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Association between high-sensitivity C-reactive protein (hsCRP) and change in mammographic density over time in the SWAN mammographic density subcohort

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Abstract

Purpose—High mammographic density (MD) is a strong risk factor for breast cancer. Chronic inflammation may be related to breast cancer risk through a mechanism involving the percent of breast area that is dense (percent MD). Longitudinal assessments, however, are lacking and thus were constructed to evaluate the relationship between chronic inflammation and percent MD.

Methods—We evaluated whether elevated (>3 mg/L) high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, was associated with change in percent MD among 653 women aged 42–52 years at baseline in the Study of Women’s Health Across the Nation, a longitudinal study of midlife women. We used a mixed model to analyze data from an average of 4.7 mammograms per woman collected during an average follow-up of 4.9 years ($SD = 1.47$).

Results—Elevated hsCRP at baseline was associated with lower baseline percent MD and a significantly slower annual decline over time of percent MD in an adjusted model that did not include body mass index (BMI) ($\beta = 0.88$, 95 % CI 0.44, 1.31). This association was attenuated

and nonsignificant when BMI was included in the model ($\beta = 0.37$, 95 % CI -0.09 , 0.84). Elevated hsCRP levels over time (time-varying elevated hsCRP levels) were also associated with a significantly slower decline in percent MD ($\beta = 0.62$, 95 % CI 0.30 , 0.94). This association was attenuated, but still significant after adjusting for baseline BMI ($\beta = 0.40$, 95 % CI 0.07 , 0.73).

Conclusion—These results suggest that inflammation may be related to slower reduction in percent MD.

Keywords

High-sensitivity C-reactive protein (hsCRP); Mammographic density (MD); Time-varying elevated hsCRP levels; Body mass index (BMI)

Introduction

Many risk factors have been identified for breast cancer, including older age, genetic mutations (e.g., *BRCA1* and *BRCA2*) [1], higher levels of estrogens and androgens and/or growth factors [2–5], and reproductive factors (e.g., earlier age at menarche, older age at first birth, nulliparity, and not breast feeding) [6–8]. These factors have in common a potential for increased proliferation of breast epithelial tissue. Percent mammographic density (MD) is the percent of breast area occupied by radiographically dense tissue [3]. High percent MD is a strong risk factor for breast cancer, conferring a four-to-six-fold increase in risk of women with 60–75 % MD compared to those with no or low percent MD [4]. Percent MD may be a marker of breast cancer risk [9, 10]. Moreover, percent MD declines with age [11–13]; thus, the longitudinal study of factors related to the rate of change in percent MD may provide more detail about the relationship than using percent MD at onetime point [14]. Chronic inflammation results in excess cell proliferation and the activation of a series of cellular actions, resulting in the induction of DNA damage, so that prolonged inflammation can lead to initiated cells, tumor growth, metastatic progression, and immunosuppression [15, 16].

CRP, produced by the liver when inflammation or infection occurs, is an established biomarker of both acute and chronic inflammation [17–23]. Many cancer cases occur at the sites of chronic inflammation [24], and circulating levels of CRP may be increased in some cancer patients [20]. Elevated high-sensitivity CRP (hsCRP) has also been related to prevalent cancer and increased risk of future cancer in healthy populations [25]. CRP is a fairly stable biomarker and has little diurnal variation [26, 27]. Breast carcinogenesis may be related to a mechanism involving both chronic inflammation, reflected by elevated circulating levels of CRP, and estrogen pathways (the latter also including percent MD) [20, 28–30].

Epidemiologic study results have been inconsistent, with some supporting a positive association between CRP and breast cancer risk [21, 24, 31–36], while others have reported no association [25, 37–40]. One cross-sectional study reported a nonsignificant negative association between CRP and percent MD in healthy postmenopausal women [41]. A longitudinal analysis of changes in CRP and percent MD is needed to understand better the relationship between inflammation and breast cancer risk.

We undertook a novel longitudinal investigation of the relation between high-sensitivity CRP (hsCRP) and changes over 6 years in percent MD among a midlife multiracial/ethnic sample of women. The aims of the present analyses were to assess whether baseline and time-varying elevated hsCRP levels were associated with change in percent MD and whether these associations were affected by use of nonsteroidal anti-inflammatory drugs (NSAIDs) or varied by race/ethnicity.

Materials and methods

SWAN study sample

The Study of Women's Health Across the Nation (SWAN) is a seven-site, community-based, longitudinal cohort study designed to investigate the biological and psychosocial characteristics of the menopausal transition among a racially/ethnically and socioeconomically diverse cohort of women, who at baseline were aged 42–52 years, reported having had a menstrual period in the prior 3 months, had an intact uterus and at least one ovary, and were not using exogenous hormones within the 3 months prior to the recruitment [42]. One minority sample was selected at each site in addition to a Caucasian sample. SWAN recruited and enrolled 3,302 women at baseline or 50 % of total eligible women; 935 were African-American (Boston, Chicago, Detroit, Pittsburgh); 1,550 were Caucasian (all sites); 250 were Chinese (Oakland); 281 were Japanese (Los Angeles), and 286 were Hispanic (Newark). SWAN participants have been evaluated at annual in-person visits since 1996 to obtain information on demographic, medical and reproductive history and events, anthropometrics, medication use, and serum and urine biomarkers of endocrine function, lipids, glucose, inflammation, and bone turnover.

Both the SWAN core study and the MD substudy protocols were approved by the institutional review boards of all participating institutions. All participating women provided written informed consent.

Mammographic density substudy

Three SWAN sites participated in the MD ancillary study: the University of California, Davis-Kaiser (Oakland), the University of California, Los Angeles (Los Angeles), and the University of Pittsburgh (Pittsburgh). Mammograms taken as part of routine medical care were obtained for women in this substudy [43]. For each woman, the “index mammogram” was the first mammogram that either followed a SWAN visit or preceded it by no more than 1 month. The SWAN visit closest to the date of this index mammogram was considered the index SWAN visit for this analysis. Mammograms that were acquired more than 1 month prior to the start of SWAN were excluded from analyses. Follow-up mammograms (i.e., mammograms after the index mammogram) were linked with later SWAN visits using the same criteria. The interval between the mammogram and corresponding SWAN visit averaged 0.41 years after the visit (standard deviation = 0.30 years), a sufficiently small interval to minimize the likelihood of major changes in hsCRP or confounders during this time. Of the 1,248 women available at the three SWAN sites at the time of enrollment into the substudy, 85 % agreed to participate. Of those who participated, 1,005 women had at least one eligible mammogram assessed for percent MD. Only women who were pre- or

early perimenopausal at baseline and who had at least one follow-up mammogram were included. Women were excluded from this analysis if they had cancer at any time during the study. In total, 801 women were pre- or early perimenopausal at baseline. After excluding those women who did not have two completed mammograms during SWAN's follow-up, a total of 653 women remained for these analyses.

Quantitative assessment of mammograms was made by Martine Salane, an established expert in measuring MD [44]. Ms. Salane's measurements have been highly correlated with computer-assisted MD measurements ($r = 0.90$) [45]. A compensating polar planimeter (LASICO, Los Angeles, CA) was used to calculate the radio-dense area (in cm^2) of the breast tissue and the total area of the breast [43]. Percent MD was calculated by dividing the dense breast area by the total area of the breast and multiplying by 100.

High-sensitivity CRP (hsCRP) assessment

The SWAN protocol included an annual blood draw after a minimum 10-h fast, which was used to measure hsCRP from baseline to visit 6 (except visit 2). HsCRP was assayed using an ultrasensitive immunophelometric method (Dade-Behring, Marburg, Germany). Because hsCRP was not measured at visit 2, the average of the two closest hsCRP measures was used as the hsCRP value for that visit. This approach was used, because for some women, the index or a follow-up mammogram was closest to visit 2, and an hsCRP value corresponding to that visit was needed for inclusion in the analyses, but hsCRP was not measured in visit 2, so it was imputed from the average of the two visits closest to visit 2. No meaningful differences were observed in the final results when the analyses were repeated without the imputed hsCRP value for visit 2 (data not shown). Details of the specimen collection and hsCRP assay have been published [46]. Although hsCRP level is a continuous variable, a cutoff for elevated hsCRP has been established for clinical use [47] and was used to categorize hsCRP into elevated ($>3\text{mg/L}$) and non-elevated ($\leq 3\text{mg/L}$) for analyses of both baseline and hsCRP levels over time.

Covariates

Time-invariant covariates obtained from the index SWAN visits were evaluated as potential confounders in the analyses. Based on the literature, the following variables were of interest: annual household income ($<\$50,000$, $\$50,000\text{--}74,000$, $\geq \$75,000$), age at menarche (in years), family history of breast cancer (yes/no based on first- and second-degree female family members who had breast cancer), race/ethnicity (Non-Hispanic Caucasian, African-American, Chinese, and Japanese) [43], parity (number of births), prior oral contraceptive use at baseline (yes/no), and education (high school or less, some college, and college and more). Because of the SWAN study design, combined information about race/ethnicity and recruitment site was categorized and used in the analyses [6]. The following variables were also considered potential confounders: use of hormone therapy (yes/no), baseline menopausal status (premenopausal or early perimenopausal), physical activity score, frequency of alcohol consumption (none, <1 drink per week, $1\text{--}7$ drinks per week, and >7 drinks per week), vitamin use (yes/no), active and passive smoke exposure (never smoker/no second hand smoking (SHS), never smoker/with SHS, former smoker/no SHS, former smoker/with SHS and current smoker [49]), and comorbidities (yes/no) from the index

SWAN visit. Physical activity was classified according to the Kaiser Permanente Activity Score [48], which includes physical activity in mutually exclusive domains of sports/exercise, household/caregiving, occupational, and daily routine [14, 48, 49].

Two time-varying covariates were of particular interest: BMI and menopausal status. In addition to the baseline values, a variable for change since the index SWAN visit was created for each of these variables. The value of BMI for a woman changed for each SWAN visit linked to a mammogram and was defined as the difference between the value at that SWAN visit and the value from the index SWAN visit. For menopausal status, the change from baseline was categorized as: (1) no change in menopausal status; (2) pre- to early perimenopausal; (3) pre- to late perimenopausal; (4) early to late perimenopausal; (5) pre-to naturally postmenopausal; (6) early peri- to naturally postmenopausal; and (7) change to no periods resulting from surgery or indetermination due to hormone use (combining surgery and hormone use because their individual numbers were relatively small, the final menstrual period could not be determined in most cases, and many women who had hysterectomies used hormones so that the effects could not be separated). In addition, a variable measured the time in years from the index to each subsequent mammogram.

Use of NSAIDs was obtained at each SWAN visit in the interviewer-administered questionnaire. Women were asked about both prescribed and “regularly used” over-the-counter medications that were taken “in the last month” (at the baseline visit) or “since your last visit” (at each follow-up visit). Regular use was defined as use two or more times per week during the previous month (at baseline), or during any month since the previous visit (at each follow-up visit). Separately for prescription and nonprescription medications, women were asked to name the medication taken with prompting by symptom (e.g., “for pain including headaches and arthritis”), with a final open question for each type (e.g., “Are there any other prescription/other-the-counter pills or medications that you have taken, that I haven’t asked you about?”).

Statistical analyses

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

The primary objective of this analysis was to assess the association between hsCRP levels and change in percent MD.

Mixed models were used to examine the association between the index hsCRP status and change in percent MD. These models included factors related to change in percent MD and random intercepts and slopes to account for between-person variability in the starting level and change over time. Model assumptions of linear change, normality, and constant variance of the residuals and bivariate normality of the random effects were checked and were met by the data.

Model building strategies were the same for all outcomes to evaluate the hypotheses of interest. We began with a simple unadjusted model that included categorized hsCRP at the index visit, time, and the interaction between these two (Model 1). Then, we evaluated potential confounders by adding one variable at a time as a main effect and an interaction

with time to that simple model and if the coefficient for elevated hsCRP or the interaction of hsCRP and time changed by more than 10 % when a single variable was added, then that variable was included in an adjusted model as either a main effect and interaction with time or just as a main effect. We constructed an adjusted model by adding all confounders identified in the previous step to the simple model.

Next, interactions between time and two time-varying variables for change in BMI and in menopausal status were added to the adjusted model to construct a final adjusted model to assess the associations of these variables with change in the outcome and whether the association between elevated hsCRP level and change in percent MD was the same with the inclusion of these interactions. Because BMI has been strongly associated with percent MD [43], we constructed models with (Model 2) and without BMI (Model 3). Finally, models were repeated using hsCRP status at each visit as a time-varying variable to reflect better a woman's status over time.

Additional analyses were performed to investigate the association of: 1) elevated hsCRP level with change in percent MD in consistent nonusers of NSAIDs and 2) hsCRP level with dense and non-dense area. Analyses of the association between continuous hsCRP level and change in percent MD and the association of frequently elevated hsCRP (hsCRP > 3 mg/L for more than half of all visits) with change in percent MD were also conducted.

Results

Approximately 20 % of women had elevated hsCRP at the index visit (Table 1). Most women were aged 45–49 years (58 %), had normal BMI 18.5–24.9 kg/m² (55 %), were non-Hispanic Caucasian (50 %), had no comorbidities (73 %), had age at menarche of 11–15 years (83 %), and were nonusers of NSAIDs (74 %). In addition, 45 % were never smokers with no exposure to second hand smoke; 37 % were not alcohol drinkers; and 38 % had a physical activity score more than 8.5 (the highest tertile). Women who were obese or African-American, moderately physically active, had comorbidities or early age at menarche, and used NSAIDs were more likely to have elevated hsCRP. The mean percent MD at baseline was 44 % (SD = 20.0 %). The average number of mammograms per woman was 4.7 (SD = 1.73; range 2–9) over an average of 4.9 years (SD = 1.47; range 0.92–8.08).

In women with non-elevated hsCRP at baseline, mean percent MD was higher (47 %), compared with women who had elevated hsCRP (31 %) ($p < 0.001$) (Fig. 1a). On average, percent MD declined 1.1 percent (SE = 0.06) per year. The percent MD for women with elevated hsCRP at baseline declined at a 0.44 percentage point (95 % CI 0.14, 0.73) slower rate than those without elevated hsCRP for an overall average rate of decline of 0.73 percent each year in the unadjusted model (Model 1, Table 2). In the adjusted model, the direction of the association of change in percent MD with elevated baseline hsCRP was the same but not significant ($\beta = 0.37$, 95 % CI –0.09, 0.84) (Fig. 1b; Model 2, Table 2). This association became significant when BMI was excluded from the model, with a 0.88 percentage point (95 % CI 0.44, 1.31) slower decline in percent MD associated with elevated hsCRP and an overall average rate of decline 1.99 percentage points each year (Table 2, Model 3). A one-unit increase in change in BMI over time was associated with a 0.13 percentage point faster

decline in percent MD per year ($SE = 0.03$, $p < 0.001$; Model 2, Table 2). The association between baseline hsCRP status and change in MD did not differ significantly by race/ethnicity (data not shown).

Women could have had hsCRP measurements at a total of 4 visits during follow-up in the MD substudy. The average number of visits with hsCRP measurement was 2.5. Women who had elevated hsCRP at over half of the visits did not differ in change in percent MD from women whose hsCRP was less frequently or never elevated ($\beta = 0.39$, 95 % CI -0.04 , 0.83). Using continuous hsCRP level in place of elevated hsCRP, significant associations between increasing baseline hsCRP levels and slower decline in percent MD were found in an unadjusted model ($p = 0.01$) and when BMI was not included in the adjusted model ($p = 0.006$).

When using hsCRP as a time-varying predictor, hsCRP was significantly associated with percent MD in both unadjusted and adjusted models (Table 3). At any point in time, women with elevated hsCRP had a 0.39 percentage point (95 % CI 0.12 , 0.66) slower rate of decline in percent MD than those with normal hsCRP for an overall average rate of decline of 0.84 percentage point each year in the unadjusted model (Model 1, Table 3). In the adjusted model that included BMI and change in BMI, women who had elevated hsCRP levels at any time point had a 0.40 percentage point (95 % CI 0.07 , 0.73) slower rate of decline in percent MD than those with normal hsCRP levels (Fig. 1c; Model 2, Table 3). In the adjusted model that did not include BMI, a 0.62 percentage point slower rate of decline (95 % CI 0.30 , 0.94) was observed for those with elevated hsCRP levels over time with an overall average rate of decline of 2.19 percentage points each year (Model 3, Table 3).

At any time point, women with elevated hsCRP also experienced a 1 % slower increase in non-dense breast tissue ($\beta = -0.01$, $SE = 0.004$, $p = 0.002$) than those with normal hsCRP levels. Similar results for non-dense breast area were found in adjusted models, including BMI ($\beta = -0.02$, $SE = 0.005$, $p = 0.001$) and excluding BMI ($\beta = -0.02$, $SE = 0.005$, $p < 0.001$). No significant association was observed with time-varying hsCRP and change in dense breast tissue in unadjusted ($\beta = 0.001$, $SE = 0.006$, $p = 0.78$) or adjusted models with or without BMI ($\beta = 0.009$, $SE = 0.008$, $p = 0.21$; $\beta = 0.01$, $SE = 0.007$, $p = 0.07$, respectively).

In analyses restricted to women who were consistent nonusers of NSAIDs across all annual visits up to visit 6 ($N = 240$), no significant association was seen between elevated hsCRP level at baseline ($\beta = -0.008$, $SE = 0.56$, $p = 0.98$) or hsCRP status over time ($\beta = -0.03$, $SE = 0.31$, $p = 0.93$) and change in percent MD. We also did not observe a statistically significant association between baseline hsCRP and change in MD in any racial/ethnic subgroup, baseline menopausal status subgroup, or in any BMI subgroup (data not shown).

Discussion

In our community-based, multiracial/ethnic sample of 653 midlife women, we observed that elevated hsCRP levels over time were statistically significantly associated with a slower decrease in percent MD in unadjusted and adjusted models (with and without BMI). We

identified only one prior study, which was cross-sectional [41], that reported a significant negative association between continuous CRP levels and age-adjusted percent MD in healthy postmenopausal women; this relation was attenuated and nonsignificant when adjusted for BMI. Our study, in contrast, was longitudinal, a benefit over the cross-sectional design. In addition, we examined women who were pre- or early perimenopause at baseline, which permitted us to examine changes in percent MD before women were postmenopausal and at a time when circulating hormones were changing [50, 51] and might thus be a potentially critical window for inflammation [52, 53]; our results suggested that the relation of hsCRP to percent MD began earlier, i.e., before menopause, in the menopausal transition or earlier. We also examined the relation of elevated hsCRP (>3 mg/L), as both baseline and time-varying, providing more information about inflammation than the one-time assessment.

A few studies have investigated the relationship between CRP and breast cancer risk, but the results have been inconsistent. A recent meta-analysis of prospective studies by Heikkila et al. [21] showed a slight, but non-statistically significant, increased breast cancer risk associated with higher levels of CRP. A few studies [31, 32, 37] have found a nonsignificant relation of elevated CRP to breast cancer risk, while the Rotterdam cohort study indicated a statistically significant 28 % increase in breast cancer risk of every one-unit increase in CRP [34]. Further, mammographic dense volume, a measure of fibroglandular tissue, has been negatively correlated with C-reactive protein (CRP) [54].

Inflammation results in excess cell proliferation [15]. In addition, CRP, an inflammation cytokine, decreases when COX-2 is inhibited [55]. COX-2 overexpression results in an increase in prostaglandins, especially prostaglandin E2 [56, 57], which increases aromatase gene expression and thus stimulates local estrogen production [58], which may also increase mammographic density [59]. Thus, our finding that time-varying elevated hsCRP was associated with a slower decline in percent MD is consistent with these hormonal changes related to inflammation.

Our study had some limitations to consider when interpreting our results. First, because women in our cohort were pre- or early perimenopausal at baseline and were followed only for 6 years, and we lacked sufficient numbers of women to evaluate the relationship of elevated hsCRP to decline in percent MD in postmenopausal women. Second, because NSAID use is related to inflammation, we included NSAID use in an adjusted model, and no substantial change was observed in the relation of elevated hsCRP to reduced decline in percent MD. However, we may have had some misclassification of information of NSAID use due to recall, particularly of the nonprescription forms of this medication, and to short and variable durations of use, which may at least partially explain the lack of an observed effect.

Our study also had many strengths. First, this is the first study of which we are aware to investigate the association of change in percent MD with elevated hsCRP using objective measures. Second, this study was a longitudinal cohort design and had over 6 years of data on percent MD in a large multiracial/ethnic sample of midlife women, so that the longitudinal relation of elevated baseline hsCRP to change in percent MD could be assessed. Third, SWAN is a multiracial/ethnic, community-based, cohort; therefore, the results of this

study are likely to be generalizable to pre- and perimenopausal US women. Fourth, all data collection was performed by well-trained staff, all using the same standard protocol so that quality control was high. Fifth, the mammograms were read by only one specialist who had very high accuracy and who was masked to hsCRP levels, thus reducing the potential for differential misclassification.

BMI appears to play an important role in the association of CRP with MD because BMI is strongly correlated with MD [31, 60, 61] and strongly correlated with CRP [35, 62]. In some studies [37, 41], and in our initial analyses, a single measure of CRP at baseline had no relation to MD when also accounting for BMI. While this may lead to the conclusion that inflammation does not independently affect breast cancer risk through a pathway that includes MD, in our longitudinal analyses examining time-varying elevated hsCRP (a more informative approach because it more directly links the hsCRP status over time with percent MD decline and takes into consideration that a woman's hsCRP level at baseline may not be indicative of her inflammation process over time), the association between elevated hsCRP over time and change in percent MD remained statistically significant even after adjusting for BMI. This result suggests that inflammation, a potential risk factor for breast cancer, may be related to a slower decline of MD over time. However, this finding requires verification in future studies because the relation of elevated hsCRP over time to a slower decline in percent MD may have been due to such women starting with a lower percent MD and thus having less ability to be much further reduced (i.e., a floor effect); 36 % of those with elevated hsCRP at baseline started with a percent MD less than 20, while only 16 % of those with non-elevated hsCRP at baseline had a percent MD less than 20. The higher proportion of women with low percent MD in those with elevated baseline CRP could at least partially explain the reduced rate of decline in percent MD in this group after adjustment for confounding variables, but the significant differences in rates of age-related decline in percent MD could also suggest that inflammation may play a role in reducing the rate of age-related decline in percent MD, a suggestion that requires further testing in larger longitudinal studies. Further studies should explore the complex processes of inflammation and change in MD and whether BMI and inflammation are on the same causal pathway of breast carcinogenesis.

To date, this is one of the largest cohort studies with longer follow-up and more mammogram and hsCRP measurements used to assess the association between hsCRP and percent MD. This is the first study of which we are aware that considered hsCRP status both at baseline and as a time-varying independent predictor of change in percent MD over time. We also controlled for many confounders in our analyses, thus reducing the chance for biased results due to residual confounding. In conclusion, our results provide limited support for the hypothesis that inflammation may play an important role in change in percent MD with age, but this role remains uncertain due to our finding that while higher baseline hsCRP was associated with lower percent MD, elevated hsCRP levels over time were associated with a slower decline in percent MD over time. Few, if any, studies have examined the association between elevated hsCRP over time and change in MD, and further study of this association is needed to clarify the role of inflammation in breast cancer, and whether this association acts through or is reflected by mammographic density.

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References

1. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995; 378:789–792.10.1038/378789a0 [PubMed: 8524414]
2. McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, Wang CY, Brunner RL, Johnson KC, Manson JE, Lewis CE, Kotchen JM, Hulka BS. Estrogen-plus-progestin use and mammographic density in postmenopausal women: women's health initiative randomized trial. *J Natl Cancer Inst*. 2005; 97:1366–1376.10.1093/jnci/dji279 [PubMed: 16174858]
3. Martin LJ, Boyd NF. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. *Breast Cancer Res*. 2008; 10:201.10.1186/bcr1831 [PubMed: 18226174]
4. Boyd NF, Lockwood GA, Byng JW, Trichler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomark Prev*. 1998; 7:1133–1144.
5. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst*. 1995; 87:1622–1629. [PubMed: 7563205]
6. Butler LM, Gold EB, Greendale GA, Crandall CJ, Modugno F, Oestreich N, Quesenberry CP Jr, Habel LA. Menstrual and reproductive factors in relation to mammographic density: the Study of Women's Health Across the Nation (SWAN). *Breast Cancer Res Treat*. 2008; 112:165–174.10.1007/s10549-007-9840-0 [PubMed: 18066689]
7. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev*. 1993; 15:36–47. [PubMed: 8405211]
8. Stuebe AM, Willett WC, Xue F, Michels KB. Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Arch Intern Med*. 2009; 169:1364–1371.10.1001/archinternmed.2009.231 [PubMed: 19667298]
9. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomark Prev*. 2006; 15:1159–1169.10.1158/1055-9965.EPI-06-0034
10. Warner E, Lockwood G, Trichler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detect Prev*. 1992; 16:67–72. [PubMed: 1532349]
11. Boyd N, Martin L, Stone J, Little L, Minkin S, Yaffe M. A longitudinal study of the effects of menopause on mammographic features. *Cancer Epidemiol Biomark Prev*. 2002; 11:1048–1053.
12. Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A 2-year soy intervention in premenopausal women does not change mammographic densities. *J Nutr*. 2004; 134:3089–3094. [PubMed: 15514280]
13. Maskarinec G, Pagano I, Lurie G, Kolonel LN. A longitudinal investigation of mammographic density: the multiethnic cohort. *Cancer Epidemiol Biomark Prev*. 2006; 15:732–739.10.1158/1055-9965.EPI-05-0798
14. Conroy SM, Butler LM, Harvey D, Gold EB, Sternfeld B, Oestreich N, Greendale GA, Habel LA. Physical activity and change in mammographic density: the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2010; 171:960–968.10.1093/aje/kwq025 [PubMed: 20354074]
15. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420:860–867.10.1038/nature01322 [PubMed: 12490959]

16. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001; 357:539–545.10.1016/S0140-6736(00)04046-0 [PubMed: 11229684]
17. Black S, Kushner I, Samols D. C-reactive Protein. *J Biol Chem*. 2004; 279:48487–48490.10.1074/jbc.R400025200 [PubMed: 15337754]
18. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. *J Intern Med*. 2008; 264:295–314.10.1111/j.1365-2796.2008.02015.x [PubMed: 18823504]
19. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, Stegger J, Overvad K, Chabbert-Buffet N, Jimenez-Corona A, Clavel-Chapelon F, Rohrmann S, Teucher B, Boeing H, Schutze M, Trichopoulou A, Benetou V, Lagiou P, Palli D, Berrino F, Panico S, Tumino R, Sacerdote C, Redondo ML, Travier N, Sanchez MJ, Altzibar JM, Chirlaque MD, Ardanaz E, Bueno-de-Mesquita HB, van Duijnhoven FJ, Onland-Moret NC, Peeters PH, Hallmans G, Lundin E, Khaw KT, Wareham N, Allen N, Key TJ, Slimani N, Hainaut P, Romaguera D, Norat T, Riboli E, Kaaks R. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. *Endocr Relat Cancer*. 2010; 17:1007–1019.10.1677/ERC-10-0053 [PubMed: 20843938]
20. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health*. 2007; 61:824–833.10.1136/jech.2006.051292 [PubMed: 17699539]
21. Heikkila K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, Ben-Shlomo Y, Ebrahim S, Lawlor DA. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. *Cancer Causes Control*. 2009; 20:15–26.10.1007/s10552-008-9212-z [PubMed: 18704713]
22. Lundin E, Dossus L, Clendenen T, Krogh V, Grankvist K, Wulff M, Sieri S, Arslan AA, Lenner P, Berrino F, Hallmans G, Zeleniuch-Jacquotte A, Toniolo P, Lukanova A. C-reactive protein and ovarian cancer: a prospective study nested in three cohorts (Sweden, USA, Italy). *Cancer Causes Control*. 2009; 20:1151–1159.10.1007/s10552-009-9330-2 [PubMed: 19301134]
23. Poole EM, Lee IM, Ridker PM, Buring JE, Hankinson SE, Tworoger SS. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor alpha receptor 2 levels and risk of ovarian cancer. *Am J Epidemiol*. 2013; 178:1256–1264.10.1093/aje/kwt098 [PubMed: 23966559]
24. Prizment AE, Folsom AR, Dreyfus J, Anderson KE, Visvanathan K, Joshi CE, Platz EA, Pankow JS. Plasma C-reactive protein, genetic risk score, and risk of common cancers in the Atherosclerosis Risk in Communities study. *Cancer Causes Control*. 2013; 24:2077–2087.10.1007/s10552-013-0285-y [PubMed: 24036889]
25. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci*. 2011; 48:155–170.10.3109/10408363.2011.599831 [PubMed: 22035340]
26. Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. *Clin Chem*. 2001; 47:426–430. [PubMed: 11238292]
27. Hardikar S, Song X, Kratz M, Anderson GL, Blount PL, Reid BJ, Vaughan TL, White E. Intraindividual variability over time in plasma biomarkers of inflammation and effects of long-term storage. *Cancer Causes Control*. 2014; 25:969–976.10.1007/s10552-014-0396-0 [PubMed: 24839050]
28. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002; 94:606–616. [PubMed: 11959894]
29. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C, Dossus L, Lukanova A, Bingham S, Khaw KT, Allen NE, Bueno-de-Mesquita HB, van Gils CH, Grobbee D, Boeing H, Lahmann PH, Nagel G, Chang-Claude J, Clavel-Chapelon F, Fournier A, Thiebaut A, Gonzalez CA, Quiros JR, Tormo MJ, Ardanaz E, Amiano P, Krogh V, Palli D, Panico S, Tumino R, Vineis P, Trichopoulou A, Kalapothaki V, Trichopoulos D, Ferrari P, Norat T, Saracci R, Riboli E. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer

- and nutrition. *Endocr Relat Cancer*. 2005; 12:1071–1082.10.1677/erc.1.01038 [PubMed: 16322344]
30. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol*. 2006; 7:910–918.10.1016/S1470-2045(06)70911-1 [PubMed: 17081916]
 31. Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, Kritchevsky SB. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol Biomark Prev*. 2005; 14:2413–2418.10.1158/1055-9965.EPI-05-0316
 32. Trichopoulos D, Psaltopoulou T, Orfanos P, Trichopoulou A, Boffetta P. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. *Cancer Epidemiol Biomark Prev*. 2006; 15:381–384.10.1158/1055-9965.EPI-05-0626
 33. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J Clin Oncol*. 2009; 27:2217–2224.10.1200/JCO.2008.19.8440 [PubMed: 19289618]
 34. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, Hofman A, Pols HA, Stricker BH. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *J Clin Oncol*. 2006; 24:5216–5222.10.1200/JCO.2006.07.1381 [PubMed: 17114654]
 35. Zeleniuch-Jacquotte A, Gu Y, Bruning PF, Bonfrer JM, Koenig KL, Arslan AA, Toniolo P, Shore RE. Re: C-reactive protein and risk of breast cancer. *J Natl Cancer Inst*. 2008; 100:443–444. author reply 444–445. 10.1093/jnci/djn016 [PubMed: 18334713]
 36. Dossus L, Jimenez-Corona A, Romieu I, Boutron-Ruault MC, Boutten A, Dupre T, Fagherazzi G, Clavel-Chapelon F, Mesrine S. C-reactive protein and postmenopausal breast cancer risk: results from the E3 N cohort study. *Cancer Causes Control*. 2014; 25:533–539.10.1007/s10552-014-0355-9 [PubMed: 24504436]
 37. Zhang SM, Lin J, Cook NR, Lee IM, Manson JE, Buring JE, Ridker PM. C-reactive protein and risk of breast cancer. *J Natl Cancer Inst*. 2007; 99:890–894.10.1093/jnci/djk202 [PubMed: 17551149]
 38. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, Mejean C, Latino-Martel P, Hercberg S, Galan P, Czernichow S. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: a nested case–control study. *Am J Epidemiol*. 2013; 177:3–13.10.1093/aje/kws359 [PubMed: 23171880]
 39. Van Hemelrijck M, Holmberg L, Garmo H, Hammar N, Walldius G, Binda E, Lambe M, Jungner I. Association between levels of C-reactive protein and leukocytes and cancer: three repeated measurements in the Swedish AMORIS study. *Cancer Epidemiol Biomark Prev*. 2011; 20:428–437.10.1158/1055-9965.EPI-10-1190
 40. Ollberding NJ, Kim Y, Shvetsov YB, Wilkens LR, Franke AA, Cooney RV, Maskarinec G, Hernandez BY, Henderson BE, Le Marchand L, Kolonel LN, Goodman MT. Prediagnostic leptin, adiponectin, C-reactive protein, and the risk of postmenopausal breast cancer. *Cancer Prev Res (Phila)*. 2013; 6:188–195.10.1158/1940-6207.CAPR-12-0374 [PubMed: 23466816]
 41. Reeves KW, Weissfeld JL, Modugno F, Diergaarde B. Circulating levels of inflammatory markers and mammographic density among postmenopausal women. *Breast Cancer Res Treat*. 2011; 127:555–563.10.1007/s10549-010-1249-5 [PubMed: 21069450]
 42. Sowers MF, Crawford S, Sternfeld B. SWAN: a multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition. In: Lobo, RA.; Kelsey, J.; Marcus, R., editors. *Menopause: biology and pathobiology*. Academic Press; New York: 2000. p. 175-188.
 43. Habel LA, Capra AM, Oestreicher N, Greendale GA, Cauley JA, Bromberger J, Crandall CJ, Gold EB, Modugno F, Salane M, Quesenberry C, Sternfeld B. Mammographic density in a multiethnic cohort. *Menopause*. 2007; 14:891–899.10.1097/gme.0b013e318032569c [PubMed: 17414171]
 44. Wellings SR, Wolfe JN. Correlative studies of the histological and radiographic appearance of the breast parenchyma. *Radiology*. 1978; 129:299–306. [PubMed: 704841]
 45. Haiman CA, Bernstein L, Berg D, Ingles SA, Salane M, Ursin G. Genetic determinants of mammographic density. *Breast Cancer Res*. 2002; 4:R5. [PubMed: 12052257]

46. Sowers MR, Matthews KA, Jannausch M, Randolph JF, McConnell D, Sutton-Tyrrell K, Little R, Lasley B, Pasternak R. Hemostatic factors and estrogen during the menopausal transition. *J Clin Endocrinol Metab.* 2005; 90:5942–5948.10.1210/jc.2005-0591 [PubMed: 16105968]
47. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003; 107:499–511. [PubMed: 12551878]
48. Sternfeld B, Ainsworth BE, Quesenberry CP. Physical activity patterns in a diverse population of women. *Prev Med.* 1999; 28:313–323.10.1006/pmed.1998.0470 [PubMed: 10072751]
49. Ainsworth BE, Sternfeld B, Richardson MT, Jackson K. Evaluation of the kaiser physical activity survey in women. *Med Sci Sports Exerc.* 2000; 32:1327–1338. [PubMed: 10912901]
50. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. *Human Reprod Update.* 2007; 13:559–565.10.1093/humupd/dmm020
51. Tepper PG, Randolph JF Jr, McConnell DS, Crawford SL, El Khoudary SR, Joffe H, Gold EB, Zheng H, Bromberger JT, Sutton-Tyrrell K. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health across the Nation (SWAN). *J Clin Endocrinol Metabol.* 2012; 97:2872–2880.10.1210/jc.2012-1422
52. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, Chandler WL, Boyko EJ, Brunzell JD. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. *J Clin Endocrinol Metabol.* 2009; 94:1104–1110.10.1210/jc.2008-0701
53. Kurtz EG, Ridker PM, Rose LM, Cook NR, Everett BM, Buring JE, Rexrode KM. Oral postmenopausal hormone therapy, C-reactive protein, and cardiovascular outcomes. *Menopause.* 2011; 18:23–29.10.1097/gme.0b013e3181e750dd [PubMed: 20647959]
54. Woolcott CG, Courneya KS, Boyd NF, Yaffe MJ, McTiernan A, Brant R, Jones CA, Stanczyk FZ, Terry T, Cook LS, Wang Q, Friedenreich CM. Association between sex hormones, glucose homeostasis, adipokines, and inflammatory markers and mammographic density among postmenopausal women. *Breast Cancer Res Treat.* 2013; 139:255–265.10.1007/s10549-013-2534-x [PubMed: 23605145]
55. Bogaty P, Brophy JM, Noel M, Boyer L, Simard S, Bertrand F, Dagenais GR. Impact of prolonged cyclooxygenase-2 inhibition on inflammatory markers and endothelial function in patients with ischemic heart disease and raised C-reactive protein: a randomized placebo-controlled study. *Circulation.* 2004; 110:934–939.10.1161/01.CIR.0000139338.12464.5F [PubMed: 15302800]
56. Davies G, Martin LA, Sacks N, Dowsett M. Cyclooxygenase-2 (COX-2), aromatase and breast cancer: a possible role for COX-2 inhibitors in breast cancer chemoprevention. *Ann Oncol.* 2002; 13:669–678. [PubMed: 12075734]
57. DuBois RN. Aspirin and breast cancer prevention: the estrogen connection. *JAMA.* 2004; 291:2488–2489.10.1001/jama.291.20.2488 [PubMed: 15161901]
58. Elvin JA, Yan C, Matzuk MM. Growth differentiation factor-9 stimulates progesterone synthesis in granulosa cells via a prostaglandin E2/EP2 receptor pathway. *Proc Natl Acad Sci USA.* 2000; 97:10288–10293.10.1073/pnas.180295197 [PubMed: 10944203]
59. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Taplin S. Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. *JAMA.* 2001; 285:171–176.10.1001/jama.285.2.171 [PubMed: 11176809]
60. Boyd NF, Martin LJ, Sun L, Guo H, Chiarelli A, Hislop G, Yaffe M, Minkin S. Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol Biomark Prev.* 2006; 15:2086–2092.10.1158/1055-9965.EPI-06-0345
61. Haars G, van Noord PA, van Gils CH, Grobbee DE, Peeters PH. Measurements of breast density: no ratio for a ratio. *Cancer Epidemiol Biomark Prev.* 2005; 14:2634–2640.10.1158/1055-9965.EPI-05-0824

62. Bochud M, Marquant F, Marques-Vidal PM, Vollenweider P, Beckmann JS, Mooser V, Paccaud F, Rousson V. Association between C-reactive protein and adiposity in women. *J Clin Endocrinol Metabol.* 2009; 94:3969–3977.10.1210/jc.2008-2428

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Fig. 1.

a Mean percent MD at each mammogram visit by baseline hsCRP level. **b** Estimated trajectory by baseline hsCRP status for a reference woman (Table 2, Model 2) (adjusted model with BMI). No significant difference of decline in MD by baseline hsCRP status. **c** Estimated trajectory by time-varying hsCRP status for a reference woman (Table 3, Model 2) (adjusted model with BMI). Significantly faster decline in percent MD in a woman with consistently non-elevated hsCRP compared to a woman with consistently elevated hsCRP

Table 1Distribution of study population characteristics by baseline hsCRP level, SWAN ($n = 653$)

Characteristic	<i>n</i>	hsCRP 3 mg/L (<i>n</i> = 521) <i>N</i> (%)	hsCRP > 3 mg/L (<i>n</i> = 132) <i>N</i> (%)
Age (years)			
40–44	158 (24.2)	126 (24.2)	32 (24.2)
45–49	382 (58.5)	302 (58.0)	80 (60.6)
50–55	113 (17.3)	93 (17.8)	20 (15.2)
<i>p</i> value 0.75			
BMI (kg/m ²) *			
<18.5	12 (1.9)	10 (1.9)	2 (1.5)
18.5–24.9	358 (55.5)	334 (64.9)	24 (18.5)
25.0–29.9	168 (26.0)	131 (25.4)	37 (28.5)
30	107 (16.6)	40 (7.8)	67 (51.5)
<i>p</i> value < 0.001			
Race/ethnicity			
Non-Hispanic Caucasian	329 (50.4)	247 (47.4)	82 (62.1)
African-American	37 (5.7)	16 (3.1)	21 (15.9)
Chinese	151 (23.1)	131 (25.1)	20 (15.2)
Japanese	136 (20.8)	127 (24.4)	9 (6.8)
<i>p</i> value < 0.001			
Parity			
Nulliparous	118 (18.1)	87 (16.7)	31 (23.5)
1–2 births	389 (59.6)	319 (61.2)	70 (53.0)
3 births	146 (22.3)	115 (22.1)	31 (23.5)
<i>p</i> value 0.16			
Menopausal status			
Premenopausal	392 (60.0)	316 (60.6)	76 (57.6)
Early perimenopausal	261 (40.0)	205 (39.4)	56 (42.4)
<i>p</i> value 0.52			
Education			
High school or less	103 (15.8)	85 (16.3)	18 (13.6)
Some college	187 (28.6)	140 (26.9)	47 (35.6)
College or more	363 (55.6)	296 (56.8)	67 (50.8)
<i>p</i> value 0.14			
Household annual income *			
<\$50,000	177 (27.7)	134 (26.4)	43 (32.8)
\$50,000–74,000	169 (26.4)	131 (25.8)	38 (29.0)
\$75,000	293 (45.9)	243 (47.8)	50 (38.2)
<i>p</i> value 0.13			
Smoking status *			
Never smoker/no SHS	294 (45.1)	248 (47.7)	46 (34.8)

Characteristic	<i>n</i>	hsCRP 3 mg/L (<i>n</i> = 521) <i>N</i> (%)	hsCRP > 3 mg/L (<i>n</i> = 132) <i>N</i> (%)
Never smoker/with SHS	158 (24.2)	128 (24.6)	30 (22.7)
Former smoker/no SHS	79 (12.1)	59 (11.4)	20 (15.2)
Former smoker/with SHS	69 (10.6)	48 (9.2)	21 (15.9)
Current smoker	52 (8.0)	37 (7.1)	15 (11.4)
<i>p</i> value 0.02			
Alcohol consumption (drink per week)*			
None	183 (37.0)	138 (34.9)	45 (45.0)
Less than 1 per week	93 (18.8)	71 (18.0)	22 (22.0)
1–7 per week	181 (36.6)	152 (38.5)	29 (29.0)
More than 7 per week	38 (7.6)	34 (8.6)	4 (4.0)
<i>p</i> value 0.07			
Physical activity*			
<7.1	226 (34.9)	174 (33.8)	52 (39.4)
7.1–8.3	172 (26.6)	129 (25.0)	43 (32.6)
>8.5	249 (38.5)	212 (41.2)	37 (28.0)
<i>p</i> value 0.01			
Comorbidities ¹			
No	480 (73.5)	416 (79.9)	64 (48.5)
Yes	173 (26.5)	105 (20.1)	68 (51.5)
<i>p</i> value < 0.001			
Vitamin use ^{2,*}			
No	341 (54.6)	268 (53.6)	73 (58.9)
Yes	283 (45.4)	232 (46.4)	51 (41.1)
<i>p</i> value 0.29			
Age at menarche, years			
<12	136 (20.8)	96 (18.4)	40 (30.3)
12	192 (29.4)	149 (28.6)	43 (32.6)
13	188 (28.8)	154 (29.6)	34 (25.8)
>13	137 (21.0)	122 (23.4)	15 (11.4)
<i>p</i> value 0.001			
Ever used oral contraceptives			
No	152 (23.3)	126 (24.2)	26 (19.7)
Yes	501 (76.7)	395 (75.8)	106 (80.3)
<i>p</i> value 0.28			
Ever used hormones other than oral contraceptive*			
No	566 (86.9)	449 (86.5)	117 (88.6)
Yes	85 (13.1)	70 (13.5)	15 (11.4)
<i>p</i> value 0.52			
Family history of breast cancer ^{3,*}			
No	584 (90.1)	466 (90.0)	118 (90.8)

Characteristic	<i>n</i>	hsCRP 3 mg/L (<i>n</i> = 521) <i>N</i> (%)	hsCRP > 3 mg/L (<i>n</i> = 132) <i>N</i> (%)
Yes	64 (9.9)	52 (10.0)	12 (9.2)
<i>p</i> value 0.78			
NSAID use ^{4, *}			
No	486 (74.5)	410 (78.8)	76 (57.6)
Yes	166 (25.5)	110 (21.2)	56 (42.4)
<i>p</i> value < 0.001			
Baseline breast density, [mean (SD)]	653	47.0 (18.5)	31.1 (20.6)
Mammographic density	653	47.5 (26.1)	45.9 (30.6)
Dense breast area	653	62.4 (49.1)	135.8 (94.6)
Non-dense breast area	653	109.9 (56.3)	181.7 (97.3)

¹ Comorbidities = diabetes, hypertension, arthritis, osteoporosis, heart disease

² Vitamin use = Use of at least one of these following antioxidant vitamins/supplements: vitamin C, vitamin E, or betacarotene

³ Family history of breast cancer = 1° and 2° female family members who had breast cancer

⁴ NSAID use = Use of any one of NSAIDs two or more times per week during the previous month or during any month since the previous visit

* Missing value: BMI (*n* = 8; 6 in hsCRP ≤ 3, 2 in hsCRP > 3), household annual income (*n* = 14; 13 in hsCRP ≤ 3, 1 in hsCRP > 3), smoking (*n* = 1 in hsCRP > 3), alcohol consumption = (*n* = 158; 126 in hsCRP ≤ 3, 32 in hsCRP > 3), physical activity (*n* = 6; all in hsCRP ≤ 3), vitamin use (*n* = 29; 21 in hsCRP ≤ 3, 8 in hsCRP > 3), ever use hormones other than oral contraceptive (*n* = 2; both in hsCRP ≤ 3), family history of breast cancer (*n* = 5; 3 in hsCRP ≤ 3, 2 in hsCRP > 3), NSAID use (*n* = 1 in hsCRP ≤ 3)

Table 2

Unadjusted and adjusted longitudinal model results for change in percent mammographic density (MD) associated with baseline elevated hsCRP (>3 mg/L), Study of Women's Health Across the Nation ($n = 653$)

Characteristics	Univariate Model 1 ^a			BMI-adjusted model 2 ^b			Model 3 ^c (model 2 without BMI)		
	β	CI	p value	β	CI	p value	β	CI	p value
Time ^d	-1.17	-1.30, -1.00	<0.001	-3.21	-5.15, -1.26	0.001	-2.87	-4.85, -0.89	0.005
Baseline elevated hsCRP $\times$ time ²	0.44	0.14, 0.73	0.003	0.37	-0.09, 0.84	0.11	0.88	0.44, 1.31	<0.001
Baseline BMI $\times$ time (kg/m ²)	-	-	-	0.07	0.04, 0.10	<0.001	-	-	-
Change in BMI $\times$ time	-	-	-	-0.13	-0.18, -0.07	<0.001	-	-	-

BMI/ body mass index. hsCRP high-sensitivity C-reactive protein

Use either symbols or numbers for all footnotes

Only associations with change in percent MD are presented

^aModel 1 presents the unadjusted model for baseline hsCRP predicting annual change in percent MD

^bModel 2 is adjusted model for annual change in percent MD adjusted for baseline levels of age, race/site, baseline BMI, baseline menopausal status, presence of comorbidities, vitamin use, alcohol consumption, and smoking, as well as interactions of race/site, baseline menopausal status, change in menopausal status, baseline BMI and change in BMI, alcohol consumption, smoking, presence of comorbidities, and vitamin use with time

^cModel 3 is the same as Model 2, excluding BMI and change in BMI

^dThe beta coefficient of time reflects the average annual change in percent MD for a reference woman. In Model 1, the reference is a woman with non-elevated hsCRP level (< 3 mg/ml). In Model 2, the reference is premenopausal with no change in menopausal status, Caucasian, nondrinker, non-smoker, non-vitamin user from the Pittsburgh site who has no comorbidities and average baseline level of BMI and no change in BMI. In Model 3, the reference is premenopausal with no change in menopausal status, Caucasian, nondrinker, non-smoker, non-vitamin user from the Pittsburgh site who has no comorbidities

²The beta coefficient of elevated baseline hsCRP $\times$ time reflects the average difference in annual change in percent MD between baseline non-elevated hsCRP level (< 3 mg/ml) and elevated hsCRP level (>3 mg/ml). For example, in Model 1, the unadjusted model, percent MD in women with elevated hsCRP levels decreased 0.44 percentage points per year less than women with non-elevated hsCRP level, for an average rate of change of -0.73 (-1.17 + 0.44)

Unadjusted and adjusted longitudinal model results for change in percent mammographic density (MD) associated with time-varying elevated hsCRP (>3 mg/L), Study of Women's Health Across the Nation ($n = 653$)

Table 3

Characteristics	Univariate Model 1 ^a			BMI-adjusted Model 2 ^b			Model 3 ^c (model 2 without BMI)		
	β	CI	p value	β	CI	p value	β	CI	p value
Time ^d	-1.23	-1.38, -1.07	<0.001	-3.01	-4.92, -1.10	0.002	-2.81	-4.74, -0.88	0.004
Time-varying elevated hsCRP $\times$ time ²	0.39	0.12, 0.66	0.004	0.40	0.07, 0.73	0.02	0.62	0.30, 0.94	<0.001
Baseline BMI $\times$ time (kg/m ²)	-	-	-	0.07	0.03, 0.10	<0.001	-	-	-
Change in BMI $\times$ time	-	-	-	-0.13	-0.18, -0.07	<0.001	-	-	-

BMI/ body mass index. *hsCRP* high-sensitivity C-reactive protein

Use either symbols or numbers for all footnotes

Only associations with change in percent MD are presented

^aModel 1 presents the unadjusted model for baseline hsCRP predicting annual change in percent MD

^bModel 2 is adjusted model for annual change in percent MD adjusted for baseline levels of age, race/site, baseline BMI, baseline menopausal status, presence of comorbidities, vitamin use, alcohol consumption, and smoking, as well as interactions of race/site, baseline menopausal status, change in menopausal status, baseline BMI and change in BMI, alcohol consumption, smoking, presence of comorbidities, and vitamin use with time

^cModel 3 is the same as Model 2, excluding BMI and change in BMI

^dThe beta coefficient of time reflects the average annual change in percent MD for a reference woman. In Model 1, the reference is a woman with non-elevated hsCRP level (< 3 mg/ml). In Model 2, the reference is premenopausal with no change in menopausal status Caucasian, nondrinker, non-smoker, non-vitamin user from the Pittsburgh site who has no comorbidities and average baseline level of BMI and no change in BMI. In Model 3, the reference is premenopausal with no change in menopausal status, Caucasian, nondrinker, non-smoker, non-vitamin user from the Pittsburgh site who has no comorbidities

²The beta coefficient of time-varying elevated hsCRP $\times$ time reflects the average difference in annual change in percent MD between non-elevated hsCRP level (< 3 mg/ml) and elevated hsCRP level (>3 mg/ml) at any time point. For example, in Model 1, the unadjusted model, at any time point, MD in women with elevated hsCRP level, decreased 0.39 percentage point per year less than women with non-elevated hsCRP level, for an average rate of change of -0.84 (-1.23 + 0.39). In Model 2 and 3, elevated hsCRP was associated with change in percent MD, with a 0.40 and 0.62 percentage point slower decline on MD per year than non-elevated hsCRP