomarker significantly associated with odds of BC in fully adjusted models. However, for molecular subtypes, low HDL and high LDL were significantly associated with odds of TNBC and Luminal B subtypes, respectively. None of the other lipid biomarkers were significantly associated with BC in this cohort.

Several past studies among populations from the United States, Europe, and Asia have evaluated the association between lipid biomarkers and BC risk, however results have been inconsistent. For total cholesterol, one study in Korea noted a positive association with BC risk [25], but others in the United States and Europe, like ours, have found no association [15,26], and one study additionally observed an inverse association [27]. In the context of LDL, a case-control study among African American women in the United States found a 59% reduction in risk among those who had clinically high levels of LDL cholesterol [14]. Other studies in the United States, Asia, and Europe, like ours, have also found no association [28,13], although one Mendelian randomization study among those of European descent documented a positive association [29]. We did not observe a significant association between HDL cholesterol and odds of BC. One study in Europe found an inverse association between HDL cholesterol

and BC risk [27], while a Mendelian randomization analysis in Europe found that an increase in genetically-predicted HDL was associated with increased BC risk [30]. However, others in the United States and Europe have failed to find an association with HDL [28,31]. Regarding triglycerides, one study using the Swedish AMORIS database noted a weak protective association with risk of BC [32], while others still have reported no association [27,33]. On the contrary, two small case-control studies in India and the United States, like ours, found a positive association between triglycerides and BC [34,35]. Ultimately, there is inconclusive evidence regarding the role of lipid biomarkers in BC risk, suggesting that additional studies on this topic are still warranted, and importantly, studies from diverse populations will be needed to determine if region-specific associations may explain the disparate findings.

Our analysis of Nigerian women on the association between lipid measures and BC subtypes revealed that low HDL cholesterol level is associated with increased odds of TNBC and that high LDL is associated with increased odds of Luminal B BC. Our HDL result is consistent with findings from a study from Korea reporting that low HDL cholesterol and high triglycerides were associated with an increased risk of developing hormone receptor negative tumors among premenopausal women [16]. Further, dyslipidemia, investigated as part of metabolic syndrome, was associated with TNBC, and specifically, low HDL was associated with TNBC among patients from the United States [36]. However, our subtype findings are inconsistent with a separate study in Spain that found that BC risk increased with increasing triglyceride levels among postmenopausal Luminal A BC [37]. Due to limitations in our sample size for the molecular subtype analysis, we were unable to stratify our sample by menopausal status; given that the majority of BC in Nigeria is pre-menopausal, future studies with larger sample sizes will be needed to examine these associations. Given that epidemiologic studies evaluating the association of lipid biomarkers and BC subtypes are very limited, our findings provide important initial evidence upon which future studies can expand.

The biological mechanisms underlying the association between lipids and BC remains unclear and is an active area of research. Studies have suggested that elevated serum cholesterol levels may advance tumor progression [38], and a recent review of laboratory studies suggests that cholesterol is capable of regulating proliferation, migration, and signaling pathways in BC [39]. Research on mechanisms underlying risk by molecular BC subtype is limited, however, as suggested by Llanos et al. [14], it is possible that HDL influences overall BC risk by moderating biologically active estradiol [40], a risk factor for BC among postmenopausal women [41]. Low HDL cholesterol may reflect an unfavorable hormonal profile, and the conversion of androgens to estrogens within adipose tissues may represent a causal mechanism for the inverse association between HDL and BC risk [40]. Fernandez and Murillo demonstrated that HDL is inversely correlated with waist circumference and higher BMI [42], providing support for the mediating role of adiposity. It is also possible that HDL plays a key role in reverse cholesterol transport that may contribute to the blocking of tumor progression and ultimately BC incidence. Although reverse cholesterol transport may be its primary role, HDL has also been shown to possess antimicrobial, antioxidant, antiglycation, anti-inflammatory, antiatherogenic, and immunosuppressive properties [43-45]. The numerous functions of HDL provide a plethora of opportunities for novel research, but also make pinpointing the exact mechanism by which it may confer

protection against BC difficult. Some of the conflicting results in the epidemiology of HDL and BC risk may be explained, in part, by the observation that the environment in which HDL exists in the body may influence its effect on BC cells. Pan and colleagues used *in vivo* and *in vitro* models of BC and observed that oxidized HDL and HDL derived from diabetic patients were associated with the promotion of metastasis and invasion to surrounding tissues [46-48]. Still, these explanations are not specific to TNBC and further studies are needed to fully characterize these mechanisms by BC subtype.

Understanding the mechanism by which HDL has shown an inverse association with TNBC is further complicated by challenges related to sample size as TNBC typically accounts for an estimated 15-20% of all BCs. Further, although an estimated 80% of TNBC are classified as the basal BC intrinsic subtype [49], new research suggests that TNBC may actually be quite heterogenous with respect to cellular and molecular features [50]. African American women tend to demonstrate patterns of TNBC occurrence that map more closely with women from western and sub-Saharan Africa than they do with women from east Africa, implicating a role of genetic factors [51,52]. That clinically low HDL was associated with TNBC provides a possibility of a therapeutic target for the BC subtype that is the most aggressive, has a poor prognosis, and by definition, cannot be targeted with pharmaceutical therapy designed for ER+ cancers. Still as we point out, the mechanisms underlying the inverse association between HDL and TNBC risk requires vigorous investigations, perhaps pooled analyses across existing studies may provide additional insight.

There are several strengths and limitations of this study that may impact the interpretation of these results. Many covariates were self-reported by participants, potentially introducing recall bias into our analysis. However, our main exposures of interest, namely total cholesterol, HDL, LDL, and triglycerides were assayed for cases and controls at the same time following the same standard assay protocol, thus minimizing batch effects. Additionally, due to the case-control study design, we are unable to rule out the possibility of reverse causality. It is possible that lipid levels may be influenced by the presence of BC, producing the observed association. Strengths of our study include the use of histologically confirmed cancer cases and pathologically verified molecular subtypes assessed by a single pathologist, the availability of data on critical reproductive history and clinical characteristics for covariate adjustment, and the unique study population of Nigerian women—adding to the diversity of study populations for this topic. Although our sample size is modest compared with other large cohorts, we emphasize that our study is the first to characterize the association between lipid profile measures and BC risk in Nigeria, and one of very few studies worldwide to evaluate the association between lipid profile measures and BC risk by subtype. We lay important groundwork for future large prospective studies among African women.

In conclusion, we report a positive association between triglycerides and odds of BC, and between low HDL with TNBC, and high LDL with Luminal B BC. Lipids are easily measured in clinical settings, making this an attractive target for cancer prevention strategies that may reduce the risk of BC.

Abbreviations

BMI
body mass index
BC
breast cancer
CKD
Chronic Kidney Disease
ER
estrogen receptor
HDL
high-density lipoprotein
HER2
human epidermal growth factor-2
H3
Human Heredity and Health
LDL
low-density lipoprotein
MEND
Mechanisms for Established and Novel Risk Factors for Breast Cancer in Women of African Descent
PR
progesterone receptor
TN
triple-negative

Declarations

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Competing Interests: The authors have no competing interests to declare.

Ethics Approval: This study was approved by Duke University and the participating hospitals' Institutional Review Boards (Pro00102004). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate: All participants included provided informed consent.

Data Availability Statement: The data that support the findings of the study are available from the corresponding author upon reasonable request.

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Compliance with Ethical Standards:

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Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1
Clinical and reproductive characteristics of MEND breast cancer cases and controls

Variable	Case N = 296	Controls N = 116	P-value
Demographics			
Age (years)[a]	48.5 (42.0, 57.0)	46.0 (40.0, 54.5)	0.0328
Clinical characteristics			
Lipid Profile[a]			
Total cholesterol (mg/dL)	169.0 (142.5, 199.5)	162.0 (131.0, 190.0)	0.0384
HDL-cholesterol (mg/dL)	49.6 (39.2, 59.2)	47.4 (35.7, 55.7)	0.0683
LDL-cholesterol (mg/dL)	83.1 (66.6, 104.6)	76.2 (58.8, 97.5)	0.0376
Triglycerides (mg/dL)	87.0 (60.0, 125.0)	74.0 (57.0, 104.0)	0.0478
Total cholesterol (mg/dL)			0.3927
High (> 200)	73 (24.7)	24 (20.7)	
Low (≤ 200)	223 (75.3)	92 (79.3)	
HDL-cholesterol (mg/dL)			0.3587
Low (< 50)	151 (51.0)	65 (56.0)	
High (≥ 50)	145 (49.0)	51 (44.0)	
LDL-cholesterol (mg/dL)			0.1680
High (> 100)	89 (30.1)	27 (23.3)	
Low (≤ 100)	207 (69.9)	89 (76.7)	
Triglycerides (mg/dL)			0.1493
High (> 150)	47 (15.9)	12 (10.3)	
Low (≤ 150)	249 (84.1)	104 (89.7)	
Height (in)[a]	63.1 (61.4, 64.8)	63.0 (61.0, 65.4)	0.9311
Weight (lb)[a]	143.0 (121.0, 165.2)	152.7 (127.9, 176.4)	0.0227
Systolic BP[a]	125.0 (114.7, 140.5)	122.7 (109.2, 135.5)	0.0687
Diastolic BP[a]	79.7 (70.7, 88.7)	75.0 (68.0, 82.8)	0.0056

Variable	Case N = 296	Controls N = 116	P-value
Body Mass Index (BMI)[a]	25.4 (22.2, 29.6)	26.5 (23.1, 31.4)	0.0451
Hypertension at enrollment	87 (29.4)	25 (21.6)	0.1077
Reproductive history			
Age at menarche			0.8851
≤ 13	60 (20.3)	19 (16.4)	
> 13	230 (77.7)	76 (65.5)	
Missing	6 (2.0)	21 (18.1)	
Ever pregnant	282 (95.3)	110 (94.8)	0.8508
Number of pregnancies[a,b]	5.0 (3.0, 6.0)	5.0 (3.0, 6.0)	0.7457
Number of births[a.b]	4.0 (3.0, 5.0)	4.0 (2.0, 5.0)	0.8457
Menopausal status			0.8799
Pre- or peri-menopause	143 (48.3)	57 (49.1)	
Post-menopause	153 (51.7)	59 (50.9)	
Cancer type	N = 124	N/A[c]	
Luminal A	33 (26.6)		
Luminal B	26 (21.0)		
Triple-negative	37 (29.8)		
HER2+	28 (22.6)		

[a]Median (Q1, Q3).
[b]Among those who were ever pregnant.
[c]Cancer variables are not applicable to control participants.
Where applicable, missing values were not used to compute p-value.

Table 2. Clinical and reproductive characteristics of MEND cases and controls by quartile of total cholesterol

	Quartile of Total Cholesterol (mg/dL)				
Variable	Q1 ≤140.00 mg/dL N = 104	Q2 >140.00 - ≤167.00 mg/dL N = 105	Q3 >167.00 - ≤198.00 mg/dL N = 102	Q4 >198.00 mg/dL N = 101	P-value
Case status					0.1291
Case	66 (22.3)	75 (25.3)	78 (26.4)	77 (26.0)	
Control	38 (32.8)	30 (25.9)	24 (20.7)	24 (20.7)	
Demographics					
Age (years)[a]	44.0 (38.5, 52.0)	46.0 (41.0, 55.0)	49.0 (42.0, 59.0)	52.0 (47.0, 59.0)	0.0003
Clinical characteristics					
Height (in)[a]	63.0 (61.1, 64.9)	63.4 (62.2, 65.0)	63.0 (60.8, 64.6)	63.1 (61.6, 65.5)	0.3569
Weight (lb)[a]	137.7 (121.1, 160.7)	143.3 (120.8, 172.0)	143.3 (125.5, 174.4)	152.1 (130.1, 176.4)	0.0593
Systolic BP[a]	124.3 (111.0, 138.8)	119.7 (110.0, 134.0)	125.3 (115.7, 144.7)	130.3 (120.0, 145.0)	0.0067
Diastolic BP[a]	76.5 (69.7, 87.3)	75.0 (68.7, 82.3)	80.0 (70.7, 89.7)	80.0 (71.0, 90.0)	0.0202
Body Mass Index (BMI)[a]	24.6 (20.9, 28.7)	25.4 (21.8, 29.7)	25.9 (23.3, 30.3)	26.2 (23.1, 31.5)	0.0396
Hypertension at enrollment	26 (23.2)	20 (17.9)	29 (25.9)	37 (33.0)	0.0385
Reproductive history					
Age at menarche					0.0222
≤ 13	30 (38.0)	15 (19.0)	17 (21.5)	17 (21.5)	
>13	65 (21.2)	81 (26.5)	79 (25.8)	81 (26.5)	
Missing	9 (33.3)	9 (33.3)	6 (22.2)	3 (11.1)	
Ever pregnant	97 (24.7)	101 (25.8)	96 (24.5)	98 (25.0)	0.5878
Number of pregnancies[a,b]	4.0 (4.0, 6.0)	5.0 (3.0, 7.0)	5.0 (3.0, 6.0)	5.0 (3.0, 6.0)	0.9480

	Quartile of Total Cholesterol (mg/dL)				
Number of births[a.b]	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	0.8751
Menopausal status					0.0003
Pre- or peri-menopause	67 (33.5)	53 (26.5)	44 (22.0)	36 (18.0)	
Post-menopause	37 (17.5)	52 (24.5)	58 (27.4)	65 (30.7)	

[a]Median (Q1, Q3).
[b]Among those who were ever pregnant.
Where applicable, missing values were not used to compute p-value.

Table 3

Associations between lipid profile biomarkers and odds of cancer status

	Model 1[a] OR (95% CI)	Model 2[b] aOR (95% CI)	Model 3[c] aOR (95% CI)	Model 4[d] aOR (95% CI)
Total Cholesterol (mg/dL)				
High vs. Low	1.26 (0.75, 2.11)	1.14 (0.67, 1.94)	1.13 (0.63, 2.02)	0.61 (0.28, 1.31)
per one-unit SD increase	1.27 (1.00, 1.62)	1.23 (0.96, 1.57)	1.24 (0.94, 1.65)	0.65 (0.32, 1.33)
HDL Cholesterol (mg/dL)				
Low vs. High	0.82 (0.53, 1.26)	0.84 (0.54, 1.30)	0.94 (0.58, 1.52)	0.89 (0.54, 1.47)
per one-unit SD decrease	0.81 (0.65, 1.01)	0.82 (0.66, 1.02)	0.89 (0.69, 1.14)	0.75 (0.52, 1.08)
LDL Cholesterol (mg/dL)				
High vs. Low	1.42 (0.86, 2.33)	1.30 (0.79, 2.16)	1.54 (0.87, 2.72)	2.32 (1.10, 4.89)
per one-unit SD increase	1.23 (0.97, 1.56)	1.18 (0.93, 1.50)	1.29 (0.97, 1.72)	1.59 (0.88, 2.89)
Triglycerides (mg/dL)				
High vs. Low	1.64 (0.83, 3.21)	1.54 (0.78, 3.04)	1.61 (0.76, 3.39)	1.70 (0.79, 3.66)
per one-unit SD increase	1.32 (1.03, 1.70)	1.28 (0.99, 1.64)	1.39 (1.03, 1.86)	1.47 (1.06, 2.03)

Logistic regression models predicted odds of having cancer using lipid profile biomarkers. ORs per one-unit SD were modeled as a one-unit increase/decrease in standard deviation of the lipid profile variable from its mean-centered value. Bolded values indicate significance at $p < .05$.
High total cholesterol defined as > 200 mg/dL; low HDL defined as < 50 mg/dL; high LDL defined as > 100 mg/dL; high triglycerides defined as > 150 mg/dL.

[a]Model 1, unadjusted.

[b]Model 2, adjusted for age.

[c]Model 3, additionally adjusted for clinical characteristics: BMI, age at menarche, number of pregnancies, number of births, hypertension at enrollment, and menopausal status.

[d]Model 4, additionally adjusted for all lipid profile biomarkers: total cholesterol, LDL, HDL, and triglycerides.

Abbreviations: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; SD, standard deviation.

Table 4

Associations between lipid biomarkers and breast cancer subtype

	Luminal A	Luminal B	Triple Negative	HER2
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Total Cholesterol (mg/dL)				
High vs. Low	0.63 (0.20, 1.98)	1.38 (0.49, 3.92)	0.92 (0.35, 2.41)	1.17 (0.41, 3.31)
per one-unit SD increase	0.99 (0.64, 1.55)	1.34 (0.92, 1.96)	0.98 (0.63, 1.51)	1.01 (0.65, 1.57)
HDL Cholesterol (mg/dL)				
Low vs. High	0.92 (0.38, 2.22)	1.11 (0.44, 2.78)	2.67 (1.10, 6.49)	0.91 (0.37, 2.26)
per one-unit SD decrease	0.96 (0.64, 1.44)	0.84 (0.53, 1.32)	1.49 (0.94, 2.34)	0.93 (0.60, 1.45)
LDL Cholesterol (mg/dL)				
High vs. Low	1.96 (0.71, 5.40)	2.56 (0.92, 7.11)	2.10 (0.87, 5.11)	1.72 (0.61, 4.80)
per one-unit SD increase	1.21 (0.75, 1.98)	1.64 (1.06, 2.55)	1.34 (0.88, 2.06)	1.02 (0.60, 1.72)
Triglycerides (mg/dL)				
High vs. Low	1.03 (0.25, 4.34)	1.12 (0.28, 4.58)	1.57 (0.51, 4.85)	2.64 (0.81, 8.59)
per one-unit SD increase	1.32 (0.81, 2.15)	1.53 (0.97, 2.42)	1.38 (0.90, 2.11)	1.36 (0.85, 2.18)

Multinomial logistic regression models predicted odds of having each cancer subtype, compared to no cancer, using lipid profile biomarkers. ORs per one-unit SD were modeled as a one-unit increase/decrease in standard deviation of the lipid profile variable from its mean-centered value. Bolded values indicate significance at $p < .05$.
High total cholesterol defined as > 200 mg/dL; low HDL defined as < 50 mg/dL; high LDL defined as > 100 mg/dL; high triglycerides defined as > 150 mg/dL.
Models were adjusted for age and clinical characteristics: BMI, age at menarche, number of pregnancies, number of births, hypertension at enrollment, and menopausal status.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation.

Figures

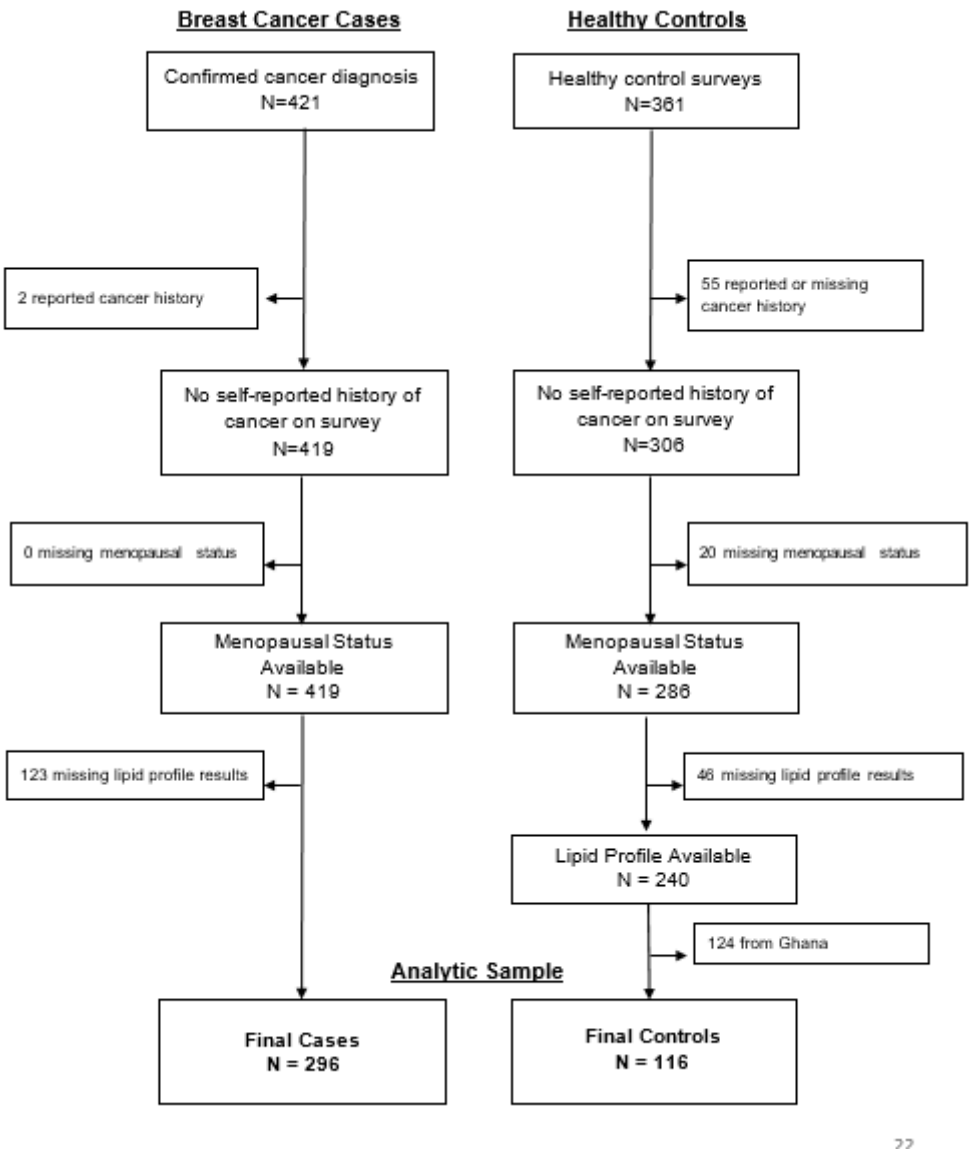

Figure 1

CONSORT diagram for MEND lipid profile analysis

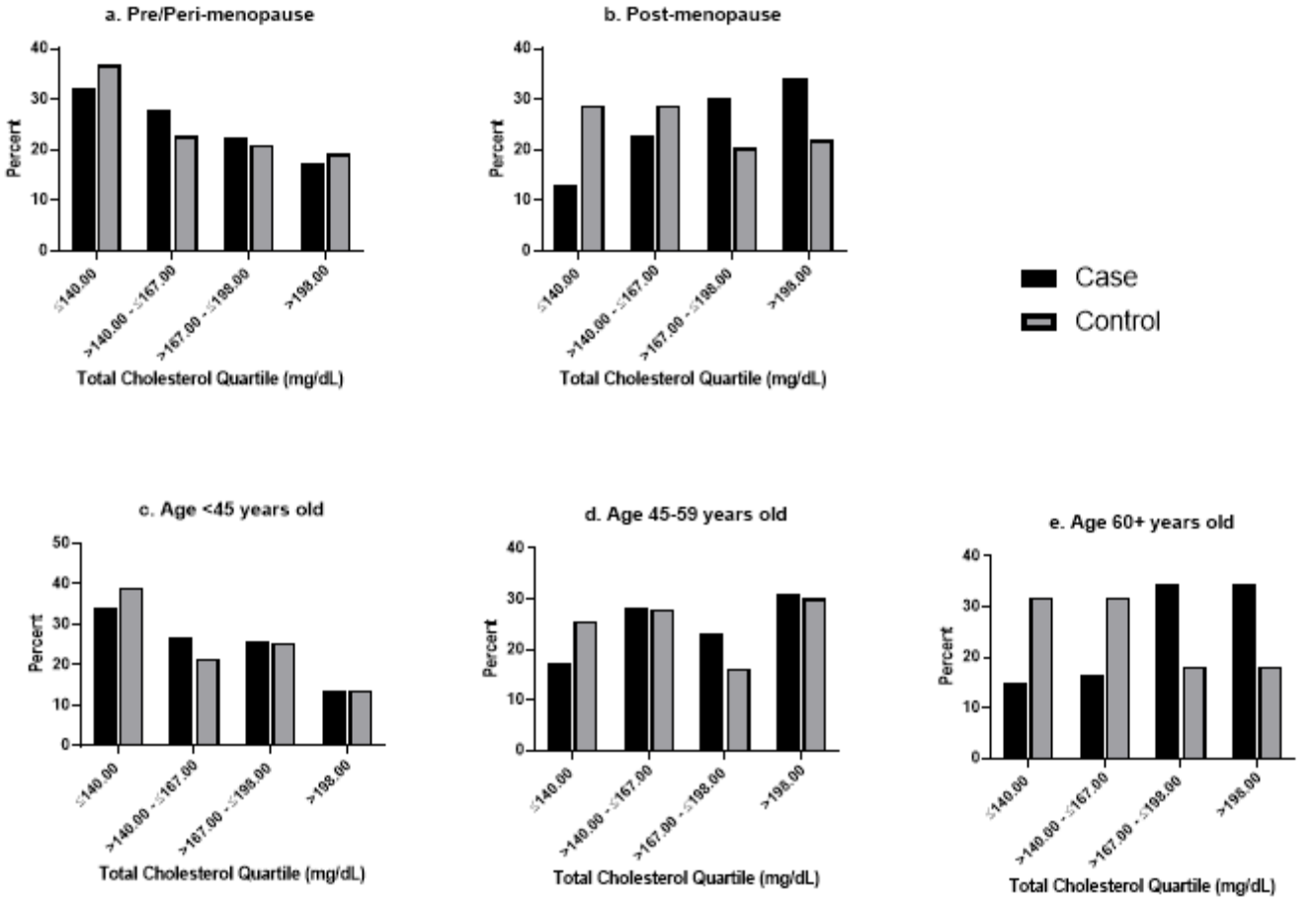

Figure 2

Total cholesterol quartile by case/control status and clinical factors

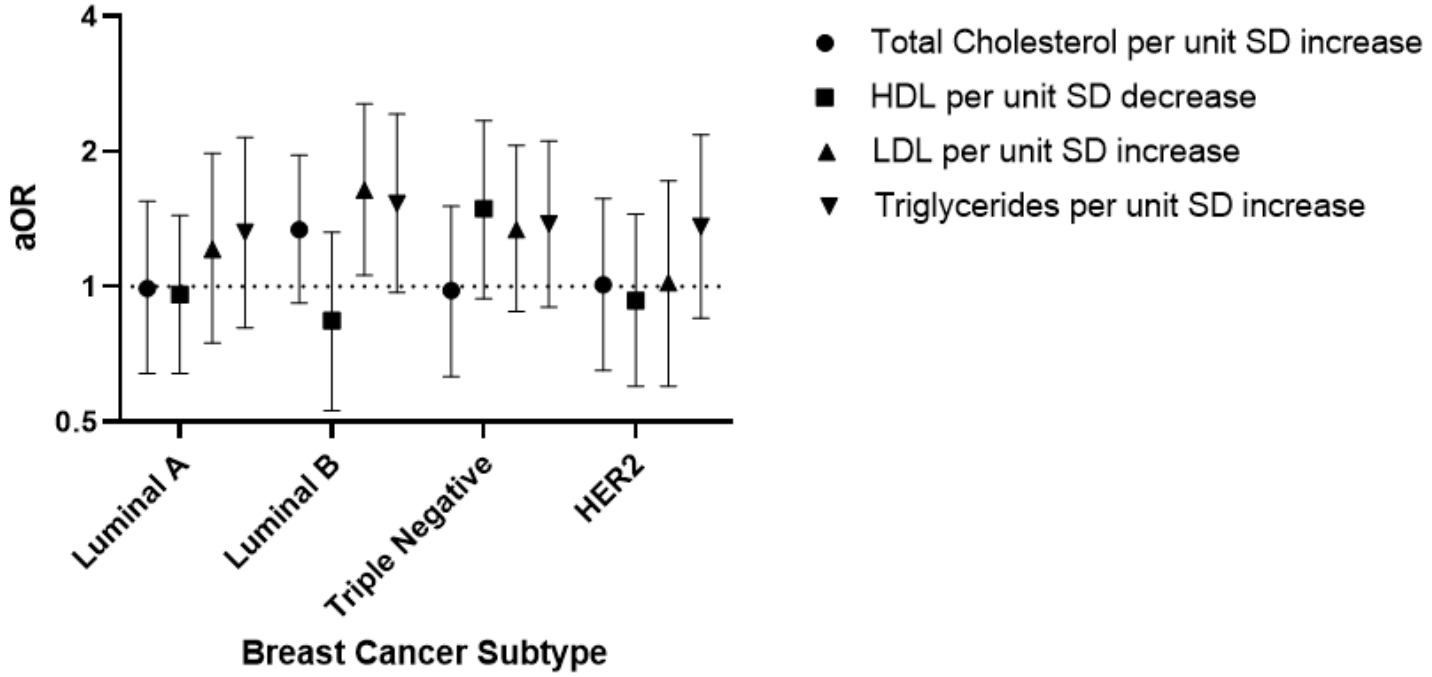

Figure 3

Associations between lipid biomarkers and breast cancer subtypes (reference group = control; adjusted for age, BMI, age at menarche, number of pregnancies, number of births, hypertension at enrollment, and menopausal status)