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Coffee, tea, caffeine, and risk of breast cancer: a twenty two-year follow-up

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Abstract

The relation between consumption of coffee, tea, and caffeine and risk of breast cancer remains unsettled. We examined data from a large, long-term cohort study to evaluate whether high intake of coffee and caffeine is associated with increased risk of breast cancer. This was a prospective cohort study with 85,987 female participants in the Nurses' Health Study. Consumption of coffee, tea and caffeine consumption was assessed in 1980, 1984, 1986, 1990, 1994, 1998, and the follow-up continued through 2002. We documented 5,272 cases of invasive breast cancer during 1,715,230 person-years. The multivariate relative risks (RRs) of breast cancer across categories of caffeinated coffee consumption were: 1.0 for <1cup/mo (reference category), 1.01 (95% confidence interval: 0.92–1.12) for 1/mo–4.9/wk, 0.92 (0.84–1.01) for 5/wk–1.9/d, 0.93 (0.85–1.02) for 2–3.9/d, 0.92 (0.82–1.03) for 4 cups per day (p for trend= 0.14). Intakes of tea and decaffeinated coffee were also not significantly associated with risk of breast cancer. RRs (95% CI) for increasing quintiles of caffeine intake were 1.00, 0.98 (0.90–1.07), 0.92 (0.84–1.00), 0.94 (0.87–1.03), and 0.93 (0.85–1.01) (p for trend=0.06). A significant inverse association of caffeine intake with breast cancers was observed among postmenopausal women; for the highest quintile of intake compared to the lowest RR 0.88 (95% CI = 0.79 to 0.97, p for trend=0.03). We observed no substantial association between caffeinated and decaffeinated coffee and tea consumption and risk of breast cancer in the overall cohort. However, our results suggested a weak inverse association between caffeine-containing beverages and risk of postmenopausal breast cancer.

Keywords

Breast cancer; Dietary practices; Coffee; Tea; Caffeine

INTRODUCTION

Coffee and tea consumption have been hypothesized both to increase and to decrease the risk of developing breast cancer. Caffeine is a naturally occurring plant alkaloid found in coffee, tea, cocoa, and as an additive in many soft drinks and medications. It belongs to a group of purine-based compounds collectively referred to as methylxanthines (1). Speculation that caffeine may increase breast cancer risk followed reports that women with benign breast disease experienced symptom relief after eliminating methylxanthines from their diet (2–4). Animal studies have indicated that caffeine can both stimulate and suppress mammary tumors, depending on the rodent species and strain as well as the tumorigenic phase (initiation/promotion) at the caffeine administration (5,6). Caffeine-rich foods such as tea, coffee, and chocolate were suggested to be carcinogenic in 1970s and 1980s (7,8).

Coffee and tea are also rich in phenolic compounds including substantial amounts of several lignans (9). These lignans can be converted into enterolactone and enterodiol which have antiestrogenic properties and can potentially reduce the risk of certain cancers (10). In addition, in vitro evidence indicates beverages high in phenolic compounds have antioxidant activity and can also protect mammalian cells against genotoxic effects, inhibit cell-replication enzymes and prevent cancer growth through anti-estrogenic pathways or mitochondrial toxicity (11–13). Coffee is the major source of the phenol chlorogenic acid (14), and a major contributor to the total antioxidant capacity of the diet in several populations (15,16). The primary antioxidant potential of tea is attributed to its catechins, chief among them, epigallocatechin gallate (EGCG) for which green tea has a higher concentration than black tea (17). In various studies, rats with breast tumors that were given green tea had reductions in tumor size and tumor growth (18, 19). Some human case-control studies suggest protective effects of polyphenols against breast cancer specifically (20). These findings, coupled with observations of lower rates of breast cancer in countries where green tea is consumed daily, suggest that green tea may protect against human breast cancer.

International comparative studies have shown a positive association between coffee and breast cancer incidence and mortality (21,22). The association between coffee and breast cancer, however, has been inconsistent in observational studies, with reports of no association (23–31), inverse association (32–36) and positive association (37,38). The associations between coffee consumption and breast cancer may be confounded by other aspects of diet or by the lack of appropriate control for nondietary confounding factors. Another concern is that tea consumption in countries that traditionally consume coffee may reflect non-coffee consumption, and the effect attributed to tea may be in fact due to the absence of coffee.

To address the relationship of caffeinated and decaffeinated coffee and tea consumption to breast cancer risk in women, we examined this association prospectively in a large population of women with long follow-up and repeated measures of intake.

MATERIALS and METHODS

Study Population

The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, 30 to 55 years of age and from 11 states in the USA, answered a mailed questionnaire on risk factors for cancer and lifestyles. Further details have been published elsewhere (39). We excluded women who did not complete more than 10 items on the 1980 dietary questionnaire, had extreme scores for total daily intake of energy (<500 kcal or >3,500 kcal), or who had greatly increased or decreased their coffee intake over the past 10 years to reduce measurement error and to capture a measure of long-term intake. We excluded women who had a prior history of cancer (except non-melanoma skin cancer), or in situ breast cancer, leaving 85,987 women who were followed from 1980 to 2002.

Exposure Assessment

In 1980, diet was assessed with a 60-item food frequency questionnaire (FFQ) which included the following caffeine-containing foods and beverages: coffee with caffeine, tea, cola and other carbonated beverages with caffeine, and chocolate. For each food, participants were asked if their use had greatly increased or decreased over the past 10 years. Decaffeinated coffee was added to an expanded FFQ (approximately 130 foods) in 1984, 1986, 1990, 1994, and 1998. For each item, participants were asked how often, on average, they had consumed a specified amount of each beverage or food over the past year. The participants could choose from nine frequency categories (never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, and 6 or more per day). Intakes of nutrients and caffeine were calculated using US Department of Agriculture food composition sources. In these calculations, we assumed the content of caffeine was 137 mg per 8 oz cup of coffee, 47 mg per 8 oz cup of tea, 46 mg per 12 oz can or bottle of cola or other caffeinated carbonated beverage, and 7 mg per 1 oz serving of chocolate candy. We assessed the total intake of caffeine by summing the caffeine content for the specified amount of each food multiplied by a weight proportional to the frequency of its use. In a validation among a subsample of our cohort, we obtained high correlations between intake of caffeinated coffee and other caffeinated beverages from the FFQ and four 1-week diet records (coffee, $r=0.78$; tea, $r=0.93$; and caffeinated sodas, $r=0.85$) (40,41). For the present analysis, caffeinated or decaffeinated coffee and tea consumption were categorized into 5 groups: less than 1 cup per month, 1 cup per month to 4.9 cups per week, 5 cups per week to 1.9 cups per day, 2 to 3.9 cups per day, and 4 or more cups per day. Caffeine intake was divided into five categories with equal number of participants.

Identification of breast cancer cases

In each biennial questionnaire, participants were asked whether they had been diagnosed as having breast cancer in the previous two years, and we attempted to interview nonrespondents by telephone. The response rates were approximately 90 percent for each questionnaire. Deaths were identified by a report from a family member, the postal service or the National Death Index. When a case of breast cancer was reported, we asked the participant (or next of kin if she had died) for permission to obtain medical records. Since self-reports have been confirmed by pathology reports in 98% of instances, we included the

few-self reported cases for whom we could not obtain medical records in the analysis. Pathology reports were also reviewed to obtain information on estrogen receptor (ER) and progesterone receptor (PR) status. 74 percent of the cases had receptor status information (51% were estrogen and progesterone receptor positive breast cancer, 23% were estrogen and progesterone receptor negative breast cancer). Cases of carcinoma in situ were not included in the analysis.

Assessment of medical history, anthropometric data and other lifestyle factors

On the 1976 baseline questionnaires, we requested information about age, weight and height, smoking status, family history of breast cancer, use of hormone therapy, and personal history of other diseases. This information (except height) has been updated on the biennial follow-up questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Alcohol intake was assessed on the FFQ from consumption of beer, wine and liquor. Other covariates included were age at menarche, parity, age at first birth, age at menopause, history of benign breast disease, physical activity, weight change after age 18.

Statistical Analysis

For each participant, we calculated person-months of follow-up from the date of return of the 1980 baseline questionnaire to the date of breast cancer, other cancer except nonmelanoma skin cancer, death, or June 1, 2002, whichever came first. Participants were classified according to levels of coffee, tea, and caffeine consumption. We used Cox proportional hazard regression models to examine the association between dietary exposures and incidence of breast cancer. Hazard ratios were calculated to estimate relative-risks (RRs) and 95% confidence intervals (CIs) using the lowest category of intake as the reference.

To reduce within-subject variation and best represent long-term effect for diet, we used the cumulative average of coffee, tea, and caffeine intakes from all available dietary questionnaires up to the start of each 2-year follow-up interval (42). For example, the coffee intake from the 1980 FFQ was used to characterize follow-up between 1980 and 1984, the average of the 1980 and 1984 intakes was used for the follow-up between 1984 and 1986, the average of the 1980, 1984 and 1986 intakes was used for the follow-up between 1986 and 1990, etc.

In alternative analyses, we used simple updating (the most recent dietary information) to study the short-term effects of caffeinated coffee, tea and caffeine on breast cancer. We also compared the results of the analysis using cumulatively averaged and updated consumption with those obtained when we stopped updating the consumption at the beginning of a time interval in which individuals developed hypertension, hypercholesterolemia, type 2 diabetes mellitus, or cardiovascular diseases. The diagnosis of these endpoints may alter intake of coffee or tea. In additional analyses, we examined various latency periods between caffeine exposure and breast cancer diagnosis using the multiple questionnaires to maximize power. For example, in analyses with a latency period of 4–7.9 years, the 1980 diet was used for cases from 1984 to 1988, the 1984 diet was used to follow-up from 1988–1990, the 1986

diet was used to follow-up from 1990–1994, and the 1990 diet was used to follow-up from 1994 to 1998, and so on.

Models were first adjusted for age, smoking status (never, past and current 1–14, 15–24, and 25 cigarettes per day), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0 kg/m²). Physical activity, history of benign breast disease, family history of breast cancer, height, weight change since age 18, age at menarche, parity, age at first birth, alcohol intake, total energy intake, age at menopause and postmenopausal hormone use were added in multivariable proportional hazard models. To test for linear trends across exposure categories, we used the median of each category as a continuous variable. SAS PROC PHREG with SAS version 8.2 was used for all analyses.

RESULTS

During the 22 years of follow-up we documented 6,552 cases of incident invasive breast cancer in the cohort who completed the 1980 dietary questionnaire. Cases were excluded for the following reasons: diagnosis before baseline (667) or after end of follow-up (93), previous diagnosis of another cancer except nonmelanoma skin cancer (495), and missing date of diagnosis (n=25). This left 5,272 incident cases of invasive breast cancer among 85,987 women for this analysis.

Characteristics of the population according to caffeinated coffee consumption in 1980 are presented in Table 1. Frequent coffee consumption was strongly associated with smoking. In addition, women who drank more coffee were more likely to drink alcohol, less likely to drink tea, and less likely to use postmenopausal hormones than those who drank little coffee. Coffee drinkers were less likely to gain weight, though current BMI was not related to coffee intake.

In age-adjusted analysis, we found a weak inverse association between the cumulative average caffeinated coffee consumption and the risk of the breast cancer (Table 2). Compared with women who drank <1 cup of caffeinated coffee per month, the relative risk for women who drank 4 cups per day was 0.91 (95% CI 0.82–1.01) and the p-value for the linear trend across all categories was 0.04. After multivariate adjustment, the RRs were somewhat attenuated and the linear trend was not significant. For tea, the multivariate relative risk and 95% confidence interval was 0.94 (0.77–1.14) for the women consuming 4 cups per day compared to the women consuming less than one cup per month. Caffeinated coffee and tea consumption were mutually adjusted in these multivariate analyses.

There was no association between decaffeinated coffee intake (Table 2) and breast cancer risk either after adjustment for age, caffeinated coffee, and multiple breast cancer risk factors. There was also no apparent association between intakes of caffeinated soft drinks and chocolates, which contribute to caffeine intake, and breast cancer occurrence (data not shown).

Analyses stratified by BMI did not reveal any statistically significant difference in the association between caffeinated coffee consumption and breast cancer in obese participants

as compared with normal and overweight participants. (p for interaction = 0.72) (Table 3). The relationship also did not differ significantly between premenopausal and postmenopausal women; the multivariable RRs for 4 cups/day were 1.00 (95% CI = 0.80–1.27, p for trend=0.79) and 0.89 (95% CI = 0.78 to 1.02, p for trend=0.08), respectively. Given the known variation in the BMI-breast cancer relationship by menopausal status, we conducted further analyses stratified by baseline BMI status restricted to postmenopausal women only. The results did not show any statistically significant difference (data not shown).

To address the issue that low consumers of coffee tend to be higher drinkers of tea and vice versa we cross-classified coffee and tea drinkers with the reference category being low consumption of both coffee and tea (i.e., < 1 cup/month). We found no significant association between risk of breast cancer and high tea consumption (i.e., 4+ cups/day) among women with low coffee intake (RR = 0.98, CI = 0.87 to 1.10) or high coffee consumption among women with low tea intake (RR=1.02, 95% CI = 0.91 to 1.15).

We observed a weak, but statistically significant inverse relation between caffeine intake and risk of breast cancer in the age-adjusted analysis; the RRs comparing the highest with the lowest quintile were 0.91 (95% CI = 0.83 to 0.99 for trend=0.01). In the multivariate analysis the trend was a slightly attenuated, but lower risk remained for the highest compared with the lowest quintile (RR 0.93, 95% CI 0.85–1.01) (Table 4). We also categorized total caffeine intakes into deciles. No additional benefit was apparent in comparisons of the highest and lowest deciles of intake. The multivariate RRs for the uppermost vs lowermost deciles of intake were 0.99 (95% CI 0.87–1.12) for total caffeine.

The association between caffeine and breast cancer was stronger among postmenopausal women; for the highest quintile of intake compared to lowest RR = 0.88 (95% CI = 0.79 to 0.97 for trend=0.03) than among premenopausal women (RR 1.09, 95% CI = 0.87–1.37 for trend=0.77).

When breast cancers were classified by estrogen and progesterone receptor status, we observed a statistically significant inverse association of caffeine intake with breast cancers that had positive estrogen and progesterone receptors (p for trend=0.01) (Table 4). Results were similar for estrogen receptor negative and progesterone receptor negative cases. However, perhaps due to lower power the linear trend was not statistically significant.

The association between caffeine and breast cancer was stronger among postmenopausal women with estrogen-receptor and progesterone-receptor positive breast cancer (RR 0.81, 95% CI = 0.70 to 0.95 for trend=0.006) than those with estrogen-receptor and progesterone-receptor negative breast cancer (RR 0.94, 95% CI = 0.70–1.26 for trend=0.97).

Alternative analyses using the most recent caffeine intake before diagnosis of breast cancer showed no association (multivariate RRs for increasing quintiles of caffeine consumption were 0.99, 0.99, 1.00, and 0.96 (95% CI = 0.87–1.05). In our main analysis, caffeine intake was calculated as cumulative averages of the diet data collected during follow-up. However, it is possible that earlier diet plays more critical role in the etiology of breast cancer. We used the repeated questionnaires to assess the temporal relationship between caffeine intake

and breast cancer risk (Table 5). No significant association was observed with a longer latency interval.

DISCUSSION

In this large cohort of women, we observed no substantial association between caffeinated or decaffeinated coffee and tea consumption and risk of breast cancer during 22 years of follow-up. We found no evidence of an effect of either recent or long-term average consumption. We observed a weak overall inverse association with caffeine intake, and this association was stronger in postmenopausal women compared to premenopausal women.

Possible explanations for null findings include a narrow range of exposure, low statistical power, or measurement error. The current study had a wide range of coffee and tea intakes with the upper categories of 4 or more cups per day. The study included 5,272 cases and 1.8 million person-years, thus confidence intervals were narrow and statistical power was not a major problem. The use of repeated measures in the analysis not only accounts for changes in coffee use over time but also decreases measurement error (43). Also, current coffee and caffeine intake had high correlations with estimates from four 1-week diet records (40,41). Many biases inherent in case-control studies are avoided by a cohort design with nearly complete follow-up. Unmeasured confounding is still possible, although we adjusted for many breast cancer risk factors.

Results from other cohort studies of coffee, caffeine and risk of breast cancer generally have been inconsistent. The preliminary results from the Nurses' Health Study by Hunter et al. showed an inverse dose-related association of caffeine with breast cancer incidence (32). Michels et al. assessed coffee consumption in relation to breast cancer cases in Swedish women (24) and reported that women who drank 4 or more cups of coffee per day had a covariate-adjusted hazard ratio of breast cancer of 0.94 (95% confidence interval (CI) 0.75–1.28) compared to women who reported drinking 1 cup a week or less. The corresponding hazard ratio for tea consumption was 1.13 (95% CI 0.91–1.40). Similarly, women in the highest quintile of self-reported caffeine intake had a hazard ratio of breast cancer of 1.04 (95% CI 0.87–1.24) compared to women in the lowest quintile. Folsom et al. assessed coffee intake prospectively in postmenopausal women; and found no apparent association between daily intake of coffee and risk of breast cancer (26). The results of the study by Vatten et al. in 14,593 Norwegian women suggested that coffee consumption reduces the risk of breast cancer in lean women, whereas coffee might have the opposite effect in relatively obese women (37). In the lean women, drinking 5 cups or more per day had an age-adjusted IRR of 0.5 (95% confidence intervals, 0.3 and 0.9) compared to women who had 2 cups or less. In more obese women there was a positive relation between coffee intake and breast cancer risk; the age-adjusted IRR was 2.1 (95% confidence intervals, 0.8 and 5.2). The reason for discrepancy between their findings and ours is not clear although the majority of the cases from the Norwegian cohort were premenopausal at the diagnosis of breast cancer, and most were certainly premenopausal at initiation phase. However, in the present study when we analyzed the coffee and breast cancer incidence stratified by menopausal status, among our premenopausal women we did not observe a significant association.

We also found caffeine to be associated with a lower risk of postmenopausal breast cancer than with premenopausal breast cancers; and this association was stronger with estrogen-receptor positive and progesterone-receptor positive breast cancer than with receptor negative breast cancer, suggesting a possible mechanistic role involving steroid hormones. Our results suggest that caffeine may be inversely associated with postmenopausal breast cancer risk, particularly in a low-estrogen environment. An inhibitory effect of caffeine on hormone-induced rat breast cancer has been reported by Petrek et al. (44), who examined the effect of two caffeine doses in rats (45), with and without diethylstilbestrol (DES). With DES, increasing caffeine dosage lengthened the time to first cancer, decreased the number of rats that developed cancers, and reduced the number of cancers overall. The inverse association observed for caffeine also may reflect beneficial effects of components of coffee and tea other than caffeine. Higher coffee consumption (or caffeine intake) has been directly associated with plasma estradiol, estrone, and sex-binding globulin levels (46, 47). Jernstrom et al. (48) reported that coffee consumption was the second most important lifestyle factor associated with increased plasma 2-OHE/16a-OHE ratio, and in some studies a relatively high 2-OHE/16a-OHE ratio has been associated with low rate of breast cancer (49,50). 2-hydroxyestrone (OHE) is catalyzed by the cytochrome P450 (*CYP*) 1A2 (51) and caffeine in turn appears to be an inducer of *CYP1A2* activity (52). Nkondock et al. reported that women with *BRCA1* or *BRCA2* mutations who consumed at least 6 cups of coffee per day to have a statistically significant reduction in breast cancer risk (OR = 0.31, 95% CI 0.13–0.71) compared to *BRCA* mutation carriers who have never drunk coffee (53).

In conclusion, no substantial association was observed between consumption of caffeinated or decaffeinated coffee and tea and risk of breast cancer for the overall cohort. Higher consumption of caffeine-containing beverages may modestly reduce risk of postmenopausal breast cancer, and this relation needs to be examined further.

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Abbreviations

NHS	Nurses Health Study
EGCG	epigallocatechin gallate
BMI	body mass index

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Table 1
Baseline characteristics by levels of coffee consumption among participants the Nurses' Health Study

	Coffee consumption, cups in women in NHS (1980 Baseline)					
	<1/mo	1/mo-4/wk	5/wk-1.9/d	2-3.9/d	>4/d	
Participants, n	19 462	5 223	11 676	28 178	21 448	
Caffeine, mg/day	116	134	219	419	794	
Tea, cups/day	1.3	1.1	0.9	0.8	0.6	
Age, y	45.5	45.3	46.6	46.6	46.3	
Current smoker, %	19.0	20.0	20.0	28.0	46.0	
BMI, kg/m2	24.8	24.5	24.5	24.3	24.2	
Physical exercise, hours/week	4.0	4.0	3.9	3.9	3.7	
Age at menarche, y	12.4	12.4	12.5	12.4	12.4	
Age at first birth, y [*]	24.4	24.5	24.6	24.4	24.2	
Parity [*]	2.9	2.8	2.9	3.0	3.0	
Postmenopausal, %	33.0	33.0	32.0	33.0	33.0	
Postmenopausal hormone use, % [†]	22.0	22.0	22.0	21.0	18.0	
Age at menopause	44.9	45.2	45.7	45.8	45.4	
Duration of PMH use, y [‡]	2.1	2.0	2.4	2.2	2.0	
History of benign breast disease, %	25.0	24.0	23.0	24.0	25.0	
Family history of breast cancer %	6.0	6.0	6.0	6.0	6.0	
Alcohol, gram/day	4.4	5.2	5.8	7.5	7.2	
Weight change since age of 18, kg	9.6	9.1	9.2	7.9	6.5	
Height, inches	64.5	64.5	64.4	64.5	64.6	

Values are means unless otherwise indicated. Data were directly standardized to the age distribution in the study population.

NHS: Nurses' Health Study; BMI: body mass index;

[†] Among postmenopausal women only;

[‡] Among current post menopausal hormone users only;

^{*} among parous women only

Multivariate RR and 95% CI of breast cancer according to cumulatively averaged and updated consumption of coffee and tea in relation to risk of breast cancer in all women.

Table 2

		Coffee and tea consumption, cups				P value for trend*
		<1/mo	1/mo-4.9/wk	5/wk-1.9/d	2-3.9/d	4/d
Coffee						
Person-years		286 165	207 883	403 471	567 032	250 650
Cases, No		837	745	1 335	1 718	637
Age-adjusted		1.0	1.06 (0.96-1.17)	0.97 (0.88-1.05)	0.96 (0.88-1.04)	0.91 (0.82-1.01)
Multivariate [†]		1.0	1.01 (0.92-1.12)	0.92 (0.84-1.01)	0.93 (0.85-1.02)	0.92 (0.82-1.03)
Tea						
Person-years		386 876	707 013	393 506	183 582	44 225
Cases, No		1 165	2 284	1 201	514	108
Age-adjusted		1.0	0.98 (0.91-1.05)	0.95 (0.88-1.04)	0.97 (0.88-1.08)	0.94 (0.77-1.14)
Multivariate		1.0	0.95 (0.89-1.02)	0.94 (0.86-1.02)	0.96 (0.86-1.07)	0.94 (0.77-1.14)
Decaffeinated coffee [‡]						
Person-years		462 124	355 046	256 056	128 400	21 133
Cases, No		1 504	1 259	979	422	70
Age-adjusted		1.00	1.00 (0.93-1.08)	1.07 (0.98-1.16)	0.97 (0.87-1.08)	1.07 (0.84-1.36)
Multivariate		1.00	0.97 (0.90-1.05)	1.01 (0.93-1.10)	0.90 (0.80-1.01)	1.03 (0.81-1.31)

* P values for trend calculated using continuous values

[†] Adjusted for: age months, smoking status (never, past, and current 1-14, 15-24, and 25 cigarettes/day), body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0 kg/m²), physical activity (quintiles of hours/week <1.0, 1.0-1.9, 2.0-3.9, 4.0-6.9, 7.0 hours/week), height (<63, 63-63.9, 64-65.9, 66 inches), alcohol intake (never, 0.1-4.9, 5.0-14.9, 15.0 g/d), family history of breast cancer in mother or a sister (yes, no), history of benign breast disease (yes, no), menopausal status, age at menopause, use of hormone therapy (postmenopausal <48 never, postmenopausal <48 past, postmenopausal <48 current <5 year, postmenopausal <48 current 5 years, postmenopausal 48-52 never, postmenopausal 48-52 current <5year, postmenopausal 48-52 current 5year, postmenopausal 53+ never, postmenopausal 53+ current<5year, postmenopausal 53+ current 5year), age at menarche (12, 13, 14years), parity and age at first birth (nulliparous, parity 2 and age at first birth<25years, parity 2 and age at first birth 25-30 years, parity 2 and age at first birth <25years, parity 3-4 and age at first birth 25-30 years, parity 3-4 and age at first birth 30, parity 5 and age at first birth <25, and parity 5 and age at first birth 25-30), weight change after 18 (loss:>4 kg, stable, gain 4.1-10 kg, gain 10.1-20 kg, gain 20.1-40 kg, gain 40.1kg and above) and duration of postmenopausal hormone use (continuous). Coffee and tea intake mutually adjusted for each other.

[‡] Follow-up from 1984, additionally adjusted for coffee intake

Table 3

Multivariate RR and 95% CI of breast cancer according to cumulatively averaged and updated coffee consumption stratified by BMI

	Coffee consumption, cups					P value for trend	P value for interaction
	<1/m	1/mo-4.9/wk	5/wk-1.9/d	2-3.9/d	4/d		
BMI < 25 kg/m ²							
Person-years	150 186	106 140	207 014	309 513	145 524		
Cases, No	421	363	656	892	353		
Multivariate	1.0	1.00 (0.86-1.15)	0.93 (0.82-1.06)	0.94 (0.83-1.06)	0.93 (0.80-1.08)	0.43	
BMI 25-29.9							
Person-years	79 896	61 403	123 467	170 149	71 118		
Cases, No	246	239	449	545	187		
Multivariate	1.0	1.09 (0.91-1.31)	0.98 (0.83-1.15)	0.94 (0.81-1.11)	0.87 (0.71-1.07)	0.06	
BMI ≥ 30							
Person-years	55 357	39 978	72 299	86 609	33 466		
Cases, No	170	142	229	277	95		
Multivariate	1.0	0.98 (0.78-1.24)	0.88 (0.71-1.08)	0.97 (0.79-1.19)	1.02 (0.78-1.33)	0.52	0.72

Models, RR (95% CI).

[†] Adjusted for the same covariates as in Table 2, except for BMI

Table 4

Multivariate RR and 95% CI of breast cancer (total, ER+/PR+ and ER-/PR-) according to quintiles of cumulatively averaged and updated caffeine intake.

	Caffeine Quintile					P value for trend
	1 (lowest)	2	3	4	5 (highest)	
Median intake (range), mg/d	51 (0–139)	191 (140–336)	363 (337–404)	501 (405–692)	816 (693)	
All cases						
Person-years	336 496	342 156	347 356	344 680	344 541	
Cases, No	1 085	1 101	1 059	1 048	979	
Multivariate	1.00	0.98 (0.90–1.07)	0.92 (0.84–1.00)	0.94 (0.87–1.03)	0.93 (0.85–1.01)	0.06
Premenopausal women						
Person-years	91 365	93 756	90 427	91 367	91 045	
Cases, No	157	202	172	162	173	
Multivariate	1.0	1.28 (1.04–1.58)	1.07 (0.85–1.33)	1.02 (0.81–1.28)	1.09 (0.87–1.37)	0.77
Postmenopausal women						
Person-years	208 178	214 244	221 842	215 627	209 067	
Cases, No	844	810	800	797	698	
Multivariate	1.0	0.91 (0.83–1.01)	0.87 (0.79–0.96)	0.92 (0.83–1.02)	0.88 (0.79–0.97)	0.03
Receptor status						
Cases, No	500	533	463	474	432	
ER+/PR+	1.0	1.01 (0.90–1.15)	0.85 (0.75–0.97)	0.90 (0.79–1.03)	0.88 (0.77–1.00)	0.01
Cases, No	153	142	163	141	132	
ER-/PR-	1.0	0.90 (0.72–1.14)	1.02 (0.82–1.28)	0.89 (0.71–1.13)	0.88 (0.69–1.12)	0.33

Models, RR (95% CI).

[†] Adjusted for the same covariates as in Table 2.

Table 5

Multivariate RR and 95% CI of breast cancer according to caffeine intake with various lag times between diet assessment and follow-up among participants in the NHS

Latency, years	N of cases	Caffeine quintile					P for trend
		1	2	3	4	5	
4–7.9 years	4642	1.0	0.91 (0.84–1.00)	0.91 (0.83–1.00)	0.94 (0.86–1.03)	0.86 (0.78–0.95)	0.01
8–11.9 years	4032	1.0	0.90 (0.82–0.99)	0.89 (0.81–0.98)	0.97 (0.88–1.07)	0.88 (0.79–0.97)	0.12
12–15.9 years	2816	1.0	0.84 (0.74–0.94)	0.87 (0.78–0.98)	0.95 (0.85–1.06)	0.82 (0.72–0.92)	0.05
16–19.9 years	1791	1.0	0.98 (0.84–1.14)	1.08 (0.94–1.25)	1.00 (0.86–1.16)	0.97 (0.83–1.13)	0.75

[†] Adjusted for the same covariates as in Table 2.