EPIDEMIOLOGY

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Associations of coffee consumption and caffeine intake with mammographic breast density

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Abstract

Purpose Previous studies suggest that coffee and caffeine intake may be associated with reduced breast cancer risk. We investigated the association of coffee and caffeine intake with mammographic breast density by woman's menopausal status and, in postmenopausal women, by hormone therapy (HT).

Methods This study included 4130 cancer-free women within the Nurses' Health Study and Nurses' Health Study II cohorts. Percent breast density (PD) was measured from digitized film mammograms using a computer-assisted thresholding technique and square root-transformed for the analysis. Average cumulative coffee/caffeine consumption was calculated using data from all food frequency questionnaires preceding the mammogram date. Information regarding breast cancer risk factors was obtained from questionnaires closest to the mammogram date. We used generalized linear regression to quantify associations of regular, decaffeinated, and total coffee, and energy-adjusted caffeine intake with percent density.

Results In multivariable analyses, decaffeinated coffee was positively associated with PD in premenopausal women (2+ cups/day: $\beta = 0.23$, p trend = 0.03). In postmenopausal women, decaffeinated and total coffee were inversely associated with PD (decaffeinated 2+ cups/day: $\beta = -0.24$, p trend = 0.04; total 4+ cups/day: $\beta = -0.16$, p trend = 0.02). Interaction of decaffeinated coffee with menopausal status was significant (p-interaction < 0.001). Among current HT users, regular coffee and caffeine were inversely associated with PD (regular coffee 4+ cups/day: $\beta = -0.29$, p trend = 0.01; caffeine 4th vs. 1st quartile: $\beta = -0.32$, p trend = 0.01). Among past users, decaffeinated coffee was inversely associated with PD (2+ cups/day $\beta = -0.70$, p trend = 0.02).

Conclusions Associations of decaffeinated coffee with percent density differ by woman's menopausal status. Associations of regular coffee and caffeine with percent density may differ by HT status.

Keywords Caffeine · Coffee intake · Breast density · Postmenopausal hormone therapy

Introduction

Mammographic breast density is a well-established and strong predictor of breast cancer risk [1]. Appearance of the breast on the mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast [2]. Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues ("mammographically dense"), whereas the dark (radiolucent) areas are primarily fat. Women with breasts of ≥ 75% density (proportion of the total breast area that appears dense on the mammogram) are at fourfold to sixfold greater risk of breast cancer compared to women with more fat tissues in the breasts [1].

A few previous studies have suggested that coffee and caffeine intake may be associated with reduced breast cancer risk [3–6]. Some of the suggested mechanisms explaining

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these associations included changes in bioavailable estrogen, antioxidative properties of coffee constituents, and changes in DNA methylation and cellular differentiation [7–13]. To date, there is limited epidemiologic evidence that diet has a strong influence on mammographic density [14–17]. The only study that examined the associations between caffeine intake and percent breast density (Minnesota breast cancer family study) found no associations [18]. In addition to the very limited evidence on the association between coffee and caffeine consumption and breast density, it is unknown if there is an interaction between postmenopausal hormone use and caffeine intake in relation to breast density. Postmenopausal hormones have been shown to consistently increase mammographic breast density [19–22]. As coffee has stimulating effects on variety of enzymes, including those involved in estrogen and xenobiotic metabolism [11], it is possible that the effect of postmenopausal hormones on breast density could potentially be modified by the coffee consumption. To address these knowledge gaps, we examined the associations of coffee and caffeine intake with percent breast density in healthy pre- and postmenopausal women using prospective data from the Nurses' Health Study and Nurses' Health Study II cohorts. The associations in postmenopausal women were further examined separately by woman's hormone therapy (HT) status.

Methods

Study population

Women included in this study were selected from participants of the nested case–control study within Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. These prospective cohorts followed registered nurses in the United States who were 30–55 years (NHS) or 25–42 years old (NHSII) at enrollment. After administration of the initial questionnaire, the information on breast cancer risk factors and any diagnoses of cancer or other diseases was updated through biennial questionnaires [2, 23].

A nested case–control approach was originally used to examine the association between selected biomarkers and breast cancer risk within the NHS and NHS II [2, 24]. Using incidence density sampling, women without cancer history (other than non-melanoma skin cancer) at the time of the case's cancer diagnosis (controls) were matched 1:1 or 1:2 with women diagnosed with in situ or invasive breast cancer (cases) on age at the time of blood collection, menopausal status, and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw; for NHS II, additional matching included race/ethnicity and day in the luteal phase [25]. Our analysis included controls from this nested case–control study as well as additional women

within NHSII cohort without a history of any cancer other than non-melanoma skin who were not included in the original nested breast cancer case–control study. We attempted to obtain mammograms closest to the time of blood collection (or ~ 1997 for those who did not provide blood samples). From all eligible women, 4342 women provided consent and had a usable mammogram for density estimation. Of these women, 4130 (95%) had data on coffee and caffeine intake. This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Consent was obtained or implied by return of questionnaires.

Dietary assessment

Usual dietary intake and coffee consumption during the past year were assessed with a semi-quantitative food frequency questionnaire (FFQ) with approximately 130 items which was included in the 1991, 1995, 1999, 2003, and 2007 questionnaires for NHSII [26]. In NHS, information on diet within the preceding 1 year was first collected with 61-item FFQ in 1980 and then expanded to 116 items in 1984, 1986, 1990, 1994, and 1998 [27]. Responses on both NHS and NHSII FFQs were recorded in nine categories of intake frequency ranging from "never or less than once per month" to "six or more per day". Caffeine intake was derived from self-reported intakes of coffee, soda, tea, and chocolate by multiplying the frequency of consumption of each item by their caffeine content per serving and then summing across all items, as previously described [7].

We separately examined the associations with regular coffee, decaffeinated coffee, total coffee, and caffeine intake. Average cumulative coffee and caffeine intake were calculated using data available from all the questionnaires preceding the mammogram date. Consistent with previous studies in these cohorts [7], coffee consumption categories were defined as ≤ 6 cups/week, 1 cup/day, 2–3 cups/day, and 4+ cups/day. Decaffeinated coffee was categorized as ≤ 1–3 cups/month, 1–6 cups/week, 1 cup/day, and 2+ cups/day. Energy-adjusted caffeine intake was modeled as quartiles based on the distribution among pre- and postmenopausal women (premenopausal: < 94 mg, 94 to < 224 mg, 224 to < 383 mg, and ≥ 383 mg; postmenopausal: < 134 mg, 134 to < 262 mg, 262 to < 400 mg, and ≥ 400 mg). In a secondary analysis, we also explored the associations of recent consumption (preceding and closest to the mammogram date) with percent mammographic density.

Assessment of mammographic breast density

To quantify mammographic density, the craniocaudal views of both breasts for all mammograms in the NHS and for the first two batches of mammograms in the NHSII were digitized at 261 μm per pixel with a Lumisys 85 laser film

scanner (Lumisys, Sunnyvale, California). The third batch of NHSII mammograms was digitized using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) and comparable resolution of 150 dots per inch and 12 bit depth). The Cumulus software (University of Toronto, Toronto, Canada) was used for computer-assisted determination of the percent mammographic density on all mammograms [2, 28]. As reported previously, the measure of breast density from NHS mammograms was highly reproducible (within-person intraclass correlation coefficient = 0.93) [2]. All NHSII images were read by a single reader. Although within batch reproducibility was high (intraclass correlation coefficient ≥ 0.90) [29], density measures varied across the NHSII batches. We included a small subset of identical mammograms in all batches to account for batch drift in density measurement readings. The density measures from the second and third batches of NHSII mammograms were adjusted to account for the batch effect (whether due to intra-reader variability or scanner), as previously described [30]. Additionally, to assess the potential variability in percent density by scanner, we conducted a pilot study of 50 mammograms. These mammograms were scanned using both the Lumysis 85 laser scanner and the VIDAR CAD PRO Advantage scanner. The correlation between percent density as measured by the same observer from the two scanners was 0.88.

Percent breast density was measured as percentage of the total area occupied by epithelial/stromal tissue (absolute dense area) divided by the total breast area. Because breast densities of the right and left breast for an individual woman are strongly correlated [28], the average density of both breasts was used in this analysis.

Covariates

Information on breast cancer risk factors was obtained from the biennial questionnaires closest to the date of the mammogram. Women were considered to be postmenopausal if they reported: (1) no menstrual periods within the 12 months before blood collection with natural menopause, (2) bilateral oophorectomy, or (3) hysterectomy with one or both ovaries retained, and were 54 years or older for ever smokers or 56 years or older for never smokers [31, 32].

Statistical analysis

We used generalized linear regression to examine the associations of coffee and caffeine intake with percent density. Because percent mammographic density was non-normally distributed, we used square root transformation to improve normality in all the regression analyses. The lowest intake category for each of the exposures was used as the reference. The regression estimates were adjusted for age (continuous),

body mass index (continuous), age at menarche (< 12, 12–13, > 13 years), parity and age at first child's birth (nulliparous, parous with age at first birth < 25 years, and parous with age at first birth of ≥ 25 years), a confirmed history of benign breast disease (yes, no), a family history of breast cancer (yes, no), alcohol consumption (0, 0 to < 5, ≥ 5 g/day, unknown), study cohort, and in postmenopausal women also for hormone therapy (none, current, past, past with unknown current) and age at menopause (< 46, 46 to < 50, 50 to < 55, ≥ 55, unknown). In a secondary analysis, among current HT users the regression estimates were additionally adjusted for duration of HT.

To assess the overall trend for each of the exposure variables, we used respective medians within each category. For coffee consumption, the intake frequencies were first converted into servings and then the median servings in each quartile were used in the trend analysis. Differences in the associations of exposure variables with breast density by menopausal status were evaluated with two-way interactions and using Wald Chi square test. We used respective medians within each of the exposure categories to model the interaction. The same approach was used to test interactions of exposure variables with HT among postmenopausal women. Statistical significance in all the analyses was assessed at 0.05 level. The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

In this study of 4130 cancer-free women, the average age at the mammogram was 53 years (range 30–84). Of these women, 1823 were premenopausal and 2307 were postmenopausal. Pre- and postmenopausal women in the highest caffeine intake quartile had a mean percent density of 37.4 and 25.5%, respectively, as compared with 40.6 and 26.2% in women from the lowest quartile. Distributions of breast cancer risk factors by the quartiles of caffeine intake in pre- and postmenopausal women are presented in Table 1. Women in the highest quartile of caffeine intake as compared with the lowest quartile consumed more alcohol, where less likely to have a history of benign breast disease, and in postmenopausal women, less likely to be currently on HT. Premenopausal women in the highest caffeine quartile had greater BMI as compared with women in the lowest quartile. Distributions of other risk factors were similar across the caffeine intake quartiles.

In multivariable analysis, decaffeinated coffee was positively associated with percent density in premenopausal women ($\beta = 0.19$ for 1 cup/day and $\beta = 0.23$ for 2+ cup/day; p trend = 0.03) (Table 2). In a secondary analysis with untransformed percent density, drinking 2 and more cups of decaffeinated coffee was associated with 2.6% increase in

Table 1 Age-adjusted characteristics of postmenopausal women in the study (NHS and NHSII) at the time of the mammogram, by caffeine consumption quartile (cumulative average before the mammogram date)

Characteristic	Premenopausal women				Postmenopausal women			
	< 94 mg ($n = 455$)	94 < 224 mg ($n = 452$)	224 to < 383 mg ($n = 460$)	≥ 383 mg ($n = 456$)	< 134 mg ($n = 574$)	134 to < 262 mg ($n = 583$)	262 to < 400 mg ($n = 573$)	≥ 400 mg ($n = 577$)
Mean (SD)								
Percent mammographic density	40.6 (19.3)	38.8 (19.0)	41.5 (18.3)	37.4 (19.5)	26.2 (17.4)	26.4 (17.92)	26.1 (18.5)	25.5 (17.9)
Age (years)[a]	44.9 (4.4)	46.0 (4.4)	46.3 (4.5)	47.2 (4.0)	57.5 (8.5)	58.5 (8.2)	58.3 (7.5)	57.9 (7.4)
Age at menarche (years)	12.4 (1.5)	12.4 (1.4)	12.5 (1.4)	12.4 (1.5)	12.4 (1.4)	12.6 (1.4)	12.5 (1.5)	12.6 (1.4)
Age at menopause (years)	NA	NA	NA	NA	47.4 (6.1)	47.7 (6.1)	47.6 (5.9)	47.5 (5.9)
Body mass index (kg/m^2)	25.7 (5.6)	25.7 (5.4)	25.2 (5.2)	26.0 (5.4)	26.4 (5.8)	26.3 (5.4)	26.0 (4.8)	26.0 (5.0)
Alcohol consumption, g/day	2.0 (4.3)	3.6 (5.7)	6.0 (9.5)	6.5 (9.3)	3.0 (6.6)	5.2 (9.8)	6.1 (8.8)	6.2 (9.4)
Percentages								
Parity/age at first birth								
Nulliparous	14	13	15	13	9	8	11	8
Parous, age < 25 years	33	34	31	37	45	47	47	47
Parous, age ≥ 25 years	53	53	54	50	45	44	42	45
Family history of breast cancer	8	9	9	10	13	13	11	11
Benign breast disease	20	17	17	15	26	21	25	20
Never used HT	NA	NA	NA	NA	32	36	33	39
Past HT use	NA	NA	NA	NA	19	20	19	22
Current HT use	NA	NA	NA	NA	48	44	47	39

SD standard deviation, *HT* postmenopausal hormone therapy

[a]Value not age adjusted

percent density. Regular and total coffee consumption and caffeine intake were not associated with percent breast density. The risk estimates for regular and decaffeinated coffee remained similar after mutually adjusting for these two variables (data not shown).

In postmenopausal women, decaffeinated and total coffee consumption were inversely associated with percent breast density (decaffeinated coffee: β = − 0.12 for 1 cup/day and β = − 0.24 for 2+ cups/day, p trend = 0.04, p-interaction with menopausal status < 0.001; total coffee: β = − 0.17 for 2–3 cups/day and β = − 0.16 for 4+ cups/day, p trend = 0.02) (Table 2). In a secondary analysis with untransformed percent density, drinking 2 and more cups/day of decaffeinated coffee was associated with 2.4% decrease in percent density and intake of 4 and more cups of total coffee per day was associated with 1.2% decrease in percent density. We found a marginal inverse association of caffeine intake with percent density (p = 0.10). The

risk estimates for regular and decaffeinated coffee remained similar after mutually adjusting for these two variables (data now shown). We found no interactions of regular and total coffee as well as caffeine intake with menopausal status (p-interaction > 0.05 for all).

In the stratified analysis by woman's HT status, none of the exposure variables were associated with percent breast density among women with no HT (Table 3). Among current postmenopausal hormone users, regular coffee and caffeine intake were inversely associated with percent density (regular coffee: β = − 0.37 for 2–3 cups/day and β = − 0.29 for 4+ cups/day, p trend = 0.01; caffeine intake: β = − 0.20 for 3rd quartile and β = − 0.32 for 4th quartile, p trend = 0.01). These associations remained similar after additional adjustment for HT duration (data not shown). In a secondary analysis with untransformed percent density among current HT users, drinking 2–3 cups of regular coffee per day was associated with 3.8%

Table 2 Associations of coffee and caffeine consumption with mammographic percent breast density (square root-transformed), by menopausal status

Intake category (category median for pre-/postmenopausal)	Premenopausal		Postmenopausal	
	N	Full models, β and 95% CI[a]	N	Full models, β and 95% CI[b]
Regular coffee consumption				
≤ 6 cups/week (0/0.05)	765	Ref	730	Ref
1 cup/day (1.50/1.50)	453	0.18 (0.01, 0.35)	714	− 0.02 (− 0.19, 0.14)
2–3 cups/day (2.63/3.00)	453	− 0.15 (− 0.32, 0.02)	600	− 0.24 (− 0.41, − 0.07)
4+ cups/day (5.00/5.13)	108	− 0.13 (− 0.42, 0.15)	157	− 0.02 (− 0.29, 0.25)
p trend	1779	0.14	2201	0.08
Decaffeinated coffee				
≤ 1–3 cups/month (0/0)	970	Ref	873	Ref
1–6 cups/week (0.33/0.36)	378	0.09 (− 0.08, 0.26)	493	− 0.09 (− 0.26, 0.09)
1 cup/day (1.25/1.29)	320	0.19 (0.01, 0.38)	645	− 0.12 (− 0.28, 0.04)
2 + cups/day (2.60/2.67)	107	0.23 (− 0.06, 0.51)	183	− 0.24 (− 0.49, 0.01)
p trend	1775	0.03	2194	0.04
Total coffee				
≤ 6 cups/week (0/0.05)	584	Ref	455	Ref
1 cup/day (1.54/1.67)	439	0.08 (− 0.10, 0.26)	619	0.09 (− 0.10, 0.28)
2–3 cups/day (3.00/3.16)	558	0.05 (− 0.12, 0.22)	771	− 0.17 (− 0.36, 0.02)
4 + cups/day (5.21/5.36)	198	− 0.14 (− 0.38, 0.09)	357	− 0.16 (− 0.38, 0.07)
p trend	1779	0.43	2202	0.02
Caffeine intake (mg) quartile[c]				
1st (37/74)	442	Ref	539	Ref
2nd (153/195)	442	− 0.06 (− 0.25, 0.13)	556	− 0.05 (− 0.24, 0.13)
3rd (311/329)	444	0.09 (− 0.10, 0.28)	549	− 0.15 (− 0.34, 0.03)
4th (504/522)	447	− 0.17 (− 0.37, 0.02)	556	− 0.15 (− 0.33, 0.04)
p trend	1775	0.18	2200	0.10

[a]Adjusted for age (continuous), BMI (continuous), age at menarche (< 12, 12, 13, > 13), a family history of breast cancer (yes/no), a history of benign breast disease (yes/no), NHS cohort (NHSI, NHSII), alcohol use (none, > 0 to < 5, ≥ 5 g/day), and parity and age at first child's birth (nulliparous, parous with age at first birth < 25, parous with age at first birth ≥ 25)

[b]Adjusted for age (continuous), BMI (continuous), age at menarche (< 12, 12, 13, > 13), a family history of breast cancer (yes/no), a history of benign breast disease (yes/no), NHS cohort (NHSI, NHSII), alcohol use (none, > 0 to < 5, ≥ 5 g/day), hormone therapy (none, past, current, past/unknown current), age at menopause (< 46, 46 to < 50, 50 to < 55, ≥ 55, unknown), and parity and age at first child's birth (nulliparous, parous with age at first birth < 25, parous with age at first birth ≥ 25)

[c]Caffeine quartile definition in premenopausal women: 1st: < 94 mg, 2nd: 94 to < 224 mg, 3rd: 224 to < 383 mg, and 4th: 383 mg or greater; quartile definition if postmenopausal women: 1st: < 134 mg, 2nd: 134 to < 262 mg, 3rd: 262 to < 400 mg, and 4th: 400 mg or greater

decrease in percent density and drinking 4 or more cups per day was associated with 2.9% decrease in percent density. In this analysis, the highest caffeine intake quartile was associated with 3.3% decrease in percent density.

Among past hormone users, decaffeinated coffee was inversely associated with percent density (β = − 0.45 for 1 cup/day and β = − 0.70 for 2+ cups/day, *p* trend = 0.02). In a secondary analysis with untransformed percent density among past HT users, drinking 1 cup of decaffeinated coffee per day was associated with 4% decrease in percent density and drinking 2 and more cups of decaffeinated coffee was associated with 6% decrease in percent density.

We found no interactions of coffee and caffeine intake with the status of HT.

In a secondary analysis examining recent coffee and caffeine intake, the findings were similar (data not shown).

Discussion

In this study of cancer-free women, we investigated the associations of coffee consumption and caffeine intake with mammographic percent density in pre- and postmenopausal women and by the woman's HT status. Decaffeinated and

Table 3 Associations of coffee/caffeine with percent breast density (square root-transformed) by woman's hormone therapy use status at time of mammogram

Intake category (category median)	Never used hormones N = 776		Past hormone users N = 430		Current hormone users N = 980	
	N	β and 95% CI	N	β and 95% CI	N	β and 95% CI
Regular coffee consumption						
≤ 6 cups/week (0.05)	248	Ref	129	Ref	346	Ref
1 cup/day (1.50)	243	− 0.02 (− 0.30, 0.25)	151	− 0.13 (− 0.51, 0.24)	317	− 0.01 (− 0.25, 0.23)
2–3 cups/day (3.00)	224	− 0.15 (− 0.43, 0.13)	123	− 0.13 (− 0.53, 0.28)	248	− 0.37 (− 0.62, − 0.11)
4+ cups/day (5.13)	61	0.02 (− 0.40, 0.45)	27	0.72 (0.05, 1.38)	69	− 0.29 (− 0.69, 0.11)
p trend	776	0.58	430	0.28	980	0.01
Decaffeinated coffee						
≤ 1–3 cups/month (0)	324	Ref	139	Ref	407	Ref
1–6 cups/week (0.36)	162	− 0.16 (− 0.44, 0.13)	100	− 0.57 (− 0.98, − 0.16)	223	0.19 (− 0.07, 0.45)
1 cup/day (1.29)	232	− 0.18 (− 0.45, 0.08)	136	− 0.45 (− 0.83, − 0.07)	275	0.04 (− 0.21, 0.28)
2+ cups/day (2.67)	54	− 0.09 (− 0.53, 0.35)	55	− 0.70 (− 1.19, − 0.20)	72	− 0.12 (− 0.51, 0.27)
p trend	772	0.38	430	0.02	977	0.52
Total coffee						
≤ 6 cups/week (0.05)	166	Ref	64	Ref	221	Ref
1 cup/day (1.67)	207	− 0.04 (− 0.35, 0.28)	118	− 0.30 (− 0.79, 0.19)	290	0.28 (0.01, 0.56)
2–3 cups/day (3.16)	262	− 0.24 (− 0.54, 0.07)	173	− 0.50 (− 0.96, − 0.03)	331	− 0.04 (− 0.31, 0.23)
4+ cups/day (5.36)	141	− 0.17 (− 0.52, 0.18)	76	− 0.22 (− 0.77, 0.32)	138	− 0.16 (− 0.50, 0.18)
p trend	776	0.18	431	0.37	980	0.10
Caffeine intake (mg) quartile						
1st (74)	170	Ref	101	Ref	263	Ref
2nd (195)	205	− 0.14 (− 0.45, 0.17)	113	− 0.03 (− 0.46, 0.40)	236	0.02 (− 0.25, 0.30)
3rd (329)	180	− 0.06 (− 0.38, 0.27)	104	− 0.17 (− 0.62, 0.28)	260	− 0.20 (− 0.47, 0.07)
4th (522)	221	− 0.11 (− 0.42, 0.20)	111	0.15 (− 0.29, 0.59)	221	− 0.32 (− 0.60, − 0.04)
p trend	776	0.67	429	0.51	980	0.01

Adjusted for age (continuous), BMI (continuous), age at menarche (< 12, 12, 13, > 13), a family history of breast cancer (yes/no), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), alcohol use (none, > 0 to < 5, ≥ 5 g/day), age at menopause (< 46, 46 to < 50, 50 to < 55, ≥ 55, unknown), and parity and age at first child's birth (nulliparous, parous with age at first birth < 25, parous with age at first birth ≥ 25)

total coffee intakes were inversely associated with percent density in postmenopausal women and decaffeinated coffee intake was positively associated with percent density in premenopausal women. Inverse associations of regular coffee and caffeine with percent density were limited to current hormone users. Our findings contribute to the very limited evidence on the association of coffee and caffeine intake with breast density.

The only previous study that examined association between caffeine consumption and breast density among 1508 cancer-free women participating in the Minnesota Breast Cancer Family Study (MBCFS), found no statistically significant association overall and when stratified by menopausal status [18]. In contrast, we observed inverse associations of total and decaffeinated coffee intake with percent breast density among postmenopausal women and a positive association of decaffeinated coffee with percent density in premenopausal women. Several aspects of study design and methods could potentially explain inconsistencies

in the findings between the two studies. First, our study had considerably larger sample size and included 4130 women (1823 pre- and 2307 postmenopausal) in contrast to 1508 women in MBCFS (81.2% postmenopausal) thus substantially improving our statistical power in both overall and stratified analysis. MBCFS utilized a cross-sectional design with a single measure of caffeine intake while our study was prospective in nature and measured coffee and caffeine intake at multiple time points before the mammogram date thus allowing us to calculate cumulative average exposure measures. Next, two studies differed with respect to breast density estimation. In MBCFS, breast density was estimated visually by a radiologist from the mediolateral oblique view in contrast to computer-assisted density estimation from the craniocaudal views in our study. As the authors of MBCSF noted in their discussion, the study had a smaller proportion of women with dense breasts as compared with other studies as the result of using breast density estimation from mediolateral views which produces systematically lower

density estimates as compared with craniocaudal views [18]. Further, the two studies differed with respect to statistical methods, including analytical approach and covariates used for adjustment. As individuals in MBCSF did not represent independent observations, the study implemented bootstrapping procedure to account for the family-based sampling design in which generalized linear models were used for each randomly selected sample followed by the use of standard errors and the pooled parameter estimate for hypothesis testing. In addition, unlike our study, the density measures were not transformed in MBCSF. Finally, multivariate models from MBCSF included smoking. As caffeine has been shown to be positively correlated with smoking [33–35], this approach may have resulted in over-adjustment and attenuation of the effects.

In the stratified analysis by hormone therapy status, we noted an inverse association of regular coffee and caffeine intake with percent density and, among past users, an inverse association of decaffeinated coffee with percent density. Previous studies consistently show increase in breast density in HT users [19–22]. Even though we did not find any statistically significant interactions of regular coffee and caffeine intake with HT, our findings suggest that simultaneous intake of coffee might reduce the effect of HT on breast density which could potentially have implications for breast cancer prevention.

Several biological mechanisms were suggested as a possible explanation for potential effects of coffee and caffeine on breast cancer risk and breast density, including an influence on circulating estrogen levels and bioavailable estrogen [7–9], antioxidative potential due to a high content of wide variety of phytochemicals [10], stimulating effects on variety of enzymes, including those involved in estrogen and xenobiotic metabolism [11], and inhibition of DNA methylation [12] all of which eventually can disrupt normal cell proliferation and differentiation.

Our study is the largest study to date that systematically investigated associations of coffee and caffeine intake with mammographic breast density by menopausal status. We examined, for the first time, these associations in postmenopausal women by the status of HT. The analysis used data from the NHS and NHSII cohorts with more than 25 years of follow-up, ascertainment of disease status, and comprehensive information on breast cancer risk factors and breast density.

Our study has a few limitations. The examined associations are based on the density measures from a single mammogram which might not be reflective of the woman's life-long density pattern; however, studies have suggested that a single measure can predict breast cancer risk for up to 10 years in both pre- and postmenopausal women [36, 37]. Despite the prospective nature of the cohort, potential errors in recall of coffee consumption are possible. However,

previous validation studies suggest that reasonable reproducibility and validity of the data from food frequency questionnaires for the use in studies of associations between diet and health outcomes in epidemiologic studies [38, 39].

In conclusion, we investigated the associations of coffee and caffeine intake with percent mammographic density. Our findings suggest that inverse associations of decaffeinated and total coffee intake with mammographic percent density in postmenopausal women and a positive association of decaffeinated coffee with percent density in premenopausal women. Our results also suggest that these associations may differ by woman's HT status. If these association patterns are confirmed in subsequent studies, then the finding may translate into important public health messages for women using HT.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Consent was obtained or implied by return of questionnaires.

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