DISSERTATION

EXAMINATION OF THE COMPLEX RELATIONSHIPS AMONG DIETARY COMPONENTS, TYPE II DIABETES, WEIGHT CHANGE, AND BREAST CANCER RISK AMONG SINGAPOREAN CHINESE WOMEN

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ABSTRACT

EXAMINATION OF THE COMPLEX RELATIONSHIPS AMONG DIETARY COMPONENTS, TYPE II DIABETES, WEIGHT CHANGE, AND BREAST CANCER RISK AMONG SINGAPOREAN CHINESE WOMEN

Type II diabetes and breast cancer are on the rise in Asian populations that have typically had lower burdens of disease. Intake of dietary components high in nutrients with anti-oxidative and anti-inflammatory properties, such as green tea, soy, fruits and vegetables, may protect against the development of type II diabetes and may improve HbA1c (glycated hemoglobin) levels, a clinically relevant biomarker of diabetes and prediabetes. Furthermore, modifiable lifestyle factors such as diabetes, weight change and diet that influence endogenous hormone levels and the insulin pathway may play a role in the development of breast cancer. This dissertation includes three aims that examined different aspects of the complex relationships between diet, diabetes, weight change, and breast cancer risk in the Singapore Chinese Health Study, a prospective cohort study that enrolled 63,257 Chinese men and women aged 45-74 years between 1993 and 1998. First, we examined the association between intake of green tea, soy, and a vegetable-fruit-soy dietary pattern on HbA1c levels among self-reported, nondiabetic men and women, examined separately (Aim 1). We also evaluated type II diabetes and weight change (separately) in relation to risk of breast cancer, as well as the potential interaction of diet (soy and green tea intake) with the exposures of interest among women only (Aims 2 and 3). Dietary intake was assessed at baseline (1993-1998) by in-person interviews using a validated 165-item food frequency questionnaire. HbA1c levels were measured from blood samples collected in the follow-up period after baseline enrollment (1999-2004), and self-reported diabetes diagnosis was determined at the follow-up interview. Self-reported weights at the

baseline and follow-up interviews were used to determine weight change. Multivariable linear regression (Aim 1) and proportional hazards regression models (Aims 2 and 3) were used to evaluate these associations. In Aim 1, adjusted mean HbA1c levels were inversely related to soy protein intake (p-value = 0.02; p for trend across the four quartiles of soy protein intake = 0.05) among women; the mean HbA1c difference between the highest and lowest quartile of soy protein intake of 0.07%. We also observed higher HbA1c levels for women with higher green tea intake (p for trend of 0.11), which was in the direction opposite to that hypothesized. In Aim 2, we observed a non-statistically significant increase in breast cancer risk among women with type II diabetes (adjusted hazard ratio [HR]=1.24, 95% confidence interval [CI]: 0.82, 1.86). The assessment of the joint effects of diabetes and lower soy isoflavone intake suggested a weak non-significant interaction between these variables on breast cancer risk; the HR for breast cancer was slightly elevated among those with lower soy isoflavone intake, while among those with higher isoflavone intake the HR was consistent with a null association. There was no evidence of interaction when evaluating soy food, soy protein and green tea intake on the diabetes and breast cancer association. In Aim 3, we did not observe evidence of an increase in breast cancer risk among women reporting weight gain between baseline and follow-up interviews; however, we observed an increase in risk among women who lost between 3 and 5 kilograms between baseline and follow-up interviews (HR=1.31, 95% CI: 0.94, 1.83), which was in the direction opposite of what was hypothesized. This result was similar when we removed breast cancer cases diagnosed within the first two years of follow-up. There was no evidence of interaction between weight change and soy and green tea intake. In conclusion, we provide suggestive evidence that soy protein intake is associated with decreased HbA1c levels among self-reported nondiabetic women. Furthermore, our results suggest that soy isoflavone intake may weakly modify the association between type II diabetes and breast cancer risk. Collectively, the results of these three studies indicate that soy intake may be protective for the development and progression of type II diabetes and could also attenuate the adverse impact of

type II diabetes on breast cancer risk. However, given that these results are suggestive for different soy components and the short follow-up time of the prospective evaluation of breast cancer risk, further research is needed to investigate this question. Furthermore, research among populations with varying levels of soy intake is also needed to assess these associations.

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I would like to express my sincerest appreciation to my parents, Leovardo and Irma Canales, for their unwavering love, encouragement, and support; you are the key to my success. I am thankful to all of my family and friends who have been encouraging and caring. I finally did it!

DEDICATION

This dissertation is dedicated to my parents, Leovardo and Irma Canales. Life is not a fairytale; thank you for allowing me to follow my dreams.

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Chapter 1: Introduction

Type II diabetes is a rapidly growing health concern worldwide and has been implicated as a risk factor for breast cancer. A review article among Western populations reported that type II diabetes was associated with a 20% elevated risk of breast cancer among women and a 45% increased risk of breast cancer when the analyses were restricted to studies among Asian populations (Larsson et al. 2007). Although the exact mechanism of the association between type II diabetes and breast cancer risk is largely unknown, it has been postulated that the hyperinsulinemic state, which is a defining characteristic of type II diabetes, may increase breast cancer risk by acting on breast tissue directly or by increasing endogenous hormone concentrations (Kaaks 1996). Type II diabetes and weight gain have been shown to impact the insulin pathway and endogenous hormone levels and were evaluated comprehensively with respect to breast cancer among postmenopausal women to provide insight regarding these complex relationships.

Modifiable risk factors (soy and green tea intake; type II diabetes; weight change) that are associated with alterations in endogenous hormone levels may also influence the risk of breast cancer among women. Increased soy and green tea intake were associated with decreased circulating estrogen levels in Singaporean Chinese women (Wu et al. 2002; Wu et al. 2005). Along with demonstrated associations with endogenous estrogen levels, soy and green tea independently have been found to influence the insulin pathway and subsequently glucose homeostasis (Chacko et al. 2010; Kwon et al. 2010). Because soy and green tea influence both endogenous estrogen levels and the insulin pathway, these dietary factors were evaluated with respect to HbA1c levels in a subset of individuals of the Singapore Chinese Health Study; their potential modifying role on the relationship between type II diabetes and weight gain on the risk of breast cancer was also evaluated among postmenopausal women.

Together, the following research aims allowed for a comprehensive examination of the

complex relationships among dietary factors (that impact the insulin pathway and endogenous estrogen levels), type II diabetes, weight change, and the risk of breast cancers among Singaporean Chinese women. Type II diabetes, weight gain, and green tea and soy intake are all modifiable risk factors; elucidating the independent and potential modifying effects of these risk factors on breast cancers was warranted to provide the greatest public health impact.

Figure 1 illustrates the proposed mechanism, observed associations, and proposed associations among dietary variables, diabetes, weight change, and breast cancer risk. Although the exact mechanism is unknown, the proposed mechanism in the literature by which diet, diabetes, and weight change influence breast cancer risk is through the insulin pathway and endogenous hormone levels (Figure 1; orange arrow).

Established associations among different populations in the literature are joined by blue arrows (Figure 1). Soy and green tea intake, HbA1c levels, and weight change are associated with the insulin pathway (Figure 1; blue arrows). Weight change is also associated with hormone levels and diabetes risk (Figure 1; blue arrows). Furthermore, endogenous hormone level is an established risk factor for the development of breast cancer (Figure 1; blue arrow).

The relationships that were assessed in this dissertation are connected by red arrows. Cross-sectional analyses of the associations between soy and green tea intake and HbA1c levels were evaluated in this dissertation (Figure 1; Aim 1). The associations between type II diabetes and weight change (independently) and risk of breast cancer were evaluated prospectively in the Singapore Chinese Health Study (Figure 1; Aims 2 and 3; red arrows). Associations between soy and green tea intake and endogenous hormone levels and breast cancer risk have previously been reported in the Singapore Chinese Health Study (Figure 1; green arrow); effect modification of dietary variables on the association between type II diabetes and weight change and risk of breast cancer were proposed due to previously established associations in the Singapore Chinese Health Study, as well as the effect modification of these variables in other populations. The literature on the proposed mechanism and observed

associations will be discussed in further detail in Chapters 3 through 6 of this dissertation.

Objective: To examine the interplay of modifiable risk factors such as dietary habits and lifestyle factors on chronic diseases, particularly type II diabetes and breast cancer. The objective was examined through evaluation of the following aims:

Aim 1: Examine the association between soy, green tea, and vegetable-fruit-soy intake and glycated hemoglobin (HbA1c) levels, a diagnostic measure for diabetes and prediabetes, among self-reported nondiabetic women.

Aim 2: Examine the association between self-reported history of type II diabetes and risk of breast cancer among women using existing data from the SCHS.

Aim 2a: Examine potential effect modification of soy and green tea intake on the association of diabetes and breast cancer risk described in Aim 2.

Aim 3: Examine the association between weight gain since baseline enrollment and risk of breast cancer among Singaporean Chinese women.

Aim 3a: Examine potential effect modification of soy and green tea intake on the association of weight gain and breast cancer described in Aim 3.

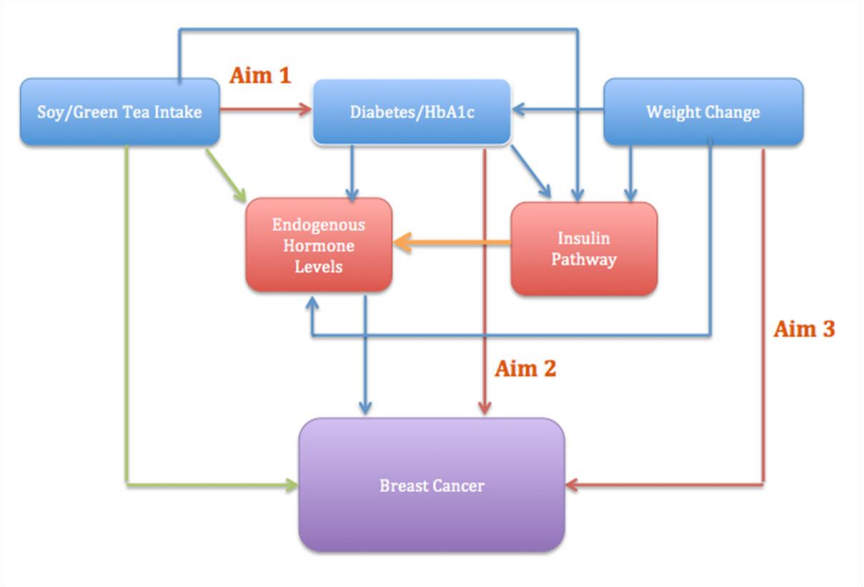

Figure 1: Observed Associations, Proposed Associations, and Proposed Mechanism between Diet, Diabetes, Weight Change, and Breast Cancer

Legend:

- Associations reported in the literature
- Proposed mechanism described in the literature
- Associations previously reported in the SCHS
- Associations evaluated for this dissertation in the SCHS

Chapter 2: The Singapore Chinese Health Study

The design of the Singapore Chinese Health Study has been previously described in detail (Yuan et al. 2003). Approximately three-fourths of the Singaporeans currently residing in the country are of Chinese decent, making Chinese the largest ethnic group in Singapore (Ministry of Health 2013). The Singapore Chinese Health Study was originally developed to evaluate dietary and environmental factors in relation to the etiology of cancer. The development of the SCHS was originally funded through the National Cancer Institute.

Briefly, the cohort consists of 27,959 men and 35,298 women recruited between April 1993 and December 1998, who were permanent residents or citizens of Singapore aged 45–74 years and resided in government-built housing estates (86 % of the Singapore population resided in such facilities) at the time of enrollment. The study was restricted to those individuals belonging to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese, who originated from the contiguous provinces of Fujian and Guangdong in southern China.

The SCHS was developed to study the role of diet and environmental factors on the etiology of cancer. More than 60 peer-reviewed articles have been published utilizing the SCHS, several of which are directly relevant to this proposal. Wu et al. (2008) observed inverse associations of soy intake and breast cancer risk. Furthermore, previous SCHS publications have reported associations between soy intake and markers for breast cancer that include mammographic density and serum estrogen levels (Jakes et al. 2002; Wu et al. 2008). The green tea intake-breast cancer/mammographic density relationships have also been elucidated in the SCHS (Yuan et al. 2005; Wu et al. 2008). Additionally, self-reported diabetes risk was associated with an elevated risk of colorectal cancer among study participants (Seow et al. 2006). Extensive research on diet and environmental factors and cancer outcomes continues within the SCHS. More recently investigators have begun to elucidate the relationships between

environmental factors and respiratory diseases among this population (David et al. 2005; Butler et al. 2006).

Baseline Questionnaire: Enrollment in the cohort entailed completing a baseline, in-person interview in the participant's home. The questionnaire elicited information on smoking, diet, demographics, current physical activity, occupational exposure, medical history, reproductive history, and history of hormone use. A 165-item quantitative food frequency questionnaire (FFQ) that was developed for and validated in this population was used to assess usual diet over the past year (Hankin et al. 2001). Comparison means between the FFQ and 24-h recall responses for the major macro- and micronutrients were within 10% deviation of each other and thus deemed comparable (Hankin et al. 2001). Validation of other dietary components, such as isoflavones, was evaluated independently and will be explained in greater detail below.

Follow-up of Cohort: The first follow-up period of the cohort members began in 1999. By April 2005, all surviving cohort participants had been re-contacted for biospecimen donation. Samples were obtained from 32,543 subjects (28,330 bloods, 4,400 buccal cells, 31,895 urines), representing a consent rate of approximately 60 percent. Along with the biospecimen collection, the cohort has been followed for death, cancer occurrence, and other major health outcome occurrences through regular record linkage with the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths, and through telephone follow-up interviews. The observed numbers of incident cancers and deaths within the cohort are comparable to corresponding expected numbers based on age- and sex-specific incidence rates for all Chinese in Singapore (Seow et al. 2006). For the publication of the manuscripts, we will have updated breast cancer cases through December 31, 2013.

Chapter 3: Background and Literature Review

Breast Cancer

Breast cancer incidence is estimated to occur in 12% of women and has historically been highest in developed countries (Howlader et al. 2011). Breast cancer is the most commonly diagnosed cancer and remains the leading cause of cancer mortality among women worldwide and in Singapore (Parkin et al. 2005; SCR 2012). However, in places like Singapore that have traditionally had lower rates, incidence of breast cancer has increased rapidly in recent decades (Seow et al. 2004 and Singapore Cancer Registry 2012). Of all Singaporean women, those of Chinese decent have the highest age-standardized rates of breast cancer; at 60.8 per 100,000 in 2010, the age-standardized rates of breast cancer have tripled since 1970 (Teo and Soo 2013). It has been hypothesized that increases in breast cancer risk in populations with traditionally lower incidence rates are rapidly rising due to modernization and uptake of Western lifestyles that include modifiable lifestyle factors such as diet, type II diabetes, and weight change, all of which may influence endogenous hormone levels (Lee and Gourley 1986).

Increased age and change in menopausal status are well-established risk factors for breast cancer risk (Howlader et al. 2011; Beral et al. 2011). Factors contributing to endogenous hormone levels are associated with increased breast cancer risk, particularly among postmenopausal women (Missmer et al. 2004). Increased mammographic density and increased abdominal body fat are also associated with increased breast cancer risk. Women having an oophorectomy have a decreased risk of breast cancer development when compared to natural menopause later in life, also indicating a change endogenous hormone levels as a risk factor for breast cancer (Titus-Ernstoff et al. 1998; Domcheck et al, 2010). Hormone replacement therapy has been associated with increased mammographic density, as well as increased breast cancer risk among postmenopausal women (Chlebowski et al. 2010; Stomper

et al. 1990). Decreased age at menarche, later age at first birth, and being nulliparous are also established risk factors for breast cancer (Brinton et al. 1988; Ewertz et al. 1990; MacMahon et al. 1970).

Other modifiable risk factors that contribute to breast cancer risk are dietary factors, vitamin use, physical activity, and smoking. Vegetable consumption and vitamin C intake have been associated with decreased breast cancer risk (Gandini et al. 2000; Freudenheim et al. 1996), while saturated fat consumption has been associated with an increased risk of breast cancer (Smith-Warner et al., 2001 and Cho et al., 2003). Soy and green tea intake are staples of Asian diets that have also been implicated as risk factors for breast cancer (Wu et al. 2008; Zhang et al. 2007). Furthermore, lifestyle factors such as alcohol consumption, smoking, and lack of physical activity are also associated with increased breast cancer risk (Xue, et al. 2011; Longecker 1994; Friedenreich and Cust, 2008).

Additionally, family history of breast cancer, breast cancer 1-early onset (BRCA1), and breast cancer 2-early onset (BRCA2) genes are risk factors for breast cancer (Antoniou et al. 2003; Colditz et al. 2011). More recently, type II diabetes has been implicated as a risk factor for breast cancer (Jee et al. 2005; Larsson et al. 2007; Vona-Davis et al. 2007).

Although most epidemiological studies evaluating risk factors for breast cancer have focused on Western populations that have traditionally had higher breast cancer rates (Larsson et al. 2007), the same risk factors have been found to be associated with breast cancer risk among Chinese women (Tao et al. 1988; Yuan et al. 1988). Additionally, Singaporean Chinese populations follow similar trends as Western populations with respect to reproductive and lifestyle risk factors for breast cancer (i.e. parity, later age at first birth, education, and dietary factors) (Ministry of Health 2013; Singapore Cancer Registry 2012).

Type II Diabetes

Type II diabetes is a growing health concern worldwide (Centers for Disease Control and Prevention 2011); prevalence of type II diabetes in Asian populations has increased abruptly in

the last few decades. Type II diabetes is on the rise among the Singaporean population; between 1975-2000, there was more than a four-fold increase in diabetes among residents of Singapore. The overall diabetes prevalence in Singapore has risen from approximately 2% in 1975 to 9% in 1998 (Lee 2000). Through 2010, the prevalence of diabetes among Singaporeans rose even more, to approximately 11.3%, as determined by a two-hour oral glucose tolerance test (Institute for Health Metrics and Evaluation 2013). Although the Singaporean Chinese population accounts for more than 70% of the entire population of Singapore (Cheah et al. 1985), the Chinese population has the lowest prevalence of diabetes in Singapore when compared to Malays and Indians (Lee 2000). Of the Chinese population in Singapore, the diabetes prevalence was approximately 8.4% in 1998 (Lee 2000). These results are consistent with the proportion of individuals in the SCHS that self-reported having physician diagnosed diabetes at baseline (8.9%; Seow et al. 2006).

The prevalence of type II diabetes is often underestimated in populations due to the asymptomatic nature of the disease. Two features of type II diabetes are glucose intolerance and reduced insulin sensitivity (Alberti and Simmet 1998); these indicators are asymptomatic and may go undiagnosed for an extended period of time. Because the prevalence of diabetes may be different with respect to aspects of clinical diagnosis, examination of a clinically relevant biomarker of diabetes is essential. The prevalence of type II diabetes is often underestimated in populations due to the asymptomatic nature of the disease. Two main features of type II diabetes are glucose intolerance and reduced insulin sensitivity (Alberti and Simmet 1998). Although these indicators may be indicative of diabetes, they are asymptomatic and may go undiagnosed for an extended period of time. Individuals may be unaware of their clinical diabetes status, which may result in the underreporting of diabetes.

Further complicating the diagnosis of diabetes is that diagnostic criteria may vary depending on the test implemented to determine diabetes status. Recently, there has been a shift towards the use of glycated hemoglobin (HbA1c) levels to clinically diagnose type II

diabetes. HbA1c level is an indicator of glycated hemoglobin in blood over a two to three month period (American Heart Association 2012). Diabetic and pre-diabetic ranges have been determined for HbA1c levels; among the determined ranges, 5.7-6.4% HbA1c is the pre-diabetic range and HbA1c levels of greater than 6.5% are considered to be in the diabetic range (American Heart Association 2012).

Diet and Type II Diabetes

The relationship between diabetes and breast cancer risk has not been studied extensively among Asian populations that differ from Western populations with regard to lifestyle factors, dietary factors, and body composition. There is limited information regarding the association between dietary variables and HbA1c levels. However, there are epidemiological studies indicating that dietary factors such as the vegetable-fruit-soy dietary pattern, soy, and green tea may be protective against the development of type II diabetes in the Singapore Chinese Health Study (Odegaard et al. 2008; Odegaard et al. 2011; Iso et al. 2006). Furthermore, randomized control trials have indicated that soy intake may slightly improve the HbA1c profile of individuals (Jayagopal 2002).

Tea: Studies examining the relationship between tea consumption and risk of type II diabetes are inconsistent. In the SCHS, researchers found a suggestive protective effect between black tea intake and type II diabetes risk (RR: 0.86, 95% CI: 0.74, 1.00) and a trend towards a positive association between green tea on diabetes risk (Odegaard et al. 2008). A study among a Japanese population reported an inverse association between green tea consumption and diabetes risk; the same study did not find an association between black or oolong tea intake on risk of type II diabetes (Iso et al. 2006). A randomized control trial reported that supplementation with green and black tea extracts resulted in an improvement of glucose control, determined by improvement of HbA1c profiles, among diabetic patients after intake for a three-month period (MacKenzie et al. 2007).

Toxicological studies have also shown a positive impact of green tea on indicators of diabetes. Green tea polyphenols were associated with improvements in glucose metabolism in rats (Sabu and Kuttan 2002). Green tea contains flavonoids that have been shown to be protective against the development and progression of diabetes. The primary green tea catechin epigallocatechin gallate (EGCG) has been shown to influence glucose metabolism and have glucose-lowering effects (Sabu and Kuttan 2002). A study by Waltner-Law et al. indicated that the mechanism in which EGCG works is through the regulation of genes that encode glucose production and regulate gluconeogenesis (2002).

Soy: A prospective study evaluating the effects of soy isoflavones and type II diabetes risk in the SCHS indicated that soy was protective against type II diabetes risk when comparing consumption of unsweetened soy intake greater than or equal to 5 times per week to no soy intake (HR: 0.72, 95% CI: 0.59, 0.89; Mueller et al. 2012). Other epidemiological studies assessing the relationship between soy food and/or soy variables and diabetes risk are not consistent. A prospective study examining the relationship between soy protein intake and self-reported diabetes among an Asian population found no association, while the same study found soybean food intake was associated with a reduced risk for type II diabetes (Villegas et al. 2008). Furthermore, randomized trials have reported that soy improves biomarkers of diabetes among women; among these was an intervention study that found that supplementation with soy foods improves blood triglycerides and total serum cholesterol among diabetic patients (Shabazian et al. 2006).

The effects of soy foods and isoflavones on glucose homeostasis have been studied to a lesser extent. Randomized control trials evaluating soy foods as a method to improve the diabetic state in comparison to the American Diabetes Association (ADA) recommended diet have reported that diets containing soy food may be more beneficial than the ADA recommended diets. Soy food replacement was effective in improving fasting plasma glucose levels; soy food replacement also resulted in decreased levels of HbA1c levels when compared

to the ADA recommended diet; the control diet included consumption of less than 30% calories from fat, approximately 10-20% dietary intake of protein, and approximately 55-65% dietary intake of carbohydrates (Li et al. 2005).

Along with observational and randomized control trials, experimental animal studies suggest that soy intake was beneficial in the improvement of blood lipid profiles; however, study results vary and have been inconsistent. There are experimental studies, however, indicating that HbA1c levels were significantly reduced when rats were supplemented with isoflavones at a dose that was approximately 8 times higher than that of normal human consumption (Hsu et al. 2003).

There are several mechanisms in which soy is thought to influence chronic disease. Isoflavones are biologically active compounds that are derived primarily through soybeans; they are known for their antioxidant capabilities and have recently been implicated for their roles as phytoestrogens, their biological activity, and their anti-diabetic effects (Nielson and Williamson 2007). Soy isoflavones have been shown to improve insulin levels and lower blood glucose levels, indicating better glycemic control after supplementation with soy foods (Lui et al. 2011). Genistein is a soy isoflavonoid that has been shown to improve blood glucose levels and insulin levels; more specifically, Fu et al. (2010) showed that genistein acted as a cell cycle regulator of beta cells in diabetic mice. Genistein supplementation was effective in beta cell proliferation and survival, indicating its role in the improvement of insulin sensitivity and glucose homeostasis (Fu et al. 2010).

Vegetable-Fruit-Soy Dietary Pattern: In the Singapore Chinese Health Study, the vegetable-fruit-soy dietary pattern was associated with decreased breast cancer risk among postmenopausal women (Butler et al. 2010) and decreased type II diabetes risk among men and women (Odegaard et al. 2011). Other epidemiological studies examining the relationship between diets and risk of type II diabetes suggest that diets high in fruits, vegetables, whole grains, low-fat dairy, and fish were protective for type II diabetes risk (Fung et al. 2004; van Dam

et al. 2002; Villegas et al. 2010, Lui et al. 2004).

In the European Prospective Investigation into Cancer (EPIC), high fruit and vegetable intake was associated with decreased HbA1c levels, indicating that consumption of fruits and vegetables may beneficially influence glucose homeostasis (Sargeant et al. 2001). In a Chinese population, researchers found that vegetable intake was associated with lower risk of type II diabetes. When comparing highest quintile of intake to the lowest quintile of intake, the relative risk for type II diabetes was 0.72 (95% CI: 0.61, 0.85); the same study did not find a similar relationship with fruit consumption (Villegas et al. 2008). In the SCHS, researchers found that the vegetable-fruit-soy dietary pattern was inversely associated with type II diabetes risk among nonsmokers (RR: 0.75, 95% CI: 0.64, 0.90 when comparing 5^{th} quintile to 1^{st} quintile; Odegaard et al. 2011). Green leafy vegetables have consistently been associated with decreased risk of diabetes. Intake was associated with a 14% reduction in diabetes risk in a meta-analysis that evaluated the associations between fruit and vegetable intake and risk for diabetes (CI: 0.77, 0.97; Carter et al. 2010). Green leafy vegetables have also been associated with improvement of diabetes risk among obese women in the Women's Health Study (WHS; Liu et al. 2004); the same study, however, did not report an association of other fruits and vegetables with reduced diabetes risk.

Fruits and vegetables are major sources of polyphenolic compounds; flavonoids and phenolic acids are the primary types of these compounds. These polyphenolic compounds have antioxidant and anti-inflammatory properties. Furthermore, these compounds have been shown to reduce oxidative stress and improve glycemic control (Schroder 2007; Carter et al. 2010).

Because of the previously mentioned difficulties with self-reported physician-diagnosed diabetes and the asymptomatic nature of type II diabetes, the associations between dietary variables and HbA1c levels were investigated in the Singapore Chinese Health Study.

Type II Diabetes and Breast Cancer Risk

Diabetes is associated with increasing circulating estrogen and testosterones levels, altering endogenous hormone levels (Kaaks 1996), as well as increasing breast cancer risk among Western populations (Wolf et al. 2005). Epidemiological studies evaluating the relationship between diabetes and breast cancer risk have shown that diabetes is associated with an elevated risk of breast cancer, particularly in Western populations (Larsson et al. 2007 and Vona-Davis et al. 2007). A meta-analysis evaluating the relationship between diabetes and breast cancer among published studies found that women with diabetes had a 20% increased risk of breast cancer when compared to those without diabetes (95% CI: 1.12, 1.28, Larsson et al. 2007).

The relationship between diabetes and breast cancer has been evaluated to a lesser extent in Asian populations. In the meta-analysis by Larsson et al. (2007), the summary RR for the 4 Asian studies was 1.45 (95% CI: 1.07, 1.97). When diabetes (assessed by blood glucose levels and diabetes medication use) was evaluated with respect to breast cancer risk in a prospective study of Korean subjects, a RR of 2.23 (95% CI: 1.49, 3.33) was reported (Jee et al. 2005). A population based case-control study evaluating diabetes and risk of breast cancer in an Asian-American population found an increased risk of breast cancer among women with diabetes (OR 1.68, 95% CI: 1.15, 2.47). These associations were more profound after stratification by BMI and soy intake, with elevated risk observed among women with lower BMI and among women with low or intermediate soy intake (Wu et al. 2007).

There are several hypothesized mechanisms by which diabetes impacts breast cancer risk. Type II diabetes has been associated with increasing circulating estrogen and testosterones levels, altering endogenous hormone levels (Kaaks 1996). The hyperinsulinemic state results in the stimulation of aromatase activity, which results in an increase of estrogens (Randolph 1987). Insulin is also a regulator of sex hormone-binding globulin (SHBG); in the hyperinsulinemic state, SHBG is suppressed, which may result in an increase in estrogens (Xue

and Michels 2007). Elevated circulating estrogens have also been associated with increased risk for breast cancer (Missmer et al. 2004).

Because of the unique body composition of Asians and increase in diabetes development and the increasing prevalence of diabetes and incidence of breast cancer, this association was investigated among the women in the Singapore Chinese Health Study. This was of particular interest since recently Asians have become more prone to the development of diabetes, even at much lower body mass index than that observed among Western populations (World Health Organization 2004). Although some epidemiological studies do not differentiate between juvenile diabetes and type II diabetes, there is limited research on the associations of juvenile diabetes on breast cancer risk. Therefore, we investigated the association between a type II diabetes diagnosis and breast cancer risk among this population.

Weight Change and Breast Cancer Risk

Increasing weight has become a major health concern among all women worldwide (James et al. 2001). Weight gain has been associated with elevated endogenous hormone levels (Missmer et al. 2006), and therefore, may result in an increased risk of breast cancer, particularly among postmenopausal women (Eliassen et al. 2006; deWaard et al. 1982); additionally, weight loss has been associated with a decrease in circulating estrogen levels (deWaard et al. 1982).

Obesity as determined by BMI, is a well-established risk factor for breast cancer (Cleary and Maihle 1997; Stephenson and Rose 2003; Harvie et al. 2003). The associations of BMI with respect to breast cancer differ after stratification by menopausal status. Higher BMI has been shown to be inversely related to breast cancer risk among premenopausal women; it is hypothesized that higher BMI among premenopausal women may result in more frequent ovulation and alterations in endogenous hormone levels (van den Brandt et al. 2000). Higher BMI was positively associated with breast cancer risk among postmenopausal women in a pooled analysis of seven prospective studies (van den Brandt et al. 2000). Along with obesity,

patterns in adiposity influence breast cancer risk. When examining the relationship prospectively, waist to hip ratio and waist circumference were associated with increased breast cancer risk in women in the NHS (Huang et al. 1999).

Breast cancer risk in relation to weight change has not been studied extensively. Few studies have shown that weight change can influence breast cancer risk among women, particularly among primarily white populations and among postmenopausal women. In the Nurses' Health Study, weight gain was associated with an increase in breast cancer risk. Postmenopausal women who gained more than or equal to 10 kg since menopause had an increased risk of breast cancer when compared to women who had a stable weight (RR: 1.18, 95% CI 1.03-1.35); weight reduction since menopause was inversely associated with breast cancer risk when comparing women who lost more than 10 kg since menopause and had never been on hormone replacement therapy to women whose weight remained stable (RR: 0.43, 95% CI: 0.21, 0.86). The findings of this study were in the same direction but more robust when evaluating the associations of weight gain since age of 18 and breast cancer risk (Eliassen et al. 2006). Another study evaluating weight change prospectively among women in 6 European countries found that risk of breast cancer was increased among previous hormone replacement therapy users that had gained more than 20 kg when compared to women who had a stable weight after 5.8 years of follow up time (HR: 1.52, 95% CI: 1.08, 2.13); adjustments were made for age at recruitment, weight at age 20, age at menarche, age at first birth/parity, education, height, alcohol intake, smoking status, and leisure physical activity (Lahmann et al. 2005).

Furthermore, the weight change and breast cancer association has been studied to a lesser extent in primarily Asian populations, where the body composition is different from that of women in Western populations (Odegaard et al. 2010). A population based case-control study evaluating breast cancer risk among Asian-American women showed that women that were in their 50s that gained more than or equal to 11 pounds in the previous decade had a greater than 2-fold increase in breast cancer risk when compared to women who had no weight change

(RR: 2.26, 95% CI 1.21, 4.21). After stratification by BMI, women in their 50s that had a BMI greater than 27.3 kg/m^2 and had recently gained more than 10 pounds had a RR of 3.01 for breast cancer when compared to those women who did not recently gain weight (95% CI: 1.45, 6.25; Ziegler et al. 1996).

As a potential modifier of endogenous levels resulting from higher adiposity, it is plausible that excess weight gain may increase risk of breast cancer development. Adiponectin is a proposed mechanism through which increased weight (and BMI in general) may influence the risk for breast cancer. Low plasma or adiponectin levels have been associated with an increased risk for breast cancer. Along with the biological mechanisms, increased adiposity results in a hyperinsulinemic state, which may also influence the development of breast cancer (Vona-Davis et al. 2007). The weight change and breast cancer association was evaluated in the Singapore Chinese Health Study.

Potential for Effect Modification by Soy and Green Tea Intake

Hormone-modifying diets high in soy and green tea are inversely associated with the development of breast cancer among women in the Singapore Chinese Health Study (Wu et al. 2008; Yuan et al. 2005). Soy and green tea contain compounds that have high antioxidant and/or anti-inflammatory properties (Hirose et al. 1994; Messina et al. 1994). Furthermore, increased soy (highest quartile of soy protein vs. lower three quartiles of soy protein) and green tea (drinker vs. non/irregular drinkers) intake were also associated with decreased circulating estrogen levels in a cross-sectional study among postmenopausal Singaporean Chinese women (Wu et al. 2002; Wu et al. 2005).

Tea: Results from epidemiological studies evaluating tea consumption and breast cancer risk are equivocal depending on the population of interest and the type of tea being evaluated. Western populations may differ significantly from other populations, particularly because of the type of tea consumption; black tea is most commonly consumed among Western populations, and green tea is not as commonly consumed among these populations (Sun et al. 2006). Asian

diets consist of more green tea consumption when compared to Western populations and can be useful in providing more insight into the protective effects of green tea (Trock et al. 2006). A population-based case-control study among Asian-American women by Wu et al. (2003) reported an inverse association between green tea intake and breast cancer risk when comparing women who drank more than 85.7 mL of green tea per day to those that were non-green tea drinkers (OR: 0.53, 95% CI: 0.35, 0.78).

A case-control study among Chinese women showed that green tea consumption duration was associated with decreased risk of breast cancer (Zhang et al. 2007). Women drinking tea for greater than or equal to 20 years had a 42% reduced risk of breast cancer when compared to the referent group (0 years of green tea consumption); women drinking green tea at least twice a day had a 52% decreased risk of breast cancer diagnosis when compared to the referent group (never or seldom drinks green tea). Furthermore, women consuming greater than or equal to 750 grams of green tea per year had a 49% decreased risk of breast cancer diagnosis when compared to the referent group (0 grams of green tea per year). When determining the dose-response relationship between green tea intake and breast cancer risk, the p for trend for the duration of green tea consumption, number of cups of green tea, and grams of dried tealeaves were all statistically significant after adjustment for traditional risk factors ($p<0.001$, Zhang et al. 2007).

The protective effects of green tea consumption also vary depending on individual characteristics such as genetic composition. In the Singapore Chinese Health Study, researchers used a nested case-control study to determine the effects of green tea consumption among women with different genotypes. The low activity ACE genotype was associated with reduced breast cancer risk among women, and the high activity ACE genotype was associated with increased breast cancer risk (Koh et al. 2003). Researchers showed that green tea intake resulted in decreased breast cancer risk among women with high activity ACE genotype (Yuan et al. 2005).

Many mechanisms of green tea's anti-carcinogenic effects have been suggested; one mechanism is the antioxidant properties of green tea. Green tea polyphenols, specifically the catechins, contribute to the anti-carcinogenic effects of green tea consumption (Sun et al. 2006). In vitro studies have shown that epigallocatechin gallate (EGCG), which is the most abundant catechin, was effective in the suppression of MCF-7 breast cancer cell proliferation (Komori et al. 1993). Additionally, Hirose et al. (1994) found that green tea extract exposure increased survival in adult female Sprague-Dawley rats with chemically induced mammary cancer.

Green tea intake has been shown to be associated with both breast cancer risk and diabetes risk in the Singapore Chinese Health Study. The effect modification of the green tea on the diabetes and breast cancer association was evaluated among women in the Singapore Chinese Health Study.

Soy: Epidemiological studies examining the association between soy intake and breast cancer risk vary depending on the populations of interest. Breast cancer rates among Asian-born women are substantially lower than rates among American women (Parkin et al. 1992). However, migration of Asian women to the United States has been shown to result in increased risk of breast cancer among Asian immigrants (Ziegler et al. 1993). The migration of Asian women to the United States resulted in lifestyle changes, particularly changes in diets that are often associated with an increased risk of breast cancer development (Wu et al. 1998). Therefore, Asian diets are the focus of preventative and protective factors of breast cancer (Trock et al. 2006).

Wu et al. (2008) reported that soy isoflavone intake was inversely related to breast cancer risk in postmenopausal women in the Singapore Chinese Health Study (Wu et al. 2008). Postmenopausal women consuming greater than or equal to 10.6 mg of soy isoflavones were at a decreased risk of developing breast cancer when compared to postmenopausal women consuming less that 10.6 mg of soy isoflavones (RR: 0.74, 95% CI: 0.61, 0.90 after adjustment for traditional risk factors). The protective effect of soy isoflavones was more pronounced

among women above the median BMI of all women (RR: 0.67, 95% CI: 0.51, 0.88; Wu et al. 2008).

The timing of soy intake is also of particular importance in the development of breast cancer. A study by Wu et al. 2002 demonstrated that increased tofu intake during adolescence resulted in decreased risk of breast cancer during adulthood in Asian-American women (Chinese, Japanese, and Filipino subgroups) with an OR of 0.51 (95% CI: 0.31, 0.84, highest quartile vs. reference, P trend=0.002, after adjustment for traditional risk factors). However, statistical significance varied by subgroups of Asian-American women. Similar results were seen in the association of adult soy consumption and breast cancer risk among this population (P for trend = 0.003; Wu et al. 2002).

There are several proposed mechanisms by which soy components, such as isoflavones, protect against the development of breast cancer. Isoflavones, particularly genistein, have been shown to act as an estrogenic agonist, resulting in the down-regulation of estrogen receptors (Sathyamoorthy and Wang 1997). Furthermore, in vitro studies of genistein on breast cancer cell lines have shown that genistein inhibited the growth of cancer cells (Messina et al. 1994).

The effect modification of soy on the diabetes and breast cancer association has only been evaluated in a case-control study among Asian Americans. The study reported that among women with low/moderate soy intake, those with diabetes had an increased risk of breast cancer when compared to women without diabetes; furthermore, there was not an observed association between diabetes and breast cancer among women who were high soy consumers (Wu et al. 2007). There is evidence that soy isoflavones may beneficially influence blood glucose, insulin levels, and development of type II diabetes via the insulin pathway. The effect modification of soy intake on the diabetes and breast cancer association has not been evaluated using a prospective study design; the effect modification of diet (soy and green tea) on the diabetes and breast cancer association was evaluated among women in the Singapore

Chinese Health Study.

The effects of soy and green tea intake on weight change have not been evaluated prospectively; however, randomized control trials indicate green tea extract and soy replacements may be effective in weight loss and a potential for the protective effect of soy and green tea with respect to obesity (Bhathena and Velasquez 2002; Thielecke and Boschmann 2009). The effect modification of diet (soy and green tea) on the weight change and breast cancer association was evaluated among women in the Singapore Chinese Health Study.

Chapter 4: Manuscript 1: Selected Dietary Variables and HbA1C Levels among Self-Reported Nondiabetics in the Singapore Chinese Health Study (Aim 1)

Synopsis

Diabetes is one of the most common non-communicable diseases in the world. It is on the rise even in Asian populations that have typically had lower incidence than Western populations; there was more than a four-fold increase in diabetes among residents of Singapore between 1975 and 2000. Intake of dietary factors high in nutrients with antioxidative and anti-inflammatory properties, such as green tea, soy, fruits and vegetables, may protect against the development of diabetes and may improve HbA1c (glycated hemoglobin) levels, a clinically relevant biomarker of diabetes. The use of HbA1c offers further public health relevance in that it is recognized to have important implications for concentrations below those in the diabetic range. We examined the association between intake of green tea, soy, and a vegetable-fruit-soy dietary pattern on HbA1c levels among self-reported, nondiabetic subjects in the Singapore Chinese Health Study. Dietary intake was assessed by in-person interviews using a validated 165-item food frequency questionnaire. Linear regression was used to assess the relationships between dietary intake and HbA1c levels. Least square mean HbA1c levels for quartiles of dietary variables and 95% confidence intervals (CI) surrounding the means were determined. Mean HbA1c levels were 5.81% (95% CI: 5.74, 5.88) for quartile one (lowest intake) of soy protein and 5.74% (95% CI: 5.68, 5.81) for quartile four (highest intake) of soy protein (p-value = 0.02; p for trend across the four quartiles = 0.05); there were no significant differences in HbA1c means when evaluating quartiles of soy food or soy isoflavones. Similar results were not observed among men. There was a borderline significant p for trend with increasing intake of green tea (p for trend of 0.11) in the direction opposite to that hypothesized; however, the small number of daily green tea drinkers in this subsample may have influenced these results. There were no differences in HbA1c means between quartiles of the vegetable-fruit-soy dietary

pattern. In conclusion, we provide suggestive evidence that soy protein intake is associated with decreased HbA1c levels among self-reported nondiabetic women.

Introduction

Diabetes affects 285 million people worldwide (Hu 2011), with type II diabetes accounting for 90% of the disease burden (Chen et al. 2012). Although Asian populations have typically had lower incidence levels of type II diabetes than Western populations, Asia now accounts for approximately 60% of those affected by diabetes in the world (Chen et al. 2012). Furthermore, there was more than a four-fold increase in diabetes among residents of Singapore between 1975 and 2000 (Lee 2000). Because of the typically asymptomatic nature of the disease, the prevalence of type II diabetes is often underestimated (Odegaard et al. 2010). Therefore, there has been a shift towards the use of HbA1c (glycated hemoglobin), a clinically relevant biomarker of diabetes, to determine diabetic status, rather than self-reported diabetes status (American Heart Association 2012) or blood glucose levels, which are often limited by an individual's fasting status (Sacks 2011).

Evaluating factors in relation to HbA1c may provide valuable insight into the growing public health problem surrounding type II diabetes. Lifestyle factors that affect body weight and body fat distribution such as physical activity and diet are known to influence the prevalence of diabetes (American Diabetes Association 2012). For example, increased consumption of certain dietary components (e.g., vegetables and fruits) have traditionally been linked to lower incidence of type II diabetes and improvement of diabetes risk profiles (e.g. blood glucose concentrations) among Western populations; however, there is a lack of research evaluating lifestyle factors and HbA1c levels. Additionally, these relationships have been studied to an even lesser extent among Asian populations (Iso et al. 2006; Odegaard et al. 2008; Odegaard et al. 2011).

Interest surrounding the potential protective effects of fruits, vegetables, green tea, and soy are driven by the antioxidant and anti-inflammatory properties of these dietary components.

Isoflavones are antioxidant compounds that are derived primarily through soybeans; these compounds have recently been implicated for their anti-diabetic effects (Nielson and Williamson 2007). Similarly, green tea contains flavonoids that may be protective against the development and progression of diabetes; experimental evidence suggests that epigallocatechin gallate (EGCG), a green tea catechin, may have glucose-lowering effects (Sabu and Kuttan 2002). Furthermore, fruits and vegetables are major sources of flavonoids and polyphenolic compounds that have been shown to improve glycemic control (Carter et al. 2010; Schroder 2007).

Identifying modifiable factors, such as diet, that are associated with HbA1c levels may inform actionable public health strategies. Because of the limitations associated with the accuracy of self-reported physician-diagnosed diabetes and the asymptomatic nature of type II diabetes, it is useful to examine the relationships between dietary variables and an objective, clinically relevant biomarker of diabetes, such as HbA1c. Additionally, the use of HbA1c offers further public health relevance in that it is recognized to have important implications for concentrations below those in the diabetic range (American Heart Association 2012). Here we present the first evaluation of the associations between selected dietary variables (soy, green tea, and a vegetable-fruit-soy dietary pattern) and HbA1c levels among self-reported nondiabetic men and women in the Singapore Chinese Health Study (SCHS). Previous research suggests that HbA1c is more strongly related to risk of chronic disease among women than among men (Pradhan et al. 2007; Singer et al. 1992); therefore, we evaluated the associations between selected dietary variables and HbA1c levels among men and women separately.

Methods

Study Population: The design of the Singapore Chinese Health Study has been previously described in detail (Yuan et al. 2003). Briefly, the cohort consists of 27,959 men and 35,298 women recruited between April 1993 and December 1998 who were permanent

residents or citizens of Singapore, aged 45–74 years, and resided in government-built housing estates (86% of the Singapore population resided in such facilities) at the time of enrollment. We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese.

After the follow-up interview, approximately 65% of the population consented to provide blood samples. The participants for the current study were a random selection of individuals from the full study population who consented to provide blood, who did not report a history of diabetes or CVD at the baseline or follow-up interview and who reported no history of cancer at baseline. This nondiabetic group was established to serve in future SCHS analyses as a comparison group to incident cases of type II diabetes from the full SCHS population (Bancks et al. 2014). To confirm the self-reported diabetic status of these participants, HbA1c levels were measured in blood; HbA1c levels were not determined for the type II diabetic incident cases. For the current study, we utilized this sample of self-reported nondiabetic men and women with HbA1c measures, regardless of HbA1c status for a total of N=6,586 participants. Men and women were evaluated separately (n= 3,028 for men and n=3,558 for women).

Diet: Enrollment in the cohort entailed completing a baseline, in-person interview and a food frequency questionnaire (FFQ) in the participant's home. We used the 165-item quantitative FFQ, developed for and validated in this population, to assess usual diet over the past year (Hankin et al. 2001). Correlation coefficients from the FFQ and 24-hour recall responses for the energy and nutrient variables were between 0.24 and 0.79, which is comparable to dietary calibration studies among other populations evaluating dietary intake using a FFQ (Hankin et al. 2001).

Tea: Subjects were asked in the FFQ to identify their intake frequency, in cups consumed, of green and black tea separately over the past 12 months from nine predefined responses: never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day, and 6 or more times a day. For these

analyses, subjects reporting being never or hardly ever drinkers were categorized as nondrinkers, those reporting 1-3 times a month were categorized as monthly drinkers, 1-6 times a week were categorized as weekly drinkers, and those reporting 1-6 times a day were categorized as daily drinkers.

Soy: Information on the seven common fermented soy products (food and drinks) in the Singapore Chinese diet was obtained using the FFQ. Total soy intake (combining information on the seven soy products) was expressed using three different metrics: total soy foods per day (equivalent amounts of tofu and soybean drink; energy adjusted; g/Kcal), total soy protein per day (presented as percent of total protein), and total isoflavones per day (energy adjusted; mg/Kcal) (Wu et al., 2002). Equivalent amounts of tofu and soybean drink per day were calculated to facilitate comparison with a known dietary item while taking into account the varying water contents across the seven soy foods. The total soy foods intake for each subject was estimated as the summation of all foods expressed in units of plain tofu and soybean drink equivalent. Total soy protein intake per day was calculated using the Singapore Food Composition Table, as previously described (Hankin et al, 2001). Total soy isoflavone intake per day was estimated from the summation of the genistein, daidzein, and glycitein contents that had previously been measured in samples of common soy foods in Singapore (Hankin et al. 2001). The soy variables were categorized using quartiles determined by the total baseline cohort population.

Vegetable-Fruit-Soy and Meat-Dim Sum Dietary Patterns: Using principal components analysis among the baseline cohort (n = 63,257), patterns were identified from the food frequency responses as previously described (Butler et al. 2004). Briefly, extraction of principal components was followed by orthogonal rotation. The number of components retained for rotation was based primarily on examination of scree plots and factor interpretability, but eigenvalues (> 1.0) and percentage of variance explained were also considered. For each dietary pattern, a component score was computed as a linear composite of the foods with

meaningful loading scores (e.g., ≥ 0.30). Scores were calculated by taking the unweighted sum of standardized frequencies of intake for each food associated with the pattern, then dividing them into quartiles based on the distribution of the total baseline cohort population. Principal components analyses were conducted using the Factor Procedure in SAS version 9 (SAS Institute, Cary, NC). The dietary patterns identified were vegetable-fruit-soy and meat-dim sum patterns. The vegetable-fruit-soy dietary pattern was characterized by diets high in fruits, vegetables, fish, and white meat intake, while the meat-dim sum pattern was characterized by diets high in fat and sugars.

Additional Covariates: The questionnaire administered at baseline elicited information on smoking, diet, demographics, current physical activity, occupational exposure, medical history, reproductive history, alcohol use, and history of hormone use. Covariates that were assessed for inclusion as potential confounders in the multivariable models were age at baseline interview (years, assessed continuously), year of baseline interview (1993–1995, 1996–1998), dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary), menopausal status (premenopausal, postmenopausal), body mass index (BMI) (assessed continuously), moderate physical activity (none, 0.5-3 hours/week, ≥4 hours/week), smoking (current/former [defined as smoking at least one cigarette a day for a year or longer], never), alcohol intake (drinker [defined as monthly, weekly, or daily], nondrinker), and weekly vitamin/mineral supplement use (yes, no).

HbA1c (glycated hemoglobin): Red blood cells were isolated from whole blood and frozen until analysis was performed at the University of Minnesota as described previously by Bancks et al. (2014). Percentage of HbA1c was analyzed in a Clinical Laboratory Improvement Amendments–certified laboratory using an automated high-performance liquid chromatography (HPLC) method in which whole blood samples are treated with ethylenediaminetetraacetic acid(EDTA) on a Tosoh G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA). Using the standards developed in the National Glycohemoglobin

Standardization Program, this method of percentage of HbA1c assessment was calibrated to the reference range of 4.3–6.0% (23–42 mmol/mol) and a laboratory coefficient of variation range 1.4–1.9% (Bancks et al. 2014; Steffes et al. 2005).

Statistical Analyses: Linear regression was used to assess the relationships between dietary intakes (green tea, the soy variables, and the vegetable-fruit-soy dietary pattern) and continuous HbA1c levels (as the dependent variable) in separate models. Least square mean HbA1c levels for each category of dietary variables, 95% confidence intervals surrounding the means, p-values comparing the means to the mean of the referent category, and p-values for trend were calculated. Assessments were performed to evaluate the assumptions of linear regression (Weisberg 2014). Additive interaction between sex and the dietary variables of interest was assessed by introducing interaction terms in the models. Final results presented were adjusted for the following covariates: age, dialect, education, menopausal status, physical activity, smoking status, BMI, and vitamin use. The inclusion of additional covariates (year of baseline interview and alcohol use) did not appreciably change the results. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). All p values were two-sided and were considered statistically significant if $p < 0.05$ ($p < 0.10$ for interaction terms).

Sensitivity Analyses: We performed the statistical analysis described above among postmenopausal women only and nonsmokers only. We also examined models for each dietary variable of interest further adjusted for the other dietary variables of interest, as well as for total carbohydrate intake, total protein intake, total caffeine intake, black tea intake, and the meat-dim sum dietary pattern. We also conducted analyses excluding individuals with HbA1c levels in the diabetic range (i.e. HbA1c levels ≥ 6.5%). Additionally, HbA1c levels were assessed based as categorical variables based on diagnostic cut-points (nondiabetes: HbA1c levels ≤5.7%, prediabetes: HbA1c levels 5.8%-6.4%, diabetes: HbA1c levels ≥6.5%) (American Heart Association 2012) using multinomial logistic regression.

Results

Table 1 presents selected baseline characteristics for this subsample of self-reported nondiabetic subjects in the Singapore Chinese Health Study, as well as means HbA1c levels by the same characteristics. The average age at baseline was 56.7 years (standard deviation [SD] 7.4, range: 44-74) (Table 1). The average BMI was 22.8 kg/m^2 (SD 3.2) (for men, mean = 22.7 kg/m^2, range: 13.1-48.5 kg/m^2; for women, mean = 22.9 kg/m^2, range: 14.0-57.8 kg/m^2). Approximately 5% of women and 22% of men reported ever drinking alcohol in the baseline interviews, while 8% of women and 55% of men indicated they were current or former smokers. The majority of the subjects (77%) reported not being physically active and having either a primary or secondary level of education (77%). Postmenopausal women accounted for the majority of the women in these analyses (77%).

HbA1c levels among women ranged from 3.1-14.9% (mean=5.77%, SD=0.60) and among men from 3.3-12.3% (mean=5.76%, SD=0.61). Among these self-reported nondiabetics, 221 (6.2%) women and 194 (6.4%) men had HbA1c levels in the diabetic range (HbA1c level ≥ 6.5%); 1,357 (38.4%) and 1,132 (37.4%), respectively, had HbA1c levels in the pre-diabetic range (HbA1c level 5.8%-6.4%) (American Heart Association 2012). Increasing age, lower education level, increasing BMI, Cantonese dialect, postmenopausal status (among women), and ever smoking were associated with higher HbA1 levels (Table 1). Over half of the study population reported they did not regularly drink green tea; 15% of men and 10% of women reported drinking green tea on a daily basis (Table 2). The range of green tea intake for daily drinkers was between one and six cups of green tea per day (data not shown). Total soy protein intake per day ranged from 0% to 28.7% in women and 0% to 26.0% in men.

Adjusted mean HbA1c levels by categories of the dietary variables of interest are presented in Table 2. We observed lower HbA1c levels with higher levels of total soy protein intake among women (p-value for trend = 0.05); mean HbA1c levels were 5.81% (95% CI: 5.74, 5.88) for quartile one of total soy protein intake and 5.74% (95% CI: 5.68, 5.81) for quartile four

(p-value = 0.02). A similar, although weaker, pattern was observed for the other soy variables. We did not observe the same trend among men (p-value for interaction = 0.07). We observed higher mean HbA1c levels with higher reported green tea intake, particularly for women who reported drinking green tea daily compared to nondrinkers. Similar, although weaker, patterns were observed among men. Mean HbA1 levels did not vary across quartiles of the vegetable-fruit-soy dietary intake pattern for either men or women. The results did not change meaningfully in any of the sensitivity analyses (Appendix A).

Discussion

In a subset of men and women of the Singapore Chinese Health Study, 45% of self-reported nondiabetic subjects were in the diabetic and pre-diabetic ranges for HbA1c, indicating a substantial underreporting of diabetes in the SCHS. Our results evaluating the association of dietary variables with HbA1c levels suggest that higher soy intake was associated with lower HbA1c levels among women. In contrast, higher green tea consumption was associated with higher HbA1c levels in both men and women. Mean HbA1c levels did not vary across quartiles of the vegetable-fruit-soy dietary pattern.

To our knowledge, this is the first observational study evaluating the association between soy food intake and HbA1c levels; our findings of the protective effects of soy intake are consistent with other epidemiological studies evaluating HbA1c and related endpoints. Our cross-sectional results for soy intake among self-reported nondiabetics are consistent with a prospective evaluation of soy food intake and the development of type II diabetes among the entire Singapore Chinese Health Study cohort; Mueller et al. (2012) reported that unsweetened soy food intake was protective against type II diabetes risk when comparing consumption of unsweetened soy products greater than or equal to five times per week to no intake of unsweetened soy (hazard ratio [HR]: 0.72; 95% CI: 0.59, 0.89). Our results are also consistent with experimental studies. Supplementation with soy in randomized controlled trials improved biomarkers of diabetes (i.e., fasting blood glucose concentrations and HbA1c levels) when

compared to a control group (Li et al. 2005) and when compared to those randomized to American Diabetes Association recommended diets (Shabazian et al. 2006). Not all interventions studies have consistently reported beneficial effects of soy foods (Lui et al. 2010); however, comparison across studies and populations (i.e. Japanese, Western populations) is difficult due to differing measurements, definitions, and ranges of consumption of soy foods. Furthermore, many of the previous interventions have been short term (e.g., 2-3 months) and among small numbers of diabetic patients.

It is not clear why we observed a stronger effect on HbA1c for total soy protein compared to total soy food or total soy isoflavone. It is possible that protein in general is protective for diabetes risk. However, we evaluated a nutrient variable defined as the percentage of soy protein out of all protein sources to eliminate the potential impact of other protein sources. Additionally, the results did not change when total protein consumption was added as a covariate. Although it is often suggested that isoflavones may be the mechanistically relevant component of soy, these results suggest that soy components other than isoflavones may also be associated with improved glycemic control (Bhathena and Velasquez 2002).

Results from the limited number of studies examining the association between tea consumption and HbA1c or type II diabetes have been inconsistent, and the exact mechanisms of the different varieties of tea are not known (Iso et al. 2006; Odegaard et al. 2011). Due to the suspected beneficial effects of green tea on diabetes risk, we hypothesized that higher green tea consumption would be associated with lower HbA1c levels in our subset of nondiabetic subjects. However, we observed the opposite of our hypothesis. Our results are similar to the positive but not statistically significant association reported in a cross-sectional analysis among a Japanese population (Pham et al. 2014). Rebello et al. (2011) observed no association between green tea and HbA1c among a Singaporean population. Our results are also consistent with a prospective evaluation of green tea intake and type II diabetes in the SCHS. Odegaard et al. (2008) observed a suggestive increase in risk of type II diabetes for daily green

tea drinkers compared to weekly green tea drinkers and monthly/non-green tea drinkers (p for trend=0.09). Contrary to our results, an inverse association between green tea and diabetes risk was observed among a Japanese population with much higher observed levels of green tea intake as compared to our study population (Iso et al. 2006). As with the evaluation of soy intake, direct comparisons between study populations are difficult due to the differences in tea composition and in methods for assessing the frequency of tea intake. Furthermore, there were a relatively small number of daily green tea drinkers in the SCHS (15% of men and 10% of women); the range of green tea intake among the daily drinkers was between one and six cups per day. Additionally, 53% of the population reported that they do not drink green tea. Therefore our ability to evaluate a dose-response across levels of green tea intake was limited. Finally, we cannot rule out the possibility that the daily green tea drinkers in our population are different with regards to unmeasured or poorly measured confounders such as smoking and physical activity that may be responsible for the observed pattern.

The use of dietary patterns to evaluate chronic disease risks could be advantageous compared to evaluation of individual nutrient and food variables because these patterns can be overall indicators of lifestyles within a population (Villegas et al. 2010). In the full SCHS, investigators have reported that the vegetable-fruit-soy dietary pattern was inversely associated with type II diabetes risk among nonsmokers (RR: 0.75, 95% CI: 0.64, 0.90 when comparing the 5^{th} quintile to the 1^{st} quintile of intake; Odegaard et al. 2011). Other epidemiological studies examining the relationship between diets and risk of type II diabetes suggest that diets high in fruits and vegetables are protective for type II diabetes risk (Lui et al. 2004; Sargeant et al. 2001; Villegas et al. 2010). We did not observe evidence of a protective association between the vegetable-fruit-soy dietary pattern and HbA1c levels similar to what has previously been reported in other studies that evaluated the effects of similar diets (Lui et al. 2004; Sargeant et al. 2001). Discrepancies may be due to the evaluation of HbA1c levels in a lower concentration range that than observed among physician-diagnosed diabetics. Furthermore, our results may

implicate the importance of specific nutrients, such as soy, as compared to more general indicators of diet for influencing HbA1c levels in apparently healthy populations.

This study had several limitations. Accurately defining dietary nutrient variables, dietary patterns, cooking practices, and food content is difficult and often inconsistent in epidemiologic studies (Flegal 1999) and is likely to result in measurement error. The food frequency questionnaire used in this study, however, was developed for and validated in the study population (Hankin et al. 2001); furthermore, dietary soy and vegetable intake have been validated with urinary isoflavone and isothiocyanate levels, respectively in this population (Seow et al. 1998; Seow et al. 1998). As previously mentioned, another limitation is that possible confounders, such as smoking, were often measured crudely; therefore, the results may be impacted by residual confounding. Our models adjusted for variables that may represent healthy lifestyles (e.g. physical activity and smoking behaviors); however we cannot rule out the potential that residual confounding influenced our results. Furthermore, since HbA1c levels were only assessed at one time point, it is possible that misclassification of the dependent variables may have occurred in this study. However, the use of a clinical biomarker of diabetes is also a strength of our study. Measured HbA1c is an indicator of an individual's blood glucose levels over the previous 2-3 month period (American Heart Association 2012). Additionally, the sensitivity of HbA1c levels is high among undiagnosed individuals (Rohlfing et al. 2000).

The relationship between dietary variables and HbA1c levels was assessed in a restricted sample of self-reported nondiabetic subjects of the SCHS, resulting in limited generalizability. However, our observational results among those without a disease diagnosis have broad public health relevance due to the growing epidemic of diabetes worldwide and the resulting campaigns to halt disease development. Previously, HbA1c levels have been shown to predict diabetes risk among nondiabetic women in the Women's Health Study, which further emphasizes the need for evaluating HbA1c levels among individuals in the normal and pre-diabetic ranges with respect to type II diabetes development and prevention (Pradhan et al.

2007). Intervention studies among individuals with elevated risk of type II diabetes (overweight individuals, impaired glucose tolerance, and family history of disease) suggest that changes in diet and physical activity result in the prevention of progression to type II diabetes (Lindstrom et al. 2003; Tuomilehto et al. 2001). Our results from a cross-sectional evaluation should be confirmed in larger observational studies as well as longer-term intervention studies. Additionally, although the clinical relevance of small differences in HbA1c levels is unknown and should be evaluated further, our results among a relatively large sample of self-reported nondiabetics point to the importance of evaluating modifiable variables that can influence diabetes risk among currently disease-free populations. Furthermore, HbA1c levels increased with increasing age and BMI, giving us confidence in our results. The results from this study may lead to the development of more specific dietary recommendations to combat the development and progression of type II diabetes. Our results using a continuous marker of glycemic control further emphasize the potential beneficial effects of soy consumption, even among nondiabetics and pre-diabetics.

Conclusions: Higher intake of total soy protein was associated with lower HbA1c levels among self-reported nondiabetic women in the SCHS. Therefore, soy protein may be beneficial in preventing the progression of type II diabetes; however, further research is needed to specifically address this question.

Table 1: HbA1C Levels by Selected Baseline Characteristics among Self-Reported Nondiabetic Men and Women in the Singapore Chinese Health Study (n=6,586)

	Overall (n=6,586)		Men (n=3,028)		Women (n=3,558)	
	n (%)	Mean HbA1c (SD)	n (%)	Mean HbA1c (SD)	n (%)	Mean HbA1c (SD)
Age (years)						
≤ 50	1,691 (25.7)	5.72 (0.58)	822 (27.2)	5.72 (0.58)	869 (24.4)	5.70 (0.61)
51-55	3,159 (22.3)	5.75 (0.54)	636 (21.0)	5.75 (0.54)	832 (23.4)	5.74 (0.51)
56-61	4,805 (75.0)	5.75 (0.57)	770 (25.4)	5.75 (0.57)	876 (24.6)	5.80 (0.67)
62-74	1,781 (27.0)	5.81 (0.70)	800 (26.4)	5.81 (0.70)	981 (27.6)	5.85 (0.59)
Dialect group						
Hokkien	3,250 (49.4)	5.73 (0.55)	1,387 (45.8)	5.73 (0.55)	1,863 (52.4)	5.77 (0.59)
Cantonese	3,336 (50.6)	5.78 (0.65)	1,641 (54.2)	5.78 (0.65)	1,695 (47.6)	5.78 (0.61)
Highest level of education						
No formal education	1,533 (23.3)	5.86 (0.86)	246 (8.1)	5.86 (0.86)	1,287 (36.2)	5.81 (0.57)
Primary	2,953 (44.8)	5.75 (0.59)	1,521 (50.2)	5.75 (0.59)	1,432 (40.3)	5.78 (0.67)
≥ Secondary	2,100 (31.9)	5.74 (0.57)	1,261 (41.6)	5.74 (0.57)	839 (23.6)	5.71 (0.50)
BMI (kg/m^2)						
<20	1,155 (17.5)	5.67 (0.53)	533 (17.6)	5.67 (0.53)	622 (17.5)	5.65 (0.39)
20-24	3,535 (53.7)	5.72 (0.55)	1,626 (53.7)	5.72 (0.55)	1,909 (53.7)	5.76 (0.62)
24-28	1,520 (23.1)	5.86 (0.71)	727 (24.0)	5.86 (0.71)	793 (22.3)	5.86 (0.65)
>28	376 (5.7)	5.97 (0.77)	142 (4.7)	5.97 (0.77)	234 (6.6)	5.96 (0.61)
Menopausal Status						
Premenopausal					826 (23.2)	5.71 (0.62)
Postmenopausal					2,732 (76.7)	5.80 (0.59)
Physical activity (moderate)						
None	5,063 (76.9)	5.97 (0.77)	2,269 (74.9)	5.97 (0.77)	2,794 (78.5)	5.80 (0.60)
30 minute-3hours/week	944 (14.3)	5.68 (0.44)	473 (15.6)	5.68 (0.44)	471 (13.2)	5.78 (0.54)
>3hours/week	579 (8.8)	5.82 (0.70)	286 (9.5)	5.82 (0.70)	293 (8.22)	5.78 (0.65)
Smoking Status						

Never	4,631 (70.3)	5.69 (0.57)	1,365 (45.1)	5.69 (0.57)	3,266 (91.8)	5.78 (0.60)
Ex/Current	1,955 (29.7)	5.81 (0.63)	1,663 (54.9)	5.81 (0.63)	292 (8.2)	5.80 (0.47)
Alcohol Intake						
Never	5,729 (87.0)	5.76 (0.60)	2,356 (77.8)	5.76 (0.60)	3,373 (94.8)	5.77 (0.59)
Ever	857 (13.0)	5.76 (0.63)	672 (22.2)	5.76 (0.63)	185 (5.2)	5.77 (0.47)
Weekly Vitamin Use						
No	6,091 (92.5)	5.76 (0.61)	2,869 (94.8)	5.76 (0.61)	3,222 (90.6)	5.78 (0.59)
Yes	495 (7.5)	5.74 (0.57)	159 (5.2)	5.74 (0.57)	336 (9.4)	5.75 (0.63)

BMI=Body Mass Index

SD=Standard Deviation

Table 2: Mean HbA1c Levels by Intake of Selected Soy Variables, Green Tea, and Vegetable-Fruit-Soy Dietary Pattern among Men and Women in the Singapore Chinese Health Study

	Men (n=3,028)				Women (n=3,558)			
	N (%)	Mean HbA1c (%)*	95% CI	p-value	N (%)	Mean HbA1c (%)*#	95% CI	p-value
Soy Food, Adjusted (g/1000 Kcal)								
≤ 36.9	919 (30.3)	5.77	(5.70, 5.37)		736 (20.7)	5.80	(5.73, 5.87)	
36.9-60.4	753 (24.9)	5.76	(5.69, 5.83)	0.91	822 (23.1)	5.77	(5.70, 5.83)	0.26
60.4-92.5	731 (24.1)	5.83	(5.76, 5.91)	0.12	959 (27.0)	5.76	(5.70, 5.82)	0.18
>92.5	625 (20.6)	5.80	(5.72, 5.87)	0.53	1,041 (29.3)	5.76	(5.70, 5.82)	0.16
p-value for trend				0.31				0.19
Soy Protein, Percent Total Protein (%kcal)								
≤ 0.79	1,046 (34.5)	5.79	(5.73, 5.86)		638 (17.9)	5.81	(5.74, 5.88)	
0.80-1.28	842 (27.8)	5.79	(5.72, 5.85)	0.86	774 (21.8)	5.76	(5.69, 5.82)	0.09
1.29-1.94	662 (21.9)	5.79	(5.71, 5.86)	0.94	993 (27.9)	5.78	(5.71, 5.84)	0.23
>1.95	478 (15.8)	5.78	(5.70, 5.87)	0.85	1,153 (32.4)	5.74	(5.68, 5.81)	0.02
p-value for trend				0.82				0.05
Total Soy Isoflavone, Adjusted (mg/1000 Kcal)								
≤ 5.77	897 (29.6)	5.77	(5.70, 5.84)		737 (20.7)	5.80	(5.73, 5.86)	
5.78-9.83	771 (25.5)	5.78	(5.71, 5.85)	0.45	807 (22.7)	5.78	(5.71, 5.84)	0.45
9.84-15.42	715 (23.6)	5.79	(5.71, 5.86)	0.06	972 (27.3)	5.74	(5.68, 5.81)	0.06
>15.43	645 (21.3)	5.83	(5.75, 5.90)	0.29	1,042 (29.3)	5.77	(5.71, 5.83)	0.29
p-value for trend				0.32				0.21
Green Tea								
Nondrinker	1,600 (52.8)	5.74	(5.68, 5.79)		2,228 (62.6)	5.76	(5.71, 5.82)	
Monthly	342 (11.3)	5.78	(5.69, 5.87)	0.36	387 (10.9)	5.77	(5.70, 5.85)	0.77
Weekly	635 (21.0)	5.77	(5.70, 5.84)	0.34	606 (17.0)	5.76	(5.69, 5.82)	0.82
Daily	451 (14.9)	5.78	(5.70, 5.86)	0.31	337 (9.5)	5.85	(5.77, 5.93)	0.02
p-value for trend				0.01				0.11
Vegetable-Fruit-Soy Pattern								
Quartile 1 (lowest)	675 (22.3)	5.80	(5.73, 5.88)		747 (21.0)	5.76	(5.69, 5.87)	

Quartile 2	754 (24.9)	5.78	(5.71, 5.85)	0.95	925 (26.0)	5.76	(5.69, 5.82)	0.95
Quartile 3	809 (26.7)	5.81	(5.74, 5.88)	0.17	949 (26.7)	5.80	(5.74, 5.86)	0.17
Quartile 4	790 (26.1)	5.77	(5.70, 5.83)	0.95	937 (26.3)	5.76	(5.70, 5.82)	0.95
p-value for trend				0.48				0.62

95% CI= 95% Confidence Interval

Chapter 5: Manuscript 2: Effect Modification of Soy and Green Tea Intake on the Diabetes and Breast Cancer Association among Singaporean Chinese Women (Aim 2)

Synopsis

Breast cancer is the leading cause of cancer mortality among women worldwide. Modifiable lifestyle factors such as type II diabetes and diet that influence endogenous hormone levels may play a role in the development of breast cancer. Prospective data are needed to evaluate the effects of type II diabetes on breast cancer and the potential effect modification of soy and green tea on this association among Asian populations. We examined the association between type II diabetes on breast cancer risk in the Singapore Chinese Health Study, a prospective cohort that enrolled 63,257 Chinese men and women aged 45-74 years between 1993 and 1998. Self-reported diabetes diagnosis was determined at follow-up interview. Dietary intake was assessed at baseline interview using a validated 165-item food frequency questionnaire. As of December 2007, 305 postmenopausal women developed breast cancer. Multivariable proportional hazards regression models were used to evaluate the associations between type II diabetes and breast cancer risk and the interaction of soy variables and green tea on the diabetes and breast cancer association. We observed a non-statistically significant increase in breast cancer risk among women with type II diabetes (adjusted hazard ratio [HR]=1.24, 95% confidence interval [CI]: 0.82, 1.86). The assessment of the interaction between diabetes and lower soy isoflavone intake suggested a weak interaction; an elevated HR for breast cancer was observed only among those with lower soy isoflavone intake. There was no evidence of interaction when evaluating soy food, soy protein and green tea intake on the diabetes and breast cancer association. In conclusion, our prospective data suggest that higher levels of soy isoflavone intake may attenuate the association between type II diabetes and breast cancer risk.

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide, accounting for 23% of cancer diagnoses (Jemal et al. 2011); it is also the leading cause of cancer mortality among women worldwide (Howlader et al. 2011). Although Singapore has traditionally had lower rates of breast cancer, incidence has increased rapidly over the past 35 years (Seow et al. 2004; Singapore Cancer Registry 2012). Traditional reproductive risk factors such as lower parity and late age at first childbirth may contribute to the recent increases (American Cancer Society 2006); however, lifestyle factors may also play a role. More specifically, changes in modernization and uptake of Western lifestyles have been attributed to the rapid increase of breast cancer in Asian populations (Lee and Gourley 1986). Type II diabetes is a largely preventable disease that has also become a growing health concern worldwide (Centers for Disease Control and Prevention 2011). Although Asian populations have customarily had lower incidence rates of type II diabetes when compared to Western populations, Asian countries now account for approximately 60% of individuals affected by diabetes in the world (Chen et al. 2012). Among residents of Singapore, there was more than a four-fold increase in diabetes between 1975 and 2000 (Lee 2000).

Epidemiological studies evaluating the relationship between diabetes and breast cancer risk have reported positive associations, particularly in Western populations (Larsson et al. 2007; Vona-Davis et al. 2007; Wolf et al. 2005). However, the relationship between diabetes and breast cancer risk has not been studied extensively among Asian populations that differ from Western populations with regard to lifestyle factors, dietary factors, and body composition (Wu et al. 2007). The comprehensive mechanism of breast cancer development is unknown; however, hormone-modifying lifestyle factors have been implicated (Kaaks 1996; Missmer et al. 2004; Wolf et al. 2005; Wu et al. 2008; Yuan et al. 2005). Therefore, diabetes is thought to influence breast cancer risk through alterations in endogenous hormone levels (Kaaks 1996). Furthermore, certain features common to Asian diets may also influence endogenous hormone

levels; increased soy intake was associated with decreased circulating estrogen levels in a cross-sectional study among postmenopausal women in the Singapore Chinese Health Study (SCHS) (Wu et al. 2005). Diets high in soy and green tea were also protective for the development of breast cancer among women in the SCHS (Wu et al. 2008; Yuan et al. 2005), leading to the hypothesis that these dietary variables may modify the association between diabetes and breast cancer. In support of this hypothesis, Wu et al. (2008) provided suggestive evidence that the relationship between diabetes and breast cancer was attenuated among women with higher consumption of soy food (as compared to lower consumption of soy food) in a case-control study among Asian-American women.

Here we present a prospective evaluation of the association between diabetes and breast cancer among postmenopausal Singaporean Chinese women. We also present the first prospective evaluation of the potential effect modification of soy and green tea intake on the association between diabetes and breast cancer risk.

Methods

Study Population: The design of the Singapore Chinese Health Study has been previously described in detail (Yuan et al. 2003). Briefly, the cohort consists of 27,959 men and 35,298 women recruited between April 1993 and December 1998, who were permanent residents or citizens of Singapore aged 45–74 years and resided in government-built housing estates (86% of the Singapore population resided in such facilities at the time of enrollment). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. For these analyses, we counted person-years starting at the follow-up interview for 23,677 postmenopausal women who did not have a history of cancer diagnosis at baseline (1993-1998) or follow-up interview (1999-2004), based on self-report and computer-assisted record linkage analysis with the population-based Singapore Cancer Registry database, nor a self-reported diagnosis of diabetes at the baseline interview. This was to ensure that diet assessed at baseline was not influenced by a diabetes diagnosis

and that diabetes diagnosis preceded breast cancer diagnosis.

Breast Cancer Case Ascertainment: Incident breast cancer cases diagnosed after the follow-up interview through December 31, 2007 were identified using linkage with the Singapore Cancer Registry database. This nationwide cancer registry was established in 1968 and is complete in the recording of cancer cases (Parkin et al. 2002).

Exposure and Covariate Assessment: Enrollment in the cohort entailed completing a baseline, in-person interview in the participant's home. The questionnaire elicited information on smoking, diet, demographics, current physical activity, occupational exposure, medical history, and reproductive history. A 165-item quantitative food frequency questionnaire (FFQ) developed for and validated in this population was used to assess usual diet over the past year (Hankin et al. 2001). Means comparing values obtained from the FFQ and 24-hour recall responses for the major macro- and micronutrients were within 10% deviation of each other and thus very comparable (Hankin et al. 2001).

Type II Diabetes: Self-reported physician diagnosed type II diabetes was evaluated at the follow-up interview (1999-2004). Diabetes status (yes/no) was assessed by the following question "Please tell me if you have been told by a doctor to have any of these conditions: Diabetes (high blood sugar)?" If yes: "Please also tell me the age at which you were first diagnosed with this condition."

Tea: Subjects were asked in the FFQ to identify their intake frequency, in cups consumed, of green and black tea separately over the past 12 months from nine predefined responses: never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day, and 6 or more times a day. For these analyses, subjects reporting being never or hardly ever drinkers were categorized as nondrinkers, those reporting 1-3 times a month were categorized as monthly drinkers, 1-6 times a week were categorized as weekly drinkers, and those reporting 1-6 times a day were categorized as daily drinkers.

Soy: Information on the seven common fermented soy products (food and drinks) in the Singapore Chinese diet was obtained using the FFQ. Total soy intake (combining information on the seven soy products) was expressed using three different metrics: total soy foods per day (equivalent amounts of tofu and soybean drink; energy adjusted; g/Kcal), total soy protein per day (presented as percent of total protein), and total isoflavones per day (energy adjusted; mg/Kcal) (Wu et al., 2002). Equivalent amounts of tofu and soybean drink per day were calculated to facilitate comparison with a known dietary item while taking into account the varying water contents across the seven soy foods. The total soy foods intake for each subject was estimated as the summation of all foods expressed in units of plain tofu and soybean drink equivalent. Total soy protein intake per day was calculated using the Singapore Food Composition Table, as previously described (Hankin et al, 2001). Total soy isoflavone intake per day was estimated from the summation of the genistein, daidzein, and glycitein contents that had previously been measured in samples of common soy foods in Singapore (Hankin et al. 2001). The soy variables were assessed using quartiles (sex-specific, energy adjusted) determined by the total baseline cohort population (covariate assessment) and median values for the entire baseline cohort (interaction assessment).

Covariate Assessment: Covariates that were assessed for inclusion as potential confounders in the multivariable models were age at baseline interview (years, assessed continuously), year of baseline interview (1993–1995, 1996–1998), dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary), body mass index (BMI) (kg/m2, assessed continuously and as quartiles based on the total population), moderate physical activity (none, 0.5-3 hours/week, ≥4 hours/week), smoking (current/former [defined as smoking at least 1 cigarette a day for a year or longer], never), alcohol intake (drinker [defined as monthly, weekly, or daily], nondrinker), weekly vitamin/mineral supplement use (yes, no), and family history of breast cancer (yes, no). Reproductive factors that were also assessed for potential confounding were age at regularity (never regular, ≥17, 15-16, 13-14, <13 years), age

at first menarche (≥17, 15-16, 13-14, <13), age at first birth (nulliparous, ≥31, 26-30, 21-25, ≤20 years), number of full term births (0, 1-2, >3), and postmenopausal hormone use (no, yes). Along with green tea intake and soy food intake (described above), omega-3 fatty acid intake was evaluated as a covariate (sex-specific, energy adjusted intake evaluated as quartiles based on the entire baseline cohort).

Statistical Analyses: Descriptive analyses for risk factors and potential confounders of interest were performed. Hazard ratios (HRs) for breast cancer and their corresponding 95% confidence intervals for self-reported diabetes were calculated using Cox proportional hazards regression methods. Model assumptions were evaluated using time dependent variables and Kaplan-Meier Curves. The non-informative censoring assumption was satisfied due to the cohort study design. Person-years of follow-up were enumerated from the date of the follow-up interview to the date of diagnosis of breast cancer, death, migration out of Singapore, or December 31, 2007, whichever occurred first.

For the main analyses evaluating the association between diabetes and breast cancer risk, three adjusted models were evaluated among postmenopausal women. The base model was adjusted for age, date of baseline interview, and father's dialect. The second model additionally adjusted for baseline lifestyle and reproductive characteristics (BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, and postmenopausal hormone use). The final model additionally adjusted for dietary variables (sex-specific, energy-adjusted omega-3 fatty acid intake [quartiles], sex-specific, energy-adjusted total soy food intake [quartiles], and green tea intake) that have been shown to be associated with breast cancer in the Singapore Chinese Health Study (Gago-Dominguez et al. 2003; Wu et al. 2008; Yuan et al. 2005).

Interaction terms between diabetes status (no, yes) and soy and green tea intake were introduced into the model to assess potential additive and multiplicative effect modification (in separate models); the soy and green tea variables were dichotomized (based on the median

value of the baseline cohort for the soy variables and nondrinker versus drinker (daily, weekly, monthly) for green tea. Models assessing the interaction between diabetes and soy variables/green tea intake were adjusted for age, baseline interview date, and dialect. A p for interaction was used to evaluate the multiplicative interaction. The relative excess risk for interaction (RERI) was used to evaluate additive interaction (Rothman et al. 2008).

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). All p-values were two-sided and were considered statistically significant if $p < 0.05$ ($p < 0.10$ for interaction terms).

As a sensitivity analysis we included premenopausal women. Additionally, we included women who reported a type II diabetes diagnosis at baseline to determine the impact of inclusion of all diabetic women in the Singapore Chinese Health Study on the association between diabetes and breast cancer, regardless of the possible change in diet due to a diabetes diagnosis. Furthermore, we conducted a sensitivity analysis after removing the first two years of follow-up for all subjects in the study.

Results

Through December 31, 2007, an average of 6.4 years (standard deviation [SD] = 3.8 years) after the follow-up interview, 305 postmenopausal women had developed breast cancer. The average age of breast cancer diagnosis was 65.3 years (SD=8.0 years). At baseline interview, women evaluated in these analyses had a mean age of 56.2 years (SD=7.5 years) (Table 3). Primary and secondary education (compared to no formal education), increasing BMI, older age at first birth, fewer number of full term births, and postmenopausal hormone use were associated with an increased risk of breast cancer in univariate analyses (Table 3). Furthermore, increasing age, fewer years of education, increasing BMI, weekly vitamin use, earlier age at first birth, increased parity, and postmenopausal hormone use were associated with increased type II diabetes prevalence among postmenopausal women of the SCHS (Table 4).

We observed a non-statistically significant increase in breast cancer risk among women reporting a type II diabetes diagnosis (Table 5). After adjusting for age, baseline interview data, and dialect (Table 5, Model 1), the HR for the diabetes and breast cancer association among postmenopausal women was 1.24 (95% CI: 0.82, 1.86). Further adjustment for additional baseline characteristics and dietary variables did not meaningfully change the results (Table 5, Models 2 and 3).

The mean energy adjusted total soy isoflavone intake among all women at baseline was 9.8 grams/day (SD=8.5). The results suggested a weak interaction of type II diabetes and low soy isoflavone intake (Table 6); the risk of breast cancer was increased only among those women who had low soy isoflavone intake. The RERI value for total soy isoflavone and diabetes on breast cancer was 0.70, indicating a slightly greater than additive interaction. Furthermore, there was an increase in risk of breast cancer among postmenopausal women who consumed less than the median soy isoflavone intake and who reported a type II diabetes diagnosis (HR=2.04; 95% CI: 1.23, 3.39).

At baseline, 62.3% of women reported no consumption of green tea and only 10.0% of women reported consuming green tea daily. There was no evidence of interaction between green tea intake and type II diabetes among postmenopausal women (Table 6).

The results did not meaningfully change when including premenopausal women, when including women who reported diabetes at baseline, or when removing the first two years of follow-up from the analyses (Appendix B).

Discussion

Among women in the Singapore Chinese Health Study, we observed a suggestive increase in risk of breast cancer in relation to type II diabetes. Our results evaluating the interaction of dietary variables on the association between diabetes and breast cancer risk indicated the potential beneficial effects of increased soy isoflavone intake; however, the modification was weak, and the power to detect a statistically significant interaction was limited.

Although we did not observe a statistically significant positive association between diabetes and breast cancer risk, the magnitude of effect that we observed is similar to effects previously observed in other epidemiological studies evaluating this relationship (Larsson et al. 2007; Vona-Davis et al. 2007; Wolf et al. 2005). Our study was one of only a few studies prospectively evaluating the association between a self-reported type II diabetes diagnosis and risk of breast cancer among an Asian population that has recently had a dramatic increase in both diabetes prevalence and breast cancer diagnoses (Lee 2000; Seow et al. 2004). Our results were similar to an epidemiological study evaluating self-reported type II diabetes and breast cancer risk prospectively in a Japanese population (HR=1.27; 95%CI: 0.51, 3.14) (Khan et al. 2006). Another study among a Korean cohort evaluating blood glucose levels and medication use as an indicator of diabetes status found a significant increase in breast cancer risk associated with diabetes (Jee et al. 2005), indicating a possible advantage of using a biomarker of diabetes (as compared to self-report) to evaluate this relationship.

To our knowledge, this is the first prospective study evaluating the effect modification of dietary variables on the association between type II diabetes and breast cancer. Our findings of the potential beneficial effect of soy isoflavone intake on the association between type II diabetes and breast cancer risk among postmenopausal women is consistent with a case-control study among Asian-American women which found a protective effect of soy food intake on the diabetes and breast cancer association (Wu et al. 2008). However, the timing of soy intake between the two studies varied. The study by Wu et al. (2008) evaluated soy food intake during the lifetime of the subject (adolescence and adulthood), and the current study evaluated soy food intake during adulthood, estimating intake during the year prior to the baseline assessment. The results of our study evaluating the interaction of soy food intake and type II diabetes on breast cancer risk should be interpreted with caution. Although there was a suggestive interaction between total soy isoflavone intake and diabetes, similar results were not observed for total soy food intake or for total soy protein intake and type II diabetes. These

results, however, may support the beneficial role of soy isoflavones on the development of breast cancer that has previously been reported in the SCHS (Wu et al. 2008). Our study is the first prospective evaluation of the green tea intake and type II diabetes interaction on breast cancer risk; however, the majority of women in the Singapore Chinese Health Study did not report drinking green tea and a low proportion reported high levels of intake, making it difficult to assess this interaction by varying levels of green tea intake. Although there was limited power to evaluate the effect modification of dietary variables and type II diabetes on the breast cancer risk, the results of this study are novel and may provide valuable public health implications in reducing the burden of breast cancer.

In these analyses, we used a conservative approach to evaluate the association between type II diabetes and breast cancer risk. Women who reported type II diabetes at baseline were excluded from the primary analyses. Only type II diabetes diagnoses that developed during and were reported at the follow-up interview were assessed; furthermore, only breast cancer cases that occurred after the follow-up period were assessed. This approach was taken to determine the diabetes and breast cancer association independent of a possible change in behaviors (diet, physical activity, and BMI) due to a diabetes or breast cancer diagnosis; diet, physical activity, and BMI assessments were based on baseline interviews. Although this exclusion resulted in limited power, the conservative approach was beneficial in that a temporal relationship between dietary variables, type II diabetes diagnosis, and breast cancer risk could be established.

In addition to limited power, there are several potential limitations of this study. Type II diabetes is often underreported; it is possible that misclassification of exposure could have occurred in these analyses. Self-reported diabetes among the cohort may be lower than the actual diabetes burden. Any effect of underreporting of type II diabetes would likely be non-differential with respect to breast cancer diagnoses; therefore, the underreporting would likely attenuate a true association between diabetes and breast cancer risk and result in a bias

towards the null (Seow 2006). Diabetes case validation within the SCHS has been shown to have a high positive predictive value when evaluating symptoms and diagnostic tests for diabetes (Odegaard et al. 2011). Furthermore, because diabetes status was assessed at the follow-up interview, length of follow-up was relatively short in this study (mean=6.4 years, SD=3.8 years).

The baseline questionnaire gathered information on lifestyle factors such as physical activity, alcohol use, and smoking status, which may be confounders of the association between type II diabetes and breast cancer; these variables, however, were only assessed at baseline. Although alcohol use and cigarette smoking have been implicated as being associated with breast cancer risk (American Cancer Society 2006), there were no associations between these variables and breast cancer risk when a univariate assessment was performed within our study. Although there were only a small proportion of women who consume alcohol and smoke in this population, crude classification of confounders may result in residual confounding. Other potentially confounding variables such as mammographic density and other environmental exposures that may contribute to breast cancer risk were unmeasured in this cohort and therefore cannot be assessed in this study.

There are several strengths of the study. An advantage of evaluating the diabetes and breast cancer association among women in the Singapore Chinese Health Study is that the potential for confounding by weight or BMI, factors known to be associated with both diabetes and breast cancer risk, may be reduced. This is of particular interest since Asians have become more prone to the development of diabetes in recent years, even at much lower BMIs than that observed among Western populations (World Health Organization 2004). Furthermore, along with the conservative approach used to evaluate these temporal relationships, the Singapore Chinese Health Study is a well-established prospective cohort study. Because of the cohort study design, it is unlikely that a selection bias occurred in this study. Loss of follow-up in this cohort is minimal, with less than 1% of individuals of the cohort being lost to migration, and the

response rate in the cohort is very high. Additionally, the food frequency questionnaire used for these analyses was developed for and validated in the study population (Hankin et al. 2001). Specifically, dietary soy intake was validated with urinary isoflavone levels (Seow et al. 1998). Finally, breast cancer case ascertainment is considered to be complete within the Singapore Chinese Health Study due to the nation-wide cancer registry in place in Singapore.

Conclusions: The identification of the potential effect modification of soy isoflavones on the association between diabetes and breast cancer risk may be beneficial in determining modifiable risk factors to reduce the burden of breast cancer worldwide; however, further research to reproduce results among larger Asian as well as non-Asian populations is needed.

Table 3: Baseline* Characteristics by Breast Cancer Status after Follow-up among Postmenopausal Women in the Singapore Chinese Health Study (n=23,677)

	Breast Cancer		
	No (n=23,372)	Yes (n=305)	
	N (%)	N (%)	HR (95% CI)
Person-Years of follow-up, mean (SD)	6.48 (1.4)	3.50 (2.1)	
Age, years, mean (SD)	56.2 (7.5)	55.6 (7.7)	
Age, years			
<50	5,209 (22.3)	76 (24.9)	1.00 (reference)
50-54	5,697 (24.4)	87 (28.5)	1.02 (0.75, 1.39)
55-61	6,503 (27.8)	73 (23.9)	0.77 (0.56, 1.06)
>62	5,963 (25.5)	69 (22.6)	0.84 (0.61, 1.17)
Dialect group			
Hokkien	11,354 (48.6)	162 (53.1)	1.00 (reference)
Cantonese	12,018 (51.4)	143 (46.9)	0.83 (0.67, 1.05)
Education			
No formal education	9,320 (39.9)	95 (31.2)	1.00 (reference)
Primary	9,376 (40.1)	127 (41.6)	1.29 (0.99, 1.68)
≥ Secondary	4,676 (20.0)	83 (27.2)	1.69 (1.26, 2.27)
BMI, kg/m^2, mean (SD)	23.2 (3.3)	23.6 (3.3)	
BMI, kg/m^2			
<20	3,571 (15.3)	32 (10.5)	1.00 (reference)
20-24	12,831 (54.9)	165 (54.1)	1.43 (0.98, 2.09)
24-28	5,203 (22.3)	80 (26.2)	1.71 (1.13, 2.57)
>28	1,767 (7.6)	28 (9.2)	1.78 (1.07, 2.96)
Moderate Physical Activity			
None	18,582 (79.5)	245 (80.3)	1.00 (reference)
30 minute-3 hours/week	2,979 (12.8)	36 (11.8)	0.90 (0.63, 1.27)
>3 hours/week	1,811 (7.8)	24 (7.9)	0.96 (0.63, 1.46)
Cigarette Smoking			
Never	21,471 (91.9)	284 (93.1)	1.00 (reference)
Ever	1,901 (8.1)	21 (6.9)	0.89 (0.57, 1.38)
Alcohol use			
Never	24,607 (95.2)	342 (97.7)	1.00 (reference)
Ever	1,238 (4.8)	8 (2.3)	0.55 (0.27, 1.12)
Weekly Vitamin/Mineral Supplement Use			
No	21,573 (92.3)	275 (90.2)	1.00 (reference)
Yes	1,799 (7.7)	30 (9.8)	1.30 (0.89, 1.90)
Age at Regularity, years (missing=5)			
< 13	2,775 (11.9)	35 (11.5)	1.00 (reference)
13-14	8,065 (34.5)	123 (40.3)	1.27 (0.90, 1.81)
15-16	8,072 (34.5)	100 (32.8)	1.11 (0.77, 1.59)
≥17	3,694 (15.8)	39 (12.8)	0.89 (0.58, 1.37)

Never Regular	761 (3.3)	8 (2.6)	0.75 (0.35, 1.60)
Age at First Menarche, years (missing=5)			
< 13	3,217 (13.8)	40 (13.1)	1.00 (reference)
13-14	8,856 (37.9)	132 (43.3)	1.19 (0.84, 1.70)
15-16	8,240 (35.3)	102 (33.4)	1.00 (0.69, 1.44)
≥17	3,054 (13.1)	31 (10.2)	0.83 (0.52, 1.32)
Age at First Birth, years (missing=19)			
≤20	4,416 (18.9)	42 (13.8)	1.00 (reference)
21-25	8,945 (38.3)	87 (28.5)	1.00 (0.69, 1.45)
26-30	6,032 (25.8)	97 (31.8)	1.62 (1.13, 2.33)
≥31	2,360 (25.8)	44 (31.8)	1.87 (1.23, 2.86)
Nulliparous	1,600 (6.9)	35 (11.5)	2.25 (1.44, 3.52)
Number of Full Term Births			
≥3	15,305 (65.5)	169 (55.4)	1.00 (reference)
1-2	6,467 (27.7)	101 (33.1)	1.39 (1.09, 1.78)
0	1,600 (6.9)	35 (11.5)	1.98 (1.37, 2.84)
Ever Postmenopausal Hormone Use (missing=346)			
No	20,229 (87.8)	247	1.00 (reference)
Yes	2,801 (12.2)	54	1.53 (1.14, 2.05)
Family History of Breast Cancer			
No	23,063 (98.7)	301 (98.7)	1.00 (reference)
Yes	309 (1.3)	4 (1.3)	0.99 (0.37, 2.66)

*All characteristics were from the baseline interview except for postmenopausal hormone use, which was from the follow-up interview.

BMI=Body Mass Index
HR=Hazard Ratio
SD=Standard Deviation
95% CI=95% Confidence Interval

Table 4: Baseline* Characteristics by Diabetes Status at the Follow-up Interview among Postmenopausal Women in the Singapore Chinese Health Study (n=23,677)

	Diabetes		
	No (n=21,966)	Yes (n=1,711)	
	N (%)	N (%)	p-value
Age, years, mean (SD)	56.2 (7.5)	57.3 (7.4)	
Age, years			<0.0001
<50	4,977 (22.7)	308 (18.0)	
50-54	5,400 (24.6)	384 (22.4)	
55-61	6,080 (27.7)	496 (29.0)	
>62	5,509 (25.1)	523 (30.6)	
Dialect group			0.01
Hokkien	10,737 (48.9)	779 (45.5)	
Cantonese	11,229 (51.1)	932 (54.5)	
Education			<0.0001
No formal education	8,623 (39.3)	792 (46.3)	
Primary	8,826 (40.1)	677 (39.6)	
≥ Secondary	4,517 (20.6)	242 (14.1)	
BMI, kg/m^2, mean (SD)	23.0 (3.2)	24.8 (3.7)	
BMI, kg/m^2			<0.0001
<20	3,492 (15.9)	111 (6.5)	
20-24	12,210 (55.6)	786 (45.9)	
24-28	4,764 (21.7)	519 (30.3)	
>28	1,500 (6.8)	295 (17.2)	
Moderate Physical Activity			0.59
None	17,465 (79.5)	1362 (79.6)	
30 minute-3 hours/week	2,807 (12.8)	208 (12.2)	
>3 hours/week	1,694 (7.7)	141 (8.2)	
Cigarette Smoking			0.51
Never	20,190 (91.9)	1565 (91.5)	
Ever	1,776 (8.1)	146 (8.5)	
Alcohol use			<0.0001
Never	20,891 (95.1)	1666 (97.4)	
Ever	1,075 (4.9)	45 (2.6)	
Weekly Vitamin/Mineral Supplement Use			<0.0001
No	20,225 (92.1)	1623 (94.9)	
Yes	1,741 (7.9)	88 (5.1)	
Age at Regularity, years (missing=5)			1.00
< 13	2,605 (11.9)	205 (12.0)	
13-14	7,596 (34.6)	592 (34.6)	
15-16	7,582 (34.5)	590 (34.5)	
≥17	3,462 (15.8)	271 (7.3)	
Never Regular	716 (3.3)	53 (3.1)	

Age at First Menarche, years (missing=5)			0.90
< 13	3,022 (13.8)	235 (13.7)	
13-14	8,340 (38.0)	648 (37.9)	
15-16	7,747 (35.3)	595 (34.8)	
≥17	2,852 (13.0)	233 (13.6)	
Age at First Birth, years, (missing=19)			<0.0001
≤20	4,054 (18.5)	404 (23.6)	
21-25	8,361 (38.1)	671 (39.2)	
26-30	5,708 (26.0)	421 (24.6)	
≥31	2,263 (10.3)	141 (8.3)	
Nulliparous	1,562 (7.1)	73 (4.3)	
Number of Full Term Births			<0.0001
≥3	14,212 (64.7)	1262 (73.8)	
1-2	6,192 (28.2)	376 (22.0)	
0	1,562 (7.1)	73 (4.3)	
Ever Postmenopausal Hormone Use (missing=346)			<0.001
No	18,933 (87.5)	1543 (91.4)	
Yes	2,709 (12.5)	146 (8.6)	
Family History of Breast Cancer			0.15
No	21,669 (98.7)	1695 (99.1)	
Yes	297 (1.3)	16 (0.9)	
Breast Cancer			0.51
No	21,686 (98.7)	1686 (98.5)	
Yes	280 (1.3)	25 (1.5)	

*All characteristics were from the baseline interview except for postmenopausal hormone use, which was from the follow-up interview.

Table 5: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Diabetes in relation to Breast Cancer Risk among Postmenopausal Women in the Singapore Chinese Health Study

Diabetes	Breast Cancer Cases	HR (95%CI)*	HR (95%CI) [#]	HR (95%CI) [¥]
No	280	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	25	1.24 (0.82, 1.86)	1.20 (0.79, 1.81)	1.20 (0.79, 1.81)

*Model 1 adjusted for age, baseline interview date, and dialect

[#]Model 2 adjusted for age, baseline interview date, dialect, BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, postmenopausal hormone use

[¥]Model 3 adjusted for age, baseline interview date, dialect, BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, postmenopausal hormone use, energy adjusted omega-3 intake, energy adjusted soy food intake, and green tea intake

HR=Hazard Ratio
95% CI=95% Confidence Interval

Table 6. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Joint Effects of Dietary Soy/Green Tea Intake and Diabetes among Postmenopausal Women in the Singapore Chinese Health Study

	n	HR (95% CI) *
Soy Food (g/1000Kcal)		
≥ Median (60.4)		
No Diabetes	123	1.00 (reference)
Diabetes	13	1.44 (0.81, 2.55)
< Median (60.4)		
No Diabetes	157	1.32 (1.04, 1.67)
Diabetes	12	1.42 (0.79, 2.57)
p for multiplicative interaction		0.49
RERI		-0.39 (-3.18, 2.40)
Soy Protein (g, % total protein)		
≥ Median (2.3)		
No Diabetes	125	1.00 (reference)
Diabetes	14	1.55 (0.89, 2.70)
< Median (2.3)		
No Diabetes	155	1.23 (0.97, 1.56)
Diabetes	11	1.21 (0.65, 2.24)
p for multiplicative interaction		0.27
RERI		-0.52 (-2.39, 1.35)
Soy Isoflavones (mg/1000Kcal)		
≥ Median (9.8)		
No Diabetes	121	1.00 (reference)
Diabetes	8	0.92 (0.45 1.88)
< Median (9.8)		
No Diabetes	159	1.38 (1.09, 1.75)
Diabetes	17	2.04 (1.23, 3.39)
p for multiplicative interaction		0.29
RERI		0.70 (-2.82, 2.42)
Green Tea		
Drinker		
No Diabetes	106	1.00 (reference)
Diabetes	10	1.24 (0.65, 2.36)
Nondrinker		
No Diabetes	174	1.00 (0.78, 1.27)
Diabetes	15	1.23 (0.72, 2.12)
p for multiplicative interaction		0.99
RERI		0.03 (-2.09, 1.83)

*Adjusted for age, baseline interview date, and dialect
HR=Hazard Ratio
95% CI=95% Confidence Interval
RERI=Relative Excess Risk Due to Interaction

Chapter 6: Manuscript 3: Weight Change, Diet, and Breast Cancer Risk among Women in the Singapore Chinese Health Study (Aim 3)

Synopsis

Breast cancer is the leading cause of cancer mortality among women worldwide. Modifiable lifestyle factors such as weight change and diet that influence endogenous hormone levels may play a role in the development of breast cancer. Few prospective studies have evaluated the effects of weight change on breast cancer risk as well as the potential effect modification of soy and green tea on this association among Asian populations, which differ from Western populations with respect to body size and composition. We examined the association between weight change from baseline to follow-up interview (approximately 6 years) on breast cancer risk in the Singapore Chinese Health Study, a prospective cohort study that enrolled 63,257 Chinese men and women aged 45-74 years between 1993 and 1998. Self-reported weights at baseline and follow-up interviews were used to determine weight change. Dietary intake was assessed at baseline interview using a validated 165-item food frequency questionnaire. As of December 2007, 267 postmenopausal women developed breast cancer. Multivariable proportional hazards regression models were used to evaluate the associations between weight change and breast cancer risk and the interaction of soy variables and green tea on the weight change and breast cancer association. We did not observe evidence of an increase in breast cancer risk among women reporting weight gain between baseline and follow-up interviews; however, we observed an increase in risk among women who lost between 3 and 5 kilograms between baseline and follow-up interviews (HR=1.31, 95% CI: 0.94, 1.83). There was no evidence of interaction between weight change and either soy and green tea intake. In conclusion, our prospective data did not suggest an association between weight change and risk of breast cancer among postmenopausal women in the Singapore Chinese Health Study.

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide, accounting for 23% of cancer diagnoses (Jemal et al. 2011); it is also the leading cause of cancer mortality among women (Howlader et al. 2011). Although Singapore has traditionally had low rates of breast cancer, incidence has increased rapidly over the past 35 years (Seow et al. 2004; Singapore Cancer Registry 2012). Traditional reproductive risk factors such as lower parity and late age at first childbirth may contribute to the recent increases (American Cancer Society 2006); however, modifiable exposures may also play a role. More specifically, changes in modernization and uptake of Western lifestyles have been attributed to the rapid increase of breast cancer in Asian populations (Lee and Gourley 1986).

Weight gain and obesity have become a major health concern among all women worldwide (James et al. 2001). Weight gain has been associated with elevated endogenous hormone levels (Missmer et al. 2006), and therefore, may result in an increased risk of breast cancer, particularly among postmenopausal women (Eliassen et al. 2006; deWaard et al. 1982), while weight loss has been associated with a decrease in circulating estrogen levels (deWaard et al. 1982).

Epidemiological studies evaluating postmenopausal weight change and breast cancer risk have reported a positive association, particularly among Western populations (Eliassen et al. 2006; Lahmann et al. 2005). Furthermore, a study among Asian-American women reported a suggestive association with weight gain and breast cancer risk (Ziegler et al. 1996). This relationship, however, has not been evaluated extensively in primarily Asian women, for whom body composition of women differs from that of women in Western populations (Odegaard et al. 2011).

The exact mechanism of breast cancer development is unknown; however, hormone-modifying lifestyle factors that include weight change and diet have been implicated in the role on breast cancer development (Kaaks 1996; Missmer et al. 2004; Wolf et al. 2005; Wu et al.

2008; Yuan et al. 2005). Weight change is thought to influence breast cancer risk through alterations in endogenous hormone levels (Kaaks 1996); weight gain is associated with elevated endogenous hormone levels (Missmer et al. 2006), while weight loss was associated with decreased circulating estrogen levels (deWaard et al. 1982). Furthermore, certain features common to Asian diets may also influence endogenous hormone levels; increased soy intake was associated with decreased circulating estrogen levels in a cross-sectional study among postmenopausal Singaporean Chinese women (Wu et al. 2005). Diets high in soy and green tea were also inversely associated with the development of breast cancer among women in the Singapore Chinese Health Study (SCHS) (Wu et al. 2008; Yuan et al. 2005), leading to the hypothesis that these dietary variables may modify the association between weight change and breast cancer. However, no studies to date have evaluated the possible modifying effect of dietary variables on the relationship between weight change and risk of breast cancer.

Here we present an evaluation of the association between weight change and breast cancer among postmenopausal Singaporean Chinese women. We also present the first prospective evaluation of the effect modification of soy and green tea intake on the association between weight change and breast cancer risk.

Methods

Study Population: The design of the Singapore Chinese Health Study has been previously described in detail (Yuan et al. 2003). Briefly, the cohort consists of 27,959 men and 35,298 women recruited between April 1993 and December 1998, who were permanent residents or citizens of Singapore aged 45–74 years and resided in government-built housing estates (86% of the Singapore population resided in such facilities at the time of enrollment). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. For these analyses, we used data from the 20,163 postmenopausal women who did not have a history of cancer diagnosis at baseline (1993-1998) and follow-up interview (1999-2004), based on self-report and computer-assisted record linkage

analysis with the population-based Singapore Cancer Registry database.

Breast Cancer Case Ascertainment: Incident breast cancer cases diagnosed after the follow-up interview through December 31, 2007 were identified using linkage with the Singapore Cancer Registry database. This nationwide cancer registry was established in 1968 and is complete in the recording of cancer cases (Parkin et al. 2002).

Exposure and Covariate Assessment: Enrollment in the cohort entailed completing a baseline, in-person interview in the participant's home. The questionnaire elicited information on smoking, diet, demographics, current physical activity, occupational exposure, medical history, and reproductive history. A 165-item quantitative food frequency questionnaire (FFQ) developed for and validated in this population was used to assess usual diet over the past year (Hankin et al. 2001). Mean values obtained from the FFQ and 24-hour recall responses for the major macro- and micronutrients were within 10% deviation of each other and thus very comparable (Hankin et al. 2001).

Weight Change: Weight change for each individual was determined using self-reported weight at the baseline (1993-1998) and follow-up interviews (1999-2004). The weight change of individuals was categorized into five categories for the multivariable analyses based on the distribution of weight change in our population. The categories were weight loss of greater than 5 kilograms, weight loss between 3 and 5 kilograms, no weight change (weight loss of 2 kilogram or weight gain of 2 kilogram, reference category), weight gain between 3 and 5 kilograms, and weight gain greater than 5 kilograms. Women with imputed or missing weights at baseline and women with missing weights at follow-up were excluded from these analyses (n=4012, 16.6%).

Tea: Subjects were asked in the FFQ to identify their intake frequency, in cups consumed, of green and black tea separately over the past 12 months from nine predefined responses: never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day, and 6 or more times a day. For these

analyses, subjects reporting being never or hardly ever drinkers were categorized as nondrinkers, those reporting 1-3 times a month were categorized as monthly drinkers, 1-6 times a week were categorized as weekly drinkers, and those reporting 1-6 times a day were categorized as daily drinkers.

Soy: Information on the seven common fermented soy products (food and drinks) in the Singapore Chinese diet was obtained using the FFQ. Total soy intake (combining information on the seven soy products) was expressed using three different metrics: total soy foods per day (equivalent amounts of tofu and soybean drink; energy adjusted; g/Kcal), total soy protein per day (presented as percent of total protein), and total isoflavones per day (energy adjusted; mg/Kcal) (Wu et al. 2002). Equivalent amounts of tofu and soybean drink per day were calculated to facilitate comparison with a known dietary item while taking into account the varying water contents across the seven soy foods. The total soy foods intake for each subject was estimated as the summation of all foods expressed in units of plain tofu and soybean drink equivalent. Total soy protein intake per day was calculated using the Singapore Food Composition Table, as previously described (Hankin et al, 2001). Total soy isoflavone intake per day was estimated from the summation of the genistein, daidzein, and glycitein contents that had previously been measured in samples of common soy foods in Singapore (Hankin et al. 2001). The soy variables were assessed using quartiles (sex-specific, energy adjusted) determined by the total baseline cohort population (covariate assessment) and median values for the entire baseline cohort (interaction assessment).

Covariate Assessment: Covariates that were assessed for inclusion as potential confounders in the multivariable models were age at baseline interview (years, assessed continuously), year of baseline interview (1993–1995, 1996–1998), dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary), body mass index (BMI) (kg/m^2, assessed continuously and as quartiles based on the total population), moderate physical activity (none, 0.5-3 hours/week, ≥4 hours/week), smoking (current/former [defined as

smoking at least one cigarette a day for a year or longer], never), alcohol intake (drinker [defined as monthly, weekly, or daily], nondrinker), weekly vitamin/mineral supplement use (yes, no), and family history of breast cancer (yes, no). Reproductive factors that were also assessed for potential confounding were age at regularity (never regular, ≥17, 15-16, 13-14, <13 years), age at first menarche (≥17, 15-16, 13-14, <13), age at first birth (nulliparous, ≥31, 26-30, 21-25, ≤20 years), number of full term births (0, 1-2, >3), and postmenopausal hormone use (no, yes). Along with green tea intake and soy food intake (described above), omega-3 fatty acid intake was evaluated as a covariate (sex-specific, energy adjusted intake evaluated as quartiles based on the entire baseline cohort).

Statistical Analyses: Descriptive analyses for risk factors and potential confounders of interest were performed. Hazard ratios (HRs) for breast cancer and their corresponding 95% confidence intervals for self-reported diabetes were calculated using Cox proportional hazards regression methods. Model assumptions were evaluated using time dependent variables and Kaplan-Meier Curves. The non-informative censoring assumption is satisfied due to the cohort study design. Person-years of follow-up were enumerated from the date of the follow-up interview to the date of diagnosis of breast cancer, death, migration out of Singapore, or December 31, 2007, whichever occurred first.

For the main analyses evaluating the association between weight change and breast cancer risk, three adjusted models were evaluated. The base model was adjusted for age, date of baseline interview, and father's dialect. The second model additionally adjusted for baseline lifestyle and reproductive characteristics (BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, and postmenopausal hormone use). The final model additionally adjusted for dietary variables (sex-specific, energy-adjusted omega-3 fatty acid intake [quartiles], sex-specific, energy-adjusted total soy food intake [quartiles], and green tea intake) that have been shown to be associated with breast cancer in the Singapore Chinese Health Study (Gago-Dominguez et al. 2003; Wu et al. 2008; Yuan et al. 2005).

Interaction terms between weight change and soy and green tea intake were introduced into the model to assess potential additive and multiplicative effect modification. Weight change (weight gain less than or equal to 2 kilograms and weight gain greater than or equal to 3 kilograms), soy (based on the median value of the baseline cohort for the soy variables), and green tea intake (daily, weekly, monthly and nondrinker) were dichotomized. Models assessing the interaction between diabetes and soy variables/green tea intake were adjusted for age, baseline interview date, and dialect. A p-value for interaction was used to evaluate the multiplicative interaction. The relative excess risk for interaction (RERI) was used to evaluate additive interaction (Rothman 2008).

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). All p-values were two-sided and were considered statistically significant if $p < 0.05$ ($p < 0.10$ for interaction terms).

As a sensitivity analysis we included premenopausal women; additionally, we included women who had imputed weights at baseline to determine the impact of inclusion of all women in the Singapore Chinese Health Study on the association between weight change and breast cancer. Furthermore, we conducted a sensitivity analysis after removing the first two years of follow-up from all subjects in the study. We also performed a sensitivity analysis with different categories of weight change (≥10 kg loss, 5-9 kilogram loss, 2-4 kilogram loss, loss or gain of <2. kilogram (referent), 2-4 kilogram gain, 5-9 kilogram gain, and ≥10 kilogram gain) based on weight change categories that have been previously used (Eliassen et al. 2006). In order to determine the impact of adjusting for BMI, we conducted a sensitivity analysis without BMI as a covariate.

Results

At baseline interview, women evaluated in these analyses had a mean age of 55.8 years (standard deviation [SD] =7.3 years) (Table 7). The majority of women (n=9,602) reported no weight change (weight loss or gain of less than or equal to 2 kilograms), which served as the

reference group for these analyses (Table 7). Women in the various weight change categories (weight loss of greater than 5 kilograms, weight loss between 3 and 5 kilograms, no weight change, weight gain between 3 and 5 kilograms and weight gain greater than 5 kilograms) did not vary meaningfully with respect to baseline characteristics. Women with greater weight loss had higher baseline weights, while women with greater weight gain had higher follow-up weights (Table 7). Women with imputed weights at baseline did not differ with respect to demographic characteristics when compared to women in these analyses.

Through December 31, 2007, an average of 6.4 years (SD = 3.8 years) after the follow-up interview, 267 postmenopausal women had developed breast cancer. The average age at diagnosis was 65.3 years (SD = 8.0). Increasing education, increasing BMI, earlier age at first birth, decreased parity, and postmenopausal hormone use were associated with an increased risk of breast cancer among postmenopausal women in univariate analyses (Table 8).

After adjusting for age, baseline interview, and dialect, we did not observe an increase in breast cancer risk with weight gain compared to little or no weight gain/loss among postmenopausal women in the Singapore Chinese Health Study (Table 9). We did observe a suggestive increase in risk in relation to a weight loss of 3 to 5 kilograms compared to little or no weight gain or loss (HR=1.31, 95% CI: 0.94, 1.83) (Table 9). Further adjustment for additional baseline characteristics and dietary variables did not meaningfully change the results (Table 9, Models 2 and 3).

The median baseline intake of soy food was 60.4 g/1000 Kcal. At baseline, 60.9% of women reported no consumption of green tea and only 10.5% of women reported consuming green tea daily. There was no evidence of interaction on the multiplicative or scale for intake of soy or green tea (Table 10), with the p for interactions for weight gain and soy food intake, soy protein intake, soy isoflavones intake, and green tea intake being 0.43, 0.45, 052, and 0.66, respectively. Additionally, the RERI values for weight gain and soy food intake, soy protein intake, soy isoflavones intake, and green tea intake (-0.25, 0.23, -0.20, and 0.13 respectively)

did not indicate evidence of interaction on the additive scale.

The results did not meaningfully change when including premenopausal women, when including women who had imputed weights at baseline, when removing the first two years of follow-up from the analyses, or when evaluating different categories of weight change based on the literature (Appendix C).

Discussion

Among women in the Singapore Chinese Health Study, we did not observe an association between weight change from baseline to follow-up interviews and risk of breast cancer. Furthermore, we did not observe evidence of interaction of soy or green tea intake with weight change on the risk of breast cancer.

Previous studies have reported a positive association between weight gain and breast cancer risk (Eliassen et al. 2006; Lahmann et al. 2005; Ziegler et al. 1996). These studies, however, differed from our study with respect to stratifying variables and study designs. A population based case-control study among Asian-American women reported that 50 year old women gaining more than or equal to 11 pounds in the previous decade had a greater than two-fold increase in breast cancer risk when compared to women who had no weight change (RR=2.26, 95% CI: 1.21, 4.21) (Ziegler et al. 1996). In the Nurses' Health Study, a prospective cohort with more than twenty years of follow-up, women who gained more than or equal to 10 kg since menopause had an increased risk of breast cancer when compared to women who had no weight change (RR=1.18, 95% CI 1.03-1.35); weight reduction was inversely associated with breast cancer risk when comparing women who lost more than 10 kg since menopause to women who had no weight change (RR=0.43, 95% CI: 0.21, 0.86) (Eliassen et al. 2006). We did not have the power to investigate more refined categories of weight change similar to Eliassen et al. (2006) for our primary analyses. We observed an association contrary to the hypothesized direction, with women losing between 3 and 5 kilograms between baseline and follow-up interviews demonstrating a suggestive increased risk for breast cancer (HR=1.31, 95% CI: 0.94,

1.83). Although reverse causation may have influenced the positive observed association between weight loss and breast cancer risk (i.e., a woman in early stages of breast cancer but not yet diagnosed may lose weight), we observed similar results after removing the first two years of follow-up. The differences in the results observed between the current study and what has previously been reported may be a consequence of varying lengths of follow-up, as well as differences in baseline characteristics of the study populations. The length of follow-up for the current study was rather short when compared to the long follow-up in the Nurses' Health Study (Eliassen et al. 2006). The average baseline age of the women was comparable between the current study and that of the Nurses' Health Study (Eliassen et al. 2006); however, the women evaluated in the population based case-control study by Ziegler et al. (1996) were much younger than the current study (age range between 20 and 55 years). Additionally, the current study is the first prospective evaluation of the association between weight change and breast cancer among Asian women living in an Asian country; it is likely that modernization and uptake of Western lifestyle of women in the Singapore Chinese Health Study is not as extensive as the Westernization of the Asian-American women examined in the study by Ziegler et al. (1996).

There was no evidence of interaction between weight gain and soy or green tea intake in this population. To our knowledge, this is the first prospective study evaluating the effect modification of dietary variables on the association between weight gain and breast cancer. Statistical power was likely limited when evaluating the effect modification by soy variables and green tea intake on the association between weight gain and breast cancer. Additionally, the evaluation may have been limited by low variation in intake, particularly for green tea.

In addition to limited power, there were several limitations of this study. Weight at baseline and follow-up were self-reported. Weight is often underreported, which may have introduced measurement error in this study. We decided to exclude individuals with imputed weight at baseline from the primary analysis to decrease the potential for measurement error. The prospective study design, however, allows for the measurement of exposure (weight

change from baseline to follow-up interviews) to occur before the cancer diagnosis. Therefore, it is likely that any potential measurement error would result in non-differential misclassification; the direction of the bias with multiple categories of weight change cannot be predicted. Additionally, given the short follow-up time for this study, the association between weight change and breast cancer should be re-evaluated after a longer period of follow-up.

The baseline questionnaire gathered information on lifestyle factors such as physical activity, alcohol use, and smoking status, which may be confounders of the association between type II diabetes and breast cancer; these variables, however, were only assessed at baseline. Although alcohol use and cigarette smoking have been implicated as being associated with breast cancer risk (American Cancer Society 2006), there were no associations between these variables and breast cancer risk when a univariate assessment was performed within our study. Although there were only a small proportion of women who consume alcohol and smoke in this population, crude classification of confounding variables may result in residual confounding. It is also possible that other confounding variables such as adiposity, mammographic density, and other environmental exposures that may contribute to breast cancer risk were unmeasured in this cohort and therefore cannot be assessed in this study.

There are several strengths of the study. To our knowledge, this is the first prospective evaluation of weight change and breast cancer risk among an Asian population that is a typically leaner than Western populations. The Singapore Chinese Health Study is a well-established prospective cohort study. Because of the cohort study design, it is unlikely that a selection bias occurred in this study. Loss of follow-up in this cohort is minimal, with less than 1% of individuals of the cohort being lost to migration, and the response rate in the cohort is very high. The food frequency questionnaire used for these analyses was developed for and validated in the study population (Hankin et al. 2001). Additionally, urinary biomarkers of soy intake were assessed in the Singapore Chinese Health Study; self-reported dietary soy intake was validated with urinary isoflavone levels (Seow et al. 1998). Finally, breast cancer case ascertainment is

considered to be complete within the Singapore Chinese Health Study due to the nation-wide cancer registry in place in Singapore.

Conclusions: We did not observe an association between weight change and risk of breast cancer among postmenopausal women in the Singapore Chinese Health Study; furthermore, our results did not indicate evidence of effect modification by soy or green tea on the weight change and breast cancer association.

Table 7: Baseline* Characteristics by Weight Change from Baseline to Follow-up among Postmenopausal Women in the Singapore Chinese Health Study (n=20163)

	Weight loss >-5 kg	Weight loss -3 to -5 kg	-2 to 2 kg	Weight gain 3 to 5 kg	Weight gain >5 kg
No. of Subjects	2343	2938	9602	2988	2292
Age, years, mean (SD)	57.9 (7.6)	56.2 (7.3)	55.4 (7.1)	55.0 (7.1)	55.9 (7.5)
Age, years					
≤49	390 (16.7)	636 (21.7)	2380 (24.8)	811 (27.1)	564 (24.6)
50-54	478 (20.4)	724 (24.6)	2525 (26.3)	780 (26.1)	568 (24.8)
55-60	696 (29.7)	839 (28.6)	2700 (28.1)	791 (26.5)	611 (26.7)
≥61	779 (22.3)	739 (25.2)	1997 (20.8)	606 (20.3)	549 (24.0)
Dialect group (%)					
Hokkien	1184 (50.5)	1491 (50.8)	4904 (51.1)	1477 (49.4)	971 (42.4)
Cantonese	1159 (49.5)	1447 (49.2)	4698 (48.9)	1511 950.6)	1321 (57.6)
Education					
No formal	1059 (45.2)	1068 (36.4)	3054 (31.8)	963 (32.2)	990 (43.2)
Primary	907 (38.7)	1281 (43.6)	4123 (42.9)	1232 (41.2)	892 (38.9)
≥ Secondary	377 (16.1)	589 (20.1)	2425 (25.3)	793 (26.5)	410 (17.9)
BMI, kg/m^2, mean (SD)	25.5 (4.5)	23.7 (3.5)	22.9 (3.3)	22.6 (3.4)	22.2 (3.4)
BMI, kg/m^2					
<20	149 (6.4)	372 (12.7)	1786 (18.6)	678 (22.7)	605 (26.4)
20-24	752 (32.1)	1304 (44.4)	4549 (47.4)	1368 (45.8)	1075 (46.9)
24-28	894 (38.2)	931 (31.7)	2543 (26.5)	730 (24.4)	485 (21.2)
>28	548 (23.4)	331 (11.3)	724 (7.5)	212 (7.1)	127 (5.5)
Cigarette Smoking					
Never	2120 (90.5)	2693 (91.7)	8968 (93.4)	2783 (93.1)	2074 (90.5)
Ever	223 (9.5)	245 (8.3)	634 (6.6)	205 (6.9)	218 (9.5)
Moderate Physical Activity					
None	1893 (79.5)	2253 (76.7)	7340 (76.4)	2278 (76.2)	1898 (82.8)
30 minute-3 hours/week	302 (12.9)	443 (15.1)	1375 (14.3)	434 (14.5)	243 (10.6)
>3 hours/week	178 (7.6)	242 (8.2)	887 (9.2)	276 (9.2)	151 (6.6)

Weekly Vitamin/Mineral Supplement Use					
No	2200 (93.9)	2711 (92.3)	8618 (89.8)	2735 (91.5)	2140 (93.3)
Yes	143 (6.1)	227 (7.7)	984 (10.2)	253 (8.5)	152 (6.6)
Alcohol Use					
Never	2247 (95.9)	2808 (95.6)	9149 (95.3)	2846 (95.3)	2189 (95.5)
Ever	96 (4.1)	130 (4.4)	453 (4.7)	142 (4.7)	103 (4.5)
Age at Regularity, years (missing=3)					
< 13	258 (11.0)	353 (12.0)	1295 (13.5)	400 (13.4)	235 (10.3)
13-14	847 (36.2)	990 (33.7)	3345 (34.8)	1058 (35.4)	755 (33.0)
15-16	789 (22.7)	1044 (35.5)	3202 (33.4)	1012 (33.9)	854 (37.3)
≥17	375 (16.0)	451 (15.4)	1434 (14.9)	427 (14.3)	381 (16.6)
Never Regular	73 (3.1)	100 (3.4)	325 (3.4)	91 (3.1)	66 (2.9)
Age at first menarche, years (missing=3)					
< 13	306 (13.1)	417 (14.1)	1505 (15.7)	464 (15.5)	284 (12.4)
13-14	947 (40.4)	1096 (37.3)	3677 (38.3)	1164 (39.0)	864 (37.7)
15-16	800 (34.2)	1065 (36.3)	3294 (34.3)	1012 (33.9)	846 (36.9)
≥17	289 (12.3)	360 (12.3)	1125 (11.7)	348 (11.7)	297 (13.0)
Age at First Birth, years (missing=17)					
≤20	505 (21.6)	512 (17.4)	1556 (16.2)	546 (18.3)	494 (21.6)
21-25	886 (37.9)	1173 (39.9)	3658 (38.1)	1131 (37.9)	911 (39.8)
26-30	563 (24.1)	783 (26.7)	2736 (28.5)	782 (26.2)	541 (23.7)
≥31	225 (9.6)	285 (9.7)	968 (10.1)	307 (10.3)	206 (9.0)
Nulliparous	161 (6.9)	185 (6.3)	675 (7.0)	221 (7.4)	136 (5.9)
Ever Postmenopausal Hormone Use (missing=323)					
No	2136 (92.4)	2547 (87.9)	7965 (84.5)	2482 (84.3)	1995 (88.5)
Yes	176 (7.6)	352 (12.1)	1467 (15.5)	462 (15.7)	258 (11.5)
Number of Full Term Births					
≥3	1595 (68.1)	1964 (66.9)	5992 (62.4)	1861 (62.3)	1591 (69.4)
1-2	587 (25.1)	789 (26.9)	2935 (30.6)	906 (30.3)	565 (24.7)
0	161 (6.9)	185 (6.3)	675 (7.0)	221 (7.4)	136 (5.9)
Family History of Breast Cancer					

No	2318 (98.9)	2902 (98.8)	9439 (98.3)	2943 (98.5)	2270 (99.0)
Yes	25 (1.1)	36 (1.2)	163 (1.7)	45 (1.5)	22 (1.0)
Breast Cancer					
No	2317 (98.9)	2890 (98.4)	9482 (98.8)	2946 (98.6)	2261 (98.7)
Yes	26 (1.1)	48 (1.6)	120 (1.2)	42 (1.4)	31 (1.3)
Baseline Weight, Mean (SD)	61.4 (10.8)	56.9 (8.6)	55.2 (8.5)	54.5 (8.7)	53.6 (8.8)
Follow-up Weight, Mean (SD)	51.2 (9.0)	53.0 (8.7)	55.2 (8.5)	58.4 (8.8)	63.5 (9.7)

*All characteristics were from the baseline interview except for postmenopausal hormone use, which was from the follow-up interview.

BMI=Body Mass Index
SD=Standard Deviation

Table 8: Hazard Ratios (HR) of Study Population Characteristics in relation to Breast Cancer after Follow-up among Postmenopausal Women in the Singapore Chinese Health Study (n=20163)

	Cases, n	HR (95% CI)
Age, years		
≤49	66	1.00 (reference)
50-54	76	1.08 (0.77, 1.49)
55-60	65	0.84 (0.60, 1.19)
≥61	60	0.99 (0.70, 1.41)
Dialect group		
Hokkien	142	1.00 (reference)
Cantonese	125	0.77 (0.61, 0.98)
Education		
No formal	77	1.00 (reference)
Primary	116	1.31 (0.98, 1.75)
Secondary +	74	1.58 (1.15, 2.18)
BMI, kg/m^2		
<20	35	1.00 (reference)
20-24	115	1.28 (0.88 1.88)
24-28	87	1.58 (1.07, 2.35)
>28	30	1.62(0.99, 2.63)
Smoking Status		
Never	247	1.00 (reference)
Ever	20	1.01 (0.64, 1.59)
Any Weekly Moderate Physical Activity		
None	210	1.00 (reference)
30 minute-3 hours/week	34	0.88 (0.62, 1.27)
>3 hours/week	23	0.92 (0.60, 1.41)
Weekly Vitamin/Mineral Supplement Use		
No	233	1.00 (reference)
Yes	34	1.44 (1.05, 2.35)
Alcohol Intake		
Never	259	1.00 (reference)
Ever	8	0.66 (0.33, 1.33)
Age at Regularity, years (missing=3)		
< 13	36	1.00 (reference)
13-14	102	0.97 (0.67, 1.42)
15-16	89	0.84 (0.57, 1.23)
≥17	35	0.75 (0.47, 1.20)
Never Regular	5	0.53 (0.21, 1.35)
Age at first menarche (missing=3)		
< 13	40	1.00 (reference)
13-14	110	1.00 (0.70, 1.43)

15-16	91	0.90 (0.62, 1.30)
≥17	26	0.75 (0.46, 1.23)
Age at First Birth, years (missing=17)		
≤20	36	1.00 (reference)
21-25	77	1.00 (0.67, 1.48)
26-30	89	1.69 (1.15, 2.48)
≥31	34	1.74 (1.09, 2.79)
Nulliparous	31	2.36 (1.46, 3.81)
Ever Postmenopausal Hormone Use (missing=323)		
No	221	1.00 (reference)
Yes	52	1.61 (1.19, 2.18)
Number of Full Term Births		
≥3	146	1.00 (reference)
1-2	90	1.44 (1.11, 1.87)
0	31	2.10 (1.43, 3.09)
Family History of Breast Cancer		
No	264	1.00 (reference)
Yes	3	0.84 (0.27, 2.63)

HR=Hazard Ratio
95% CI=95% Confidence Interval

Table 9: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in Relation to Breast Cancer Risk among Postmenopausal Women in the Singapore Chinese Health Study (n=20163)

Weight Change	Cases, n	HR (95%CI)*	HR (95%CI) [#]	HR (95%CI) [¥]	HR (95%CI) [##]	HR (95%CI) [¥¥]
<-5 kg	26	0.90 (0.59, 1.37)	0.80 (0.52, 1.25)	0.80 (0.52, 1.25)	0.93 (0.60, 1.42)	0.92 (0.60, 1.41)
-3 to -5 kg	48	1.31 (0.94, 1.83)	1.30 (0.93, 1.82)	1.29 (0.92, 1.81)	1.35 (0.97, 1.89)	1.34 (0.96, 1.87)
-2 to 2 kg	120	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3 to 5 kg	42	1.12 (0.79, 1.59)	1.13 (0.80, 1.61)	1.13 (0.80, 1.61)	1.12 (0.79, 1.59)	1.12 (0.79, 1.59)
>5 kg	31	1.09 (0.73, 1.61)	1.18 (0.79, 1.75)	1.17 (0.79, 1.75)	1.13 (0.76, 1.69)	1.13 (0.76, 1.68)

*Model 1 adjusted for age, baseline interview date, and dialect

[#]Model 2 adjusted for age, baseline interview date, dialect, menopausal status, BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, hormone use

[¥]Model 3 adjusted for age, baseline interview date, dialect, menopausal status, BMI, moderate physical activity, education, family history of breast cancer, age at regularity, parity, hormone use, energy adjusted omega-3 intake, energy adjusted soy food intake, and green tea intake

[##]Model 2 adjusted for age, baseline interview date, dialect, menopausal status, moderate physical activity, education, family history of breast cancer, age at regularity, parity, hormone use

[¥¥]Model 3 adjusted for age, baseline interview date, dialect, menopausal status, moderate physical activity, education, family history of breast cancer, age at regularity, parity, hormone use, energy adjusted omega-3 intake, energy adjusted soy food intake, and green tea intake

Table 10: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Joint Effects of Dietary Soy/Green Tea Intake and Weight Change among Postmenopausal Women in the Singapore Chinese Health Study (n=20163)

	n	HR (95% CI)*
Soy Food (g/1000Kcal)		
> Median (60.4)		
No Weight Gain and Weight Loss	88	1.00 (reference)
Weight Gain ≥3kg	38	1.19 (0.81, 1.74)
< Median (60.4)		
No Weight Gain and Weight Loss	106	1.25 (0.94, 1.66)
Weight Gain ≥3kg	35	1.19 (0.81, 1.76)
p for interaction		0.43
RERI		-0.25 (-2.62, 2.13)
Soy Protein (%total protein)		
> Median (2.3)		
No Weight Gain and Weight Loss	88	1.00 (reference)
Weight Gain ≥3kg	37	1.18 (0.80, 1.73)
< Median (2.3)		
No Weight Gain and Weight Loss	106	1.19 (0.90, 1.58)
Weight Gain ≥3kg	36	1.14 (0.77, 1.68)
p for interaction		0.45
RERI		-0.23 (-2.51, 2.04)
Soy Isoflavones (mg)		
> Median (9.8)		
No Weight Gain and Weight Loss	85	1.00 (reference)
Weight Gain ≥3kg	36	1.17 (0.79, 1.72)
< Median (9.8)		
No Weight Gain and Weight Loss	109	1.35 (1.02, 1.80)
Weight Gain ≥3kg	37	1.32 (0.90, 1.94)
p for interaction		0.52
RERI		-0.20 (-2.82, 2.42)
Green Tea		
Drinker		
No Weight Gain and Weight Loss	79	1.00 (reference)
Weight Gain ≥3kg	30	1.14 (0.75, 1.74)
Nondrinker		
No Weight Gain and Weight Loss	115	0.97 (0.73, 1.29)
Weight Gain ≥3kg	43	0.98 (0.67, 1.42)
p for interaction		0.66
RERI		-0.13 (-2.09, 1.83)

*Adjusted for age, baseline interview date, and dialect

HR=Hazard Ratio
95% CI=95% Confidence Interval

Chapter 7: Summary and Conclusions

Modifiable lifestyle factors that include diet, diabetes, and weight change may influence endogenous hormone levels and may directly or indirectly influence risk of breast cancer (Chacko et al. 2010; Kaaks 1996; Kwon et al. 2010). Although the literature on the complex relationships between these modifiable risk factors is expanding, there are only a few studies that have focused on the evaluation of these modifiable risk factors among Asian populations (Jee et al. 2005; Khan et al. 2006). Asian populations generally differ from Western populations with respect to modifiable risk factors like diet, diabetes prevalence, and weight/weight change over time (Institute for Health Metrics and Evaluation 2013; Lee 2000; Seow et al. 2006). Although Asian populations have traditionally had lower breast cancer rates, these populations have recently experienced a rapid increase in chronic diseases, particularly in type II diabetes (assessed as both an outcome and a risk factor in this dissertation) and breast cancer (Lee 2000; Seow et al. 2004). Therefore, the multifaceted associations between diet, type II diabetes, weight change, and breast cancer risk were examined among participants of the Singapore Chinese Health Study.

Together, the results of this dissertation suggest that soy components, particularly soy protein and soy isoflavones may play a beneficial role in the prevention and progression of type II diabetes and breast cancer. Among the various aims of this dissertation, either total soy protein or soy isoflavones intake was shown to be beneficial with different outcomes assessed; increased soy protein intake was beneficial with respect to HbA1c levels (as a marker for diabetes/prediabetes), while increased soy isoflavone intake was beneficial when evaluating the interaction of dietary variables on the type II diabetes and breast cancer association (i.e. a slightly stronger association between type II diabetes and breast cancer was observed among women with lower isoflavone intake when compared to those with higher isoflavone intake). These results may indicate the beneficial role of individual soy components as opposed to soy

food intake. Due to the observational nature of this study, it is not known if the beneficial effects of the various soy components are biologically relevant. An explanation for the beneficial effects of soy components may be that they are measured with less error than soy food intake; alternatively, individual soy components may be more correlated with other unmeasured variables, which may have resulted in the beneficial observed effects. More research of the experimental nature is needed to determine if different soy components are more beneficial than others.

Evaluating the associations between soy and green tea intake and HbA1c levels, a clinically relevant biomarker for diabetes, was valuable in determining the potential impact of specific dietary components on the progression of type II diabetes. Although we found statistically significant results for the effects of diet on HbA1c levels in an apparently healthy subset of self-reported nondiabetic subjects of the SCHS, the clinical relevance of the small observed changes in HbA1c levels needs to be further assessed.

Evaluating soy intake among participants in the Singapore Chinese Health study was advantageous because of the detailed dietary information that allowed for the evaluation of several specific components of soy intake within the cohort. Intake of soy among Singapore Chinese Health Study participants was comparable to soy intake among Asian-American populations (Wu et al. 2008) and less than soy intake of Chinese populations living in China (Lee et al. 2009). Although this study may not be generalizable to non-Asian Western populations, it may provide an estimate of the association between soy consumption and chronic disease risk that is between Chinese populations living in China and Asian-American populations. More research among populations with varying levels of soy intake is warranted.

Although green tea intake among participants of the Singapore Chinese Health Study is more than those of Western populations, there were a large percentage of participants in this study who reported not drinking green tea. Therefore, we may have had limited power to assess

interactions by varying levels of green tea intake.

Evaluation of risk factors (type II diabetes and weight change) for breast cancer among an Asian population that does not have type II diabetes prevalence rates and weight changes as large as Western populations was difficult due to limited power. However, evaluating the associations between diabetes/weight change and breast cancer risk and the effect modification of dietary variables (soy and green tea intake) on these associations in a primarily Asian population were novel and provided insight into the interplay between modifiable risk factors for breast cancer. Although power was limited in these analyses, the Singapore Chinese Health Study cohort has been followed through 2013; planned inclusion of additional breast cancer cases through December 31, 2013 may result in increased power to detect associations of type II diabetes/weight change on breast cancer risk.

Overall, there was suggestive evidence indicating the beneficial effects of soy intake with respect to diabetes and breast cancer among women in the Singapore Chinese Health Study. There was suggestive evidence that soy protein intake was associated with decreased HbA1c levels among self-reported nondiabetic women. Additionally, our prospective data suggested that soy isoflavone intake may modify the association between type II diabetes and breast cancer risk. More research is needed to determine the beneficial effects of different soy components.

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Appendix A: Selected Dietary Variables and HbA1C Levels among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

We performed the statistical analysis described above among postmenopausal women only and nonsmokers only. We also examined models for each dietary variable of interest further adjusted for the other dietary variables of interest, as well as for total carbohydrate intake, total protein intake, total caffeine intake, black tea intake, and the meat-dim sum dietary pattern. We also conducted analyses excluding individuals with HbA1c levels in the diabetic range (i.e. HbA1c levels ≥ 6.5%). Additionally, HbA1c levels were assessed based as categorical variables based on diagnostic cut-points (nondiabetes: HbA1c levels ≤5.7%, prediabetes: HbA1c levels 5.8%-6.4%, diabetes: HbA1c levels ≥6.5%) (American Heart Association 2012) using logistic regression.

Table A1: Baseline Characteristics of Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	Overall (n=3558)	Premenopausal (n=826)	Postmenopausal (n=2732)
Age, years, mean ± SD	56.7 ± 7.4	48.3 ± 2.9	5929 ± 6.4
BMI, kg/m^2, mean ± SD	22.9 ± 3.2	22.1 ± 2.8	23.1 ± 3.3
Education, n (%)			
No formal education	1,287 (36.2)	127 (15.4)	1,160 (42.5)
Primary	1,432 (40.3)	346 (41.9)	1,086 (39.8)
≥ Secondary	839 (23.6)	353 (42.7)	486 (17.8)
Physical activity (moderate), n (%)			
None	2,794 (78.5)	659 (79.8)	2,135 (78.2)
30 minutes-3hours/week	471 (13.2)	130 (15.7)	341 (12.5)
>3hours/week	293 (8.2)	37 (4.5)	256 (9.34
Menopausal Status			
Premenopausal	826 (23.2)		
Postmenopausal	2,732 (76.8)		
Alcohol use (ever), n (%)	185 (5.2)	41 (5.0)	144 (5.3)
Cigarette Smoking (ever), n (%)	292 (8.2)	11 (1.3)	281 (10.3)
Weekly Vitamin Use			
No	3,222 (90.6)	745 (90.2)	2,477 (90.7)
Yes	336 (9.4)	81 (9.8)	255 (9.3)
Soy foods, mean (SD)	76.7 (53.3)	82.4 (55.4)	75.0 (52.6)
Soy foods			
< Median	1,598 (44.9)	330 (40.0)	1,268 (46.4)
≥ Median	1,960 (55.1)	496 (60.0)	1,464 (53.6)
Soy isoflavones, mg	13.0 (9.9)	14.0 (10.1)	12.7 (9.7)
Soy isoflavones, n (%)			
< Median	1,582 (44.5)	329 (39.8)	1253 (45.9)
≥ Median	1,976 (55.5)	497 (60.2)	1479 (54.1)
Green Tea Intake			
None	2,228 (62.2)	506 (61.3)	1,722 (63.0)
Monthly	387 (10.9)	91 (11.0)	296 (10.8)
Weekly	606 (17.0)	158 (19.1)	448 (16.4)
Daily	337 (9.5)	71 (8.6)	266 (9.7)
Green Tea Intake			
Nondrinker	2,228 (62.6)	506 (61.3)	1,722 (63.0)
Drinker	1,330 (37.4)	320 (38.7)	1,010 (37.0)
Black Tea Intake			
None	2,455 (69.0)	526 (63.7)	1,929 (70.6)
Monthly	295 (8.3)	78 (9.4)	217 (7.9)
Weekly	522 (14.7)	137 (16.6)	385 (14.1)
Daily	286 (8.0)	85 (10.3)	201 (7.4)

Black Tea Intake			
Nondrinker	2,455 (69.0)	526 (63.7)	1,929 (70.6)
Drinker	1,103 (31.0)	300 (36.3)	803 (29.4)
VFS			
1	747 (21.0)	144 (17.4)	603 (22.1)
2	925 (26.0)	218 (26.4)	707 (25.9)
3	949 (26.7)	215 (26.0)	734 (26.9)
4	937 (26.3)	249 (30.2)	688 (25.1)
MDS			
1	903 (25.4)	148 (17.9)	755 (27.6)
2	892 (25.1)	185 (22.4)	707 (25.9)
3	923 (25.9)	241 (29.2)	682 (25.0)
4	840 (23.6)	252 (30.5)	588 (21.5)
HbA1c (%)	5.8 ± 0.6	5.7 ± 0.6	5.8 ± 0.6
HbA1c (%), diabetic status			
Normal (≤5.7%)	1,970 (55.4)	517 (62.6)	1,453 (53.2)
Prediabetes (5.8-6.5%)	1,413 (39.7)	283 (34.3)	1,130 (41.4)
Diabetes (≥6.6%)	175 (4.9)	26 (3.2)	149 (5.5)
HbA1c (%), median			
≤ Median (5.7)	1,970 (55.4)	517 (62.6)	1,453 (53.2)
> Median	1,588 (44.6)	309 (37.4)	1,279 (46.8)

SD=Standard Deviation

Table A2: Baseline Characteristics by Quartiles (Q) of Soy Intake for Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	Q1	Q2	Q3	Q4	p-value
No. of Subjects	736 (20.7)	822 (23.1)	959 (27.0)	1,041 (29.3)	<0.001
Age, years, mean (SD)	58.5 (7.60	56.7 (7.6)	56.3 (7.2)	55.7 (7.1)	
Age, years					<0.001
≤50	124 (16.9)	219 (26.6)	239 (24.9)	287 (27.6)	
51-55	159 (21.6)	176 (21.4)	230 (24.0)	267 (25.7)	
56-61	184 (25.0)	194 (23.6)	255 (26.6)	243 (23.3)	
62-74	269 (36.6)	233 (28.4)	235 (24.50	244 (23.4)	
Dialect group (%)					0.05
Hokkiens	409 (55.6)	447 (54.4)	490 (51.1)	517 (49.7)	
Cantonese	327 (44.4)	375 (45.6)	469 (48.9)	524 (50.3)	
Highest level of education					<0.001
No formal education	311 (42.5)	302 (36.7)	333 (34.7)	341 (32.8)	
Primary	294 (40.0)	315 (38.3)	398 (41.5)	425 (40.8)	
≥ Secondary	131 (17.8)	205 (24.9)	228 (23.8)	275 (26.4)	
BMI (kg/m^2), mean (SD)	23.2 (3.3)	22.8 (3.1)	22.8 (3.3)	23.0 (3.0)	
BMI (kg/m^2), %					0.31
<20	109 (14.8)	158 (19.2)	183 (19.1)	172 (16.5)	
20-24	398 (54.1)	429 (52.2)	518 (54.0)	564 (54.2)	
24-28	172 (23.4)	180 (21.9)	202 (21.1)	239 (23.0)	
>28	57 (7.7)	55 (6.7)	56 (5.8)	66 (6.3)	
Menopausal Status					<0.001
Still menstruating	130 (17.7)	192 (23.4)	238 (24.8)	266 (25.6)	
Postmenopausal	606 (82.3)	630 (76.6)	721 (75.2)	775 (74.4)	
Physical activity (moderate), n (%)					0.01
None	602 (81.8)	672 (81.7)	735 (76.6)	785 (75.4)	
30 minutes-3hours/week	86 (11.7)	91 (11.1)	135 (14.1)	159 (15.3)	
>3hours/week	48 (6.5)	59 (7.2)	89 (9.3)	97 (9.3)	
Smoking Status					<0.001
Never	641 (87.1)	758 (92.2)	890 (92.8)	977 (93.8)	
Ex/current	95 (12.9)	64 (7.8)	69 (7.2)	64 (6.2)	
Alcohol Intake					0.21
Never	687 (93.3)	786 (95.6)	910 (94.9)	990 (95.1)	
Ever	49 (6.7)	36 (4.4)	49 (5.1)	51 (4.9)	
Weekly Vitamin Use					0.25
No	680 (92.4)	736 (89.5)	867 (90.4)	939 (90.2)	
Yes	56 (7.6)	86 (10.5)	92 (9.6)	102 (9.8)	
Green Tea Intake					<0.001
Never	526 (71.5)	524 (63.8)	584 (60.9)	594 (57.1)	
Monthly	67 (9.1)	102 (12.4)	107 (11.2)	111 (10.7)	
Weekly	78 (10.6)	120 (14.6)	184 (19.2)	224 (21.5)	

Daily	65 (8.8)	76 (9.3)	84 (8.8)	112 (10.8)	
VFS					<0.001
1	297 (40.4)	202 (24.6)	141 (14.7)	107 (10.3)	
2	226 (30.7)	265 (32.2)	251 (26.2)	183 (17.6)	
3	145 (19.7)	208 (25.3)	294 (30.7)	302 (29.0)	
4	68 (9.2)	147 (17.9)	273 (28.5)	449 (43.1)	
Black Tea Intake					<0.001
Never	552 (75.0)	589 (71.7)	643 (67.1)	671 (64.5)	
Monthly	57 (7.7)	57 (6.9)	87 (9.0)	94 (9.0)	
Weekly	71 (9.7)	107 (13.0)	146 (15.2)	198 (19.0)	
Daily	56 (7.6)	69 (8.4)	83 (8.7)	78 (7.5)	
MDS					<0.001
1	253 (34.4)	237 (28.8)	189 (19.7)	224 (21.5)	
2	190 (25.8)	209 (25.4)	237 (24.7)	256 (24.6)	
3	171 (23.2)	194 (23.6)	266 (27.7)	292 (28.1)	
4	122 (16.6)	182 (22.1)	267 (27.8)	269 (25.8)	

Table A3: Baseline Characteristics by Frequency of Green Tea Intake among Self-Reported Nondiabetic Women of the Singapore Chinese Health Study

	Nondrinkers	Monthly	Weekly	Daily	p-value
No. of Subjects	2,228 (62.6)	387 (10.9)	606 (17.0)	337 (9.5)	<0.001
Age, years, mean (SD)	56.9 (7.4)	56.1 (7.4)	56.0 (7.5)	56.9 (7.3)	
Age, years					0.08
≤ 50	518 (23.3)	102 (26.4)	175 (28.9)	74 (22.0)	
51-55	518 (23.3)	93 (24.0)	135 (22.3)	86 (25.5)	
56-61	554 (24.8)	83 (21.5)	154 (25.4)	85 (25.2)	
62-74	638 (28.6)	109 (28.2)	142 (23.4)	92 (27.3)	
Dialect group (%)					<0.001
Hokkiens	1094 (49.1)	207 (53.5)	333 (54.9)	229 (67.9)	
Cantonese	1134 (50.9)	180 (46.5)	273 (45.1)	108 (32.1)	
Highest level of education					<0.001
No formal education	915 (41.1)	129 (33.3)	159 (26.2)	84 (24.9)	
Primary	860 (38.6)	162 (41.9)	258 (42.6)	152 (45.1)	
≥ Secondary	453 (20.3)	96 (24.8)	189 (31.2)	101 (30.0)	
BMI (kg/m^2), mean (SD)	22.9 (23.1)	23.0 (3.7)	23.0 (3.1)	23.3 (2.9)	
BMI (kg/m^2), %					<0.001
<20	408 (18.3)	72 (18.6)	101 (16.7)	41 (12.2)	
20-24	1211 (54.4)	203 (52.5)	323 (53.3)	172 (51.0)	
24-28	464 (20.8)	80 (20.7)	145 (23.9)	104 (30.9)	
>28	145 (6.5)	32 (8.3)	37 (6.1)	20 (5.9)	
Menopausal Status					0.26
Still menstruating	506 (22.7)	91 (23.5)	158 (26.1)	71 (21.1)	
Postmenopausal	1,722 (77.3)	296 (76.45	448 (73.9)	266 (78.9)	
Physical activity (moderate), n (%)					<0.001
None	1,801 (80.8)	310 (80.1)	422 (69.6)	261 (77.5)	
30 minutes-3hours/week	262 (11.8)	46 (11.9)	111 (18.3)	52 (15.4)	
>3hours/week	165 (7.4)	31 (8.0)	73 (12.1)	24 (7.1)	
Smoking Status					0.33
Never	2,031 (91.2)	357 (92.2)	564 (93.1)	314 (93.2)	
Ex/current	197 (8.8)	30 (7.8)	42 (6.9)	23 (6.2)	
Alcohol Intake					0.59
Never	2,119 (95.1)	366 (94.6	568 (93.7)	320 (95.0)	
Ever	109 (4.9)	21 (5.4)	38 (6.3)	17 (5.0)	
Weekly Vitamin Use					0.06
No	2,039 (91.5)	346 (89.4)	534 (88.1)	303 (89.9)	
Yes	189 (8.5)	41 (10.6)	72 (11.9)	34 (10.1)	
Soy food intake					<0.001
Q1	526 (23.6)	67 (17.3)	78 (12.9)	65 (19.3)	
Q2	524 (23.5)	102 (26.4)	120 (19.8)	76 (22.6)	
Q3	584 (26.2)	107 (27.6)	184 (30.4)	84 (24.9)	

Q4	594 (26.7)	111 (28.7)	224 (37.0)	112 (33.2)	
VFS intake					<0.001
1	556 (25.4)	61 (15.8)	71 (11.7)	49 (14.5)	
2	608 (27.3)	97 (25.1)	131 (21.6)	89 (26.4)	
3	567 (25.4)	112 (28.9)	176 (29.0)	94 (27.9)	
4	487 (21.9)	117 (30.2)	228 (37.6)	105 (31.2)	
Black Tea Intake					<0.001
Never	1,663 (74.6)	217 (56.1)	348 (57.4)	227 (67.4)	
Monthly	140 (6.3)	88 (22.7)	44 (7.3)	23 (6.8)	
Weekly	263 (11.8)	57 (14.7)	166 (27.4)	36 (10.7)	
Daily	162 (7.3)	25 (6.5)	48 (7.9)	51 (15.1)	
MDS					<0.001
1	615 (27.6)	82 (21.2)	134 (22.1)	72 (21.4)	
2	578 (25.9)	87 (22.5)	149 (24.6)	78 (23.2)	
3	572 (25.7)	97 (25.1)	159 (26.2)	95 (28.2)	
4	463 (20.8)	121 (31.3)	164 (27.1)	92 (27.3)	

Table A4: Baseline Characteristics by Vegetable-Fruit-Soy Intake among Self-Reported Nondiabetic Women of the Singapore Chinese Health Study

	1	2	3	4	p-value
No. of Subjects	747 (20.99)	925 (26.00)	949 (26.67)	937 (26.34)	<0.001
Age, years, mean (SD)	58.00 (7.56)	56.34 (7.31)	56.29 (7.19)	56.27 (7.48)	
Age, years					<0.001
≤ 50	141 (18.88)	236 (25.51)	243 (25.61)	249 (26.57)	
51-55	163 (21.82)	210 (22.70)	236 (24.87)	223 (23.80)	
56-61	193 (25.84)	241 (26.05)	233 (24.55)	209 (22.31)	
62-74	250 (33.47)	238 (25.73)	237 (24.97)	256 (27.32)	
Dialect group (%)					0.13
Hokkiens	364 (48.73)	484 (52.32)	508 (53.53)	507 (54.11)	
Cantonese	383 (51.27)	441 (47.68)	441 (46.47)	430 (45.89)	
Highest level of education					<0.001
No formal education	356 (47.66)	355 (38.38)	301 (31.72)	275 (29.35)	
Primary	281 (37.62)	352 (38.05)	420 (44.26)	379 (40.45)	
≥ Secondary	110 (14.73)	218 (23.57)	228 (24.03)	283 (30.20)	
BMI (kg/m2), mean (SD)	22.99 (3.00)	23.07 (3.16)	22.86 (3.19)	22.83 (3.36)	
BMI (kg/m^2), %					0.16
<20	118 (15.80)	143 (15.46)	179 (18.86)	182 (19.42)	
20-24	417 (55.82)	499 (53.95)	501 (52.79)	492 (52.51)	
24-28	169 (22.62)	227 (24.54)	201 (21.18)	196 (20.92)	
>28	43 (5.76)	56 (6.05)	68 (7.17)	67 (7.15)	
Menopausal Status					0.01
Still menstruating	144 (19.28)	218 (23.57)	215 (22.66)	249 (26.57)	
Postmenopausal	603 (80.72)	707 (76.43)	734 (77.34)	688 (73.43)	
Physical activity (moderate), n (%)					<0.001
None	637 (85.27)	744 (80.43)	730 (76.92)	683 (72.89)	
30 minutes-3hours/week	65 (8.70)	112 (12.11)	137 (14.44)	157 (16.76)	
>3hours/week	45 (6.02)	69 (7.46)	82 (8.64)	97 (10.35)	
Smoking Status					<0.001
Never	662 (88.62)	840 (90.81)	876 (92.31)	888 (94.77)	
Ex/current	85 (11.38)	85 (9.19)	73 (7.69)	49 (5.23)	
Alcohol Intake					0.33
Never	710 (95.05)	870 (94.05)	909 (95.79)	884 (94.34)	
Ever	37 (4.95)	55 (5.95)	40 (4.21)	53 (5.66)	
Weekly Vitamin Use					<0.001
No	702 (93.98)	847 (91.57)	863 (90.94)	810 (86.45)	
Yes	45 (6.02)	78 (8.43)	86 (9.06)	127 (13.55)	
Green Tea Intake					<0.001
Never	566 (75.77)	608 (65.73)	567 (59.75)	487 (51.97)	
Monthly	61 (8.17)	97 (10.49)	112 (11.80)	117 (12.49)	
Weekly	71 (9.50)	131 (14.16)	176 (18.55)	228 (24.33)	

Daily	49 (6.56)	89 (9.62)	94 (9.91)	105 (11.21)	
Soy food intake					<0.001
Q1	297 (39.76)	226 (24.43)	145 (15.28)	68 (7.26)	
Q2	202 (27.04)	265 (28.65)	208 (21.92)	147 (15.69)	
Q3	141 (18.88)	251 (27.14)	294 (30.98)	273 (29.14)	
Q4	107 (14.32)	183 (19.78)	302 (31.82)	449 (47.92)	
Black Tea Intake					<0.001
Never	555 (74.30)	639 (69.08)	653 (68.81)	608 (64.89)	
Monthly	63 (8.43)	80 (8.65)	75 (7.90)	77 (8.22)	
Weekly	83 (11.11)	119 (12.86)	144 (15.17)	176 (18.78)	
Daily	46 (6.16)	87 (9.41)	77 (8.11)	76 (8.11)	
MDS					<0.001
1	256 (34.27)	252 (27.24)	210 (22.13)	185 (19.74)	
2	224 (29.99)	259 (28.00)	237 (24.97)	172 (18.36)	
3	173 (23.16)	224 (24.22)	271 (28.56)	255 (27.21)	
4	94 (12.58)	190 (20.54)	231 (24.34)	325 (34.69)	

Table A5: Baseline Characteristics by HbA1c levels (%) of Self-Reported Nondiabetic Women of the Singapore Chinese Health Study

	Normal (≤5.7%)	Prediabetes (5.8-6.5%)	Diabetes (≥6.6%)	
No. of Subjects	1,970 (55.4)	1,413 (39.7)	175 (4.9)	p-value
Age, years, mean (SD)	55.8 (7.3)	57.6 (7.4)	58.4 (7.4)	<0.001
Age, years				
≤50	552 (28.0)	285 (20.2)	32 (18.3)	<0.001
51-55	486 (24.7)	317 (22.4)	29 16.6)	
56-61	472 (24.0)	350 (24.8)	54 (30.9)	
62-74	460 (23.3)	461 (32.6)	60 (34.3)	
Dialect group (%)				
Hokkiens	1,030 (52.3)	739 (52.3)	94 (52.7)	0.93
Cantonese	940 (47.7)	674 (47.7)	81 (46.3)	
Highest level of education				
No formal education	655 (33.2)	561 (39.7)	71 (40.6)	<0.001
Primary	808 (41.0)	551 (39.0)	73 (41.7)	
≥ Secondary	507 (25.7)	301 (21.3)	31 (17.7)	
BMI (kg/m2), mean (SD)	22.6 (3.2)	23.3 (3.1)	24.3 (2.9)	
BMI (kg/m^2), %				
<20	395 (20.1)	219 (15.5)	8 (4.6)	<0.001
20-24	1098 (55.7)	718 (50.8)	93 (53.1)	
24-28	384 (19.5)	358 (25.3)	51 (29.1)	
>28	93 (4.7)	118 (8.4)	23 (13.1)	
Menopausal Status				
Still menstruating	517 (26.2)	283 (20.0)	26 (14.9)	<0.001
Postmenopausal	1,453 (73.8)	1130 (78.0)	149 (85.1)	
Physical activity (moderate), n (%)				
None	1,549 (78.6)	1,108 (78.4)	137 (78.3)	0.97
30 minutes-3hours/week	257 (13.1)	192 (13.6)	22 (12.6)	
>3hours/week	164 (8.3)	113 (8.0)	16 (9.1)	
Smoking Status				
Never	1,828 (92.8)	1,273 (90.1)	165 (94.3)	0.01
Ex/current	142 (7.2)	140 (9.9)	10 (5.7)	
Alcohol Intake				
Never	1,865 (94.7)	1,342 (95.0)	166 (94.9)	0.92
Ever	105 (5.3)	71 (5.0)	9 (5.1)	
Weekly Vitamin Use				
No	1,776 (90.2)	1285 (90.9)	161 (92.0)	0.59
Yes	194 (9.8)	128 (9.1)	14 (8.0)	
Soy food intake				
Q1	388 (19.7)	309 (21.9)	39 (22.3)	0.71
Q2	463 (23.5)	319 (22.6)	40 (22.9)	

Q3	547 (27.8)	369 (26.1)	43 (24.6)	
Q4	572 (29.0)	416 (29.4)	53 (30.3)	
Green Tea Intake				
Never	1,259 (63.9)	862 (61.0)	107 (61.1)	0.32
Monthly	210 (10.7)	161 (11.4)	16 (9.1)	
Weekly	333 (16.9)	243 (17.2)	30 (17.1)	
Daily	168 (8.5)	147 (10.4)	22 (12.6)	
VFS intake				
1	423 (21.5)	289 (20.4)	35 (20.0)	0.55
2	524 (26.6)	360 (25.5)	41 (23.4)	
3	508 (25.8)	397 (28.1)	44 (25.1)	
4	515 (26.1)	367 (26.0)	55 (31.4)	
Black Tea Intake				
Never	1,348 (68.4)	989 (70.0)	118 (67.4)	0.63
Monthly	178 (9.0)	102 (7.2)	15 (8.6)	
Weekly	288 (14.6)	209 (14.8)	25 (14.3)	
Daily	156 (7.9)	113 (8.0)	17 (9.7)	
MDS				
1	487 (24.7)	372 (26.3)	44 (25.1)	0.57
2	514 (26.1)	340 (24.1)	38 (21.7)	
3	519 (26.4)	357 (25.3)	47 (26.9)	
4	450 (22.8)	344 (24.3)	46 (26.3)	

Table A6: Mean HbA1c Levels by Quartiles of Soy Variable Intake among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	N (%)	Mean HbA1c (%)*	95% CI	p-value	Mean HbA1c (%)**	95% CI	p-value	Mean HbA1c (%)***	95% CI	p-value
Soy Food Adjusted for Food Energy										
Q1	736 (20.7)	5.82	(5.78, 5.87)		5.80	(5.74, 5.86)		5.80	(5.73, 5.87)	
Q2	822 (23.1)	5.77	(5.73, 5.81)	0.06	5.76	(5.67, 5.82)	0.16	5.77	(5.70, 5.83)	0.26
Q3	959 (27.0)	5.76	(5.72, 5.80)	0.03	5.75	(5.70, 5.81)	0.11	5.76	(5.70, 5.82)	0.18
Q4	1,041 (29.2)	5.76	(5.72, 5.80)	0.03	5.76	(5.70, 5.81)	0.13	5.76	(5.70, 5.82)	0.16
p for trend				0.04			0.17			0.19
Soy Protein										
Q1	638 (17.9)	5.82	(5.78, 5.87)		5.81	(5.75, 5.87)		5.81	(5.74, 5.88)	
Q2	774 (21.8)	5.77	(5.72, 5.81)	0.08	5.76	(5.70, 5.82)	0.11	5.76	(5.69, 5.82)	0.09
Q3	993 (27.9)	5.78	(5.74, 5.81)	0.13	5.77	(5.72, 5.83)	0.22	5.78	(5.71, 5.84)	0.23
Q4	1,153 (32.4)	5.75	(5.72, 5.79)	0.02	5.74	(5.69, 5.80)	0.03	5.74	(5.68, 5.81)	0.02
p for trend				0.04			0.06			0.05
Total Soy Isoflavone										
Q1	737 (20.7)	5.82	(5.78, 5.86)		5.80	(5.75, 5.67)		5.80	(5.73, 5.86)	
Q2	807 (22.7)	5.78	(5.74, 5.82)	0.20	5.77	(5.73, 5.83)	0.35	5.78	(5.71, 5.84)	0.45
Q3	972 (27.3)	5.74	(5.71, 5.78)	0.01	5.74	(5.71, 5.80)	0.04	5.74	(5.68, 5.81)	0.06
Q4	1,042 (29.3)	5.77	(5.73, 5.82)	0.06	5.77	(5.73, 5.82)	0.24	5.77	(5.71, 5.83)	0.29
p for trend				0.04			0.18			0.21

*Crude Model
**Adjusted for age, dialect, education, menopausal status, physical activity, smoking status
***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use
HR=Hazard Ratio
95% CI=95% Confidence Interval

Table A7: Mean HbA1c Levels by Tea Intake among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	N (%)	Mean HbA1c (%)*	95% CI	p-value	Mean HbA1c (%)**	95% CI	p-value	Mean HbA1c (%)***	95% CI	p-value
Green Tea										
Nondrinker	2,228 (62.6)	5.77	(5.73, 5.79)		5.77	(5.73, 5.80)		5.76	(5.706, 5.819)	
Monthly	387 (10.9)	5.77	(5.72, 5.83)	0.84	5.77	(5.71, 5.84)	0.84	5.77	(5.695, 5.850)	0.77
Weekly	606 (17.0)	5.75	(5.71, 5.80)	0.63	5.76	(5.71, 5.81)	0.77	5.76	(5.689, 5.824)	0.82
Daily	337 (9.5)	5.86	(5.79, 5.92)	0.01	5.86	(5.79, 5.92)	0.01	5.85	(5.766, 5.929)	0.02
p for trend				0.11			0.10			0.11
Black Tea										
Nondrinker	2,455 (69.0)	5.78	(5.76, 5.80)		5.78	(5.74, 5.81)		5.77	(5.71, 5.83)	
Monthly	295 (8.3)	5.75	(5.68, 5.82)	0.45	5.76	(5.68, 5.83)	0.54	5.76	(5.67, 5.84)	0.33
Weekly	522 (14.7)	5.76	(5.71, 5.25)	0.58	5.77	(5.72, 5.82)	0.78	5.77	(5.70, 5.84)	0.93
Daily	286 (8.0)	5.78	(5.71, 5.85)	0.98	5.79	(5.71, 5.86)	0.81	5.78	(5.70, 5.87)	0.80
p for trend				0.67			0.96			0.81

*Crude Model
**Adjusted for age, dialect, education, menopausal status, physical activity, smoking status
***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use

Table A8: Mean HbA1c Levels by Dietary Pattern Intake among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	No. of Subjects										
		No. of Subjects	Mean HbA1c (%)	95% CI	p-value	Mean HbA1c (%)	95% CI	p-value	95% CI	Mean HbA1c (%)	
VFS											
	1	747 (21.0)	5.78	(5.73, 5.82)		5.75	(5.70, 5.81)				
	2	925 (26.0)	5.76	(5.72, 5.81)	0.63	5.75	(5.69, 5.81)		5.76	(5.69, 5.27)	
	3	949 (26.7)	5.8	(5.76, 5.84)	0.43	5.79	(5.72, 5.85)	0.95	5.76	(5.69, 5.82)	0.95
	4	937 (26.3)	5.76	(5.72, 5.80)	0.55	5.75	(5.69, 5.81)	0.18	5.80	(5.74, 5.86)	0.17
p for trend					0.86			0.97	5.76	(5.70, 5.82)	0.95
								0.68			0.62
MDS											
	1	903 (25.4)	5.78	(5.74, 5.81)		5.74	(5.68, 5.80)				
	2	892 (25.1)	5.76	(5.72, 5.80)	0.6	5.74	(5.67, 5.80)		5.76	(5.69, 5.82)	
	3	923 (25.9)	5.78	(5.74, 5.81)	0.97	5.76	(5.670, 5.83)	1	5.75	(5.69, 5.82)	0.86
	4	840 (23.6)	5.79	(5.75, 5.83)	0.62	5.79	(5.72, 5.85)	0.43	5.77	(5.70, 5.83)	0.69
p for trend					0.52			0.1	5.8	(5.74, 5.86)	0.13

*Crude Model
**Adjusted for age, dialect, education, menopausal status, physical activity, smoking status
***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use

Table A9: Mean HbA1c Levels by Dietary Variables among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study (Excluding Diabetics)

	No. of Subjects	Mean HbA1c (%)***	95% CI	p-value
Soy Protein				
Q1	602 (17.8)	5.71	(5.66, 5.75)	
Q2	734 (21.7)	5.68	(5.64, 5.72)	0.22
Q3	946 (28.0)	5.71	(5.71, 5.67)	0.98
Q4	1,101 (32.5)	5.69	(5.66, 5.73)	0.50
p for trend				0.88
Green Tea				
Nondrinker	2,121 (62.7)	5.69	(5.65, 5.72)	
Monthly	371 (11.0)	5.71	(5.66, 5.75)	0.39
Weekly	576 (17.0)	5.70	(5.66, 5.74)	0.64
Daily	315 (9.3)	5.75	(5.70, 5.77)	0.01
p for trend				0.02
VFS				
1	712 (21.1)	5.70	(5.65, 5.74)	
2	884 (26.1)	5.69	(5.65, 5.73)	0.88
3	905 (26.7)	5.72	(5.68, 5.76)	0.13
4	882 (26.1)	5.68	(5.64, 5.72)	0.42
p for trend				0.78

***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use

Table A10: Green Tea by Cups of Intake Per Month among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	No. of Subjects	Mean HbA1c (%)***	95% CI	p-value
Nondrinker	2,228	5.76	(5.71, 5.82)	
1-4 cups	633	5.76	(5.69, 5.83)	0.99
5-19 cups	297	5.77	(5.69, 5.86)	0.73
≥20 cups	400	5.82	(5.75, 5.90)	0.06
p for trend				0.09

***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use

Table A11: Mean HbA1c Levels by Dietary Variables Using Log HbA1c among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

	No. of Subjects	Mean HbA1c (%)***	95% CI	p-value
Soy Food Adjusted for Food Energy				
Q1	736 (20.7)	1.75	(1.74, 1.76)	
Q2	822 (23.1)	1.75	(1.74, 1.76)	0.34
Q3	959 (26.9)	1.75	(1.74, 1.76)	0.15
Q4	1,041 (29.3)	1.75	(1.74, 1.76)	0.23
p for trend				0.23
Soy Protein				
Q1	638 (17.9)	1.75	(1.74, 1.76)	
Q2	774 (21.8)	1.75	(1.74, 1.76)	0.11
Q3	993 (27.9)	1.75	(1.74, 1.76)	0.32
Q4	1,153 (32.4)	1.74	(1.74, 1.75)	0.04
p for trend				0.09
Green Tea				
Nondrinker	2,228 (62.6)	1.75	(1.74, 1.76)	
Monthly	387 (10.9)	1.75	(1.74, 1.76)	0.64
Weekly	606 (17.0)	1.75	(1.74, 1.76)	1.00
Daily	337 (9.5)	1.76	(1.75, 1.77)	0.01
p for trend				0.05
VFS				
1	747 (21.0)	1.75	(1.74, 1.76)	
2	925 (26.0)	1.75	(1.74, 1.76)	0.88
3	949 (26.7)	1.75	(1.74, 1.76)	0.14
4	937 (26.3)	1.75	(1.74, 1.76)	1.00
p for trend				0.62

***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use

Table A12: Normal vs. Prediabetes/Diabetes Logistic Regression Results for HbA1c Levels among Self-Reported Nondiabetic Women in the Singapore Chinese Health Study

		Model 3
	No. of Subjects	OR (95% CI)***
Soy Food Adjusted for Food Energy		
Q1	736 (20.7)	1.00
Q2	822 (23.1)	0.95 (0.78, 1.17)
Q3	959 (27.0)	0.94 (0.77, 1.14)
Q4	1,041 (29.3)	1.03 (0.84, 1.25)
p for trend		0.77
Soy Protein		
Q1	638 (17.9)	1.00
Q2	774 (21.8)	0.82 (0.66, 1.01)
Q3	993 (27.9)	0.98 (0.80, 1.20)
Q4	1,153 (32.4)	0.88 (0.72, 1.07)
p for trend		0.54
Green Tea		
Nondrinker	2,228 (62.6)	1.00
Monthly	387 (10.9)	1.12 (0.90, 1.40)
Weekly	606 (17.0)	1.11 (0.92, 1.34)
Daily	337 (9.5)	1.30 (1.02, 1.64)
p for trend		0.03
VFS		
1	747 (21.0)	1.00
2	925 (26.0)	1.06 (0.87, 1.29)
3	949 (26.7)	1.24 (1.01, 1.51)
4	937 (26.3)	1.18 (0.97, 1.44)
p for trend		0.04

***Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use
95% CI=95% Confidence Interval

Table A13: Mean HbA1c Levels by Intake of Selected Soy Variables, Green Tea, and Vegetable-Fruit-Soy Dietary Pattern among Men and Women in the Singapore Chinese Health Study (additionally adjusted for omega-3 fatty acid intake and parity among women)

	Men (n=3,028)				Women (n=3,558)			
	N (%)	Mean HbA1c (%)*[#]	95% CI	p-value	N (%)	Mean HbA1c (%)**[#]	95% CI	p-value
Soy Food, Adjusted (g/1000 Kcal)								
≤ 36.9	919 (30.3)	5.74	(5.67, 5.80)		736 (20.7)	5.79	(5.73, 5.86)	
36.9-60.4	753 (24.9)	5.75	(5.68, 5.82)	0.62	822 (23.1)	5.76	(5.70, 5.83)	0.32
60.4-92.5	731 (24.1)	5.82	(5.75, 5.89)	0.01	959 (27.0)	5.76	(5.69, 5.82)	0.22
>92.5	625 (20.6)	5.76	(5.69, 5.84)	0.41	1,041 (29.3)	5.76	(5.69, 5.82)	0.24
p-value for trend				0.06				0.09
Soy Protein, Percent Total Protein (%kcal)								
≤ 0.79	1,046 (34.5)	5.75	(5.68, 5.81)		638 (17.9)	5.81	(5.74, 5.88)	
0.80-1.28	842 (27.8)	5.8	(5.73, 5.86)	0.1	774 (21.8)	5.75	(5.69, 5.82)	0.1
1.29-1.94	662 (21.9)	5.76	(5.69, 5.83)	0.74	993 (27.9)	5.77	(5.71, 5.84)	0.25
>1.95	478 (15.8)	5.75	(5.67, 5.83)	0.99	1,153 (32.4)	5.74	(5.68, 5.80)	0.03
p-value for trend				0.57				0.16
Total Soy Isoflavone, Adjusted (mg/1000 Kcal)								
≤ 5.77	897 (29.6)	5.74	(5.67, 5.809)		737 (20.7)	5.79	(5.72, 5.86)	
5.78-9.83	771 (25.5)	5.76	(5.69, 5.83)	0.41	807 (22.7)	5.77	(5.71, 5.84)	0.52
9.84-15.42	715 (23.6)	5.78	(5.71, 5.85)	0.17	972 (27.3)	5.74	(5.68, 5.80)	0.09
>15.43	645 (21.3)	5.79	(5.72, 5.86)	0.13	1,042 (29.3)	5.77	(5.70, 5.83)	0.4
p-value for trend				0.8				0.37
Green Tea								
Nondrinker	1,600 (52.8)	5.74	(5.68, 5.80)		2,228 (62.6)	5.76	(5.70, 5.82)	
Monthly	342 (11.3)	5.8	(5.72, 5.88)	0.08	387 (10.9)	5.77	(5.69, 5.85)	0.71
Weekly	635 (21.0)	5.78	(5.71, 5.85)	0.15	606 (17.0)	5.76	(5.69, 5.82)	0.87
Daily	451 (14.9)	5.79	(5.72, 5.87)	0.08	337 (9.5)	5.85	(5.76, 5.93)	0.01
p-value for trend				0.03				0.05

Vegetable-Fruit-Soy Pattern								
Quartile 1 (lowest)	675 (22.3)	5.76	(5.69, 5.83)		747 (21.0)	5.75	(5.68, 5.82)	
Quartile 2	754 (24.9)	5.76	(5.69, 5.83)	0.95	925 (26.0)	5.75	(5.69, 5.81)	0.99
Quartile 3	809 (26.7)	5.8	(5.73, 5.86)	0.25	949 (26.7)	5.8	(5.73, 5.86)	0.14
Quartile 4	790 (26.1)	5.75	(5.68, 5.82)	0.74	937 (26.3)	5.76	(5.70, 5.83)	0.77
p-value for trend				0.35				0.43

*[#]Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use, and omega-3 fatty acid intake
**[#]Adjusted for age, dialect, education, menopausal status, physical activity, smoking status, BMI, vitamin use, omega-3 fatty acid intake, and parity

95% CI=95% Confidence Interval

Appendix B: Effect Modification of Soy and Green Intake on the Diabetes and Breast Cancer Association among Singaporean Chinese Women

As a sensitivity analysis we included premenopausal women. Additionally, we included women who reported a type II diabetes diagnosis at baseline to determine the impact of inclusion of all diabetic women in the Singapore Chinese Health Study on the association between diabetes and breast cancer, regardless of the possible change in diet due to a diabetes diagnosis. Furthermore, we conducted a sensitivity analysis after removing the first two years of follow-up for all subjects in the study.

Table B1: Baseline Characteristics by Breast Cancer Diagnosis among Women in the Singapore Chinese Health Study (n=26195)

	Breast Cancer		
	No	Yes	HR (95% CI)
No. of Subjects	25845 (98.66)	350 (1.34)	
Person-Years, mean (SD)	6.49 (1.38)	3.51 (2.09)	
Age, years			
≤49	7535 (29.15)	117 (33.43)	1.00 (reference)
50-54	5838 (22.59)	92 (26.00)	0.98 (0.74, 1.29)
55-61	6507 (25.18)	73 (20.86)	0.72 (0.54, 0.97)
>61	5965 (23.08)	69 (19.71)	0.79 (0.59, 1.07)
Dialect group (%)			
Hokkiens	12667 (49.01)	184 (52.57)	1.00 (reference)
Cantonese	13178 (50.99)	166 (47.43)	0.87 (0.70, 1.07)
Education			
No formal	9586 (37.06)	99 (28.29)	1.00 (reference)
Primary	10452 (40.44)	144 (41.14)	1.30 (1.00, 1.67)
Secondary +	5807 (22.47)	107 (30.57)	1.74 (1.33, 2.29)
BMI			
<20	3993 (15.45)	39 (11.14)	1.00 (reference)
20-24	14116 (54.62)	191 (54.57)	1.38 (0.98, 1.95)
24-28	5783 (22.38)	88 (25.14)	1.55 (1.06, 2.26)
>28	1953 (7.56)	32 (9.14)	1.69 (1.06, 2.70)
Any Weekly Moderate Physical Activity			
None	20591 (79.67)	282 (80.57)	1.00 (reference)
30 minutes-3hours/week	3336 (12.91)	41 (11.71)	0.88 (0.63, 1.22)
>3hours/week	1918 (7.42)	27 (7.71)	0.98 (0.66, 1.45)
Smoking Status			
Never	23903 (92.49)	328 (93.71)	1.00 (reference)
Ever	1942 (7.51)	22 (6.29)	0.88 (0.57, 1.35)
Alcohol Intake			
Never	24607 (95.21)	342 (97.71)	1.00 (reference)
Ever	1238 (4.79)	8 (2.29)	0.48 (0.24, 0.96)
Weekly Vitamin/Mineral Supplement Use			
No	23822 (92.17)	318 (90.86)	1.00 (reference)
Yes	2023 (7.83)	32 (9.14)	1.18 (0.82, 1.70)
Age at Regularity, years (missing=5)			
< 13	3288 (12.72)	40 (11.43)	1.00 (reference)
13-14	9013 (34.88)	141 (40.29)	1.27 (0.90, 1.81)
15-16	8686 (33.61)	118 (33.71)	1.11 (0.77, 1.59)
≥17	3971 (15.37)	43 (12.29)	0.89 (0.58, 1.37)
Never Regular	882 (3.41)	8 (2.29)	0.75 (0.35, 1.60)
Age at First Menarche, years (missing=5)			

< 13	3838 (14.85)	48 (13.71)	1.00 (reference)
13-14	9939 (38.46)	153 (43.71)	1.22 (0.88, 1.69)
15-16	8862 (34.30)	116 (33.14)	1.04 (0.74, 1.46)
≥17	3201 (12.39)	33 (9.43)	0.83 (0.53, 1.29)
Age at First Birth, years (missing=20)			
≤20	4658 (18.04)	47 (13.43)	1.00 (reference)
21-25	9789 (37.91)	106 (30.29)	1.05 (0.75, 1.48)
26-30	6864 (26.58)	107 (30.57)	1.49 (1.06, 2.10)
≥31	2676 (10.36)	52 (14.86)	1.85 (1.25, 2.74)
Nulliparous	1838 (7.12)	38 (10.86)	2.01 (1.31, 3.08)
Number of Full Term Births			
≥3	16378 (63.37)	190 (54.29)	1.00 (reference)
1-2	7629 (29.52)	122 (34.86)	1.36 (1.09, 1.71)
0	1838 (7.11)	38 (10.86)	1.78 (1.26, 2.53)
Menopausal Status (missing=3)			
Still menstruating	2470 (9.56)	45 (12.86)	1.00 (reference)
Postmenopausal	23372 (90.44)	305 (87.14)	0.72 (0.53 0.99)
Ever Postmenopausal Hormone Use (missing=2610)			
No	20835 (89.50)	256 (83.93)	1.00 (reference)
Yes	2445 (10.50)	49 (16.07)	1.61 (1.18, 2.18)
Family History of Breast Cancer			
No	25493 (98.64)	344 (98.29)	1.00 (reference)
Yes	352 (1.36)	6 (1.71)	1.26 (0.56, 2.82)

BMI=Body Mass Index
SD=Standard Deviation

Table B2: Baseline Characteristics by Diabetes Status at Follow-up among Women in the Singapore Chinese Health Study (n=26195)

	Diabetes		
	No	Yes	p-value
No. of Subjects	24405 (93.17)	1790 (6.83)	
Age, years			<0.001
≤49	7273 (29.80)	379 (21.17)	
50-54	5537 (22.69)	392 (21.90)	
55-61	6084 (24.93)	496 (27.71)	
>61	5511 (22.58)	523 (29.22)	
Dialect group (%)			0.01
Hokkien	12027 (49.28)	824 (46.03)	
Cantonese	12378 (50.72)	966 (53.97)	
Education			<0.001
No formal	8886 (36.41)	799 (44.64)	
Primary	9871 (40.45)	725 (40.50)	
Secondary +	5648 (23.14)	266 (14.86)	
BMI			<0.001
<20	3917 (16.05)	115 (6.42)	
20-24	13490 (55.28)	817 (45.64)	
24-28	5325 (21.82)	546 (30.50)	
>28	1673 (6.86)	312 (17.43)	
Any Weekly Moderate Physical Activity			0.27
None	19449 (79.69)	1424 (79.55)	
30 minutes-3hours/week	3159 (12.94)	218 (12.18)	
>3hours/week	1797 (7.36)	148 (8.27)	
Smoking Status			0.20
Never	22589 (92.56)	1642 (91.73)	
Ever	1816 (7.44)	148 (8.27)	
Alcohol Intake			<0.001
Never	23206 (95.09)	1743 (97.37)	
Ever	1199 (4.91)	47 (2.63)	
Weekly Vitamin/Mineral Supplement Use			<0.001
No	22443 (91.96)	1697 (94.80)	
Yes	1962 (8.04)	93 (5.20)	
Age at Regularity, years (missing=5)			0.93
< 13	831 (3.41)	59 (3.30)	
13-14	3734 (15.30)	280 (15.64)	
15-16	8194 (33.58)	610 (34.08)	
≥17	8530 (34.96)	624 (34.86)	
Never Regular	3111 (12.75)	217 (12.12)	
Age at First Menarche, years (missing=5)			0.61
< 13	3634 (14.89)	252 (14.08)	

13-14	9404 (38.54)	688 (38.44)	
15-16	8364 (34.28)	614 (34.30)	
≥17	2998 (12.29)	236 (13.18)	
Age at First Birth, years (missing=20)			<0.001
≤20	4285 (17.57)	420 (23.48)	
21-25	9194 (37.70)	701 (39.18)	
26-30	6532 (26.79)	439 (24.54)	
≥31	2577 (10.57)	151 (8.44)	
Nulliparous	1798 (7.37)	78 (4.36)	
Number of Full Term Births			<0.001
≥3	15264 (62.54)	1304 (72.85)	
1-2	7343 (30.09)	408 (22.79)	
0	1798 (7.37)	78 (4.36)	
Menopausal Status (missing=3)			<0.001
Still menstruating	2436 (9.98)	79 (4.41)	
Postmenopausal	21966 (90.02)	1711 (95.59)	
Ever Postmenopausal Hormone Use (missing=2610)			<0.001
No	19505 (89.13)	1586 (93.18)	
Yes	2378 (10.87)	116 (6.82)	
Family History of Breast Cancer			0.12
No	24064 (98.60)	1773 (99.05)	
Yes	341 (1.40)	17 (0.95)	

Table B3: Using Hazard Ratios (HR) to Evaluate Confounding for Diabetes-Breast Cancer Relationship

	Overall		Premenopausal		Postmenopausal	
	No	Yes	No	Yes	No	Yes
Diabetes	1.00 (ref)	1.25 (0.85, 1.84)	1.00 (ref)	1.40 (0.71, 2.75)	1.00 (ref)	1.24 (0.77, 1.99)
Education	1.00 (ref)	1.31 (0.89, 1.93)	1.00 (ref)	1.46 (0.74, 2.87)	1.00 (ref)	1.27 (0.79, 2.03)
BMI	1.00 (ref)	1.18 (0.80, 1.74)	1.00 (ref)	1.39 (0.70, 2.75)	1.00 (ref)	1.13 (0.70, 1.82)
Age at First Birth, years	1.00 (ref)	1.31 (0.89, 1.92)	1.00 (ref)	1.45 (0.74, 2.85)	1.00 (ref)	1.29 (0.84, 2.07)
Menopausal Status	1.00 (ref)	1.29 (0.88, 1.90)				
Ever Postmenopausal Hormone Use					1.00 (ref)	1.26 (0.79, 2.02)
Number of Full Term Births	1.00 (ref)	1.304 (0.89, 1.92)	1.00 (ref)	1.44 (0.73, 2.83)	1.00 (ref)	1.28 (0.80, 2.06)
Weekly Vitamin/Mineral Supplement Use	1.00 (ref)	1.257 (0.85, 1.85)	1.00 (ref)	1.39 (0.71, 2.74)	1.00 (ref)	1.25 (0.78, 2.00)
Smoking	1.00 (ref)	1.252 (0.85, 1.84)	1.00 (ref)	1.40 (0.71, 2.75)	1.00 (ref)	1.24 (0.77, 1.98)
Alcohol	1.00 (ref)	1.236 (0.84, 1.82)	1.00 (ref)	1.37 (0.70, 2.70)	1.00 (ref)	1.23 (0.77, 1.97)

Table B4: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Diabetes in relation to Breast Cancer Risk

Diabetes	Cases, n	HR (95%CI)*	HR (95%CI)**	HR (95%CI)***
Overall				
No	322	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	28	1.29 (0.88, 1.90)	1.28 (0.86, 1.89)	1.27 (0.86, 1.88)
Premenopausal Women				
No	42	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	3	2.25 (0.70, 7.28)	2.36 (0.71, 7.83)	2.44 (0.73, 8.15)
Postmenopausal Women				
No	280	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	25	1.28 (0.86, 1.89)	1.21 (0.80, 1.83)	1.21 (0.80, 1.83)

*Adjusted for dialect, baseline interview date, age
**Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity
***Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.
HR=Hazard Ratio
95% CI=95% Confidence Interval

Table B5. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for the Joint Effects of Dietary Soy/Green Tea Intake and Diabetes among Women of the Singapore Chinese Health Study

	All Women*		Premenopausal Women**		Postmenopausal Women***	
Soy Food (g/1000Kcal)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
> Median/No Diabetes	150	1.00 (reference)	28	1.00 (reference)	122	1.00 (reference)
< Median/No Diabetes	16	1.61 (0.96, 2.70)	14	0.61 (0.31, 1.20)	13	1.47 (0.83, 2.60)
> Median/Diabetes	172	1.18 (0.95, 1.47)	3	3.97 (1.15, 13.63)	158	1.29 (1.02, 1.64)
< Median/Diabetes	12	1.23 (0.70, 2.21)	0	-	12	1.37 (0.76, 2.48)
p for interaction		0.27		0.99		0.43
Soy Protein (% total protein/%Kcal)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
> Median/ No Diabetes	155	1.00 (reference)	30	1.00 (reference)	125	1.00 (reference)
< Median/ No Diabetes	16	1.57 (0.94, 2.62)	12	0.39 (0.20, 0.78)	14	1.48 (0.85, 2.58)
> Median/ Diabetes	167	1.08 (0.87, 1.34)	2	3.07 (0.69, 13.65)	155	1.23 (0.97, 1.57)
< Median/ Diabetes	12	1.14 (0.64, 2.06)	1	0.96 (0.13, 7.19)	11	1.19 (0.64, 2.21)
p for interaction		0.33		0.86		0.31
Soy Isoflavones (mg/1000Kcal)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
> Median/ No Diabetes	149	1.00 (reference)	28	1.00 (reference)	121	1.00 (reference)
< Median/ No Diabetes	11	1.12 (0.61, 2.07)	14	0.61 (0.31, 1.21)	8	0.92 (0.45 1.89)
> Median/ Diabetes	173	1.20 (0.97, 1.50)	3	4.23 (1.22, 14.66)	159	1.33 (1.05, 1.68)
< Median/ Diabetes	17	1.75 (1.06, 2.89)	0	-	17	1.95 (1.17, 3.25)
p for interaction		0.52		0.99		0.29
Green Tea	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
Drinker/ No Diabetes	120	1.00 (reference)	14	1.00 (reference)	106	1.00 (reference)
Nondrinker/ No Diabetes	10	1.19 (0.62, 2.26)	28	1.64 (0.85, 3.14)	10	1.24 (0.65, 2.36)
Drinker/ Diabetes	202	1.05 (0.84, 1.32)	0	-	174	0.96 (0.78, 1.27)
Nondrinker/ Diabetes	18	1.45 (0.88, 2.39)	3	7.32 (2.01, 26.63)	15	1.23 (0.72, 2.12)
p for interaction		0.71		0.99		0.99

*Adjusted for dialect, baseline interview date, age

**Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity

***Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea

Table B6: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Diabetes in relation to Breast Cancer Risk among Postmenopausal Women after Removal of First Two Years of Follow-up

Diabetes	Breast Cancer Cases	HR (95%CI)*	HR (95%CI) **	HR (95%CI) ***
No	206	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	21	1.44 (0.92, 2.26)	1.36 (0.87, 2.15)	1.37 (0.87, 2.16)

*Adjusted for dialect, baseline interview date, age

**Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity

***Adjusted for dialect, baseline interview date, age, BMI, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

Appendix C: Weight Change, Diet, and Breast Cancer among Women in the Singapore Chinese Health Study

As a sensitivity analysis we included premenopausal women; additionally, we included women who had imputed weights at baseline to determine the impact of inclusion of all women in the Singapore Chinese Health Study on the association between weight change and breast cancer. Furthermore, we conducted a sensitivity analysis after removing the first two years of follow-up from all subjects in the study. We also performed a sensitivity analysis with different categories of weight change (≥10 kg loss, 5-9 kilogram loss, 2-4 kilogram loss, loss or gain of <2. kilogram (referent), 2-4 kilogram gain, 5-9 kilogram gain, and ≥10 kilogram gain) based on weight change categories that have been previously used (Eliassen et al. 2006). In order to determine the impact of adjusting for BMI, we conducted a sensitivity analysis without BMI as a covariate.

Table C1: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in relation to Breast Cancer Risk among Postmenopausal Women in the Singapore Chinese Health Study without Adjusting for BMI (n=20163)

Weight Change	Cases, n	HR (95%CI)*	HR (95%CI) **	HR (95%CI) ***
<5 kg	26	0.90 (0.59, 1.37)	0.93 (0.60, 1.42)	0.92 (0.60, 1.41)
-3 to -5 kg	48	1.31 (0.94, 1.83)	1.35 (0.97, 1.89)	1.34 (0.96, 1.87)
-2 to 2 kg	120	1.00 (reference)	1.00 (reference)	1.00 (reference)
3 to 5 kg	42	1.12 (0.79, 1.59)	1.12 (0.79, 1.59)	1.12 (0.79, 1.59)
>5 kg	31	1.09 (0.73, 1.61)	1.13 (0.76, 1.69)	1.13 (0.76, 1.68)

*Adjusted for dialect, baseline interview date, age
**Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity
***Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

HR=Hazard Ratio
95% CI=95% Confidence Interval

Table C2: Baseline Characteristics by Weight Change from Baseline to Follow-up (n=26173)

	-20 to -10 kg	-10 to -3 kg	-3 to 3 kg	3 to 10 kg	10 to 20 kg	p-value
No. of Subjects	1,303 (5.0)	5,636 (21.5)	13,322 (50.9)	4,789 (18.3)	1,123 (4.3)	
Person-Years, mean (SD)	6.1 (1.8)	6.4 (1.5)	6.5 (1.4)	6.4 (1.5)	6.3 (1.6)	
Age, years, mean (SD)	58.6 (8.1)	56.2 (7.1)	54.5 (7.4)	54.8 (7.6)	56.2 (7.9)	
Age, years						<.001
≤49	223 (17.1)	1,369 (24.3)	4,268 (32.0)	1,496 (31.2)	296 (26.4)	
49-54	244 (18.7)	1,249 (22.2)	3,143 (23.6)	1,102 (23.0)	220 (19.6)	
54-61	351 (26.9)	1,513 (26.9)	3,313 (24.9)	1,184 (24.7)	306 (27.3)	
>61	485 (37.2)	1,505 (26.7)	2,598 (19.5)	1,007 (21.0)	301 (26.8)	
Dialect group (%)						<.001
Hokkiens	648 (49.7)	2,823 (50.1)	6,752 (50.7)	2,187 (45.7)	436 (38.8)	
Cantonese	655 (50.3)	2,813 (49.9)	6,570 (49.3)	2,602 (54.3)	687 (61.2)	
Education						<.001
No formal	647 (49.7)	2,232 (39.6)	4,114 (30.9)	1,789 (37.4)	552 (49.2)	
Primary	496 (38.1)	2,325 (41.3)	5,612 (42.1)	1,914 (40.0)	429 (38.2)	
Secondary +	160 (12.3)	1,079 (19.1)	3,596 (27.0)	1,086 (22.7)	142 (12.6)	
BMI, kg/m^2, mean (SD)	25.2 (3.3)	24.0 (3.1)	22.9 (3.2)	22.6 (3.1)	22.7 (2.6)	
BMI, kg/m^2						<.001
<20	31 (2.4)	475 (8.4)	2,325 (17.5)	985 (20.6)	166 (14.8)	
20-24	679 (52.1)	2,955 (52.4)	6,926 (52.0)	2,647 (55.3)	772 (68.7)	
24-28	329 (25.3)	1,587 (28.2)	3,188 (23.9)	896 (18.7)	152 (13.5)	
>28	264 (20.3)	619 (11.0)	883 (6.6)	261 (5.5)	33 (2.9)	
Age at Regularity, years (missing=5)						<.001
< 13	140 (10.8)	666 (11.8)	1,857 (13.9)	617 (12.9)	121 (10.8)	
13-14	440 (33.8)	1,946 (34.5)	4,741 (35.6)	1,684 (35.2)	387 (34.5)	
15-16	479 (36.8)	1,919 (34.1)	4,297 (32.3)	1,625 (33.9)	400 (35.7)	
≥17	200 (15.4)	917 (16.3)	1,954 (14.7)	706 (14.7)	180 (16.0)	
Never Regular	42 (3.2)	187 (3.3)	472 (3.5)	157 (3.3)	34 (3.0)	
Age at first menarche, years (missing=5)						<.001
< 13	164 (12.6)	786 (14.0)	2,168 (16.3)	716 (15.0)	140 (12.5)	

13-14	483 (37.1)	2,155 (38.2)	5,213 (39.1)	1,864 (38.9)	431 (38.4)	
15-16	475 (36.5)	1,970 (35.0)	4,415 (11.5)	1,634 (34.1)	401 (35.7)	
≥17	179 (13.8)	724 (12.9)	1,525 (11.5)	575 (12.0)	150 (13.4)	
Age at First Birth, years (missing=20)						<.001
≤20	295 (22.7)	1,033 (18.3)	2,126 (16.0)	938 (19.6)	300 (26.7)	
21-25	488 (37.5)	2,161 (38.4)	5,044 (37.9)	1,825 (38.1)	443 (39.5)	
26-30	271 (20.9)	1,445 (25.7)	3,804 (28.6)	1,210 (25.3)	249 (22.2)	
≥31	149 (11.5)	602 (10.7)	1,376 (10.3)	483 (10.1)	85 (7.6)	
Nulliparous	97 (7.5)	392 (7.0)	963 (7.2)	329 (6.9)	45 (4.0)	
Menopausal Status (missing=5)						<.001
Still menstruating	235 (18.1)	1,512 (26.8)	4,589 (34.5)	1,585 (33.1)	302 (26.9)	
Postmenopausal	1,066 (81.9)	4,123 (73.2)	8,732 (65.5)	3,204 (66.9)	820 (73.1)	
Ever Postmenopausal Hormone Use (missing=8228)						<.001
No	1,043 (97.8)	3,874 (94.0)	7,904 (90.5)	2,957 (92.3)	784 (95.7)	
Yes	23 (2.2)	249 (6.0)	828 (9.5)	247 (7.7)	36 (4.3)	
Number of Full Term Births						<.001
≥3	892 (6,856)	3,665 (65.0)	8,098 (60.8)	3,114 (65.0)	826 (73.6)	
1-2	314 (24.0)	1,579 (28.0)	4,261 (32.0)	1,346 (28.1)	252 (22.4)	
0	97 (7.4)	392 (7.0)	963 (7.2)	329 (6.9)	45 (4.0)	
Smoking Status						<.001
Never	1,164 (89.3)	5,157 (91.5)	12,476 (93.6)	4,435 (92.6)	1,019 (90.7)	
Ever	139 (10.7)	479 (8.5)	846 (6.4)	354 (7.4)	104 (9.3)	
Any Weekly Moderate Physical Activity						0.09
None	1,060 (81.4)	4,457 (79.1)	10,320 (77.5)	3,877 (81.0)	944 (84.0)	
30 minutes-3hours/week	160 (12.3)	772 (13.7)	1,894 (14.2)	570 (11.9)	112 (10.0)	
>3hours/week	83 (6.3)	407 (7.2)	1,108 (8.3)	342 (7.1)	67 (6.0)	
Weekly Vitamin/Mineral Supplement Use						<.001
No	1,238 (95.0)	5,263 (93.4)	12,044 (90.4)	4,451 (92.9)	1,064 (94.7)	
Yes	65 (5.0)	373 (6.6)	1278 (9.6)	338 (7.1)	59 (5.3)	
Alcohol Intake						0.08
Never	1,260 (96.7)	5,386 (95.6)	12,679 (95.2)	4,578 (95.6)	1,079 (96.1)	

Ever	43 (3.3)	250 (4.4)	643 (4.8)	211 (4.4)	44 (3.9)	
Family History of Breast Cancer						0.07
No	1,287 (98.8)	5,572 (98.9)	13,112 (98.4)	4,716 (98.5)	1,113 (99.1)	
Yes	16 (1.2)	64 (1.1)	210 (1.6)	73 (1.5)	10 (0.9)	
Breast Cancer						0.99
No	1,285 (98.6)	5,559 (98.6)	13,144 (98.7)	4,722 (98.6)	1,108 (98.7)	
Yes	18 (1.4)	77 (1.4)	178 (1.3)	67 (1.4)	15 (1.3)	
Baseline Weight, Mean (SD)	60.8 (8.4)	57.5 (8.2)	55.1 (8.1)	54.3 (8.1)	54.3 (7.2)	
Follow-up Weight, Mean (SD)	47.7 (8.5)	52.2 (8.3)	55.4 (8.2)	60.1 (8.3)	68.0 (7.6)	

SD=Standard Deviation

Table C3: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Study Population Characteristics in Relation to Breast Cancer

	Cases, n	HR (95% CI)
Dialect group		
Hokkiens	186	1.00 (reference)
Cantonese	169	0.88 (0.71, 1.08)
Education		
No formal	98	1.00 (reference)
Primary	148	1.27 (0.99, 1.64)
Secondary +	109	1.68 (1.28, 2.20)
BMI		
<20	42	1.00 (reference)
20-24	184	1.25 (0.90 1.75)
24-28	95	1.47 (1.02, 2.12)
>28	34	1.61 (1.02, 2.53)
Age at Regularity, years		
< 13	42	1.00 (reference)
13-14	141	1.23 (0.87, 1.74)
15-16	123	1.14 (0.80, 1.61)
≥17	43	0.88 (0.57, 1.34)
Never Regular	6	0.54 (0.23, 1.27)
Age at First Birth, years		
≤20	47	1.00 (reference)
21-25	107	1.05 (0.75, 1.48)
26-30	113	1.56 (1.11, 2.19)
≥31	51	1.82 (1.23, 2.71)
Nulliparous	37	1.99 (1.30, 3.07)
Menopausal Status (missing=5)		
Still menstruating	137	1.00 (reference)
Postmenopausal	218	0.74 (0.60, 0.92)
Ever Postmenopausal Hormone Use		
No	191	1.00 (reference)
Yes	27	1.70 (1.45, 2.54)
Number of Full Term Births		
≥3	191	1.00 (reference)
1-2	127	1.41 (1.13, 1.77)
0	37	1.77 (1.25, 2.52)
Smoking Status		
Never	330	1.00 (reference)
Ever	25	1.01 (0.67, 1.52)
Any Weekly Moderate Physical Activity		
None	283	1.00 (reference)
30 minutes-3hours/week	44	0.90 (0.65, 1.23)

>3hours/week	28	0.97 (0.66, 1.43)
Weekly Vitamin/Mineral Supplement Use		
No	319	1.00 (reference)
Yes	36	1.28 (0.91, 1.81)
Alcohol Intake		
Never	347	1.00 (reference)
Ever	8	0.49 (0.24, 0.99)
Family History of Breast Cancer		
No	349	1.00 (reference)
Yes	6	1.20 (0.53, 2.68)

HR=Hazard Ratio
95% CI= 95% Confidence Intervals

Table C4: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in relation to Breast Cancer Risk without Adjusting for BMI

Weight Change in Kilograms	N	HR (95% CI)*	HR (95% CI)**	HR (95% CI)***
-20 to -10 kg	18	1.00 (reference)	1.00 (reference)	1.00 (reference)
-10 to -3 kg	77	0.98 (0.59, 1.65)	0.92 (0.55, 1.54)	0.93 (0.56, 1.56)
-3 to 3 kg	178	0.95 (0.58, 1.57)	0.85 (0.52, 1.38)	0.86 (0.53, 1.40)
3 to 10 kg	67	1.06 (0.62, 2.23)	0.92 (0.55, 1.56)	0.93 (0.55, 1.58)
10 to 20 kg	15	1.12 (0.56, 2.23)	0.97 (0.49, 1.93)	0.98 (0.49, 1.95)
p for trend		0.63	0.92	0.94

*Adjusted for dialect, baseline interview date, age
**Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity
***Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

Table C5: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Joint Effects of Dietary Soy/Green Tea Intake and Weight Change among All Women in the SCHS

Soy Food (g/1000Kcal)	n	HR (95% CI)*
> Median/No Weight Gain and Weight Loss	131	1.00 (reference)
< Median/No Weight Gain and Weight Loss	142	1.09 (0.83, 1.42)
> Median/Weight Gain >3kg	34	0.94 (0.64, 1.37)
< Median/Weight Gain >3kg	48	1.39 (0.97, 1.98)
p for trend		0.19
p for interaction		0.27
Green Tea		
Drinker/No Weight Gain and Weight Loss	113	1.00 (reference)
Nondrinker/No Weight Gain and Weight Loss	160	0.95 (0.75, 1.22)
Drinker/Weight Gain >3kg	26	0.88 (0.58, 1.36)
Nondrinker/Weight Gain >3kg	56	1.20 (0.86, 1.67)
p for trend		0.41
p for interaction		0.46

*Adjusted for dialect, baseline interview date, age

Table C6: Hazard ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in relation to Breast Cancer Risk among Postmenopausal Women after Removal of Subjects in the 1st and 99th Percentiles

Weight Change	Cases, n	HR (95%CI)*	HR (95%CI) #	HR (95%CI) ¥	HR (95%CI)**	HR (95%CI)***
<-5 kg	22	0.86 (0.54, 1.35)	0.78 (0.49, 1.24)	0.78 (0.49, 1.24)	0.89 (0.56, 1.40)	0.88 (0.56, 1.39)
-3 to -5 kg	48	1.33 (0.95, 1.86)	1.30 (0.93, 1.83)	1.29 (0.92, 1.81)	1.37 (0.98, 1.91)	1.35 (0.97, 1.89)
-2 to 2 kg	120	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3 to 5 kg	42	1.14 (0.80, 1.62)	1.15 (0.81, 1.64)	1.15 (0.81, 1.64)	1.13 (0.80, 1.61)	1.13 (0.80, 1.61)
>5 kg	28	1.09 (0.72, 1.65)	1.18 (0.78, 1.79)	1.18 (0.78, 1.78)	1.14 (0.75, 1.72)	1.14 (0.75, 1.72)

*Adjusted for dialect, baseline interview date, age

#Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity

¥Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

** Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity

***Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

Table C7: Hazard ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in relation to Breast Cancer Risk among Postmenopausal Women after Removal of First Two Years of Follow-up

Weight Change	Cases, n	HR (95%CI)*	HR (95%CI) #	HR (95%CI) ¥	HR (95%CI)**	HR (95%CI)***
<-5 kg	21	1.06 (0.66, 1,72)	0.95 (0.58, 1.56)	0.95 (0.58, 1.55)	1.10 (0.68, 1.78)	1.08 (0.67, 1.76)
-3 to -5 kg	37	1.44 (0.98, 2.11)	1.43 (0.97, 2.10)	1.42 (0.96, 2.09)	1.48 (1.00, 2.18)	1.47 (1.00, 2.16)
-2 to 2 kg	86	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3 to 5 kg	31	1.18 (0.78, 1.77)	1.18 (0.78, 1.78)	1.18 (0.78, 1.79)	1.17 (0.77, 1.76)	1.17 (0.78, 1.76)
>5 kg	22	1.12 (0.70, 1.79)	1.21 (0.76, 1.94)	1.21 (0.75, 1.93)	1.17 (0.73, 1.87)	1.17 (0.73, 1.87)

*Adjusted for dialect, baseline interview date, age

#Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity

¥Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

** Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity

***Adjusted for dialect, baseline interview date, age, moderate physical activity, education, family history of breast cancer, menopausal status, age at regularity, parity, omega-3, soy and green tea.

Table C8: Weight Change Variable by Diabetes Status (Baseline and Follow-up)

Diabetes Status	<-5 kg	-3 to -5 kg	-2 to 2 kg	3 to 5 kg	>5 kg
Baseline					
No	2035 (86.9)	2624 (89.3)	8907 (92.8)	2831 (94.8)	2139 (93.3)
Yes	308 (13.1)	314 (10.7)	314 (7.2)	157 (5.2)	153 (6.7)
Follow-up					
No	1793 (76.5)	2400 (81.7)	8393 (87.4)	2718 (91.0)	2012 (87.8)
Yes	550 (23.5)	538 (18.3)	1209 (12.6)	270 (9.0)	280 (12.2)

Table C9: Hazard ratios (HR) and 95% Confidence Intervals (CI) for Weight Change in relation to Breast Cancer Risk among Postmenopausal Women with Additional Adjustment for Diabetes Status in the Singapore Chinese Health Study (n=20163)

Weight Change	Cases, n	HR (95%CI)**	HR (95%CI)***
<-5 kg	26	0.82 (0.53, 1.28)	0.83 (0.53, 1.28)
-3 to -5 kg	48	1.31 (0.94, 1.83)	1.31 (0.94, 1.83)
-2 to 2 kg	120	1.00 (reference)	1.00 (reference)
3 to 5 kg	42	1.15 (0.81, 1.64)	1.15 (0.81, 1.63)
>5 kg	31	1.20 (0.81, 1.79)	1.20 (0.81, 1.79)

**Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity, baseline diabetes status
**Adjusted for dialect, baseline interview date, age, moderate physical activity, BMI, education, family history of breast cancer, menopausal status, age at regularity, parity, follow-up diabetes status

Table C10: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for the Joint Effects of Baseline BMI and Weight Change among Postmenopausal Women in the SCHS (n=20163)

< Median BMI (24 kg/m^2)	n	HR (95%CI)*
No Weight Gain and Weight Loss	102	1.00 (reference)
Weight Gain ≥3kg	48	1.15 (0.82, 1.62)
≥ Median BMI		
No Weight Gain and Weight Loss	92	1.38 (1.04, 1.83)
Weight Gain ≥3kg	25	1.44 (0.93, 2.23)
p for interaction		0.73
RERI		-0.09

*Adjusted for dialect, baseline interview date, age

Appendix D: Role of Soy and Green Tea on Ovarian Cancer Risk among Singaporean Chinese Women

We evaluated the associations between soy and tea intake in relation to ovarian cancer risk among women in the Singapore Chinese Health Study. We reported a positive association between higher soy intake and ovarian cancer risk among postmenopausal women. We also reported a positive association with black tea intake. These results should be interpreted cautiously given that the analyses were based on data from only 124 ovarian cancer cases, and thus produced imprecise rate estimates. Future prospective studies among women with high soy intake are needed to evaluate whether soy intake among postmenopausal women may increase the risk of developing ovarian cancer.

Table D1: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Study Population Characteristics in Relation to Ovarian Cancer

	No. of Cases	HR (95% CI)*
Education		
No formal/Primary	103	1.00 (reference)
Secondary/A level/University	21	0.80 (0.49, 1.32)
BMI		
<20	15	1.00 (reference)
20-24	71	1.28 (0.73, 2.24)
24-28	27	1.21 (0.64, 2.27)
>28	11	1.39 (0.64, 3.04)
Age at Regularity, years		
≥17 or Never Regular	23	1.00 (reference)
15-16	46	1.13 (0.68, 1.87)
13-14	40	0.95 (0.57, 1.60)
< 13	15	1.01 (0.52, 1.97)
Age at First Birth, years		
Nulliparous	21	1.00 (reference)
≥31	9	0.30 (0.14, 0.65)
26-30	25	0.33 (0.19, 0.59)
21-25	38	0.34 (0.20, 0.58)
≤20	31	0.56 (0.32, 0.99)
Menopausal Status		
Still menstruating	34	1.00 (reference)
Postmenopausal	90	0.84 (0.50, 1.43)
Ever Postmenopausal Hormone Use		
No	84	1.00 (reference)
Yes	6	1.01 (0.43, 2.37)
Number of Full Term Births		
0	21	1.00 (reference)
1-2	36	0.44 (0.26, 0.76)
≥3	67	0.34 (0.21, 0.56)
Smoking Status		
Never	113	1.00 (reference)
Ever	11	1.02 (0.54, 1.92)
Any Weekly Strenuous/Vigorous Physical Activity		
No	119	1.00 (reference)
Yes	5	0.66 (0.27, 1.63)
Weekly Vitamin/Mineral Supplement Use		
No	112	1.00 (reference)
Yes	12	1.29 (0.71, 2.35)
Alcohol Intake		
None	116	1.00 (reference)

≥1 drinks/week	8	0.69 (0.34, 1.42)
Family History of Breast Cancer		
No	123	1.00 (reference)
Yes	1	0.62 (0.09, 4.43)

*Adjusted for age, father's dialect group, and interview year

HR=Hazard Ratio
95% CI=95% Confidence Interval

Table D2: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Soy Intake in relation to Ovarian Cancer Risk

	Overall		Premenopausal		Postmenopausal	
	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*
Soy Food (g)						
Median						
< 85.7 g	59	1.00 (reference)	19	1.00 (reference)	40	1.00 (reference)
≥ 85.7 g	65	1.16 (0.79, 1.71)	15	0.69 (0.33, 1.45)	50	1.42 (0.90, 2.25)
Tertiles						
T1 (30.0 g)	36	1.00 (reference)	14	1.00 (reference)	22	1.00 (reference)
T2 (89.4 g)	53	1.52 (0.99, 2.35)	14	0.79 (0.37, 1.69)	39	2.03 (1.19, 3.47)
T3 (811.8 g)	35	1.08 (0.65, 1.82)	6	0.33 (0.12, 0.95)	29	1.70 (0.92, 3.14)
p for trend		0.69		0.04		0.08
Soy Isoflavones (mg)						
Median						
< 14.2 mg	61	1.00 (reference)	19	1.00 (reference)	42	1.00 (reference)
≥ 14.2 mg	63	1.07 (0.73, 1.57)	15	0.67 (0.32, 1.40)	48	1.28 (0.82, 2.01)
Tertiles						
T1 (4.8 mg)	39	1.00 (reference)	11	1.00 (reference)	28	1.00 (reference)
T2 (14.8 mg)	49	1.26 (0.82, 1.94)	15	1.09 (0.49, 2.42)	34	1.33 (0.80, 2.22)
T3 (147.3 mg)	26	0.99 (0.56, 1.63)	8	0.61 (0.22, 1.68)	28	1.18 (0.66, 2.11)
p for trend		0.99		0.37		0.56
Soy Protein (g)						
Median						
< 4.5 g	53	1.00 (reference)	17	1.00 (reference)	36	1.00 (reference)
≥ 4.5 g	71	1.47 (1.00, 2.17)	17	0.93 (0.45, 1.95)	54	1.77 (1.12, 2.80)
Tertiles						
T1 (1.6 g)	39	1.00 (reference)	15	1.00 (reference)	24	1.00 (reference)
T2 (4.7 g)	51	1.34 (0.87, 2.05)	14	0.73 (0.35, 1.54)	37	1.74 (1.03, 2.94)
T3 (32.1 g)	34	0.95 (0.56, 1.58)	5	0.25 (0.08, 0.74)	29	1.53 (0.83, 2.79)
p for trend		0.91		0.01		0.16

*Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI.
p for interaction for menopausal status and soy food tertiles: 0.2337; P for interaction menopausal status and soy protein tertiles. 0.194.

Table D3: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Green and Black Tea Intake in relation to Ovarian Cancer Risk

	Overall		Premenopausal		Postmenopausal	
	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*
Green Tea						
Non-Green Tea Drinker	82	1.00 (reference)	19	1.00 (reference)	63	1.00 (reference)
Monthly	15	0.96 (0.55, 1.67)	6	1.52 (0.61, 3.82)	9	0.76 (0.38, 1.53)
Weekly	18	0.88 (0.52, 1.46)	7	1.28 (0.53, 3.06)	11	0.75 (0.39, 1.42)
Daily	9	0.63 (0.31, 1.26)	2	0.54 (0.12, 2.35)	7	0.66 (0.30, 1.45)
P for trend		0.21		0.82		0.18
Non-Green Tea Drinker	82	1.00 (reference)	19	1.00 (reference)	63	1.00 (reference)
Drinker	42	0.83 (0.57, 1.22)	15	1.15 (0.58, 2.28)	27	0.73 (0.46, 1.15)
Black Tea						
Non-Black Tea Drinker	86	1.00 (reference)	20	1.00 (reference)	66	1.00 (reference)
Monthly	13	1.41 (0.79, 2.54)	5	1.92 (0.72, 5.13)	8	1.22 (0.59, 2.55)
Weekly	11	0.65 (0.35, 1.23)	2	0.40 (0.09, 1.71)	9	0.78 (0.39, 1.57)
Daily	14	1.59 (0.90, 2.81)	7	2.68 (1.12, 6.39)	7	1.15 (0.53, 2.52)
P for trend		0.59		0.26		0.93
Non-Black Tea Drinker	86	1.00 (reference)	20	1.00 (reference)	66	1.00 (reference)
Drinker	38	1.09 (0.74, 1.61)	14	1.37 (0.69, 2.72)	24	0.99 (0.62, 1.59)

*Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI, tea intake-cups/month [black tea intake for green tea categories and green tea intake for black tea categories].
**Drinkers are defined as any tea (green or black) intake (e.g., ≥monthly)

Table D4: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Joint Effects of Soy and Green Tea Intake

	Green tea			
	Nondrinker		Drinker	
	Cases, n	HR (95% CI)*	Cases, n	HR (95% CI)*
Overall				
Soy intake				
≥median	44	1.00 (referent)	21	0.63 (0.37, 1.06)
<median	38	0.70 (0.44, 1.11)	21	0.79 (0.46, 1.35)
Premenopausal				
Soy intake				
≥median	10	1.00 (referent)	5	0.60 (0.21, 1.78)
<median	9	0.84 (0.33, 2.15)	10	1.80 (0.72, 4.47)
Postmenopausal				
Soy intake				
≥median	34	1.00 (referent)	16	0.65 (0.36, 1.18)
<median	29	0.65 (0.38, 1.10)	11	0.51 (0.25, 1.02)

* Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI, black tea intake-cup/month.
Green tea intake was defined as follows: No= non-green tea drinkers; Yes=any green tea intake (e.g., ≥monthly).
P for interactions: green tea 4 levels X menopausal status= 0.1868; green tea 2 levels X menopausal status= 0.1027.

Table D5: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Joint Effects of Soy and Black Tea Intake

	Black tea			
	Nondrinker		Drinker	
	Cases, n	HR (95% CI)*	Cases, n	HR (95% CI)*
Overall				
Soy intake				
≥median	47	1.00 (referent)	18	0.75 (0.44, 1.31)
<median	39	0.68 (0.43, 1.07)	20	1.11 (0.65, 1.89)
Premenopausal				
Soy intake				
≥median	9	1.00 (referent)	6	1.11 (0.39, 3.14)
<median	11	1.19 (0.47, 3.00)	8	2.15 (0.80, 5.72)
Postmenopausal				
Soy intake				
≥median	38	1.00 (referent)	12	0.68 (0.35, 1.30)
<median	28	0.56 (0.33, 0.95)	12	0.85 (0.43, 1.65)

* Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI, green tea intake-cup/month
Black tea intake was defined as follows: No= non-black tea drinkers; Yes=any black tea intake (e.g., ≥monthly).
P for interaction: black tea 4 level X menopausal status=0.3772; black tea 2 level X menopausal status=0.1131.

Table D6: Hazard Ratios (HR) 95% Confidence Intervals (CI) by Median of Soy Food Intake and BMI in relation to Ovarian Cancer among All Women in the Singapore Chinese Health Study

	Overall		< BMI median		≥ BMI median	
	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*
Soy Food Adjusted for Food Energy						
<Median	59	1	26	1	33	1
≥ Median	65	1.16 (0.79, 1.71)	32	1.03 (0.73, 2.07)	33	1.07 (0.65,1.74)
Green Tea						
Non-Green Tea Drinker	82	1	41	1	41	1
Drinker	42	0.84 (0.58, 1.23)	17	0.72 (0.41, 1.27)	25	0.96 (0.58, 1.58)

* Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI, black tea intake-cup/month

Green tea intake was defined as follows: No= non-green tea drinkers; Yes=any green tea intake (e.g., ≥monthly).

Median BMI 23.2 kg/m^2

Table D7: Hazard Ratios (HR) and 95% Confidence Intervals (CI) by Median Soy Food Intake and BMI in relation to Ovarian Cancer among Postmenopausal Women in the Singapore Chinese Health Study

			< BMI median		≥ BMI median	
	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*	Cases, n	HR (95%CI)*
Soy Food Adjusted for Food Energy						
<Median	40	1.00 (ref)	16	1.00 (ref)	24	1.00 (ref)
≥ Median	50	1.43 (0.94, 2.17)	25	1.72 (0.91, 3.24)	25	1.22 (0.69, 2.15)
Green Tea						
Non-Green Tea Drinker	63	1.00 (ref)	28	1.00 (ref)	35	1.00 (ref)
Drinker	27	0.73 (0.47, 1.16)	13	0.85 (0.43, 1.50)	14	0.65 (0.35, 1.22)

* Adjusted for age, father's dialect group, interview year, number of full term births, education, BMI, black tea intake-cup/month

Green tea intake was defined as follows: No= non-green tea drinkers; Yes=any green tea intake (e.g., ≥monthly).

Median BMI 23.2 kg/m^2