THESIS

COFFEE CONSUMPTION INCREASES RISK OF ADVANCED BREAST CANCER AMONG SINGAPORE CHINESE WOMEN

Submitted by

Lei Zhu

Department of Environmental and Radiological Health Sciences

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Master's Committee:

Advisor: Annette Bachand
Co-Advisor: Lesley Butler

Tracy Nelson-Ceschin

ABSTRACT

COFFEE CONSUMPTION INCREASES RISK OF ADVANCED BREAST CANCER AMONG SINGAPORE CHINESE WOMEN

Background: Experimental data support both a protective and risk enhancing effect of coffee compounds on breast cancer development. A few retrospective studies conducted before 1988 also reported inconsistent findings. However, more recent prospective epidemiological data do not support a relationship between coffee intake and breast cancer risk among western populations, and well-conducted studies among Asian population are lacking. Coffee is one of the most commonly consumed beverages, but more among western populations than most Asian populations. In Singapore with relatively recent economic development, aspects of western diet and lifestyle, including coffee consumption, have become more prevalent. Even though the breast cancer incidence rate kept increasing in Singapore during last three decades, it is still much lower than western countries. Since many contributing factors (such as diet and lifestyle) to the lower risk profile among Asian women compared with US women, conducting prospective studies on evaluating the association between coffee intake and breast cancer risk among this Asian population help us have opportunity to observe the breast cancer-coffee association if there is one, among this lower breast cancer profile population.

Objective: To evaluate the effect of coffee consumption and overall caffeine intake on breast cancer incidence among women in the Singapore Health Study. To achieve this objective, we

have the following analysis strategies: 1) Evaluate the effect of coffee consumption and overall caffeine intake on breast cancer incidence; 2) Restrict the analysis to the subgroup group: late stage breast cancer cases (metastatic or ≥5cm or present in lymph nodes vs. localized disease), since we only observed the statistically significant findings among the advanced disease cases; 3) Conduct subgroup analysis by estrogen/progesterone receptor (ER/PR) status; 4) Conduct stratified analyses by potential effect modifier: below and above median BMI.

Methods: At baseline, between 1993 and 1998, information on dietary history from 35,303 Singaporean Chinese women aged 45 to 74 years was collected by trained interviewers using a structured questionnaire. Using Cox regression models, we calculated hazard ratios (HR) and 95% confidence intervals (CIs) adjusted for potential confounders. Stratified analyses by menopausal status, stage of disease, and body mass index (BMI) were conducted to evaluate potential effect modification.

Results: After a mean follow-up of 10 years, 629 women developed breast cancer. Average intake among coffee drinkers (80% of the study population) was 1.5 cups/day (interquartile range=0.8, 2.3), compared with average 3.2 cups/day coffee consumption in United States. Restricting the analysis to coffee, overall, women consuming ≥2 cups of coffee per day had a statistically non-significant increase in risk of breast cancer compared with coffee nondrinkers or monthly drinkers (HR=1.23; 95% CI: 0.98, 1.54). There was no association with either coffee or caffeine intake and localized breast cancer risk. However, the positive

overall association strengthened and became statistically significant when the analysis was restricted to advanced breast cancer (n=272) (HR=1.90; 95% CI: 1.30, 2.77). Considering total caffeine consumed, results were similar (HR = 2.23; 95% CI: 1.52, 3.26) comparing the highest (median amount (IQR) = 244.96 mg (60.79)) to the lowest quartile (median amount (IQR) = 18.59 mg (32.77)) of caffeine intake. The associations between overall coffee and caffeine intake and advanced breast cancer did not differ by menopausal status. We conducted stratified analyses by BMI and found that the adverse effect of coffee intake on the development of advanced breast cancer was present only among heavier women (BMI ≥median, 23 kg/m^2) (HR=2.35; 95% CI: 1.51, 3.66; P for interaction=0.02).

Conclusion: We provide the first prospective evidence among Chinese women suggesting an adverse effect of coffee consumption at relatively low levels of intake on advanced stage breast cancer. Our data suggest that a higher BMI ≥23 kg/m^2, may increase the adverse effect of coffee on advanced breast cancer development.

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DEDICATION

This thesis was dedicated to my wonderful parents, grandparents, and the best friends. I always know how lucky I am to have them in my life. I cannot love them enough.

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CHAPTER 1: INTRODUCTION

1.1 The Singapore Chinese Health Study

The Singapore Chinese Health Study is a population-based prospective cohort study. This study was originally designed for the long-term study of genetic, dietary and other environmental determinants of cancer and other chronic diseases. The study population consisted of permanent residents or citizens of Singapore who resided in government-built housing estates (86% of population was included). The study was restricted to individuals who were belonging to two major dialect groups of Chinese in Singapore: the Hokkiens and the Cantonese. Between April 1993 and December 1998, 63,257 individuals (aged 45 to 74 years old), approximately 85% of those eligible, were enrolled. The cohort has been followed for mortality, cancer incidence, and other major health outcome occurrences through the Singapore Cancer Registry and the Singapore Registry of Births and Deaths, as well as the address/telephone updates. During 1999-2004 and 2006-2012, telephone and in-person interviews were conducted to update smoking, drinking, tea, coffee, exercise, medical history and for women, menstrual history. Additionally, the Singapore Chinese Health Study provides information on coffee consumption from a food frequency questionnaire, which was specifically developed and validated in this population; the response rate was high (83%) and data were collected through face to face interviews by trained interviewers. There was little loss follow-up.

1.2 Rationale

Experimental studies suggested both a positive and negative effect of coffee and its compounds on breast cancer risk. Before 1988, retrospective epidemiologic studies also reported inconsistent findings for an association between coffee consumption and breast cancer risk [1-6]. More recently, many prospective studies have been conducted among western populations to evaluate the association between breast cancer and coffee consumption [7-15], and none reported a significant association overall. However, some association among late stage of breast cancer [10] and higher BMI [16] was found in two of the prospective studies. Therefore, we investigated the overall breast cancer-coffee intake association and the association among late stage and higher BMI in the Singapore Chinese Health Study.

While the Singapore Chinese population is at a low-risk of breast cancer, in comparison to the US and many Europe countries, recently, discernible rises in breast cancer incidence have been observed, which most likely due at least in part to the changes in diet and lifestyle resembling a shift from ‘traditional’ to Western cultural influences. Additionally, Asian population has many contributing factors to the lower risk profile due to different diet and life style, compared with US women [17]. Since well-conducted large prospective studies on this topic are lacking among Asian population are lacking, we evaluate coffee-breast cancer association among Singapore Chinese population, a unique population who drink both tea and coffee.

1.3 Study Aim

To evaluate the effect of coffee consumption and overall caffeine intake on breast cancer incidence among women in the Singapore Health Study.

Analysis strategies:

① Evaluate the effect of coffee consumption and overall caffeine intake on breast cancer incidence.

② Restrict the analysis to late stage breast cancer cases.

③ Further restrict the analysis to late stage breast cancer cases with known ER/PR status.

④ Conduct stratified analyses by potential effect modifier: menopausal status, duration of follow up, and BMI.

CHAPTER 2: LITERATURE REVIEW

2.1 Breast cancer prevalence: Singapore vs. other parts of the world

Breast cancer is the most commonly diagnosed cancer among women in the world [18]. Chinese women in Singapore had among the lowest rates of breast cancer worldwide until 1972. However, in Singapore, the breast cancer incidence has increased over the last 40 years, nearly three-fold, from 20 per 100,000 per year for 1968-1972 [19, 20] to its current level, 61 per100,000 per year [21]. The increase may be due in part to increased use of mammography, and a shift to consuming a more western diet and lifestyle that includes an increase in coffee intake.

2.2 Breast cancer risk factors

The established risk factors of breast cancer include having a family history of breast cancer, mutations in genes BRCA1 and/or BRCA2, younger age at menarche (age 12 or younger), older age at menopause, shorter menstrual cycle length, older age at first full-term pregnancy, having fewer or no children, exogenous estrogens at menopause, and higher circulating hormones (e.g. estrogens, progesterone, and prolactin) [8, 15, 22-32]. Other possible risk factors include dietary factors, such as red and processed meat [33], smoking [34], alcohol consumption [33, 34]. The magnitude of association for these risk factors is different, from weak, modest, to strong risk factors [35], as what we see below (Figure 1).

A major factor involved in the development of breast cancer is lifetime exposure to estrogens. Experimental studies reported that higher circulating estrogens are established risk factors for breast cancer [36]. The Women's Health initiative was the first randomized controlled trial to confirm that estrogen plus progestin increase the breast cancer risk [37].

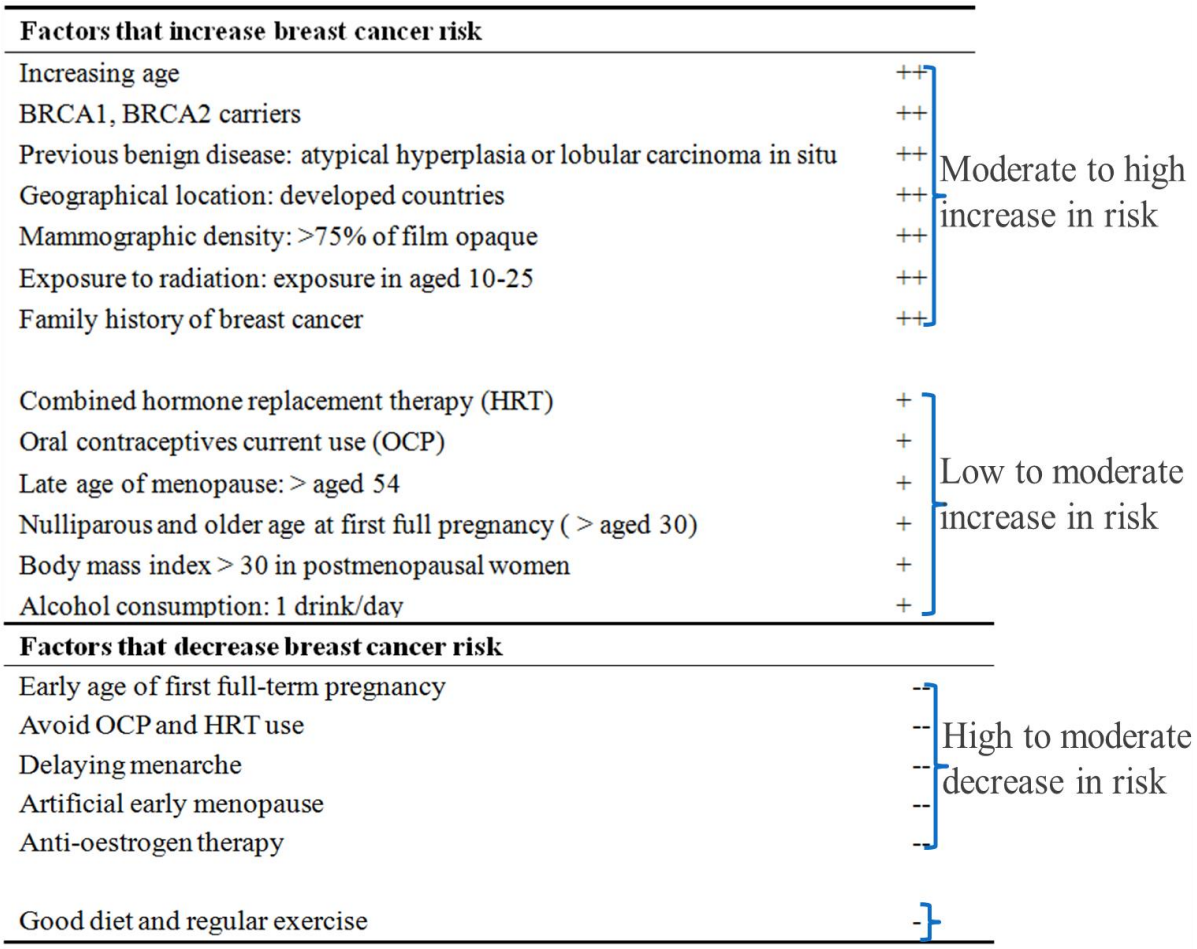

Figure 1: Magnitude of association for the breast cancer risk/protective factors

2.3 Components of coffee

2.3.1 Caffeine

Caffeine consumption promotes differentiation of neoplastic mammary gland tumors (promoting phase, not the initiating phase) in vivo [38]. Possible explanations for the promoting effect of caffeine are: 1) Caffeine inhibits 3', 5'-phosphhodiesterase; cyclic nucleotides (eg. cAMP, cGMP) affect tumorigenesis in mammary gland. 2) Caffeine alters the secretion and/or metabolism of the hormones, which influence mammary gland tumorigenesis. 3) Caffeine increases serum-free fatty acid levels, which may be important to mammary gland tumorigenesis. 4) Caffeine raises Ca^{2+} levels in mammalian tissues, and intracellular Ca^{2+} levels have been reported to be elevated in tumor cells.

Except coffee-breast cancer association, caffeine-breast cancer association was also evaluated, because caffeine is the major component of coffee among Singapore Chinese population. Caffeine was hypothesized to increase risk of breast cancer in previous studies [39-41], but their findings were inconsistent.

2.3.2 Trigonelline

Trigonelline, a proved novel phytoestrogen [42], is the second richest alkaloid compound in raw coffee beans [43] and constitutes about 1% of the dry roasted coffee beans [44]. Previous studies reported that trigonelline stimulates the proliferation of estrogen-dependent breast cancer cells through mediation of estrogen receptors in vitro [42].

Therefore, the potential effect of trigonelline on circulating estrogen levels may explain how coffee increases the risk of breast cancer.

2.3.3 Polyphenolic component (including chlorogenic acid, caffeic acid and caffeic acid phenethyl ester (CAPE))

In previous study, the authors reported that catechol-containing coffee polyphenols are highly effective inhibitors of placental catechol-O-methyltransferase (COMT)-mediated O-methylation of catechol estrogens in vitro [45]. Combined with an earlier study, which suggested that a COMT polymorphism with a lower catalytic activity enzyme may be associated with increased risk of breast cancer in humans [46], we may speculate that the polyphenolic component (including chlorogenic acid, caffeic acid and caffeic acid phenethyl ester (CAPE)) in coffee increases the risk for developing estrogen-induced breast cancer.

2.3.4 Acrylamide

Acrylamide is a probable human carcinogen, which formed during high-temperature processing of many commonly consumed foods, such as coffee [47]. Some epidemiology studies and animal studies have reported positive association between dietary acrylamide intake and breast cancer [48-51]. A cohort reported a positive risk of breast cancer among postmenopausal women with higher acrylamide intake, and the association is stronger for smokers and estrogen receptor positive cancers [52].

2.4 Experimental studies of coffee and breast cancer

Coffee contains hundreds of compounds, some of which have chemopreventive properties (e.g., casfestol and kahweol), while others have mutagenic and/or carcinogenic properties (e.g., acrylamide). While cafestol and kahweol may act through anti-inflammatory mechanisms to reduce breast cancer development [41, 53], previous studies of the effects of caffeine have not shown consistent direction of the effects caused by caffeine. Animal studies have shown that caffeine can significantly reduce the size of benign mammary gland tumors. Early in vivo evidence suggests that caffeine may promote mammary tumors [54], but more recent evidence suggests that caffeine may instead have a cancer protective role in arresting cell cycle and inducing apoptosis [55], as well as promoting the differentiation of neoplastic mammary gland tumors as shown in carcinogen-treated female Sprague-Dawley rats [41]. In addition to caffeine, coffee is also a main dietary source of acrylamide, a probable human carcinogen [47, 56]. Caffeine may have opposing effects on breast carcinogenesis. It may cause DNA damage, or play a role in arresting cell cycle or inducing apoptosis, which may impact carcinogen metabolism [55].

2.5 Epidemiologic studies of coffee/caffeine and breast cancer

2.5.1 1996 to May 2008: Studies included in a recent Meta-analysis

Based on a recent meta-analysis [15], there were nine case-control studies and nine prospective cohort studies that reported no associations between coffee consumption and

breast cancer from 1966 to 2008. The combined summary OR from all studies was 0.98 (95% CI: 0.96-1.00) for an increment of 2 cups/day of coffee consumption on the risk of breast cancer; after stratification by study design, summary estimate among nine prospective cohort studies was RR=0.95; 95% CI: 0.88-1.02 and among the nine population-based case-control studies was OR=0.95; 95% CI: 0.87-1.04. Only three of eighteen studies were conducted among Asian populations (others are among US and European population). Two of the Asian studies were prospective studies conducted in Japan (≥5 cups/week vs. ≤1 cups/week, OR=1.19; 95% CI: 0.93-1.52) [57] and (≥1 cups/day vs. never, OR=0.81; 95% CI: 0.55-1.18) [58], and the third was a case-control study in Israel [3]. The summary OR for the three studies was 0.92 (95% CI: 0.64-1.33). The case control study in Israel reported a statistically non-significant inverse association for breast cancer with coffee intake (≥4 cups/day vs. ≤1 cups/week, OR=0.6; 95% CI: 0.2- 0.9) [3, 59]. Observational data do not support an overall relationship between coffee intake and breast cancer risk.

2.5.2 May 2008-2011: Summary of findings from studies published since the meta-analysis

There have been eight prospective studies of coffee consumption published since the meta-analysis and none have reported a significant association between coffee intake and breast cancer risk [7-14].

After stratification by menopausal status, an inverse association between breast cancer risk and coffee intake was reported among premenopausal women. [15, 60, 61], but not among postmenopausal women [8, 9, 62, 63].

Furthermore, after stratification by BMI, a prospective study reported a statistically non-significant positive association (IRR (incidence rate ratios) = 1.8; 95% CI= 0.6, 5.4) between coffee consumption (≥7 vs. <2 cups/day) and breast cancer risk among Norwegian women having BMI greater than 24 kg/m^2 [16].

In addition, the relationship between BMI and breast cancer depends on tumor stage, and some cohort studies reported that the increased risk was stronger for advanced tumors than for localized tumors [64-66]. A possible mechanism is that hyperinsulinemia, activating insulin receptor and PI3K signaling pathway, altered adipocytokine profile, which leads to stimulatory effect on breast cancer cells [67, 68].

Eleven prospective studies have investigated the association between total caffeine and breast cancer risk, and none reported a significant association [7-11, 16, 57, 62, 63, 69-72]. An exception was observed among postmenopausal women where Hunter et al. reported a statistical significant inverse association (RR=0.88; 95% CI: 0.79, 0.97). Further, one large cohort study, the Women's Health Study, reported a statistically significant positive association between caffeine consumption (the fourth quartiles vs. the first quartile) and breast cancer with tumor size >2 cm (RRs=1.79; 95% CI: 1.18, 2.72) [10].

2.6 Breast cancer-BMI association

Experimental study reported that increased adiposity (fat tissue) is associated with higher aromatase activity and higher estrogen levels for postmenopausal women [73]. Additionally, retrospective studies observed an overall positive association between of breast cancer and higher BMI [74, 75]. Two large prospective studies reported that obesity increase risk of advanced tumors only, not localized tumors [64-66].

2.7 Coffee/caffeine-hormone association

Previous study reported a positive association between coffee/caffeine intake and luteal progesterone levels among premenopausal women [76]. In addition, one study reported a positive association between caffeine intake and estrone, which may suggest that some chronic conditions may be mediated by an effect on endogenous sex steroid [77].

2.8 Summary

Most epidemiologic studies did not report any significant association between coffee intake and breast cancer risk [15], including the nine most recent prospective studies among western populations [7-14, 78]. Additionally, some studies focusing on caffeine-breast cancer association reported similar null findings [7, 8, 10, 11, 62, 69].

However, one large prospective study in United States reported a significant association between caffeine intake and breast cancer risk among late stage of breast cancer with tumor

sizes >2 cm [10]. A Norwegian study found a positive association between coffee intake and breast cancer among higher BMI (≥24 kg/m^2) [16].

Figure 2 showed a brief summary for the coffee-breast cancer association studies.

	No association	**Positive association**	**Inverse association**
Experimental study			
-In vitro		√	√
-In vivo		√	√
Observational study			
-Retrospective studies	√ (5 studies)		√ (2 studies)
-Prospective studies			
Caffeine-breast cancer	√		
Coffee-breast cancer	√ (18 studies)		
Subgroup or stratified analysis			
-Women Health study		√ advanced disease	
-Norwegian study		√ higher BMI	√ lower BMI

Figure 2. Previous findings on coffee-breast cancer risk association

CHAPTER 3: MATERIALS AND METHODS

3.1 Study population

The design and subject recruitment of the Singapore Chinese Health Study have been described previously [79]. Briefly, Chinese women and men, from permanent residents or citizens of Singapore who resided in government-built housing estates (86% of the Singapore population resided in such facilities), aged 45-74 years belonging to the Hokkien or Cantonese dialect group were enrolled in the study between April 1993 and December 1998. For these analyses, we used data from the 35,303 female participants who did not have a history of cancer at base-line, based on self-report and linkage with the Singapore Cancer Registry. The study was approved by the Institutional Review Boards of the National University of Singapore and the University of Pittsburgh.

3.2 Baseline exposure assessment

At recruitment, information on demographics, lifetime use of tobacco, current physical activity, menstrual/reproductive history, occupational exposure, medical history, and family history of cancer was obtained through in-person interviews. The dietary questionnaire included 165-item semi-quantitative food frequency questionnaire (FFQ) assessing current diet, which was subsequently validated against a series of 24-h-diet recalls among a sub-population drawn randomly among the cohort participants [80]. The FFQ included

questions concerning consumption of coffee. Levels of caffeine intake were derived from self-report of coffee, black tea, green tea, and soda intake. Coffee contributes to 82% of caffeine intake in this population.

To assess beverage consumption including coffee and tea, participants were asked to choose their level of consumption from the following pre-defined categories: never or hardly ever, 1 to 3 times a month, once a week, 2 to 3 times a week, 4 to 6 times a week, once a day, 2 to 3 times daily, 4 to 5 times daily, and 6 or more times daily. Average daily intake of roughly 100 nutrient and non-nutrient compounds, including caffeine, was computed for each study subject based on the Singapore Food Composition Database [80]. The trained interviewers did not ask about intake of decaffeinated coffee separately, because Singapore Chinese rarely consume decaffeinated coffee.

3.3 Case ascertainment

3.3.1 Definition of breast cancer cases

Breast cancer cases were identified through the population-based cancer registry in Singapore. The nationwide cancer registry has existed since 1968 and has kept comprehensive recording of cancer cases [81]. To date, only 27 cancer cases were known to be lost to follow-up due to migration from Singapore. As of December 31, 2005, with an average of 10.7 years of follow-up, 629 women in the cohort had developed breast cancer. Histologic and staging information on all breast cancer diagnoses were confirmed by manual review of the pathology reports and clinical charts.

3.3.2 Definition of stage of breast cancer

Stage of disease at diagnosis was determined for 97.9% of breast tumors based on TMN staging system for breast cancer. TMN stands for primary tumor, distant metastasis, and regional lymph nodes, respectively. We defined localized disease as either carcinoma in-situ (CIS) (n=79) or invasive disease with tumors ≤5cm in their greatest dimension, without positive nodes and without metastasis.

All other cases with stage information were defined as having advanced disease (n=272), which included the cancer is not metastatic (has not spread to another part of the body), but the tumor is greater than 5 cm; is growing into the skin or muscle of the chest or is present in the lymph nodes in the armpit, and these lymph nodes are either stuck to each other, or to other structures; or the cancer is metastatic (has spread to another part of the body).

Figure 3 presents the definition of stage of breast cancer.

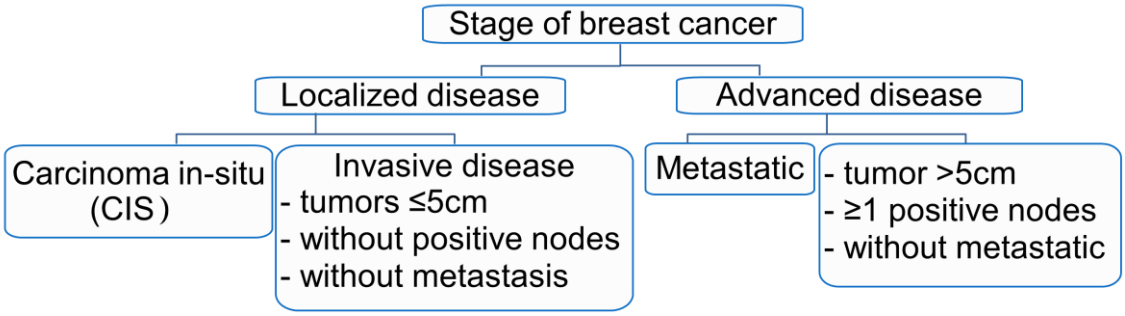

Figure 3. Definition of Stage of Breast Cancer

3.3.3 Definition of Breast cancer estrogen receptor/ progesterone receptor (ER/PR) status

Estrogen and progesterone hormone receptor (ER/PR) status was obtained for 63% (n=394) of the breast tumors. ER/PR status stands for hormone receptor status of the breast cancer cells. The cancer cells growing in the presence of estrogen or progesterone have hormone receptors on the cell surfaces. The breast cancer cells with or without the receptors are called ER positive, ER negative, PR positive, PR negative.

3.4 Statistical methods

3.4.1 Overall

For each study subject, person-years of follow-up, stratified simultaneously by calendar time and age at recruitment, were counted from the date of recruitment to the data of diagnosis of breast cancer, death, migration, or 31 December 2005, whichever occurred first. Cox proportional hazards regression methods were used to examine the association between categories of coffee and caffeine consumption and breast cancer risk. The strength of association was measured by the hazard ratio (HR) and its 95% CIs with p for trend to assess the association. We used SAS version 9.3 (SAS Institute Inc, Cary, NC). All P values were 2-sided and were considered statistically significant if < 0.05.

We created four variables for coffee consumption:

1) Five categories: non/monthly, weekly, daily, 2-3 cups/day, ≥4 cups/day;

   To compare results from the Singapore Chinese population with the results from western populations who used these five categories for their studies.

2) Four categories: non/monthly, weekly, 1 cup/day, ≥2 cups/day;

   To allow enough levels to show us the various levels of information by coffee intake.

3) Three categories: non/monthly, weekly, ≥daily;

   For the stratified analysis, we used three categories coffee variable to obtain enough power for the analysis.

4) Two categories: non/monthly/weekly, ≥daily.

   For subgroups analysis by ER/PR status and stage of breast cancer, we collapsed categories to ensure sufficient numbers of cases in each category.

The Singapore Food Composition Table is a food-nutrient database that lists the levels of 96 nutritive/nonnutritive components (including caffeine) per 100 g of cooked food and beverages in the Chinese diet. By combining information obtained from the food frequency questionnaire with nutrient values provided in this food-nutrient database, we were able to compute the mean daily intake of caffeine [80].

For caffeine intake (mg/day values), we used

1) Quartiles: median caffeine amount (IQR): 18.59 mg (32.77), 88.25 mg (11.37), 139.01 mg (66.97), 244.96 mg (60.79).

For presenting various levels of information for caffeine intake, hence we are able to estimate the low to moderate caffeine consumption-breast cancer association.

2) Tertiles: IQR: 43.57 mg (54.98), 106.22 mg (29.22), 227.16 mg (39.17).

For getting enough power for the analysis, while presenting various levels of information for caffeine intake, hence we are able to estimate the low to moderate caffeine consumption-breast cancer association.

3) Dichotomous: median: <101mg, ≥101 mg.

For the stratified analysis, we used two categories for caffeine intake to obtain enough power for the analysis.

3.4.2 Subgroups analysis by stage of breast cancer and ER/PR status

We estimated the hazard ratios and corresponding 95% CIs with two-sided p-value for trend stratified by stage of disease (localized, advanced) and/or ER/PR status (ER+, ER-, PR+, PR-) to assess the relation between coffee and breast cancer within subgroups. In our study, the investigator went back to hospital to update the ER/PR information, and 58% of the cases have ER and PR status ascertained.

3.4.3 Evaluation of effect modification

For assessing effect modification, stratified analysis by menopausal status (premenopausal, postmenopausal women), duration of follow up (<5 years, ≥5 years; or <5

years, 5-10 years, ≥10 years), and median BMI (<23, ≥23 kg/m^2) were conducted, in the full data set, among advanced cases, and among advanced cases plus cases with ER/PR status. If we observed a statistically significant effect modifier, we would present them as our main findings.

3.4.5 Adjusted for confounding

First, we have base/minimally-adjusted model, which includes three design variables: age at recruitment (years), year of recruitment (1993-1995, and 1996-1998), dialect group (Cantonese and Hokkien). We made this decision because all the previous Singapore Chinese Health Study adjusted for these three covariates.

Additionally, by reviewing the previous Singapore Chinese Health studies, which were conducted to evaluate the breast cancer or coffee related association, we considered the confounders they used for their adjusted model as our potential confounders. They are: physical activity (yes/no weekly vigorous activity), BMI (<20, 20-23.9, 24-27.9, ≥28 m/kg^2), median soy intake, frequency of green tea intake (nondrinkers, monthly drinkers, weekly or more frequent drinkers), smoking status (ever/ never), consumption of alcoholic beverages (nondrinkers, <7 drinks/week, or ≥7 drinks/week), family history of first-degree relative with diagnosis of breast cancer, menopausal status (premenopausal/ postmenopausal), age when period started (<13, 13-14, 15-16, ≥17 years), age at menopause (<50, 50-54, ≥55), age at first live birth (<21, 21-25, 26-30, ≥31, nulliparous women) number of live births (none, 1-2, 3-4 and 5+), ever use of oral contraception, and postmenopausal hormone use by calculating

the HR (95% CI), education level (none/primary education, secondary or higher), and age when period became regular (<13, 13-14, 15-16, ≥17 years or periods never became regular); and for postmenopausal women, postmenopausal hormones use was also considered. And then, we used the criteria to determine the confounding: the covariate should 1) be related to disease; 2) be related to exposure; 3) be not in the direct biological pathway between disease and exposure. Last, the potential confounders selected by the above mentioned three criteria were introduced into the models to determine the extent to which they might influence any effect. A potential confounder was retained in the model if inclusion changed the HR of coffee consumption by more than 10% [82] (Table 5). The figure 4 presents the criteria of determining confounders for the final adjusted model.

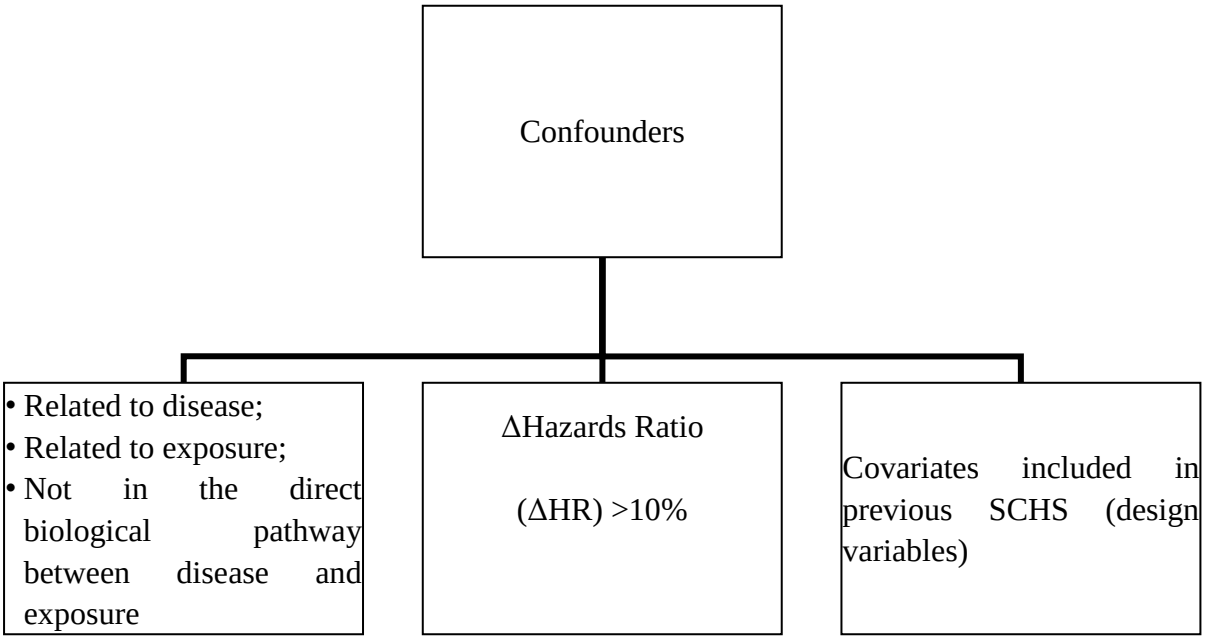

Figure 4. Criteria of determine confounding for the adjusted model

CHAPTER 4: RESULTS

4.1 Confounding

In all analyses, we adjusted for the following potential confounders: age at recruitment, year of recruitment, dialect group, education level, and age when period became regular. Additional adjustment was made for use of hormone replacement therapy in analyses among postmenopausal women.

4.2 Baseline characteristics by levels of coffee intake (four coffee categories)

At baseline among 34,028 women, the median age was 55 years (interquartile range (IQR) = 13 years) (we present the median and IQR, instead of the mean and SD, because the data were skewed due to a few very old participants). In this cohort, 21.5% were non-drinkers of coffee or monthly coffee drinkers, 8.9% were weekly coffee drinkers, 40.1% were daily coffee drinkers, and 29.5% consumed ≥2 cups/day of coffee. Compared with women who never or hardly ever drank coffee, women who were drinking more than 2 cups/day of coffee were more likely to have no or little education (83.2% vs. 74.3%), drink less tea, consume more caffeine (227.9 vs. 18.0 mg/day), be older when their periods became regular, and to have more live births (Table 1).

4.3 Results after adjusting for confounding

4.3.1 Overall

Overall, we observed a statistically non-significant positive association (HR=1.23; 95%: 0.98, 1.54; P for trend=0.11) between coffee intake (≥2 cups/day vs. none or infrequent intake) and breast cancer risk (Table 2). The weak positive association did not depend on the level of intake.

The majority (82%) of caffeine consumed in our study population was from coffee. The next highest source was black tea (12%) (Table 7). We observed a non-statistically significant positive association between caffeine intake (Q4 vs. Q1) and overall breast cancer risk (HR=1.33; 95%: 1.05, 1.68; P for trend=0.12) (Table 2). However, instead of a dose-dependent trend, we observed the strongest associations for the second (HR=1.32; 95%: 1.06, 1.66) and fourth quartile of intake, compared with the first (Table 2).

4.3.2 By stage of disease

After stratification by stage of disease, a significant positive dose-dependent trend was observed for coffee intake (four categories) and risk of advanced breast cancer (HR=1.90; 95%: 1.30, 2.77; P for trend<0.01) (Table 2). Women who consumed coffee ≥2 cups/day had a 1.9-fold increase in risk of advanced disease. Stronger positive associations were observed for the second (HR=2.10; 95%: 1.45, 3.05; P for trend<0.01) and fourth quartiles (HR=2.23; 95%: 1.52, 3.26; P for trend<0.01) of caffeine intake, vs. the first quartile.

Different categorize for coffee intake to assess the association among subgroup classified by stage of disease were presented in Table 10 (five categories for coffee intake). For women diagnosed with advanced breast cancer, we found a non-statistically significant positive association between coffee intake ≥4 cups/day vs. none or monthly intake (HR=2.03; 95%: 0.98, 4.20; P for trend<0.001) (Table 10). The positive dose-dependent trend was observed for coffee intake (five categories of coffee intake) and risk of advanced breast cancer. Even though the 95% CI for the five category ≥4 cups/day showed it is not statistically significant, it may due to the very small sample size (n=9) in this category.

4.3.3 By ER/PR status

For coffee intake, estrogen receptor negative (ER-) cancer cells (HR=1.87; 95% CI: 1.17, 2.98) and progesterone receptor positive (PR+) cancer cells (HR=1.85; 95% CI: 1.13, 3.01) status of breast cancer among advanced disease cases showed a positive association. PR- status breast cancer was the only stratum that showed a significant positive association between caffeine intake (tertiles) and advanced breast cancer (HR=1.77; 95% CI: 1.05, 2.96; P for trend=0.03) (Table 4). These data showed the adverse effect of caffeine on breast cancer risk is for ER- cancer cells, and especially for PR- cancer cells (tertile 1) (Table 4).

4.4 Effect modification

4.4.1 Overall

1) Menopausal status

Although the trend for increasing breast cancer risk with increasing coffee intake (highest versus lowest intake) was somewhat more obvious among postmenopausal women, the HRs for none/monthly vs. ≥2 cups/day coffee intake did not depend on menopausal status (HR=1.26; 95% CI: 0.96, 1.66; P for trend=0.1); while the similar association was reported for premenopausal women though the p trend is not statistically significant (HR for premenopausal women=1.18; 95% CI: 0.78, 1.77; P for trend=0.7). When we used five categories for coffee intake, a slight attenuation was observed for four or more cups per day compared with none/monthly intake (HR=0.93; 95% CI: 0.52, 1.64; P for trend=0.2) (Table 9). Overall, we did not find significant finding by stratified analysis by menopausal status.

2) Duration of follow-up

The positive associations between coffee/caffeine intake were similar after further stratification by duration of follow-up (when stratified by duration of follow-up into 2 (<5 years; ≥5 years) and 3 categories (<5 years; 5-10 years; ≥10 years) (Table 12, 13).

3) BMI

Stratified analysis by above and below median BMI (23 kg/m^2) suggested no significant association (median BMI ≥23kg/m^2: HR=1.16; 95% CI: 0.91, 1.47; median BMI <23kg/m^2:

HR=1.05; 95% CI: 0.81, 1.36; P for interaction=0.45) (Table 14). The caffeine-breast cancer association assessment showed similar findings (Table 14).

4.4.2 By advanced stage of breast cancer

1) Menopausal status

Among premenopausal women, our data showed that compared with none or monthly coffee drinker, two or more than two cups of coffee drinker have a non-statistically positive risk to have advanced breast cancer (HR=1.86; 95% CI: 0.91, 3.79; *P* trend = 0.12). However, the positive association is statistically significant among postmenopausal women (HR=1.91; 95% CI: 1.22, 2.98; *P* trend = 0.001).

For caffeine intake and advanced breast cancer association, the statistically positive association also only exists among postmenopausal women (HR=2.20; 95% CI: 1.41, 3.43; *P* trend = 0.01) compared the highest quartile to the lowest quartile (Table 9).

2) Duration of follow-up

The HRs for advanced breast cancer and ≥2 cups/day vs. none or monthly coffee drinker were similar for the <5 years' follow-up and ≥5 years' follow-up population (<5 years' follow-up: HR=1.90; 95% CI: 1.30, 2.77; *P* trend < 0.001; ≥5 years' follow-up: HR=1.58; 95% CI: 0.96, 2.59; *P* trend=0.04) (Table 11).

3) BMI

We examined association between coffee intake and breast cancer risk after stratification by median BMI in the advanced breast cancer subgroup. We found a highly significant positive association between coffee consumption and risk of developing advanced breast cancer, only for BMI larger than 23 kg/m^2; the multivariable HR was 2.55 (95% CI, 1.49, 4.35, p for trend <0.001) (the third category vs. the first one) (Table 3). However, when the BMI was less than 23 kg/m^2, the association between advanced breast cancer risk and coffee intake was no longer observed (Table 3). The p for trend for the interaction between median BMI and coffee/ caffeine consumption to advanced breast cancer risk was statistically significant (<0.001 for three coffee category) (Table 3).

Since BMI is calculated by using both height and weight, we explored whether height or weight was the more important factor. There was no statistically finding when we stratified analysis by median weight (55kg) and median height (155cm) to evaluate the association between coffee consumption and advanced breast cancer (Table 16, 17).

Additionally, we examined the association between caffeine consumption and breast cancer risk further stratified by median BMI (23 kg/m^2) among the advanced breast cancer cases. We found a strong statistically significant positive association between caffeine consumption and risk of developing advanced breast cancer, however, this statistically significant association only exists among women with a BMI larger than 23 kg/m^2; the HR was 1.58 (95% CI, 1.07, 2.33, p for trend = 0.02) (third tertile vs. the first tertile) (Table 3). When the median BMI was less than 23 kg/m^2, there was no association between advanced breast cancer risk and caffeine intake (Table 3). The p for trend for the interaction between

median BMI and caffeine consumption on advanced breast cancer risk was strongly significant (0.03 for caffeine tertiles) (Table 3).

Tables

Table 1. Baseline Characteristics of the Cohort by Levels of Coffee Intake, Singapore, 1993-1998

Characteristic	None/monthly	Weekly	Daily	≥2 cups/day
Total Person-years	71,868	29,282	135,683	101,408
Age, median (IQR), years	55 (14)	54 (13)	55(14)	55(13)
Dialect group, % Hokkien	50.0	52.7	51.4	54.6
Education level, % None or primary education	74.3	73.1	80.6	83.2
BMI, median (IQR), kg/m^2	23.2 (3.3)	23.3 (3.9)	23.3 (3.5)	23.3 (3.5)
Tea intake, %				
Never/monthly	58.3	47.9	60.8	66.2
Green tea only	17.7	16.7	18.8	15.3
Black tea only	14.4	22.3	12.7	12.0
Green and Black tea	9.6	13.2	7.6	6.6
Caffeine intake, median (IQR), mg/day	18.0 (38.7)	52.7 (39.8)	95.4 (26.7)	227.9 (40.5)
Soy intake, median (IQR), g/1000kcal	65.1 (62.4)	70.5 (63.7)	65.5 (57.9)	61.9 (54.3)
Alcohol intake, % non-drinkers	92.7	91.5	91.1	89.3
Family history, % with breast cancer among first-degree relative	1.3	1.4	1.3	1.3
% Premenopausal	29.2	30.8	27.5	27.6
Age when period became regular, %, years				
<13	13.4	12.8	12.3	11.2
13-14	35.0	35.0	35.4	34.2

Table 1 (Continued)

15-16	32.3	33.8	33.8	35.2
≥17	15.8	14.7	15.4	16.0
Never became regular	3.5	3.8	3.1	3.4
Number of live births, %				
0	8.0	6.9	6.9	6.6
1-2	30.0	31.1	28.0	26.2
≥3	62.0	62.1	65.2	67.2
Oral contraception, % ever used	25.7	27.8	26.7	26.2
Postmenopausal hormones, % ever used	27.2	11.6	38.8	22.4

Abbreviation: IQR, interquartile range; BMI: Body mass index

Table 2. Multivariate-Adjusted Hazard Ratios for Association between Coffee and Caffeine Consumption and Breast Cancer Risk According to Different Stage of Disease, Singapore, 1993-1998

	Overall Breast Cancer				Localized Breast Cancer				Advanced Breast Cancer			
Variable	No.	HR[a]	95% CI	*P* Value[d]	No.	HR	95% CI	*P* Value	No.	HR	95% CI	*P* Value
Coffee[b]												
None/Monthly	121	1.00	Referent		79	1.00	Referent		38	1.00	Referent	
Weekly	60	1.21	0.89, 1.66		40	1.24	0.84, 1.81		19	1.23	0.71, 2.14	
Daily	251	1.13	0.91, 1.41		126	0.88	0.66, 1.16		119	1.70	1.18, 2.45	
≥ 2 cups/day	197	1.23	0.98 1.54	0.11	99	0.95	0.70, 1.28	0.41	96	1.90	1.30, 2.77	<0.01
Caffeine[c]												
Q1	134	1.00	Referent		88	1.00	Referent		41	1.00	Referent	
Q2	177	1.32	1.06, 1.66		86	0.98	0.73, 1.32		86	2.10	1.45, 3.05	
Q3	168	1.07	0.85, 1.34		99	0.95	0.72, 1.27		68	1.41	0.96, 2.08	
Q4	150	1.33	1.05, 1.68	0.12	71	0.96	0.70, 1.31	0.74	77	2.23	1.52, 3.26	<0.01

Abbreviation: CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

[a] All model adjusted for age at recruitment (years), year of recruitment (1993-1995, 1996-1998), and dialect group (Hokkien, Cantonese), education, age when period became regular; All variables are coded as ordinal; and there are 13 cases missing stage information (see Methods);

[b] Categorized coffee consumption as four categories.

[c] Categorized caffeine intake as quartiles (Q), and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

[d] *P* value for the difference between none/monthly and ≥ 2 cups/day coffee consumption; or the difference between Q1 and Q4 caffeine intake.

Table 3. Adjusted Hazard Ratios for the Association between Coffee and Caffeine Intake and Advanced Breast Cancer Risk Stratified by Body Mass Index (BMI), Singapore, 1993-1998

	BMI < median (23 kg/m^2)			BMI ≥ median (23 kg/m^2)			*P* Value[e]
	Cases, n	HR[a]	95% CI	Cases, n	HR	95% CI	
Coffee[b]							
None /Monthly	23	1.00	Referent	15	1.00	Referent	
Weekly	11	1.25	0.61, 2.57	8	1.29	0.55, 3.04	
≥ daily	84	1.31	0.82, 2.08	131	2.55	1.49, 4.35	
P for trend[d]			0.27			0.0002	0.02
Caffeine[c]							
T1	46	1.00	Referent	44	1.00	Referent	
T2	29	0.91	0.57, 1.45	48	1.49	0.99, 2.24	
T3	43	1.20	0.79, 1.82	62	1.58	1.07, 2.33	
P for trend			0.42			0.02	0.34

Abbreviation: BMI: Body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

[a] All model adjusted for age at recruitment (years), year of recruitment (1993-1995, 1996-1998), and dialect group (Hokkien, Cantonese), education, age when period became regular; All variables are coded as ordinal.

[b] Categorized coffee consumption as three categories.

[c] Categorized caffeine intake as tertiles (T), and coded it as dummy variable. the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

[d] *P* for trend for the difference between none/monthly and ≥daily coffee intake; or the difference between T1 and T4 caffeine intake.

[e] *P* value for the interaction between BMI and coffee/caffeine intake on advanced breast cancer risk.

Table 4. Adjusted Hazards Ratios for the Association between Coffee and Caffeine Intake on Advanced Breast Cancer Risk According to Estrogen Receptor (ER) and Progesterone Receptor (PR) Status, Singapore, 1993-1998

	ER+			ER-		
	Cases, n	HR[a]	95% CI	Cases, n	HR	95% CI
Cases, n	77			114		
Coffee[b]						
None/Monthly/Weekly	16	1.00	Referent	22	1.00	Referent
Daily	61	1.66	0.95, 2.88	92	1.87	1.17, 2.98
Caffeine[c]						
T1	26	1.00	Referent	37	1.00	Referent
T2	23	1.23	0.70, 2.15	35	1.32	0.83, 2.09
T3	28	1.24	0.73, 2.12	42	1.35	0.87, 2.10
P for trend[d]			0.43			0.19
	ER+			ER-		
	Cases, n	HR[a]	95% CI	Cases, n	HR	95% CI
Cases, n	104					104
Coffee[b]						
None/Monthly/Weekly	20	1.00	Referent	18	1.00	Referent
Daily	84	1.85	1.13, 3.01	66	1.63	0.96, 2.74
Caffeine[c]						
T1	38	1.00	Referent	24	1.00	Referent
T2	33	1.21	0.76, 1.92	24	1.39	0.79, 2.45
T3	33	1.01	0.63, 1.62	36	1.77	1.05, 2.96
P for trend[d]			0.93			0.03

Table 4 (Continued)

Abbreviation: ER: Estrogen Receptor; PR: Progesterone Receptor; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

[a] All model adjusted for age at recruitment (years), year of recruitment (1993-1995, 1996-1998), and dialect group (Hokkien, Cantonese), education, age when period became regular; All variables are coded as ordinal.

[b] Categorized coffee consumption as three categories.

[c] Categorized caffeine intake as tertiles (T), and coded it as dummy variable. the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

[d] P for trend for the difference between none/monthly and ≥daily coffee intake; or the difference between T1 and T4 caffeine intake.

CHAPTER 5: DISCUSSION

5.1 Summary

5.1.1 Overall findings

We present the prospective results from an Asian population evaluating the relationship between coffee/caffeine intake and breast cancer risk. Our study found a statistically non-significant increase in risk of breast cancer among women consuming ≥2 cups of coffee per day compared with coffee nondrinkers or monthly drinkers overall (HR=1.23). Since both 95% CI and P for trend are not statistically significant, and compared with HR=1.9 among advanced disease, HR=1.23 could be count as no association. Therefore, our finding for coffee among all women was consistent with most previous prospective studies in which no association between coffee consumption and risk of overall breast cancer was observed [7-11, 14, 15, 69]. One of the possible reasons may be because the different amount of coffee drinking between different populations. Americans drink 3.2 cups of coffee per day [83], while Swedish people drink 6 cups of coffee per day on average [84]. This is much higher than among Singapore women (1-2 cups/day). Therefore, it is possible that the protective effect of coffee shown in other studies is due to high amounts of coffee consumption. More studies need to be done to further clarify this assumption. Similarly, we found no association between caffeine intake and breast cancer.

5.1.2 Subgroup analysis by stage of breast cancer

When breast cancer cases were restricted to those at an advanced stage, we found a statistically significant positive association between coffee intake and advanced breast cancer; and a statistically significant association with a dose-dependent trend for the association between caffeine intake and breast cancer. One previous study reported similar positive caffeine-advanced breast cancer (defined as breast tumor>2 cm) association [10].

5.1.3 Effect modifier by median BMI

Body size was an important effect modifier on the coffee-breast cancer relationship, in our data. Among women with a higher BMI (≥23 kg/m^2), daily coffee consumption was associated with a statistically significant 2.4-fold increase in risk of advanced breast cancer in our study. This result is consistent with a Norwegian study, which reported an adverse effect among women with higher BMI (≥24 kg/m^2) [16].

After restricting the analysis to advanced stage breast cancer cases, coffee intake was a significant risk factor among women with a BMI greater than 23 kg/m^2.

5.1.4 Additional analysis

To further evaluate the association between coffee consumption and advanced breast cancer, we repeated the analysis among all cases without carcinoma in-situ (CIS) or localized

breast cancer cases without CIS. Our hypothesis is that there is no significant association between coffee consumption and invasive localized breast cancer. Localized disease was defined as either CIS or invasive disease with tumors ≤5cm in the greatest dimension, without positive nodes and without metastasis. We found no significant association between coffee/caffeine consumption and localized disease, as we see from Table 29. Therefore, we conclude that 1) there is no association between coffee consumption and localized invasive disease in this population; 2) the association between coffee intake and breast cancer is only for advanced disease.

Furthermore, previous studies of the association between coffee and caffeine and other disease outcomes included both coffee and caffeine in the same model in order to determine whether coffee-breast cancer association was explained at least in part by caffeine. Therefore, we conducted additional analyses including both coffee and caffeine in the same model. The association between coffee consumption and advanced disease are similar with or without caffeine covariates in the model (Table 23). Previous studies of the association between other exposure and breast cancer also included covariates: number of live births (ordinal variable: 0, 1-2, 3+), BMI, smoking (ever/never), physical activity (yes/no any weekly vigorous or moderate activity), soy intake (>, <median) and green tea intake (drinker/nondrinker) in the model. Therefore, we also included the above covariates in the same model to rerun the model to evaluate coffee-breast cancer association; we got the similar findings as what we got from our final adjusted model.

Additionally, while alcohol consumption, a known risk factor for breast cancers [33, 34], is very low in the Singapore population, it is not zero. Therefore, we restricted our population to non- alcohol drinkers to evaluate the breast cancer-coffee association in the overall population and among advanced stage breast cancer cases and evaluated effect modification by BMI (Table 24, 25, 26, 27, 28). The null findings we got showed that alcohol consumption does not affect the coffee- advanced breast cancer association in this population, also does not affect this association when we conducted the stratified analysis by median BMI to evaluate the coffee-advanced breast cancer.

5.2 Possible interpretations

The followings are three possible interpretations we would like to use to interpret for our findings:

1) Explained by components of coffee that may be related to breast cancer development;
2) Coffee may increase the risk of breast cancer development by acting through a hormonally-related mechanism as promoter;
3) Asian coffee replacement is different with the coffee replacement among Western population.

5.2.1 Components of coffee that may be related to breast cancer development

Due to the complex components of coffee, component of coffee, such as trigonelline and acrylamide (probable human carcinogen) can also be measured to help us better understand the association between coffee and breast cancer.

First, caffeine is the major component of coffee, which coffee contributes 82% of caffeine intake in Singapore Chinese population. Experimental study reported that caffeine may promote differentiation of neoplastic mammary gland tumors through promoting phase, not the initiating phase in vivo [38].

Second, trigonelline, a proved novel phytoestrogen [42], is the second richest alkaloid compound in raw coffee beans [43], which increases the risk for developing estrogen-induced breast cancer through catechol-O-methyltransferase (COMT) mediation [42]. Therefore, trigonelline could be one of the coffee components to affect the development of breast cancer through a hormone related pathway.

Third, acrylamide, a probable human carcinogen, is formed during high-temperature processing of many consumed foods in, such as coffee [47]. Animal experiment reported that high level of acrylamide in drinking water causes several types of hormone-sensitive cancers, including mammary tumors in female rats [48, 49]. Hence, measuring acrylamide during coffee brew may be helpful to help us understand the underlying mechanisms of coffee-breast cancer association.

Last, polyphenolic components, including chlorogenic acid, caffeic acid and caffeic acid phenethyl ester (CAPE), increases the risk for developing estrogen-induced breast cancer

through catechol-O-methyltransferase (COMT) mediation [45]. Therefore, by evaluating the polyphenolic components, we may further explore the association between coffee-breast cancer through a hormone related pathway.

5.2.2 Coffee plays a promoter role to breast cancer risk

Coffee may increase the risk of breast cancer development by acting through a hormonally related mechanism. Positive associations between coffee or caffeine intake and circulating estrogen levels have been reported [76, 77, 85, 86], with most consistent results from studies among postmenopausal women [76, 77]. Compounds in coffee, such as polyphenols components, have estrogenic effects. Previous study suggested that a COMT polymorphism [87] with a lower catalytic activity enzyme may be associated with increased risk of breast cancer in humans [46]. Therefore, the effect of coffee to breast cancer development is through a hormone related pathway; and this is also confirmed by the effect modifier (BMI) evaluation we conducted. Since we only found significant positive association between coffee intake and advanced breast cancer among above median BMI women, it implies a higher estrogen levels among these women. Previous studies reported the increased adiposity is associated with higher aromatase activity and higher estrogen levels in postmenopausal women, which is associated with worse breast cancer outcomes [64-66].

What's more, given that women in Singapore can receive free mammography screening (which does a great job at detecting CIS and localized invasive disease) once per two years;

and we observed a positive association between coffee consumption and advanced breast cancer only (not localized breast cancer), we think coffee may be acting as a breast cancer promoter, and the effect of coffee is highly possible to through a estrogenic effect to breast cancer development. Also, coffee is a promoter, which explains the association with late stage disease.

5.2.3 Asian coffee replacement is different with the Western coffee replacement

In Singapore, the increase in coffee consumption likely leads to a concurrent decrease in green or black tea consumption. In western countries, increased coffee consumption may mean decreased consumption of soft drinks or sweet juice. Hence, it is possible that coffee drinking in Western countries partially replaces an unhealthy beverage but replaces a healthy beverage in Singapore. Further study needs to be done to show whether tea has protective effect to breast cancer.

5.3 Potential limitations

Potential limitations of this study include the lack of ER/PR status for all cohort participants. The receptor status among Singapore Chinese women was only known for 58%. The missing of ER/PR status could lead to selection bias. However, by comparing the HRs between coffee intake and breast cancer among women with and without ER/PR status, as well as the characteristics of breast cancer cases with and without ER/PR status according to

coffee consumption (Table 2), we found no statistically significant difference between the subgroup with ER/PR information and the overall group with the missing ER/PR information. We conclude that missing of ER/PR status in this population does not lead to selection bias.

Additionally, we only had baseline coffee and caffeine consumption data, which did not account for changes in coffee intake over the follow-up time period. Therefore, measurement error due to the individuals' coffee intake changes is inevitable. However, at baseline, most of women included in our study were between 40 to 74 years old and are likely to have had a relative stable coffee consumption pattern, since older people are more likely to have certain dietary habits. Also, coffee intake has been shown to be consistent over longer time periods. Because the number of case patients in some exposure categories and categories of tumor characteristics was not large enough, our statistical power was limited in some subgroup analyses. Even though this coffee self-report had some error, this would most likely result in non-differential misclassification with respect to disease status, which likely leads to the bias towards or away the null since coffee has more than two categories in this study.

Another concern is the availability of specific coffee information, such as caffeinated or decaffeinated or instant coffee; filtered or boiled way to brew coffee. To our knowledge, the majority of Singaporeans drink caffeinated coffee. Additionally, in Singapore, the coffee is brewed in a silver pot on a charcoal grill and strained through a bag, which is similar to the filtered brewing method.

5.4 Strengths

5.4.1 Strengths of Singapore Chinese Health Study

The Singapore Chinese Health Study has information on coffee consumption and breast cancer. First, the food frequency questionnaire was validated. Second, this study has high participant response rate (83%). Third, it has very little loss of follow-up, which provides a more accurate estimate of Hazards Ratios. Moreover, this study has complete case ascertainment, with the nationwide cancer registry in Singapore.

5.4.2 Strengths of prospective study

First, prospective study has good temporality, because all the people developed disease after knowing their exposure status. Also, prospective study is less likely to have recalled bias. The recalled bias does not cause confounding, because all the people did not know their disease status yet when they got their exposure measured.

5.4.3 Strengths of the low breast cancer profile population

Asian women have overall lower circulating hormone level compared with western population [17], therefore, we have opportunity to observe breast cancer-coffee association if there is one with lower breast cancer profile in Singapore Chinese women.

5.5 Conclusion

In summary, high consumption of coffee (≥2 cups/day) was statistically significantly associated with advanced breast cancer among Singaporean Chinese women. In addition, among women with a higher BMI (≥23 kg/m^2), coffee consumption increased advanced breast cancer risk about two fold. Interactions between above and below median BMI (23 kg/m^2) and coffee consumption is leading to advanced breast cancer was statistically significant. Our findings are consistent with most previous studies. For clarifying the specific role of the constituents in coffee further studies are warranted to help us better understand the underlying mechanisms.

Using a large prospective cohort of Asian women, we report 2 or more cups of coffee per day increase the risk of developing breast cancer, particularly advanced disease. Daily coffee intake was associated with a 2.6-fold increase in advanced breast cancer risk among heavier women. One large prospective study in US reported a significant association between caffeine intake and breast cancer risk among late stage cases [10]. A Norwegian study found a positive association between coffee intake and breast cancer among higher BMI (≥24 kg/m^2) [16]. Our data support a hypothesis for an adverse effect of coffee on breast cancer development that may act through a hormonally driven mechanism, given the synergistic effects of higher BMI and higher coffee intake on breast cancer risk that we observed. A possible reason for why we observed a positive association while most previous prospective findings from Western populations show no association may be due in part to the underlying lower breast cancer risk profile among Asian women compared with white women.

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APPENDIX I

Table 5 Baseline characteristics by coffee tertiles

	Non-drinker/monthly	Weekly	Daily	2+ cups/day	p-value
Person-years	71,868	29,282	135,683	101,408	
Median Age (IQR), yrs	55 (14)	54 (13)	55 (14)	55 (13)	
Dialect group, % (Hokkien)	49.97	52.69	51.38	54.56	<.0001
None or primary education only, %	74.25	73.05	80.56	83.16	<.0001
Median BMI (IQR), kg/m^2	23.19 (3.25)	23.29 (3.90)	23.31 (3.46)	23.29 (3.45)	
Tea intake, %					
Nondrinkers	21.36	6.32	39.55	32.77	<.0001
Green tea, at least weekly	22.95	10.4	41.48	25.17	<.0001
Black tea, at least weekly	23.54	14.41	37.15	24.9	<.0001
Alcohol intake, % (nondrinkers)	92.68	91.53	91.05	89.27	<.0001
Family history: first-degree relative with diagnosis of breast cancer, %	1.30	1.38	1.26	1.29	0.9590
Menopausal status, % (premenopausal)	29.19	30.77	27.50	27.64	<.0001
Age when period became regular, yrs, %					0.0002
<13	13.39	12.75	12.29	11.20	
13-14	34.96	35.02	35.38	34.17	

Table 5 (Continued)

15-16	32.34	33.77	33.78	35.22	
17+	15.81	14.66	15.42	16.01	
Never	3.51	3.79	3.13	3.40	
Number of live births, %					<.0001
None	7.96	6.85	6.85	6.61	
1-2	30.01	31.07	27.98	26.22	
3-4	36.03	37.33	37.06	37.86	
5+	25.99	24.74	28.11	29.31	
Ever use of oral contraception, %	25.68	27.78	26.71	26.16	0.1200
Ever use either estrogens/ progesterone, %	26.36	11.74	38.73	23.17	<.0001

Table 6 Minimally- adjusted model building

	HRs for coffee				ΔOR %			>10%
	Non & monthly	weekly	daily	2+				
For All Women								
Base model	1.00	1.22	1.10	1.17				
+Education[1]	1.00	1.21	1.13	1.23	0.01	-0.03	-0.05	
+Education[2]	1.00	1.21	1.14	1.23	0.01	-0.04	-0.05	
+BMI[1]	1.00	1.21	1.10	1.16	0.01	0.00	0.01	
+BMI[2]	1.00	1.21	1.10	1.16	0.01	0.00	0.01	
+Soy intake, g/1000 kcal	1.00	1.23	1.10	1.16	-0.01	0.00	0.01	
+Family history: first-degree relative with diagnosis of breast cancer	1.00	1.22	1.10	1.17	0.00	0.00	0.00	
+Menopausal status	1.00	1.21	1.10	1.17	0.01	0.00	0.00	
+Age when period became regular[1]	1.00	1.22	1.10	1.17	0.00	0.00	0.00	
+Age when period became regular[2]	1.00	1.22	1.10	1.17	0.00	0.00	0.00	
+Age at menopause[1]	1.00	1.22	1.10	1.17	0.00	0.00	0.00	
+Age at menopause[2]	1.00	1.21	1.09	1.16	0.01	0.01	0.01	
+Age at first live birth[1]	1.00	1.23	1.12	1.20	-0.01	-0.02	-0.03	
+Age at first live birth[2]	1.00	1.23	1.12	1.20	-0.01	-0.02	-0.03	
+Number of live births[1]	1.00	1.22	1.12	1.20	0.00	-0.02	-0.03	
+Number of live births[2]	1.00	1.22	1.12	1.20	0.00	-0.02	-0.03	
+Ever use of oral contraception	1.00	1.22	1.11	1.17	0.00	-0.01	0.00	

Table 6 (continued)

Postmenopausal Women								
Base model	1.00	1.10	1.15	1.19				
+ Ever use either estrogens/ progesterone	1.00	1.10	1.17	1.22	0.00	-0.02	-0.02	
+Age at menopause1	1.00	1.09	1.13	1.18	0.01	0.02	0.01	
+Age at menopause^2	1.00	1.09	1.13	1.18	0.01	0.02	0.01	

*** All above adjusted for age at recruitment (years), year of recruitment (1993-1995, 1996-1998), and dialect group (Hokkien, Cantonese)

1: Regard the variable as dummy variable to get the HR;

2: Regard the variable as ordinal variable to get the HR.

Table 7 Pearson Correlation between caffeine and coffee/ green tea/ black tea

r	Coffee/ cups/ day	Green tea/ cups/ day	Black tea/ cups/ day
Caffeine/ mg	0.89	0.32	0.17

The majority of caffeine consumed in the study population was from coffee (81.8%) and black tea (12.0%). Green tea and soda were the minor contributors to caffeine (0.2%, 0.7%, respectively) in the study population.

Table 8 Breast cancer and coffee/ caffeine association among overall, premenopausal and postmenopausal women

	Total women			Premenopausal women			Postmenopausal women		
All cases	Cases, n	HR (95% CI)[1]	p trend	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)[2]	p trend
Coffee-4[3]									
None/Monthly	121	1.0 (ref)		39	1.0 (ref)		82	1.0 (ref)	
Weekly	60	1.21 (0.89, 1.66)		24	1.45 (0.87, 2.42)		36	1.09 (0.74, 1.62)	
Daily	251	1.13 (0.91, 1.41)		69	1.03 (0.70, 1.53)		182	1.19 (0.92, 1.54)	
≥ 2 cups/day	197	1.23 (0.98 1.54)	0.11	58	1.18 (0.78, 1.77)	0.69	139	1.26 (0.96, 1.66)	0.08
Coffee-5[4]									
None/Monthly	121	1.0 (ref)		39	1.0 (ref)		82	1.0 (ref)	
Weekly	60	1.21 (0.89, 1.66)		24	1.45 (0.87, 2.42)		36	1.09 (0.74, 1.62)	
Daily	251	1.13 (0.91, 1.41)		69	1.03 (0.70, 1.53)		182	1.19 (0.92, 1.54)	
2-3 cups/day	184	1.26 (1.00, 1.58)		53	1.17 (0.77, 1.78)		131	1.31 (0.99, 1.73)	
≥4 cups/day	13	0.93 (0.52, 1.64)	0.15	5	1.22 (0.48, 3.11)	0.68	8	0.81 (0.39, 1.67)	0.13
Caffeine[5]									
Q1	134	1.0 (ref)		39	1.0 (ref)		95	1.0 (ref)	
Q2	177	1.32 (1.06, 1.66)		58	1.53 (1.02, 2.30)		119	1.25 (0.96, 1.64)	
Q3	168	1.07 (0.85, 1.34)		48	1.01 (0.66, 1.54)		120	1.10 (0.84, 1.44)	
Q4	150	1.33 (1.05, 1.68)	0.12	45	1.35 (0.88, 2.07)	0.57	105	1.33 (1.01, 1.76)	0.12

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal

2: Model 1 plus variable hormone use (hormoneuse);

3: Categorized coffee consumption as four categories (D35_7_4); 4: Categorized coffee consumption as five categories (D35_7_5);

5: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 9 Coffee and caffeine intake in relation to advanced breast cancer risk, stratified by menopausal status

	Premenopausal women			Postmenopausal women		
	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)	p trend
Coffee-4[2]						
None/Monthly	11	1.0 (ref)		27	1.0 (ref)	
Weekly	9	1.93 (0.80, 4.66)		10	0.94 (0.45, 1.93)	
Daily	31	1.67 (0.84, 3.34)		88	1.71 (1.11, 2.64)	
≥ 2 cups/day	25	1.86 (0.91, 3.79)	0.12	71	1.91 (1.22, 2.98)	0.001
Caffeine[3]						
Q1	11	1.0 (ref)		30	1.0 (ref)	
Q2	27	2.56 (1.27, 5.16)		59	1.94 (1.25, 3.01)	
Q3	17	1.29 (0.60, 2.75)		51	1.47 (0.93, 2.30)	
Q4	21	2.29 (1.10, 4.76)	0.19	56	2.20 (1.41, 3.43)	0.01

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal.

2: Categorized coffee consumption as four categories (D35_7_4);

3: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 10 Coffee (five categories) and advanced breast cancer association

	Advanced BC		
All cases	Cases, n	HR (95% CI)[1]	p trend
Coffee-5[4]			
None/Monthly	38	1.0 (ref)	
Weekly	19	1.23 (0.71, 2.14)	
Daily	119	1.70 (1.18, 2.45)	
2-3 cups/day	87	1.89 (1.29, 2.77)	
≥4 cups/day	9	2.03 (0.98, 4.20)	0.0004

Table 11 Coffee and caffeine intake in relation to breast cancer risk, stratified by stage of disease and duration of follow-up

	Localized Cases			Advanced Cases		
	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)	p trend
Overall[1]						
Coffee-4[2]						
None/Monthly	79	1.0 (ref)		38	1.0 (ref)	
Weekly	40	1.24 (0.84, 1.81)		19	1.23 (0.71, 2.14)	
Daily	126	0.88 (0.66, 1.16)		119	1.70 (1.18, 2.45)	
≥ 2 cups/day	99	0.95 (0.70, 1.28)	0.41	96	1.90 (1.30, 2.77)	<0.01
Caffeine[3]						
Q1	88	1.0 (ref)		41	1.0 (ref)	
Q2	86	0.98 (0.73, 1.32)		86	2.10 (1.45, 3.05)	
Q3	99	0.95 (0.72, 1.27)		68	1.41 (0.96, 2.08)	
Q4	71	0.96 (0.70, 1.31)	0.74	77	2.23 (1.52, 3.26)	<0.01
Duration of follow-up, < 5 years[4]						
Coffee-4						
Non/Monthly	33	1.0 (ref)		15	1.0 (ref)	
Weekly	18	1.23 (0.84, 1.80)		10	1.23 (0.71, 2.14)	
Daily	62	0.88 (0.66, 1.16)		56	1.70 (1.18, 2.46)	
≥ 2 cups/day	39	0.95 (0.71, 1.28)	0.42	47	1.90 (1.30, 2.77)	<0.001
Caffeine						
Q1	36	1.0 (ref)		16	1.0 (ref)	
Q2	40	0.98 (0.73, 1.32)		40	2.10 (1.45, 3.04)	

Table 11 (Continued)

Q3	47	0.95 (0.72, 1.27)		34	1.41 (0.96, 2.08)	
Q4	29	0.96 (0.70, 1.31)	0.74	38	2.22 (1.52, 3.25)	0.002
Duration of follow-up, ≥ 5 years						
Coffee-4						
Non/Monthly	46	1.0 (ref)		23	1.0 (ref)	
Weekly	22	1.19 (0.72, 1.98)		9	0.99 (0.46, 2.14)	
Daily	64	0.76 (0.52, 1.10)		63	1.48 (0.92, 2.39)	
≥ 2 cups/day	60	0.95 (0.64, 1.39)	0.45	49	1.58 (0.96, 2.59)	0.04
Caffeine						
Q1	52	1.0 (ref)		25	1.0 (ref)	
Q2	46	0.88 (0.59, 1.31)		46	1.84 (1.13, 3.00)	
Q3	52	0.83 (0.56, 1.22)		34	1.15 (0.69, 1.93)	
Q4	42	0.92 (0.61, 1.38)	0.58	39	1.82 (1.10, 3.01)	0.14

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1);

2: Categorized coffee consumption as four categories (D35_7_4);

3: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively;

4: Median duration of follow-up (5 yrs) value among cases.

*All variables are coded as ordinal.

Table 12 Coffee and caffeine intake in relation to risk of overall breast cancer, stratified by median duration of follow-up

	< 5 years[3]			≥ 5 years		
	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
Coffee-4[1]						
Non & monthly-drinker	49	1.0 (ref)		72	1.0 (ref)	
Weekly	29	1.41 (0.89, 2.23)		31	1.08 (0.71, 1.64)	
Daily	122	1.37 (0.98, 1.91)		129	0.97 (0.73, 1.29)	
≥ 2 cups/day	87	1.39 (0.98, 1.98)	0.08	110	1.11 (0.83, 1.50)	0.59
Caffeine[2]						
Q1	54	1.0 (ref)		80	1.0 (ref)	
Q2	84	1.56 (1.11, 2.20)		93	1.16 (0.86, 1.56)	
Q3	81	1.30 (0.92, 1.83)		87	0.91 (0.67, 1.23)	
Q4	68	1.55 (1.09, 2.22)	0.06	82	1.18 (0.86, 1.60)	0.70

1: Categorized coffee consumption as four categories (D35_7_4);

2: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively;

3: Median duration of follow-up (5 yrs) value among cases.

Table 13 Coffee and caffeine intake in relation to risk of breast cancer by duration of follow-up (3 categories)

	0 to 5 years			5 to < 10 years			≥ 10 years		
	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
Coffee-4[1]									
None/ monthly	49	1.0 (ref)		60	1.0 (ref)		12	1.0 (ref)	
Weekly	29	1.41 (0.89, 2.23)		26	1.08 (0.68, 1.71)		5	1.07 (0.38, 3.03)	
Daily	122	1.37 (0.98, 1.91)		100	0.91 (0.66, 1.25)		29	1.28 (0.65, 2.50)	
≥2 cups/day	87	1.39 (0.98, 1.98)	0.08	83	1.03 (0.74, 1.43)	0.95	27	1.54 (0.78, 3.04)	0.19
Caffeine[2]									
Q1	54	1.0 (ref)		67	1.0 (ref)		13	1.0 (ref)	
Q2	84	1.56 (1.11, 2.20)		70	1.05 (0.75, 1.46)		23	1.75 (0.89, 3.46)	
Q3	81	1.30 (0.92, 1.83)		72	0.90 (0.65, 1.26)		15	0.94 (0.45, 1.98)	
Q4	68	1.55 (1.09, 2.22)	0.06	60	1.04 (0.73, 1.48)	0.91	22	1.85 (0.93, 3.67)	0.30

1: Categorized coffee consumption as four categories (D35_7_4);

2: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 14 Coffee and caffeine intake in relation to risk of overall and localized breast cancer, stratified by body mass index (BMI)

	BMI < median (23 kg/m^2)		BMI ≥ median (23 kg/m^2)		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Overall[1]					
Coffee-2[2]					
Non-drinker or less frequent than weekly	87	1.0 (ref)	94	1.0 (ref)	
Daily	187	1.05 (0.81, 1.36)	261	1.16 (0.91, 1.47)	
					0.45
Caffeine[3]					
T1	115	1.0 (ref)		1.0 (ref)	
T2	61	0.77 (0.56, 1.05)		1.06 (0.82, 1.38)	
T3	98	1.08 (0.83, 1.42)		1.15 (0.90, 1.47)	
P for trend		0.64		0.26	0.63
Localized Disease					
Coffee-2					
Non-drinker or less frequent than weekly	52	1.0 (ref)	67	1.0 (ref)	
Daily	101	0.94 (0.67, 1.32)	124	0.78 (0.58, 1.05)	
					0.44

Table 14 (Continued)

Caffeine				
T1	66	1.0 (ref)	1.0 (ref)	
T2	32	0.70 (0.46, 1.07)	0.86 (0.60, 1.24)	
T3	55	1.06 (0.74, 1.52)	0.97 (0.69, 1.34)	
P for trend		0.84	0.82	0.34

1: Overall model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal;

2: Categorized coffee consumption as dichotomous (D35_7_2c);

3: Categorized caffeine intake (N4_34) as tertiles, and coded it as dummy variable; the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

Table 15 Coffee and caffeine intake in relation to risk of advanced breast cancer, stratified by body mass index (BMI)

	BMI < median (23 kg/m^2)		BMI ≥ median (23 kg/m^2)		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Coffee-2[1]					
Non-drinker or less frequent than weekly	34	1.0 (ref)	23	1.0 (ref)	
Daily	84	1.22 (0.82, 1.83)	131	2.35 (1.51, 3.66)	
					0.02
Caffeine[2]					
<101 mg	59	1.0 (ref)	68	1.0 (ref)	
≥101 mg	59	1.04 (0.72, 1.49)	86	1.23 (0.90, 1.69)	
					0.51

1: Categorized coffee consumption as dichotomous (D35_7_2c);

2: Categorized caffeine intake as dichotomous (N1_34_2); the median caffeine intake is 101 (mg).

Table 16 Coffee and caffeine intake in relation to risk of advanced breast cancer, stratified by Weight (kg)

	Weight < median (55 kg)		Weight ≥ median (55 kg)		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Coffee-2[1]					
Non-drinker or less frequent than weekly	30	1.0 (ref)	27	1.0 (ref)	
Daily	93	1.45 (0.96, 2.19)	122	1.94 (1.28, 2.94)	
					0.26
Caffeine[2]					
T1	46	1.0 (ref)	44	1.0 (ref)	
T2	30	0.94 (0.60, 1.50)	47	1.44 (0.96, 2.18)	
T3	47	1.28 (0.85, 1.93)	58	1.47 (1.00, 2.18)	0.64
P for trend		0.25		0.05	

1: Categorized coffee consumption as dichotomous (D35_7_2c);

2: Categorized caffeine intake (N4_34) as tertiles, and coded it as dummy variable; the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

Table 17 Coffee and caffeine intake in relation to risk of advanced breast cancer, stratified by Height (cm)

	Height < median (155 cm)		Height ≥ median (155 cm)		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Coffee-2[1]					
Non-drinker or less frequent than weekly	25	1.0 (ref)	32	1.0 (ref)	
Daily	78	1.34 (0.85, 2.11)	137	1.92 (1.30, 2.82)	
					0.32
Caffeine[2]					
T1	37	1.0 (ref)	53	1.0 (ref)	
T2	26	0.98 (0.60, 1.63)	51	1.32 (0.90, 1.94)	
T3	40	1.24 (0.79, 1.95)	65	1.42 (0.99, 2.05)	0.80
P for trend		0.35		0.06	

1: Categorized coffee consumption as dichotomous (D35_7_2c);

2: Categorized caffeine intake (N4_34) as tertiles, and coded it as dummy variable; the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

Table 18 Coffee (two categories) and caffeine (two categories) intake in relation to risk of advanced breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status

Advanced disease	ER+		ER-	
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)
Total	77		114	
Coffee-2[1]				
Non-drinker or less frequent than weekly	16	1.0 (ref)	22	1.0 (ref)
Daily	61	1.66 (0.95, 2.88)	92	1.87 (1.17, 2.98)
Caffeine[2]				
<101 mg	40	1.0 (ref)	51	1.0 (ref)
≥101 mg	37	0.91 (0.58, 1.42)	63	1.24 (0.85, 1.79)
	PR+		PR-	
Total	104		84	
Coffee-2[1]				
Non-drinker or less frequent than weekly	20	1.0 (ref)	18	1.0 (ref)
Daily	84	1.85 (1.13, 3.01)	66	1.63 (0.96, 2.74)
Caffeine[2]				
<101 mg	58	1.0 (ref)	31	1.0 (ref)

Table 18 (Continued)

≥101 mg	46	0.79 (0.53, 1.16)	53	1.70 (1.09, 2.65)

1: Categorized coffee consumption as dichotomous (D35_7_2c);

2: Categorized caffeine intake as dichotomous (N1_34_2); the median caffeine intake is 101 (mg).

Table 19 Coffee (three categories) and caffeine (three categories) intake in relation to risk of advanced breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status

	ER+			ER-		
Advanced disease	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
Coffee-3[2]						
Non & monthly	8	1.0 (ref)		17	1.0 (ref)	
Weekly	8	2.43 (0.91, 6.49)		5	0.73 (1.23, 2.89)	
≥Daily	61	2.35 (1.12, 4.92)	0.03	92	1.72 (1.03, 2.89)	0.02
Caffeine[3]						
T1	26	1.0 (ref)		37	1.0 (ref)	
T2	23	1.23 (0.70, 2.15)		35	1.32 (0.83, 2.09)	
T3	28	1.24 (0.73, 2.12)	0.43	42	1.35 (0.87, 2.10)	0.19
	PR+			PR-		
	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
Coffee-3[2]	12	1.0 (ref)		13	1.0 (ref)	
Non & monthly	8	1.64 (0.67, 4.01)		5	0.94 (0.34, 2.65)	
Weekly	84	2.19 (1.19, 4.01)	0.01	66	1.60 (0.88, 2.90)	0.09
≥Daily						
Caffeine[3]	38	1.0 (ref)		24	1.0 (ref)	
T1	33	1.21 (0.76, 1.92)		24	1.39 (0.79, 2.45)	
T2	33	1.01 (0.63, 1.62)	0.93	36	1.77 (1.05, 2.96)	0.03

Table 19 (Continued)

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1);

2: Coffee (D35_7_3c);

3: Regard caffeine as dummy variable & caffeine (N4_34);

*Except the ones specially mentioned above, all other category variables are coded as ordinal.

Table 20 Coffee-4 and caffeine-4 intake in relation to risk of overall breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status

	ER+			ER-		
	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
Coffee-4[2]						
None/ monthly	25	1.0 (ref)		53	1.0 (ref)	
Weekly	14	1.36 (0.71, 2.62)		22	1.02 (0.62, 1.67)	
Daily	52	1.14 (0.71, 1.83)		105	1.09 (0.78, 1.52)	
≥2 cups/day	46	1.39 (0.85, 2.27)	0.25	77	1.12 (0.79, 1.59)	0.50
Caffeine[3]						
Q1	27	1.0 (ref)		57	1.0 (ref)	
Q2	42	1.56 (0.96, 2.53)		69	1.22 (0.86, 1.73)	
Q3	38	1.20 (0.73, 1.96)		72	1.08 (0.76, 1.53)	
Q4	30	1.32 (0.78, 2.22)	0.55	59	1.25 (0.87, 1.80)	0.38
	PR+			PR-		
Coffee-4[2]	Cases, n	HR (95%CI)	P trend	Cases, n	HR (95%CI)	P trend
None/ monthly	41	1.0 (ref)		36	1.0 (ref)	
Weekly	20	1.19 (0.70, 2.03)		16	1.09 (0.60, 1.96)	
Daily	84	1.13 (0.78, 1.64)		70	1.06 (0.71, 1.59)	
≥2 cups/day	62	1.17 (0.79, 1.74)	0.49	60	1.26 (0.83, 1.91)	0.30
Caffeine[3]						
Q1	45	1.0 (ref)		38	1.0 (ref)	
Q2	65	1.46 (0.99, 2.13)		44	1.16 (0.75, 1.79)	
Q3	49	0.93 (0.62, 1.39)		59	1.32 (0.88, 1.99)	
Q4	48	1.29 (0.86, 1.93)	0.75	41	1.28 (0.83, 2.00)	0.20

Table 20 (Continued)

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1);

2: Coffee (D35_7_4);

3: Regard caffeine as dummy variable; & caffeine (N5_34)

Table 21 Coffee and caffeine intake and advanced breast cancer association

	All (control+cases without ER/PR information)		Subgroup (control+cases with any ER/PR information)	
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)
Coffee[1]				
None/Monthly	13	1.00 (ref)	26	1.00 (ref)
Weekly	6	1.16 (0.44, 3.04)	13	1.28 (0.65, 2.50)
Daily	29	1.23 (0.64, 2.37)	90	1.94 (1.25, 3.03)
≥ 2 cups/day	33	1.93 (1.01, 3.67)	63	1.89 (1.19, 3.01)
p trend		0.04		0.003
Caffeine[2]				
Q1	15	1.00 (ref)	26	1.00 (ref)
Q2	21	1.42 (0.73, 2.75)	65	2.49 (1.58, 3.93)
Q3	17	0.96 (0.48, 1.92)	51	1.68 (1.05, 2.69)
Q4	28	2.21 (1.18, 4.15)	49	2.24 (1.39, 3.61)
p trend		0.04		0.02

1: Categorized coffee consumption as four categories (D35_7_4);

2: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 22 Frequency of coffee intake among advanced cases with or without ER/PR status on coffee and caffeine intake

	Cases without ER/PR information	Cases with any ER/PR information
Coffee-4[1], %		
None/Monthly	16.05	13.09
Weekly	7.41	6.81
Daily	35.80	47.12
≥ 2 cups/day	40.74	32.98
x^2 P value	0.05	
Caffeine[2] , %		
Q1	18.52	13.61
Q2	25.93	34.03
Q3	20.99	26.70
Q4	34.57	25.65
x^2 P value	0.04	

1: Categorized coffee consumption as four categories (D35_7_4);

2: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively

Table 23 Coffee intake (four categories) and breast cancer association for overall and different stage of disease

	Advanced disease[1]			Advanced disease (plus caffeine)[2]		Advanced disease (plus additional covariates)[3]	
	Cases, n	HR (95% CI)[1]	p trend	HR (95% CI)	p trend	HR (95% CI)	p trend
Coffee-4[4]							
None/Monthly	38	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Weekly	19	1.23 (0.71, 2.14)		1.21 (0.70, 2.11)		1.24 (0.71, 2.15)	
Daily	119	1.70 (1.18, 2.45)		1.59 (1.04, 2.45)		1.70 (1.18, 2.46)	
≥ 2 cups/day	96	1.90 (1.30, 2.77)	<0.01	1.66 (0.91, 3.02)	0.05	1.88 (1.29, 2.75)	<0.001

1: Model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal;

2: Model 1 plus caffeine (N5_34) in the model (coded as quartiles, run as an ordinal variable);

3: Model 1 plus the following covariates: number of live births (ordinal variable: 0, 1-2, 3+) <D52_14_>, BMI <D2>, smoking (ever/never) <D14_1_1>, physical activity (yes/no any weekly vigorous or moderate activity) <D51_4>, soy intake (>, <median) <FD1_5_1_> and green tea intake (drinker/nondrinker) <D35_5_1>;

4: Categorized coffee consumption as four categories (D35_7_4).

Table 24 Alcohol intake percentage by four levels of coffee intake

	Non-drinker/monthly	weekly	daily	≥2 cups/day
Alcohol intake, %				
Non-drinkers	92.68	91.53	91.05	89.27
<7 drinks/week	6.57	7.78	7.81	9.13
≥7 drinks/week	0.75	0.69	1.14	1.60

1: Categorized coffee consumption as four categories (D35_7_4);

2: Categorized alcohol consumption as three categories (D37_1_1_) < Non-drinkers, <7 drinks/week, ≥7 drinks/week >.

Table 25 Coffee and caffeine intake and breast cancer association (overall cases and different stage of disease) among non-drinkers of alcohol

	Overall			Localized disease			Advanced disease		
	Cases, n	HR (95% CI)[1]	p trend	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)	p trend
Coffee[2]									
None/Monthly	118	1.0 (ref)		76	1.0 (ref)		38	1.0 (ref)	
Weekly	56	1.18 (0.86, 1.62)		37	0.88 (0.65, 1.20)		18	1.18 (0.67, 2.07)	
Daily	232	1.09 (0.87, 1.36)		116	0.86 (0.64, 1.14)		111	1.61 (1.11, 2.32)	
≥ 2 cups/day	171	1.13 (0.89, 1.43)	0.39	85	1.21 (0.82, 1.79)	0.23	84	1.70 (1.16, 2.50)	<0.01
Caffeine[3]									
Q1	131	1.0 (ref)		85	1.0 (ref)		41	1.0 (ref)	
Q2	165	1.28 (1.02, 1.62)		80	0.97 (0.71, 1.31)		81	2.01 (1.38, 2.92)	
Q3	152	1.02 (0.81, 1.29)		91	0.94 (0.70, 1.26)		60	1.29 (0.87, 1.92)	
Q4	129	1.29 (1.02, 1.62)	0.37	58	0.86 (0.61, 1.20)	0.37	69	2.10 (1.42, 3.09)	<0.01

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal.

2: Categorized coffee consumption as four categories (D35_7_4);

3: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 26 Coffee intake and breast cancer association for overall and different stages of disease (adding alcohol and other covariates into models)

	Advanced disease[1]			Advanced disease (plus alcohol)[2]		Advanced disease (plus additional covariates)[3]	
	Cases, n	HR (95% CI)[1]	p trend	HR (95% CI)	p trend	HR (95% CI)	p trend
Coffee-4[4]							
None/Monthly	38	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Weekly	19	1.23 (0.71, 2.14)		1.24 (0.71, 2.14)		1.24 (0.71, 2.15)	
Daily	119	1.70 (1.18, 2.45)		1.71 (1.18, 2.46)		1.71 (1.18, 2.46)	
≥ 2 cups/day	96	1.90 (1.30, 2.77)	<0.01	1.91 (1.31, 2.79)	<0.01	1.89 (1.30, 2.77)	<0.01

1: Model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal;

2: Model 1 plus alcohol (drinkers/nondrinkers) in the model;

3: Model 2 plus the following covariates: number of live births (ordinal variable: 0, 1-2, 3+) <D52_14_>, BMI <D2>, smoking (ever/never) <D14_1_1>, physical activity (yes/no any weekly vigorous or moderate activity) <D51_4>, soy intake (>, <median) <FD1_5_1_> and green tea intake (drinker/nondrinker) <D35_5_1>;

Table 27 Coffee intake and advanced breast cancer association stratified by median body mass index (BMI) among non-drinkers of alcohol

	BMI < median (23 kg/m^2)		BMI ≥ median (23 kg/m^2)		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Coffee[1]					
Non-drinker or less frequent than weekly	33	1.0 (ref)	23	1.0 (ref)	
Daily	76	1.15 (0.76, 1.73)	119	2.17 (1.39, 3.39)	0.03

1: Categorized coffee consumption as dichotomous (D35_7_2c).

Table 28 Alcohol (two categories and three categories) intake and breast cancer association for overall and different stages of disease

	Overall			Localized disease			Advanced disease		
	Cases, n	HR (95% CI)[1]	p trend	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)	p trend
Alcohol-2[2]									
Nondrinker	577	1.0 (ref)		314	1.0 (ref)		251	1.0 (ref)	
Drinker	52	0.93 (0.70, 1.23)		30	0.98 (0.67, 1.42)		21	0.86 (0.55, 1.35)	
Alcohol-3[3]									
Nondrinker	577	1.0 (ref)		314	1.0 (ref)		251	1.0 (ref)	
<7 drinks per week	46	0.93 (0.69, 1.26)		28	1.03 (0.70, 1.52)		18	0.84 (0.52, 1.36)	
≥7 drinks per week	6	0.88 (0.39, 1.98)	0.58	2	0.56 (0.14, 2.23)	0.71	3	0.99 (0.32, 3.08)	0.58

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); number of live births (ordinal variable: 0, 1-2, 3+) <D52_14_>, BMI <D2>, smoking (ever/never) <D14_1_1>, physical activity (yes/no any weekly vigorous or moderate activity) <D51_4>, soy intake (>, <median) <FD1_5_1_> and green tea intake (drinker/nondrinker) <D35_5_1>; All variables are coded as ordinal;

2: Categorized alcohol consumption as two categories (D37_1_1_1) < Non-drinkers, drinker >;

3: Categorized alcohol consumption as three categories (D37_1_1_) < Non-drinkers, <7 drinks/week, ≥7 drinks/week >.

Table 29 Coffee intake and breast cancer association for general population and localized disease without carcinoma in-situ

	General excluding CIS*			Localized disease without CIS		
	Cases, n	HR (95% CI)[1]	p trend	Cases, n	HR (95% CI)	p trend
Coffee[2]						
N	550			265		
None/Monthly	108	1.0 (ref)		66	1.0 (ref)	
Weekly	45	1.02 (0.72, 1.45)		25	0.93 (0.59, 1.47)	
Daily	215	1.09 (0.86, 1.37)		90	0.75 (0.55, 1.03)	
≥ 2 cups/day	182	1.27 (1.00 1.62)	0.05	84	0.97 (0.70, 1.34)	0.61

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1); All variables are coded as ordinal.

2: Categorized coffee consumption as four categories (D35_7_4);

*CIS=Carcinoma in-situ

Table 30 Confounding assessment for green tea by evaluating coffee/caffeine intake and breast cancer association for overall, different stages of disease with model including green tea covariate

	Overall			Localized disease			Advanced disease		
	Cases, n	HR (95% CI)[1]	p trend	Cases, n	HR (95% CI)	p trend	Cases, n	HR (95% CI)	p trend
Coffee[2]									
None/Monthly	121	1.0 (ref)		79	1.0 (ref)		38	1.0 (ref)	
Weekly	60	1.21 (0.89, 1.66)		40	1.24 (0.84, 1.81)		19	1.23 (0.71, 2.14)	
Daily	251	1.13 (0.91, 1.41)		126	0.88 (0.66, 1.16)		119	1.70 (1.18, 2.45)	
≥ 2 cups/day	197	1.23 (0.98 1.54)	0.11	99	0.95 (0.70, 1.28)	0.41	96	1.90 (1.30, 2.77)	<0.01
Caffeine[3]									
Q1	134	1.0 (ref)		88	1.0 (ref)		41	1.0 (ref)	
Q2	177	1.32 (1.06, 1.66)		86	0.98 (0.73, 1.32)		86	2.10 (1.45, 3.05)	
Q3	168	1.07 (0.85, 1.34)		99	0.95 (0.72, 1.27)		68	1.41 (0.96, 2.08)	
Q4	150	1.33 (1.05, 1.68)	0.12	71	0.96 (0.70, 1.31)	0.74	77	2.23 (1.52, 3.26)	<0.01

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1), green tea intake; All variables are coded as ordinal.

2: Categorized coffee consumption as four categories (D35_7_4);

3: Categorized caffeine intake (N5_34) as quartiles, and coded it as dummy variable; the median caffeine amount (IQR) for each quartile are 18.59 (32.77), 88.25 (11.37), 139.01 (66.97), 244.96 (60.79), respectively.

Table 31 Coffee/caffeine and breast cancer association stratified analysis by green tea drinking

	Non-Green tea drinker		Green tea drinker		p for interaction
	Cases, n	HR (95%CI)	Cases, n	HR (95%CI)	
Total	118		154		
Coffee-2[1]					
Non/ weekly/monthly	34	1.0 (ref)	23	1.0 (ref)	
Daily	84	1.22 (0.82, 1.83)	131	2.35 (1.51, 3.66)	
					0.02
Caffeine-3[2]					
T1	46	1.0 (ref)	44	1.0 (ref)	
T2	29	0.91 (0.57, 1.45)	48	1.49 (0.99, 2.24)	
T3	43	1.20 (0.79, 1.82)	62	1.58 (1.07, 2.33)	0.34
p for trend		0.42		0.02	

1: Categorized coffee consumption as dichotomous (D35_7_2c);

2: Categorized caffeine intake (N4_34) as tertiles, and coded it as dummy variable; the median caffeine amount (IQR) for each tertile are 43.77 (54.98), 106.22 (29.22), 227.16 (39.17), respectively.

Table 32 Coffee and caffeine intake and breast cancer association, after removing the first year of follow-up

	Advanced Cases		
	Cases, n	HR (95% CI)	*p* trend
Overall[1]			
Coffee-4			
None/Monthly	34	1.0 (ref)	
Weekly	18	1.31 (0.74, 2.32)	
Daily	111	1.77 (1.21, 2.60)	
≥ 2 cups/day	89	1.96 (1.32, 2.92)	0.0004
Coffee-3			
None/Monthly	34	1.0 (ref)	
Weekly	18	1.31 (0.74, 2.32)	
Daily	200	1.85 (1.29, 2.67)	0.0005
Caffeine			
Q1	38	1.0 (ref)	
Q2	77	2.03 (1.37, 2.99)	
Q3	66	1.48 (0.99, 2.20)	
Q4	71	2.21 (1.49, 3.27)	0.002
Caffeine			
T1	82	1.0 (ref)	
T2	72	1.21 (0.89, 1.67)	
T3	98	1.39 (1.03, 1.86)	0.03

1: All model adjusted for age at recruitment (years) (D1), year of recruitment (1993-1995, 1996-1998) (V3), and dialect group (Hokkien, Cantonese) (V15), education (V25_), age when period became regular (D52_2_1);

*All variables are coded as ordinal; N= 47 breast cancer cases removed from this analysis; N= 158 non-cases removed from this analysis.

Table 33 Association between family history/hormone use and stage of disease

	Localized disease			Advanced disease		
	Cases, n	HR (95% CI)[1]	*p* trend	Cases, n	HR (95% CI)	*p* trend
Family history: first-degree relative with diagnosis of breast cancer						
No	340	1.0 (ref)		266	1.0 (ref)	
Yes	4	0.83 (0.31, 2.24)		6	1.68 (0.75, 3.79)	
Hormone use						
Ever	308	1.0 (ref)		257	1.0 (ref)	
Never	36	1.82 (1.28, 2.59)		15	0.97 (0.57, 1.65)	

APPENDIX II

Table 34 Coffee & Breast Cancer association studies

Reference	Study Population (US, xx Study, Case/Cohort, N)	Cut points	Overall Results	Notes (stratified/interaction); Con't: Other findings	*Related discussion contents
[16]; Coffee & BC.	Norway, Norwegian study; Prospective Cohort (12 ys fu); 152 cases /14,593 (35-51 ys); <1974->; FFQ+24hs recall among a subsample; NO QUESTIONS in primary questionnaire related to risk factors for BC, like menarche.	Coffee: ≤2cups/day, 3-4 cups/day, 5-6 cups/ day, ≥7 cups/day;	Overall coffee: non-sig weak negative association OR=0.8 (0.5, 1.4), p=0.37, x^2 =0.81.	-BMI (<24; ≥24 kg/m^2): coffee sig inverse associated among lean women (<24), IRR=0.5 (0.3-0.9), p=0.02, x^2 trend=5.07 (≥5 cups/day vs. 2 cups/day); coffee positive associated among women with BMI ≥24, IRR=2.1 (0.8-5.2), p=0.13, x^2 trend=2.33 ; -Interaction BMI & coffee was statistically sig <x^2 interaction=2.33; p=0.02>.	1.Protective effect of obesity on the risk of BC is restricted to premenopausal women [75]; 2. may BMI – ovarian activity
Con't				-Height: increase risk of BC, IRR=1.5, p=0.02, (≥163 vs. <163 cm); -Relative overweight: inversely related to BR risk; -Total serum cholesterol: non-sig negative association, IRR=-.8, p=0.2, cholesterol	

				equal or above median <6.6 mmol/l>vs. lower than median; -Menopausal <premenopausal: by defined as age 47 or younger>: no materially alter the negative association.	
[60]; <in meta>; Coffee & pre-meno BC.	US, Hospital based Case-control; 1932 cases/ 1895 hospital control with non-neoplastic conditions.	Coffee: None, <1 cup/day, 2-3 cups/day, ≥4 cups/day;	Among premenopausal women: Inversed associated coffee, OR=0.62 (0.39, 0.98), p=0.03, ≥4 cups/day vs. none drinker; Among postmenopausal women: No association, OR=0.99 (0.79, 1.23), p=0.57.	Caffeinated coffee: Inverse associated with coffee; Decaffeinated coffee: No association.	BBD without atypia has no association with coffee consumption, atypical hyperplasia is related; see following.
[88]; Coffee & BRCA1 & 2.	US, Canada, Poland, Israel; Matched Case-control; 1690 BRCA+ control/1690 cases.	Coffee: Non-drinker, 1-3 cups/day, 4-5 cups/day, ≥6 cups/day;	0 (reference), nondrinker; 0.90 (0.72, 1.12), 1-3 cups/day; 0.75 (0.47, 1.19), 4-5 cups/day; 0.31 (0.13, 0.71), ≥6 cups/day; P trend=0.02.	Inversed association between coffee & BC among high-risk women <BRCA mutations>.	1. Assessed high-risk women (BRCA); 2. Carrying CYP1A2- also inverse associated [89].

[78]; Anti-oxidant beverages & BC.	French, French Supplementation en Vitamins' and Mineral Antioxidants Study; 95/4396 women (35-60 yrs); Cohort study (median 8 yrs fu); <1994-2002>.	Coffee: 112-252 ml/day, >252 ml/day;	1.07 (0.64, 1.79), 112-252 ml/day; 1.10 (0.66, 1.84), >252 ml/day, p trend=0.71.		
[15]; Coffee & BC.	Meta-analysis; 25,250 cases and 375,169 non-cases; 9 case-controls & 9 cohort studies, Europe, US, Asia, <1966-May 2008>;	Coffee: Highest, non/lowest consumption; 2 cups/day increment;	Combined RR coffee: borderline significant influence <I think no association>, RR=0.95 (0.9-1.0), highest vs. non/lowest coffee consumption; & RR= 0.98 (0.96, 1.0), increment of 2 cups/day;	Case-control: <I think no association> -1) high coffee consumption: RR=0.95 (0.87-, 1.04); -2) 2 cups/day increment: RR=0.98 (0.95. 1.01); Cohort: <I think no association> -1) high coffee consumption: RR=0.95 (0.88, 1.02); -2) 2 cups/day increment: RR=0.98 (0.96, 1.01).	1. Few mechanism in introduction & discussion related to positive association mechanism, see following.
Con't				For case-control, separated by hospital-based, and population-based, no difference; Stratified by geographic region <Europe, US, Asia>, <I think no association for all three>. RR=0.95 (0.86, 1.06), 0.94 (0.87, 1.01), 0.92 (0.64, 1.33), respectively.	2. Many mechanisms in discussion part show inverse association mechanisms/ evidence.

[69]; Coffee/caffeine & BC. (in meta)	US, Nurses' Health Study; Prospective Cohort (22 ys fu); 6552 cases / 85,987 (30-35 ys; 11 states); <1976-1980-2002>. 1980: 60-item FFQ; 1984, 1986, 1990, 1994, 1998: 130-item FFQ <include decaffeinated coffee>	Coffee (137 mg caffeine/ 8 oz cup): ≤1cup/month, 1cup/month-4.9 cups/week, 5cups/week-1.9 cups/day, ≥4 cups/day; Caffeine (quintile): with equal number of participants (didn't report actual number in paper).	Overall coffee: no association; -Caffeinated coffee RR=0.92 (0.82-1.03), ≥4 cups/day vs. <1 cup/month, p=0.14; -Decaffeinated coffee: not significant associated; Overall caffeine: weak inverse association; -Caffeine intake RR=0.93 (0.85-1.01), p=0.06, 4 vs. 1; postmenopausal women: significant inverse association, RR=0.88 (0.79-0.97), p=0.03;	-Menopausal status: <Postmenopausal women> significant inverse association between caffeine and breast cancer (RR=0.88, (0.79-0.97), p=0.03) <association stronger than premenopausal women>; -ER/PR: caffeine sig inverse associated, for ER+/PR+, RR=0.88 (0.79, 0.97), p=0.01; -postmenopausal women: caffeine sig inverse associated, for ER+/PR+, RR=0.81 (0.70-0.95), p=0.006;	1.caffeine-fibrocystic disease-breast cancer <mentioned in introduction>;
Con't				No association <caffeinated coffee> by stratify: -BMI (<25; 25-29.9; ≥30 kg/m^2), <p for interaction=0.72>;	

				-meno-status (pre-meno; post-meno): no significant difference; -BMI/for post-meno: no significant difference; No association <caffeine> by stratify: Latency interval <4-7.9; 8-11.9; 12-15.9; 16-19.9 yrs>	
[10]; Caffeine& BC (also has coffee&BC)	US, Women Health Study; Prospective Cohort(10ys fu); 1188 invasive /38,432 (≥45 ys); <1992-2004>	Caffeine (quintile):≤68, >68-181, >181-352.2, >352.2-486.3, >486.3; Coffee (137mg caffeine per coffee): almost never, <1cup/day, 1cup/day, 2-3cups/day, ≥4 cups/day.	Overall (coffee & caffeine): no association; -coffee RR=1.08 (0.89-1.30), p=0.27, ≥4 cups/day vs. almost never.	Benign B disease (BBD): -coffee & with BBD RR=1.35 (1.01-1.80), p=0.08, ≥4 cups/day vs. almost never; coffee & without BBD RR=0.91 (0.71-1.18), p=0.96;	Caffeine & breast carcinogenesis mechanism: 1. apoptosis; 2. stimulate/suppress mammary tumors (rodents studies); 3. adenosine, ERαpathway. (following)
Con't				No association by stratify: 1.meno-status;2.hormone use;3.BMI;4.tumor lymph node metastasis;5.tumor histologic grading & differential	
[11]; Coffee/	Sweden; Swedish Mammography	Coffee (120 mg caffeine/cup of	Overall coffee: no association,	Subgroup_ ER/PR status: no association with coffee;	1. only three (include this

caffeine & BC.	Cohort study; 2,952/ 61,433 women (40-76 yrs); ER/PR status: (ER+/PR+, 1,286 (62.4%), ER+/PR-, 417 (20.2%), ER-/PR-, 266 (12.9%), ER-/PR+, 93 (4.5%)); Cohort study (mean 17.4 yrs fu); <1987-1990 baseline> 350 items FFQ.	coffee): <1 cup/day, 1 cup/day, 2-3 cups/day, ≥4 cups/day; Caffeine: highest vs. lowest category, but did not report actual number;	RR=1.02 (0.87, 1.20), p=0.74, ≥4 cups/day vs. <1 cup/day.		one) papers investigated on ER/PR status on coffee & BC; 2. This one talked about ER/PR TUMOR! Not cancer subtype. 3. the following showed a short summary for ER/PR.
Con't			Overall caffeine: no association, RR=1.00 (0.89, 1.12), highest vs. lowest category.	Coffee: Association did not differ by <u>menopausal status, postmenopausal hormone use, or BMI</u> (p for interaction ≥0.10 for all); Caffeine: No association with any subtype defined by <u>ER/PR</u> status.	4. They did not report ER+/PR-, since the number is small.
(Nilsson, 2010 #9); Coffee <boiled & filtered>	Sweden, Vasterbotten Intervention project (15 ys fu); 429 cases/64,603 (median=50 yrs), 109	Coffee: <1 cup/day, 1-3 cups/day, ≥4 cups/day;	<u>Boiled</u> coffee: Overall: sig-inverse associated, HR=0.52 (0.3-0.88), p=0.247, ≥4 cups vs. <1	<u>Total and filtered</u> coffee: -<u>menopausal status</u>: -<u>Pre</u>-menopausal: non-sig positive associated, RR $_{total}$=1.69 (0.96, 2.98), p=0.015 & sig positive associated, RR	1. Boiled coffee- high diterpene; 2. Drip-filtered coffee- low

& BC.	pre-meno & 320 post-meno; <1985-2007>; 84-item FFQ (1992-1996);		cup/day; Total and filtered coffee: -Overall women: no association	$_{filtered}$ = 1.76 (1.04-3.00), p=0.045; - Post-menopausal: non-sig inverse associated, RR $_{total}$ =0.6 (0.39-0.93), p=0.0006 & sig inverse associated, RR $_{filtered}$ = 0.52 (0.30-0.88), p=0.045.	diterpene; 3. Diterpenes against tumorigenesis <following>.
[7]; Coffee & BC.	US, African-American women, Black Women's Health Study; 1268/52,062 women (21-69 yrs); Cohort study (12 yrs fu); <1995-2007>; 85-item FFQ, mailed every 2 years; 408 participants using a 3-day dietary record and up to three 24-h recalls by telephone.	Caffeinated coffee (137 mg caffeine/cup of coffee): Never & <1/month, <1/day, 1/day, 2-3/day, ≥4 cups/day; Decaffeinated coffee: Never & <1/month, <1/day, 1/day, ≥2 cups/day; Caffeine: <16, 16-42, 43-92, 93-208, ≥209 mg/day;	Overall caffeinated coffee: no association, IRR=1.03 (0.77, 1.39), ≥4 cups/day vs. none; Overall caffeine: no association, IRR=1.04 (0.87, 1.24), top quintile vs. bottom quintile.	For both coffee and caffeine: No association with BC according to menopausal status or hormone receptor status: -Caffeinated or decaffeinated coffee: Decaffeinated seems to show non-sig, weak inverse association, IRR=0.82 (0.61, 1,11), p=0.33; -Menopausal status: -For caffeinated coffee, Premenopausal: weak non-sig positive, IRR=1.33 (0.83, 2.11), p=0.31; Postmenopausal: weak non-sig inverse, IRR=0.85 (0.55, 1.32), p=0.28; -Joint asso _ menopausal status & ER/PR status: ER+/PR+ & 1) premenopausal: weak non-sig positive, IRR= 1.14 (0.67, 1.94), p=0.83; 2) Postmenopausal: weak non-sig inverse,	1. African-American women (AAW) are more likely to be diagnosed with hormone receptor–negative tumors [90]. Dietary habits differ, with AAW drinking less coffee than white women [91]; 2. Coffee & sex hormone-binding globulin in postmenopausa

				IRR=0.89 (0.55, 1.43), p=0.77.	l women [76, 77], which may be one mechanism for inverse association.
[14]; Coffee & BC.	Netherlands, Dutch, EPIC-NL study <Prospect & MORGEN cohorts>; 681/27,323 <mostly> postmenopausal women (20-70 yrs); Cohort study (average 9.6 yrs fu) <1993-2004/2007>; 77 main items FFQ; Twelve 24-h recalls among 121 men & women.	Coffee: 0, 0.1-1.0, 1.1-2.0, 2.1-3.0, 3.1-5.0, >5 cups/day;	Overall coffee: no association, HR=0.94 (0.72, 1.24), >5 cups/day vs. none.	Stratified by BMI <25 kg/m^2>: No association; -My interpreting: --BMI≤25 kg/m^2: weak positive, non-sig associated, HR=1.2 (0.81, 1.78); --BMI> 25 kg/m^2: weak negative, non sig associated, RR=0.83 (0.59, 1.16); But those association only for 3.1-5.0 cups/day vs. none, not 5 cups/day vs. None.	1. Netherlands is one of the top 10 countries in the world for coffee consumption per capita; 2. Author restricted the analyses to BC cases occurring after 2 yrs of fu; 3. Harmful effect of coffee to BC, see following.
[8]; Coffee/caffeine & BC.	French, E3N cohort study; 2,868/67,703 women (40-65 yrs), 2268	Coffee: (72.8 mg caffeine/125 ml coffee): None, ≤ 1,	Overall coffee & caffeine: no association;	Sub-analyses by - tumor receptor status, -menopausal status, -type of coffee (regular or decaffeinated),	1. since author thinks caffeine-glucose

	(79%) ER/PR status cases; Cohort study (Median 11 yrs fu), <1993-2005>; 208-iyems FFQ.	1.1-3, >3 cups/day; Caffeine: <88, 88-163, 164-262, >262;		-meals at which beverage were drunk did not show difference.	metabolism-<glucose absorption, glucose hepatic output and storage_ so caffeine & BC may differ by the time of day at which the beverage is drunk>.
Con't				ER-/PR+ <to me> showed non-sig inverse association with both coffee & caffeine, RR coffee=0.66 (0.39, 1.12), p=0.1.	
[12]; Coffee & postmenopausal BC.	Sweden; 2,818 cases/ 3,111 controls women (50-74 yrs), 65.4% women have ER/PR status information; controls were , frequency-matched by age; postmenopausal women is 54-55 yrs due to smoking status, 280 cases/ 303	Coffee: ≤1 cup, 2-3 cups, 4-5 cups, >5 cups/day;	Overall cancer & coffee: non-sig negative association, OR=0.84 (0.66, 1.06), p trend=0.127, >5 cups/day vs. ≤1 cup/day;	ER-: a significant inverse association, OR=0.43 (0.25, 0.72), p<0.001; PR-: non-significant inverse association, OR=0.67 (0.44, 1.01), P=0.034; Validation study: Overall cancer & coffee: no association, OR=0.87 (0.71, 1.07), P=0.173; ER-: non-significant inverse association, OR=0.67 (0.43, 1.05), p=0.326; PR-: non-significant inverse association, OR=0.70 (0.49, 1.00), P=0.280.	1. One possible explanation of the weaker association with breast cancer risk in the MA RIE study may thus be due to the primarily use of filtered coffee in

	controls; Large population-based case-control study, <1993>;				Germany, and boiled coffee in Scandinavia [92]. 2. Caffeine may not be a valid substitute for measuring coffee effect, see following.
Con't				-Validation study design: Germany, Mamma Carcinoma Risk factor Investigation study; 3,464 cases/ 6,657 controls postmenopausal women (50-74 yrs), but final study include 2,651 cases/ 5,395 control; Controls were frequency-matched by year of birth and study region, 2 controls per case; 176 food items FFQ.	
[9]; Coffee & BC.	US, NIH-AARP diet and health study cohort; 9,915/ 198,404 women (50-71); 2051 ER+/PR+, 453 ER-/PR-;	Coffee: ≤2 cups/week, 3-6 cups/week, 1 cup/day, 2-3 cups/day, ≥4 cups/day;	Overall breast cancer: no association, RR=0.98 (0.91, 1.07), P=0.38, (≥4 cups vs. Never drank coffee>.	-ER/PR: No association; -Stage <in situ, invasive; grade1, grade2, grade 3+>: No association; -Histology <ductal, lobular, mixed>: No association. -No difference between Caffeinated coffee	1. Latest one 'coffee & BC' paper.

	Cohort study <1995-2006>; 124-items FFQ.			& Decaffeinated coffee regarding to the risks.	
Con't				-BMI and history of benign breast biopsy, HT use, smoking status, alcohol, history of breast biopsy and family history of breast cancer, did not alter the association between coffee intake and BC risk. (p for interaction >0.10); -Sensitivity analysis: restricted to postmenopausal women, no dif.	

Table 35 Caffeine & breast cancer association studies

Reference	Study Population (US, xx Study, Case/Cohort, N)	Cut points	Overall Results	Notes (stratified/interaction); Con't: Other findings	*Related discussion contents
[69]; Coffee/caffeine & BC.	US, Nurses' Health Study; Prospective Cohort (22 ys fu); 6552 cases / 85,987 (30-35 ys; 11 states); <1976-1980-2002>. 1980: 60-item FFQ; 1984, 1986, 1990, 1994, 1998: 130-item FFQ <include decaffeinated coffee>	Caffeine (quintile): with equal number of participants (didn't report actual number in paper).	Overall caffeine: weak inverse association; -Caffeine intake RR=0.93 (0.85-1.01), p=0.06, 4 vs. 1; postmenopausal women: significant inverse association, RR=0.88 (0.79-0.97), p=0.03;	-Menopausal status: <Postmenopausal women> significant inverse association between caffeine and breast cancer (RR=0.88, (0.79-0.97), p=0.03) <association stronger than premenopausal women>; -ER/PR: caffeine sig inverse associated, for ER+/PR+, RR=0.88 (0.79, 0.97), p=0.01; -postmenopausal women: caffeine sig inverse associated, for ER+/PR+, RR=0.81 (0.70-0.95), p=0.006;	
Con't				No association <caffeinated coffee> by stratify: -BMI (<25; 25-29.9; ≥30 kg/m^2), <p for interaction=0.72>; -meno-status (pre-meno; post-meno): no significant difference; -BMI/for post-meno: no significant difference; No association <caffeine> by stratify: Latency interval <4-7.9; 8-11.9; 12-15.9; 16-19.9 yrs>	

[10]; Caffeine&BC (also has coffee&BC)	US, Women Health Study; Prospective Cohort(10ys fu); 1188 invasive /38,432 (≥45 ys); <1992-2004>	Caffeine (quintile):≤68, >68-181, >181-352.2, >352.2-486.3, >486.3;	Overall (coffee & caffeine): no association; -caffeine RR=1.02 (0.84-1.22), p=0.45, 4 vs. 1;	Benign B disease: (p for interaction: marginally sig) -borderline sig positive association for caffeine RR=1.32 (0.99-1.76), p=0.10, 4 vs. 1; ER/PR: caffeine sig positive associated, RR=1.68 (1.01-2.81) for ER-/PR-, p=0.02; Tumors size: caffeine sig positive associated, RR=1.79 (1.18-2.72) for breast tumors >2 cm, p=0.02.	
Con't				No association by stratify: 1.meno-status;2.hormone use;3.BMI;4.tumor lymph node metastasis;5.tumor histologic grading & differential	
[11]; Coffee/ caffeine & BC.	Sweden; Swedish Mammography Cohort study; 2,952/ 61,433 women (40-76 yrs); ER/PR status: (ER+/PR+, 1,286 (62.4%), ER+/PR-, 417 (20.2%), ER-/PR-, 266 (12.9%), ER-/PR+, 93 (4.5%)); Cohort study (mean 17.4 yrs fu); <1987-1990 baseline>	Caffeine: highest vs. lowest category, but did not report actual number;	Overall caffeine: no association, RR=1.00 (0.89, 1.12), highest vs. lowest category.		

	350 items FFQ.				
[7]; Coffee & BC.	US, African-American women, Black Women's Health Study; 1268/52,062 women (21-69 yrs); Cohort study (12 yrs fu); <1995-2007>; 85-item FFQ, mailed every 2 years; 408 participants using a 3-day dietary record and up to three 24-h recalls by telephone.	Caffeine: <16, 16-42, 43-92, 93-208, ≥209 mg/day;	Overall caffeine: no association, IRR=1.04 (0.87, 1.24), top quintile vs. bottom quintile.	For caffeine: No association with BC according to menopausal status or hormone receptor status	
[8]; Coffee/caffeine & BC.	French, E3N cohort study; 2,868/67,703 women (40-65 yrs), 2268 (79%) ER/PR status cases; Cohort study (Median 11 yrs fu), <1993-2005>; 208-iyems FFQ.	Caffeine: <88, 88-163, 164-262, >262;	Overall caffeine: no association;	Sub-analyses by - tumor receptor status, -menopausal status, -type of coffee (regular or decaffeinated), -meals at which beverage were drunk did not show difference.	
Con't				ER-/PR+ <to me> showed non-sig inverse association with caffeine, RR caffeine=0.66 (0.39, 1.61), p=0.15.	
[62]; Caffeine & BC_postmenopausal	Iowa Women's Health Study; 580/34,388 women (55–69 yrs), <1986-1990>;	Caffeine: quintile; Median caffeine intake= 212 mg/day for BC;	Overall: no association for caffeine, coffee, and caffeinated foods.		

Table 36 Acrylamide and breast cancer association studies

Reference	Study Population (US, xx Study, Case/Cohort, N)	Cut points	Overall Results	Notes (stratified/interaction) Con't: Other findings	Related discussion contents
[69, 93] ; Acrylamide & BC.	Dutch, The Netherlands cohorts study; Prospective cohort (11.3 yrs fu); 1,835 cases/ 62,573 (55-69 yrs); <1986-1997>; FFQ;	Acrylamide medians (quintile): 9.5, 14.0, 17.9, 24.3, 36.8 μg/d;	Acrylamide & BC: no association; - Acrylamide intake HR=0.93 (0.73-1.19), p=0.79, lowest (8.9 μg/d) vs. highest quintile (40.2 μg/d);	- For never smokers: HR=1.10 (0.80-1.52), p=0.55;	
[50]; Acrylamide & BC.	Sweden, Swedish Mammography Cohort; Prospective cohort (17.4 yrs fu); 2,952 cases/ 61,433 women; <1987-1990>; 350 items FFQ;	Acrylamide (quartile): <19.9, 19.9-24.2, 24.3-28.8, ≥28.9 μg/d;	Acrylamide & overall BC: no association; -RR=0.91 (0.80-1.02), lowest vs. highest;	Acrylamide & BC by ER/PR: no association; -For ER+PR+: RR=0.89 (0.74-1.08); - For ER+PR-: RR=1.17 (0.84-1.64); - For ER-PR-: RR=0.91 (0.61-1.38); lowest vs. highest quintile; Not differ by smoking status;	

[94]; Acrylamide & BC (Premeno).	US, the Nurses' Health Study II; Prospective cohort; 1,179 premenopausal cases/90,628 premenopausal women; <1991-2005>; 130 items FFQ;	Acrylamide mean (quintile): 10.8, 16.6, 20.2, 24.6, 37.8 μg/d;	Acrylamide & premenopausal BC: no association; - Acrylamide intake HR=0.92 (0.76-1.11), p=0.61, lowest (8.9 μg/d) vs. highest quintile;	No differ by smoking status or estrogen and progesterone receptor status of the tumors;	
[52]; Acrylamide & BC (Postmeno).	Denmark, the Danish diet, cancer and health study; Nested case-control; 374 case-control pairs;	Non-smokers: average daily intake of acrylamide= o.57μg/d;	Acrylamide-hemoglobin levels and BC: no association;		Nested case-control: not include in my study.
[95]; Acrylamide & BC (Postmeno).	Dutch, The Netherlands cohorts study; Prospective cohort (13.3 yrs fu); 1,835 cases/ 62,573 (55-69 yrs); <1986-1999>; FFQ;	Acrylamide medians (quintile): 9.5, 14.0, 17.9, 24.3, 36.8 μg/d;	Acrylamide & overall postmenopausal BC: no association; Acrylamide & ER-, PR-, or ER-PR- postmenopausal BC: no association; Not differ by smoking status;	For non-smokers: -Acrylamide & ER+, PR+, or ER+PR+ postmenopausal BC: non-significant positive association; ER+ HR=1.31 (0.87-1.97), p=0.26; PR+ HR=1.47 (0.86-2.51), p=0.16; ER+PR+ HR=1.43 (0.83-2.46), P=0.16; lowest (9.5 μg/d) vs. highest quintile (36.8	

				μg/d);	
[96]; Acrylamide & BC.	US, the Nurses' Health Study II; Prospective cohort; 6,301 cases/88,672 women; <1980-2006>; FFQ;	Acrylamide mean (quintile): 9, 13, 16, 19, 26 μg/d;	Acrylamide & overall and by ER/PR status BC: no association; Not differ by smoking status;		