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ORIGINAL PAPER

Circulating lipids, mammographic density, and risk of breast cancer in the Nurses' Health Study and Nurses' Health Study II

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Abstract

Purpose Epidemiologic evidence supports an association between high mammographic density and increased breast cancer risk yet etiologic mechanisms remain largely unknown. Mixed evidence exists as to whether circulating lipid levels influence mammographic density and breast cancer risk. Therefore, we examined these associations in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), two large prospective cohorts with information on PMD and circulating lipid measures, long follow-up, and breast cancer risk factor and outcome data.

Methods We conducted a nested case–control study among women in the NHS and NHSII. Percent mammographic density (PMD) was measured using Cumulus software, a computer-assisted method, on digitized film mammograms. Cross-sectional associations between circulating lipids [total cholesterol ($n = 1{,}502$), high-density lipoprotein (HDL-C; $n = 579$), and triglycerides ($n = 655$)] and PMD were evaluated among controls. All analyses were stratified by menopausal status at time of mammogram. Relative risks for breast cancer by lipid and PMD measures were estimated among postmenopausal women in the full nested case–control study (cases/controls for cholesterol, HDL-C, and triglycerides were 937/975, 416/449, and 506/537, respectively).

Results There were no significant associations between circulating lipid levels and PMD among healthy women, irrespective of menopausal status. The association between PMD and breast cancer risk among postmenopausal women was not modified by circulating lipid levels (p interaction = 0.83, 0.80, and 0.34 for total cholesterol, HDL-C, and triglycerides, respectively).

Conclusion Overall, no association was observed between lipid levels and PMD, and there was no evidence that lipid levels modified the association between PMD and breast cancer risk.

Keywords Breast neoplasms · Mammography · Lipids · Cholesterol · Breast density

Introduction

High percent mammographic density (PMD), indicating the presence of a high amount of fibroglandular tissue relative to adipose tissue in the breast, is strongly and consistently

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associated with increased risk of breast cancer [1]. Epidemiologic evidence indicates that the risk of breast cancer is 1.5- to 2-times greater for women with extremely dense breasts [> 75% dense; Breast Imaging Reporting and Data System score of 4 (BIRADS-4)] compared to women with average PMD (25–50% dense; BIRADS-2) [2]. High mammographic density is common and generally decreases with age and parity [3], with an estimated 37% of premenopausal and 12% of postmenopausal women having breast densities > 50% [1]. While consistent epidemiologic evidence supports a link between dense breasts and increased risk of breast cancer, the etiologic mechanisms by which higher fractions of connective and ductal tissue, compared to adipose tissue, in the breast contribute to the carcinogenic process remain largely hypothetical [4, 5].

Circulating lipids, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides, play key physiologic roles in cholesterol transport and in energy expenditure within the human body. To date, the few studies that have investigated the potential links between various circulating lipids and mammographic density have been inconclusive, with Aiello et al. [6] observing positive associations between total cholesterol and LDL-C, but not HDL-C, and mammographic density only in former hormone therapy users and Flote et al. [7] observing positive associations between HDL-C and PMD. Two additional studies have observed no associations between LDL-C, HDL-C, or triglycerides and breast density after adjustment for potential confounders [8, 9]. Methodological limitations such as modest sample size [6, 7, 9] and inclusion of only pre- [7, 9] or postmenopausal women [6] may contribute to the difficulty in interpreting these findings.

It has been hypothesized that HDL-C and LDL-C may influence cancer risk because of their roles in transporting cholesterol-a sterol involved in, among many biological processes, the biosynthesis of steroid hormones [10]. Estrogen levels, in particular, may play a role, as prior studies have observed associations between HDL-C and estrogen [7, 11] as well as between estrogen and breast cancer risk [12, 13]. Nevertheless, the evidence connecting circulating lipids with breast cancer risk is mixed, with several studies showing positive associations between HDL-C levels and breast cancer risk [9, 11, 14, 15] while others show inverse associations [16–18]. Prior investigation within the Nurses' Health Study showed no association between self-reported cholesterol and breast cancer risk [19]. Of these prior studies, only tangential investigation of any connections between circulating lipids, mammographic density, and breast cancer risk has been done, with one study restricted to women with high PMD (> 50%) showing significant associations between HDL-C and breast cancer risk [OR for 75th v. 25th percentile: 1.23 (95% CI 1.00, 1.51)] [15].

These prior studies provide some information on the potential connections between circulating lipids, PMD, and breast cancer risk, but no study has investigated all three factors jointly within a population of women with varying mammographic densities. To elucidate these relationships more clearly, we examined these associations in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), two large prospective cohorts with information on PMD and circulating lipid measures, long follow-up, and breast cancer risk factor and outcome data.

Methods

Study population

The NHS and the NHSII are long-standing prospective cohort studies. NHS was established in 1976 and included 121,701 registered female nurses residing in the United States between the ages of 30–55 at enrollment. NHSII is an ongoing cohort of 116,429 women who were between 25 and 42 years old at baseline in 1989. Nurses in both cohorts complete self-administered questionnaires every 2 years to collect updated information on diseases and risk factors, including weight, age at menarche, parity, alcohol use, menopause hormone therapy (MHT), and medication use.

Circulating lipid measures

Blood samples were collected from 32,826 cancer-free women in NHS between 1989 and 1990 and from 29,611 women in NHSII between 1996 and 1999. Briefly, blood was collected in heparin-treated tubes, stored on ice during transport to the laboratory, centrifuged, separated into plasma, red blood cell and white blood cell components, and divided into aliquots. As fasting status was not the same across all samples, information on fasting time was collected for each sample. All blood samples were stored in liquid nitrogen freezers (− 196° C) after collection. Greater detail on sample collection and design in this nested case–control study can be found in prior publications [20–22].

Breast cancer cases were identified in NHS through 1 June 2011 and in NHSII through 1 June 2007. Cases and controls were matched on age (± 2 years), menopausal status at blood draw, MHT, month/year of blood collection, time of blood draw (± 2 h), and fasting status, with NHSII cases and controls additionally matched on race and luteal day for premenopausal women (± 1 day). It should be noted that these matched pairs could not be maintained through this study, as PMD measures were not obtained for all cases and controls.

For the NHS, incident breast cancer cases were identified at each follow-up cycle and circulating lipid levels were assayed in their respective blood samples as well as those

of selected controls. For the NHSII, circulating lipid levels were assayed in 2011 for all incident cases over the follow-up and the identified controls. Total cholesterol, high-density lipoprotein, and triglyceride levels (mg/dL) were assayed with enzymatic methods using Roche Diagnostics reagents as previously described [23, 24]. Plasma total cholesterol was assayed in 12 batches for NHS and 4 batches for NHSII, yielding 5,840 women with cholesterol measures. Plasma triglyceride levels were assayed in eight batches in NHS for 2,685 women. High-density lipoprotein levels were assayed in three batches for 1,467 women in NHS. Case–control pairs were always assayed in the same batch and were placed next to each other in random order. To account for batch-to-batch variation in lipid measures and to facilitate reporting absolute levels, all batches were recalibrated to achieve a distribution comparable to an 'average' batch for each lipid separately, independent of BMI, age, menopausal status, and case–control status, according to methods previously outlined [25]. The range for within-run mean CVs for total cholesterol, HDL-C, and triglycerides were (1.3–14.0%), (5.8–14.7%), and (5.9–15.7%), respectively.

Mammographic density measures

Mammograms were successfully obtained from approximately 80% of eligible women, and those who provided mammograms had similar breast cancer risk factors compared with those who did not [20, 26]. PMD was assessed using films from the most recent mammogram procedures to blood collection (median time from blood collection to mammogram: 14 months; interquartile range: (-55 months, 1 month) among controls). For all films from NHS and the first two batches of NHSII, mammogram films of both breasts using the craniocaudal views were digitized at 261 μm/pixel with a Lumisys 85 laser film scanner covering the range of 0–4.0 absorbance. The third batch of mammograms from NHSII was scanned using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, Virginia) at a resolution of 150 dots per inch and 12-bit depth. In a sample of 50 mammograms digitized with both scanners, the correlation between percent mammographic density measurements from the digitized images from each scanner was 0.88 with a mean difference of 2.3 percentage points. Total dense area and total breast area were quantified using Cumulus software [27]. Percent density measures were calculated by dividing absolute dense area by total breast area. Two individuals read images collected for NHS, and all images for NHSII were read by one of these same individuals. No batch effects were present for NHS mammograms, but there was evidence of between-batch variability for the NHSII mammograms. To address this variability, we fitted multivariable linear regression models to estimate the effect of batch on density measures while adjusting for age, menopausal status, BMI, and case status [20]. The second and third batches from NHSII were then adjusted to estimate the density values that would have been obtained had they been in the first batch. Percent density was averaged across both breasts.

Statistical analyses

For the final analyses, women were excluded if missing information on BMI at the time of blood draw ($n=2$) or at age 18 ($n=109$). An indicator variable for missingness was utilized for the alcohol use variable ($n=67$, 27, and 32 controls and $n=59$, 30, and 33 cases for total cholesterol, HDL-C, and triglyceride analyses, respectively). Separate cross-sectional analyses of the association between each circulating lipid and PMD were conducted among controls for total cholesterol on 1,502 women (527 premenopausal; 975 postmenopausal), for HDL-C on 579 women (130 premenopausal; 449 postmenopausal), and for triglycerides on 655 women (118 premenopausal; 537 postmenopausal). Measures for all three markers were available for a small group of controls (46 and 257 pre- and postmenopausal women, respectively).

To analyze the association between circulating lipid levels and PMD, we conducted a cross-sectional analysis among controls, stratifying women by menopausal status at the time of mammographic evaluation. Multivariable linear regression models were fit using PMD (for normality purposes, square root-transformed PMD was used) as the dependent variable and quartile of lipid level as the independent variable. Models were run separately for total cholesterol, HDL-C, and triglycerides. Minimal models were run, adjusting for age, BMI at blood draw, time and fasting status of blood draw. Full models were adjusted for parity and age at first birth (nulliparous; 1–2 children and < 25 years; 1–2 children and 25-29 years; 1–2 children and ≥ 30 years; 3 + children and < 25 years; 3 + children and ≥ 25 years), alcohol intake (none, < 5, ≥ 5 g/day, missing), race (white, non-white), cohort (NHS, NHSII), fasting status (> 8 h, ≤ 8 h), age at menarche (< 12 (reference), 12, 13, ≥ 14 years), use of MHT (never, past, current), age at blood draw (continuous), BMI at age 18 (continuous), BMI at blood draw (continuous), family history of breast cancer (yes, no), and biopsy-confirmed history of benign breast disease (yes, no). These variables were selected due to their status as established predictors of mammographic density and/or breast cancer. For triglyceride and HDL-C models, the 'cohort' variable was not included as all samples were obtained only from NHS. Tests for trend were conducted using the median lipid level of each quartile as a continuous variable.

Additional models were stratified by BMI category (Normal [≤ 25 kg/m^2] and Overweight/Obese [> 25 kg/m^2]) in order to further investigate the intersection between menopausal status,

BMI, and mammographic density. Associations were also modeled for total cholesterol and HDL-C restricting to control women with high PMD (> 50% average percent density) to replicate conditions from the recent Martin et al. [2015] study. In secondary analyses, we investigated the outcomes of absolute dense and non-dense breast area as alternative measures of breast density. Analyses were also conducted in the group with complete measures on all three markers ($n = 257$ controls). Sensitivity analyses were also conducted in which we excluded women who were taking cholesterol-lowering drugs ($n = 122$ excluded) or on MHT ($n = 509$, 210, and 282 excluded for total cholesterol, HDL-C, and triglycerides, respectively) at time of blood draw, as these treatments may have been potential confounders.

Prospective analyses of the association between circulating lipids and PMD on breast cancer risk among postmenopausal women were conducted for total cholesterol among 1,912 women (937 cases, 975 controls), for HDL-C on 865 women (416 cases, 449 controls), and for triglycerides on 1,043 women (506 cases, 537 controls). Due to low numbers, it was not possible to estimate the association between circulating lipids and PMD on breast cancer risk among premenopausal women. Analyses were also conducted among the 257 postmenopausal controls and 217 postmenopausal cases with complete measures for all lipid markers.

To determine if the association between circulating lipid levels and breast cancer risk varied by mammographic density among postmenopausal women, we used unconditional logistic regression modeling as a cross-classified variable between lipid tertile and average percent density tertile with the lowest tertile of lipid measure and lowest tertile of average percent density as the reference category. Tertiles were calculated using the distribution of markers among controls. Models were adjusted for age, BMI, blood matching factors, alcohol consumption, race, family history of breast cancer, prior diagnosis of benign breast disease, age at menarche, MHT, and parity/age at first birth. Odds ratios, p trend statistics, p interaction statistics, and 95% confidence intervals (CI) were calculated. We also conducted models after excluding cases diagnosed within 12 months of blood collection ($n = 59$, 48, and 45 for total cholesterol, HDL-C, and triglyceride analyses, respectively).

All analyses were conducted using SAS version 9.4 for UNIX (SAS Institute, Cary, NC). All p values were based on two-sided tests and considered statistically significant if < 0.05.

Results

Demographic characteristics

Established risk factors for breast cancer were examined in relation to circulating total cholesterol (Table 1). Total cholesterol level was inversely associated with benign breast disease (BBD) and current use of MHT among postmenopausal women. Total cholesterol was positively associated with BMI at time of blood draw for both pre- and postmenopausal women, age at blood draw and mammogram, and family history of breast cancer among premenopausal women.

HDL-C level was positively associated with alcohol among postmenopausal women, while inversely associated with MHT in postmenopausal women and BMI at blood draw among all women (Table S1). Triglyceride level was positively associated with BMI at age 18 in premenopausal women, inversely associated with parity and family history of breast cancer in postmenopausal women, and positively associated with BMI among pre- and postmenopausal women (Table S2).

Cross-sectional associations between circulating lipoproteins and mammographic density

Among premenopausal women, increasing levels of total cholesterol were weakly inversely associated with average PMD in the minimally adjusted model (Table 2; p trend: 0.12). There was little evidence of confounding by other covariates in the fully adjusted model [Estimate (EST) for Q4 vs. Q1: −0.24 (95% CI −0.59, 0.11); Table 2). Among postmenopausal women (Table 3), there was no association between total cholesterol and PMD (p trend: 0.36 for full model). While not statistically significant for either pre- or postmenopausal women, HDL-C levels appeared to be positively associated with PMD [e.g., in premenopausal women: EST for Q4 vs. Q1: 0.74 (95% CI −0.11, 1.58); p trend: 0.10]. Triglyceride levels were not associated with PMD for either pre- or postmenopausal women [e.g., for postmenopausal women: EST for Q4 vs. Q1: −0.13 (95% CI −0.51, 0.25)]. The results were similar when excluding women taking cholesterol-lowering drugs (or with unknown use of cholesterol-lowering drugs) at time of blood draw (data not shown). When restricting the analyses to women not currently on MHT (Table 3), no clear differences from the analyses including current MHT users were apparent. Restriction to women with measures on all three markers also did not qualitatively alter the results (data not shown).

Upon stratification by BMI, no significant associations were seen between lipids and PMD among overweight/obese postmenopausal women [e.g., EST for Q4 vs. Q1 in HDL-C: 0.64 [95% CI −0.23, 1.50); Table 4]. Among postmenopausal lean women, HDL-C was significantly positively associated with square root percent density [EST for Q4 vs. Q1: 0.61 (95% CI −0.03, 1.26); p trend: 0.03]; however, there was no evidence of significant statistical interaction between BMI and HDL-C (p interaction: 0.56). When analyses were restricted to the subset of women who were currently not

Table 1 Demographic characteristics at blood collection for breast cancer controls in NHS and NHSII by quartile of serum total cholesterol (mg/dL), stratified by menopausal status

	Premenopausal controls ($n=527$) Quartiles of circulating total cholesterol				Postmenopausal controls ($n=975$) Quartiles of circulating total cholesterol			
	Q1 ($n=131$)	Q2 ($n=134$)	Q3 ($n=128$)	Q4 ($n=134$)	Q1 ($n=243$)	Q2 ($n=244$)	Q3 ($n=243$)	Q4 ($n=245$)
Total cholesterol (median, mg/dL)	161.6 (12.2)	184.9 (5.5)	205.1 (6.7)	235.4 (24.2)	177.6 (14.1)	206.0 (6.8)	228.9 (7.2)	260.6 (20.0)
Square root mammographic density (%)	6.5 (1.7)	6.3 (1.7)	6.2 (1.8)	5.8 (1.7)	4.7 (1.8)	4.8 (1.9)	4.8 (1.8)	4.6 (1.9)
Age at blood draw (y)	44.5 (4.7)	44.9 (4.6)	45.3 (4.1)	46.9 (4.4)	55.7 (6.7)	56.3 (6.9)	56.9 (6.8)	57.2 (6.1)
Age at mammogram (y)	46.0 (4.3)	45.9 (4.4)	46.2 (3.9)	47.9 (4.4)	58.6 (7.2)	59.3 (7.4)	59.1 (7.2)	60.0 (7.3)
BMI at age 18 (kg/m^2)	20.8 (2.4)	21.1 (3.1)	21.1 (2.7)	21.6 (2.9)	21.2 (2.8)	21.2 (3.1)	21.0 (2.9)	21.3 (3.0)
Current BMI (kg/m^2)	24.2 (4.6)	25.3 (6.2)	25.0 (5.1)	26.5 (5.1)	25.1 (5.2)	25.4 (4.8)	25.5 (4.9)	26.1 (5.0)
Parity (children)	2.3 (1.3)	2.2 (1.4)	2.2 (1.3)	2.2 (1.2)	3.0 (1.7)	2.9 (1.7)	3.1 (1.9)	2.9 (1.7)
Age at first birth (y)	26.2 (4.0)	25.8 (4.0)	25.3 (3.7)	25.5 (3.8)	24.8 (2.9)	25.2 (3.4)	25.1 (3.5)	25.2 (3.7)
Alcohol use (g/day)	3.8 (7.2)	4.6 (7.5)	4.8 (7.4)	4.7 (7.3)	4.9 (7.5)	6.7 (11.6)	5.8 (9.2)	6.1 (8.8)
Family history of breast cancer (%)	8	8	10	12	12	10	9	11
Diagnosis of biopsy-confirmed BBD (%)	19	14	20	20	26	21	20	18
Menopause hormone therapy (%)	*NA*	*NA*	*NA*	*NA*				
Current					58	54	53	44
Past					17	20	18	20
Never					25	26	29	36

Values are means (SD) or percentages

Among premenopausal controls, $n=218$ from NHS and $n=309$ from NHSII. Among postmenopausal controls, $n=872$ from NHS and $n=103$ from NHSII

on MHT ($n=239$), a non-significant positive association between HDL-C and PMD was seen for both lean and overweight/obese women [EST for Q4 vs. Q1 for lean women: 0.76 (95% CI −0.28, 1.80)]. There was no association between total cholesterol and triglycerides with mammographic density among lean or heavy women in the full dataset (Table 4), but we saw a significant inverse association between triglyceride level and PMD among lean postmenopausal women when restricting to women who were not currently on MHT [EST for Q4 vs. Q1: −0.89 (95% CI −1.63, −0.14); p trend: 0.03]. Upon testing for interaction among women not currently on MHT, no significant interaction between BMI and triglyceride level was apparent (p interaction = 0.17).

In analyses investigating lipid levels and absolute dense breast area, no significant associations with HDL-C were observed, but total cholesterol was positively associated with dense area among postmenopausal women [EST for Q4 vs. Q1: 0.41 (95% CI 0.04, 0.79); p trend: 0.03; Table S3]. For non-dense area analyses (Table S4), HDL-C was inversely associated [EST for Q4 vs. Q1: −0.92 (95% CI −1.79, −0.05); p trend: 0.03] while triglycerides were positively associated [EST for Q4 vs. Q1: 0.91 (95% CI 0.36, 1.46); p trend: 0.001] with non-dense area among postmenopausal women. Upon restriction to women with PMD > 50% ($n=101$ for total cholesterol, $n=55$ for HDL-C), no association between lipids and PMD was observed.

Circulating lipoproteins, mammographic density, and breast cancer risk

Across all lipid analyses, cases had greater PMD, more frequently reported a family history of breast cancer, and were more likely to report a prior diagnosis of biopsy-confirmed BBD than control women (Table S5). Among postmenopausal women, there was no association between total cholesterol and breast cancer risk regardless of extent of PMD [e.g., OR for T3 vs. T1 total cholesterol among T1 of PMD: 1.10 (95% CI 0.71, 1.70); Table 5]. As expected, compared to women with low PMD, women in the top tertile of PMD had approximately twice the risk of breast cancer (OR 2.27, 95% CI 1.75, 2.94; data not shown), but the association did not vary by cholesterol level (p interaction: 0.83). Similar results were observed for HDL-C (Table 5; p interaction: 0.80). In contrast, higher triglyceride concentrations were associated with increased risk of breast cancer among

Table 2 Beta estimates, representing the predicted change in square root percent mammographic density for each respective quartile of circulating lipid compared to the lowest quartile, among premenopausal controls[a]

Total cholesterol ($n=527$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=131$)	$Q2$ ($n=134$)	$Q3$ ($n=128$)	$Q4$ ($n=134$)	
Age-adjusted[c]	Ref.	−0.14 (−0.55, 0.27)	−0.28 (−0.69, 0.14)	−0.57 (−0.99, −0.15)	**0.01**
Minimal model[d]	Ref.	0.03 (−0.33, 0.38)	−0.16 (−0.52, 0.20)	−0.24 (−0.60, 0.13)	0.13
Full model[e]	Ref.	0.03 (−0.31, 0.37)	−0.12 (−0.46, 0.23)	−0.24 (−0.59, 0.11)	0.12
HDL-C ($n=130$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=32$)	$Q2$ ($n=33$)	$Q3$ ($n=33$)	$Q4$ ($n=32$)	
Age-adjusted[c]	Ref.	1.01 (0.08, 1.93)	1.45 (0.52, 2.38)	1.33 (0.41, 2.26)	**0.01**
Minimal model[d]	Ref.	0.71 (−0.15, 1.57)	0.99 (0.10, 1.88)	0.55 (−0.37, 1.47)	0.28
Full model[e]	Ref.	0.76 (−0.10, 1.62)	0.87 (0.03, 1.72)	0.74 (−0.11, 1.58)	0.10
Triglycerides ($n=118$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=29$)	$Q2$ ($n=30$)	$Q3$ ($n=30$)	$Q4$ ($n=29$)	
Age-adjusted[c]	Ref.	0.15 (−0.62, 0.92)	−0.22 (−0.99, 0.55)	−0.82 (−1.60, −0.04)	**0.01**
Minimal model[d]	Ref.	0.17 (−0.52, 0.85)	−0.21 (−0.89, 0.53)	−0.18 (−0.90, 0.53)	0.43
Full model[e]	Ref.	0.40 (−0.30, 1.09)	−0.02 (−0.74, 0.69)	0.01 (−0.72, 0.74)	0.62

[a]Total Cholesterol Quartiles: Q1 (116.2–175.5 mg/dL), Q2 (175.6–194.0 mg/dL), Q3 (194.1–218.2 mg/dL), Q4 (218.3–399.3 mg/dL); HDL-C Quartiles: Q1 (27.7–47.5 mg/dL), Q2 (47.6–55.6 mg/dL), Q3 (56.0–67.8 mg/dL), Q4 (68.3–112.2 mg/dL); Triglyceride Quartiles: Q1 (28.7–58.9 mg/dL), Q2 (59.0–82.5), Q3 (82.6–120.2 mg/dL), Q4 (120.3–361.9 mg/dL)

[b]Trend test based on median value of each quartile as a continuous variable in the multivariable model

[c]Adjusted for age at blood draw

[d]Adjusted for BMI at blood draw, age at blood draw, time of blood draw, cohort (cholesterol analyses only), and fasting status

[e]Additionally adjusted for alcohol consumption, race, family history of breast cancer, prior diagnosis of benign breast disease, age at menarche, BMI at age 18, and parity/age at first birth

women in the lowest and middle tertiles of PMD [e.g., OR for T3 (143.9–761.3 mg/dL) v. T1 (12.8–91.5 mg/dL) among women with low PMD: 1.95 (1.01, 3.77)] However, the interaction was not statistically significant (p interaction: 0.49). Restriction to women with measures on all three markers and exclusion of cases diagnosed within 12 months of blood collection did not qualitatively alter the results (data not shown).

Discussion

In this study of pre- and postmenopausal women in the NHS and NHSII, we observed no association between circulating lipids and average PMD. Additionally, there was no evidence that lipid levels modified the association between mammographic density and risk of breast cancer in postmenopausal women.

In HDL-C analyses, we saw no associations between circulating levels and mammographic density in the fully adjusted models, which is consistent with the null findings reported by Boyd et al. [9] and Sung et al. [2010]. However, these results are in contrast to the Flote et al. [7] study, which reported a positive association between HDL-C and PMD among premenopausal women. These inconsistencies may be due to the differences in adjustment sets, as HDL-C was significantly positively associated with PMD in models with minimal adjustment within the present study as well as in Boyd et al. [9] and Sung et al. [8]. As several epidemiologic studies have linked low HDL-C levels to elevated estrogen levels [7, 11] and current results on whether endogenous estrogen levels are linked to mammographic density are mixed [28, 29], it is possible that varying adjustment for birth control measures and/or MHT as well as menopausal status makes comparison of these studies difficult. While we did see evidence suggestive of a negative association between HDL-C and mammographic density among lean postmenopausal women, the HDL-C and PMD association did not vary significantly by BMI, decreasing our confidence of a true interaction. To our knowledge, no prior study has looked at this association stratified by BMI, therefore further analyses are needed to confirm or deny its existence. While a significant negative association between HDL-C and absolute non-dense area was observed in secondary analyses, it is probable that this primarily reflects the strong correlation between non-dense tissue and body fat [30].

Table 3 Beta estimates, representing the predicted change in square root percent mammographic density for each respective quartile[a] of circulating lipid compared to the lowest quartile, among postmenopausal controls

Total cholesterol ($n=975$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=243$)	$Q2$ ($n=244$)	$Q3$ ($n=243$)	$Q4$ ($n=245$)	
Age-adjusted[c]	Ref.	0.05 (−0.27, 0.37)	0.16 (−0.16, 0.49)	−0.07 (−0.39, 0.26)	0.81
Minimal model[d]	Ref.	0.06 (−0.23, 0.35)	0.20 (−0.09, 0.49)	0.08 (−0.21, 0.37)	0.44
Full model[e]	Ref.	0.05 (−0.23, 0.33)	0.19 (−0.09, 0.47)	0.10 (−0.18, 0.38)	0.36
No current MHT use ($n=466$)[e]	Ref.	−0.06 (−0.48, 0.36)	0.29 (−0.12, 0.71)	0.02 (−0.38, 0.43)	0.63
HDL-C ($n=449$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=112$)	$Q2$ ($n=112$)	$Q3$ ($n=113$)	$Q4$ ($n=112$)	
Age-adjusted[c]	Ref.	0.40 (−0.13, 0.92)	0.81 (0.29, 1.33)	1.20 (0.68, 1.72)	**<0.0001**
Minimal model[d]	Ref.	0.13 (−0.34, 0.59)	0.34 (−0.13, 0.80)	0.30 (−0.19, 0.78)	0.19
Full model[e]	Ref.	0.11 (−0.34, 0.56)	0.37 (−0.10, 0.83)	0.29 (−0.19, 0.78)	0.19
No current MHT ($n=239$)[e]	Ref.	0.05 (−0.51, 0.61)	0.27 (−0.34, 0.89)	0.30 (−0.41, 1.00)	0.34
Triglycerides ($n=537$)	Plasma lipid quartiles				p trend[b]
	$Q1$ ($n=134$)	$Q2$ ($n=132$)	$Q3$ ($n=137$)	$Q4$ ($n=134$)	
Age-adjusted[c]	Ref.	−0.34 (−0.75, 0.07)	−0.26 (−0.75, 0.07)	−0.58 (−0.99, −0.17)	**0.01**
Minimal model[d]	Ref.	−0.08 (−0.45, 0.28)	0.19 (−0.18, 0.56)	0.02 (−0.35, 0.40)	0.74
Full model[e]	Ref.	−0.18 (−0.54, 0.18)	−0.05 (−0.31, 0.41)	−0.13 (−0.51, 0.25)	0.71
No current MHT ($n=255$)[e]	Ref.	−0.46 (−0.96, 0.03)	0.03 (−0.49, 0.55)	−0.34 (−0.85, 0.18)	0.43

[a]Total Cholesterol Quartiles: Q1 (123.2–192.6 mg/dL), Q2 (192.7–216.4 mg/dL), Q3 (216.5–243.0 mg/dL), Q4 (234.1–351.8 mg/dL); HDL-C Quartiles: Q1 (26.8–49.6 mg/dL), Q2 (49.8–59.1 mg/dL), Q3 (59.3–72.0 mg/dL), Q4 (72.4–124.2 mg/dL); Triglyceride Quartiles: Q1 (25.5–79.6 mg/dL), Q2 (79.7–114.5 mg/dL), Q3 (114.8–167.9 mg/dL), Q4 (168.0–734.7 mg/dL)

[b]Trend test based on median value of each quartile as a continuous variable

[c]Adjusted for age at blood draw

[d]Adjusted for BMI at blood draw, age, time of blood draw, cohort (cholesterol analyses only), and fasting status

[e]Additionally adjusted for alcohol consumption, race, family history of breast cancer, prior diagnosis of benign breast disease, age at menarche, BMI at age 18, menopause hormone therapy, and parity/age at first birth

Additionally, we saw no significant associations between HDL-C level and breast cancer risk, in contrast to the recent report of inverse association by His et al. [16]. We also did not replicate the association between breast cancer risk and HDL-C that was observed by Martin et al. [15], when restricting our analyses to women with high percent mammographic density (> 50%). Nevertheless, the number of women with PMD > 50% was relatively low in this study ($n=55$ for HDL-C) compared to Martin et al. [15] ($n_{cases}=279$; $n_{controls}=588$) and thus these associations were measured with poor precision.

Prior studies evaluating the relationship between total cholesterol (which includes a combined measure of HDL-C and LDL-C), triglyceride levels, and mammographic density have shown a mix of null [8, 9] and positive associations [6]. The inverse relationship between total cholesterol and percent mammographic density we observed for premenopausal women was also seen, while not statistically significant, by Sung et al. [8]. This association was not observed in other studies [9]. Because of the composite nature of total cholesterol measures, variation in the results may be attributable to variation in the relative concentrations of HDL-C and LDL-C between studies (e.g., LDL-C/HDL-C ratios < 2.0 in [9] vs. ≥ 2.8 in [6]). Should a true association between one component and PMD or breast cancer risk exist, combining this component with others that are not associated with PMD or breast cancer may result in dilution of any effect.

In the main analysis, we did not observe any significant associations between triglycerides and PMD, though triglycerides were significantly negatively associated with PMD among lean postmenopausal women not using MHT. Serum triglyceride levels, which are involved in the regulation of glucose and adipose fat transfer, were significantly inversely associated with percent mammographic density in one prior study before adjustment for potential confounders [9] but were non-significant in a more recent study by Sung et al. [8], which unfortunately did not look at the results stratified by MHT use. The weak negative association between triglycerides and PMD observed in this study as well as prior studies may be due to residual confounding despite adjustment for BMI, as higher body adiposity is positively associated with triglyceride level and inversely associated

Table 4 Beta estimates, representing the predicted change in square root percent mammographic density for each respective quartile of circulating lipid compared to the lowest quartile, for fully adjusted models among pre- and postmenopausal control women, stratifying by BMI

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* trend[a]	*p* interaction[b]
Total cholesterol						
Premenopausal women						
BMI ≤ 25 (*n* = 307)	Ref.	0.00 (−0.38, 0.39)	−0.01 (−0.40, 0.38)	−0.42 (−0.85, 0.01)	0.08	0.86
BMI > 25(*n* = 220)	Ref.	−0.05 (−0.72, 0.61)	−0.13 (−0.80, 0.55)	0.07 (−0.56, 0.70)	0.76	
Postmenopausal women						
BMI ≤ 25 (*n* = 542)	Ref.	0.09 (−0.27, 0.46)	0.28 (−0.09, 0.65)	0.06 (−0.32, 0.44)	0.55	0.98
BMI > 25 (*n* = 433)	Ref.	−0.01 (−0.46, 0.45)	0.15 (−0.30, 0.60)	0.07 (−0.37, 0.51)	0.63	
BMI ≤ 25–no current MHT (*n* = 238)	Ref.	0.23 (−0.37, 0.83)	0.74 (0.13, 1.34)	0.30 (−0.29, 0.88)	0.20	0.14
BMI > 25–no current MHT (*n* = 228)	Ref.	−0.24 (−0.89, 0.41)	−0.04 (−0.64, 0.56)	−0.27 (−0.87, 0.34)	0.51	
HDL-C						
Premenopausal women						
BMI ≤ 25 (*n* = 75)	Ref.	0.59 (−0.46, 1.65)	0.79 (−0.20, 1.78)	0.23 (−0.72, 1.19)	0.83	0.41
BMI > 25 (*n* = 55)	Ref.	0.96 (−0.42, 2.34)	1.24 (−0.22, 2.70)	1.25 (−0.43, 2.92)	0.07	
Postmenopausal women						
BMI ≤ 25 (*n* = 246)	Ref.	0.09 (−0.62, 0.80)	0.65 (−0.03, 1.32)	0.61 (−0.03, 1.26)	**0.03**	0.56
BMI > 25 (*n* = 203)	Ref.	0.30 (−0.33, 0.92)	0.22 (−0.48, 0.93)	0.64 (−0.23, 1.50)	0.18	
BMI ≤ 25–no current MHT (*n* = 114)	Ref.	0.47 (−0.63, 1.57)	0.64 (−0.36, 1.63)	0.76 (−0.28, 1.80)	0.17	0.07
BMI > 25–no current MHT (*n* = 125)	Ref.	0.07 (−0.63, 0.76)	0.21 (−0.72, 1.13)	0.72 (−0.66, 2.10)	0.34	
Triglycerides						
Premenopausal women						
BMI ≤ 25 (*n* = 68)	Ref.	0.96 (0.13, 1.78)	0.22 (−0.55, 0.99)	0.70 (−0.35, 1.74)	0.68	0.63
BMI > 25 (*n* = 50)	Ref.	−0.33 (−1.55, 0.89)	0.20 (−1.16, 1.56)	−0.38 (−1.49, 0.73)	0.52	
Postmenopausal women						
BMI ≤ 25 (*n* = 314)	Ref.	−0.11 (-0.55, 0.30)	0.10 (−0.36, 0.56)	−0.30 (−0.79, 0.19)	0.32	0.60
BMI > 25 (*n* = 223)	Ref.	−0.62 (−1.34, 0.10)	−0.17 (−0.84, 0.50)	−0.55 (−1.22, 0.11)	0.27	
BMI ≤ 25–no current MHT (*n* = 132)	Ref.	−0.32 (−0.95, 0.30)	−0.07 (−0.81, 0.67)	−0.89 (−1.63, −0.14)	**0.03**	0.17
BMI > 25–no current MHT (*n* = 123)	Ref.	−0.34 (−1.22, 0.54)	0.58 (−0.27, 1.43)	−0.02 (−0.85, 0.80)	0.73	

Models were adjusted for age, BMI at blood draw, time of blood draw, fasting status, race, alcohol consumption, age at menarche, parity, prior diagnosis of biopsy-confirmed BBD, BMI at age 18, menopause hormone therapy, cohort (cholesterol analyses only), and family history of breast cancer

[a]Trend test based on median value of each quartile as a continuous variable in the multivariable model

[b]p-value associated with the coefficient of an interaction term between BMI (continuous) and lipid level (continuous) in the unstratified model

with percent mammographic density. It is worth noting that in the secondary analyses on absolute dense area, which is thought to be less confounded by body fat [31], we observed statistically non-significant positive associations between triglyceride levels and absolute dense area, results which may be worth investigating in future studies.

No significant association was observed in this study for triglycerides, PMD, and BC risk, a result which is consistent with prior studies on triglycerides and BC [15, 16]. Nevertheless, we did see some evidence of a higher risk of breast cancer in postmenopausal women with high triglyceride levels and low PMD, a result in the opposite direction to that seen by Martin et al. [15] between triglycerides and BC among postmenopausal women with no MHT use. These differences may be partially explained by the fact the Martin et al. [15] study was conducted only among women with high PMD. Triglycerides are hypothesized to influence breast cancer risk through their role in fatty acid oxidation, which may be associated with higher aggressiveness in tumors [32].

The connection between HDL-C, PMD, and breast cancer is hypothesized to arise through steroid hormone pathways.

Table 5 Adjusted odds ratio of incident breast cancer among postmenopausal women, according to tertiles of plasma lipid and square root average percent mammographic density

Tertile of total cholesterol	Tertile of square root average percent mammographic density		
	T1 (0.0–3.84 sqrt.%)	*T2* (3.85–5.58 sqrt.%)	*T3* (5.58–9.41 sqrt.%)
T1 (117.2–202.0 mg/dL)	1.0 (ref.)	1.55 (1.01, 2.37)	2.67 (1.74, 4.11)
Cases/controls	64/102	102/117	157/107
T2 (202.0–232.9 mg/dL)	0.96 (0.62, 1.50)	1.85 (1.20, 2.86)	1.86 (1.22, 2.85)
Cases/controls	69/110	99/94	126/121
T3 (233.0–351.8 mg/dL)	1.10 (0.71, 1.70)	1.46 (0.96, 2.23)	2.60 (1.69, 4.00)
Cases/controls	80/113	102/114	138/97
p trend[a]	*0.86*	*0.87*	*0.45*
Tertile of HDL-C	Tertile of square root average percent mammographic density		
	T1 (0.0–3.66 sqrt.%)	*T2* (3.67–5.65 sqrt.%)	*T3* (5.67–9.41 sqrt.%)
T1 (10.4–52.9 mg/dL)	1.0 (ref.)	1.65 (0.93, 2.94)	3.32 (1.79, 6.15)
Cases/controls	47/67	46/49	65/34
T2 (52.9–67.0 mg/dL)	0.70 (0.37, 1.32)	1.58 (0.84, 2.98)	1.71 (0.93, 3.13)
Cases/controls	23/53	37/40	54/56
T3 (67.1–125.9 mg/dL)	1.17 (0.57, 2.42)	1.33(0.73, 2.43)	2.52 (1.39, 4.58)
Cases/controls	19/29	45/61	80/60
p trend[a]	*0.51*	*0.78*	*0.83*
Tertile of triglycerides	Tertile of square root average percent mammographic density		
	T1 (0.0–3.84 sqrt.%)	*T2* (3.85–5.37 sqrt.%)	*T3* (5.37–9.41 sqrt %)
T1 (12.8–91.4 mg/dL)	1.0 (Ref.)	1.53 (0.77, 3.05)	3.32 (1.75, 6.30)
Cases/controls	19/49	36/63	88/69
T2 (91.5–143.8 mg/dL)	1.41 (0.71, 2.79)	2.95 (1.52, 5.72)	3.13 (1.62, 6.04)
Cases/controls	39/63	64/53	75/61
T3 (143.9–761.3 mg/dL)	1.95 (1.01, 3.77)	2.25 (1.16, 4.34)	3.38 (1.73, 6.62)
Cases/controls	57/67	60/63	68/49
p trend[a]	*0.67*	*0.74*	*0.90*

Adjusted for BMI at blood draw, fasting status, time of blood draw, age, alcohol consumption, race, family history of breast cancer, prior diagnosis of benign breast disease, age at menarche, BMI at age 18, menopause hormone therapy, and parity/age at first birth

[a]Trend test based on continuous lipid measure in multivariable models within strata of square root percent mammographic density tertiles. Test for interaction for cholesterol ($p = 0.83$), for HDL-c ($p = 0.80$), and for triglycerides ($p = 0.34$)

One promising potential connection between cholesterol and breast cancer involves the cholesterol metabolite 27-hydroxycholesterol, which has been shown to be positively associated with cell growth and tumor progression in estrogen receptor-positive tumors [33]. Alternatively, HDL-C has been shown to be inversely associated with insulin growth factor I (IGF-I) among premenopausal women [34], a marker for which increased levels are associated with increases in breast density [35]. Studies also show that exogenous use of hormones (e.g., estrogen + progesterone therapy) influences mammographic density [12, 36] and breast cancer risk, with a recent study suggesting that the increased risk of breast cancer is entirely mediated through increases in mammographic density [12]. Estrogen and other sex hormones have also been associated with breast cancer risk independently from mammographic density [13]. While an analysis stratified by estrogen receptor tumor status is beyond the power of this study primarily due to low numbers of estrogen receptor-negative tumors ($n = 118$, 67, and 56 in total cholesterol, HDL-C, and triglyceride analyses, respectively) and missingness, further studies with a greater number of cases would be interesting for further investigating this intersection.

We saw no difference in the association between circulating lipids and mammographic density after excluding those on cholesterol-lowering drugs at time of blood draw, which is partially consistent with a recent study by Skarping et al. [37] that found no association between statin use and absolute dense area density but did observe a clear association between statin use and percent dense volume

[37]. It should be noted that the data on statin use at time of blood draw did not include duration of use, though this is not of great concern as statin drugs made their clinical debut not long before the NHS and NHSII mammograms were conducted.

There are several key strengths to this analysis. The NHS and NHSII cohorts utilized in this study are large and well established with extensive demographic data, including complete information on important risk factors for both breast cancer and mammographic density. High-quality biomarker data are also available for several circulating lipids, including total cholesterol, HDL-C, and triglycerides, with assays conducted following rigorous, standardized laboratory protocols and batch effects being taken into account.

This study is limited by the lack of biomarker data on other important lipoprotein factors, specifically ApoA1 and ApoB, that several prior studies have shown to be associated with mammographic density and breast cancer risk [9, 15, 38]. While we had sufficient power to evaluate cross-sectional associations of biomarkers with mammographic density in premenopausal women, there were too few breast cancer cases among premenopausal women for meaningful analysis of breast cancer associations in this group. It is also possible that the important biologic window for lipids to influence mammographic density may be earlier in development, and we would have been unable to observe an association, as the lipid and mammographic density measures were obtained contemporaneously during late adulthood.

Potential associations between circulating lipid levels, mammographic density, and breast cancer risk have been reported in prior studies, but we did not observe any such associations in this study in NHS and NHSII, with the possible exception of triglycerides and breast cancer incidence. While we may have been underpowered to detect weak-to-moderate associations, our findings support the conclusions that there is little association between circulating lipid levels and mammographic density and that the association between mammographic density and breast cancer risk is most likely not explained by lipid levels.

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Compliance with ethical standards

Conflict of interest Dr. Borgquist reports receiving consultant fees and research support from Novartis and Roche. No conflict of interest was disclosed by the other authors.

References

1. Vachon CM, van Gils CH, Sellers TA et al (2007) Mammographic density, breast cancer risk and risk prediction. Breast Cancer Res 9:217. https://doi.org/10.1186/bcr1829
2. Kerlikowske K, Cook AJ, Buist DSM et al (2010) Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol 28:3830–3837. https://doi.org/10.1200/JCO.2009.26.4770
3. Checka CM, Chun JE, Schnabel FR et al (2012) The relationship of mammographic density and age: implications for breast cancer screening. Am J Roentgenol 198:134–139. https://doi.org/10.2214/AJR.10.6049
4. Pettersson A, Graff RE, Ursin G et al (2014) Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst. https://doi.org/10.1093/jnci/dju078
5. Trichopoulos D, Lipman RD (1992) Mammary gland mass and breast cancer risk. Epidemiology 3:523–526
6. Aiello EJ, Tworoger SS, Yasui Y et al (2005) Associations among circulating sex hormones, insulin-like growth factor, lipids, and mammographic density in postmenopausal women. Cancer Epidemiol Biomark Prev 14:1411–1417
7. Flote VG, Frydenberg H, Ursin G et al (2015) High-density lipoprotein-cholesterol, daily estradiol and progesterone, and mammographic density phenotypes in premenopausal women. Cancer Prev Res 8:535–544. https://doi.org/10.1158/1940-6207.CAPR-14-0267
8. Sung J, Song Y-M, Stone J et al (2011) High-density lipoprotein cholesterol, obesity, and mammographic density in Korean women: the Healthy Twin study. J Epidemiol 21:52–60. https://doi.org/10.2188/jea.JE20100078
9. Boyd NF, Connelly P, Byng J et al (1995) Plasma lipids, lipoproteins, and mammographic densities. Cancer Epidemiol Biomark Prev 4:727–733
10. Hanukoglu I (1992) Steroidogenic enzymes: structure, function, and role in regulation of steroid hormone biosynthesis. J Steroid Biochem Mol Biol 43:779–804. https://doi.org/10.1016/0960-0760(92)90307-5
11. Furberg A, Jasienska G, Bjurstam N et al (2005) Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. Cancer Epidemiol Biomark Prev 14:33–40
12. Byrne C, Ursin G, Martin CF et al (2017) Mammographic density change with estrogen and progestin therapy and breast cancer risk. JNCI J Natl Cancer Inst 109:djx001. https://doi.org/10.1093/jnci/djx001
13. Tamimi RM, Byrne C, Colditz GA, Hankinson SE (2007) Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 99:1178–1187. https://doi.org/10.1093/jnci/djm062
14. Cowan L, O'Connell D, Criqui M et al (1990) Cancer mortality and lipid and lipoprotein levels: the lipid research clinics program mortality follow-up study. Am J Epidemiol 3:468–482
15. Martin LJ, Melnichouk O, Huszti E et al (2015) Serum lipids, lipoproteins, and risk of breast cancer: a nested case-control study using multiple time points. J Natl Cancer Inst 107:1–9. https://doi.org/10.1093/jnci/djv032

16. His M, Zelek L, Deschasaux M et al (2014) Prospective associations between serum biomarkers of lipid metabolism and overall, breast and prostate cancer risk. Eur J Epidemiol 29:119–132. https://doi.org/10.1007/s10654-014-9884-5
17. Han C, Zhang H-T, Du L et al (2005) Serum levels of leptin, insulin, and lipids in relation to breast cancer in China. Endocrine 26:19–24. https://doi.org/10.1385/ENDO:26:1:019
18. Høyer AP, Engholm G (1992) Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. Cancer Causes Control 3:403–408. https://doi.org/10.1007/BF00051352
19. Eliassen AH, Colditz GA, Rosner B et al (2005) Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med 165:2264–2271
20. Bertrand KA, Eliassen AH, Hankinson SE et al (2012) Urinary estrogens and estrogen metabolites and mammographic density in premenopausal women. Breast Cancer Res Treat 136:277–287. https://doi.org/10.1007/s10549-012-2240-0
21. Graff RE, Cho E, Lindstrom S et al (2014) Premenopausal plasma ferritin levels, HFE polymorphisms, and risk of breast cancer in the nurses' health study II. Cancer Epidemiol Biomark Prev 23:516–524. https://doi.org/10.1158/1055-9965.EPI-13-0907
22. Bertone-Johnson ER, Chen WY, Holick MF et al (2005) Plasma 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Bioiomark Prev 14:1991–1997. https://doi.org/10.1158/1055-9965.EPI-04-0722
23. Qi Q, Liang L, Doria A et al (2012) Genetic predisposition to dyslipidemia and type 2 diabetes risk in two prospective cohorts. Diabetes 61:745–752. https://doi.org/10.2337/db11-1254
24. Allain CC, Poon LS, Chan CSG et al (1974) Enzymatic determination of total serum cholesterol. Clin Chem 20:470–475
25. Rosner B, Cook N, Portman R et al (2008) Determination of blood pressure percentiles in normal-weight children: some methodological issues. Am J Epidemiol 167:653–666. https://doi.org/10.1093/aje/kwm348
26. Colditz GA, Hankinson SE (2005) The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer 5:388–396. https://doi.org/10.1038/nrc1608
27. Byng JW, Boyd NF, Little L et al (1996) Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev 5:319–327
28. Walker K, Fletcher O, Johnson N et al (2009) Premenopausal mammographic density in relation to cyclic variations in endogenous sex hormone levels, prolactin, and insulin-like growth factors. Cancer Res 69:6490–6499. https://doi.org/10.1158/0008-5472.CAN-09-0280
29. Martin LJ, Boyd NF (2008) Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res 10:201. https://doi.org/10.1186/bcr1831
30. Haars G, Van Noord PAH, Van Gils CH et al (2005) Measurements of breast density: no ratio for a ratio. Cancer Epidemiol Biomark Prev 14:2634–2640. https://doi.org/10.1158/1055-9965.EPI-05-0824
31. Stone J, Warren RML, Pinney E et al (2009) Determinants of percentage and area measures of mammographic density. Am J Epidemiol 170:1571–1578. https://doi.org/10.1093/aje/kwp313
32. Wang YY, Attané C, Milhas D et al (2017) Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells. JCI Insight. https://doi.org/10.1172/jci.insight.87489
33. Lee W-R, Ishikawa T, Umetani M (2014) The interaction between metabolism, cancer and cardiovascular disease, connected by 27-hydroxycholesterol. Clin Lipidol 9:617–624. https://doi.org/10.2217/clp.14.53
34. Kawachi SI, Takeda N, Sasaki A et al (2005) Circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 are associated with early carotid atherosclerosis. Arterioscler Thromb Vasc Biol 25:617–621. https://doi.org/10.1161/01.ATV.0000154486.03017.35
35. Verheus M, Peeters PHM, Kaaks R et al (2007) Premenopausal insulin-like growth factor-I serum levels and changes in breast density over menopause. Cancer Epidemiol Biomark Prev 16:451–457. https://doi.org/10.1158/1055-9965.EPI-06-0642
36. McTiernan A, Martin CF, Peck JD et al (2005) Estrogen-plus-progestin use and mammographic density in postmenopausal women: women's health initiative randomized trial. J Natl Cancer Inst 97:1366–1376. https://doi.org/10.1093/jnci/dji279
37. Skarping I, Brand JS, Hall P, Borgquist S (2015) Effects of statin use on volumetric mammographic density: results from the KARMA study. BMC Cancer 15:435. https://doi.org/10.1186/s12885-015-1457-9
38. Borgquist S, Butt T, Almgren P et al (2016) Apolipoproteins, lipids and risk of cancer. Int J Cancer 138:2648–2656. https://doi.org/10.1002/ijc.30013