CAFFEINE INTAKE AND INVASIVE BREAST CANCER INCIDENCE AMONG POSTMENOPAUSAL WOMEN IN THE WOMEN'S HEALTH INITIATIVE

by

Kan Hong Zheng
15 May 2018

A thesis submitted to the
Faculty of the Graduate School of
the University at Buffalo, State University of New York
in partial fulfillment of the requirements for the
degree of

Master of Science

Department of Epidemiology and Environmental Health

ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Lina Mu, for her guidance throughout my time in the program. Her encouragements and unwavering support has allowed me to actively engage in many facets of epidemiological research.

I would also like to thank my committee members, Dr. Michael LaMonte, Dr. Jo Freudenheim, and Dr. Jean Wactawski-Wende. Their expertise and insights were instrumental in the completion of this thesis. Their guidance has expanded my knowledge of the topic and allowed me to develop my skills in critical thinking and research methodology.

Thank you to Ms. Kathleen Hovey and Dr. Ajay Myneni for the invaluable insights and suggestions throughout the data analysis portion of this project, and Ms. Karen Degarmo for her indispensable assistance and encouragements. I am also grateful for my friends and classmates that have stood by me throughout graduate and medical school.

Lastly, I would also like to give special thanks to the many participants in the Women's Health Initiative cohort and the members of the research team. Without their dedication and hard work, this and many other studies would not have been made possible.

My journey with this thesis has been circuitous, and I could not have completed the program without everyone's patience and unyielding support along the way.

TABLE OF CONTENTS

LIST OF TABLES

ABSTRACT

Background. Results of research on the effects of caffeine consumption and invasive breast cancer remains inconsistent. The aim of this study was to determine the association between caffeine intake from coffee and tea on incident invasive breast cancer in a large cohort of postmenopausal women.

Methods. This analysis included 79,871 women without previous invasive breast cancer in the Women's Health Initiative Observational Study prospective cohort. Coffee and tea intake were self-reported in a baseline questionnaire. Cox proportional hazard models were used to estimate crude and multivariate-adjusted hazards ratios (HR) and 95% confidence intervals (CIs) for invasive breast cancer incidence. Subgroup analyses by beverage type, age, race/ethnicity, smoking status, BMI, sleep duration, history of hormone therapy use, and invasive breast cancer receptor subtypes were also assessed.

Results. A total of 4,719 incident cases of invasive breast cancer were identified with a mean follow-up time of 13.5 years. No significant association was found between overall reported caffeine intake from coffee and tea and invasive breast cancer incidence. In the beverage-specific analysis, participants consuming 2-3 cups/day of caffeinated or decaffeinated coffee, compared to non-drinkers, were at increased risk of invasive breast cancer in a multivariate model adjusting for age, race/ethnicity, education, and other caffeinated beverages (caffeinated coffee HR = 1.12, 95% CI = 1.02-1.24; decaffeinated coffee HR = 1.24, 95% CI = 1.09-1.41). Invasive breast cancer risk was not associated with tea consumption. In analysis of invasive breast cancer receptor subtypes, there was decreased risk of ER+/PR- breast cancer among those in the highest quartile (279 – 736 mg/d) of caffeine consumption compared to the lowest (0 – 93 mg/d) (HR = 0.74, 95% CI = 0.59, 0.93).

Conclusion. Our findings suggest that total caffeine intake from coffee and tea is not associated with invasive breast cancer incidence. Consumption of 2-3 cups/day of coffee is associated with increased incidence of invasive breast cancer. There was no association of risk with tea consumption.

BACKGROUND

Caffeine Consumption

Caffeine is a widely consumed food constituent that is found in natural cocoa, coffee beans, kola nuts, and tea leaves. It can also be commercially added to products, such as soft drinks, energy drinks, energy shots, alcoholic beverages, and medications [1]. A report by the Food and Drug Administration (FDA) estimates 97% of caffeine consumption in teenagers and adults and 95% of caffeine consumption in children ages 2-13 years of age come from beverage sources [1]. Additionally, a comprehensive survey estimated that 85% of the U.S. population ages ≥2 years consumes at least one caffeinated beverage per day [2]. Adults primarily consume caffeine through coffee while children primarily consume it through carbonated soft drinks. More specifically, adults 51-70 years old consume 71% of total caffeine from coffee, 18% from tea, 10% from soda, and 1% from other beverages and food products. Adults >70 years old similarly consume 80% of total caffeine from coffee, 13% from tea, 5% from soda, and the remainder from other beverages and food products [3].

Caffeine Consumption and Health Effects

This common consumption of caffeine from coffee, tea, and other beverage sources has led many researchers to study its potential positive or negative effects on multiple health outcomes. Coffee contains caffeine and numerous phenolic compounds, such as chlorogenic, caffeic, vanillic, and ferulic acids, that are important for their antioxidant activities [4]. Coffee has been widely studied and shown to have both adverse and beneficial health effects. For example, the caffeine content in coffee has shown to increase blood pressure and plasma homocysteine, which are risk factors for cardiovascular disease [5, 6]. However, studies have

also found that coffee consumption may prevent type 2 diabetes mellitus, Parkinson's disease, and liver disease, and is inversely related with deaths due to heart disease, respiratory disease, stroke, diabetes, accidents, and infections [5, 7]. Tea also contains high concentrations of antioxidants, such as flavonoids, catechins, and tannins [8]. Consumption of tea has shown to have antiobesity and antidiabetic effects, lower the risk of coronary heart disease, and have a positive effect on bone mineral density [9, 10]. Adversely, there is also presence of aluminum in tea, which can accumulate in the body of patients with renal failure and lead to neurological diseases [9]. Catechins have a high iron affinity, which may decrease iron bioavailability in the body. Soft drinks have shown to increase the risks for type 2 diabetes, coronary heart disease, and gout in women [11-14]. Soft drinks are also associated with increased energy consumption and reduced intakes of calcium and other nutrients. These consequences may be attributed to the high fructose corn syrup content of many soft drinks, which can increase insulin concentrations and inflammatory molecules leading to adverse effects [12]. Finally, energy drinks have been associated with trouble sleeping, anxiety, cardiovascular events, and seizures [15].

Several studies have assessed the effects of caffeine, coffee, tea, and soft drinks on cancer risk, but the results have been inconsistent depending on the cancer site. For example, tea or coffee consumption appears to be protective against colorectal, liver, and mouth and throat cancer, but coffee consumption is associated with increased risk of lung cancer [9, 10, 16-18]. Carbonated soft drinks were not associated with cancer risk [19].

Several biological mechanisms have been proposed to explain how caffeine, coffee, and tea may affect cancer development. Caffeine has been shown to modulate tumor suppression by alternative splicing of a subset of cancer-associated genes, with a positive shift in immunity by antagonizing adenosine receptors to reduce tumor incidence [20, 21]. Both coffee and tea contain

antioxidant polyphenols, such as lignin phytoestrogens and flavonoids, which may have anti-carcinogenic properties [22, 23]. It has been suggested that coffee phytochemicals inhibit oxidative stress and damage, regulate DNA repair, phase II enzymatic activity, apoptosis, inflammation, and have antimetastatic effects [24]. Tea consumption may protect against cancer by modulating phase II metabolism, altering the redox environment, inhibiting growth factor signaling, slowing cancer progression, and modifying expression of biomarkers relevant to carcinogenesis in animal and human studies [25].

Breast Cancer

Breast cancer is the most common type of cancer and second leading cause of death for women of all race/ethnicities in the United States [26]. There are 246,660 new breast cancer cases annually according to the 2016 Surveillance, Epidemiology, and End Results Program (SEER) estimates, which consists of 14.6% of all new cancer cases in females [27]. Furthermore, 89.7% of women survive five years or more after breast cancer diagnosis. The median age of breast cancer diagnosis is 61 years old [28].

Breast cancer is staged from 0 to IV depending on size of the tumor and whether the cancer has spread. Knowing the stage of the breast cancer allows for better understanding of the prognosis and success of treatments. Staging requires knowing if a breast cancer is either invasive or *in situ*, meaning that the cancer cells have not spread to the surrounding tissue. *In situ* breast cancers are categorized as stage 0 since they have not invaded deeper breast tissue. About 1 in 5 of new breast cancer cases will be ductal carcinoma in situ (DCIS), which may remain *in situ* or become invasive. Nearly all women diagnosed with DCIS at this stage can be cured. About 80% of invasive breast cancer cases are ductal carcinoma (IDC), which begin in the milk

ducts of the breast, and 10% lobular carcinoma (ILC), which start in the milk-producing glands [29]. The prognosis and 5-year survival rate for invasive breast cancers depend on the stage of the breast cancer. The 5-year survival for stage 0 and I is close to 100%, for stage II about 93%, for stage III about 72%, and for stage IV about 22% [29]. A study by Toikkanen et al. has shown that ILC may have better a prognosis and survival rate compared to IDC due to the primary tumor size, axillary nodal status, and presence of tumor necrosis [30]. Less common types of breast cancer include inflammatory breast cancer (1-3%), Paget disease of the nipple (1%), phyllodes tumor, and angiosarcoma. Paget disease of the nipple is categorized as stage 0 breast cancer since there is no underlying tumor mass. Inflammatory breast cancer is categorized as stage III, with both a higher chance of spreading and with a worse prognosis compared to IDC and ILC.

Breast cancers also differ by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor type 2 (HER2/neu) hormone receptor status, which can influence prognosis of the cancer and guide treatment options. About 2 of 3 breast cancer cases have either the estrogen or progesterone receptors present or both. These reproductive hormones can help fuel the growth of breast cancer cells by inhibiting apoptosis and stimulating metastasis [29, 31]. Hormone receptor positive breast cancers (ER+ and PR+) have better prognosis compared to hormone receptor negative breast cancers and respond better to hormone therapy [31-33]. HER2 is a protein on the surface of some breast cancer cells that is important for cellular growth and survival. The overexpression of HER2 has been associated with greater disease recurrence and shorter survival time [34]. The development of the drug trastuzumab has improved the prognosis and survival of HER2+ breast cancer as it works to block HER2+ cells from replicating [35]. Triple-negative breast cancers lack estrogen, progesterone, and HER2 receptors, and this

receptor subtype has shown to be more aggressive, have higher rates of relapse, and have poorer prognosis compared to other subtypes [36, 37]. Although responsive to chemotherapy, triple-negative breast cancer does not respond to receptor-targeted treatments.

Age is an important risk factor for breast cancer because of the decline in overall health and well-being of an individual, and the increased likelihood of abnormal cellular changes during the aging process [38]. The risk of being diagnosed with breast cancer is 1 in 42 at 50 years, 1 in 28 at 60 years, and 1 in 26 at 70 years of age [29]. The risk of breast cancer varies greatly by race/ethnicity. The age-adjusted incidence rates per 100,000 persons are 123 for white, 120 for African-American, 91 for Hispanic, 90 for Asian/Pacific Islander, and 68 for American Indian/Alaskan native women [26]. Although white women have the highest risk, African-American women tend to have more aggressive breast cancer because they are more likely to develop higher grade tumors and to have tumors with triple-negative receptor status [39]. This higher likelihood of developing more aggressive breast cancers results in poorer prognosis and survival rates for African-American women compared to other race/ethnicity groups [26]. It is, therefore, important to study breast cancer by age and race/ethnicity groups given these risk differences.

There are several other important and established risk factors for breast cancer. They include personal and family history of breast cancer, use of hormone replacement therapy, older age at first birth or never having given birth, early age at menarche, later age at starting menopause, alcohol consumption, physical inactivity, and obesity (for postmenopausal women) [40, 41]. Although presence of these risk factors may contribute to the development of breast cancer, the etiology differs by cancer subtype resulting in differing prognoses and survival rates. For example, ILC occurs more often for women in their early 60s compared to the mid- to late

50s for IDC. Also, as previously mentioned, African-American women are more susceptible to having triple-negative receptor breast cancer. It is, therefore, important to not only study breast cancer overall, but also by its histological and receptor-status subtypes.

Association Between Caffeine Consumption and Breast Cancer

Numerous epidemiological studies have tested the association between caffeine, coffee, or tea consumption with breast cancer incidence [42-59]. However, these studies have produced inconsistent results. Several research groups have found inverse associations between coffee or tea consumption and breast cancer. For example, a study with Asian-Americans found a significant inverse association between green tea consumption and breast cancer development when comparing high consumption (>85mL/day) to no consumption (0mL/day) (Odds ratio, OR = 0.53; 95% Confidence interval, CI = 0.35, 0.78) [58]. A population-based case-control study by Kumar et al. in the United States also found a protective effect of consuming three or more cups of tea per day against overall and subtype-specific breast cancers, such as lobular or ductal, in women less than 50 years of age (OR = 0.63, 95% CI = 0.44, 0.89) [59]. Additionally, the Ontario Women's Diet Study also suggests protection against ER- breast cancer with high coffee intake (≥5 cups/day) compared to never drinkers (OR = 0.41, 95% CI = 0.19, 0.92) [49]. Nonetheless, studies conducted in France, Israel, Sweden, Italy, the United Kingdom, the Roswell Park Cancer Institute, the Black Women's Health Study, and the Iowa Women's Study suggested no significant association between caffeine, coffee, or tea consumption and overall or subtype-specific breast cancer incidence [42-45, 47, 50, 51, 55-57]. Further, a study using the Swedish Women's Lifestyle and Health cohort found increased risk for developing overall breast cancer (Relative risk, RR = 1.14; 95% CI = 1.0, 1.24) and ER+/ PR+ breast cancer (RR = 1.21,

95% CI = 1.09, 1.34) per 1 cups of tea/day increase [52].

Interestingly, studies have indicated an inverse relation between caffeine consumption and breast cancer risk among postmenopausal women. The Nurses' Health Study found no overall association between caffeine consumption and breast cancer, but they did observe a protective effect in postmenopausal women with an RR of 0.88 (95% CI = 0.79, 0.97) [46]. Similarly, the Ontario Women's Diet and Health and the Swedish Women's Lifestyle and Health studies also found an inverse association between coffee and breast cancer incidence in postmenopausal women showing an OR of 0.63 (95% CI = 0.43, 0.94) and RR of 0.81 (95% CI = 0.70, 0.94), respectively [49, 52]. Two post-hoc meta-analyses additionally found a protective effect of coffee and caffeine intake against breast cancer in postmenopausal women with pooled RRs of 0.94 (95% CI = 0.8, 0.99) and 0.95 (95% CI = 0.90, 1.00) summarizing the study-specific comparisons between higher and lower intakes [60, 61]. Therefore, although the association between caffeine consumption and breast cancer incidence remains somewhat inconsistent among published studies, there does appear to be a more consistent finding of an inverse relation in postmenopausal women.

The inconsistencies across the aforementioned studies may be attributed to the variation in sample sizes (range of N = 501 to N = 9,915 cases of breast cancer in the Asian-American and NIH-AARP diet and health studies, respectively), the distinction in how caffeine affects pre- and postmenopausal breast cancer, the specific caffeinated beverages evaluated, or the constrained variation in caffeinated beverage that might be attributed to race/ethnic or cultural influences on dietary habits. Therefore, to better understand the association between coffee, tea, and caffeine intake and breast cancer risk, further investigation is needed in a large cohort of postmenopausal women with racial/ethnic diversity, a large age range, and breast cancer subtypes data.

Although fewer studies have been done to assess the association between soft drinks and breast cancer incidence, the Nurses' Health Study and a meta-analysis by Boyle et al. reported no association [19, 46].

Caffeine and Breast Cancer Mechanisms

Several proposed biological mechanisms support a potential role of caffeine in specifically reducing breast cancer incidence. Caffeine up-regulates tumor suppressor proteins p16, p21, p53, and Cav-1 which prevent tumor growth; reduces expression and secretion of various cytokines important in cancer signaling pathways; inactivates breast stromal myofibroblasts; and suppresses the paracrine proangiogenic effect of cancer-associated fibroblasts cells through down-regulation of HIF-1a and its downstream effectors [62]. Co-treatment by incubating cells first with cisplatin, a cancer treatment drug, then with caffeine has shown to induce apoptosis in the human breast cancer cell line MCF-7 [63]. Caffeine can reverse genistein-induced G2/M phase arrest in breast cancer cell lines, increase their sensitivity to the phytoestrogen genistein, and enhance genistein-induced inhibition of cell growth [64]. Additionally, caffeine can suppress ER+ and ER- cells, significantly reduce ER and cyclin D1 abundance in ER+ cells, reduce insulin-like growth factor-I receptor (IGFIR) and pAkt levels in ER+ and ER- cells to impair cell-cycle progression and enhance cell death [65]. High levels of caffeine intake can also significantly lower levels of micronuclei suggesting a chemopreventive effect, which may be associated with improved capacity to efficiently repair DNA damage [66]. While these mechanisms have been identified through which caffeine could potentially benefit breast cancer risk, the epidemiologic evidence for an association between caffeine intake and breast cancer incidence remains inconsistent. Additional studies are needed to clarify the

presence and nature of an association between caffeine intake and incidence of breast cancer.

Summary

In summary, findings from research on the association between caffeine, coffee, and/or tea and breast cancer risk is largely inconsistent. However, this association appears to be consistently inverse specifically among postmenopausal women. On average, women enter menopause at age 51 years, which coincides with the highest reported rates of caffeine consumption according to a 2010 report by the Food and Drugs Administration using data from the National Health and Nutrition Examination (NHANES) 2005 – 2006 survey (225.3mg per day for women aged 50 to 59 years) [1]. Additionally, the rates of breast cancer are lower in women younger than 40 years of age; median age at diagnosis is 61 in the United States [28]. This overlap of age at menopause, median age at diagnosis of breast cancer, and high consumption of caffeine adds to the importance of studying this association in postmenopausal women. Presently, few studies have assessed the association between caffeine consumption and breast cancer risk among different race/ethnicity groups [47, 49, 50, 53], specifically in a cohort of postmenopausal women [45, 47, 57], or by histological or receptor-specific breast cancer subtypes [42, 44, 46-49, 52, 59]. The Women's Health Initiative (WHI) will uniquely allow for an evaluation of this association overall and by all of the above-mentioned subgroups. The WHI's observational study include a large number of invasive breast cancer cases overall and by subtypes, and comprehensive coffee and tea measurements exclusively among postmenopausal women [67-69]. The cohort's extensive follow-up period, adjudication of breast cancer outcome, availability of receptor-type breast cancer information, and inclusion of women from multiple race/ethnic groups allowed for a more complete understanding of the association based on

analysis within selected cohort subgroups. Furthermore, the cohort's age range of 50 to 99 years allowed for assessment of the different effects of caffeine on mechanisms for early and late postmenopausal breast cancer.

We report here on the association between caffeine consumption and invasive breast cancer incidence in a well-characterized, race-ethnically diverse cohort of postmenopausal women with more than 20 years' follow-up for incident cases. Our study contributes to the existing body of evidence on the association between caffeine intake and breast cancer incidence.

STUDY AIMS

Primary Aim: We examined the association between self-reported total caffeine consumption and invasive breast cancer incidence in postmenopausal women.

Secondary Aim: We explored whether an association between caffeine consumption and breast cancer differs among subgroups defined by: race/ethnicity, age, smoking status, BMI, sleep duration, history of HT use, and invasive breast cancer receptor subtypes.

METHODS

Study Population

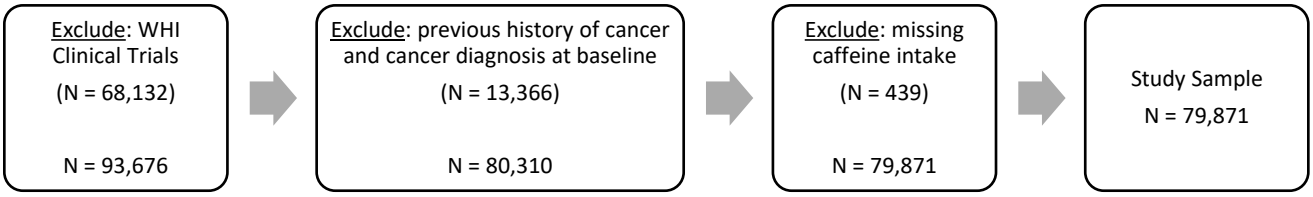
The Women's Health Initiative (WHI) is a multi-center prospective cohort study established by the National Institutes of Health (NIH) in 1991 and launched in 1992 to address the most common causes of death and disease in postmenopausal women between the ages of 50 – 79 years. The study enrolled from 40 study centers across the U.S. in 24 states and the District of Columbia. Enrollment into the cohort began in 1993 and ended in 1998. The WHI observational study (OS), which included 93,676 participants, aimed to explore predictors and biomarkers of morbidity and mortality [69].

The main follow-up activities of the WHI OS concluded between 2004-2005, but interested participants were offered to continue in the subsequent WHI Extension Studies and re-consented for continuation. The first extension study followed re-consenting participants for five additional years (2005 – 2010) and collected updates on health outcomes annually. The extension study aimed to understand the longer-term effects of the original interventions, document change in hormone use in the hormone therapy trials, build on the existing pool of data to support additional investigations. The second extension study added an additional five-year follow-up period (2010 – 2020) with a focus on cardiovascular events and aging. It continued collecting annual health updates from re-consenting women from the first extension study.

Follow-up questionnaires were mailed to the OS participants annually to obtain information on study outcomes and health updates. The most recent identification of verified primary cancers for OS participants were collected through September 30, 2015.

Study Sample Selection Flow Chart

The study was limited to participants of the WHI OS. Participants from the three clinical trials, having a history of cancer or cancer diagnosis at baseline, or missing coffee, decaffeinated coffee, or tea intake information were excluded.



Exposure and Outcome Assessment

Baseline characteristics collected from participants include information on demographics and general health characteristics, personal and family medical history, dietary intake, other lifestyle factors including smoking, alcohol intake, physical activity, anthropometric measures of body size, and medication use. For our present analyses, we used information on age, race/ethnicity, body mass index (BMI), education, smoking status, smoking intensity, secondhand smoking exposure, alcohol intake and frequency, recreational physical activity, total energy intake, sleep duration, hormone therapy (HT) use, age at menarche, age at menopause, age at first birth, parity, and family history of breast cancer.

Caffeine Consumption Assessment

The Observational Study Questionnaire (Form 42) assessed any regular (caffeinated) coffee, decaffeinated coffee, and regular tea intake at baseline by asking the following questions: "How many cups of regular coffee (not decaf) do you usually drink each day [count tall (12 oz or more) cups and espresso drinks made with double shots as 2 cups]," "How many cups of decaf coffee do you usually drink each day? [count tall (12 oz or more) cups and espresso drinks made

with double shots of espresso as 2 cups]," and "How many cups of tea do you usually drink each day? (do not include decaf or herbal tea)." Participants reported their intake of coffee and/or tea in the following frequency categories for numbers of servings: none, 1 cup, 2-3 cups, 4-5 cups, 6 or more cups. Caffeine intake from soft drink consumption and foods, such as chocolate, was not included in this study as assessment of their intake were not included in the WHI Observational Study Questionnaire.

The self-administered, standardized food frequency questionnaire (FFQ) was used to collect food intakes over the previous 3-month period, and determined usual frequency and portion size of 122 foods or food groups [70]. Although total caffeine intake (mg/d) was assessed at baseline and 3 years after entry into the OS, the FFQ did not differentiate between caffeinated, decaffeinated, or caffeine-free coffee, tea, or soft drinks. In addition, the FFQ collected information over the previous 3-month period whereas the Observational Study Questionnaire assessed any consumption without a given time frame. Therefore, we did not use the FFQ data for our current analysis due to the inability to differentiate the different caffeine contents of beverages and the different time frames used.

Creating total caffeine variable from coffee and tea variables. The variable for total caffeine consumption at baseline in mg/d was calculated using the individual beverage information from the Observational Study Questionnaire, and was used as the primary exposure variable to assess total caffeine intake from coffee and tea. Coffee consumption information was gathered from question 5 and tea information from gathered from question 6 in the questionnaire, and the specific questions were as described above. Participants that were missing information on cups/d of regular (caffeinated) coffee intake, decaffeinated coffee intake, and tea intake were cross-

checked with the original questions “Do you usually drink coffee each day?” and “Do you usually drink tea each day?” Participants that answered “No” to these two questions, but were missing information on cups/d were placed in the “None” cups/d category. The caffeine content of decaffeinated coffee, caffeinated coffee, and tea were estimated and converted from cups/d to mg/d using information from the U.S. Department of Agriculture National Nutrient Database for Standard Reference [71]. The database estimates 137 mg caffeine per 8 oz cup of coffee and 47 mg caffeine per 8 oz cup of tea. Decaffeinated coffee was included in the analyses as it also contains caffeine, but in smaller amounts (5 mg per 8 oz) [72-74]. The variables for regular coffee, decaffeinated coffee, and tea were then converted to mg/d of caffeine by creating new variables from multiplying the original variables by its respective caffeine amount (mg) per 8 oz cup. The three new variables for regular coffee, decaffeinated coffee, and tea in mg/d were summed up to create a total caffeine intake variable. Four hundred thirty-nine participants with missing information on total tea and coffee caffeine intake were excluded from the study per the third exclusion criteria. The total tea and coffee caffeine consumption variable was categorized into quartiles to ensure that there were enough study participants per group for analysis purposes.

Breast Cancer Outcome Assessment

Health questionnaire updates were mailed to participants to obtain self-report of breast cancer diagnoses annually in the OS. Participants were asked “Has a doctor told you for the first time that you have a new cancer or a malignant tumor? What kind of cancer or malignant tumor was it?” Self-reported diagnoses of cancer were followed by requesting and reviewing medical record documentation and adjudication by trained physicians at local clinical centers using standard criteria [67]. Incident invasive breast cancers were ascertained and adjudicated. Data

collected included breast cancer stage, tumor type, size, nodal status, grade, histology (ductal, lobular), and receptor status (ER, PR, HER2). The National Cancer Institute Surveillance, Epidemiology, End Results (SEER) coding guidelines are used for central cancer coding. Follow-up time for each participant was accrued from the date of enrollment to the date breast cancer diagnosis or censor date as a loss to follow-up or completion of the follow-up interval. The final number of incidence invasive breast cancer cases in this study was 4,719.

Analytic Plan

Potential Covariates

Based on *a priori* knowledge and current literature, we selected the following potential covariates: age, race-ethnicity, education, smoking status, pack-years of smoking, alcohol consumption, BMI, recreational physical activity, total energy intake, sleep duration, HT use, age at menarche, age at menopause, and age at first birth, parity, and family history of breast cancer.

These variables were evaluated as potential confounders by determining if they were 1) associated with main exposure, 2) associated with the main outcome, and 3) if they were not an intermediate in the causal pathway. Mean and total N (%) differences of those selected variables were compared across breast cancer case and non-case status and quartiles of caffeine consumption (Tables 1 and 2). If the $p<0.05$, then the covariate meets the criteria to be considered a potential confounder. Next, to determine which of these potential confounders will be included in the final multivariate model, we used the parsimonious method for model building. Each covariate was added one at a time to the base model, which includes total caffeine intake and age. Continuous and categorical forms of each variable were added and assessed

separately in the base model. If the covariate results in a nominal change in HR estimate by 10% or more, then it was considered a confounder and included in the final multivariate model.

In our model building, none of the potential confounders changed the HR estimate by 10% or more when added individually in the base model. To remain consistent with current literature and to address any potential confounding that may occur in our analyses, we decided include the covariates by creating four models based on the type of variable. Model 1 was the crude model. Model 2 included demographic variables (age, race/ethnicity, and education). Model 3 included the variables in Model 2 and lifestyle variables (smoking, pack-years of smoking, alcohol intake, total energy intake, recreational physical activity, BMI, and sleep duration). Model 4 included the variables in Model 2 and gynecological variables (family history of breast cancer, OC use, history of hormone use, age at menarche, age at menopause, age at first birth, and number of live births).

Descriptive Statistics

The main exposure variable, main outcome variable, and all covariates were evaluated for missing, and data were imputed with the mode if the missing exceeded 5%. The variable for age at first birth was missing 19.91% (N = 15,986) and was cross-checked with number of live births variable. The missing age at first birth variables were then imputed with the most common response of those in the number of live births variable.

This analysis used invasive breast cancer incidence as the primary, dependent outcome variable as defined by case and non-case status. Caffeine intake from coffee and tea (mg/d) at baseline is the primary, independent exposure variable. The total caffeine intake variable is categorized into quartiles of consumption in mg/d throughout the study. We used means and

standard deviations to describe continuous variables, and total N and percent to describe categorical variables. Means and distributions of variables are presented by case status (incident breast cancer cases and non-cases) (Table 1), as well as by quartiles of total caffeine intake (Table 2). Next, *t*-tests were used to compare continuous covariate means between invasive breast cancer cases and non-cases. The Satterthwaite *t*-test was used for continuous variables with unequal variances and the pooled *t*-test was used for continuous covariates with equal variances as determined by the F-test. Analysis of variance (ANOVA) was used to compare continuous variables across quartiles of caffeine intake. Normality of the covariates was assessed using goodness-of-fit tests to satisfy the assumption prior to running the *t*-test and ANOVA. Chi-square test of independence was conducted to compare proportions of categorical covariates between invasive breast cancer cases and non-cases, and across caffeine intake quartiles. If more than 20% of the contingency cells have expected values <5, the Fisher's exact test was used instead.

Regression Analysis

Overall invasive breast cancer analysis. Cox proportional hazards regression was performed to estimate HRs and 95% CIs where the primary outcome variable was time to occurrence of first invasive breast cancer incidence. Follow-up time for incident invasive breast cancer outcome events was calculated from baseline to date of diagnosis, date of death from a disease other than breast cancer, date that follow-up ends, or date of censoring for loss-to-follow-up, whichever came first. The lowest quartile of caffeine intake (0 – 93 mg/d) was used as the referent group in determining the association between total caffeine intake from coffee and tea, and total invasive breast cancer incidence.

Analysis in subgroups. Cox proportional hazards regression was also performed to determine HRs and 95% CI in the subgroup analyses. We tested for effect modification of race/ethnicity, age, smoking status, BMI, sleep duration, and history of HT use by assessing multiplicative interaction. Product terms were first created between total caffeine intake and race/ethnicity, categorical age, smoking status, categorical BMI, categorical sleep duration, and history or hormone use variables. Multiplicative interaction is present if significance is observed when the product terms are included in the multivariate model.

Caffeinated beverage-specific analysis. We also calculated the HRs of total invasive breast cancer by cups/d of caffeine intake by beverage type (decaffeinated and caffeinated coffee, and tea) using Cox proportional hazards regression and the "None" cups/d as the referent group (Table 4). The ≥4 cups/d category for each beverage type combined the 4-5 and 6 or more cups/d categories to obtain sufficient sample sizes for analysis.

RESULTS

A total of 4,719 cases of incident invasive breast cancer were documented in this study in participants who completed the baseline Observational Study Questionnaire and had information on coffee and tea consumption. The mean follow-up time for total invasive breast cancer was 13.5 years (7.7 for cases and 13.8 years for non-cases). The mean follow-up time was 6.1 years longer for non-cases compared to cases due to censorship at incidence.

Characteristics of study participants by invasive breast cancer case and non-case status are shown in Table 1. Due to the large sample size, significant differences between the groups were estimated although the differences were small. Invasive breast cancer cases were similar to non-cases in age (63.2 and 63.4 years, respectively) with a mean age of 63.4 years. There were more cases who were former smokers (46.3%); more of the non-cases were more likely to be never smokers (51.5%). On average, cases had higher energy consumption (1578.6 kcal vs. 1545.4 kcal) and were more likely to be current alcohol drinkers. Cases were also more likely to be non-Hispanic white, have more education, have a family history of breast cancer, have used oral contraceptives, be current hormone therapy users, be nulliparous, have an earlier age at menarche (≤11 years), later age at menopause (48.8 years vs. 48.3 years), later age at first birth (≥30 years), have longer sleep durations per day (≥8 hours/day), and drink coffee. There was no significant difference between caffeine intake mg/d from coffee and tea between cases and non-cases.

Characteristics of study participants by caffeine intake quartiles are shown in Table 2. Compared to those in Quartile 4 (279 – 736 mg/d) of caffeine intake, participants in Quartile 1 (0 – 93 mg/d) were more likely to be non-Hispanic white, have higher BMI (27.4 kg/m^2 vs. 27.0 kg/m^2), be never smokers or alcohol drinkers, have lower mean total energy intake (1505.8 kcal

vs. 1631.5 kcal), and have higher total mean recreational activity (14.2 MET-hr/wk vs. 13.7 MET-hr/wk). Quartile 1 participants were also less likely to have a history of hormone therapy use, have an earlier age at menarche (≤11 years) and age at menopause (48.2 years vs. 48.4 years), be nulliparous, and have a shorter sleep duration (≤5 hours/day) compared to Quartile 4.

Using Quartile 1 as the referent group, the association between total caffeine intake and invasive breast cancer incidence was examined (Table 3). Overall, there are no statistically significant associations of caffeine intake and invasive breast cancer risk in crude or multivariate models. Any coffee consumption was associated with an increased risk of total invasive breast cancer in the crude analysis (HR = 1.07, 95% CI = 1.01, 1.15) compared to non-consumption, but the association was lost in the multivariate models.

Caffeinated beverage-specific associations with invasive breast cancer are shown in Table 4. Participants who consumed 2-3 cups/d of caffeinated coffee had a statistically significant 14% increase risk of invasive breast cancer compared to non-drinkers (HR = 1.14, 95% CI = 1.03-1.25) in the crude model. The risks were similar in Model 2 adjusting for demographic variables (age, race/ethnicity, education) and other caffeinated beverages (HR = 1.12, 95% CI = 1.02-1.24), and Model 4, which adjusted for gynecological variables (HR = 1.12, 95% CI = 1.01-1.24). In a model adjusting for behavioral variables (smoking status and packyears, alcohol intake, energy intake, physical activity, BMI, and sleep duration), results were similar, but did not reach formal statistical significance (Model 3; HR = 1.05, 95% CI = 0.95, 1.17). Increased risk of invasive breast cancer was also found for decaffeinated coffee in models adjusting for demographic variables (HR = 1.24, 95% CI = 1.09-1.41), lifestyle variables (HR = 1.18, 95% CI = 1.03-1.36), and gynecological variables (HR = 1.17, 95% CI = 1.03-1.35). There was no association found between tea consumption and invasive breast cancer risk.

To assess the differences in invasive breast cancer risk by race/ethnicity, age, smoking status, BMI, sleep duration, and history of HT use, stratified analyses of total caffeine intake and invasive breast cancer incidence within these groups were examined (Table 5). Although various statistically significant results were found within age group 49 – 59 years, former and current smokers, normal and overweight BMI, and former HT users, there were no significant multiplicative interactions in the stratified analyses (P-for-interactions >0.05).

Associations between caffeine intake and invasive breast cancer receptor subtypes are presented in Table 6. Quartile 4 of caffeine consumption is significantly associated with an increased risk of estrogen receptor negative (ER-) (HR = 1.27, 95% CI = 1.02-1.59) and estrogen receptor negative/progesterone receptor negative (ER-/PR-) (HR = 1.28, 95% CI = 1.01-1.62) invasive breast cancers compared to those in Quartile 1 after adjusting for lifestyle variables. Quartile 2 also has a weak significant association with estrogen receptor negative/progesterone receptor negative/HER2 receptor negative (ER-/PR-/HER2-) compared to Quartile 1 (HR = 1.02, 95% CI = 1.00-1.03). Conversely, Quartile 4 of caffeine consumption shows a decreased risk of estrogen receptor positive/progesterone receptor negative (ER+/PR-) invasive breast cancer compared to Quartile 1 in the crude model (HR = 0.75, 95% CI = 0.60-0.94). This association increases after adjusting for demographic variables (HR = 0.74, 95% CI = 0.59, 0.93), lifestyle variables (HR = 0.73, 95% CI = 0.57, 0.92), and gynecological factors (HR = 0.71, 95% CI = 0.56, 0.90). Although not as strong, Quartile 3 also shows a decrease risk of ER+/PR- invasive breast cancer after adjusting for lifestyle variables (HR = 0.77, 95% CI = 0.60, 0.99) and gynecological variables (HR = 0.75, 95% CI = 0.59, 0.96) compared to Quartile 1.

DISCUSSION

In this analysis of a large prospective cohort of postmenopausal women, total caffeine intake from coffee and tea beverages was not associated with risk of invasive breast cancer. However, analyses of those with the highest amounts of total tea and coffee caffeine intake indicated a potential protective effect against ER+/PR- invasive breast cancer. Caffeinated and decaffeinated coffee consumption was weakly associated with an increase in risk of total invasive breast cancer.

Our findings in the association between caffeine intake and breast cancer incidence agrees with several meta-analyses and studies in other cohorts, such as the Swedish Mammography Cohort, the Black Women's Health Study, the Iowa's Women's Health Study, and the NIH-AARP Diet and Health Study [43-45, 47, 48, 51, 55, 57, 60, 75]. Nevertheless, current epidemiologic studies on caffeine, coffee, or tea consumption and breast cancer are largely inconsistent. The Nurses' Health Study as suggested an inverse association between total caffeine consumption from coffee, tea, soft drinks, and chocolate and breast cancer incidence in postmenopausal women [46]. Similarly, EPIC cohort study reported lower risk of postmenopausal breast cancer in the high caffeinated coffee intake category compared to low intake [76]. On the other hand, Lehrer et al. found increased breast cancer mortality in women consuming larger amounts of coffee [77].

Our study also found weakly positive associations between invasive breast cancer and consumption of 2-3 cups/d of caffeinated or decaffeinated coffee. These statistically significant associations may be due to the larger number of participants in the 2-3 cups/d category of consumption for both types of beverages. Alternatively, this association may also be attributed to

another chemical component of coffee or a participant characteristic or behavior that was not accounted for. Further investigation is needed to understand this association more clearly.

The potential biological effects that caffeine has on breast cancer development remain uncertain. Changes in hormone levels may elucidate how caffeine affects breast cancer development. A few studies have found caffeine intake to be positively associated with estrone and sex hormone-binding globulin (SHBG) levels, and negatively associated with free luteal estradiol levels [78-80]. While circulating levels of androgens and estrogens are positively associated with breast cancer risk, high levels of SHBG has shown to reduce the risk [81-83]. In an animal study, caffeine was shown to inhibit hormone-induced breast cancer development in rats [84].

Caffeine, however, is just a component of coffee and tea, and the numerous other substances may also exert effects on breast cancer from these specific beverages. For example, cafestol and kahweol, two diterpenes found in coffee, have been found to have anticarcinogenic properties through induction of cancer chemopreventive enzymes [85, 86]. Antioxidant properties of caffeine is mainly mediated by its chlorogenic acid content, which is increased during the roasting process and at maximum in medium-roast coffee [86, 87]. Similarly, tea also contains high levels of antioxidants, such as flavonoids, catechins, and tannins, although levels vary among the various types of teas and amount of oxidation [88]. While caffeine and other compounds found in coffee and tea appear to provide protection against cancer and inflammation, coffee as a whole has shown to increase serum lipid levels through the effects diterpenes on LDL receptors, ultimately leading to the accumulation of cholesterol. Caffeine specifically has also shown to acutely increase blood pressure although this elevation was not observed in postmenopausal women [87, 89]. The heterogeneity of caffeine, coffee, and tea

effects on breast cancer risk and overall health therefore makes it difficult to pinpoint their exact mechanisms of action within different disease processes.

Our subgroup analysis by breast cancer types indicated a weakly positive association between the highest quartile of caffeine intake and ER-/PR- invasive breast cancer. This finding is consistent with a study by Ishitani et al., which also suggested an increased risk of ER-/PR- breast cancer with caffeine consumption (RR = 1.68, 95% CI = 1.01-2.81) [48]. The inverse association that was found between the highest quartile of caffeine intake and ER+/PR- invasive breast cancers also agrees with a study by Oh et al. that determined a reduced risk of breast cancer in their highest tertile of caffeine intake (RR = 0.64, 95% CI = 0.45-0.92) [52]. However, some studies found an inverse association between ER- breast cancers and coffee consumption in postmenopausal women, findings of which we did not replicate [49, 90, 91].

Caffeine's effects on levels of circulating estrogen and estrogen-positive receptors may provide some insight as to why differences are observed in the association between caffeine consumption and breast cancer receptor subtype incidence. Estradiol and free estradiol has been shown to increase the risk of breast cancer among women 60 years and older [83]. Caffeine has shown to increase levels of SHBG in addition to the increase in levels during the 6^{th} decade of life, and higher levels of SHBG has been associated with lower incidence of postmenopausal breast cancer in both hormone and non-hormone users [78, 79, 82, 83, 92]. This may be due to the binding of SHBG to estrogen and converting the estrogen to its inactive form, which will in turn reduce estrogen signaling in ER+ breast cancer cells. Caffeine has also shown to reduce levels of cyclin D1, insulin-like growth factor-I receptor, and pAkt, which impaired tumor cell cycle progression and enhanced cell death in ER+ breast cancer [65].

Our study was limited by the self-report nature of coffee and tea consumption from the Observational Study Questionnaire, which may be subject to misclassification errors. The questionnaire also did not indicate the amount of time the participant has been consuming the indicated amount of coffee or tea, such as in the past three months, year, or lifetime. This prevents us from determining if the association between coffee and tea caffeine and invasive breast cancer is influenced by the length of time a participant has been consuming the beverages. However, we assume that this assessment of usual intake corresponds to consumption in the last year and would not change very much within the time frame. Moreover, the questionnaire was not reassessed during the year-3 follow-up of the cohort, which does not allow us to assess beverage consumption consistency. Recent studies have shown that different brewing techniques and preparation methods can affect the quantity and quality of bioactive compounds and caffeine in coffee [93, 94]. This in turn can impact how much caffeine and other constituents an individual consumed per cup of coffee. Although information on coffee brewing methods, such as boiling, dripping, or percolating, is available in the WHI, we did not assess whether these various methods influenced the caffeine content of the beverage in the present analysis although it will be considered in later studies. The caffeine amount calculated in our study only includes those found in coffee and tea, which underestimates the total amount of caffeine consumed by a given person from other additional food sources, such as soft drinks or chocolate. This underestimation of caffeine may lead to misclassification bias from measurement error since not all caffeine-containing beverages and foods were accounted for in the calculation of the total caffeine variable. Nevertheless, the caffeine contents of soft drinks, chocolate, and other foods is far lower than that of coffee and tea [95]. This is relative to the amount of each foods an individual consumes. Additionally, adults >51 years old consume most of their caffeine from

coffee and tea. Therefore, the caffeine intake from coffee and tea may be a close representation of the total amount of caffeine consumed in this cohort although further studies will need to be done to account for the potential misclassification bias, such as controlling for the other caffeinated drinks and foods. Participants of the WHI OS prospective cohort are more likely to be non-Hispanic white and educated, and consumed less caffeine at baseline compared to other studies [46, 47, 52]. For example, 40.5% of our participants did not consume caffeinated coffee whereas 39% of women consumed 2-3 cups/d in the NIH-AARP cohort. Due to these characteristics of our participants, our findings may not be representative of the general population of postmenopausal women. Our study was also unable to differentiate whether the effects of coffee and tea on invasive breast cancer incidence is due to caffeine-specific effects or other substances within the beverages.

Despite these limitations, our study is strengthened by its large size and prospective nature, which provided more power and allowed for the measurement of temporality and incidence of invasive breast cancer. The WHI is a unique cohort that includes postmenopausal women from multiple racial/ethnic groups and geographic sites from across the United States. Cases of invasive breast cancer were also reviewed and adjudicated by physicians. The availability of a comprehensive dataset afforded us the ability to investigate the multiple subtypes of breast cancer, types of caffeinated beverages.

Caffeine is a widely consumed food constituent, and its effects on overall health has become an important topic in public health and research. Other recent studies in the Women's Health Initiative have investigated the association between caffeine or coffee consumption and multiple disease processes, such as hypertension, cognitive impairment, sudden cardiac death, and endometrial cancer [89, 96-98]. These studies have shown caffeine consumption to be

inversely related to age-related cognitive impairment or endometrial cancer risk and not associated with risk of hypertension or sudden cardiac death in postmenopausal women. Nevertheless, continued research is necessary to further understand how caffeine influences the development and progression of different disease processes. Our study will contribute to the current body of knowledge on caffeine consumption from coffee and tea sources and invasive breast cancer incidence.

CONCLUSION

In conclusion, we did not find evidence of an association between caffeine intake from coffee and tea and invasive breast cancer incidence. However, there was some evidence of an association of caffeine intake with a reduced risk of ER+/PR- invasive breast cancers. Conversely, caffeinated and decaffeinated coffee were associated with a weak increase in incidence of total invasive breast cancer. Further research is warranted to confirm these findings.

TABLES

Table 1. Characteristics of study participants overall and by invasive breast cancer case and non-case status in the Women's Health Initiative Observational Study

Characteristic	Overall N (%)	Cancer case N (%)	Non-case N (%)	P [a]
Total	79,871	4719 (5.9)	75,152 (94.1)	
Age, y, mean (SD)	63.4 (7.3)	63.2 (7.0)	63.4 (7.5)	0.1788
49 – 59	26201 (32.8)	1517 (32.2)	24684 (32.9)	0.0001
60 – 69	35227 (44.1)	2208 (46.8)	33019 (43.9)	
70 – 81	18443 (23.1)	994 (21.1)	17449 (23.2)	
Race/Ethnicity				
Non-Hispanic White	66340 (83.3)	4190 (89.0)	62150 (82.9)	<0.0001
Black	6540 (8.2)	256 (5.4)	6284 (8.4)	
Hispanic	3087 (3.9)	105 (2.2)	2982 (4.0)	
Other	3694 (4.6)	157 (3.3)	3537 (4.7)	
Missing	*210 (0.3)*	*11 (0.2)*	*199 (0.3)*	
Education				
0 – 8y	1297 (1.6)	25 (0.5)	1272 (1.7)	<0.0001
Some high school	2702 (3.4)	107 (2.3)	2595 (3.5)	
High school diploma/GED	12939 (16.3)	662 (14.1)	12277 (16.5)	
School after high school	28819 (36.4)	1598 (34.1)	27221 (36.5)	
College degree or higher	33474 (42.3)	2294 (49.0)	31180 (41.8)	
Missing	*640 (0.8)*	*33 (0.7)*	*607 (0.8)*	
BMI, kg/m^2, mean (SD)	27.2 (5.8)	27.3 (5.7)	27.2 (5.9)	0.2222
Underweight, <18.5	943 (1.2)	36 (0.8)	907 (1.2)	0.0484
Normal, 18.5 – 24.9	31561 (40.0)	1873 (40.1)	29688 (40.0)	
Overweight, 25 – 29.9	26908 (34.1)	1582 (33.9)	25326 (35.0)	
Obese, ≥30	19536 (24.8)	1175 (25.2)	18361 (24.7)	
Missing	*923 (1.2)*	*53 (1.1)*	*870 (1.2)*	
Smoking				
Never smoker	40419 (51.3)	2227 (47.8)	38192 (51.5)	<0.0001
Past smoker	33495 (42.5)	2158 (46.3)	31337 (42.3)	
Current smoker	4883 (6.2)	272 (5.8)	4611 (6.1)	
Missing	*1074 (1.3)*	*62 (1.3)*	*1012 (1.4)*	
Pack-years of Smoking, mean (SD)	9.7 (18.3)	10.8 (19.0)	9.6 (18.2)	<0.0001
Never smoker	40419 (52.5)	2227 (48.9)	38192 (52.7)	<0.0001
>0 – 4.9	11435 (14.9)	682 (15.0)	10753 (14.8)	
5 – 19.9	11054 (14.4)	725 (15.9)	10329 (14.3)	
≥20	14086 (18.3)	920 (20.2)	13166 (18.2)	
Missing	*2877 (3.6)*	*165 (3.5)*	*2712 (3.6)*	
Total Energy Intake, kcal, mean (SD)	1547.3 (692.9)	1578.6 (635.2)	1545.4 (696.3)	0.0005
Alcohol Intake				
Never drinker	8977 (11.3)	428 (9.1)	8549 (11.4)	<0.0001
Past drinker	14696 (18.5)	742 (15.8)	13954 (18.7)	
Current drinker, <7 drinks/week	45720 (57.6)	2762 (58.8)	42958 (57.5)	
Current drinker, 7+ drinks/week	10005 (12.6)	767 (16.3)	9238 (12.4)	
Missing	*473 (0.6)*	*20 (0.4)*	*453 (0.6)*	
Total Recreational Activity, MET-hr/wk, mean (SD)	13.8 (14.4)	13.8 (13.6)	13.8 (14.4)	0.9212
No activity	10674 (13.5)	571 (12.2)	10103 (13.6)	0.0397
>0 – 6.8	20445 (25.9)	1194 (25.6)	19251 (25.9)	
6.8 – 16.6	23021 (29.2)	1385 (29.7)	21636 (29.1)	
≥16.7	24845 (31.5)	1516 (32.5)	23329 (31.4)	
Missing	*886 (1.1)*	*53 (1.1)*	*833 (1.1)*	
Family History of Breast Cancer				
No	62663 (81.6)	3475 (76.2)	59188 (81.9)	<0.0001
Yes	14150 (18.4)	1088 (23.8)	13062 (18.1)	
Missing	*3058 (3.8)*	*156 (3.3)*	*2902 (3.9)*	
Oral Contraceptive Use Ever				

No	47324 (59.3)	2706 (57.3)	44618 (59.4)	0.006
Yes	32547 (40.8)	2013 (42.7)	30534 (40.6)	
History of HT Use [b]				
Never	31345 (39.3)	1610 (34.2)	29735 (39.6)	<0.0001
Former	10880 (13.6)	601 (12.8)	10279 (13.7)	
Current	37572 (47.1)	2501 (53.1)	35071 (46.7)	
Missing	*74 (0.1)*	*7 (0.2)*	*67 (0.1)*	
History of Unopposed E Use [b]				
Never	50392 (63.1)	3041 (64.5)	47351 (63.1)	0.0215
Former	9049 (11.3)	552 (11.7)	8497 (11.3)	
Current	20376 (25.5)	1124 (23.8)	19252 (25.6)	
Missing	*54 (0.1)*	*2 (0.04)*	*52 (0.1)*	
History of E + P Use [b]				
Never	55955 (70.1)	2943 (62.4)	53012 (70.6)	<0.0001
Former	6690 (8.4)	394 (8.4)	6296 (8.4)	
Current	17196 (21.5)	1377 (29.2)	15819 (21.1)	
Missing	*30 (0.04)*	*5 (0.1)*	*25 (0.03)*	
Age at Menarche				
≥9 – 11	17442 (21.9)	1087 (23.1)	16355 (21.9)	0.0263
12 – 13	43890 (55.2)	2598 (55.3)	41292 (55.2)	
≥14	18219 (22.9)	1013 (21.6)	17206 (23.0)	
Missing	*320 (0.4)*	*21 (0.5)*	*299 (0.4)*	
Age at Menopause, y, mean (SD)	48.28 (6.3)	48.8 (5.9)	48.3 (6.3)	<0.0001
<40	6717 (8.8)	307 (6.7)	6410 (8.9)	<0.0001
40 – 49	29784 (38.9)	1697 (37.1)	28087 (39.0)	
≥50	40146 (52.4)	2570 (56.2)	37576 (52.1)	
Missing	*3224 (4.0)*	*145 (3.1)*	*3079 (4.1)*	
Age at First Birth [c]				
<20	8928 (11.3)	433 (9.2)	8495 (11.4)	<0.0001
20 – 29	54380 (68.6)	3151 (67.3)	51229 (68.7)	
≥30	6028 (7.6)	423 (9.0)	5605 (7.5)	
Never had term pregnancy	2170 (2.7)	143 (3.1)	2027 (2.7)	
Never pregnant	7806 (9.8)	535 (11.4)	7271 (9.7)	
Missing	*559 (0.7)*	*34 (0.7)*	*525 (0.7)*	
Number of Live Births				
None	2279 (2.9)	148 (3.2)	2131 (2.9)	<0.0001
1	7362 (9.3)	432 (9.2)	6930 (9.3)	
2 – 4	51921 (65.5)	3093 (66.0)	48828 (65.4)	
≥5	9944 (12.5)	9944 (12.5)	9467 (12.7)	
Never pregnant	7806 (9.8)	535 (11.4)	7271 (9.7)	
Missing	*559 (0.7)*	*34 (0.7)*	*525 (0.7)*	
Sleep Duration, hrs/day, N (%)				
≤5	7529 (9.5)	344 (7.3)	7185 (9.6)	<0.0001
6-7	21918 (27.6)	1204 (25.6)	20714 (27.7)	
8-9	36287 (45.7)	2258 (48.0)	34029 (45.5)	
≥10	13763 (17.3)	897 (19.1)	12866 (17.2)	
Missing	*374 (0.5)*	*16 (0.3)*	*358 (0.5)*	
Caffeine Intake [d], mg/d, mean (SD)	166.09 (151.0)	169.6 (150.0)	165.9 (151.1)	0.0991
Quartile 1 (0 – 93 mg/d)	29748 (37.3)	1696 (35.9)	28052 (37.3)	0.2268
Quartile 2 (94 – 230 mg/d)	17938 (22.5)	1061 (22.5)	16877 (22.5)	
Quartile 3 (231 – 278epic mg/d)	14852 (18.6)	907 (19.2)	13945 (18.6)	
Quartile 4 (279 – 736mg/d)	17333 (21.7)	1055 (22.4)	16278 (21.7)	
Coffee Intake [e]				
No	22965 (28.8)	1277 (27.1)	21688 (28.9)	0.0078
Yes	56779 (71.1)	3436 (72.8)	53343 (71.0)	

[a] P-value between cases and non-cases calculated from t-tests for continuous variables and chi-square tests for categorical variables
[b] HT = hormone therapy; unopposed E use = unopposed estrogen use; E + P use = estrogen + progesterone use
[c] Age at first birth missing N = 15,986 (19.91%) and was imputed with the most common response of those who responded the number of live births variable
[d] Total beverage caffeine intake (mg/d) from coffee and tea at baseline
[e] Includes caffeinated and decaffeinated coffee consumption at baseline

Table 2. Characteristics of study participants by beverage caffeine intake at baseline in the Women's Health Initiative Observational Study

Characteristic	Overall N (%)	Caffeine Intake, mg/d [a] Quartile 1 0 – 93mg/d N (%)	Quartile 2 94 – 230mg/d N (%)	Quartile 3 231 – 278mg/d N (%)	Quartile 4 279 – 736mg/d N (%)	P [b]
Total	79871	29748 (37.3)	17938 (22.5)	14852 (18.6)	17333 (21.7)	
Age, y, mean (SD)	63.4 (7.3)	63.3 (7.4)	63.7 (7.4)	63.3 (7.3)	63.2 (7.2)	<0.0001
49 – 59	26201 (32.8)	9894 (33.3)	5577 (31.1)	5000 (33.7)	5730 (33.1)	<0.0001
60 – 69	35227 (44.1)	12909 (43.4)	7912 (44.1)	6473 (43.6)	7933 (45.8)	
70 – 81	18443 (23.1)	6945 (23.4)	4449 (24.8)	3379 (22.8)	3670 (21.2)	
Race/Ethnicity						
Non-Hispanic White	66340 (83.3)	23570 (79.5)	14535 (81.3)	12580 (84.9)	15655 (90.5)	<0.0001
Black	6540 (8.2)	3689 (12.4)	1461 (8.2)	902 (6.1)	488 (2.8)	
Hispanic	3087 (3.9)	1011 (3.4)	844 (4.7)	685 (4.6)	547 (3.2)	
Other	3694 (4.6)	1398 (4.7)	1045 (5.8)	648 (4.4)	603 (3.5)	
Missing	*210 (0.3)*	*80 (0.3)*	*53 (0.3)*	*37 (0.3)*	*40 (0.2)*	
Education						
0 – 8y	1297 (1.6)	473 (1.6)	305 (1.7)	250 (1.7)	269 (1.6)	<0.0001
Some high school	2702 (3.4)	999 (3.4)	584 (3.3)	531 (3.6)	588 (3.4)	
High school diploma/GED	12939 (16.3)	4788 (16.2)	2763 (15.5)	2478 (16.8)	2910 (16.9)	
School after high school	28819 (36.4)	10450 (35.4)	6347 (35.7)	5581 (37.8)	6441 (37.4)	
College degree or higher	33474 (42.3)	12789 (43.4)	7778 (43.8)	5911 (40.1)	6996 (40.7)	
Missing	*640 (0.8)*	*249 (0.8)*	*161 (0.9)*	*101 (0.7)*	*129 (0.7)*	
BMI, kg/m^2, mean (SD)	27.2 (5.8)	27.4 (6.1)	27.1 (5.8)	27.2 (5.7)	27.0 (5.5)	<0.0001
Underweight, <18.5	943 (1.2)	390 (1.3)	210 (1.2)	125 (0.9)	218 (1.3)	<0.0001
Normal, 18.5 – 24.9	31561 (40.0)	11642 (39.6)	7343 (41.4)	5750 (39.2)	6826 (39.8)	
Overweight, 25 – 29.9	26908 (34.1)	9702 (33.0)	5925 (33.4)	5162 (35.2)	6119 (35.7)	
Obese, ≥30	19536 (24.8)	7666 (26.1)	4245 (24.0)	3631 (24.8)	3994 (23.4)	
Missing	*923 (1.2)*	*348 (1.2)*	*215 (1.2)*	*184 (1.2)*	*176 (1.0)*	
Smoking						
Never smoker	40419 (51.3)	16880 (57.5)	9610 (54.4)	6649 (45.4)	7280 (42.6)	<0.0001
Past smoker	33495 (42.5)	11463 (39.0)	7265 (41.1)	6837 (46.7)	7930 (46.4)	
Current smoker	4883 (6.2)	1037 (3.5)	794 (4.5)	1165 (8.0)	1887 (11.0)	
Missing	*1074 (1.3)*	*368 (1.2)*	*269 (1.5)*	*201 (1.4)*	*236 (1.4)*	
Pack-years of Smoking, mean (SD)	9.7 (18.3)	7.6 (16.3)	8.3 (16.8)	11.1 (19.0)	13.5 (21.4)	<0.0001
Never smoker	40419 (52.5)	16880 (58.7)	9610 (55.7)	6649 (46.5)	7280 (43.7)	<0.0001
>0 – 4.9	11435 (14.9)	4094 (14.2)	2634 (15.3)	2250 (15.7)	2457 (14.7)	
5 – 19.9	11054 (14.4)	3743 (13.0)	2345 (13.6)	2342 (16.4)	2624 (15.7)	
≥20	14086 (18.3)	4048 (14.1)	2672 (15.5)	3053 (21.4)	4313 (25.9)	
Missing	*2877 (3.6)*	*983 (3.3)*	*677 (3.8)*	*558 (3.8)*	*659 (3.8)*	
Total Energy Intake, kcal, mean (SD)	1547.3 (692.9)	1505.8 (681.3)	1531.4 (661.8)	1551.6 (690.4)	1631.5 (737.3)	<0.0001
Alcohol Intake						
Never drinker	8977 (11.3)	4502 (15.2)	2015 (11.3)	1108 (7.5)	1352 (7.8)	<0.0001
Past drinker	14696 (18.5)	6681 (22.6)	3027 (17.0)	2218 (15.0)	2770 (16.1)	
Current drinker, <7 drinks/week	45720 (57.6)	15885 (53.8)	10595 (59.5)	8775 (59.4)	10465 (60.7)	
Current drinker, 7+ drinks/week	10005 (12.6)	2486 (8.4)	2184 (12.3)	2672 (18.1)	2663 (15.4)	
Missing	*473 (0.6)*	*194 (0.7)*	*117 (0.7)*	*79 (0.5)*	*83 (0.5)*	
Total Recreational Activity, MET-hr/wk, mean (SD)	13.8 (14.4)	14.2 (14.7)	13.6 (14.1)	13.3 (14.2)	13.7 (14.3)	<0.0001
No activity, N (%)	10674 (13.5)	3883 (13.2)	2376 (13.4)	2129 (14.5)	2286 (13.3)	<0.0001
>0 – 6.8	20445 (25.9)	7355 (25.0)	4617 (26.0)	3947 (26.9)	4526 (26.4)	
6.8 – 16.6	23021 (29.2)	8506 (28.9)	5251 (29.6)	4231 (28.8)	5033 (29.4)	
≥16.7	24845 (31.5)	9665 (32.9)	5512 (31.0)	4376 (29.8)	5292 (30.9)	
Missing	*886 (1.1)*	*339 (1.1)*	*182 (1.0)*	*169 (1.1)*	*196 (1.1)*	
Family History of Breast Cancer						
No	62663 (81.6)	23165 (81.0)	14087 (81.8)	11709 (81.7)	13702 (82.2)	0.0145
Yes	14150 (18.4)	5424 (19.0)	3129 (18.2)	2625 (18.3)	2972 (17.8)	
Missing	*3058 (3.8)*	*1159 (3.9)*	*722 (4.0)*	*518 (3.5)*	*659 (3.8)*	
Oral Contraceptive Use Ever						
No	47324 (59.3)	17752 (59.7)	10776 (60.1)	8602 (57.9)	10194 (58.8)	0.0002

Yes	32547 (40.8)	11996 (40.3)	7162 (39.9)	6250 (42.1)	7139 (41.2)	
History of HT Use [c]						
Never	31345 (39.3)	11586 (39.0)	6932 (38.7)	5685 (38.3)	7142 (41.2)	<0.0001
Former	10880 (13.6)	4051 (13.6)	2465 (13.8)	1971 (13.3)	2393 (13.8)	
Current	37572 (47.1)	14080 (47.4)	8523 (47.6)	7183 (48.4)	7786 (45.0)	
Missing	*74 (0.1)*	*31 (0.1)*	*18 (0.1)*	*13 (0.1)*	*12 (0.1)*	
History of Unopposed E Use [c]						
Never	50392 (63.1)	18395 (61.9)	11189 (62.4)	9416 (63.4)	11392 (65.8)	<0.0001
Former	9049 (11.3)	3412 (11.5)	2044 (11.4)	1620 (10.9)	1973 (11.4)	
Current	20376 (25.5)	7917 (26.6)	4691 (26.2)	3809 (25.7)	3959 (22.9)	
Missing	*54 (0.1)*	*24 (0.1)*	*14 (0.1)*	*7 (0.1)*	*9 (0.1)*	
History of E + P Use [c]						
Never	55955 (70.1)	21153 (71.1)	12557 (70.0)	10207 (68.8)	12038 (69.5)	<0.0001
Former	6690 (8.4)	2421 (8.1)	1543 (8.6)	1263 (8.5)	1463 (8.4)	
Current	17196 (21.5)	6163 (20.7)	3832 (21.4)	3374 (22.7)	3827 (22.1)	
Missing	*30 (0.04)*	*11 (0.04)*	*6 (0.03)*	*8 (0.1)*	*5 (0.03)*	
Age at Menarche						
≥9 – 11	17442 (21.9)	6497 (21.9)	3780 (21.2)	3197 (21.6)	3968 (23.0)	0.0010
12 – 13	43890 (55.2)	16334 (55.1)	9882 (55.3)	8259 (55.8)	9415 (54.5)	
≥14	18219 (22.9)	6790 (22.9)	4212 (23.6)	3339 (22.6)	3878 (22.5)	
Missing	*320 (0.4)*	*127 (0.4)*	*64 (0.4)*	*57 (0.4)*	*72 (0.4)*	
Age at Menopause, y, mean (SD)	48.28 (6.3)	48.17 (6.4)	48.38 (6.3)	48.25 (6.3)	48.40 (6.2)	0.0002
<40	6717 (8.8)	2660 (9.3)	1466 (8.5)	1208 (8.5)	1383 (8.3)	0.0004
40 – 49	29784 (38.9)	11057 (38.8)	6617 (38.4)	5644 (39.7)	6466 (38.8)	
≥50	40146 (52.4)	14811 (51.9)	9134 (53.1)	7373 (51.8)	8828 (52.9)	
Missing	*3224 (4.0)*	*1220 (4.1)*	*721 (4.0)*	*627 (4.2)*	*656 (3.8)*	
Age at First Birth [d]						
<20	8928 (11.3)	3231 (10.9)	1880 (10.6)	1794 (12.2)	2023 (11.8)	<0.0001
20 – 29	54380 (68.6)	20181 (68.3)	12241 (68.7)	10124 (68.6)	11834 (68.8)	
≥30	6028 (7.6)	2266 (7.7)	1451 (8.1)	1085 (7.4)	1226 (7.1)	
Never had term pregnancy	2170 (2.7)	840 (2.8)	491 (2.8)	419 (2.8)	420 (2.4)	
Never pregnant	7806 (9.8)	3023 (10.2)	1753 (9.8)	1333 (9.0)	1697 (9.9)	
Missing	*559 (0.7)*	*207 (0.7)*	*122 (0.7)*	*97 (0.7)*	*133 (0.8)*	
Number of Live Births						
None	2279 (2.9)	887 (3.0)	512 (2.9)	429 (2.9)	451 (2.6)	<0.0001
1	7362 (9.3)	2857 (9.7)	1681 (9.4)	1348 (9.1)	1476 (8.6)	
2 – 4	51921 (65.5)	19192 (65.0)	11658 (65.4)	9801 (66.4)	11270 (65.5)	
≥5	9944 (12.5)	3582 (12.1)	2212 (12.4)	1844 (12.5)	2306 (13.4)	
Never pregnant	7806 (9.8)	3023 (10.2)	1753 (9.8)	1333 (9.0)	1697 (9.9)	
Missing	*559 (0.7)*	*207 (0.7)*	*122 (0.7)*	*97 (0.7)*	*133 (0.8)*	
Sleep Duration, hrs/day, N (%)						
≤5	7529 (9.5)	2958 (10.0)	1771 (9.9)	1319 (8.9)	1481 (8.6)	<0.0001
6-7	21918 (27.6)	8175 (27.6)	4763 (26.7)	4017 (27.2)	4963 (28.8)	
8-9	36287 (45.7)	13197 (44.6)	8183 (45.9)	6819 (46.1)	8088 (46.9)	
≥10	13763 (17.3)	5269 (17.8)	3125 (17.5)	2641 (17.9)	2728 (15.8)	
Missing	*374 (0.5)*	*149 (0.5)*	*96 (0.5)*	*56 (0.4)*	*73 (0.4)*	

[a] Total beverage caffeine intake (mg/d) from coffee and tea at baseline

[b] P-value for differences between quintiles of caffeine intake calculated from ANOVA tests for continuous variables and chi-square tests for categorical variables

[c] HT = hormone therapy; unopposed E use = unopposed estrogen use; E + P use = estrogen + progesterone use

[d] Age at first birth missing N = 15,986 (19.91%) and was imputed with the most common response of those who responded the number of live births variable

Table 3. Associations between beverage caffeine intake at baseline and risk of total invasive breast cancer in the Women's Health Initiative Observational Study

		Caffeine Intake, mg/d [a]				
Total Invasive Breast Cancer	**Overall**	**Quartile 1** 0 – 93mg/d	**Quartile 2** 94 – 230mg/d	**Quartile 3** 213 – 278mg/d	**Quartile 4** 279 – 736mg/d	**P-for-trend**
No. Cases (%)	4719	1696 (35.9)	1061 (22.5)	907 (19.2)	1055 (22.4)	
Model 1 Adjusted HR[b] (95% CI)		*Referent*	1.04 (0.96, 1.12)	1.07 (0.98, 1.16)	1.05 (0.97, 1.13)	0.15
Model 2 Adjusted HR[c] (95% CI)		*1*	1.04 (0.96, 1.12)	1.07 (0.98, 1.16)	1.04 (0.96, 1.12)	0.20
Model 3 Adjusted HR[d] (95% CI)		*1*	1.01 (0.93, 1.09)	1.02 (0.94, 1.12)	1.00 (0.93, 1.09)	0.81
Model 4 Adjusted HR[e] (95% CI)		*1*	1.05 (0.97, 1.13)	1.08 (0.99, 1.18)	1.07 (0.99, 1.16)	0.06

		Coffee Intake [f]		
Total Invasive Breast Cancer	**Overall**	**No**	**Yes**	**P-value**
No. Cases (%)	4713	1277 (27.1)	3436 (72.9)	
Model 1 Adjusted HR[b] (95% CI)		*Referent*	**1.07 (1.01, 1.15)**	**0.02**
Model 2 Adjusted HR[c] (95% CI)		*1*	1.06 (1.00, 1.14)	0.06
Model 3 Adjusted HR[d] (95% CI)		*1*	1.02 (0.95, 1.09)	0.68
Model 4 Adjusted HR[e] (95% CI)		*1*	1.07 (1.00, 1.14)	0.06

[a] Total beverage caffeine intake (mg/d) from coffee and tea at baseline
[b] Model 1 is the crude model
[c] Model 2 adjusted for age, race/ethnicity, and education
[d] Model 3 adjusted for variables adjusted in Model 2, smoking, pack-years of smoking (continuous), alcohol intake, total energy intake (continuous), recreational physical activity (continuous), BMI (continuous), and sleep duration
[e] Model 4 adjusted for variables adjusted in Model 2, family history of breast cancer, OC use, history of unopposed E use, history of E + P use, age at menarche, age at menopause (continuous), age at first birth, and number of live births
[f] Includes caffeinated and decaffeinated coffee consumption at baseline

Table 4. Associations between caffeine intake at baseline by beverage caffeine type and risk of total invasive breast cancer in the Women's Health Initiative Observational Study

Beverage Type [a]	Total	Cancer cases	Non-cases	Model 1 Crude HR [b] (95% CI)	Model 2 Adjusted HR [c] (95% CI)	Model 3 Adjusted HR [d] (95% CI)	Model 4 Adjusted HR [e] (95% CI)
	N (%)	N (%)	N (%)				
Total	79,871	4,719	75,152				
Caffeinated Coffee, cups/day							
Overall	38860	2253	36607				
None	15736 (40.5)	845 (37.5)	14891 (40.7)	*Referent*	*1*	*1*	*1*
1	5463 (14.1)	318 (14.1)	5145 (14.1)	1.11 (0.97, 1.26)	1.10 (0.97, 1.26)	1.04 (0.91, 1.19)	1.12 (0.98, 1.28)
2-3	12681 (32.6)	788 (35.0)	11893 (32.5)	**1.14 (1.03, 1.25)**	**1.12 (1.02, 1.24)**	1.05 (0.95, 1.17)	**1.12 (1.01, 1.24)**
≥4	4969 (12.8)	302 (13.4)	4667 (12.8)	1.10 (0.96, 1.25)	1.08 (0.95, 1.24)	1.02 (0.88, 1.17)	1.09 (0.95, 1.26)
Missing	*11 (0.03)*	*0*	*11 (0.03)*				
P-for-trend				**0.02**	**0.05**	0.53	**0.05**
Decaffeinated Coffee, cups/day	N (%)	N (%)	N (%)				
Overall	24632	1410	23222				
None	15736 (63.9)	845 (59.9)	14891 (64.1)	*Referent*	*1*	*1*	*1*
1	2975 (12.1)	167 (11.8)	2808 (12.1)	1.04 (0.88, 1.23)	1.01 (0.86, 1.20)	0.98 (0.82, 1.17)	1.01 (0.85, 1.20)
2-3	4465 (18.1)	315 (22.3)	4150 (17.9)	**1.27 (1.12, 1.45)**	**1.24 (1.09, 1.41)**	**1.18 (1.03, 1.36)**	**1.17 (1.03, 1.35)**
≥4	1428 (5.8)	82 (5.8)	1346 (5.8)	1.01 (0.81, 1.27)	0.97 (0.77, 1.22)	0.95 (0.75, 1.21)	0.93 (0.73, 1.18)
Missing	*28 (0.1)*	*1 (0.1)*	*27 (0.1)*				
P-for-trend				**0.01**	**0.05**	0.20	0.24
Tea, cups/day	N (%)	N (%)	N (%)				
Overall	23106	1285	21821				
None	15736 (68.1)	845 (65.8)	14891 (68.2)	*Referent*	*1*	*1*	*1*
1	2592 (11.2)	143 (11.1)	2449 (11.2)	1.00 (0.84, 1.20)	0.96 (0.81, 1.16)	0.97 (0.81, 1.17)	0.94 (0.78, 1.14)
2-3	3248 (14.1)	196 (15.3)	3052 (14.0)	1.09 (0.94, 1.28)	1.07 (0.92, 1.26)	1.06 (0.90, 1.24)	1.03 (0.87, 1.21)
≥4	1278 (5.5)	83 (6.5)	1195 (5.5)	1.17 (0.94, 1.47)	1.16 (0.92, 1.45)	1.19 (0.95, 1.50)	1.19 (0.94, 1.50)
Missing	*252 (1.1)*	*18 (1.4)*	*234 (1.1)*				
P-for-trend				0.11	0.19	0.19	0.31

[a] Participants drinking either of the other beverage types have been excluded from each beverage analysis. Those included are exclusive drinkers of such beverage.
[b] Model 1 is the unadjusted, crude model
[c] Model 2 adjusted for age, race/ethnicity, education, and other caffeinated beverages
[d] Model 3 adjusted for variables adjusted in Model 2, smoking, pack-years of smoking (continuous), alcohol intake, total energy intake (continuous), recreational physical activity (continuous), BMI (continuous), and sleep duration
[e] Model 4 adjusted for variables adjusted in Model 2, family history of breast cancer, OC use, history of unopposed E use, history of E + P use, age at menarche, age at menopause (continuous), age at first birth, and number of live births

Table 5. Associations between total caffeine intake at baseline and risk of total breast cancer among race/ethnicity, age, smoking status, BMI, sleep duration, and history HT use subgroups in the Women's Health Initiative Observational Study

RACE/ETHNICITY

Caffeine Intake, mg/d[a]	No. Cases (%)	Model 1 Crude HR[b] (95% CI)	Model 2 Adjusted HR[c] (95% CI)	Model 3 Adjusted HR[d] (95% CI)	Model 4 Adjusted HR[e] (95% CI)
			Non-Hispanic White		
Overall	4190				
Quartile 1	1452 (34.7)	*Referent*	*1*	*1*	*1*
Quartile 2	941 (22.5)	1.05 (0.97, 1.14)	1.05 (0.97, 1.14)	1.03 (0.94, 1.12)	1.06 (0.97, 1.15)
Quartile 3	815 (19.5)	1.06 (0.97, 1.15)	1.06 (0.97, 1.16)	1.02 (0.93, 1.12)	1.08 (0.99, 1.18)
Quartile 4	982 (23.4)	1.02 (0.94, 1.11)	1.03 (0.95, 1.12)	1.00 (0.91, 1.08)	1.06 (0.98, 1.16)
P-for-trend		0.53	0.40	0.95	0.11
			Black		
Overall	256				
Quartile 1	138 (53.9)	*Referent*	*1*	*1*	*1*
Quartile 2	59 (23.1)	1.09 (0.80, 1.48)	1.10 (0.81, 1.50)	1.06 (0.77, 1.45)	1.18 (0.86, 1.62)
Quartile 3	39 (15.2)	1.16 (0.81, 1.65)	1.18 (0.83, 1.68)	1.08 (0.73, 1.57	1.08 (0.73, 1.59)
Quartile 4	20 (7.8)	1.06 (0.66, 1.69)	1.05 (0.65, 1.69)	1.02 (0.62, 1.68)	0.99 (0.59, 1.67)
P-for-trend		0.50	0.47	0.76	0.74
			Hispanic		
Overall	105				
Quartile 1	39 (37.1)	*Referent*	*1*	*1*	*1*
Quartile 2	21 (20.0)	0.67 (0.40, 1.15)	0.69 (0.41, 1.17)	0.59 (0.34, 1.02)	0.72 (0.40, 1.28)
Quartile 3	25 (23.8)	1.00 (0.61, 1.65)	1.01 (0.61, 1.66)	0.92 (0.55, 1.54)	1.18 (0.69, 2.01)
Quartile 4	20 (19.1)	0.99 (0.58, 1.70)	1.01 (0.59, 1.73)	0.88 (0.50, 1.56)	1.09 (0.61, 1.94)
P-for-trend		0.86	0.82	0.79	0.51
			Other		
Overall	157				
Quartile 1	62 (39.5)	*Referent*	*1*	*1*	*1*
Quartile 2	37 (23.6)	0.83 (0.55, 1.25)	0.82 (0.55, 1.24)	0.78 (0.51, 1.20)	0.84 (0.55, 1.29)
Quartile 3	27 (17.2)	0.93 (0.59, 1.46)	0.93 (0.59, 1.46)	0.97 (0.61, 1.55)	0.95 (0.60, 1.51)
Quartile 4	31 (19.8)	1.13 (0.73, 1.73)	1.14 (0.74, 1.75)	1.13 (0.72, 1.78)	1.22 (0.78, 1.90)
P-for-trend		0.67	0.65	0.62	0.48
P-for-interaction		0.52	0.52	0.62	0.56

AGE AT BASELINE

			49 – 59 years		
Overall	1517				
Quartile 1	530 (34.9)	*Referent*	*1*	*1*	*1*
Quartile 2	338 (22.3)	1.13 (0.99, 1.30)	1.12 (0.98, 1.29)	1.09 (0.95, 1.26)	1.11 (0.96, 1.28)
Quartile 3	298 (19.6)	1.11 (0.96, 1.28)	1.11 (0.96, 1.28)	1.03 (0.89, 1.20)	1.15 (0.99, 1.33)
Quartile 4	351 (23.1)	1.13 (0.98, 1.29)	1.11 (0.97, 1.28)	1.08 (0.94, 1.24)	**1.16 (1.01, 1.33)**
P-for-trend		0.08	0.11	0.37	0.03
			60 – 69 years		
Overall	2208				
Quartile 1	791 (35.8)	*Referent*	*1*	*1*	*1*
Quartile 2	502 (22.7)	1.04 (0.93, 1.17)	1.05 (0.94, 1.18)	1.02 (0.91, 1.15)	1.05 (0.94, 1.18)
Quartile 3	426 (19.3)	1.08 (0.96, 1.21)	1.08 (0.96, 1.21)	1.05 (0.93, 1.19)	1.07 (0.95, 1.21)
Quartile 4	489 (22.2)	0.99 (0.89, 1.11)	0.98 (0.88, 1.10)	0.94 (0.84, 1.06)	0.99 (0.88, 1.11)
P-for-trend		0.85	0.99	0.50	0.94
			70 – 81 years		
Overall	994				
Quartile 1	375 (37.7)	*Referent*	*1*	*1*	*1*
Quartile 2	221 (22.2)	0.90 (0.76, 1.06)	0.90 (0.76, 1.06)	0.88 (0.74, 1.05)	0.94 (0.79, 1.12)
Quartile 3	183 (18.4)	0.98 (0.83, 1.17)	0.99 (0.83, 1.18)	0.96 (0.80, 1.15)	1.01 (0.83, 1.21)
Quartile 4	215 (21.6)	1.06 (0.90, 1.25)	1.06 (0.90, 1.25)	1.03 (0.86, 1.23)	1.11 (0.93, 1.32)
P-for-trend		0.49	0.50	0.75	0.27
P-for-interaction		0.24	0.26	0.55	0.51

SMOKING					
			Never Smoker		
Overall	2227				
Quartile 1	944 (42.4)	*Referent*	*1*	*1*	*1*
Quartile 2	512 (23.0)	0.95 (0.85, 1.06)	0.95 (0.85, 1.06)	0.93 (0.84, 1.04)	0.96 (0.86, 1.08)
Quartile 3	356 (16.0)	0.95 (0.84, 1.07)	0.95 (0.84, 1.08)	0.95 (0.83, 1.07)	0.97 (0.86, 1.10)
Quartile 4	415 (18.6)	0.99 (0.88, 1.11)	0.98 (0.88, 1.10)	0.98 (0.87, 1.11)	0.99 (0.88, 1.12)
P-for-trend		0.70	0.62	0.61	0.81
			Former Smoker		
Overall	2158				
Quartile 1	682 (31.6)	*Referent*	*1*	*1*	*1*
Quartile 2	488 (22.6)	**1.13 (1.01, 1.27)**	**1.12 (1.00, 1.26)**	1.11 (0.98, 1.25)	**1.13 (1.00, 1.27)**
Quartile 3	464 (21.5)	**1.13 (1.00, 1.27)**	**1.13 (1.00, 1.27)**	1.09 (0.96, 1.23)	1.12 (0.99, 1.27)
Quartile 4	524 (24.3)	1.08 (0.96, 1.21)	1.07 (0.95, 1.20)	1.06 (0.94, 1.20)	1.10 (0.98, 1.24)
P-for-trend		0.16	0.19	0.32	0.10
			Current Smoker		
Overall	272				
Quartile 1	50 (18.4)	*Referent*	*1*	*1*	*1*
Quartile 2	44 (16.2)	1.17 (0.78, 1.76)	1.16 (0.77, 1.74)	1.07 (0.71, 1.62)	1.21 (0.78, 1.87)
Quartile 3	78 (28.7)	1.40 (0.98, 2.00)	1.37 (0.95, 1.95)	1.24 (0.86, 1.78)	**1.50 (1.02, 2.20)**
Quartile 4	100 (36.8)	1.09 (0.77, 1.52)	1.05 (0.74, 1.48)	0.98 (0.69, 1.39)	1.18 (0.82, 1.70)
P-for-trend		0.66	0.82	0.92	0.40
P-for-interaction		0.52	0.40	0.34	0.26
BMI, kg/m^2					
			Underweight, <18.5		
Overall	943				
Quartile 1	19 (52.8)	*Referent*	*1*	*1*	*1*
Quartile 2	5 (13.9)	0.50 (0.19, 1.33)	0.56 (0.21, 1.52)	0.56 (0.21, 1.54)	0.56 (0.20, 1.53)
Quartile 3	4 (11.1)	0.64 (0.22, 1.89)	0.65 (0.22, 1.91)	0.57 (0.19, 1.74)	0.75 (0.24, 2.30)
Quartile 4	8 (22.2)	0.75 (0.33, 1.72)	0.74 (0.32, 1.71)	0.62 (0.26, 1.50)	0.78 (0.33, 1.85)
P-for-trend		0.43	0.42	0.25	0.56
			Normal, 18.5 – 24.9		
Overall	1873				
Quartile 1	649 (34.7)	*Referent*	*1*	*1*	*1*
Quartile 2	421 (22.5)	1.03 (0.91, 1.17)	1.03 (0.91, 1.16)	0.99 (0.88, 1.13)	1.04 (0.92, 1.18)
Quartile 3	368 (19.7)	**1.16 (1.02, 1.32)**	**1.17 (1.03, 1.33)**	1.10 (0.96, 1.26)	**1.18 (1.04, 1.35)**
Quartile 4	435 (23.2)	**1.14 (1.01, 1.28)**	**1.14 (1.01, 1.29)**	1.08 (0.96, 1.22)	**1.19 (1.05, 1.35)**
P-for-trend		**0.01**	**0.01**	0.15	**0.002**
			Overweight, 25 – 29.9		
Overall	1582				
Quartile 1	583 (36.9)	*Referent*	*1*	*1*	*1*
Quartile 2	354 (22.4)	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)	0.97 (0.85, 1.11)	0.99 (0.86, 1.13)
Quartile 3	299 (18.9)	0.95 (0.83, 1.09)	0.95 (0.82, 1.09)	0.91 (0.78, 1.05)	0.96 (0.83, 1.11)
Quartile 4	346 (21.9)	0.92 (0.80, 1.05)	0.91 (0.80, 1.05)	0.88 (0.76, 1.01)	0.95 (0.83, 1.09)
P-for-trend		0.18	0.16	**0.04**	0.44
			Obese, ≥30		
Overall	1175				
Quartile 1	430 (36.6)	*Referent*	*1*	*1*	*1*
Quartile 2	263 (22.4)	1.11 (0.96, 1.30)	1.11 (0.96, 1.30)	1.11 (0.95, 1.30)	1.13 (0.96, 1.32)
Quartile 3	223 (19.0)	1.09 (0.92, 1.28)	1.08 (0.92, 1.28)	1.08 (0.91, 1.28)	1.08 (0.91, 1.28)
Quartile 4	259 (22.0)	1.12 (0.96, 1.30)	1.10 (0.94, 1.28)	1.09 (0.93, 1.28)	1.07 (0.91, 1.26)
P-for-trend		0.15	0.23	0.29	0.42
P-for-interaction		0.52	0.35	0.48	0.16
SLEEP DURATION					
			≤7 Hours		
Overall	1548				
Quartile 1	572 (37.0)	*Referent*	*1*	*1*	*1*

Quartile 2	332 (21.5)	1.00 (0.87, 1.14)	0.99 (0.86, 1.13)	0.97 (0.84, 1.12)	1.04 (0.90, 1.19)
Quartile 3	295 (19.1)	1.08 (0.94, 1.24)	1.08 (0.94, 1.25)	1.03 (0.89, 1.19)	1.12 (0.96, 1.29)
Quartile 4	349 (22.6)	1.02 (0.89, 1.17)	1.02 (0.89, 1.16)	0.97 (0.84, 1.12)	1.04 (0.91, 1.20)
P-for-trend		0.53	0.55	0.86	0.36
			≥8 Hours		
Overall	3155				
Quartile 1	1118 (35.4)	*Referent*	*1*	*1*	*1*
Quartile 2	725 (23.0)	1.06 (0.96, 1.16)	1.06 (0.96, 1.16)	1.02 (0.93, 1.13)	1.05 (0.95, 1.16)
Quartile 3	608 (19.3)	1.05 (0.95, 1.16)	1.07 (0.96, 1.17)	1.02 (0.92, 1.13)	1.06 (0.96, 1.17)
Quartile 4	704 (22.3)	1.06 (0.97, 1.17)	1.06 (0.96, 1.17)	1.02 (0.92, 1.12)	1.09 (0.99, 1.20)
P-for-trend		0.19	0.21	0.77	0.09
P-for-interaction		0.82	0.62	0.75	0.60
HISTORY OF HT USE					
			Never		
Overall	1610				
Quartile 1	593 (36.8)	*Referent*	*1*	*1*	*1*
Quartile 2	355 (22.1)	1.01 (0.88, 1.15)	1.01 (0.88, 1.15)	0.99 (0.87, 1.14)	1.06 (0.92, 1.22)
Quartile 3	298 (18.5)	1.03 (0.90, 1.18)	1.02 (0.89, 1.18)	1.00 (0.87, 1.16)	1.08 (0.93, 1.26)
Quartile 4	364 (22.6)	0.97 (0.85, 1.10)	0.96 (0.84, 1.09)	0.93 (0.81, 1.07)	1.03 (0.89, 1.18)
P-for-trend		0.73	0.63	0.38	0.59
			Former		
Overall	601				
Quartile 1	198 (33.0)	*Referent*	*1*	*1*	*1*
Quartile 2	126 (21.0)	1.05 (0.84, 1.31)	1.06 (0.85, 1.33)	0.95 (0.75, 1.21)	1.07 (0.85, 1.34)
Quartile 3	133 (22.1)	**1.37 (1.10, 1.70)**	**1.36 (1.09, 1.70)**	1.25 (0.99, 1.58)	**1.38 (1.10, 1.72)**
Quartile 4	144 (24.0)	1.20 (0.97, 1.49)	1.21 (0.97, 1.50)	1.14 (0.91, 1.42)	1.19 (0.95, 1.48)
P-for-trend		**0.02**	**0.02**	0.10	**0.03**
			Current		
Overall	2501				
Quartile 1	902 (36.1)	*Referent*	*1*	*1*	*1*
Quartile 2	578 (23.1)	1.06 (0.95, 1.17)	1.05 (0.94, 1.16)	1.03 (0.92, 1.14)	1.03 (0.93, 1.15)
Quartile 3	474 (19.0)	1.02 (0.92, 1.14)	1.03 (0.92, 1.15)	0.98 (0.87, 1.10)	1.02 (0.91, 1.14)
Quartile 4	547 (21.9)	1.08 (0.97, 1.20)	1.08 (0.97, 1.20)	1.04 (0.93, 1.17)	1.07 (0.96, 1.19)
P-for-trend		0.20	0.21	0.64	0.28
P-for-interaction		0.36	0.91	0.49	0.90

[a] Total beverage caffeine intake (mg/d) from coffee and tea at baseline
[b] Model 1 is the crude model
[c] Model 2 adjusted for age, race/ethnicity, and education
[d] Model 3 adjusted for variables adjusted in Model 2, smoking, pack-years of smoking (continuous), alcohol intake, total energy intake (continuous), recreational physical activity (continuous), BMI (continuous), and sleep duration
[e] Model 4 adjusted for variables adjusted in Model 2, family history of breast cancer, OC use, history of unopposed E use, history of E + P use, age at menarche, age at menopause (continuous), age at first birth, and number of live births

Table 6. Associations between total caffeine intake at baseline and risk of receptor-specific invasive breast cancer in the Women's Health Initiative Observational Study

Invasive Breast Cancer Subtypes[b]	Overall	Caffeine Intake, mg/d[a] Quartile 1 0 – 93mg/d	Quartile 2 94 – 230mg/d	Quartile 3 231 – 278mg/d	Quartile 4 279 – 736mg/d	P-for-trend
ER+						
No. Cases (%)	3721	1322 (35.5)	837 (22.5)	715 (19.2)	847 (22.8)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	1.00 (0.91, 1.09)	0.96 (0.88, 1.05)	0.95 (0.87, 1.04)	0.18
Model 2 Adjusted HR[d] (95% CI)		*1*	1.01 (0.92, 1.10)	0.98 (0.90, 1.08)	0.96 (0.88, 1.05)	0.38
Model 3 Adjusted HR[e] (95% CI)		*1*	1.00 (0.91, 1.09)	0.98 (0.89, 1.08)	0.97 (0.89, 1.06)	0.46
Model 4 Adjusted HR[f] (95% CI)		*1*	1.00 (0.91, 1.09)	0.99 (0.90, 1.09)	0.96 (0.87, 1.05)	0.35
ER-						
No. Cases (%)	651	230 (35.3)	160 (24.6)	122 (18.7)	139 (21.4)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.98 (0.80, 1.20)	1.00 (0.80, 1.24)	1.18 (0.96, 1.46)	0.18
Model 2 Adjusted HR[d] (95% CI)		*1*	0.98 (0.80, 1.20)	1.00 (0.80, 1.25)	1.17 (0.94, 1.45)	0.21
Model 3 Adjusted HR[e] (95% CI)		*1*	1.02 (0.82, 1.26)	1.09 (0.86, 1.37)	**1.27 (1.02, 1.59)**	**0.04**
Model 4 Adjusted HR[f] (95% CI)		*1*	1.01 (0.82, 1.25)	1.00 (0.79, 1.26)	1.21 (0.97, 1.52)	0.15
PR+						
No. Cases (%)	3143	1121 (35.7)	698 (22.2)	604 (19.2)	720 (22.9)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	1.00 (0.91, 1.10)	0.99 (0.90, 1.09)	1.00 (0.91, 1.09)	0.88
Model 2 Adjusted HR[d] (95% CI)		*1*	1.01 (0.92, 1.11)	1.02 (0.92, 1.12)	1.02 (0.92, 1.12)	0.73
Model 3 Adjusted HR[e] (95% CI)		*1*	1.00 (0.90, 1.10)	1.02 (0.92, 1.13)	1.02 (0.93, 1.13)	0.61
Model 4 Adjusted HR[f] (95% CI)		*1*	1.01 (0.91, 1.12)	1.04 (0.94, 1.15)	1.01 (0.91, 1.11)	0.76
PR-						
No. Cases (%)	1165	410 (35.2)	283 (24.3)	218 (18.7)	254 (21.8)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.97 (0.83, 1.12)	0.90 (0.77, 1.06)	0.94 (0.80, 1.09)	0.28
Model 2 Adjusted HR[d] (95% CI)		*1*	0.96 (0.82, 1.11)	0.90 (0.76, 1.06)	0.92 (0.79, 1.08)	0.22
Model 3 Adjusted HR[e] (95% CI)		*1*	0.98 (0.84, 1.15)	0.91 (0.77, 1.09)	0.96 (0.82, 1.14)	0.49
Model 4 Adjusted HR[f] (95% CI)		*1*	0.95 (0.81, 1.11)	0.86 (0.72, 1.02)	0.91 (0.77, 1.07)	0.15
ER+/PR+						
No. Cases (%)	3089	1102 (35.7)	684 (22.1)	595 (19.3)	708 (22.9)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	1.01 (0.91, 1.11)	1.00 (0.90, 1.10)	1.00 (0.91, 1.09)	0.88
Model 2 Adjusted HR[d] (95% CI)		*1*	1.02 (0.93, 1.12)	1.02 (0.92, 1.13)	1.02 (0.92, 1.12)	0.73
Model 3 Adjusted HR[e] (95% CI)		*1*	1.00 (0.91, 1.11)	1.02 (0.92, 1.14)	1.02 (0.92, 1.13)	0.62
Model 4 Adjusted HR[f] (95% CI)		*1*	1.02 (0.92, 1.12)	1.04 (0.94, 1.16)	1.01 (0.91, 1.11)	0.76
ER-/PR-						
No. Cases (%)	589	210 (35.7)	143 (24.3)	111 (18.9)	125 (21.2)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	1.00 (0.81, 1.24)	1.02 (0.81, 1.28)	1.18 (0.94, 1.47)	0.20
Model 2 Adjusted HR[d] (95% CI)		*1*	1.00 (0.81, 1.24)	1.02 (0.80, 1.28)	1.17 (0.93, 1.46)	0.23
Model 3 Adjusted HR[e] (95% CI)		*1*	1.02 (0.81, 1.28)	1.10 (0.87, 1.41)	**1.28 (1.01, 1.62)**	**0.05**
Model 4 Adjusted HR[f] (95% CI)		*1*	1.03 (0.83, 1.29)	1.00 (0.78, 1.28)	1.21 (0.95, 1.53)	0.19
ER+/PR-						
No. Cases (%)	570	197 (34.7)	139 (24.4)	106 (18.6)	128 (22.5)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.93 (0.75, 1.15)	0.80 (0.63, 1.01)	**0.75 (0.60, 0.94)**	**0.01**
Model 2 Adjusted HR[d] (95% CI)		*1*	0.91 (0.73, 1.13)	0.81 (0.64, 1.03)	**0.74 (0.59, 0.93)**	**0.01**
Model 3 Adjusted HR[e] (95% CI)		*1*	0.91 (0.72, 1.15)	**0.77 (0.60, 0.99)**	**0.73 (0.57, 0.92)**	**0.004**
Model 4 Adjusted HR[f] (95% CI)		*1*	0.86 (0.68, 1.08)	**0.75 (0.59, 0.96)**	**0.71 (0.56, 0.90)**	**0.002**
ER-/PR+						
No. Cases (%)	54	19 (35.2)	14 (25.9)	9 (16.7)	12 (22.2)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.63 (0.31, 1.28)	0.66 (0.29, 1.54)	1.09 (0.52, 2.27)	0.93
Model 2 Adjusted HR[d] (95% CI)		*1*	0.70 (0.32, 1.52)	0.75 (0.31, 1.82)	1.22 (0.54, 2.75)	0.6
Model 3 Adjusted HR[e] (95% CI)		*1*	0.60 (0.24, 1.49)	0.80 (0.28, 2.31)	1.68 (0.61, 4.59)	0.35
Model 4 Adjusted HR[f] (95% CI)		*1*	0.65 (0.28, 1.51)	0.82 (0.27, 2.55)	1.17 (0.46, 2.96)	0.60
HER2+						
No. Cases (%)	475	164 (34.5)	102 (21.5)	97 (20.4)	112 (23.6)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.80 (0.63, 1.03)	0.85 (0.66, 1.09)	0.98 (0.77, 1.24)	0.77
Model 2 Adjusted HR[d] (95% CI)		*1*	0.80 (0.62, 1.02)	0.86 (0.67, 1.11)	0.99 (0.78, 1.26)	0.89
Model 3 Adjusted HR[e] (95% CI)		*1*	0.82 (0.63, 1.07)	0.88 (0.67, 1.15)	1.01 (0.77, 1.31)	0.93
Model 4 Adjusted HR[f] (95% CI)		*1*	0.80 (0.61, 1.04)	0.84 (0.64, 1.10)	1.00 (0.78, 1.30)	0.96
HER2-						
No. Cases (%)	2971	1054 (35.5)	683 (23.0)	565 (19.0)	669 (22.5)	

Model 1 Adjusted HR[c] (95% CI)		*Referent*	1.01 (0.92, 1.11)	0.96 (0.87, 1.07)	0.96 (0.87, 1.06)	0.34
Model 2 Adjusted HR[d] (95% CI)		*1*	1.01 (0.92, 1.11)	0.98 (0.88, 1.08)	0.97 (0.88, 1.06)	0.41
Model 3 Adjusted HR[e] (95% CI)		*1*	1.01 (0.91, 1.11)	0.98 (0.88, 1.10)	0.99 (0.89, 1.09)	0.74
Model 4 Adjusted HR[f] (95% CI)		*1*	1.01 (0.91, 1.12)	0.98 (0.88, 1.09)	0.96 (0.87, 1.07)	0.44
ER-/PR-/HER2-						
No. Cases (%)	346	130 (37.6)	90 (26.0)	59 (17.1)	67 (19.4)	
Model 1 Adjusted HR[c] (95% CI)		*Referent*	0.98 (0.75, 1.29)	0.88 (0.65, 1.20)	1.14 (0.85, 1.54)	0.67
Model 2 Adjusted HR[d] (95% CI)		*1*	0.99 (0.75, 1.31)	0.85 (0.62, 1.17)	1.14 (0.84, 1.53)	0.74
Model 3 Adjusted HR[e] (95% CI)		*1*	1.02 (0.92, 1.12)	**1.02 (1.00, 1.03)**	1.04 (0.88, 1.22)	0.33
Model 4 Adjusted HR[f] (95% CI)		*1*	1.05 (0.78, 1.41)	0.88 (0.63, 1.23)	1.20 (0.87, 1.64)	0.54

[a] Total beverage caffeine intake (mg/d) from coffee and tea at baseline
[b] HER2NEU status was not available for breast cancer diagnosis early in the cohort and was not investigated
[c] Model 1 is the crude model
[d] Model 2 adjusted for age, race/ethnicity, and education
[e] Model 3 adjusted for variables adjusted in Model 2, smoking, pack-years of smoking (continuous), alcohol intake, total energy intake (continuous), recreational physical activity (continuous), BMI (continuous), and sleep duration
[f] Model 4 adjusted for variables adjusted in Model 2, family history of breast cancer, OC use, history of unopposed E use, history of E + P use, age at menarche, age at menopause (continuous), age at first birth, and number of live births

REFERENCES

1. Somogyi, L. *Caffeine intake by the U.S. population*. 2010.

2. Mitchell, D.C., et al., *Beverage caffeine intakes in the U.S.* Food and Chemical Toxicology, 2014. **63**: p. 136-142.

3. Drewnowski, A. and C.D. Rehm, *Sources of Caffeine in Diets of US Children and Adults: Trends by Beverage Type and Purchase Location.* Nutrients, 2016. **8**(3): p. 154.

4. Gomez-Ruiz, J.A., D.S. Leake, and J.M. Ames, *In vitro antioxidant activity of coffee compounds and their metabolites.* J Agric Food Chem, 2007. **55**(17): p. 6962-9.

5. Higdon, J.V. and B. Frei, *Coffee and health: a review of recent human research.* Crit Rev Food Sci Nutr, 2006. **46**(2): p. 101-23.

6. James, J.E., *Critical review of dietary caffeine and blood pressure: a relationship that should be taken more seriously.* Psychosom Med, 2004. **66**(1): p. 63-71.

7. Freedman , N.D., et al., *Association of Coffee Drinking with Total and Cause-Specific Mortality.* New England Journal of Medicine, 2012. **366**(20): p. 1891-1904.

8. Wierzejska, R., *Tea and Health - A Review of the Current State of Knowledge.* Przegl Epidemiol, 2014. **68**: p. 501-506.

9. Chacko, S.M., et al., *Beneficial effects of green tea: A literature review.* Chin Med, 2010. **5**: p. 13.

10. Gardner, E.J., C.H. Ruxton, and A.R. Leeds, *Black tea--helpful or harmful? A review of the evidence.* Eur J Clin Nutr, 2007. **61**(1): p. 3-18.

11. Choi, H.K., W. Willett, and G. Curhan, *Fructose-rich beverages and risk of gout in women.* Jama, 2010. **304**(20): p. 2270-8.

12. Fung, T.T., et al., *Sweetened beverage consumption and risk of coronary heart disease in women.* Am J Clin Nutr, 2009. **89**(4): p. 1037-42.

13. Malik, V.S., et al., *Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis.* Diabetes Care, 2010. **33**(11): p. 2477-83.

14. Vartanian, L.R., M.B. Schwartz, and K.D. Brownell, *Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis.* Am J Public Health, 2007. **97**(4): p. 667-75.

15. Higgins, J.P., et al., *Energy Drinks: A Contemporary Issues Paper.* Curr Sports Med Rep, 2018. **17**(2): p. 65-72.

16. Tang, N., et al., *Coffee consumption and risk of lung cancer: a meta-analysis.* Lung Cancer, 2010. **67**(1): p. 17-22.

17. Hildebrand, J.S., et al., *Coffee, Tea, and Fatal Oral/Pharyngeal Cancer in a Large Prospective US Cohort.* American Journal of Epidemiology, 2012.

18. Petrick, J.L., et al., *Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project.* Cancer Epidemiol Biomarkers Prev, 2015. **24**(9): p. 1398-406.

19. Boyle, P., A. Koechlin, and P. Autier, *Sweetened carbonated beverage consumption and cancer risk: meta-analysis and review.* Eur J Cancer Prev, 2014. **23**(5): p. 481-90.

20. Eini, H., et al., *Caffeine promotes anti-tumor immune response during tumor initiation: Involvement of the adenosine A2A receptor.* Biochem Pharmacol, 2015. **98**(1): p. 110-8.

21. Lu, G.Y., et al., *Caffeine induces tumor cytotoxicity via the regulation of alternative splicing in subsets of cancer-associated genes.* Int J Biochem Cell Biol, 2014. **47**: p. 83-92.

22. Bhatti, S.K., J.H. O'Keefe, and C.J. Lavie, *Coffee and tea: perks for health and longevity?* Curr Opin Clin Nutr Metab Care, 2013. **16**(6): p. 688-97.

23. Ramos, S., *Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways.* Mol Nutr Food Res, 2008. **52**(5): p. 507-26.

24. Bohn, S.K., R. Blomhoff, and I. Paur, *Coffee and cancer risk, epidemiological evidence, and molecular mechanisms.* Mol Nutr Food Res, 2014. **58**(5): p. 915-30.

25. Lambert, J.D., *Does tea prevent cancer? Evidence from laboratory and human intervention studies.* Am J Clin Nutr, 2013. **98**(6 Suppl): p. 1667S-1675S.

26. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2012 Incidence and Mortality Web-based Report*. 2015; Available from: www.cdc.gov/uscs.

27. National Cancer Institute. *SEER Cancer Statistics Factsheets: Female Breast Cancer*. 2016; Available from: http://seer.cancer.gov/statfacts/html/breast.html.

28. Howlader, N., et al., *SEER Cancer Statistics Review, 1975-2012, National Cancer Institute.* SEER web site, 2015.

29. American Cancer Society. *Breast Cancer*. 2014 05/16/16]; Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/index.

30. Toikkanen, S., L. Pylkkanen, and H. Joensuu, *Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma.* Br J Cancer, 1997. **76**(9): p. 1234-40.

31. Kim, H.S., et al., *Analysis of the Potent Prognostic Factors in Luminal-Type Breast Cancer.* J Breast Cancer, 2012. **15**(4): p. 401-6.

32. Bentzon, N., et al., *Prognostic effect of estrogen receptor status across age in primary breast cancer.* Int J Cancer, 2008. **122**(5): p. 1089-94.

33. Fisher, B., et al., *Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06.* J Clin Oncol, 1988. **6**(7): p. 1076-87.

34. Slamon, D., et al., *Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene.* Science, 1987. **235**(4785): p. 177-182.

35. Piccart-Gebhart, M.J., et al., *Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.* N Engl J Med, 2005. **353**(16): p. 1659-72.

36. Anders, C. and L.A. Carey, *Understanding and Treating Triple-Negative Breast Cancer.* Oncology (Williston Park), 2008. **22**(11): p. 1233-43.

37. Voduc, K.D., et al., *Breast cancer subtypes and the risk of local and regional relapse.* J Clin Oncol, 2010. **28**(10): p. 1684-91.

38. Yashin, A.I., et al., *Health decline, aging and mortality: how are they related?* Biogerontology, 2007. **8**(3): p. 291-302.

39. Amend, K., D. Hicks, and C.B. Ambrosone, *Breast cancer in African-American women: differences in tumor biology from European-American women.* Cancer Res, 2006. **66**(17): p. 8327-30.

40. Howell, A., et al., *Risk determination and prevention of breast cancer.* Breast Cancer Research, 2014. **16**(5): p. 1-19.

41. Singletary, S.E., *Rating the Risk Factors for Breast Cancer.* Ann Surg, 2003. **237**(4): p. 474-82.

42. Baker, J.A., et al., *Consumption of coffee, but not black tea, is associated with decreased risk of premenopausal breast cancer.* J Nutr, 2006. **136**(1): p. 166-71.

43. Boggs, D.A., et al., *Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study.* Cancer Causes Control, 2010. **21**(11): p. 1941-8.

44. Fagherazzi, G., et al., *No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study.* Public Health Nutr, 2011. **14**(7): p. 1315-20.

45. Folsom, A.R., et al., *No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study.* Am J Epidemiol, 1993. **138**(6): p. 380-3.

46. Ganmaa, D., et al., *Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up.* Int J Cancer, 2008. **122**(9): p. 2071-6.

47. Gierach, G.L., et al., *Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort.* Int J Cancer, 2012. **131**(2): p. 452-60.

48. Ishitani, K., et al., *Caffeine consumption and the risk of breast cancer in a large prospective cohort of women.* Arch Intern Med, 2008. **168**(18): p. 2022-31.

49. Lowcock, E.C., et al., *High coffee intake, but not caffeine, is associated with reduced estrogen receptor negative and postmenopausal breast cancer risk with no effect modification by CYP1A2 genotype.* Nutr Cancer, 2013. **65**(3): p. 398-409.

50. Lubin, F., et al., *Coffee and methylxanthines and breast cancer: a case-control study.* J Natl Cancer Inst, 1985. **74**(3): p. 569-73.

51. Michels, K.B., et al., *Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women.* Ann Epidemiol, 2002. **12**(1): p. 21-6.

52. Oh, J.K., et al., *Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden.* Int J Cancer, 2015. **137**(8): p. 1979-89.

53. Phelps, H.M. and C.E. Phelps, *Caffeine ingestion and breast cancer. A negative correlation.* Cancer, 1988. **61**(5): p. 1051-4.

54. Pozner, J., et al., *Association of tumor differentiation with caffeine and coffee intake in women with breast cancer.* Surgery, 1986. **100**(3): p. 482-8.

55. Rosenberg, L., et al., *Breast cancer and the consumption of coffee.* Am J Epidemiol, 1985. **122**(3): p. 391-9.

56. Smith, S.J., J.M. Deacon, and C.E. Chilvers, *Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. UK National Case-Control Study Group.* Br J Cancer, 1994. **70**(1): p. 112-9.

57. Tavani, A., et al., *Coffee consumption and the risk of breast cancer.* Eur J Cancer Prev, 1998. **7**(1): p. 77-82.

58. Wu, A.H., et al., *Green tea and risk of breast cancer in Asian Americans.* Int J Cancer, 2003. **106**(4): p. 574-9.

59. Kumar, N., et al., *Tea consumption and risk of breast cancer.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(1): p. 341-5.

60. Jiang, W., Y. Wu, and X. Jiang, *Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies.* Gynecol Oncol, 2013. **129**(3): p. 620-9.

61. Tang, N., et al., *Coffee consumption and risk of breast cancer: a metaanalysis.* Am J Obstet Gynecol, 2009. **200**(3): p. 290 e1-9.

62. Al-Ansari, M.M. and A. Aboussekhra, *Caffeine mediates sustained inactivation of breast cancer-associated myofibroblasts via up-regulation of tumor suppressor genes.* PLoS One, 2014. **9**(3): p. e90907.

63. Niknafs, B., *Induction of apoptosis and non-apoptosis in human breast cancer cell line (MCF-7) by cisplatin and caffeine.* Iran Biomed J, 2011. **15**(4): p. 130-3.

64. Li, Z., et al., *Caffeine overcomes genistein-induced G2/M cell cycle arrest in breast cancer cells.* Nutr Cancer, 2008. **60**(3): p. 382-8.

65. Rosendahl, A.H., et al., *Caffeine and Caffeic Acid Inhibit Growth and Modify Estrogen Receptor and Insulin-like Growth Factor I Receptor Levels in Human Breast Cancer.* Clin Cancer Res, 2015. **21**(8): p. 1877-87.

66. Nikitina, D., et al., *Relationship between Caffeine and Levels of DNA Repair and Oxidative Stress in Women with and without a BRCA1 Mutation.* J Nutrigenet Nutrigenomics, 2015. **8**(4-6): p. 174-184.

67. Curb, J.D., et al., *Outcomes ascertainment and adjudication methods in the Women's Health Initiative.* Ann Epidemiol, 2003. **13**(9 Suppl): p. S122-8.

68. Hays, J., et al., *The women's health initiative recruitment methods and results.* Annals of Epidemiology, 2003. **13**(9, Supplement): p. S18-S77.

69. Langer, R.D., et al., *The women's health initiative observational study: baseline characteristics of participants and reliability of baseline measures.* Annals of Epidemiology, 2003. **13**(9, Supplement): p. S107-S121.

70. Patterson, R.E., et al., *Measurement characteristics of the Women's Health Initiative food frequency questionnaire.* Ann Epidemiol, 1999. **9**(3): p. 178-87.

71. U.S. Department of Agriculture, A.R.S., Nutrient Data Laboratory, *USDA National Nutrient Databse for Standard Reference, Release 28.* **Version Current: September 2015**.

72. Chin, J.M., et al., *Caffeine content of brewed teas.* J Anal Toxicol, 2008. **32**(8): p. 702-4.

73. Heckman, M.A., J. Weil, and E. Gonzalez de Mejia, *Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters.* J Food Sci, 2010. **75**(3): p. R77-87.

74. McCusker, R.R., et al., *Caffeine content of decaffeinated coffee.* J Anal Toxicol, 2006. **30**(8): p. 611-3.

75. Alicandro, G., A. Tavani, and C. La Vecchia, *Coffee and cancer risk: a summary overview.* Eur J Cancer Prev, 2017. **26**(5): p. 424-432.

76. Bhoo-Pathy, N., et al., *Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study.* Breast Cancer Research : BCR, 2015. **17**(1): p. 15.

77. Lehrer, S., S. Green, and K.E. Rosenzweig, *Coffee Consumption Associated with Increased Mortality of Women with Breast Cancer.* J Caffeine Res, 2013. **3**(1): p. 38-40.

78. Ferrini, R.L. and E. Barrett-Connor, *Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study.* Am J Epidemiol, 1996. **144**(7): p. 642-4.

79. Kotsopoulos, J., et al., *Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women.* Cancer, 2009. **115**(12): p. 2765-74.

80. Nagata, C., M. Kabuto, and H. Shimizu, *Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women.* Nutr Cancer, 1998. **30**(1): p. 21-4.

81. Hankinson, S.E., *Endogenous hormones and risk of breast cancer in postmenopausal women.* Breast Dis, 2005. **24**: p. 3-15.

82. Key, T., et al., *Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies.* J Natl Cancer Inst, 2002. **94**(8): p. 606-16.

83. Tworoger, S.S., et al., *Plasma sex hormone concentrations and subsequent risk of breast cancer among women using postmenopausal hormones.* J Natl Cancer Inst, 2005. **97**(8): p. 595-602.

84. Petrek, J.A., et al., *The inhibitory effect of caffeine on hormone-induced rat breast cancer.* Cancer, 1985. **56**(8): p. 1977-81.

85. Higgins, L.G., et al., *Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein.* Toxicol Appl Pharmacol, 2008. **226**(3): p. 328-37.

86. Neuwirthova, J., et al., *[Coffee in Cancer Chemoprevention]*. Klin Onkol. **30**(2): p. 106-114.

87. Grosso, G., et al., *Coffee, Caffeine, and Health Outcomes: An Umbrella Review.* Annu Rev Nutr, 2017. **37**: p. 131-156.

88. Friedman, M., et al., *Distribution of catechins, theaflavins, caffeine, and theobromine in 77 teas consumed in the United States.* Journal of food science, 2005. **70**(9).

89. Rhee, J.J., et al., *Coffee and caffeine consumption and the risk of hypertension in postmenopausal women.* Am J Clin Nutr, 2016. **103**(1): p. 210-7.

90. Li, J., et al., *Coffee consumption modifies risk of estrogen-receptor negative breast cancer.* Breast Cancer Res, 2011. **13**(3): p. R49.

91. Li, X.J., et al., *Coffee Consumption and Risk of Breast Cancer: An Up-To-Date Meta-Analysis.* PLoS One, 2013. **8**(1).

92. Maggio, M., et al., *Sex hormone binding globulin levels across the adult lifespan in women - The role of body mass index and fasting insulin.* J Endocrinol Invest, 2008. **31**(7): p. 597-601.

93. Caprioli, G., et al., *The influence of different types of preparation (espresso and brew) on coffee aroma and main bioactive constituents.* Int J Food Sci Nutr, 2015. **66**(5): p. 505-13.

94. Fuller, M. and N.Z. Rao, *The Effect of Time, Roasting Temperature, and Grind Size on Caffeine and Chlorogenic Acid Concentrations in Cold Brew Coffee.* Sci Rep, 2017. **7**(1): p. 17979.

95. Heckman, M.A., J. Weil, and E.G.D. Mejia, *Caffeine (1, 3, 7-trimethylxanthine) in Foods: A Comprehensive Review on Consumption, Functionality, Safety, and Regulatory Matters.* Journal of Food Science, 2010. **75**(3): p. R77-R87.

96. Bertoia, M.L., et al., *Long-term alcohol and caffeine intake and risk of sudden cardiac death in women.* Am J Clin Nutr, 2013. **97**(6): p. 1356-63.

97. Driscoll, I., et al., *Relationships Between Caffeine Intake and Risk for Probable Dementia or Global Cognitive Impairment: The Women's Health Initiative Memory Study.* J Gerontol A Biol Sci Med Sci, 2016. **71**(12): p. 1596-1602.

98. Giri, A., et al., *Caffeinated coffee, decaffeinated coffee and endometrial cancer risk: a prospective cohort study among US postmenopausal women.* Nutrients, 2011. **3**(11): p. 937-50.