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Caffeine Consumption and Risk of Breast Cancer in a Large Prospective Cohort of Women

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Abstract

Background—Prospective data relating caffeine consumption to breast cancer risk are limited. We evaluated the association among women enrolled in a completed cancer prevention trial.

Methods—Detailed dietary information was obtained at baseline (1992–1995) among 38,432 women aged ≥45 years and free of cancer. During an average of 10 years of follow-up, we identified 1188 invasive breast cancer cases.

Results—Consumption of caffeine and caffeinated beverages and foods was not statistically significantly associated with overall risk of breast cancer. The multivariable relative risks (RRs) of breast cancer were 1.02 (95% confidence interval [CI], 0.84–1.22) for caffeine (top vs. bottom quintile), 1.08 (95% CI, 0.89–1.30) for coffee (≥4 cups/day vs. almost never), and 1.03 (95% CI, 0.85–1.25) for tea (≥2 cups/day vs. almost never). However, among women with benign breast disease, a borderline significant positive association with breast cancer risk was observed for the highest quintile of caffeine (RR = 1.32; 95% CI, 0.99–1.76) and for the highest category of coffee (≥4 cups/day) (RR = 1.35; 95% CI, 1.01–1.80); tests for interaction were marginally significant. Caffeine consumption was also significantly positively associated with risk of developing ER−PR−breast cancer (RR = 1.68; 95% CI, 1.01–2.81) and breast tumors of >2 cm in size (RR = 1.79; 95% CI, 1.18–2.72).

Conclusions—Data show no overall association between caffeine consumption and breast cancer risk. The possibility of an increased risk among women with benign breast disease or for tumors that are ER−PR− or greater than 2 cm in size warrants further study.

Caffeine (1,3,7-trimethylxanthine), a natural purine alkaloid, is probably the most frequently consumed drug in the world.[1, 2] Common beverages (coffee, tea, and soft drinks), cocoa or chocolate-containing food products, and certain medications, including headache or pain remedies, and over-the-counter stimulants, are important sources of caffeine.[1, 3] In North America, coffee (60–75%) and tea (15–30%) are the primary sources of caffeine in the adult diet.[1]

Caffeine was hypothesized to increase risk of breast cancer after a report that women with benign breast disease experienced relief from symptoms after elimination of caffeine from their

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diet,[2, 4] because benign breast disease, particularly atypical hyperplasia, is a marker of increased breast cancer risk.[5] However, clinical studies have yielded inconsistent results for the effect on symptoms of benign breast disease when caffeine is eliminated or reduced or for the effect of caffeine on the development of benign breast disease.[2, 6]

Most case-control investigations reported no association between caffeine and/or caffeinated beverages and foods and breast cancer risk,[7–17] but several case-control studies found either an inverse association[18–20] or a weak positive association.[19, 21–23] In three case-control studies that have evaluated the association according to menopausal status, two studies observed either a positive association or an inverse association only among premenopausal women,[23, 24] and another study found an inverse association for coffee only among postmenopausal women and no association for tea regardless of menopausal status.[25] Data from prospective studies, which are less prone to methodological bias, are limited and in general do not support an overall association,[26–33] except that two studies showed a nonsignificant positive association for black tea[34, 35] and one study found a significant inverse association only in postmenopausal women.[33] In a few studies that have examined the association according to history of benign breast disease, no significant association was observed among women with benign breast disease.[15, 18, 27] A Norwegian cohort reported that coffee reduced risk in lean women, whereas it increased risk in relatively overweight women.[31] However, in three other large cohorts,[27, 30, 33] and a large population-based case-control study,[15] no association was observed in any stratum of body mass index.

Breast cancer consists of diverse subtypes with different risk factors and clinical responsiveness to treatments.[36] However, only a few studies have evaluated the association according to hormone receptor status of breast tumors.[27, 33] To our knowledge, no previous studies have evaluated the association by tumor size, lymph node metastasis, and tumor differentiation, which reflect the stage of the carcinogenic process. With large numbers of cases and detailed information on tumor characteristics, we conducted a comprehensive analysis in the Women's Health Study, a large prospective cohort.

METHODS

STUDY COHORT

The Women's Health Study was established in 1992 when 39,876 female US health professionals (registered nurses, 75%) aged 45 years or older and free of cancer and cardiovascular disease at baseline were enrolled in a randomized trial of low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease.[37, 38] All participants completed a baseline questionnaire inquiring about their medical history and lifestyle factors. As of the end of the trial, March 31, 2004, the average duration of follow-up was 10 years, and follow-up rates for morbidity and mortality were 97.2% and 99.4%, respectively.[37, 38] The current analysis was restricted to 38,432 women after the exclusion of 1444 women who did not provide information on beverages and diet, had implausible total energy intakes (<600 kcal/day or >3500 kcal/day), left >70 food items blank, or had pre-randomization cancers that were reported after randomization and confirmed by medical record review.

ASSESSMENT OF CAFFEINE CONSUMPTION

At baseline, 39,310 (98.6 %) women in the Women's Health Study also completed a 131-item food frequency questionnaire, a format that has been used and validated in the Nurses' Health Study.[39–41] The questionnaire assessed average consumption over the past year of a specific amount of foods, including coffee, decaffeinated coffee, tea, caffeinated cola, decaffeinated cola, low-calorie caffeinated cola, low-calorie decaffeinated cola, and chocolate, and allowed

nine responses, ranging from "never" to "six or more times per day." Intakes of nutrients and caffeine consumption were calculated using the US Department of Agriculture food composition data[42] and supplemented by food manufactures. In these calculations, we assumed the content of caffeine was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola beverage, and 7 mg per serving of chocolate candy.[43] Validation studies in a similar cohort (Nurses' Health Study) revealed high correlations between self-reported intake of coffee and other caffeinated beverages assessed by the food frequency questionnaire and by 4 weeks of diet records (r = .78 for coffee; r = .93 for tea; and r = .85 for caffeinated sodas).[39] Coffee was the primary source of caffeine intake at baseline (81%), with fewer contributions by tea (10%), low-calorie caffeinated cola (6%), caffeinated cola (1%), chocolate (0.3%), and other foods (1.7%).

ASCERTAINMENT OF BREAST CANCER CASES

The primary endpoint for this analysis was invasive breast cancer, which was initially identified by self-report from the yearly follow-up questionnaires and then confirmed by medical record review. Deaths of participants were identified through reports from family members, postal authorities, and a search of the National Death Index. Medical records and other relevant information were sought and reviewed by an Endpoints Committee consisting of physicians for the confirmation of medical diagnoses. Medical record review confirmed 98% of self-reported breast cancer cases in the Women's Health Study.[44] During an average of 10 years of follow-up, we ascertained 1188 confirmed cases of invasive breast cancer. We also extracted detailed information on breast tumor characteristics at diagnosis from medical records, including estrogen receptor (ER) and progesterone receptor (ER) status (ER+PR+, n = 803 [67.6%]; ER+PR−, n = 125 [10.5%]; ER−PR+, n = 23 [1.9%]; ER−PR−, n = 166 [14.0%]; and unknown, n = 71 [6.0%]), tumor size (≤2 cm, n = 863 [72.6%]; >2 cm, n = 274 [23.1%]; any size with direct extension to chest wall or skin, n = 5 [0.4%]; and unknown, n = 46 [3.9%]), lymph node metastasis (absent, n = 839 [70.6%]; present, n = 284 [23.9%]; and unknown, n = 65 [5.5%]), and histologic grading and differentiation (well, n = 264 cases [22.2%]; moderately, n = 488 [41.1%]; poorly, n = 277 [23.3%]; and unknown, n = 159 [13.4%]). Tumor ER and PR status was determined by the laboratories affiliated with hospitals where breast cancer cases were diagnosed.

STATISTICAL ANALYSIS

We first compared mean values or proportions of baseline risk factors for breast cancer according to the categories of coffee consumption, the primary source of caffeine, to evaluate potential confounding by these variables.

Person-years were calculated for each participant, ranging from the date of randomization to the date of confirmed cancer diagnosis, death, or March 31, 2004, whichever occurred first. Cox proportional hazards regression models were used to calculate the relative risks (RRs) and 95% confidence intervals (CIs).[45] We estimated the RRs according to quintiles of caffeine consumption and categories of caffeinated beverages and foods with adjustment for age (in years) and randomized treatment assignment (aspirin vs. placebo, vitamin E vs. placebo). We also conducted a multivariable analysis that additionally adjusted for known or potential risk factors for breast cancer at baseline, including alcohol consumption (none, >0–<10, ≥10–<15, ≥15–<30, or ≥30 g/day), body mass index (<23, ≥23–<25, ≥25–<27, ≥27–<30, or ≥30 kg/m^2), family history of breast cancer in a first-degree relative (yes or no), history of hysterectomy (yes or no), bilateral oophorectomy (yes or no), smoking status (never, past, or current), history of benign breast disease (yes or no), age at menarche (≤11, 12, 13, 14 or ≥15 years), parity (0,1–2, 3–4, 5 or ≥6), age at first birth (≤24, 25–29, or ≥30 years), physical activity (kcal/week, in quartiles), total energy intake (kcal/day, in quintiles), multivitamin use (never, past, or current), age at menopause (<45, 45–49, 50–54, 55–59, or ≥60 years), menopausal status

(premenopausal, postmenopausal, or uncertain/unknown), and postmenopausal hormone use (never, past, current <5 years, or current ≥5 years). We also conducted analyses excluding incident cases of breast cancer diagnosed within the first two years of follow-up with additional adjustment for mammography screening that was asked on the 12-month questionnaire, or stratifying by menopausal status (pre- or postmenopausal women), history of benign breast disease (yes or no), body mass index (<25 kg/m^2 or ≥25 kg/m^2), and postmenopausal hormone use (never or current). Tests for multiplicative interaction were performed by log likelihood ratio tests comparing the models with or without interaction terms.

We also performed an analysis according to combined ER and PR status (ER+PR+, ER+PR−, ER−PR−), tumor size (≤2 and >2 cm), lymph node metastasis (with and without metastasis), and histologic grading and differentiation (well, moderately, and poorly differentiated). All statistical tests were two-sided.

RESULTS

In this population, median and 90th percentile values of caffeine intake at baseline were 283.4 mg/day and 658.2 mg/day, respectively. At baseline, 9262 (24.1%) women never drank coffee, 4996 (13.0%) drank less than 1 cup per day, 5448 (14.2%) drank 1 cup per day, 12623 (32.8%) drank 2 to 3 cups per day, 5900 (15.4%) drank at least 4 cups per day, and 203 (0.5%) had missing information on coffee intake (Table 1).

Table 1 presents the distributions of baseline risk factors for breast cancer according to the frequency of coffee consumption. Women who drank more cups of coffee were more likely to be leaner, less physically active, postmenopausal, current smokers, and have larger number of births. However, they were less likely to experience late age at menarche, late age at first birth, take postmenopausal hormones, have a history of hysterectomy, bilateral oophorectomy, or benign breast disease, and undergo mammography screening. They also tended to consume more caffeine, alcohol, and total energy, but were less likely to consume tea, decaffeinated coffee, decaffeinated cola with sugar, or low-calorie decaffeinated cola. Age, age at menopause, family history of breast cancer, or consumption of caffeinated cola with sugar, low-calorie caffeinated cola, and chocolate did not appear to differ substantially according to coffee consumption.

Intakes of caffeine, coffee, tea, caffeinated cola, low-calorie caffeinated cola, chocolate, decaffeinated coffee, decaffeinated cola, and low-calorie decaffeinated cola were not statistically significantly associated with overall risk of breast cancer in the models adjusted for age and randomized treatment assignment (Table 2). Additional adjustment for risk factors for breast cancer did not materially change the results; the multivariable RR comparing the highest to the lowest quintile of caffeine consumption was 1.02 (95% CI, 0.84–1.22). Compared with almost never users, the multivariable RRs were 1.08 (95% CI, 0.89–1.30) for coffee (≥4 cups/day), 1.03 (95% CI, 0.85–1.25) for tea (≥2 cups/day), 1.17 (95% CI, 0.87–1.57) for caffeinated cola (≥1 can or bottle/day), 0.88 (95% CI, 0.68–1.13) for low-calorie caffeinated cola (≥2 cans or bottles/day), and 0.97 (95% CI, 0.78–1.20) for chocolate (>1 bar or packet/week). The results did not appreciably change after excluding breast cancer cases diagnosed within the first two years of follow-up with additional adjustment for mammography screening that was asked on the 12-month questionnaire; the multivariable RRs were 1.02 (95% CI, 0.83–1.25) for caffeine (top vs. bottom quintile), 1.04 (95% CI, 0.85–1.28) for coffee (≥4 cups/day vs. almost never), 1.12 (95% CI, 0.92–1.37) for tea (≥2 cups/day vs. almost never), 1.16 (95% CI, 0.84–1.60) for caffeinated cola (≥1 can or bottle/day vs. almost never), 0.92 (95% CI, 0.70–1.20) for low-calorie caffeinated cola (≥2 cans or bottles/day vs. almost never), and 1.01 (95% CI, 0.81–1.27) for chocolate (>1 bar or packet/week vs. almost never).

Among women with a history of benign breast disease, a borderline significantly increased risk of breast cancer was seen for the highest quintile of caffeine (multivariable RR = 1.32; 95% CI, 0.99–1.76) and for consumption of ≥4 cups/day of coffee (multivariable RR = 1.35; 95% CI, 1.01–1.80) (Table 3); tests for interaction were marginally significant (*P* = .05 for caffeine and *P* = .05 for coffee). The associations between consumption of caffeine, coffee, decaffeinated coffee, and tea and risk of breast cancer did not appear to differ by body mass index (*P* for interaction = .23 for caffeine) (Table 3), menopausal status (*P* for interaction = . 53 for caffeine) and postmenopausal hormone use (*P* for interaction = .08 for caffeine) (Table 4). Although decaffeinated coffee consumption was not associated with risk of breast cancer among all postmenopausal women, a significant inverse association for decaffeinated coffee was observed among never users of postmenopausal hormones (multivariable RR = 0.58; 95% CI, 0.36–0.93; *P* = .02 for trend) (Table 4).

Separate analyses according to hormone receptor status revealed a significant positive association between caffeine consumption and risk of developing ER−PR− breast cancer; the multivariable RR was 1.68 (95% CI, 1.01–2.81, *P* = .02 for trend) (top vs. bottom quintile) (Table 5). In addition, a significant positive association for caffeine consumption was found for developing tumors that were >2 cm in size; the multivariable RR was 1.79 (95% CI, 1.18–2.72, *P* = .02 for trend) (top vs. bottom quintile) (Table 5). There were no significant associations between caffeine consumption and breast cancer risk according to tumor lymph node metastasis, or tumor histological grading and differentiation (Table 5).

COMMENT

In this large cohort of women, we found that consumption of caffeine and caffeinated beverages and foods was not significantly associated with overall risk of breast cancer. There were also no significant associations according to menopausal status, postmenopausal hormone use, body mass index, tumor lymph node metastasis, and tumor histologic grading and differentiation. However, among women with a history of benign breast disease, we observed a borderline significant positive association between consumption of >486.3 mg/day of caffeine or ≥4 cups/day of coffee (the primary source of caffeine) and breast cancer risk. We also found a significant positive association between caffeine consumption and risk of developing breast tumors that were ER−PR−or >2 cm in size.

Previous findings on the association between caffeine or coffee consumption and breast cancer risk have been inconclusive. An ecological analysis showed a strong inverse association between coffee/tea consumption and breast cancer mortality.[46] However, higher caffeine consumption has not been associated with risk of breast cancer in most case-control studies.[7–17] Several case-control studies have found a weak positive association, but there were no clear trends of increased risk with increasing consumption,[21–23, 47] and a few others have observed an inverse association.[18–20, 25, 48] A recent meta-analysis of 13 case-control and cohort studies indicate a lower risk of breast cancer associated with higher green tea consumption (the main tea consumed in Asia), but conflicting results for black tea (the main tea consumed in US and Europe) -- black tea consumption was associated with a reduced risk of breast cancer in case-control studies, but a slightly increased risk in cohort studies.[49]

Lack of overall association between consumption of caffeine, coffee, tea (black tea), decaffeinated coffee, soft drinks, and chocolate and risk of breast cancer observed in the Women's Health Study is generally consistent with the findings from previous prospective cohort studies in North America and Europe, including the Seventh-Day Adventists cohort,[26] the Iowa Women's Health Study,[27, 32] the New York State Cohort,[28] a Norwegian cohort,[50] the Swedish Mammography Screening Cohort,[30] and the Nurses' Health Study.[33] In a French cohort study, consumption of coffee and tea was not associated with risk of breast

cancer, however, consumption of herbal tea was significantly associated with a reduced risk of breast cancer.[51] A nonsignificant positive association for black tea was also observed in the Netherlands Cohort Study.[34] In a Japanese cohort, while coffee and black tea consumption was not associated with breast cancer risk, green tea consumption was nonsignificantly inversely associated with risk.[29] In two other Japanese cohorts, coffee and green tea consumption was nonsignificantly inversely associated with risk of breast cancer, but black tea was nonsignificantly positively association with risk of breast cancer.[35]

The mechanisms by which caffeine may affect breast carcinogenesis are complex and remain unclear. Caffeine has been reported to suppress cell cycle and proliferation and induce apoptosis.[52] Caffeine also has been positively associated with blood levels of estrone[53] and sex hormone-binding globulin,[53–55] but negatively associated with plasma free estradiol.[55] Caffeine and coffee can both stimulate and suppress the development of mammary tumors, depending on the phases of tumorigenesis (initiation/promotion) when caffeine and coffee are administered in rodents.[2, 56] Caffeine is a known antagonist of the adenosine receptor.[2, 57] Adenosine, an endogenous bioactive substance, exerts its diverse biologic effects through the activation of specific cell surface adenosine receptor.[57] In breast cancer cell lines, high concentrations of adenosine inhibited cell growth and induced cell cycle arrest at G2-M phase, but had no effect on ERα levels,[58] suggesting that, through antagonism of adenosine receptor, caffeine might be able to stimulate breast cell proliferation independent of ERα pathway.

In the present investigation, caffeine consumption was associated with increased risk of developing breast cancers negative for both ER and PR or with a size of greater than 2 cm, which have less favorable prognoses. These findings indicate that caffeine consumption may affect breast cancer progression and such effect may be independent of the estrogen pathway. These findings, however, are not in line with the results from the Iowa Women's Health Study and the Nurses' Health Study, in which there were no associations between caffeine consumption and risk of breast cancer according to ER and PR status, although the caffeine intake levels were generally similar between the Women's Health Study and the Iowa Women's Health Study cohorts.

Consistent with the hypothesis that caffeine may increase the risk of breast cancer among women with benign breast disease,[2, 4] we found a significantly increased risk associated with the highest quintile of caffeine and consumption of ≥4 cups/day of coffee among women with a history of benign breast disease. These findings suggest that high caffeine consumption may promote the progression from premalignant breast lesions to breast cancers as most types of invasive breast cancer are thought to arise from certain premalignant lesions such as atypical hyperplasia.[5] Of note, the increased risk was only apparent among those with the highest amount of intake, and there was no association in those consuming less than 4 cups/day of coffee. However, such findings are inconsistent with the results from the Iowa Women's Health Study cohort[27] and two large case-control studies,[15, 18] in which they have found no positive association between caffeine or coffee intake and breast cancer risk among those with benign breast disease.

A Norwegian cohort reported that coffee consumption was associated with a lower risk of breast cancer in lean women, but an increased risk in overweight women.[31] However, we, along with the Iowa Women's Health Study,[27] the Swedish Mammography cohort,[30] the Nurses' Health Study,[33] and a large case-control study,[15] found no significant association between consumption of caffeine and coffee and breast cancer risk according to categories of body mass index.

The strengths of this study include the prospective design and high follow-up rates, which minimize the possibility that our findings are a result of methodological biases. We also

minimized the confounding by other risk factors through controlling for established risk factors for breast cancer comprehensively. Our results are also unlikely to be explained by the potential bias that breast cancer itself (before it was diagnosed) may have affected caffeine consumption because the RRs, after excluding case patients who were diagnosed with breast cancer within the first 2 years after randomization, were similar to those using all case patients. In addition, this study had over 1000 incident breast cancer cases with 38,432 women followed for at least 10 years and detailed information on tumor characteristics, which enabled us to evaluate comprehensively the caffeine-breast cancer association according to tumor characteristics. This study also has limitations. Because we used the information on consumption of caffeine and caffeinated beverages and foods only at baseline, which did not account for changes in caffeine consumption over time, measurement error due to random within-person variation is inevitable. Such misclassification in prospective studies tends to weaken any true associations. In addition, because the number of case patients in some exposure categories and categories of tumor characteristics was relatively modest, we had limited statistical power in some subgroup analyses. Finally, we cannot exclude the possibility that our findings in some subgroups may be a result of chance because a large number of subgroups were evaluated. More studies are needed to refute or confirm the associations that we observed in some subgroups.

In conclusion, the findings from this prospective study suggest that caffeine consumption is not related to overall risk of breast cancer. However, our data suggest that high caffeine consumption may increase risk of breast cancer among women with a history of benign breast disease or of breast tumors that are ER−PR− or >2 cm in size, but these findings may be due to chance and warrant further study.

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Table 1

Age-standardized baseline characteristics* by coffee consumption in the Women's Health Study

	Coffee Consumption (Cups/Day)				
	None	<1	1	2–3	≥4
Number of participants	9262	4996	5448	12623	5900
Mean					
Age, years	54.2	54.5	55.4	54.7	54.4
Body mass index, kg/m^2	26.4	26.4	26.0	25.7	25.7
Physical activity, kcal/week	1007	999	968	987	853
Age at menopause, years†	47.0	46.9	47.1	47.1	46.9
Total caffeine, mg/day	71.1	112.5	198.4	406.1	731.5
Tea, cups/day	0.87	0.77	0.63	0.53	0.42
Decaffeinated coffee, cups/day	0.77	1.00	0.65	0.37	0.25
Caffeinated cola with sugar, cans or bottles/day	0.14	0.12	0.11	0.09	0.11
Decaffeinated cola with sugar, cans or bottles/day	0.04	0.04	0.03	0.02	0.02
Low-calorie caffeinated cola, cans or bottles/day	0.45	0.37	0.36	0.42	0.45
Low-calorie decaffeinated cola, cans or bottles/day	0.38	0.28	0.22	0.18	0.15
Chocolate, bars or packets/day	0.12	0.11	0.10	0.10	0.12
Alcohol intake, g/day	2.7	3.3	4.1	5.4	4.6
Total energy intake, kcal/day	1678	1726	1712	1732	1808
Percent					
Age at menarche, ≥13 years	47.5	47.0	47.0	47.5	46.1
Age at first pregnancy lasting ≥6 months, ≥30 years‡	10.9	12.5	12.1	11.8	9.5
Parity, ≥3	47.6	48.0	47.2	49.0	51.4
Postmenopausal	54.0	55.1	53.4	54.2	55.5
Current postmenopausal hormone users†	66.8	66.9	65.4	64.6	55.6
Prior hysterectomy	36.6	34.6	34.1	31.7	31.4
Prior bilateral oophorectomy	17.2	16.5	15.7	14.4	14.1
Current smokers	7.4	8.2	7.8	13.2	30.4
History of benign breast disease	36.0	34.9	34.9	32.8	31.0
Mother or sister with breast cancer	6.2	6.1	6.0	5.9	6.3
Mammography screening§	63.5	63.2	62.5	60.3	53.2

*All factors except age are directly standardized.

†Among postmenopausal women only.

‡Among parous women only.

§From the 12-month follow-up questionnaire

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Table 2

Relative risks (RRs) and 95% confidence intervals (CIs) of breast cancer according to quintiles of caffeine and categories of coffee, tea, decaffeinated coffee, caffeinated beverages, and chocolate

Intake	No. of cases	RR (95% CI)†	RR (95% CI)‡
Caffeine, mg/day			
≤68.0	242	1.00 [Reference]	1.00 [Reference]
>68.0, ≤181.0	212	0.90 (0.74–1.08)	0.89 (0.74–1.07)
>181.0, ≤352.2	251	1.05 (0.88–1.26)	1.04 (0.87–1.24)
>352.2, ≤486.3	245	1.02 (0.85–1.22)	1.02 (0.85–1.23)
>486.3	238	1.01 (0.84–1.20)	1.02 (0.84–1.22)
P value for trend*		.53	.45
Coffee			
Almost never	274	1.00 [Reference]	1.00 [Reference]
<1 cup/day	145	0.97 (0.80–1.19)	0.97 (0.79–1.18)
1 cup/day	166	0.99 (0.82–1.20)	0.98 (0.81–1.19)
2–3 cups/day	405	1.06 (0.91–1.24)	1.05 (0.89–1.22)
≥4 cups/day	191	1.08 (0.90–1.30)	1.08 (0.89–1.30)
P value for trend*		.22	.27
Decaffeinated coffee			
Almost never	629	1.00 [Reference]	1.00 [Reference]
<1 cup/day	275	1.04 (0.90–1.20)	0.99 (0.86–1.14)
1 cup/day	94	0.84 (0.68–1.05)	0.79 (0.64–0.99)
≥2 cups/day	169	1.00 (0.85–1.19)	0.93 (0.78–1.10)
P value for trend*		.72	.23
Tea			
Almost never	388	1.00 [Reference]	1.00 [Reference]
<1 cup/day	498	1.01 (0.88–1.15)	1.02 (0.89–1.17)
1 cup/day	130	0.90 (0.74–1.10)	0.92 (0.75–1.12)
≥2 cups/day	155	1.01 (0.84–1.21)	1.03 (0.85–1.25)
P value for trend*		.84	.99
Caffeinated cola			
Almost never	879	1.00 [Reference]	1.00 [Reference]
<1 can/day	254	0.94 (0.81–1.08)	0.95 (0.82–1.09)
≥1 can/day	48	1.16 (0.86–1.55)	1.17 (0.87–1.57)
P value for trend*		.45	.40
Decaffeinated cola			
Almost never	1063	1.00 [Reference]	1.00 [Reference]
1–3 cans/month	59	0.83 (0.64–1.08)	0.81 (0.62–1.06)
≥1 can/week	48	0.83 (0.62–1.11)	0.83 (0.62–1.11)
P value for trend*		.15	.15
Low-calorie caffeinated cola			
Almost never	602	1.00 [Reference]	1.00 [Reference]
<1 can/day	421	1.04 (0.91–1.17)	1.05 (0.93–1.19)
1 can/day	87	0.86 (0.69–1.08)	0.89 (0.71–1.11)
≥2 cans/day	69	0.83 (0.65–1.07)	0.88 (0.68–1.13)
P value for trend*		.06	.16
Low-calorie decaffeinated cola			
Almost never	750	1.00 [Reference]	1.00 [Reference]
<1 can/day	308	0.88 (0.77–1.01)	0.88 (0.77–1.01)
1 can/day	50	0.76 (0.57–1.02)	0.77 (0.58–1.03)
≥2 cans/day	57	1.29 (0.99–1.70)	1.30 (0.99–1.71)
P value for trend*		.27	.25
Chocolate			
Almost never	459	1.00 [Reference]	1.00 [Reference]
1–3 bars or packets/month	424	1.07 (0.94–1.22)	1.08 (0.94–1.23)
1 bar or packet/week	183	1.12 (0.94–1.32)	1.11 (0.93–1.33)
>1 bar or packet/week	112	0.98 (0.79–1.20)	0.97 (0.78–1.20)
P value for trend*		.91	.78

*The test for trend was calculated using the median intake in each category as a continuous variable.

†Adjustments for age and randomized treatment assignment

‡Adjustments for age, randomized treatment assignment, body mass index, physical activity, total energy intake, alcohol intake, multivitamin use, age at menopause, age at menarche, age at first pregnancy lasting ≥6months, number of pregnancies lasting ≥6months, menopausal status, postmenopausal hormone use, prior hysterectomy, prior bilateral oophorectomy, smoking status, family history of breast cancer in mother or a sister, and history of benign breast disease

Table 3

Relative risks (RRs) and 95% confidence intervals (CIs) of breast cancer according to quintiles of caffeine and categories of coffee, decaffeinated coffee, and tea, by history of benign breast disease (BBD) and body mass index (BMI)

	With BBD		Without BBD		BMI <25 kg/m		BMI ≥25 kg/m^2	
	No. of cases	RR (95% CI)[†]	No. of cases	RR (95% CI)[†]	No. of cases	RR (95% CI)[‡]	No. of cases	RR (95% CI)[‡]
Caffeine, mg/day								
≤68.0	97	1.00 [Reference]	145	1.00 [Reference]	119	1.00 [Reference]	123	1.00 [Reference]
>68.0, ≤181.0	100	1.10 (0.83–1.46)	112	0.76 (0.59–0.97)	127	1.11 (0.87–1.43)	85	0.69 (0.52–0.91)
>181.0, ≤352.2	110	1.23 (0.93–1.63)	141	0.91 (0.72–1.15)	142	1.20 (0.93–1.54)	109	0.88 (0.68–1.15)
>352.2, ≤486.3	89	1.03 (0.77–1.39)	156	1.00 (0.79–1.27)	128	1.02 (0.79–1.32)	117	1.03 (0.79–1.34)
>486.3	108	1.32 (0.99–1.76)	130	0.84 (0.66–1.08)	141	1.16 (0.90–1.50)	97	0.87 (0.66–1.14)
P value for trend[*]		.10		.71		.43		.85
Coffee								
Almost never	116	1.00 [Reference]	158	1.00 [Reference]	146	1.00 [Reference]	128	1.00 [Reference]
<1 cup/day	61	0.99 (0.73–1.36)	84	0.94 (0.72–1.22)	75	0.95 (0.72–1.26)	70	0.97 (0.73–1.30)
1 cup/day	79	1.18 (0.89–1.58)	87	0.85 (0.66–1.11)	99	1.06 (0.82–1.37)	67	0.87 (0.65–1.18)
2–3 cups/day	159	1.08 (0.84–1.38)	246	1.02 (0.83–1.25)	219	0.99 (0.80–1.23)	186	1.11 (0.88–1.39)
≥4 cups/day	89	1.35 (1.01–1.80)	102	0.91 (0.71–1.18)	115	1.13 (0.88–1.46)	76	0.99 (0.74–1.32)
P value for trend[*]		.08		.96		.41		.53
Decaffeinated coffee								
Almost never	244	1.00 [Reference]	385	1.00 [Reference]	341	1.00 [Reference]	288	1.00 [Reference]
<1 cup/day	115	0.94 (0.75–1.17)	160	1.04 (0.86–1.25)	146	0.89 (0.73–1.09)	129	1.11 (0.90–1.37)
1 cup/day	51	0.95 (0.70–1.29)	43	0.67 (0.49–0.92)	55	0.77 (0.58–1.03)	39	0.83 (0.59–1.16)
≥2 cups/day	85	0.96 (0.74–1.23)	84	0.90 (0.71–1.15)	104	0.97 (0.77–1.21)	65	0.87 (0.66–1.14)
P value for trend[*]		.78		.16		.76		.15
Tea								
Almost never	143	1.00 [Reference]	245	1.00 [Reference]	221	1.00 [Reference]	167	1.00 [Reference]
<1 cup/day	226	1.23 (1.00–1.52)	272	0.90 (0.76–1.07)	265	1.00 (0.84–1.20)	233	1.04 (0.85–1.27)
1 cup/day	64	1.24 (0.92–1.67)	66	0.74 (0.56–0.98)	75	0.96 (0.74–1.25)	55	0.86 (0.63–1.16)
≥2 cups/day	67	1.24 (0.92–1.66)	88	0.92 (0.72–1.18)	85	1.02 (0.79–1.31)	70	1.05 (0.80–1.40)
P value for trend[*]		.37		.51		.93		>.99

[*] The test for trend was calculated using the median intake in each category as a continuous variable.

[†] Adjustments for variables in multivariable analysis in footnote to Table 2, except for history of benign breast disease

[‡] Adjustments for variables in multivariable analysis in footnote to Table 2, except for body mass index

Table 4

Relative risks (RRs) and 95% confidence intervals (CIs) of breast cancer according to quintiles of caffeine and categories of coffee, decaffeinated coffee, and tea, by menopausal status and postmenopausal hormone use.

	Premenopausal women		Postmenopausal women		Postmenopausal hormone never users		Postmenopausal hormone current users	
	No. of cases	RR (95% CI)†	No. of cases	RR (95% CI)†	No. of cases	RR (95% CI)‡	No. of cases	RR (95% CI)‡
Caffeine, mg/day								
≤68.0	52	1.00 [Reference]	160	1.00 [Reference]	34	1.00 [Reference]	101	1.00 [Reference]
>68.0, ≤181.0	48	0.85 (0.58–1.27)	130	0.86 (0.68–1.09)	45	1.45 (0.92–2.29)	76	0.76 (0.56–1.03)
>181.0, ≤352.2	67	1.18 (0.81–1.70)	149	0.97 (0.77–1.22)	44	1.33 (0.84–2.11)	85	0.86 (0.64–1.15)
>352.2, ≤486.3	63	1.16 (0.80–1.69)	150	0.93 (0.74–1.17)	47	1.41 (0.90–2.23)	84	0.81 (0.60–1.08)
>486.3	45	0.88 (0.58–1.33)	153	1.01 (0.80–1.27)	44	1.19 (0.75–1.89)	93	1.10 (0.82–1.47)
P value for trend*		.97		.66		.78		.34
Coffee								
Almost never	67	1.00 [Reference]	161	1.00 [Reference]	38	1.00 [Reference]	104	1.00 [Reference]
<1 cup/day	31	0.89 (0.58–1.36)	104	1.14 (0.89–1.46)	21	0.89 (0.53–1.51)	68	1.13 (0.83–1.54)
1 cup/day	39	1.07 (0.72–1.59)	98	0.90 (0.70–1.16)	36	1.15 (0.73–1.81)	52	0.78 (0.56–1.09)
2–3 cups/day	100	1.10 (0.80–1.51)	254	1.05 (0.86–1.28)	80	1.26 (0.86–1.84)	143	0.93 (0.72–1.20)
≥4 cups/day	38	0.97 (0.64–1.46)	118	1.08 (0.85–1.38)	34	1.01 (0.63–1.61)	71	1.22 (0.89–1.66)
P value for trend*		.85		.50		.45		.45
Decaffeinated coffee								
Almost never	147	1.00 [Reference]	383	1.00 [Reference]	129	1.00 [Reference]	204	1.00 [Reference]
<1 cup/day	61	0.87 (0.64–1.18)	176	1.06 (0.89–1.27)	45	0.93 (0.66–1.31)	114	1.22 (0.96–1.54)
1 cup/day	21	0.78 (0.49–1.24)	64	0.86 (0.66–1.13)	17	0.78 (0.47–1.31)	40	0.92 (0.65–1.29)
≥2 cups/day	43	1.05 (0.75–1.49)	104	0.92 (0.74–1.14)	20	0.58 (0.36–0.93)	71	1.13 (0.86–1.49)
P value for trend*		.74		.26		.02		.75
Tea								
Almost never	87	1.00 [Reference]	244	1.00 [Reference]	69	1.00 [Reference]	140	1.00 [Reference]
<1 cup/day	115	1.01 (0.76–1.34)	319	1.07 (0.91–1.27)	94	1.23 (0.90–1.69)	187	1.01 (0.81–1.27)
1 cup/day	30	0.91 (0.60–1.38)	78	0.91 (0.70–1.18)	21	0.93 (0.57–1.53)	50	0.95 (0.68–1.31)
≥2 cups/day	40	1.05 (0.72–1.53)	89	1.02 (0.80–1.31)	26	1.16 (0.74–1.84)	54	1.03 (0.75–1.42)
P value for trend*		.88		.76		.93		.93

*The test for trend was calculated using the median intake in each category as a continuous variable.

†Adjustments for variables in multivariable analysis in footnote to Table 2, except for menopausal status. The variables of age at menopause, postmenopausal hormone use, prior hysterectomy, and prior bilateral oophorectomy were adjusted in multivariable models for postmenopausal women only.

‡Among postmenopausal women with adjustments for variables in multivariable analysis in footnote to Table 2, except for menopausal status and postmenopausal hormone use

Table 5

Relative risks and 95% confidence intervals (CI) of invasive breast cancer according to quintiles of caffeine consumption, by tumor characteristics

Characteristics	Quintile of Total Caffeine					
	1 (lowest)	2	3	4	5 (highest)	*P* value for trend*
Hormone receptor status						
ER+PR+						
No. of cases	178	147	164	168	146	
Person-years	75841	76017	76145	76122	76409	
Incidence rate (cases per 100000 person-years)	234.7	193.4	215.4	220.7	191.1	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.85 (0.68–1.05)	0.93 (0.76–1.16)	0.95 (0.77–1.18)	0.84 (0.67–1.05)	.31
Multivariate adjusted‡	1.00 [Reference]	0.85 (0.68–1.06)	0.93 (0.75–1.16)	0.93 (0.75–1.16)	0.84 (0.67–1.06)	.30
ER+PR−						
No. of cases	24	20	27	27	27	
Person-years	76569	76664	76780	76769	77017	
Incidence rate (cases per 100000 person-years)	31.3	26.1	35.2	35.2	35.1	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.85 (0.47–1.54)	1.15 (0.67–2.00)	1.13 (0.65–1.95)	1.17 (0.67–2.03)	.36
Multivariate adjusted‡	1.00 [Reference]	0.84 (0.46–1.53)	1.10 (0.62–1.94)	1.28 (0.72–2.26)	1.38 (0.78–2.46)	.11
ER−PR−						
No. of cases	25	26	41	32	42	
Person-years	76584	76650	76668	76751	76911	
Incidence rate (cases per 100000 person-years)	32.6	33.9	53.5	41.7	54.6	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	1.03 (0.60–1.79)	1.64 (1.00–2.70)	1.28 (0.76–2.15)	1.67 (1.01–2.73)	.03
Multivariate adjusted‡	1.00 [Reference]	0.98 (0.56–1.69)	1.60 (0.96–2.65)	1.27 (0.74–2.17)	1.68 (1.01–2.81)	.02
Tumor size						
≤2 cm						
No. of cases	195	140	184	177	167	
Person-years	75696	75900	75934	76008	76226	
Incidence rate (cases per 100000 person-years)	257.6	184.5	242.3	232.9	219.1	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.73 (0.59–0.91)	0.96 (0.78–1.17)	0.91 (0.75–1.12)	0.87 (0.71–1.07)	.78
Multivariate adjusted‡	1.00 [Reference]	0.73 (0.59–0.91)	0.95 (0.77–1.17)	0.90 (0.73–1.10)	0.86 (0.69–1.06)	.61
>2 cm						
No. of cases	38	59	58	60	59	
Person-years	76418	76355	76531	76522	76705	
Incidence rate (cases per 100000 person-years)	49.7	77.3	75.8	78.4	76.9	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	1.60 (1.06–2.40)	1.56 (1.04–2.35)	1.60 (1.06–2.40)	1.60 (1.07–2.41)	.08
Multivariate adjusted‡	1.00 [Reference]	1.56 (1.03–2.35)	1.53 (1.01–2.32)	1.69 (1.12–2.55)	1.79 (1.18–2.72)	.02
Lymph node metastasis						
Absent						
No. of cases	177	132	171	185	174	
Person-years	75732	75953	75883	75932	76119	

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Characteristics	Quintile of Total Caffeine					
	1 (lowest)	2	3	4	5 (highest)	*P* value for trend*
Incidence rate (cases per 100000 person-years)	233.7	173.8	225.3	243.6	228.6	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.76 (0.61–0.95)	0.98 (0.80–1.21)	1.06 (0.86–1.30)	1.01 (0.82–1.24)	.20
Multivariate adjusted‡	1.00 [Reference]	0.76 (0.61–0.96)	0.98 (0.79–1.22)	1.04 (0.84–1.29)	1.01 (0.81–1.25)	.23
Present						
No. of cases	53	67	65	48	51	
Person-years	76317	76298	76472	76539	76772	
Incidence rate (cases per 100000 person-years)	69.4	87.8	85.0	62.7	66.4	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	1.28 (0.89–1.84)	1.23 (0.85–1.76)	0.90 (0.61–1.33)	0.96 (0.65–1.41)	.29
Multivariate adjusted‡	1.00 [Reference]	1.23 (0.86–1.77)	1.15 (0.80–1.67)	0.92 (0.62–1.36)	0.98 (0.66–1.45)	.43
Histological grading and differentiation						
Well						
No. of cases	56	49	54	44	61	
Person-years	76170	76213	76281	76383	76524	
Incidence rate (cases per 100000 person-years)	73.5	64.3	70.8	57.6	79.7	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.90 (0.61–1.31)	0.99(0.68–1.43)	0.79 (0.53–1.17)	1.12 (0.78–1.62)	.55
Multivariate adjusted‡	1.00 [Reference]	0.91 (0.62–1.34)	1.02 (0.70–1.50)	0.78 (0.52–1.17)	1.21 (0.83–1.76)	.40
Moderately						
No. of cases	115	76	102	103	92	
Person-years	75909	76077	76062	76074	76354	
Incidence rate (cases per 100000 person-years)	151.5	99.9	134.1	135.4	120.5	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	0.68 (0.51–0.91)	0.90 (0.69–1.18)	0.91 (0.70–1.19)	0.82 (0.63–1.08)	.68
Multivariate adjusted‡	1.00 [Reference]	0.68 (0.51–0.91)	0.89 (0.68–1.17)	0.92 (0.70–1.21)	0.82 (0.62–1.10)	.70
Poorly						
No. of cases	46	56	57	65	53	
Person-years	76216	76187	76223	76260	76556	
Incidence rate (cases per 100000 person-years)	60.4	73.5	74.8	85.2	69.2	
Relative risk (95% CI)						
Age and treatment adjusted†	1.00 [Reference]	1.23 (0.83–1.81)	1.25 (0.85–1.84)	1.40 (0.96–2.04)	1.15 (0.77–1.70)	.52
Multivariate adjusted‡	1.00 [Reference]	1.17 (0.79–1.73)	1.15 (0.77–1.71)	1.39 (0.94–2.04)	1.11 (0.74–1.67)	.56

*The test for trend was calculated using median intake of caffeine consumption in each category as a continuous variable.

†Adjustments for age and randomized treatment assignment

‡Adjustments for variables in multivariable analysis in footnote to Table 2