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Coffee and Tea Consumption and the Risk of Lung Cancer in a Population of Postmenopausal Women

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COFFEE AND TEA CONSUMPTION AND THE RISK OF LUNG CANCER IN A POPULATION OF POSTMENOPAUSAL WOMEN

A Thesis Presented

by

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DEDICATION

For everyone who has ever encouraged me to grow.

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I would first like to thank the many professors who assisted me in the past two years. From Dr. Sturgeon, who has spent countless hours guiding me, to Dr. Reeves and Dr. Qian who took time to provide me with thoughtful and insightful suggestions, I could not have completed this thesis without my committee members. I would also like to thank all of the professors in the Epidemiology and Biostatistics Department who have provided the foundations that will be used for the rest my career.

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ABSTRACT

COFFEE AND TEA CONSUMPTION AND THE RISK OF LUNG CANCER IN A POPULATION OF POSTMENOLPAUSAL WOMEN
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Lung cancer has been the leading cause of cancer death in women for the past three decades. Although smoking is the most important risk factor for lung cancer, not all lung cancer deaths in American women are attributed to smoking and the role of dietary exposures remain unclear. In particular, the effect of coffee consumption and tea consumption on lung cancer risk remains inconclusive. Therefore we assessed these associations prospectively in 83,777 women between the ages of 50-79 and did not have a previous history of cancer at enrollment. Daily coffee and tea consumption (cups/d) were assessed via a baseline questionnaire while the 1,038 lung cancer cases included in analysis were self-reported and physician adjudicated. Cox proportional hazard models, adjusted for important lung cancer risk factors, were used to model the associations. Seventy-one percent of women reported drinking coffee daily while only 26% of participants drank tea. Analyses initially conducted in a full multivariate model, which was controlled for smoking, suggested a significant increase in lung cancer risk for regular (HR=1.47, 95% CI 1.21-1.79), decaffeinated (HR=1.56, 95% CI 1.17-2.07) and total coffee (HR= 1.58, 95% CI 1.29-1.93) when comparing those in the highest consumption categories to non-daily drinkers, but no significant results were observed in these consumption groups in an analysis conducted among only non-smokers. Results for daily tea consumption was not statistically significant with those is the highest consumption category having a 27% reduction in risk (HR= 0.73, 95% CI 0.47-1.11) when compared to those that did not drink tea daily. Our data suggests that there is no

association between coffee consumption and lung cancer risk or tea consumption and lung cancer risk.

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CHAPTER 1

INTRODUCTION

Due to increasing trends in smoking in the female population since 1965, lung cancer has been the leading cause of cancer death in women since 1985. The American Cancer Society has predicted 110,110 women will be diagnosed with lung cancer in 2013 and 72,220 will die due to their diagnosis.[1] Although tobacco use is the most common lung cancer risk factor, women who have never smoked also received lung cancer diagnoses; 10% of all lung cancer deaths that occur in American women are not attributed to smoking.[2] Environmental factors, such as exposure to second hand smoke, asbestos, and radon have become established risk factors for lung cancer, but the effects of dietary exposures, especially coffee and tea, remain unclear.

Coffee is the most common source of caffeine in the United States.[3] Composed of over 1,000 chemical compounds, coffee possesses both well-established cancer promoting compounds as well as cancer preventing antioxidants. Mutagens, such as chlorogenic acid, methylglyoxal[4] and caffeine, have been implicated as an inhibitor of DNA repair and represent some of the main cancer promoting chemicals of concern.[5] Yet coffee also contains polyphenols, specifically phytoestrogens, flavonoids, and catechins, which have been shown to have antioxidant effects.[6] These seemingly contradictory components have made determining the physiological mechanism for coffee and lung cancer difficult to identify. Recent scientific discussion has implicated two components of coffee as the most probable explanation for coffee's protective effects against cancers: diterpenes known as cafestol and kahweol. Animal studies conducted in rats have shown that both cafestol and kahweol reduce the genotoxicity of several carcinogens including DMBA, AFB(1), B[a]P, and PhIP.[7] Therefore there is a biological plausibility that coffee could reduce the risk of lung cancer, yet most studies suggest a promoting effect for coffee.

Due to this complex nature of coffee, a mechanism to suggest how coffee could impact lung cancer risk has not been confirmed. Studies conducted over the past thirty years looking at this association have reported contradictory results. Studies that have reported results for high amounts of coffee consumption have reported results that have a range of results with some suggesting as high as a 200% increase in risk[8] while others suggest a 50% reduction in risk.[9] A recent meta-analysis of five cohort and eight case-control studies suggest a 27% (95% CI 1.04-1.54) increase in risk in coffee drinkers.[10] When the results of the studies were stratified by study design, prospective studies had a reported relative risk of 1.57 (95% CI 1.15-2.14) while case-control studies had a reported RR of 1.13 (95% CI 0.90-1.41).[10] It is important to note that smoking was classified and controlled for differently in each of the five cohort studies. A majority of the studies included in the analysis controlled for just smoking status and one study did not control for smoking at all. With this fact in mind it is possible that Tang et al's reported RR was also impacted by residual confounding due to smoking. An increase in risk was also demonstrated in two case-control studies that have been conducted since the meta-analysis' publication.[8,11] De Stefani et al. reported a odds ratio of 2.30 (95% CI 1.35-3.90) for those who were in the highest consumption categories compared to those who had low consumption levels while Ganesh and colleagues reported a 3 times increase in lung cancer risk for those who have ever consumed coffee compared to those who had never consumed coffee. De Stefani et. al controlled for smoking status including amount of years since quitting (former smokers) and the amount of cigarettes per a day (current) while Ganesh et.al controlled for smoking by classifying participants as smokers or not smokers.

On a global scale, tea is the second most common beverage consumed.[12] Like coffee, tea is composed of a variety of natural components which could impact one's risk of developing lung cancer. One cup of black tea, the most common type of tea consumed in America, contains catechins, flavonols, lignans, and phenolic acids.[12] These chemical components have been

recently shown to have an inhibitory effect on tumor growth, including lung cancer, in animal studies.[12] More recent epidemiological studies conducted in human populations to look at the effects of tea consumption and lung cancer risks have also identified epicatechin[13] and polyphencol [14]as two components of tea that demonstrate a chemopreventative effect even in populations that included smokers. One randomized clinical trial conducted by Hakim et al. randomized half of their smoking population to drink ≥ 4 cups/day of decaffeinated tea.[14] After 4 months, members of the study who consumed tea had a 31% reduction in the amount of urinary 8- hydroxydeoxyguanosine found in their urine indicating a substantial decrease in oxidative stress, which is implicated in cancer formation. Therefore, like in the case of coffee, there is a biological plausibility that tea consumption could reduce the risk of lung cancer.

Although there is more known about the biological mechanisms of tea components, the wide variety of tea types, which differ in composition and processing methods, the true association between tea consumption and lung cancer risk also remain contradictory in the literature. A recent meta-analysis, which looked at eight prospective studies and fourteen retrospective case control studies on green and/or black tea consumption, suggest a 22% (95% CI 0.61-1.00) decrease risk in lung cancer in green tea drinkers and a 14% (95% CI 0.70-1.05) reduction in black tea drinkers.[15] When the authors stratified their results by study design type, results from cohort studies showed a 38% (95% CI 0.45-1.02) decrease in lung cancer risk in green tea consumers while findings from case-control studies suggested a smaller 13% (95% CI 0.65-1.17) reduction in risk. This difference in predicted relative risks by study group was not observed in the black tea consumption group; prospective studies had a reported RR of 0.88 (95% CI 0.64-1.21) while case-control studies reported an RR of 0.84 (95% CI 0.64-1.09).[15] Each study included in the meta-analysis controlled for smoking differently with some looking at just current smoking status to others controlling for pack years or amount of years quit (former) and amount

of cigarettes smoked daily (current). With this in mind, it is possible that the reported RR's from Tang et al.'s meta-analysis could be affected by residual confounding due to smoking.

Due to study limitations and concerns about residual confounding due to smoking, the true association of lung cancer risk in coffee drinkers and tea consumers remains elusive. No known prospective studies have explored possible differences between regular and decaffeinated coffee consumption on risk and the effects of coffee and tea consumption among smokers and nonsmokers separately. Consequently, we intend to examine the association between coffee consumption, tea consumption, and lung cancer risk in the Women's Health Initiative (WHI) Observational Study.

CHAPTER 2

METHODS

Study Population

The relationship between coffee consumption, tea consumption and lung cancer risk was examined using data from the WHI Observational Study arm. The design for this study has been described in detail in previous litertature[16-17], but briefly, the WHI Observational Study was a prospective cohort study conducted in forty sites across the United States from October 1993 to December 1998.[16] Women between the ages of 50 and 79 who had previously indicated their interest in the diet modification or hormone replacement therapy but were not able or willing to participate in the WHI controlled trials were recruited to participate in the observational study while other participants were women who were directly invited to participate.[17] Women were excluded from the study if they planned on moving in the immediate three year period after enrollment, possessed a pre-existing medical condition that predicted a survival time of less than three years, had a complicating condition (i.e dementia or substance abuse issues) or were participants in the Diet Modification or Hormone Replacement clinical trials. Upon enlistment, women received a baseline screening visit with a medical professional and completed a questionnaire related to medical history, family history, reproductive history, lifestyle/behavioral factors, and quality of life. Information about selected exposures and medical outcomes was collected annually through the use of a mailed questionnaire.[17]

This manuscript was prepared using WHIOS Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the WHIOS or the NHLBI. Of the 93,676 original participants, we excluded those who had a previous episode of any cancer prior to baseline, with the exception of non-melanoma skin cancer (n= 9,899). No women were missing the outcome

variable. Our primary analysis consisted of 83,777 women who contributed 944,444 years of follow-up. The average amount of follow-up time was 10.34 years.

Exposure Assessment

Coffee consumption was directly assessed through the use of a baseline questionnaire which asked participants about their lifestyles and behavior. Participants were asked whether or not they drank coffee daily. If the appropriate answer was yes, participants were prompted to report their daily consumption of regular and decaffeinated coffee. Participants could describe their coffee consumption in the following ways: None, 1 cup/day, 2-3 cups/day, 4-5 cups/day, or ≥ 6 cups/day.[18] Coffee consumption was classified into four groups: None, 1 cup, 2-3 cups, and ≥4 cups. Total coffee consumption was defined as the sum of reported caffeinated and decaffeinated cups of coffee per a day.

Tea consumption was also directly assessed through the use of the same baseline questionnaire described above. Participants were asked whether or not they consumed tea daily. If the appropriate answer was yes, participants were prompted to report their daily consumption of tea, excluding decaf or herbal tea. Participants could describe their tea consumption in the following ways: None, 1 cup/day, 2-3 cups/day, 4-5 cups/day, or ≥ 6 cups/day.[18] Tea consumption was classified into four groups: None, 1 cup, 2-3 cups, and ≥4 cups.

Outcome Assessment

Information about lung cancer was self-reported by participants via the annual questionnaire. Participants were asked whether or not they had lung cancer. If a woman reported a new case of lung cancer, the WHI obtained a pathology/cytology report , a hospital Face Sheet with ICD-9-CM codes , an operative report , a hospital discharge summary, or an outpatient, day surgery, or short stay recode in order to confirm the cancer diagnosis. Information about primary site locations, date of diagnosis, and type of confirmation document was abstracted and recorded

by trained medical professionals who were blinded to each participant's exposure status. [19] Cases of lung cancer reported after the first year of enrollment were included in final analyses.

Covariate Assessment

Age at enrollment (50-59, 60-69,70-79),baseline body mass index, race (Native American/ Alaskan Indian Asian/Pacific Islander, Black/ African American, Hispanic/ Latino, White, Other), education (Less than High School, High School, 1-2 years of college/Associates Degree, Bachelor Degree, Masters/PHD), region of residency (Northeast, South, Midwest, West), physical activity (METS/week), energy intake (kcal/day), Percent of calories from fat, daily fruit consumption (medium serving/day), daily vegetable consumption (medium serving/day), alcohol intake (Never, former, current), smoking status (Never, former, current), and hormone replacement therapy (Never, ever, current) use were considered as potential confounders. Tea consumption (None, 1 cup, 2-3 cups, and ≥4 cups) was included as a covariate for all coffee consumption categories, while total coffee consumption (None, 1 cup, 2-3 cups, and ≥4 cups), decaffeinated coffee consumption (None, 1 cup, 2-3 cups, and ≥4 cups), and regular coffee consumption(None, 1 cup, 2-3 cups, and ≥4 cups) were included as a covariate for tea consumption, regular consumption, and decaffeinated consumption respectively. Due to large concerns about residual effects of confounding due to smoking, amount of years since quitting (<10, 10-19, 20-29, ≥30) and the number of cigarettes smoked daily (<5, 5-14, 15-24, ≥25) were included in the smoking status variable for former and current smokers respectively. All variables listed above are known risk factors for lung cancer or were selected due to their inclusion in prior literature on coffee and lung cancer.[6,8-9,11,20-37] Information for each covariate was retrieved from the corresponding baseline questionnaire.

Statistical Analysis

General descriptive statistics were calculated through the use of summary statistics for all study variables including all potential covariates (Table 1). Using chi-square tests, we assessed covariates as potential confounders by cross-tabulating them with each coffee consumption (Table 2) and tea variable (Table 3) and lung cancer status (Table 4). ANOVA or F-tests were used to conduct analysis on all continuous variables. Cox proportional hazards were used to estimate all hazard ratios (HRs) and 95% confidence intervals (CIs). For primary analysis, follow-up time started from the second year of enrollment and ended when a woman reported an incidence of lung cancer, death, or date of last follow-up whichever came first.

Covariates were included in the initial model if their p- value was less than <0.25 during the bivariate analysis described above. Likelihood ratio tests were completed for all remaining variables starting with the variable with the highest Wald's p-value. If a variable reported a likelihood ratio p-value of greater than 0.10, it was removed from the model. The process was repeated for all variables of interest. Due to the fact that energy consumption, percent of fat consumed, daily fruit and vegetable consumption, physical activity, alcohol consumption, smoking status and hormone replacement use are known risk factors for lung cancer, they remained in the model no matter what p-value they scored. Interactions terms were created in order to look at the relationship between each coffee and tea exposure and smoking status. Interaction terms were included in the final model if they reported a p-value less than 0.05. Model sensitivity was evaluated by running the final model in nonsmokers only. Two-sided p-values <0.05 were considered statistically significant. In order to evaluate whether or not our models fulfilled the Proportional Hazards Assumption we used Schoenfeld Residuals. All analysis was completed using STATA Version 13.

CHAPTER 3

RESULTS

After excluding women who had reported a previous diagnosis of cancer (excluding non-melanoma skin cancer), 83,777 women and 944,444 person years were available for primary analysis. The average age of participants was 63.4 years while the average time of follow-up was 11.34 years. A total of 1,038 cases of lung cancer were reported and confirmed in this population.

Table 1 describes the distribution of coffee consumption, by total consumption and coffee type, as well as tea consumption at baseline. Seventy one percent of women reported consuming coffee on a daily basis while only 25% of women reported daily tea consumption. The most commonly reported consumption categories were 2-3 cups/day for total coffee consumption and regular coffee consumption and 1 cup/day for decaffeinated and tea consumption. Within regular coffee drinkers, 42.85% reported no daily consumption, 17.17% reported 1 cup/day, 28.65% reported 2-3 cups/days, and 9.38% reported consuming ≥ 4 cups/day. A majority of women did not consume decaffeinated coffee on a daily basis (66.46%). 14.6%, 12.98%, and 3.14% of women reported consuming 1 cup/day, 2-3 cups/day, and ≥ 4 cups/day of decaffeinated coffee respectively. Tea consumption was highest in the non-daily consumption category (73.56%), followed by 1 cup/day (12.14%), 2-3 cups/day (10.15%), and lastly ≥ 4 cups/day (2.61%).

After conducting a bivariate analysis, certain differences in covariate distribution within total coffee consumption categories (Table 2) and tea consumption categories (Table 3) became apparent. White women were more likely to drink coffee than their African American/ Black counterparts with 17% of white women consuming ≥ 4 cups/day compared to 5% of African American/Black women. Women who consumed higher levels of coffee had higher total energy consumption ($p<0.001$) and consumed less servings of fruit daily ($p<0.001$) even though there was very little differences in physical activity METs or reported BMI. Seventy-six percent of all women who consumed ≥4 cups of coffee/ day were current alcohol consumers compared to

58.42% of non-drinkers. It also appeared that there was an inverse relationship between tea and coffee consumption. Seventeen percent of women who did not drink tea drank ≥ 4 cups/day of coffee while only 7% of women who drank ≥ 4 cups of tea/ day drank ≥ 4 cups/day of coffee. Most importantly, women who were non-coffee drinkers were less likely to smoke when compared to those that drank ≥ 4 cups of coffee/day. Eight percent of women who consumed ≥ 4 cups/day were heavy smokers compared to only 1.45% of non-consumers while 32% of current smokers drank ≥ 4 cups/day compared to 11% of nonsmokers. Thirty-six percent of never smokers did not consume coffee while only 17% of current smokers reported no daily coffee consumption. There was very little variation observed between consumption categories for many of the variables including region of residency, race, completed education level, percent of fat, vegetable consumption, and hormone replacement use.

Tea consumption also had high homogeneity between consumption strata for race, completed education level, reported BMI, physical activity, percent of fat and hormone replacement, yet there was also some variations observed. No region consistently reported the highest consumption across each coffee consumption category. 30% of those who reported being non-tea drinkers were from the West compared to 21% who were from the Northeast while 30% of women who consumed ≥ 4cups/day were from the South compared to 16% of women from the Midwest. Women who drank tea consumed higher amount of fruits and vegetable intake increased from 2.22 servings a day in non-tea drinkers to 2.41 servings/day in those who consumed ≥ 4 cups of tea a day. The differences observed between the highest and lowest total coffee consumption levels in never and current smokers was not observed in tea consumers. Out of all women who did not consume tea, 49.95% reported being never smokers while 50.35% of woman who consumed ≥ 4 cups/day were never smokers. Only 3% of current heavy smokers reported no tea consumption compared to 5% of heavy smokers who drank ≥ 4 cups/day. The observed inverse association between coffee and tea consumption was present in tea consumers as well with 27.58% of woman who did not consume coffee reporting no tea consumption

compared to 63% of non-coffee drinkers reporting consuming 4 or more cups of tea per day. Table 4 shows the number of cases, person years, and age-adjusted hazard ratios with 95% confidence intervals for all covariates of interest.

Both age-adjusted and multivariate hazards ratios describing the association between total coffee consumption, coffee type, and tea consumption are shown in Table 5. Reported age-adjusted hazard ratios for total coffee consumption, from lowest to higher consumption levels, were 1.08 (95% CI 0.86-1.38), 1.63 (95% CI 1.38-1.93), and 2.31 (95% CI 1.92-2.78) respectively. After adjusting for smoking status (amount of years since quitting [former smokers] and the amount of cigarettes smoked daily [current smokers]), we observed an attenuation of risk with hazards ratios decreasing up to 42% in those in the higher consumption categories. Further analysis controlling for risk factors of lung cancer produced a further attenuation of risk with hazard ratios suggesting a 58% increase in lung cancer risk (HR=1.58, 95% CI 1.29-1.93) for women who consumed $\geq$ 4 cups of coffee per a day when compared to women who did not drink coffee daily. This direct association was also observed in all regular and decaffeinated analyses as well with significant increases of risk reported in the highest consumption categories after fully adjusting for all lung cancer risk factors.

When the identical analyses were conducted within a population composed only of nonsmokers, no significant associations were observed in any consumption category for total coffee consumption, regular, or decaffeinated coffee (Table 6). Reported hazard ratios from the full multivariate model increased from 0.81 (95% CI 0.48-1.35) to 1.02 (95% CI 0.58-1.78) in the lowest to the highest consumption categories. This non-significant increase in risk was also observed in both regular and decaffeinated coffee consumption groups. Multivariate adjusted hazard ratios ranged from 0.69 (95% CI 0.44-1.10) to 0.97 (95% CI 0.53-1.80) for regular coffee consumption and 1.12 (95% CI 0.74-1.70) to 1.33 (95% CI 0.54-3.27) for decaffeinated consumption.

Women who reported daily consumption of tea had a significant 18% reduction of lung cancer risk when compared to women who did not drink tea daily (HR=0.82, 95% CI 0.70-0.96). We observed a non-significant inverse relationship between tea consumption and lung cancer risk after controlling for age, age and smoking status, and a full model that included all risk factors for lung cancer in three separate models. The full multivariate model yielded a non-significant 27% reduction risk in women who drank four or more cups of tea per a day when compared to non-daily drinkers (HR=0.73, 95% CI 0.47-1.11). No statistically significant results were observed in the other consumption categories as well. No significant results were observed in analyses conducted in populations of never smokers (Table 6) and former smokers (Table 8). Analysis conducted in a population of current smokers found no significant associations as well, but did report a 48% reduction in risk for women who drank ≥ 4 cups of tea per a day when compared to non-consumers (HR=0.54, 95% CI 0.22-1.18) (Table 7). Due to the fact that no associations were seen in a population composed of only never-smokers, this result is largely attributed to residual confounding due to smoking or may suggest possible effect modification.

During the model building process we assessed the possible need for interaction terms in our analysis. Only two interaction terms appeared significant in our analysis after the conduction of a likelihood ratio test in the total population. The interaction term for decaffeinated coffee and smoking status had a p-value of 0.02 while tea consumption and smoking status had a p-value of <0.001. The hazard proportional assumption was not maintained in any of the models that we conducted.

CHAPTER 4

DISCUSSION

This analysis, conducted on the large cohort population of 83,777 postmenopausal women who participated in the WHI Observational Study, suggested that there was no significant evidence of a relationship between total, regular, or decaffeinated coffee consumption and the risk of lung cancer. We initially conducted a multivariate analysis for each coffee exposure that included a smoking variable that allowed us to not only take into account smoking status, but also the amount of years that had passed since former smokers quit, and the amount of daily cigarettes smoked in current smokers. This careful adjustment resulted in a significant attenuation of the impact of confounding due to smoking on our reported hazard ratios. Nevertheless, results from this analysis suggested that there was a still a 50 to 60% increase of lung cancer risk in those who were in the higher consumption levels for total, regular, and decaffeinated coffee. We also conducted the same analysis in four separate study population composed solely of: 1) never smokers 2) former smokers 3) current smokers and 4) former and current smokers. Results from these analyses did not suggest any significant increase in nonsmokers, but we did observe residual increase in the populations of former and current smokers suggesting that our initial findings were impacted by this residual confounding. This two staged approach was repeated for tea as well. Results from these analyses suggest that overall tea consumption resulted in a non-significant decrease of the risk of lung cancer in all consumption levels, with the largest reduction of risk seen in current smokers.

Results from our initial analyses are consistent with the general trends observed in literature surrounding total coffee consumption and tea consumption. In 2010, Tang et al.'s published a meta-analysis that looked at five prospective cohorts and eight case-control studies conducted between 1966 and 2009. [10] When researchers stratified their results by study design, prospective studies had a significant 57% (RR = 1.57, 95% CI = 1.04–1.54) increase in lung

cancer risk associated with coffee consumption. Our initial multivariate model found almost an identical with a reported hazard ratio of 1.58 (95% CI 1.29-1.93).

Many of the previous studies conducted on tea consumption explored the specific effects of a certain type of tea (e.g black or green). Although our study was not able to distinguish type of tea consumed, our observed non-significant 27% reduction risk (HR=0.73, 95% CI 0.47-1.11) appears to be similar to reported results observed in another meta-analysis conducted by Tang et al. in 2009 which focused on black and green tea consumption.[15] After taking into account five prospective studies that looked at the association between tea consumption and green tea and four prospective cohort studies that looked at black tea, Tang et al. reported an RR of 0.68 (95%CI 0.45-1.02)and RR of 0.88 (95% CI 0.64-1.21) for green tea and black tea respectively. A limitation of our study is that we could not examine effects by type of tea.

To our knowledge, only one study reported results for decaffeinated coffee on lung cancer. Baker et al. conducted a hospital based case-control study in a population of 1979 American men and women from 1982-1998.[6] Baker and colleagues reported a significant 36% decrease in risk in those who consumed ≥2 cups/day of decaffeinated coffee when compared those who drank none (HR=0.64, 95% CI 0.51–0.80). Our reported results for decaffeinated coffee consumption differed greatly from Baker et al. We found no evidence of a reduction in risk in either our initial analysis on our total population or in our analysis conducted solely in a population of nonsmokers. After adjustment, we observed a significant 56% increase in risk (HR=1.56, 95% CI 1.17-2.07) associated with consuming ≥ 4 cups of decaffeinated coffee per a day in our total population. For never smokers, we observed a non-significant 37% increase in risk (HR=1.37, 95% CI 0.56-3.4). Observed differences could be due to two reasons. The first is that the fact that Baker and colleagues conducted their study in one hospital setting composed of men and women of varying ages which makes it difficult to compare to our population of postmenopausal women. Differences in hormones or physiology of disease could impact the ability for Baker et al.'s study results to be applied to our population. Second, Baker et al. had a

large loss to follow-up with only 50% of participants responding to their survey which assessed exposure. This could result in the study results being impacted by selection bias.

Two studies have looked at the association between coffee consumption and lung cancer risk in a population of non-smokers. Hu et al. conducted a population based case-control study of non-smoking women in eight Canadian provinces from 1994-1997.[20] After controlling for 10 year age groups, province of residence, education, and social class, the authors found a non-significant 20% reduction of risk in their largest consumption category (≥17.5 cups/ week) when compared to less than one cup a week (OR=0.80, 95% CI 0.4-1.8). Nyberg et al. also conducted a population based case-control study which looked at a population of Swedish men and women from 1989-1995.[9] They also observed a reduction of lung cancer risk associated with coffee consumption with the highest reduction in risk being observed in the highest consumption category (OR=0.50, 95% CI 0.24–1.06). The results from our analysis of non-smokers were fairly similar to those of Hu et al. Our results for 2-3 cups of regular coffee per a day, the equivalent of about 14 to 21 cups/ week, found a non-significant 1% reduction in risk (HR=1.00, 95% CI 0.68-1.45). Nyberg and colleagues results also suggested a null association, but reported odds ratios that were almost half of ours. Differences in results could be due to a few reasons. Our studies differed in the covariates included in analysis. Hu et al. controlled solely for province, education, and social class while Nyberg et al. controlled for many variables including occupational exposure and second hand smoke exposure. We were not able to control for occupational exposure or second hand exposure and this limitation may explain some of those differences between our reported results. The differences observed between Nyberg and our results may also be due to differences in study populations. Nyberg et al.'s study population contained men and women from Sweden which could impact our ability to compare their results to our population of postmenopausal women from the United States.

Although our results suggest that there is no significant association between total coffee, regular coffee, decaffeinated coffee, and tea consumption and lung cancer risk, it could be argued

that we observed effect modification in both smokers who drink coffee and smokers that drank tea. Smokers who drank tea had the highest observed reduction in risk (HR=0.52, 95%CI 0.22-1.18) while smokers who drank coffee had the largest increase in risk (HR=1.79, 95% CI 1.11-2.91). This suggests that tea may reduce the risk of lung cancer in postmenopausal women who are smokers while coffee consumption may increase the risk in smokers. Observed increases in coffee consumers could be due to the wide variety of nutrients found in coffee which could have similar effects as known risk factors such as beta-carotene in our smoker population. Due to the fact that we had a very small number of cases in some of our analyses, larger studies are required to determine if this observation is correct. It is much more likely that this observed effect was due to residual confounding due to smoking.

Our study had several strengths. Use of the data from the WHI allowed us to conduct our analysis in a large population of women who contributed over 900,000 person years of follow-up that was used in preliminary analysis. This long period of observation also allowed us to also obtain a large amount of confirmed lung cancer cases. To the best of our knowledge, our study was the first to use a prospective cohort design to analyze the effects of regular and decaffeinated coffee on lung cancer risk within a postmenopausal female population. We were also able to control for a variety of covariates including dietary and behavioral risk factors for lung cancer. Minimal loss of follow-up limited the possibility of selection bias impacting the results of this study. Distribution within covariate consumption categories had very little variation suggesting that our population was fairly homogenous.

There are also several limitations with our study. A very large concern within this study was limiting the effects of residual confounding due to smoking during analysis. Although we utilized a variable that greatly attenuated the effects of smoking on our hazard ratios, the significant increase risk observed in all three coffee consumption variables was no longer present when the same analysis was restricted to never smokers in this population. With this secondary analysis in mind, it is highly probable that our reported hazard ratios were confounded by the

residual effects of smoking and thus overestimate the true association between our exposure variables and lung cancer risk. This remaining residual confounding could be attributed to the fact that the data used to assess all components of the smoking variable was taken from the baseline survey. Future analysis will include pack years. Due to the nature of self-report data, which is how we obtained information surrounding coffee ,tea consumption, and lung cancer status, it is possible that non-differential misclassification of exposure and outcome could have occurred . If this did occur, it would have biased our results toward the null. We were also not able to look at our results in comparison to a population composed of never coffee or tea drinkers. Due to the fact that the lifestyle and behavior questionnaire only asked whether or not a woman drank tea on a daily basis, women who drink tea on a weekly, monthly, or a few times a year, were included in our referent category. With this fact in mind, our referent category includes women who had been exposed to regular, decaffeinated coffee or tea which would also bias our results towards the null. As mentioned above, we were able to control for many important covariates, but we were not able to include information surrounding family history of lung cancer, second hand smoke exposure, pack years, or occupational exposures. We also did not have access to information about the type of tea consumed and thus were not able to analyze possible differences in risk for different tea consumption categories.

Another possible limitation of our study could be the models that we used to conduct our analyses. Although we carefully built our models, tests that checked whether or not the Hazard Proportional Assumption was met suggest that the assumption was not upheld in our models. This observation is due to the fact that we categorized our age variable into three categories. Schoenfeld Residuals assess time related variables and thus when we included our categorical variable in analysis, we violated this time assumption. We will re-conduct our validity analysis and stratify the proportional hazard models by age. This will generate individual baseline hazard for each age strata which will be included in our final analyses.

CHAPTER 5

CONCLUSION

In conclusion, we were able to expand upon the knowledge surrounding the association between coffee and tea consumption through the use of a large prospective study. Our data suggested that there is no association between coffee consumption and lung cancer risk while tea consumption may be protective in a population of postmenopausal women. Observed positive associations for coffee consumption were largely attributed to residual confounding due to smoking. Future studies, with a focus on reducing the residual effects of smoking and exploring the possibility of effect modification, should be conducted in order to further the information on modifiable risk factors of lung cancer.

Table 1: Reported Coffee and Tea Consumption at Baseline: WHI Observational Study (1993-2010)

	N	%
Total Coffee		
None	24,164	28.84
1 cup/day	12,131	14.48
2-3 cups/day	31,986	38.18
≥ 4 cups/day	12,156	14.51
Missing	3,340	3.99
Regular Coffee		
None	35,897	42.85
1 cup/day	14,388	17.17
2-3 cups/day	24,006	28.65
≥ 4 cups/day	7,858	9.38
Missing	1,628	1.94
Decaffeinated Coffee		
None	55,679	66.46
1 cup/day	12,229	14.6
2-3 cups/day	10,855	12.96
≥ 4 cups/day	2,628	3.14
Missing	2,386	2.85
Tea		
None	61,629	73.56
1 cup/day	10,171	12.14
2-3 cups/day	8,503	10.15
≥ 4 cups/day	2,186	2.61
Missing	1,288	1.54

Table 2. Distribution of Covariates According to Total Coffee Consumption; WHI Observational Study (1993-2010)

	None		1 cup/d		2-3 cups/d		≥ 4 cups/d	
	N	%	N	%	N	%	N	%
Age at Baseline								
50-59	8726	36.11	3506	28.90	10100	31.58	4136	34.02
60-69	10052	41.60	5347	44.08	4390	44.99	5595	46.03
70-79	5386	22.29	3278	27.02	7496	23.44	2425	19.95
Race								
Native American/ Alaskan Indian	98	0.41	59	0.49	148	0.46	61	0.50
Asian/Pacific Islander	982	4.08	629	5.20	737	2.31	134	1.10
Black/ African American	3256	13.51	1275	10.54	1670	5.23	319	2.63
Hispanic/ Latino	868	3.60	647	5.35	1215	3.81	330	2.72
White	18586	77.13	9318	77.04	27804	87.15	11167	92.08
Other	306	1.27	167	1.38	328	1.03	117	0.96
Completed Education Level								
Less than High School	1245	5.20	626	5.20	1533	4.83	597	4.95
High School	5772	24.12	3386	28.11	8301	26.13	3324	27.54
1-2 Years of College/ Associates Degree	6273	26.21	3118	25.91	8706	27.41	3233	26.79
Bachelor Degree	5819	24.31	2823	23.45	7454	23.47	2670	22.12
Masters/PHD	4826	20.16	2086	17.33	5772	18.17	2245	18.60
Region of Residence								
NorthEast	4963	20.54	3031	24.99	8086	25.28	2677	22.02
South	6239	25.82	3364	27.73	8099	25.32	2531	20.82
Midwest	5330	22.06	2107	17.37	6661	20.82	3502	28.81
West	7632	31.58	3626	29.92	9140	28.58	3446	28.35
BMI at Baseline	27.52±6.17		27.11±5.62		27.09±5.44		27.06±5.43	
Physical activity (METs/week)	13.97±14.88		13.08±13.96		13.94±14.20		13.69±14.32	
Energy Intake (kcal/ day)	1523.64±704.61		1501.97±683.60		1551.95±667.73		1642.30±765.37	
% Calories from Fat	30.09±8.44		30.20±8.34		31.14±8.78		30.48±8.46	
Daily Fruit Consumption (med. serv/day)	2.14±1.29		2.03±1.29		1.99±1.24		1.89±1.25	
Daily Vegetable Consumption (med.serv/day)	2.25±1.40		2.19±1.29		2.27±1.32		2.30±1.36	
Alcohol Intake								
Non-Drinker	4234	17.65	1533	12.72	2433	7.65	855	7.08
Past Drinker	5740	23.93	2208	18.32	4924	15.48	2094	17.33
Current Drinker	14008	58.42	8314	68.96	24499	76.87	9135	75.59
Tea Consumption								
None	16427	68.783	8778	73.05	24277	76.45	10078	83.42
1 cup/day	2719	11.38	1793	14.92	4304	13.55	1011	8.37
2-3 cups/day	3409	14.26	1221	10.16	2763	8.70	840	6.95
≥ 4 cups/day	1346	5.63	225	1.87	412	1.30	152	1.26
Smoking Status								
Never	14704	61.56	6674	55.78	14677	46.51	4585	38.24
Ever	8364	35.02	4772	39.89	14847	47.05	5809	48.44
Current	818	3.42	518	4.33	2032	6.44	1597	13.32
Smoking Status								
Never	14704	61.56	6674	55.78	14677	46.51	4585	38.24
Past:Quit < 10 years before enrollment	1014	4.25	622	5.20	2180	6.91	1114	9.29
Past: Quit 10-19 years before enrollment	2010	8.41	1288	10.77	4017	12.73	1631	13.60
Past: Quit 20-29 years before enrollment	2107	8.82	1171	93.79	3569	11.31	1521	11.02
Past: Quit ≥ 30 years before enrollment	3233	13.54	1691	14.13	5081	16.10	1743	14.54
Current: Smokes < 5 cigs/day	205	0.86	138	1.15	443	1.40	198	1.65
Current: Smokes 5-14 cigs/day	256	1.07	198	1.65	726	2.30	468	3.90
Current: Smokes 15-24 cigs/day	249	1.04	122	1.02	533	2.01	605	5.05
Current: Smokes ≥25 cigs/day	108	0.45	60	0.50	230	0.73	326	2.72
Hormone Replacement Therapy Use								
Never	9675	40.08	4640	38.30	12133	37.96	5056	41.58
Ever	3297	13.66	1720	14.20	4347	13.60	1669	13.74
Current	11168	46.26	5755	47.50	15483	48.44	5427	44.68

Table 3. Distribution of Covariates According to Tea Consumption: WHI Observational Study (1993-2010)

	None		1 cup/d		2-3 cups/d		≥ 4 cups/d	
	N	%	N	%	N	%	N	%
Age at Baseline								
50-59	20519	33.29	3096	30.44	2615	30.75	761	34.81
60-69	27104	43.98	4509	44.33	3730	43.91	967	44.24
70-79	14006	22.73	2566	25.23	2154	25.33	458	20.95
Race								
Native American/ Alaskan Indian	297	0.48	28	0.28	42	0.50	11	0.50
Asian/Pacific Islander	1620	2.64	428	4.22	389	4.59	91	4.17
Black/ African American	5607	9.12	649	6.40	432	5.10	64	2.93
Hispanic/ Latino	2569	4.18	350	3.45	255	3.01	53	2.43
White	50687	82.48	8569	84.44	7239	85.39	1938	88.74
Other	677	1.10	124	1.22	121	1.43	27	1.24
Completed Education Level								
Less than High School	3166	5.18	498	4.94	439	5.20	96	4.45
High School	15877	25.97	2602	25.79	2325	27.56	558	25.85
1-2 Years of College/ Associates Degree	16305	26.67	2704	26.85	2244	26.60	578	26.77
Bachelor Degree	14370	23.50	2389	23.67	1874	22.21	520	24.09
Masters/PHD	11420	18.68	1893	18.76	1554	18.42	407	18.85
Region of Residence								
NorthEast	12980	21.06	3243	31.88	2320	27.28	561	25.66
South	15222	24.70	2591	25.47	2493	29.32	669	30.60
Midwest	14489	23.51	1709	16.80	1409	16.57	352	16.10
West	18938	30.73	2628	25.84	2281	26.83	604	27.63
BMI at Baseline	27.29±5.73		26.87±5.44		27.08±5.56		27.2±5.93	
Physical activity (METs/week)	13.80±14.44		14.08±14.47		13.24±13.88		13.27±14.67	
Energy Intake (kcal/ day)	1531.69±686.45		1573.43±679.15		1605.40±772.40		1660.71±747.27	
% Calories from Fat	30.08±8.60		29.86±8.13		30.52±8.42		30.54±8.97	
Daily Fruit Consumption (med. serv/day)	2.00±1.30		2.12±1.29		2.04±1.28		1.97±1.34	
Daily Vegetable Consumption (med.serv/day)	2.22±1.33		2.37±1.34		2.35±1.36		2.41±1.45	
Alcohol Intake								
Non-Drinker	6861	11.20	1092	10.81	1083	12.82	280	12.93
Past Drinker	11690	19.09	1712	16.95	1478	17.49	414	19.12
Current Drinker	42693	69.71	7299	72.24	5889	69.69	1471	67.95
Total Coffee Consumption								
None	16427	27.58	2719	27.67	3409	41.41	1346	63.04
1 cup/day	8778	14.74	1793	18.25	1221	14.83	225	10.54
2-3 cups/day	24277	40.76	4304	43.80	2763	33.56	412	19.30
≥ 4 cups/day	10078	16.92	1011	10.29	840	10.20	152	7.12
Smoking Status								
Never	30363	49.95	5558	55.35	4610	54.91	1086	50.35
Ever	26423	43.57	4019	40.02	3331	39.68	877	40.66
Current	4001	6.58	465	4.63	454	5.41	194	8.99
Smoking Status								
Never	30363	49.95	5558	55.35	4610	54.91	1086	50.35
Past:Quit < 10 years before enrollment	3952	6.50	511	5.09	454	5.41	113	5.24
Past: Quit 10-19 years before enrollment	7144	11.75	985	9.81	839	9.99	210	9.74
Past: Quit 20-29 years before enrollment	6347	10.44	984	9.80	809	9.64	215	9.97
Past: Quit ≥ 30 years before enrollment	8980	14.77	1593	15.33	1229	14.64	339	15.72
Current: Smokes < 5 cigs/day	770	1.27	118	1.18	96	1.14	32	1.48
Current: Smokes 5-14 cigs/day	1384	2.28	132	1.31	141	1.68	48	2.23
Current: Smokes 15-24 cigs/day	1284	2.11	157	1.56	152	1.81	66	3.06
Current: Smokes ≥25 cigs/day	563	0.93	58	0.58	65	0.77	48	2.23
Hormone Replacement Therapy Use								
Never	24063	39.08	4022	39.63	3372	39.68	905	41.42
Ever	8337	13.54	1449	14.26	1230	14.47	287	13.14
Current	29171	47.38	4685	46.11	3892	45.85	993	45.45

Table 4: Age-Adjusted Hazard Ratios for Covariates and Risk of Lung Cancer: WHI Observational Study (1993-2010)

	Cases (N)	Person Years	HR	95 % CI	P-Value
Age at Baseline					
50-59	185	39139	1.00	Referent	
60-69	546	66616	1.05	0.87-1.21	0.26
70-79	307	50282	0.56	0.46-0.67	<0.001
Total	1038				
Race					
White	918	130223	1.00	Referent	
Native American/ Alaskan Indian	6	764	1.06	0.47-2.36	0.52
Asian/Pacific Islander	19	3915	1.02	0.65-1.61	0.67
Black/ African American	62	13292	0.72	0.55-0.93	0.13
Hispanic/ Latino	17	5649	0.55	0.34-0.89	0.87
Other	11	1749	0.88	0.49-1.60	0.17
Total	1033				
Completed Education Level					
Less than High School	51	9110	1.00	Referent	
High School	258	41583	1.09	0.81-1.47	<0.001
1-2 years of college/ Associates Degree	305	41967	1.22	0.91-1.64	<0.001
Bachelor Degree	253	3517	1.25	0.93-1.69	<0.001
Masters/PHD	163	13209	1.08	0.79-1.50	0.07
Total	1,030				
Region of Residence					
NorthEast	279	37098	1.00	Referent	
South	257	39745	0.94	0.79-1.11	<0.001
Midwest	188	32147	0.86	0.72-1.04	<0.001
West	314	47049	0.94	0.80-1.10	<0.001
Total	1038				
BMI at Baseline					
Normal	482	60101	1.00	Referent	
Underweight	8	1628	0.50	0.25-1.01	0.37
Overweight	330	51698	0.79	0.69-0.91	<0.001
Obese	210	40840	0.60	0.51-0.71	<0.001
Total	1030				
Physical activity (METs/week)					
<5	362	54112	1.00	Referent	
5 to < 10	148	26131	0.90	0.74-1.08	<0.001
10 to <20	252	38140	1.06	0.91-1.25	<0.001
20 to<30	137	18728	1.22	1.00-1.48	0.001
≥30	139	18927	1.21	1.00-147	0.02
Total	1038				
Energy Intake (kcal/ day)					
1st Quartile	272	40035	1.00	Referent	
2nd Quartile	246	38729	0.91	0.77-1.08	<0.001
3rd Quartile	271	38151	1.02	0.87-1.22	<0.001
4th Quartile	248	38952	0.90	0.76-1.07	0.007
Total	1037				
% Calories from Fat					
1st Quartile	253	37012	1.00	Referent	
2nd Quartile	248	38224	0.90	0.76-1.08	<0.001
3rd Quartile	238	39481	0.84	0.70-1.00	<0.001
4th Quartile	298	41149	0.97	0.82-1.15	0.002
Total	1037				

Daily Fruit Consumption (medium serv/day)					
1st Quartile	331	39755	1.00	Referent	
2nd Quartile	293	46284	0.78	0.67-0.92	<0.001
3rd Quartile	239	37231	0.76	0.64-0.90	<0.001
4th Quartile	174	32596	0.65	0.54-0.78	<0.001
Total	1037				
Daily Vegetable Consumption (medium serv/day)	267	40769	1.00	Referent	
1st Quartile	270	38992	1.09	0.92-1.29	<0.001
2nd Quartile	273	38050	1.15	0.97-1.36	<0.001
3rd Quartile	227	38056	0.95	0.80-1.14	<0.001
4th Quartile	1037				
Total					
Alcohol Intake					
Non-Drinker	47	17931	1.00	Referent	
Past Drinker	208	31838	2.15	1.56-2.95	0.002
Current Drinker: <1 Drink/month	86	17378	1.79	1.25-2.55	0.208
Current Drinker: <1 Drink/wk	212	30508	2.49	1.81-3.42	<0.001
Current Drinker: 1-<7 Drinks/wk	281	37471	2.73	2.00-3.72	<0.001
Current Drinker: ≥ 7 Drinks/wk	199	19709	3.36	2.44-4.62	<0.001
Total	1033				
Tea Consumption					
None	823	114882	1.00	Referent	
1 cup/day	102	18504	0.79	0.64-0.97	0.01
2-3 cups/day	76	15878	0.67	0.53-0.84	0.12
≥ 4 cups/day	23	4330	0.65	0.43-0.98	0.68
Total	1024				
Total Coffee Consumption					
None	196	44573	1.00	Referent	
1 cup/day	104	22485	1.09	0.86-1.38	<0.001
2-3 cups/day	435	59222	1.63	1.38-1.93	<0.001
≥ 4 cups/day	259	23453	2.31	1.92-2.78	0.001
Total	994				
Smoking Status					
Never	178	73915	1.00	Referent	
Former: Quit <10 years ago	161	9922	5.69	4.56-7.09	0.30
Former: Quit 10-19 years ago	205	18831	3.84	3.15-4.70	0.68
Former: Quit 20-29 years ago	112	15402	2.84	2.24-3.60	0.51
Former: Quit ≥30 years ago	115	22962	1.88	1.49-2.38	0.35
Current: < 5 cigs/day	14	1893	3.04	1.76-5.24	0.77
Current: 5-14 cigs/day	57	4180	4.02	2.98-5.43	0.93
Current: 15-24 cigs/day	108	4510	6.83	5.37-8.68	0.95
Current: ≥ 25 cigs/day	73	1977	10.96	8.30-14.47	0.21
Total	1023				
Hormone Replacement Therapy Use					
Never	418	65721	1.00	Referent	
Ever	159	23352	1.03	0.86-1.24	<0.001
Current	460	66827	1.23	1.07-1.39	<0.001
Total	1037				

Table 5. Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals for Lung Cancer Status by Daily Coffee Consmption Type and Tea; WHI Observational Study (1993-2010)

	Cases	Person Years	Age-Adjusted		Cases	Person Years	Multivariate HR¨		Cases	Person Years	Multivariate	
	N		HR	95% CI	N		HR	95% CI	N		HR	95% CI
Total Daily Coffee Consumption *												
None	196	4457	1.00	Referent	196	44043	1.00	Referent	191	42298	1.00	Referent
1 cup/day	104	22485	1.08	0.86-1.38	104	22093	1.00	0.73-1.32	100	21272	0.99	0.78-1.27
2-3 cups/day	435	59222	1.63	1.38-1.93	428	58419	1.30	1.04-1.63	415	56615	1.30	1.09-1.55
≥ 4 cups/day	259	2347	2.31	1.92-2.78	256	23128	1.34	1.03-1.76	246	22370	1.58	1.29-1.93
Total	994				984				952			
Daily Regular Coffee Consumption **												
None	340	66367	1.00	Referent	338	65519	1.00	Referent	329	62969	1.00	Referent
1 cup/day	143	26314	1.09	0.90-1.33	143	25838	1.09	0.90-1.33	131	23827	1.02	0.83-1.25
2-3 cups/day	349	44761	1.47	1.27-1.71	341	44122	1.31	1.13-1.52	321	41334	1.25	1.06-1.46
≥ 4 cups/day	184	15473	2.04	1.71-2.44	183	15267	1.52	1.26-1.83	171	14425	1.47	1.21-1.79
Total	1016				1005				952			
Daily Decaffeinated Coffee Consumption ***												
None	673	104257	1.00	Referent	668	102893	1.00	Referent	649	99324	1.00	Referent
1 cup/day	129	22515	0.92	0.76-1.11	128	22153	0.96	0.79-1.16	113	20701	0.88	0.72-1.07
2-3 cups/day	149	19705	1.22	1.02-1.46	144	19431	1.18	0.98-1.41	137	17892	1.22	1.01-1.48
≥ 4 cups/day	57	5081	1.69	1.29-2.22	57	4980	1.53	1.16-2.00	53	4637	1.56	1.17-2.07
Total	1008											
Daily Tea Consumption ****												
None	823	11488	1.00	Referent	811	113285	1.00	Referent	758	106573	1.00	Referent
1 cup/day	102	18504	0.79	0.64-0.97	102	18196	0.90	0.73-1.10	97	17111	0.93	0.75-1.15
2-3 cups/day	76	15878	0.67	0.53-0.84	76	15651	0.71	0.56-0.90	75	14807	0.81	0.64-1.03
≥ 4 cups/day	23	4330	0.65	0.43-0.98	23	4278	0.62	0.41-0.93	22	4064	0.73	0.47-1.11
Total	1024				1012				952			

¨ Adjusted for Age at Enrollment, Smoking Status (Never, Former [including years since quitting: ≥30, 20–29, 10–19, and ,10], and Current [including cigarettes smoked per day: <5, 5–14,15–24, and ≥25]),

*Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Smoking Status (Never, Former [including years since quitting: ≥30, 20–29, 10–19, and ,10], and Current [including cigarettes smoked per day: <5, 5–14,15–24, and ≥25]), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quantiles), and History of Hormone Replacement Use (Never, Ever, Current)

**Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Smoking Status (Never, Former [including years since quitting: ≥30, 20–29, 10–19, and ,10], and Current [including cigarettes smoked per day: <5, 5–14,15–24, and ≥25]), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), and Decaffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day).

*** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Smoking Status (Never, Former [including years since quitting: ≥30, 20–29, 10–19, and ,10], and Current [including cigarettes smoked per day: <5, 5–14,15–24, and ≥25]), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), and Caffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day).

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Table 6. Hazard Ratios and 95% CI of Lung Cancer Status by Daily Coffee Consumption Type and Tea in Never Smokers;WHI Observational Study (1993-2010)

	Cases	Person Years	Age-Adjusted HR	95% CI	Cases	Person Years	Multivariate HR	95% CI
Daily Total Coffee Consumption *								
None	62	259	1.00	Referent	59	24856	1.00	Referent
1 cup/day	22	11795	0.82	0.50-1.34	20	11331	0.81	0.48-1.35
2-3 cups/day	66	25447	1.09	0.77-1.54	66	24612	1.15	0.80-1.67
≥ 4 cups/day	20	7875	1.09	0.66-1.80	17	7635	1.02	0.58-1.78
Total	170				162			
Daily Regular Coffee Consumption **								
None	91	35635	1.00	Referent	86	34201	1.00	Referent
1 cup/day	24	13334	0.71	0.45-1.11	22	12266	0.70	0.44-1.12
2-3 cups/day	44	18661	0.90	0.63-1.29	43	17381	0.99	0.68-1.45
≥ 4 cups/day	15	4873	1.15	0.67-1.99	11	4586	0.96	0.58-1.81
Total	174				162			
Daily Decaffeinated Coffee Consumption ***								
None	122	50972	1.00	Referent	115	49107	1.00	Referent
1 cup/day	29	10987	1.14	0.76-1.70	25	10206	1.02	0.66-1.58
2-3 cups/day	17	8168	0.93	0.56-1.55	17	7479	0.99	0.59-1.65
≥ 4 cups/day	5	1739	1.21	0.50-2.97	5	1642	1.37	0.56-3.40
Total	173				162			
Daily Tea Consumption ****								
None	128	52899	1.00	Referent	118	49710	1.00	Referent
1 cup/day	24	9805	0.95	0.61-1.46	22	9197	0.95	0.60-1.50
2-3 cups/day	17	1997	0.88	0.53-1.46	17	7632	0.97	0.58-1.61
≥ 4 cups/day	5	8090	0.88	0.36-2.15	5	1895	0.99	0.40-2.45
Total	174							

*Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quantiles), and History of Hormone Replacement Use (Never, Ever, Current)

**Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), and Decaffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day).

*** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), and Caffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day).

**** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), and Total Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day).

Table 7. Hazard Ratios and 95% CI of Lung Cancer Status by Daily Coffee Consumption Type in Current Smokers;WHI Observational Study (1993-2010)

	Cases	Person-Years	Age-Adjusted	95% CI	Cases	Person- Years	Multivariate HR¨	95%CI	Cases	Person-Years	Multivariate HR	95% CI
Daily Total Coffee Consumption *												
None	22	2014	1.00	Referent	22	2014	1.00	Referent	22	1941	1.00	Referent
1 cup/day	19	1137	1.94	1.05-3.60	19	1137	1.94	1.05-3.60	19	1101	1.68	0.89-3.14
2-3 cups/day	88	4800	1.76	1.11-2.82	88	4800	1.76	1.11-2.82	86	4714	1.41	0.87-2.20
≥ 4 cups/day	114	4154	2.45	1.55-3.87	114	4154	2.45	1.55-3.87	111	4037	1.79	1.11-2.91
Total	243				243							
Daily Regular Coffee Consumption **												
None	44	3180	1.00	Referent	44	3180	1.00	Referent	43	3076	1.00	Referent
1 cup/day	20	1411	1.19	0.70-2.03	20	1411	1.14	0.67-1.94	20	1306	1.10	0.64-1.89
2-3 cups/day	87	4386	1.4	1.00-2.08	87	4386	1.50	1.04-2.16	83	4182	1.35	0.91-1.99
≥ 4 cups/day	97	3396	1.97	1.38-2.81	97	3396	1.80	1.26-2.58	92	3230	1.64	1.11-2.43
Total	248				248				238			
Daily Decaffeinated Coffee Consumption ***												
None	178	9058	1.00	Referent	178	9058	1.00	Referent	176	8837	1.00	Referent
1 cup/day	22	1242	0.97	0.62-1.51	22	1242	1.00	0.64-1.56	19	1167	0.93	0.57-1.50
2-3 cups/day	30	1332	1.14	0.77-1.67	30	1332	1.15	0.78-1.70	27	1238	1.24	0.81-1.88
≥ 4 cups/day	16	572	1.29	0.77-2.15	16	572	1.12	0.67-1.87	16	550	1.29	0.76-2.20
Total	246				246				238			
Daily Tea Consumption ****												
None	216	9868	1.00	Referent	216	9868	1.00	Referent	204	9371	1.00	Referent
1 cup/day	15	976	0.86	0.51-1.45	15	976	0.77	0.46-1.31	15	907	0.85	0.51-1.44
2-3 cups/day	13	1078	0.53	0.30-0.93	13	1078	0.58	0.33-1.02	13	1029	0.66	0.37-1.17
≥ 4 cups/day	7	517	0.62	0.29-1.31	7	518	0.52	0.25-1.12	6	486	0.52	0.22-1.18
Total	251				251				238			

¨Adjusted for Age at Enrollment and and Amount of cigarettes smoked daily (<5,5-14, 15-24, 25-34)

*Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quantiles),History of Hormone Replacement Use (Never, Ever, Current), and Amount of cigarettes smoked daily (<5. 5-14, 15-24, 25-34)

**Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current),Decaffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day), and and Amount of cigarettes smoked daily (<5. 5-14, 15-24, 25-34)

*** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), Caffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day), and and Amount of cigarettes smoked daily (<5. 5-14, 15-24, 25-34)

**** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current),Total Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day), andand Amount of cigarettes smoked daily (<5. 5-14, 15-24, 25-34).

Table 8. Hazard Ratios and and 95% CI of Lung Cancer Status by Daily Coffee Consumption Type and Tea in Former Smokers;WHI Observational Study (1993-2010)

	Cases	Person Years	Age- Adjusted HR	95% CI	Cases	Person Years	Multivariate HR¨	95%CI	Cases	Person Years	Multivariate HR	95% CI
Total Daily Coffee Consumption *												
None	134	18329	1.0	Referent	134	18144	1.00	Referent	132	17443	1.00	Referent
1 cup/day	82	10452	1.12	0.85-1.47	82	10298	1.13	0.86-1.49	80	9942	1.04	0.79-1.38
2-3 cups/day	367	33322	1.49	1.22-1.82	362	32972	1.47	1.21-1.80	349	32003	1.30	1.06-1.59
≥ 4 cups/day	237	15425	1.94	1.57-2.40	236	15253	1.87	1.51-2.32	229	14735	1.66	1.33-2.07
Total	820				814				790			
Daily Regular Coffee Consumption **												
None	249	30229	1.00	Referent	247	29884	1.00	Referent	243	28769	1.00	Referent
1 cup/day	119	12676	1.20	0.97-1.50	119	12504	1.22	0.98-1.51	109	11561	1.15	0.92-1.44
2-3 cups/day	301	25748	1.41	1.19-1.66	297	25462	1.39	1.17-1.64	278	23952	1.32	1.10-1.58
≥ 4 cups/day	168	10489	1.75	1.44-2.13	168	10393	1.37	1.37-2.04	160	9839	1.62	1.31-2.01
Total	837				831				790			
Daily Decaffeinated Coffee Consumption ***												
None	548	52478	1.00	Referent	546	51922	1.00	Referent	534	50218	1.00	Referent
1 cup/day	100	11291	0.89	0.72-1.10	99	11166	0.89	0.72-1.10	88	10495	0.85	0.68-1.07
2-3 cups/day	130	11415	1.14	0.94-1.38	127	11262	1.34	0.94-1.38	120	10414	1.22	0.99-1.50
≥ 4 cups/day	52	3283	1.50	1.13-1.99	52	3241	1.50	1.13-2.00	48	2996	1.60	1.18-2.16
Total	830				824				790			
Tea Consumption ****												
None	689	61064	1.00	Referent	683	60387	1.00	Referent	640	56863	1.00	Referent
1 cup/day	78	8490	0.88	0.70-1.11	78	8391	0.91	0.72-1.14	75	7914	0.95	0.75-1.21
2-3 cups/day	59	7663	0.66	0.51-0.87	59	711	0.68	0.52-0.89	58	7175	0.76	0.58-1.00
≥ 4 cups/day	18	2308	0.62	0.38-0.98	18	2280	0.60	0.37-0.96	17	2170	0.70	0.43-1.15
Total	844				838				790			

¨Adjusted for Age at Enrollment and and Amount of years since quitting (<10, 10-19, 20-29, ≥30)

*Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quantiles), History of Hormone Replacement Use (Never, Ever, Current), and Amount of years since quitting (<10, 10-19, 20-29, ≥30)

**Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), Decaffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day), and Amount of years since quitting (<10, 10-19, 20-29, ≥30)

*** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Tea Consumption (None, 1 cup/day, 2-3 cups/day,≥ 4 cups/day) , Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), Caffeinated Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day),and Amount of years since quitting (<10, 10-19, 20-29, ≥30).

**** Adjusted for Age at Enrollment (50-59, 60-69, 70-79), Race (American Indian/ Alaskian, Asian or Pacific Islander, Black or African American,Hispanic/Latino, White, Other), Education (Less than Highschool, Highschool, 1-2 Years of College/Associates Degree, Bachelor Degree, Masters/PhD) , BMI (Continuous), Recreational Physical Activity(< 5mets/wk, 5-<10 mets/wk, 10-<20 mets/wk, 20-<30 mets/wk,≥ 30 mets/wk) , Alcohol Intake (nondrinker, past drinker,and current drinker [including frequency:<1drink/month, <1 drink/week, 1 to <7 drinks/week, and ≥7 drinks/week]), Total Energy Intake (Quartiles), Percent of Calories from Fat (Quartiles), Total Fruit Intake(Quartiles), Total Vegetable Intake (Quartiles), History of Hormone Replacement Use (Never, Ever, Current), Total Coffee Consumption (None, 1 cup/day, 2-3 cups/day, 4 cups/day), and and Amount of years since quitting (<10, 10-19, 20-29, ≥30).

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