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Coffee intake and breast cancer risk in the NIH-AARP Diet and Health Cohort Study

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Abstract

There are several biologic mechanisms whereby coffee might reduce breast cancer risk. Caffeine and caffeic acid, major coffee constituents, have been shown to suppress mammary tumor formation in animal models and to inhibit DNA methylation in human breast cancer cells, respectively. Coffee may also reduce risk through decreasing inflammation and influencing estrogen metabolism. However, epidemiologic studies have been inconsistent and few studies have examined the association by estrogen and progesterone receptor (ER/PR) status. We evaluated coffee intake for its effect on incident breast cancer in the NIH-AARP Diet and Health Study cohort, which included 198,404 women aged 50–71 with no history of cancer, who in 1995–1996 completed a questionnaire capturing usual coffee intake over the past year. State cancer registry and mortality index linkage identified 9,915 primary incident breast carcinomas through December 2006; available information on hormone receptor status identified 2,051 ER+/PR+ and 453 ER−/PR− cancers. In multivariate proportional hazards models, coffee intake was not associated with breast cancer risk (p-value for trend=0.38) (relative risk=0.98, 95% confidence interval: 0.91–1.07, for ≥ 4 cups per day as compared to women who never drank coffee), and results did not vary by body mass index or history of benign breast biopsy (p-value for interaction >0.10). We found no evidence of a relationship with either caffeinated or decaffeinated coffee. Null findings persisted for risk of both hormone receptor positive and negative breast cancers. These findings from a large prospective cohort do not support a role of coffee intake in breast carcinogenesis.

Keywords

breast neoplasms; coffee; caffeine; cohort studies; epidemiology

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Conflicts of interest: none

Introduction

Since reports were published in 1979 linking methylxanthines (caffeine, theophylline and theobromine) to benign breast disease,[1–2] an established marker of increased breast cancer risk, many epidemiologic studies have examined the association between caffeine or caffeinated beverages, such as coffee, and breast cancer risk. A review of epidemiologic studies published from 1990–1999 concluded that there is no appreciable relation between coffee and breast cancer risk.[3] In 2008, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that the evidence for an association between coffee and breast cancer risk was inconclusive for both pre- and postmenopausal women.[4] Yet, summary estimates from a meta-analysis of case-control and cohort studies published that same year suggested a weak inverse relationship for the highest compared with the lowest levels of coffee consumption (RR=0.95, 95% CI: 0.95–1.00).[5] Subsequently, five additional cohort studies evaluated the association, with conflicting results.[6–10] Given the widespread consumption of coffee in the U.S. and the potential for public health impact, the association between coffee intake and breast cancer risk warrants further investigation.

There are several plausible biologic mechanisms whereby coffee intake might reduce breast cancer risk. Caffeic acid and caffeine, both major constituents of coffee, have been shown to inhibit DNA methylation in human breast cancer cells[11] and to inhibit mammary tumorigenesis in a mouse model,[12] respectively. Coffee intake has been inversely associated with circulating markers of inflammation and insulin resistance,[13–14] both of which may play a role in breast cancer.[15–16] Finally, coffee has been linked to endogenous estrogens: an elevated ratio of circulating 2-hydroxyestrone: 16 alpha-hydroxyestrone[17] and reduced levels of circulating estradiol have been observed with coffee intake in some studies.[18–19]

Although there is some evidence to suggest that coffee and/or caffeine may influence breast cancer risk in part through alterations in estrogens and metabolites, relatively few cohort studies have examined the association according to the hormone receptor (HR) status of breast tumors.[6–8, 10, 20–21] The largest of these was the Nurses' Health Study (NHS, n=5,272 cases among 85,987 women): while coffee was not related to breast cancer risk overall, intake of caffeinated coffee or tea was inversely associated with risk of HR positive breast (RR for highest vs. lowest quintile=0.88, 95% CI: 0.77–1.00; p-value for trend=0.01).[21] In contrast, the Women's Health Study (WHS, n=1,188 cases among 38,432 women) observed an increased risk of HR negative breast cancer associated with caffeine consumption (RR for highest vs. lowest quintile=1.68, 95% CI: 1.02–2.81; p-value for trend=0.02), but no association was observed for HR positive breast cancer (RR=0.84, 95% CI: 0.67–1.06; p-value for trend=0.30).[6] Consistent with these findings which suggest etiologic heterogeneity, a Swedish cohort study (n=3,034 cases among 64,603 women) recently reported an increased risk of breast cancer among younger women (<49 years) and a decreased risk among older women (>55 years) associated with drinking coffee four or more times per day;[9] although tumors in older women tend to be HR positive, HR status was not reported in this study. Of the remaining cohort studies to evaluate associations by HR status, coffee was not related to risk of either HR positive or negative tumors.[7–8, 10, 20]

The NIH-AARP cohort has several advantages for studying this association relative to other studies, including the large size necessary to detect a modest association and the availability of extensive information on potential confounding factors, including body mass index and alcohol use. In addition, this large cohort allowed us to examine relationships with clinical features of breast tumors including HR status.

Materials and methods

Study population

The NIH AARP-Diet and Health Study design and methodology have been described in detail.[22] The study was initiated in 1995–1996 when a questionnaire was mailed to 3.5 million members of the AARP (formerly known as the American Association of Retired Persons), ages 50–71 years, who resided in one of eight US states (CA, FL, PA, NJ, NC, LA, GA, and MI). This baseline questionnaire captured diet history, demographic characteristics, current weight and height, smoking status, physical activity, medical and reproductive history, menopausal status, menopausal hormone therapy (HT), history of breast biopsy, and personal and familial history of cancer. A total of 617,119 (17.6%) questionnaires were returned, of which 567,169 were satisfactorily completed; of these, 179 duplicate questionnaires were excluded.

After additionally excluding individuals who died (n=261) or moved out of the cancer registry ascertainment area (n=321) before their baseline questionnaire was received and scanned, proxy respondents to the baseline questionnaire (n=15,760), six individuals who withdrew from the study, and 325,174 men, the baseline study population included 225,468 women. The study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute, and written informed consent was obtained from study participants.

Analytic sample

We excluded 23,957 women with a personal cancer history other than non-melanoma skin cancer, 1,848 women with Box-Cox log transformed total energy intake more than two interquartile ranges from the median, 1,231 women who were missing information on coffee intake, 9 women who died on the first day of follow-up, and 19 women with non-epithelial breast tumors. Thus, 198,404 women were included in the present analysis.

Assessment of coffee intake

Usual coffee intake over the past year was assessed as part of a 124-item food frequency questionnaire (FFQ).[23] Participants could choose from ten frequency categories: none, <1 cup/month, 1–3 cups/month, 1–2 cups/week, 3–4 cups/week, 5–6 cups/week, 1 cup/day, 2–3 cups/day, 4–5 cups/day and 6+ cups/day. For the present analysis, we collapsed responses into seven groups: never, ≤ 2 cups/wk, 3–6 cups/week, 1 cup/day, 2–3 cups/day and 4+ cups/day. Participants were also asked whether they drank caffeinated or decaffeinated coffee more than half of the time.

Cohort follow-up

Cohort members were followed periodically for address changes and vital status. Address changes were identified by matching the cohort database to the U.S. Postal Service's National Change of Address database. Vital status was updated through linkage to the U.S. Social Security Administration Death Master File and the National Death Index (NDI) Plus.

Ascertainment of breast cancer

Incident *in situ* and invasive breast cancers were identified through linkage to the eight cancer registries corresponding to participants' baseline state of residence, as well as Texas and Arizona, in order to capture cancers occurring in participants who moved to these states during follow-up. Each registry has been certified by the North American Association of Central Cancer Registries for meeting the highest standards of data quality. Breast cancer estrogen receptor (ER) and progesterone receptor (PR) status were coded as described in the

American Joint Committee on Cancer's Collaborative Staging Site-Specific Factors Manual, with a threshold of >10 femtomoles (fmol) of cytosol protein per milligram for a positive tumor; however, HR status was not reported by the Florida, Pennsylvania, and Texas cancer registries. Histology was defined using International Classification of Diseases for Oncology (ICD-O) codes, 3rd edition.[24] A previous validation study in this cohort estimated that registry linkage validly identified approximately 90% of all incident cancers.[25] Date of death for fatal cancers (n=64) was identified through linkage to the NDI.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CI) for breast cancer associated with coffee intake; age was the time scale[26] and ties were handled by enumeration.[27] Follow-up began at the age at which the baseline questionnaire was received and scanned (1995–1996) and continued through the earliest of the following dates: participant diagnosed with breast cancer, moved out of her registry catchment area, died from any cause, or December 31, 2006. To test the proportional hazards assumption, we generated time-dependent covariates by including an interaction term for coffee intake and the natural log of age (the time metric); probability values were >0.05, consistent with proportional hazards.

Multivariate models were used to control for age at entry (years), race/ethnicity (white black, other/unknown), education (<high school, high school graduate, post high school/ some college, college graduate, post graduate, unknown), body mass index (BMI in kg/m^2: <20, 20–22.4, 22.5–24.9, 25–27.4, 27.5–29.9, 30–31.9, 32–33.9, 34+, unknown), smoking status and dose (non-smoker, quit and ≤ 20 cigarettes/day, quit and >20 cigarettes/day, current smoker and ≤ 20 cigarettes/day, current smoker and >20 cigarettes/day, unknown), alcohol (g/day: 0, >0–5, >5–10, >10–20, >20–35, >35), proportion of total energy from fat (quintiles), age at first live birth (nulliparous, <20, 20–24, 25–29, 30+, unknown), menopausal HT use (never, former, current, unknown), history of breast biopsy (no, yes, unknown), and family history of breast cancer in a first degree relative (no, yes, unknown). In subsequent models, we adjusted for birth year and several additional factors, including ages at menarche and menopause, parity, self-rated health quality, vigorous physical activity, and history of diabetes; results were essentially the same and are not shown here. Tests for linear trends across categories of coffee intake were calculated by using an ordinal variable containing the median value of coffee intake (cups/day) within the defined coffee categories.

We used a likelihood ratio test, comparing models with and without the interaction terms, to separately examine effect modification by BMI (<25, 25–<30, ≥ 30 kg/m^2), HT use (never, ever), smoking status (never, ever), alcohol (g/day: 0, >0–5, >5–10, >10–20, >20–35, >35), history of breast biopsy (never, ever), and family history of breast cancer (no, yes). In addition, we examined whether the relationship between coffee intake and breast cancer incidence differed by ER/PR status, stage at diagnosis (*in situ* or invasive disease), tumor grade (1, 2, 3+), and histologic type (ductal, lobular, or mixed). To test for heterogeneity in associations between coffee intake and breast cancer subtypes, we conducted case-only analyses using polytomous logistic regression models adjusting for the same covariates included in our multivariate proportional hazards models as well as age at diagnosis in order to account for duration in the cohort.

Probability values of <0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using SAS software release 9.1.3 (SAS Institute Inc., Cary, NC).

Results

The mean (SD) age at baseline was 61.8 (5.4) years, and over 96% of women were postmenopausal. The 198,404 women accrued 1,906,185 person years during an average follow-up of 5.2 years (cases) and 9.8 years (non-cases). Of the 9,915 women who developed breast carcinoma during follow-up, 1,892 tumors were *in situ*, 7,959 were invasive, and 64 were missing stage. Among the 7,959 invasive breast cancer cases, 5,139 cases were ascertained from state cancer registries reporting HR status; 2,051 were coded as ER+/PR+, 425 as ER+/PR−, 55 as ER−/PR+, 453 as ER−/PR−, 24 as borderline and 2,131 (41%) were missing either ER or PR status. The majority of invasive breast cancers were ductal carcinomas (n=5,495), followed by lobular (n=869), and mixed (n=680) histologic types; 915 cases had other histologies. Breast cancer risk factors in this population were generally consistent with established associations with age, race/ethnicity, BMI, ages at menarche, first birth and menopause, parity, menopausal HT use, vigorous physical activity, number of breast biopsies, and family history of breast cancer (data not shown).

The vast majority of women (87.9%) reported drinking coffee over the last 12 months. Among all women, 11.0% drank 2 cups per week or less, 6.8% drank 3–6 cups per week, 18.3% drank 1 cup per day, 39.0% drank 2–3 cups per day, and 12.8% drank 4 or more cups per day. Among women reporting drinking decaffeinated or caffeine-containing coffee (n=166,788), the majority (63%) drank caffeinated coffee more than half of the time. Compared with never coffee drinkers, women who more frequently drank coffee were more likely to be white, have a lower BMI, smoke, and drink alcohol (Table 1). More frequent coffee drinkers were also less likely to report fair/poor overall health status and a history of diabetes. Similar relationships were observed between these factors with both decaffeinated and caffeinated coffee consumption (data not shown).

Coffee intake and breast cancer

Associations between coffee intake and risk of breast cancer overall and according to clinical characteristics of tumors are shown in Table 2. In both age- and multivariate-adjusted proportional hazards models, coffee intake was not associated with breast cancer risk; compared with never coffee drinkers, the multivariate RR for women who reported drinking 4 or more cups per day was 0.98 (95% CI: 0.91–1.07). In addition, no statistically significant trend was observed with increasing frequency of coffee consumption (p-value for trend=0.38). The risk associated with coffee intake did not vary substantially by other factors including, BMI, HT use, smoking status, alcohol, history of breast biopsy, and family history of breast cancer (p-value for interaction >0.10, data not shown).

We further examined associations by ER/PR status, tumor stage, grade and histology. Although slight increases in risk were observed for a few subgroups of women (i.e., for ER +/PR+ breast cancer among women who reported drinking 3–6 cups per week; and for grade 2 and lobular tumors among women who reported drinking 2 cups or less per week), no clear patterns emerged in the relationships between coffee intake and risk for any of the tumor characteristics.

Because recent cohort studies have reported different risk relationships by HR status and caffeine intake, we also explored relationships between caffeinated and decaffeinated coffee consumption with overall breast cancer risk as well as with risk of tumors defined by ER/PR status (Table 3). Again, coffee showed no association with breast cancer among drinkers of either predominantly caffeinated or predominantly decaffeinated coffee. Compared with never drinkers, the RRs for drinking 4+ cups per day of caffeinated and decaffeinated coffee were 0.98 (95% CI: 0.90–1.08) and 1.00 (95% CI: 0.88–1.15), respectively. Risks associated with tumors defined by ER/PR status also did not vary in any systematic way according to

caffeinated vs. decaffeinated coffee consumption. In sensitivity analyses, we also restricted analyses to postmenopausal women. Results were similar and are not shown here.

Discussion

In this large prospective study of mostly white, postmenopausal women, coffee intake was not associated with breast cancer risk. This null relationship persisted across tumors with distinct clinical characteristics including ER/PR status, stage, grade and histology. Similarly, no association was observed for either caffeinated or decaffeinated coffee intake.

This study of 198,404 women is one of the largest cohorts to date to have evaluated the association between coffee intake and breast cancer risk. The study sample size achieved 80% power to minimally detect a reduced risk of 0.92 or an increased risk of 1.09 for those drinking four or more cups per day relative to never coffee drinkers; our observed RR of 0.98 had a corresponding 95% CI of 0.91–1.07, which includes the point estimate of 0.92 but excludes that of 1.09. Thus, it remains possible that we may have failed to detect a very weak association with coffee intake. However, the null finding we observed in our study is consistent with that observed in a recent meta-analysis of nine cohort studies (0.95, 95% CI: 0.88–1.02).[5] The lack of a dose response relationship in this current study lends further support to the evidence that coffee intake does not influence breast cancer risk.

Several previous cohorts observed associations among specific subgroups, such as lean[28] and postmenopausal women,[9, 21] or among women with benign breast disease.[6] Yet our study did not replicate these findings, nor have the finding from other cohorts.[6–8, 10, 20–21] Although there is epidemiologic data to suggest that coffee and/or caffeine may influence estrogen metabolism,[17–19] none of the six previous cohorts to evaluate associations by HR status found associations with coffee intake;[6–8, 10, 20–21] however, with caffeine, one study found decreased risk of ER+/PR+ tumors[21] whereas a second study found increased risk of ER−/PR− tumors.[6] We observed no association between coffee and breast cancer, regardless of tumor HR status or coffee caffeine content.

Limitations of our study include the inexactness of the caffeine assessment, which may have reduced our ability to detect distinct associations for caffeinated and decaffeinated coffee. While we did not collect information on the coffee brewing method, in a recent report from a large Swedish cohort, there was some indication that associations with breast cancer risk differed between filtered and boiled coffee,[9] suggesting avenues for future research. In addition, we lacked data on the clinical characteristics of tumors for a substantial proportion of our cases. Nevertheless, due to the large size of our cohort, our analyses of coffee intake and incident ER+/PR+ and ER−/PR− tumors are among the largest to date. Furthermore, the proportions of HR positive and HR negative tumors in our cohort are consistent with those among U.S. women of comparable ages at diagnosis.[29]

Despite these limitations, the large size of the NIH-AARP Diet and Health Study allowed for a wide range of coffee intake, and the most common category of intake (i.e., 2–3 cups per day) is consistent with that observed in other U.S. cohorts of women.[6, 21] Although the proportion of women in this study who drank at least 4 cups per day is somewhat lower than that reported in other populations,[6, 21] the actual number of cases occurring in heavy coffee drinkers and the corresponding power is larger than in previous studies.

In conclusion, coffee intake was not associated with breast cancer risk in this large, mostly postmenopausal cohort. Although there are several plausible biologic pathways whereby coffee might influence breast cancer risk, none of them seemed to have affected breast cancer risk in this population. Our findings are consistent with a growing body of literature

from prospective cohort studies suggesting that coffee intake is not related to overall breast cancer risk.

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List of Abbreviations Used

BMI	body mass index
CI	confidence interval
ER	estrogen receptor
HR	hormone receptor
HT	hormone therapy
ICD-O	International Classification of Diseases for Oncology
NDI	National Death Index
NHS	Nurses' Health Study
NIH	National Institutes of Health
PR	progesterone receptor
RR	relative risk
SD	standard deviation
WHS	Women's Health Study

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Novelty and impact of paper

Although there are several plausible biologic pathways where by coffee might influence breast cancer risk, epidemiologic studies have been inconsistent; a relation between coffee intake and breast cancer risk could have important public health implications. In one of the largest prospective cohort studies to date, we found no evidence of a relationship with either caffeinated or decaffeinated coffee, and null findings persisted for risk of both hormone receptor positive and negative breast cancers.

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Table 1

Distribution of select baseline characteristics across categories of coffee consumption among 198,404 women, NIH-AARP Diet and Health Study

Characteristic	Coffee Consumption											
	Never (n=24,021)		≤2 cups/week (n=21,742)		3–6 cups/week (n=13,444)		1 cup/day (n=36,384)		2–3 cups/day (n=77,450)		4+ cups/day (n=25,363)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	61.1	5.6	61.5	5.5	61.8	5.4	62.5	5.9	62.0	5.3	61.4	5.4
Body mass index (kg/m^2)	27.3	5.8	27.1	5.7	27.4	5.7	26.9	5.4	26.5	5.1	26.1	5.0
Alcohol (g/day)	3.5	15.0	4.8	15.8	4.8	14.7	5.3	15.2	7.0	16.5	6.7	17.9
	n	%*	n	%	n	%	n	%	n	%	n	%
Race/ethnicity												
Caucasian/Non-Hispanic white	21,141	88.0%	18,127	83.4%	11,238	83.6%	31,115	85.5%	71,705	92.6%	24,209	95.5%
Non-Hispanic black	1,864	7.8%	2,288	10.5%	1,356	10.1%	2,743	7.5%	2,454	3.2%	366	1.4%
Other	1,016	4.2%	1,327	6.1%	850	6.3%	2,526	6.9%	3,291	4.2%	788	3.1%
Education, ≥ college graduate	7,683	33.0%	7,428	35.3%	4,042	31.3%	10,758	30.6%	22,623	30.2%	6,669	27.1%
Smoking status												
Never	14,474	62.2%	11,348	54.2%	6,661	51.8%	17,977	51.3%	30,187	40.4%	6,572	26.8%
Former	6,883	29.6%	7,992	38.2%	5,069	39.4%	14,022	40.0%	32,689	43.7%	9,443	38.5%
Current	1,901	8.2%	1,589	7.6%	1,141	8.9%	3,073	8.8%	11,907	15.9%	8,542	34.8%
Age at menarche (years)												
<13	11,630	49.0%	10,425	48.5%	6,387	48.1%	17,511	48.6%	37,571	49.0%	12,653	50.4%
13–14	9,764	41.1%	9,002	41.9%	5,612	42.3%	15,044	41.8%	32,236	42.0%	10,117	40.3%
15+	2,361	9.9%	2,083	9.7%	1,276	9.6%	3,446	9.6%	6,903	9.0%	2,354	9.4%
Age at first live birth (years)												
Nulliparous	3,656	15.5%	3,469	16.3%	1,923	14.6%	5,119	14.3%	10,545	13.8%	3,316	13.3%
<20	4,120	17.5%	3,575	16.8%	2,382	18.1%	5,901	16.5%	13,438	17.6%	5,324	21.3%
20–24	10,319	43.7%	8,837	41.4%	5,533	42.1%	15,789	44.2%	34,373	45.1%	10,913	43.7%
25–29	4,127	17.5%	4,027	18.9%	2,445	18.6%	6,698	18.7%	13,532	17.8%	4,148	16.6%
30+	1,365	5.8%	1,425	6.7%	864	6.6%	2,240	6.3%	4,333	5.7%	1,285	5.1%
Age at menopause (years)												
Premenopausal	1,174	4.9%	894	4.1%	477	3.5%	1,110	3.1%	2,744	3.5%	806	3.2%

Characteristic	Coffee Consumption											
	Never (n=24,021)		≤2 cups/week (n=21,742)		3–6 cups/week (n=13,444)		1 cup/day (n=36,384)		2–3 cups/day (n=77,450)		4+ cups/day (n=25,363)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<45	1,496	6.2%	1,283	5.9%	843	6.3%	2,313	6.4%	5,151	6.7%	2,192	8.6%
45–49	3,544	14.8%	3,121	14.4%	1,896	14.1%	5,336	14.7%	12,396	16.0%	4,454	17.6%
50–54	6,151	25.6%	5,774	26.6%	3,460	25.7%	9,736	26.8%	21,044	27.2%	6,798	26.8%
55+	1,403	5.8%	1,302	6.0%	818	6.1%	2,284	6.3%	4,663	6.0%	1,352	5.3%
Surgical menopause	9,436	39.3%	8,601	39.6%	5,366	39.9%	14,343	39.4%	28,844	37.2%	9,023	35.6%
Postmenopausal, age unknown	817	3.4%	767	3.5%	584	4.3%	1,262	3.5%	2,608	3.4%	738	2.9%
Ever used oral contraceptives	9,562	40.4%	8,749	40.9%	5,324	40.3%	13,600	38.0%	30,789	40.3%	10,042	40.1%
Ever used menopausal HT	12,344	51.5%	11,794	54.4%	7,137	53.2%	19,477	53.7%	42,167	54.6%	12,511	49.4%
Vigorous physical activity ≥ 3 times/ week [†]	9,815	41.4%	9,005	41.9%	5,641	42.7%	14,919	41.6%	32,353	42.2%	9,805	39.1%
Self-reported general health												
Excellent/very good/good	19,861	84.2%	17,890	83.7%	11,154	84.6%	30,887	86.5%	68,046	89.2%	22,227	89.0%
Fair/Poor	3,716	15.8%	3,476	16.3%	2,031	15.4%	4,821	13.5%	8,203	10.8%	2,749	11.0%
Ever been diagnosed with diabetes	2,168	9.0%	1,889	8.7%	1,258	9.4%	3,056	8.4%	4,837	6.2%	1,344	5.3%
Ever had a breast biopsy	5,586	23.6%	5,299	24.7%	3,240	24.5%	8,649	24.1%	18,341	24.0%	5,875	23.4%
Positive family history of breast cancer in a first degree female relative	2,919	12.8%	2,626	12.7%	1,600	12.7%	4,459	12.9%	9,545	12.9%	3,143	13.0%

[*] Missing values were excluded from percentage calculations.

[†] Vigorous physical activity was defined as activity at work/home in last 12 months that lasted at least 20 minutes and caused increases in breathing or heart rate, or worked up a sweat.

HT, hormone therapy; SD, standard deviation

Table 2

Associations between coffee consumption and breast cancer risk, overall and by clinical characteristics, among 198,404 women, NIH-AARP Diet and Health Study

	Coffee consumption											
	Never	≤2 cups/week		3–6 cups/week		1 cup/day		2–3 cups/day		4+ cups/day		
Breast cancer	**RR**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	***p*-value for trend**
All cases*(No. cases=9,915)*	*1,138*		*1,114*		*662*		*1,833*		*3,951*		*1,217*	
Age-adjusted*	1.00	1.08	(1.00, 1.18)	1.03	(0.93, 1.13)	1.04	(0.96, 1.12)	1.06	(0.99, 1.13)	1.01	(0.93, 1.10)	0.89
Multivariate adjusted†	1.00	1.06	(0.97, 1.15)	1.00	(0.91, 1.10)	1.02	(0.94, 1.09)	1.02	(0.95, 1.09)	0.98	(0.91, 1.07)	0.38
Cases with ER/PR status*(No. cases=2,984)*	*313*		*355*		*223*		*518*		*1,214*		*361*	
Age-adjusted*	1.00	1.25	(1.07, 1.45)	1.26	(1.06, 1.49)	1.07	(0.93, 1.23)	1.18	(1.04, 1.34)	1.09	(0.94, 1.27)	0.52
Multivariate adjusted†	1.00	1.21	(1.04, 1.41)	1.22	(1.03, 1.45)	1.03	(0.90, 1.19)	1.13	(0.99, 1.28)	1.08	(0.92, 1.26)	0.80
ER/PR status												
ER+/PR+ (No. cases=2,051)	*210*		*235*		*158*		*368*		*834*		*246*	
Age-adjusted*	1.00	1.23	(1.02, 1.48)	1.32	(1.07, 1.62)	1.12	(0.95, 1.33)	1.20	(1.03, 1.40)	1.10	(0.92, 1.32)	0.91
Multivariate adjusted†	1.00	1.20	(0.99, 1.44)	1.29	(1.05, 1.59)	1.10	(0.92, 1.30)	1.15	(0.99, 1.35)	1.11	(0.91, 1.34)	0.93
ER+/PR− (No. cases=425)	*44*		*50*		*31*		*64*		*186*		*50*	
Age-adjusted*	1.00	1.25	(0.83, 1.87)	1.23	(0.78, 1.95)	0.92	(0.63, 1.36)	1.27	(0.92, 1.77)	1.07	(0.71, 1.60)	0.56
Multivariate adjusted†	1.00	1.21	(0.80, 1.81)	1.21	0.76, 1.92)	0.90	(0.61, 1.32)	1.18	(0.84, 1.65)	0.97	(0.64, 1.48)	0.97
ER−/PR+ (No. cases=55)	*5*		*8*		*8*		*6*		*23*		*5*	
Age-adjusted*	1.00	1.76	(0.58, 5.38)	2.81	(0.92, 8.60)	0.77	(0.24, 2.53)	1.40	(0.53, 3.68)	0.94	(0.27, 3.25)	0.50
Multivariate adjusted†	1.00	1.60	(0.52, 4.91)	2.49	(0.81, 7.68)	0.70	(0.21, 2.33)	1.26	(0.47, 3.40)	1.02	(0.29, 3.61)	0.63
ER−/PR− (No. cases=453)	*54*		*62*		*26*		*80*		*171*		*60*	
Age-adjusted*	1.00	1.29	(0.89, 1.85)	0.87	(0.55, 1.39)	1.00	(0.71, 1.41)	1.00	(0.73, 1.35)	1.06	(0.74, 1.53)	0.76
Multivariate adjusted†	1.00	1.22	(0.85, 1.77)	0.82	(0.51, 1.31)	0.95	(0.67, 1.35)	0.96	(0.70, 1.31)	1.08	(0.74, 1.58)	0.95
p-value for heterogeneity‡		0.53										
Stage												
In-situ (No. cases=1,892)	*227*		*222*		*122*		*358*		*727*		*236*	
Age-adjusted*	1.00	1.09	(0.90, 1.31)	0.96	(0.77, 1.19)	1.03	(0.87, 1.22)	0.98	(0.85, 1.14)	0.99	(0.82, 1.19)	0.45

	Coffee consumption											
	Never	≤2 cups/week		3–6 cups/week		1 cup/day		2–3 cups/day		4+ cups/day		
Breast cancer	**RR**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	***p*-value for trend**
Multivariate adjusted†	1.00	1.04	(0.86, 1.25)	0.92	(0.74, 1.15)	1.00	(0.85, 1.19)	0.97	(0.84, 1.14)	1.02	(0.85, 1.24)	0.99
Invasive (No. cases=7,959)	*905*		*881*		*534*		*1,463*		*3,203*		*973*	
Age-adjusted*	1.00	1.07	(0.98, 1.18)	1.04	(0.93, 1.16)	1.04	(0.96, 1.13)	1.08	(1.00, 1.16)	1.02	(0.93, 1.11)	0.78
Multivariate adjusted†	1.00	1.05	(0.96, 1.16)	1.02	(0.91, 1.13)	1.02	(0.94, 1.11)	1.03	(0.95, 1.11)	0.98	(0.89, 1.07)	0.37
p-value for heterogeneity‡		0.79										
Grade												
Grade 1 (No. cases=1,687)	*184*		*162*		*118*		*280*		*725*		*218*	
Age-adjusted*	1.00	0.97	(0.79, 1.20)	1.13	(0.89, 1.42)	0.97	(0.81, 1.17)	1.19	(1.01, 1.40)	1.12	(0.92, 1.36)	0.01
Multivariate adjusted†	1.00	0.93	(0.75, 1.15)	1.09	(0.86, 1.37)	0.93	(0.77, 1.12)	1.09	(0.93, 1.29)	1.04	(0.85, 1.28)	0.14
Grade 2 (No. cases=3,030)	*341*		*363*		*208*		*597*		*1,174*		*347*	
Age-adjusted*	1.00	1.18	(1.01, 1.36)	1.08	(0.91, 1.28)	1.12	(0.98, 1.28)	1.05	(0.93, 1.18)	0.96	(0.83, 1.12)	0.05
Multivariate adjusted†	1.00	1.16	(1.00, 1.35)	1.06	(0.89, 1.26)	1.11	(0.97, 1.27)	1.01	(0.89, 1.14)	0.93	(0.80, 1.09)	0.01
Grade 3+(No. cases=2,097)	*252*		*242*		*136*		*377*		*815*		*275*	
Age-adjusted*	1.00	1.07	(0.90, 1.27)	0.96	(0.78, 1.19)	0.98	(0.84, 1.15)	1.00	(0.87, 1.15)	1.04	(0.87, 1.23)	0.87
Multivariate adjusted†	1.00	1.04	(0.87, 1.25)	0.93	(0.76, 1.15)	0.96	(0.82, 1.13)	0.97	(0.84, 1.12)	1.01	(0.85, 1.21)	0.98
p-value for heterogeneity‡		0.03										
Histology												
Ductal (No. cases=5,495)	*636*		*585*		*362*		*993*		*2,233*		*686*	
Age-adjusted*	1.00	1.02	(0.91, 1.14)	1.01	(0.88, 1.15)	1.01	(0.91, 1.11)	1.07	(0.98, 1.17)	1.02	(0.92, 1.14)	0.26
Multivariate adjusted†	1.00	1.00	(0.90, 1.12)	0.99	(0.87, 1.13)	0.99	(0.90, 1.10)	1.03	(0.94, 1.13)	0.99	(0.89, 1.11)	0.74
Lobular (No. cases=869)	*83*		*110*		*50*		*162*		*364*		*100*	
Age-adjusted*	1.00	1.46	(1.09, 1.94)	1.05	(0.74, 1.49)	1.23	(0.95, 1.61)	1.32	(1.04, 1.67)	1.14	(0.85, 1.52)	0.81
Multivariate adjusted†	1.00	1.39	(1.04, 1.85)	0.99	(0.70, 1.41)	1.16	(0.89, 1.52)	1.18	(0.93, 1.51)	1.02	(0.76, 1.37)	0.51
Mixed (No. cases=680)	*76*		*87*		*60*		*125*		*256*		*76*	
Age-adjusted*	1.00	1.27	(0.94, 1.73)	1.41	(1.00, 1.97)	1.08	(0.81, 1.43)	1.04	(0.80, 1.34)	0.95	(0.69, 1.31)	0.08
Multivariate adjusted†	1.00	1.21	(0.89, 1.66)	1.34	(0.95, 1.89)	1.02	(0.76, 1.36)	0.94	(0.72, 1.22)	0.88	(0.63, 1.22)	0.02

	Coffee consumption										
	Never	≤2 cups/week		3–6 cups/week		1 cup/day		2–3 cups/day		4+ cups/day	
Breast cancer	**RR**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	***p*-value for trend**
p-value for heterogeneity[‡]		0.15										

[*]Relative risk adjusting for age (continuous). The referent category is never coffee drinkers.

[†]Relative risk adjusting for age (continuous), race/ethnicity, education, BMI (kg/m^2), smoking status and dose, alcohol, proportion of total energy from fat (quintiles), age at first live birth, menopausal hormone therapy use, history of breast biopsy, and family history of breast cancer. The referent category is never coffee drinkers.

[‡]*p*-value for heterogeneity obtained through multivariate polytomous logistic regression models where the referent category is ER+/PR+, invasive, grade 1, and ductal histology, respectively.

ER, estrogen receptor; PR, progesterone receptor

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Table 3

Associations between caffeinated and decaffeinated coffee consumption and breast cancer risk, overall and by ER/PR status, among 198,404 women, NIH-AARP Diet and Health Study

	All cases (n=9,915)			ER/PR status											
				ER+/PR+ (n=2,051)			ER+/PR− (n=425)			ER−/PR+ (n=55)			ER−/PR−(n=453)		
Characteristic	**n**	**RR†**	**(95% CI)**	**n**	**RR†**	**(95% CI)**	**n**	**RR†**	**(95% CI)**	**n**	**RR†**	**(95% CI)**	**n**	**RR†**	**(95% CI)**	***p*-value‡**
Coffee consumption																0.75
Never	1,106	1.00	referent	204	1.00	referent	43	1.00	referent	5	1.00	referent	52	1.00	referent	
Caffeinated																
≤2 cups/week	343	1.01	(0.90, 1.15)	84	1.33	(1.03, 1.72)	21	1.59	(0.94, 2.69)	3	1.79	(0.42, 7.52)	21	1.28	(0.77, 2.13)	
3–6 cups/week	305	1.09	(0.96, 1.24)	75	1.45	(1.11, 1.89)	18	1.65	(0.95, 2.88)	5	3.45	(0.99, 12.08)	7	0.52	(0.23, 1.14)	
1 cup/day	1,024	1.01	(0.93, 1.10)	205	1.08	(0.89, 1.31)	35	0.87	(0.55, 1.36)	2	0.39	(0.08, 2.04)	44	0.93	(0.62, 1.40)	
2–3 cups/day	2,580	1.00	(0.93, 1.07)	528	1.10	(0.93, 1.30)	117	1.11	(0.77, 1.59)	13	1.02	(0.36, 2.93)	103	0.86	(0.61, 1.22)	
4+ cups/day	885	0.98	(0.90, 1.08)	175	1.09	(0.88, 1.34)	37	0.98	(0.62, 1.55)	5	1.38	(0.39, 4.88)	44	1.09	(0.72, 1.65)	
p-value for trend		0.48			0.82			0.59			0.96			0.98		
Decaffeinated																
≤2 cups/week	654	1.11	(1.01, 1.22)	130	1.18	(0.95, 1.47)	23	0.98	(0.59, 1.62)	4	1.39	(0.37, 5.19)	38	1.37	(0.90, 2.09)	
3–6 cups/week	342	0.98	(0.87, 1.10)	79	1.22	(0.94, 1.58)	11	0.80	(0.41, 1.55)	3	1.74	(0.41, 7.32)	19	1.16	(0.68, 1.96)	
1 cup/day	732	1.02	(0.93, 1.13)	151	1.14	(0.93, 1.41)	25	0.89	(0.54, 1.46)	4	1.19	(0.32, 4.47)	27	0.83	(0.52, 1.33)	
2–3 cups/day	1,250	1.10	(1.01, 1.19)	282	1.33	(1.11, 1.60)	65	1.42	(0.96, 2.10)	8	1.49	(0.48, 4.63)	61	1.20	(0.82, 1.75)	
4+ cups/day	282	1.00	(0.88, 1.15)	61	1.18	(0.88, 1.57)	11	0.95	(0.49, 1.85)	0	---		14	1.13	(0.62, 2.05)	
p-value for trend		0.40			0.04			0.16			0.65			0.74		
Unknown caffeine status	412	1.09	(0.97, 1.22)	77	1.12	(0.86, 1.46)	19	1.27	(0.73, 2.18)	3	1.81	(0.43, 7.63)	23	1.28	(0.78, 2.10)	

†Relative risk adjusting for age (continuous), race/ethnicity, education, BMI (kg/m^2), smoking status and dose, alcohol, proportion of total energy from fat (quintiles), age at first live birth, menopausal hormone therapy use, history of breast biopsy, and family history of breast cancer.

‡*p*-value for heterogeneity obtained through multivariate polytomous logistic regression models where the referent category is ER+/PR+ breast cancer. ER, estrogen receptor; PR, progesterone receptor