THE ASSOCIATION BETWEEN CRUCIFEROUS VEGETABLES INTAKE AND BREAST CANCER RISK AMONG WOMEN WITH FAMILIAL BREAST CANCER

by

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ABSTRACT

Background

The effect of cruciferous vegetables consumption on breast cancer risk is controversial. Cruciferous vegetables are a primary source of glucosinolates that have shown anticarcinogenic effects in etiological studies. Some prior epidemiological and intervention studies suggested the protective effect of crucifers on breast cancer risk but the results were inconsistent. This study evaluated the effect of crucifers on breast cancer risk among women from a familial risk cohort.

Methods

To address this issue, a hospital-based case-control study was conducted among 200 cases and 200 controls matched on age at baseline and enrollment year, from the same familial risk cohort. A self-developed food frequency questionnaire was applied to assess the consumption of 25 subtypes of crucifers. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated from conditional logistic regression. Cases and controls were stratified by menopausal status and body mass index (BMI, cutoff point 25 kg/m^2) and unconditional logistic regression was used in stratified analyses.

Results

The median consumption of total crucifers was 1 serving/day in cases and less than one serving/day in controls. Total crucifers intake was not associated with breast cancer risk after adjusting for breast cancer risk

factors. Broccolini showed a protective effect that closed to significance on the development of breast cancer (adjusted OR=0.51, 95% CI = [0.25, 1.01], and *P* = 0.06). BMI modified the association between total crucifers consumption and breast cancer risk (*P* = 0.015). Most subtypes non-significantly decreased the odds of developing breast cancer among normal BMI women while non-significantly increased the odds of developing breast cancer among overweight/obese women.

Conclusions

To the best of our knowledge, this is the first study to examine the impact of cruciferous vegetables on breast cancer risk among women with a familial breast cancer risk and one of the few studies that has collected detailed information on crucifer intake. Total cruciferous vegetables intake was not associated with breast cancer risk among women with a familial risk. Our results suggested that BMI may modify the association between the cruciferous vegetables and breast cancer risk among the high-risk population.

PREFACE AND ACKNOWLEDGEMENTS

In August 2014, I began working toward a Master of Science degree in cancer epidemiology, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (JHSPH) in Baltimore, Maryland. To fulfill the requirement of my degree, I worked on my master thesis as a student research in Department of Epidemiology in JHSPH, advised by Dr. Kala Visvanathan.

My thesis is focused on examining the association between cruciferous vegetables consumption and breast cancer risk among women with a familial history of breast cancer. Diet is a modifiable risk factor that could therefore be a primary prevention strategy for women with a higher risk due to hereditary factors in addition to other lifestyle factors. A few studies in the general population have shown inverse associations between breast cancer risk and cruciferous vegetables intake. These finding are supported by preclinical studies which suggest that sulforaphane (SFN), a major nutrient of crucifers, has anti-carcinogenic effects. SFN has been shown to inhibit the growth of tumor cells active apoptosis and decrease the expression of key proteins involved in breast cancer proliferation in breast cancer cell lines. There has been no study conducted in women with a familial risk before.

To conduct this study, I took advantage of an ongoing cohort study known as the Breast and Ovarian Surveillance (BOSS) Cohort Study which has recruited men and women with a familial risk for breast and/or ovarian cancer from the Johns Hopkins Clinical Cancer Genetics and Prevention Service between 2005 and 2013. I conducted a matched case-control study to explore

the association between crucifers and breast cancer risk among women with a familial risk. Cases were confirmed by pathology records and medical record.

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I would first like to thank my thesis advisor, Dr. Kala Visvanathan, for her competent, patient, and kind mentorship during these two years. She helped me in building the idea of my thesis, providing me the dataset for the analyses and providing guidance in the analysis and interpretation of the results with me whenever she thought I needed help. Dr. Visvanathan's knowledgement and consistently support inspired and encouraged me to overcome many hurdles in my academic career. Acknowledgements are also due to Dr. Avonne Connor, as the reader of my thesis, for her meticulous and valuable comments on my thesis. I would also like to thank the BOSS research team, including Betty May, Brenna Hogan, Alpana Kaushiva, Michelle McCullough, Michele Trieb, Cody Ramin and all the investigators, researchers, and laboratory personnels, for their hardwork and commitment to producing high-quality clean data and generous help for my thesis. Specifically, thanks are due to Alpana Kaushiva for helping me organizing the dataset and discussing the methods and results. Thanks are also due to the patients in BOSS Cohort Study. I thank Aozhou Wu, and all my good friends in JHSPH for their company and support in these two years. Finally, I express my gratitude to my parents for supporting and encouraging me in pursuing the Master of Science degree throughout the two years. The accomplishment would not have been possible without them. Thank you.

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BACKGROUND

Summary of Breast Cancer

Burden of Disease

Breast cancer is the most common non-skin cancer among women in the United States and worldwide. There were 234,840 new cases and 40,290 deaths in 2015, accounting for 14.0% of all new cancer cases and 6.8% of all cancer deaths in US, respectively (1).

Figure 1 shows long-term trends of the incident cases and deaths from invasive breast cancer in US between 1992 and 2012 from the Surveillance, Epidemiology, and End Results Program (SEER) (1). As shown in Figure 1, the incidence of invasive breast cancer started to increase in the early 1980s and reached its peak at 1998. The increase during this time period may due to the introduction and prevalence of mammography screening (2), the changes in the reproductive patterns, and the rising rates of hormone replacement therapy (HRT) use in US (2, 3). Mammography screening can detect more breast tumors at an earlier stage, leading to the increase in the number of cases being detected. Changes in the reproductive patterns, such as not having children at younger age, and the increasing use of HRT increased the risk of breast cancer and resulted in more cases. After being stable for 4 years (1998-2002), the incidence of breast cancer dropped rapidly in 2002 and 2003. The rapid decrease was likely associated with the decrease of HRT use after the Women's Health Initiative randomized trial reported the

increasing risk of breast cancer among HRT users in 2002 (3, 4). The incidence became stable afterwards (1, 3). Figure 1 also presents the steady decrease in mortality of breast cancer since the 1990s. The decrease in mortality may due to the introduction of mammography screening (i.e. early detection) and the progress in breast cancer treatment (1, 3).

In the US, compared to other race/ethnicity, white women had the highest incidence of breast cancer (127.9 per 100,000 person-year), followed by African Americans (124.4 per 100,000 person-year) (data in 2015) (1). The change patterns of incidence rate of breast cancer were similar in white women and African American women (1). Compared to women aged less than 50, women aged 50 or older had a higher rate of incident invasive breast cancer, among whom the age group between 55 y to 64 y had the highest incidence of breast cancer, accounting for 25.6% of the new cases (1). The increase of invasive breast cancer between early 1980's and 1998 was largely due to the increasing number of cases among women aged 50 or older. The trend of incidence of breast cancer was stable among women aged less than 50 (1).

Subtypes of breast cancer

There are many classification systems to identify the subtypes of breast cancer reflecting the fact that breast cancer is a heterogenous group of dieases based on molecular features, gene expression, and risk factors, rather than a single disease (5). Based on the biological markers and the gene expression profiles, the "intrinsic" subtypes classification system, which is the most popular classification system of breast cancer, classifies the

breast cancer into 1) estrogen receptor (ER) positive tumors (i.e. luminal tumors); 2) basal-like ER negative tumors; 3) human epidermal growth factor receptor 2 (HER2) positive and ER negative tumors; and 4) normal breast tumors (5-7). The luminal group has been subdivided into two groups: luminal A (ER+/HER2-) and luminal B (ER+/HER2+) based on the HER2 status (7). The basal-like tumors and HER2+/ER- tumors show high gene expression for basal markers but low expression for luminal breast epithelium (6). Besides the ER, HER2, and gene expression profiles, progesterone receptor (PR), cytokeratins (CKs), and epidermal growth factor receptor (EGFR) have also been taken into account when classifying the breast cancer in the clinical settings.

Among all the subtypes, luminal A has the highest prevalence, accounting for 40% of breast cancer (5, 7). The ER- tumors are more likely to grow and spread more aggressive than the ER+ tumors (luminal A and B), resulting in a higher mortality in the short-term (5, 8). In the long-term, even though the mortality of luminal tumors remains constant over time, it becomes higher than the non-luminal tumors due to the fact that the mortality of non-luminal decreased over time (8).

Established Risk Factors of Breast Cancer

Family History of Breast and/or Ovarian Cancer

Ever since the scientists noticed breast cancer in families, a number of epidemiological studies have been conducted to evaluate the impact of family history for breast cancer. Compared to women without family history of breast and/or ovarian cancer, women with one first-degree relatives (i.e. mother,

sister or daughter) with breast/ovarian cancer had twice the risk of getting breast cancer while having two first-degree breast/ovarian cancer relatives tripled the risk(9). Among women with first-degree breast cancer relatives, women with first-degree relatives with postmenopausal breast cancer had a lower risk of breast cancer than women with first-degree relatives with premenopausal breast cancer (10). Family history increases the risk of breast cancer in all subtypes (11).

Even though family history is a strong risk factor for breast cancer, a large pooled analysis from 52 epidemiological studies indicated that only 12% of breast cancer patients had an affected first-degree relative and most of women with family history of breast and/or ovarian cancer never develop breast cancer (12).

Genetic Risk Factors

The concept of hereditary breast cancer has been known for many years. There are only 25% of familial breast cancers and 5-10% of all breast cancers are attributed to be hereditary (13, 14). In general, for *BRCA1* and *BRCA2* carriers, the penetrance ranges are 40-87% and 18-88%, respectively (10). A linkage study among women from families with multiple-breast cancer cases (i.e. families with at least four cases with onset at age < 60 y) showed that the *BRCA1* contributed to a cumulative breast cancer risk of 54% (95% CI = [27%, 71%]) by age 60 y (15). However, most of women with one or two relatives who subject with breast cancer are not *BRCA1/2* carriers (16). Other germline mutations, such as ATM (17), CDH1 (18), p53 (19), PALB2 (20), and PTEN (21), are associated with breast cancer but occur less frequently.

Environmental Risk Factors

Besides hereditary risk factors, breast cancer is strongly (relative risk > 4.0) associated with aging, breast density, and personal history of cancer. The relative risk of breast cancer is 5.8 times higher among women aged 65 or older compared to women less than 65 y (10).

Breast cancer is moderately associated with obesity among postmenopausal women, and the association is positively modified by aging (10, 22). On the other hand, high body mass index (BMI) has been reported to lower the risk of breast cancer among premenopausal women (11, 22, 23). Besides obesity, higher amount of alcohol consumption (24-26), and lower level of physical activity (27, 28) are moderately associated with breast cancer risk.

Reproductive Factors

Because of the inherant hormone dependent property of breast cancer, reproductive factors play a role in the incidence of breast cancer, with the restriction to hormone receptor (HR) positive tumors (11, 29). Nulliparity, older age at first birth, younger age at menarche, older age at menopausal and longer interval between age at menarche and age at first birth are positively associated with the HR+ breast tumors (11, 29). The impacts of reproductive factors on HR- breast cancer are inconsistent. Longer duration of breastfeeding is the most consistent association for HR- tumors, especially for triple negative breast cancer (ER-/PR-/HER2-) (29).

The increasing risk by using HRT was discovered by Women's Health Initiative (WHI) in 2002 as described before and then being reported by several clinical trials as well (3, 30-32). So it was the duration of HRT use (32). After the cessation of HRT use, the risk of breast cancer drops and then nearly disappeared 5 years later (32). The results of the effects of oral contraceptive use on breast cancer were inconsistent (22, 33).

Crucifer Vegetables and its Metabolites

Cruciferous vegetables, also known as *Brassica* vegetables, include broccoli, brussels sprouts, cabbage, cauliflower, collard greens, kale, parsnip, radish, horseradish, wasabi, Chinese cabbage, bok choy, turnips, rutabaga, kohlrabi, mustard, etc. (34, 35). The cruciferous vegetables have been recognized as protective factors of lung, colorectal, stomach, breast, prostate, and other cancers in some epidemiological studies (36-40). Biological studies have demonstrated that the anticarcinogenic effect of most of cruciferous vegetables is due to glucosinolates (41). More than 100 glucosinolates and their bioactivities have been identified in vegetables (42). Glucosinolates is converted by myrosinase enzymes in plant cells and by microflora in the gastrointestinal tract into two groups of metabolites: indoles group (e.g. indole-3-carbinol (I3C)) and isothiocyanates (ITC) group (35, 36, 43). Figure 2 showed the hydrolysis products of glucosinolates and the formation of I3C and ITC (44). The contents of glucosinolates vary across different cruciferous vegetables and have been described in Table 1 (44). Besides the subtypes,

the quantities of bioactivities of crucifers differ by the age and the fresh/frozen status of the cruciferous vegetables (45).

Isothiocyanates

Isothiocyanates (ITC) is the stable glucosinolates hydrolysis that are produced at neutral pH 6-7 (Figure 2) (43, 44). The well-established feature of ITC is that it could modulate phase I enzymes (e.g. cytochrome P450, CYP) and phase II enzymes (e.g. glutathione S-Transferase, GST) (36, 46). Phase I enzymes could promote the biotransformation of chemical carcinogens and phase II enzymes could protect cells from DNA damage by carcinogens and reactive oxygen species (42). It has been hypothesized that the anti-carcinogenic effects of isothiocyanates were induced by inhibiting the carcinogen activation of phase I enzymes or increasing the activity of phase II enzymes (42).

Sulforaphane (SFN) is one of the isothiocyanates, and is the most prominent potent inducer of phase II enzymes in cultured human cells. Phase II enzymes include quinone reductase (QR), GST, epoxide hydrolase (EH) and glucuronyltranseferase (UGT), etc. (42, 47). The genes for these phase II enzymes contain a specific sequence of DNA called an antioxidant response element (ARE). SFN increases the activity of these phase II enzymes by accelerating the transcription the genes which contain an ARE (48). Animal studies also reported that SFN could induce the cell lines' type-specific apoptosis (49), inhibit the growth of phenotypically different breast cancer cells (50) and suppress the proliferation both in breast cancer cells line and the whole animal model (51). A recent epigenetic study showed SFN could

activate DNA methylation-silenced tumor genes in the breast cancer cell lines (52).

Indole-3-carbinol

Indole-3-carbinol (I3C) is derived from the unstable glucosinolates (Figure 2) (44) and is the prominent product that has been studied as a hormonal-dependent cancer chemoprotective agent. Animal models showed that I3C could suppress the growth of both estrogen responsive (MCF-7 cell line) and estrogen independent (MDA-MB-231 cell line) human breast cancer cells (53). I3C is converted to a series of oligomeric products under acidic conditions, amongst 3,3`-diindolylmethane (DIM) is a major self-condensation product that could arrest the proliferation of human breast cancer cells (54) and induce G1/S arrest of the cell cycle as well as apoptosis (55). Scientists believed that the anti-carcinogenic effects of I3C are mediated by DIM (36). However, I3C has been found to promote or enhance the development of cancers after exposure to carcinogen in animal studies (56-59). The cancer-promoting effect of I3C was discovered in an animal tumor study of liver cancer (57) and then reported in thyroid (58), colon (59), and uterus (60) cancers. Studies in cell cultures further supported the cancer-promoting effect (61). They suggested that I3C and its acid condensation products, DIM, could enhance the transcription of estrogen-responsive gene (61). The contradictory results of animal studies suggested that further work is required to define the possible risks versus benefits of I3C (62).

Breast Cancer Risk and Cruciferous Vegetables

Table 2 is a summary from prior studies that examined cruciferous vegetables consumption and breast cancer risk. A number of studies have suggested that cruciferous vegetables intake could reduce breast cancer risk (63-70). In the Western New York Diet Study, a case-control study, conducted in Eric and Niagara, observed a marginal inverse association between broccoli consumption during the past 2 y and breast cancer risk in premenopausal women (4^{th} quartile odds ratio= 0.6; 95% confidence interval (95% CI) = [0.4, 1.0]) (63). The average consumption of broccoli among premenopausal women was 851 g/month (standard deviation = 46.2 g/month), estimated from the product of the self-reported portion size and intake frequency. Two case-control studies in China showed an inverse association with breast cancer as well as the trend of lower risk for breast cancer as the consumption of crucifers increased (*P* trend = 0.03 for the Shanghai study (67) and *P* trend < 0.001 for the Guangzhou study (69)). The FFQ in the Shanghai study asked for the frequency of consumption individually for the crucifers, but the results were shown by group (total vegetables) (67). Therefore, it is difficult to isolate the effect of the cruciferous vegetables based on this study's result. For the Guangzhou study, the investigators collected dietary information during the past 12 months and used the portion size to estimate the total consumption of cruciferous vegetables (69). Another case-control study in Sweden also suggested an inverse effect of Brassica vegetables on breast cancer but only significant in the highest quartile among postmenopausal women (71). A US-wide cohort study, the Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort study, suggested that coleslaw, cabbage, and

sauerkraut were associated with a reduced risk of invasive breast cancer in postmenopausal, BMI < 25 kg/m^2 women (relative hazard= 0.81; 95% CI= [0.66, 0.97]; and *P* trend = 0.16) (68). The investigators also reported the evidence of an interaction between BMI and the dietary pattern (68). Black Women's Health Study and Women's Healthy Eating and Living cohort reported a protective effect of cruciferous vegetables on breast cancer risk among women after 12 y and 11 y follow up, respectively (64, 65).

Overall, the results are inconsistent. A large prospective cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC) study, found a null association between cabbage consumption and breast cancer risk (*P* trend = 0.11) (72). In a literature review that consisted of 54 studies (including cohort studies and case-control studies) related to cruciferous vegetables, the majority of studies (38/54) showed inverse associations between cruciferous vegetables and cancer whereas there were 8/54 studies showed positive association while 8/54 studies showed null association, respectively (40). However, the review didn't provide the magnitude of the association. A pooled analysis of eight cohort studies, consisting of 200 incident breast cancer cases, reported a null association between three subtypes of cruciferous vegetables (i.e. broccoli, brussels sprouts and cabbage) and breast cancer risk (73). Japan Public Health Center-based Prospective Study and the After Breast Cancer Pooling Project showed null association between cruciferous vegetables and breast cancer risk (65, 66). A positive risk of breast cancer among cruciferous vegetable consumers was observed in a population-based case-control study in New York (Long Island

Breast Cancer Study Project) (OR= 1.76; 95% CI= [1.18-2.61]; and *P* trend=0.03) (74). The case-control study suggested that menopausal status interacted with the effect of vegetables and fruits on breast cancer and that vegetables and fruits tend to show protective effect on ER+ tumors (74).

The studies described above mainly focus on the general population. To our knowledge it has not been studied in the general population. A dietary intervention would be desirable for all women to reduce their risk particularly those with family history .To examine this question, we conducted a case-control study to explore the association between cruciferous vegetables intake and breast cancer risk overall and stratified by suvtype in women with a famililal risk.

METHODS

Study Design and Population

The Breast and Ovarian Surveillance Service (BOSS) Cohort Study is an ongoing prospective cohort study which recruited women and men with a familial risk for breast and/or ovarian cancer from the cancer genetics clinic at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD) in 2005-2013 (75). Institutional review board approval was obtained at Johns Hopkins Bloomberg School of Public Health and informed contest was obtained from all participants at enrollment. An extensive questionnaire collected the information on demographic characteristics, lifestyle factors, medical history, reproductive history, and dietary habits. A food frequency questionnaire (FFQ) assessed the consumption of vegetables, including detailed questions on crucifer intake at baseline as well. A detailed family history and blood samples were collected at this time. Follow up questionnaires are ongoing every 3 years.

All recruited women and men are with a familial risk, including 1) having family history of breast cancer or ovarian cancer; or 2) having documented deleterious BRCA1/2 mutation; or 3) having early onset breast cancer (75).

For this study, cases were women with incident breast cancer (N = 200) diagnosed in the 2 years prior to enrollment. All breast cancer diagnoses were confirmed based on medical pathology records. Women with a prior cancer history with the exception of cervical cancer in situ and non-melanoma skin

cancer were excluded. Controls (N = 200) were women who were cancer free at the time of cases were selected from the same cohort and individually matched to cases based on age at enrollment (± 1 year) and enrollment year (± 1 year).

Assessment of cruciferous vegetables

We assessed average consumption of total cruciferous vegetable in the last year as well as its 25 subtypes at baseline with a self-designed FFQ. Cruciferous vegetables included arugula, bok choy, broccoli raab, broccoli sprouts, broccolini, brussel sprouts, cabbage, cauliflower, Chinese cabbage, collard greens, cress/watercress, daikon, honey mustard, horseradish, kale, kimchi, kohlrhabi, mustard greens, mustard seeds, mustard, radish, rutabaga, turnips, and wasabi. The subtypes of cruciferous vegetable with a small intake proportion, including daikon, kimchi, kohlrhabi, mustard greens and rutabaga, were excluded from the analysis.

The sample questions have been shown in Table 3. In the FFQ, question 55 asked about the total consumption of broccoli, brussel sprouts, cabbage and cauliflower and question 57 specifically asked the intake of each subtype. The frequency responses of question 55 and 57 ranged from “not at all”, “< 1 serving/week”, “1-2 servings/week”, “3-6 servings/week”, “1 serving/day” to “more than 1 serving/day”. For each of the subtypes of cruciferous vegetables (except for broccoli), we modeled them as binary variables by collapsing category 2 to 6 into one category (i.e. 0 = “never eat”, and 1 = “have eaten”).

For broccoli, we modeled it as a binary variable by collapsing the first two categories and collapsing the rest of the categories (i.e. 0 = "< 1 servings/week", and 1 = "≥ 1 servings/week") due to the frequent intake of broccoli among participants (only 4 cases and 9 controls didn't eat broccoli). To calculate the total consumption of all subtypes, we assigned values to each intake frequency category: 0 for "not at all", 0.5/7 for "less than once per week", 1.5/7 for "1-2 per week", 4.5/7 for "3-6 per week", 1 for "1 per day", and 2 for "more than once per day" with the unit servings/day. For each individual, we summed up the values of all subtypes as the total consumption and classified it into categories with the cutoff points 0.5, 1.0 and 1.5 servings/day. Based on the literature review, we selected the four most frequent studied subtypes, including broccoli, brussel sprouts, cabbage and cauliflower. Under the same rationale, we modeled the sum of the four subtypes consumption as a categorical variable with cutoff points 2, and 3 servings/week. All the cutoff points were identified based on the distribution of intake frequency among controls.

Question 58 assessed the change pattern, after the diagnosis (cases) or during the past year (controls), of the consumption of broccoli, brussel sprouts, and mustard, respectively. The responses of changes were "not at all", "unchanged", "increased" or "decreased". The text was shown in Table 3.

Assessment of non-dietary exposures

Information on age at baseline, BMI, smoking status, age at menarche, parity, age at first birth, oral contraceptive use, menopausal status (age at

menopausal), HRT, education, physical activity and family history was obtained through the questionnaire at baseline. Family history included first-degree and second-degree relatives with breast cancer and/or ovarian cancer. The details of family history were confirmed through the pedigrees. First-degree relatives denoted mother, daughter, and sister. Second-degree relatives denoted aunt, niece, and grandmother. Family history was classified as “no family history”, “second-degree relatives only” and “both of first-degree and second-degree relatives with breast and/or ovarian cancer”. BMI was divided into three categories based on the cutoff points “< 25 kg/m^2 (normal)”, “25-30 kg/m^2 (overweight)” and “≥ 30 kg/m^2 (obese)” (76). Physical activity was measured as metabolic equivalents (METs) at baseline. METs evaluate the energy cost of physical activity by calculating the ratio of metabolic rate during the physical activities compared to that during the standard resting (77). Women with less than 3 METs, 3 to 6 METs, and more than 6 METs were classified as “light activity”, “moderate activity”, and “vigorous activity”, respectively (78). For menopausal status, women who reported “having periods” or “irregular periods” were classified as premenopausal, and who reported “have stopped periods” were classified as postmenopausal. Women who reported “using hormone replacement therapy” in the question pertained to menopausal status were classified as premenopausal if their age at enrollment was less than the median age of control women (48 years), and as postmenopausal if their age at enrollment was greater than the median age of controls. HRT was modeled as “never used”, “estrogen”, “progesterone” and “combination of both estrogen and progesterone”. Parity and age at first birth were combined as one exposure. The DNA sample of BRCA 1/2 testing was

collected and tested at baseline. Among cases, estrogen receptor and progesterone receptor were assessed, respectively.

Statistical Analysis

We checked the missing data of total cruciferous vegetable and its subtypes intake. Complete cases analysis was used for dietary exposure with missing data less than 10% and missing category was created for non-dietary covariates with missing data. The descriptive analyses of cruciferous vegetables as well as covariates were conducted. Cases and controls were compared using *t* test for normally distributed continuous variables and Wilcoxon rank-sum test for continuous variables not normally distributed. Pearson's Chi-square or Fisher exact tests were used for categorical variables. Baseline non-cruciferous covariates were also compared between categories of the total amount of all crucifer subtypes consumption. Cruciferous vegetable exposures were defined as binary variables (each subtype), and as a categorical variable (the total amount of all crucifer subtypes) in the analyses as described previously. The total amount of all crucifer subtypes were calculated by summing up the consumption of all subtypes under the rationale described before and then were categorized based on the intake frequency among controls. Adjusted odds ratios (ORs) and 95% confidence interval (95% CI) were calculated from conditional logistic regression models. Age at baseline and enrollment year are the matching factors for this study. ORs were adjusted for age at baseline, enrollment year, BMI, age at menarche, oral contraceptive use, menopausal

status, HRT, physical activity, family history and the total consumption of flame broiled meat, fish, and chicken. Each cruciferous vegetable was evaluated separately and then to compare results to previous studies. Based on the previous studies, we concluded that broccoli, brussel sprouts, cabbages, and cauliflower are the most frequent crucifers that have been studied. Thus, in this study we examined the associated of the combined intake of broccoli, brussel sprouts, cabbages and cauliflower and breast cancer. *P* trend for the categorical variable was test by Chi-square test.

Since the risk of breast cancer differs between pre- and postmenopausal women, stratified analyses by menopausal status at baseline were then conducted. Adjusted ORs and 95% CI were calculated through unconditional logistic regression model because cases and controls were not matched on menopausal status. Stratified analyses by BMI status were also conducted among this population (cut-off point 25 kg/m^2). The interaction terms (i.e. menopausal status * crucifer, and BMI * crucifer) were tested through *t* test in unconditional logistic regression model.

Previous studies suggested that the effect of crucifers is more sensitive to hormone receptor positive tumors (42, 74). The reason for we evaluated the effect of each subtype on ER positive and ER negative compared to controls, respectively, is to test whether the effect of crucifer is only restricted to ER positive tumors.

Both in question 57 and question 58, we asked whether the participants change the crucifers consuming pattern in selected subtypes (i.e. broccoli, brussel sprouts, and mustard). The crossing contexts were used to evaluate the performance of the FFQ. Percent agreements of responses regarding subtypes consumption frequency in these selected vegetables were calculated by the proportion of agreed responses among all women. Kappa statistic was calculated to test the reliability of the agreement. Kappa performs better than percent agreements because it takes into account the role of chance agreement. We considered a good performance for the FFQ if the value of kappa statistic was higher than 0.50 (79).

Considering that cases were more likely to increase their consumption of cruciferous vegetables after the diagnoses and thus have an impact on the measures, sensitivity analysis was conducted among women after excluding those who changed their dietary patterns. Because of the potential recall bias in this retrospective study, we conducted a sensitivity analysis among women excluding those who were diagnosed beyond one year before the enrollment.

All analyses were performed using Stata (version 13.0) and R (version 3.1.3).

RESULTS

Baseline demographics and clinical characteristics

The baseline demographics and clinical characteristics are shown in Table 4. Cases and controls were well matched on age at baseline and enrollment year. The mean value of age at baseline was 49.2 y in cases and 49.2 y in controls. The mean value of enrollment year was 2008 in cases and 2008 in controls. There were only 4% and 6% current smokers in cases and controls, respectively. The majority of cases and controls had a college degree or higher (i.e. post-college graduate) and were physically active.

Reproductive factors were evaluated at baseline. The difference of age at menarche between two groups was small (0.3 y) but significant (P = 0.03). The average age at menarche was 12.4 y in cases and 12.7 y in controls. More than half of participants had their first child at age later than 25 y but the distribution didn't differ in cases and controls (53.5% vs 60%, and P = 0.33). The menopausal status was significantly different between the cases and controls (P = 0.005): cases were more likely to be premenopausal (56%) while there were more postmenopausal controls (58%). Among the postmenopausal women, the mean age at menopause was 47.7 y in cases and 47.9 y in controls. The use of HRT in our study population was limited. Only a small proportion of women in this study had ever used HRT (21.5% in cases and 26.0% in controls). Oral contraceptive use significantly varied

between cases and controls (P = 0.003). There were more former users of oral contraceptive pills among cases (80.5% vs. 70.5%; cases vs. controls). The distribution of family history was significantly different between cases and controls (P < 0.001). The majority of controls (95%) had family history of breast and/or ovarian; while 73% of cases had family history.

Among invasive cases in this study, the average age at breast cancer diagnosis was 48 y and the average time from diagnosis to baseline was 0.78 y. Classified by the biological markers of breast tumors, there were 77.4% ER- positive tumors and 68% PR+ tumors among all invasive cases.

Table 5 presents the baseline demographics and clinical characteristics stratified by consumption of all cruciferous vegetables, based on the cutoff points (i.e. 0.5, 1.0, and 1.5 servings/day). Women with high consumption of total crucifer subtypes were more likely to be older and more physical active, and have a later menarche, higher education level (Table 5).

Cruciferous vegetables consumption and breast cancer risk

Table 6 describes the association between cruciferous vegetables intake and breast cancer risk.

The median consumption of crucifers was 1 servings/day in cases and less than one servings/day in controls (data not shown). The point estimate for the association between total cruciferous vegetable intake and breast cancer ranged from 0.58 to 1.38 depending on the number of servings.

The odds of developing breast cancer was reduced among women who consumed 0.5 to 1 serving/day of crucifers compared to women who consumed less than 0.5 serving/day (adjusted $OR_{II\ to\ I}$ = 0.58, 95% CI = [0.23, 1.43], and *P* =0.24). While the odds of developing breast cancer increased among women who consumed either 1-1.5 servings/day or more than 1.5 servings/day compared to women who consumed less than 0.5 serving/day (adjusted $OR_{III\ to\ I}$ = 1.38, 95% CI = [0.56, 3.42], and *P* =0.49; adjusted $OR_{IV\ to\ I}$ = 1.36, 95% CI = [0.55, 3.39], and *P* =0.51).

Based on the published literature, we selected the four most examined subtypes that are also the most prevalent, including broccoli, brussel sprouts, cabbage, and cauliflower, and summarized the total weekly consumption of the four subtypes. Half of the participants took the four selected subtypes during the past year (45.5% in cases and 50.5% in controls). An overall non-significant positive association was observed. The odds of developing breast cancer was higher in both women who ate 2- 3 servings/week and women who ate more than 3 servings/week compared to women who consumed the four selected subtypes less than 2 servings/week (adjusted $OR_{II\ to\ I}$ = 1.41, 95% CI = [0.68, 2.94], and *P* = 0.36; adjusted $OR_{III\ to\ I}$ = 1.84, 95% CI = [0.89, 3.77], and *P* =0.09).

The most frequent consumed subtype was broccoli. Only 4 cases (2%) and 9 controls (4.5%) didn't eat broccoli. Further, more than 50% in cases and controls took broccoli more than once per week during the past year.

Broccolini showed a protective effect that closed to significance on the development of breast cancer (adjusted OR=0.51, 95% CI = [0.25, 1.01], and *P* = 0.06) (Table 6).

Results from stratified analyses by menopausal status are presented in Table 7. Overall, there was no association between total cruciferous vegetable and breast cancer risk among premenopausal women; however, total cruciferous vegetable marginally increased the odds of developing breast cancer among postmenopausal women (adjusted OR = 1.95, 95% CI = [0.99, 3.83], and *P* = 0.05). The odds of developing breast cancer was significantly increased among premenopausal women who ate radish and turnips compared to women who didn't eat in the last year (OR_{radish} = 3.22, 95% CI = [1.53, 6.97], and *P* = 0.002; $OR_{turnips}$ = 2.78, 95% CI = [1.13, 6.97], and *P* = 0.03). The modification effect of menopausal status on breast cancer risk was noticed in radish (*P* = 0.04) as well. While the odds of developing breast cancer was higher in postmenopausal women who ate brussel sprouts ($OR_{brussel\ sprouts}$ = 2.04, 95% CI = [1.04, 4.05], and *P* = 0.04) and collard greens ($OR_{collard\ greens}$=2.3, 95% CI = [1.06, 5.19], and *P* = 0.04).

Table 8 presents the results from stratified analyses based on BMI using the cutoff point 25 kg/m^2. Null association was observed between total cruciferous vegetable consumption and breast cancer risk among normal BMI women (adjusted OR = 1.00, 95% CI = [0.52, 1.92], and *P* = 0.99). However, among overweight/obese women (BMI ≥ 25 kg/m^2), the total cruciferous vegetable consumption significantly increased the risk of breast cancer (adjusted OR =

4.91, 95% CI = [1.81, 9.30], and P = 0.001). Effect modification of BMI on the association between the total consumption of all subtypes and breast cancer risk was observed (P = 0.015). More than 10 subtypes suggested a ~30% reduce in breast cancer risk among normal BMI women, including broccoli raab, broccoli sprouts, broccolini, cauliflower, honey mustard, mustard, and wasabi. Broccolini was associated with a 52% decrease in the OR of breast cancer risk among normal BMI women. None of the associations were significant. In contrast, most of the subtypes showed increases in breast cancer risk among overweight/obese women (BMI ≥ 25 kg/m^2). The positive association was significant for brussel sprouts, radish and wasabi ($OR_{brussel\ sprouts}$ = 2.285, 95% CI = [1.08, 4.96], and P = 0.033; OR_{radish} = 2.351, 95% CI = [1.12,- 5.05], and P = 0.025; OR_{wasabi} = 3.204, 95% CI = [1.38, 7.84], and P = 0.008). In addition, the association between wasabi and breast cancer risk was modified by BMI (P = 0.027).

Table 9 presents the analyses among ER+ and ER- breast tumors. A significant increase of odds of developing ER+ breast cancer was observed among women who took arugula, Chinese cabbage, radish, and turnips. Brussel sprouts was significantly associated with ER- breast tumors in our study ($OR_{brussel\ sprouts}$ = 3.29, 95%CI = [1.31, 9.05], and P = 0.01).

Evaluation of the reliability for the FFQ

To evaluate the reliability of the FFQ, the percent agreements and Kappa statistics of responses were calculated in three selected subtypes of

cruciferous vegetables where we had information from two sources (i.e. broccoli, brussel sprouts, and mustard) (Table 10). The agreements, based on Kappa, for broccoli intake (Kappa = 0.74), brussel sprouts intake (Kappa = 0.65) and mustard (Kappa = 0.52) was good.

Change of cruciferous vegetables consumption

Table 11 describes the patterns of change in three selected cruciferous vegetables: broccoli, brussel sprouts, and mustard. Significantly more cases had increased their consumption of Brussel sprouts post-diagnosis than controls had during the past year. A similar change in consumption of both broccoli and mustard was observed between cases and controls, irrespectively of frequency of intake.

Sensitivity analysis

Table 12 presents the results from the sensitivity analyses. Considering that cases may prefer to increase their consumption of cruciferous vegetables after diagnosis, we conducted sensitivity analysis by excluding both cases and controls women who changed their dietary patterns either after diagnosis or during the past year. For the three selected subtype (i.e. broccoli, mustard and brussel sprouts) with information on change patterns, the measures of association were similar, comparing to the primary analyses.

We were concerned about the potential recall bias in our primary analyses; therefore, we conducted sensitivity analyses by only including women who were diagnosed within one year before the enrollment (*N* = 372). The results of the sensitivity analyses were similar in magnitude and direction to the primary analyses as well. Of note, the inverse association between broccolini and breast cancer risk became significant after the exclusion ($OR_{broccolini}$ = 0.44, 95% CI = 0.20- 0.94, and *P* = 0.04). The positive association between Chinese cabbage and breast cancer also became significant after the exclusion of the women who were diagnosed greater than one year ($OR_{Chinese\ cabbage}$ = 2.23, 95% CI = 1.06- 4.68, and *P* = 0.03).

DISCUSSION and CONCLUSION

Consumption of cruciferous vegetables and breast cancer risk

To the best of our knowledge, this is the first study to examine the impact of cruciferous vegetables on breast cancer risk among women with a familial risk and one of the few studies that has collected detailed information on crucifer intake.

Consumption of cruciferous vegetables among all women

No association between total amount of cruciferous vegetables and breast cancer risk was observed in this study. Our findings are consistent with prospective cohort studies that reported a null association between total cruciferous vegetables intake and breast cancer risk (66, 72, 73, 80). Smith-Warner SA and colleagues (73) pooled eight prospective cohorts and suggested no association between the consumption of total fruit and vegetables and breast cancer risk. They studied the effects of broccoli, brussels sprouts, and cabbage, on breast cancer risk without information on the frequency of consumption on each subtype. None of the three vegetables showed significant results, which were consistent with our study. The median consumption of total cruciferous in our study was 0.75 serving/day, which was higher than the general population in US (0.3 and 0.4 serving/day in women < 50 y and women ≥ 50 y, respectively) (63).

In contrast, Black Women's Health Survey (64) observed an inverse association between the consumption of total cruciferous vegetables (including broccoli, collard/mustard greens, and cabbage/coleslaw) and breast cancer risk (OR = 0.8). However, consistent with our study, when they evaluated the vegetables individually, none of the vegetables (broccoli, collard greens, and cabbage) showed a significant protective effect on breast cancer risk.

Several case-control studies also observed that the intake of total cruciferous vegetables had no impact on breast cancer risk (63, 67, 71, 74, 81-83). Potischman N et al. (83) found no association between the early-stage breast cancer risk and total crucifers intake in a case-control study. The median intake of total crucifers among controls in their study was 1.7 servings/week. However, some case-control studies reported a protective effect of total crucifers on breast cancer risk. Zhang CX et al. (69) found the total crucifer consumption (including Chinese cabbage, cabbage, broccoli, and cauliflower) was inversely associated with breast cancer risk when the consumption exceeded one serving/day.

Our study suggested an inverse association between broccolini intake and breast cancer risk. To the best of our knowledge, the protective effect of broccolini has not been reported in previous studies. Broccolini contains a high level of SFN and is served as raw in most dishes. An etiological study showed that raw vegetables could keep approximately 36% glucosinolate, the precursors of isothiocyanates, than the cooked vegetables (84). Therefore,

even though the frequency of consumption in broccolini was relatively low compared to other subtypes, it is plausible that there was a protective effect on breast cancer risk. The lack of association between breast cancer risk and other subtypes, such as brussels sprouts, cabbage, bok choy, may due to the overcooking as this would decrease the contents of glucosinolates.

Consumption of cruciferous vegetables stratified by menopausal status

In our study, the total consumption of cruciferous vegetable was not found to be associated with breast cancer risk regardless of the menopausal status. No effect modification by menopausal status was observed between the total crucifers and breast cancer risk. The results are consistent with Ambrosone CB and colleagues' study (63) and the Long Island Breast Cancer Study Project (LIBCSP) (74). In individual subtypes, Ambrosone CB et al. (63) found that broccoli was related to a reduction in breast cancer risk among premenopausal women; however, our study showed a null association between broccoli intake and breast tumors risk, regardless of the menopausal status.

Consumption of cruciferous vegetables stratified by BMI status

To the best of our knowledge so far, there are no previous studies that have stratified the association between crucifers consumption and breast cancer risk by women's BMI status. Our study showed an inverse association between some subtypes and breast cancer risk among normal BMI women. However, among overweight/obese women, these subtypes showed an

increase in breast cancer risk. BMI significantly modified the effect of the consumption of total crucifer and wasabi on breast cancer risk, respectively.

The human gut microbiome is associated with both obesity and cruciferous digestion. Obesity alters the gene expression of bacterial genes and metabolic pathways (85). A recent review suggested that obesity was one of the well-established risk factors of dysbiosis of gut microbiome environment (86) by decreasing the proportion of Bacteroidetes, one group of the beneficial bacteria dominant in the human gut (87). On the other hand, individuals' dietary habits shape their core microbiome community (88); in return, the human gut microbiome has an impact on the digestion of cruciferous vegetables. Supported by animal models and feeding studies, researches have proven that the environment in the human digestive tract alters the metabolism of isothiocyanates and other glucosinolates bioactivities (89-93). The process of hydrolyzing of glucosinolates into isothiocyanates requires the enzyme myrosinase, which is stored in plants and activated when the plant tissues were destroyed (89). Human digestive tract is another source of myrosinase (89). To the best of our knowledge, there have not been any previous etiological studies focused on the association between gut microbiome, cruciferous vegetables and breast cancer risk. A recent animal model, which studied the effect of dietary fiber on colorectal cancer, suggested that the inconsistent results for the association between fiber consumption and colorectal cancer risk in previous epidemiologic studies may be partially explained by the variation in microbiota among the participants (94). We hypothesize that the variation in microbiome community between

normal BMI and overweight/obese women may modify the metabolism process through the the enzymes activity, such as myrosinase, and ultimately modify the association between cruciferous vegetables and breast cancer risk. In this condition, it is plausible that BMI plays a role in the association between cruciferous vegetables consumption and breast cancer risk.

Consumption of cruciferous vegetables among ER+ and ER- tumors

Few studies have studied the association between crucifers consumption and the risk of subtypes of breast cancer. Inconsistent with previous studies (64, 74), our study suggested an increase odds of developing ER+ breast tumors in relation to total crucifers. Moreover, arugula, Chinese cabbage, radish, and wasabi increased the odds of developing the ER+ breast cancer as well. Riby JE et al. (95) suggested that one major product of indole-3-carbionol (I3C), an unstable bioactivity of isothiocyanates, was a “strong agonist of estrogen receptor signaling pathway” in breast cancer cell (MDA-MD-231). Another animal study reported that 3,3'-diindolylmethane, another major product of I3C, promoted the breast cancer by serving as an estrogen in rainbow trout (96). Therefore, it is biological plausible that the bio-products derived from I3C may increase the risk of ER+ tumors. Gaudet MM et al. (2004) (74) reported a null association between the intake of total cruciferous vegetables regardless of the hormone receptor status of breast cancers among general population. They included cabbage, coleslaw, sauerkraut, broccoli, cauliflower, brussel sprouts, mustard greens, turnip greens, collards, and kale and transformed the total amount into a continuous variable with the unit 0.5 cup per serving per week. The subtypes that included in our study were different from Gaudet

and colleagues' study. The positive association suggested by our study seems to be driven by arugula, Chinese cabbage, radish and turnips. The inconsistent results may due to the differential contents of glucosinolates bioactivities, including SFN and I3C, in these crucifer subtypes.

Reasons for the inconsistent results from previous epidemiologic and intervention studies

Firstly, the study population differed between studies. Based on our inclusion criteria, both of the cases and controls in our study were *BRCA1/2* mutation carriers, or had family history, or had early breast cancer onset. The study population in our study has a higher risk of breast cancer than the general population, which was the target population in most of the previous studies. Furthermore, our study population was a group of well-educated women. They might have more access to the healthcare education and live in a healthier way than general population. Our results suggested that women in our study were indeed more likely to consume more cruciferous vegetables and have more physical activities, than general women.

Secondly, the assessment methods of cruciferous vegetables and statistical approaches while handling the dietary data were different across studies. In our study, we assessed the consumption of each subtype with a frequency format response, translated the answer into an ordinal value, summed up the total amount of all subtypes with the unit servings/day, and then categorized it into four categories with the cutoff points 0.5, 1, and 1.5 servings/day. Different from ours, some studies used continuous scale, such as g/month

(63) or g/day (66, 69, 80) while some adopted portion size scale, such as servings/week or servings/month with different definitions of “servings” (64, 65, 70, 71, 74, 81-83, 97). Even though the measurement error within each study was non-differential, the differential approaches and scales in collecting dietary data across studies may introduce differential measurement errors between studies. Eventually, such differential measurement errors may result in inconsistent conclusions.

Thirdly, different edible methods may account for the inconsistent studies observed across the studies. An etiological study showed that the contents of glucosinolate were significantly different between raw and cooked vegetables (84). Available data showed that the average losses of glucosinolate in cruciferous vegetables during the cooking process were approximately 36% (84). Most studies, including ours, did not specify the status of vegetable when women consumed it in the questionnaire. Franceschi S et al. (71) evaluated the association of both raw and cooked crucifers and breast cancer risk. They indicated that only raw vegetables could reduce the risk of breast cancer while cooked vegetables showed no effect on the risk of breast cancer. A case-control study meticulously asked the edible methods of cruciferous vegetable and concluded that only raw crucifers protected individuals from bladder cancer risk while no association was observed between cooked crucifers consumption and bladder cancer risk (98).

Assessment of the data quality

To evaluate the potential recall bias in the case-control study, we compared the baseline characteristics between cases and controls. We assumed that cases should be more likely to report a healthier lifestyle than controls, including overestimating the consumption of crucifers, the level of physical activity and BMI value. Therefore, if cases reported an overall lower BMI and higher physical activity level than controls, the recall bias between cases and controls may be differential. In Table 4, we observed that the distribution of BMI categories was similar between cases and controls. Table 4 also suggested that controls had a higher level of physical activity than cases, which was expected if the recall bias did not differ between cases and controls. Therefore, we considered the recall bias to be non-differential in our study.

By evaluating the Kappa statistics of responses in selected subtypes (i.e. broccoli, brussel sprouts, and mustard), all of which were beyond 0.5, we believe the questionnaire worked well in our study. The change patterns of selected subtypes were not related to the case status except for brussel sprouts. In the sensitivity analyses which excluded women with changed patterns, the results were consistent to the primary analyses among all women. Therefore, in our opion, the results in the primary analyses are reliable.

The sensitivity analyses which excluded women who were diagnosed beyond one year before the enrollment showed a same direction and magnitude

association compared to the primary analyses among all women. Such results further supports the validity and reliability of our primary results.

Limitations and strengths

To our best of knowledge, this is the first study focused on the association between cruciferous vegetables and breast cancer risk among women with a higher risk due to the hereditary factors. Both cases and controls in our study were selected from the same familial risk cohort. The high agreements of responses and non-differential recall bias between cases and controls suggested a high reliability of our conclusions. Our study investigated more than 20 subtypes of crucifers, which contains the highest number of subtypes in one study to date. Such a large number of different subtypes further supported the reliability.

Another strength of our study is the accuracy of the family history details. Previous studies have suggested that the accuracy of recalling family history decreases as the relatives become more distant (15). Our study used a pedigree of each family to identify the family history for each participant and thus reduced the measurement error in family history.

Our study is a case-control study, which has an inherent recall bias. We reduced the recall bias by limiting the cases who were diagnosed within two years before the enrollment. Moreover, by 1) evaluating the baseline characteristics, 2) checking the agreements of responses in different

questionnaires, and 3) conducting sensitivity analyses among women who did not change their dietary habits or women who were diagnosed within one year at baseline, we concluded that the potential recall bias should be balanced between cases and controls in our study.

The generalizability of our study is limited. The conclusion of our study may be limited to women with a familial breast and/or ovarian cancer risk and a high education level. All recruited women in our study have a family history of breast and/or ovarian cancer, or *BRCA1/2* mutation, or early breast cancer onset. They experience a higher risk than the general population, and their awareness of breast cancer prevention may be higher than that of other women. Our baseline characteristics supported such conclusion: more than 70% women in our study were vigorous active, 80% women were non-obese, and only 3.5% of them were current smokers.

Inevitably, our study might have been subjected to measurement errors of dietary assessments, which happens frequently in nutritional research. To reduce the error, we asked participants to recall their intake in a precise way by providing the frequency of consumption with six clearly defined levels (i.e. “not at all”, “less than once per week”, “1-2 per week”, “3-6 per week”, “1 per day”, and “more than once per day”). This type of frequency format choice provided an easier way for the participants to recall their intake of vegetables precisely compared to a continuous scale, such as g/day. Moreover, we asked about 25 subtypes in order to obtain a more comprehensive picture of the consumption of cruciferous vegetables, which could make the total

consumption of crucifers more reliable than the previous studies, most of which included less than five subtypes.

It is challenging to isolate the key factors in nutritional study due to the high correlation between dietary factors, such as fruits, vitamins and other vegetables. To better evaluate the effect of cruciferous vegetables consumption on breast cancer risk, we conducted another sensitivity analysis by further adjusting for fruits and other vegetables in the model (data not shown), the results were consistent with the primary analyses.

In conclusion, our results suggested that total cruciferous vegetables intake was not associated with breast cancer risk among women with a familial risk. BMI may modify the association between the cruciferous vegetables consumption and breast cancer risk among the high-risk population. Future studies should include a larger sample size, test for the gene-dietary interactions and evaluate the effect of crucifers intake on the risk of breast cancer subtypes.

TABLES

Table 1. Glucosinolate contents of selected cruciferous vegetables (84, 99).

Cruciferous vegetables	Total glucosinolates content (mg/100g)
Broccoli	61.1
Brussels sprouts	226.2
Bok choy (pak-choi)	54.1
Cabbage	108.9
Collards	200.7
Cauliflower	62.0
Cress	120.7
Horseradish	160.1
Mustard greens	281.5
Kale	89.4
Kohlrabi	109.3
Radish	12.5
Watercress	95.0
Turnip	56.0

Table 2. Characteristics and results of studies reporting measure and 95% confidence intervals (95% CI) of the association between cruciferous vegetable intake and breast cancer events

Study (year)	Country	Study Population	Type of cruciferous vegetables examined	Intake frequency	Measure of association (95%CI)[a]	P_{trend}
Case-control studies						
Population-based case-control study (2004) (63)	Erie and Niagara (cases); US (controls)	740 cases, 810 controls	Broccoli, cabbage, cauliflower, sauerkraut, coleslaw, and brussels sprouts	Premenopausal, g/mo Cases:1531.0 ± 85.8 Controls: 1649 ± 69.1 Postmenopausal, g/mo Cases:1368.4 ± 52.3 Controls: 1479 ± 59.9	OR: 0.7 (0.5, 1.2) OR: 0.6 (0.8, 1.4)	
			Broccoli	Premenopausal, g/mo Cases:779.6 ± 55.0 Controls: 851 ± 46.2 Postmenopausal, g/mo Cases:639.9 ± 36.7 Controls: 675 ± 40.2	OR: 0.6 (0.4, 1.0) OR: 1.0 (0.7, 1.4)	
Long Island Breast Cancer Study Project (1996) (74)	US	1463 cases, 1500 controls	Coleslaw/cabbage/sauerkraut, broccoli, cauliflower/brussels sprouts, and mustard greens/turnips/collards/kale	Premenopausal: ser/wk 0-0.5: 128/154 1: 115/121 1.5: 48/53 2-2.5: 63/81 >3: 102/72 Postmenopausal:ser/wk 0-0.5: 305/291 1: 233/196 1.5: 109/107 2-2.5: 167/162 >3: 147/181	OR: 1.76 (1.18-2.61) OR: 0.80 (0.60, 1.05)	0.03 0.12
Population-based case-control study (2009) (69)	China	438 cases, 438 controls	Chinese cabbage, cabbage, broccoli, cauliflower	Controls: 52.96 ± 58.53 g/day	OR: 0.49 (0.32, 0.74)	<0.001
Hospital-based case-control study (1982) (81)	US	1803 cases, 917 controls	Cruciferous vegetables[c]	Servings/month: >20: 102/54 12-19: 286/173	OR: 1.00	>0.05

				4-11: 1082/513 0-3: 335/177		
Hospital-based case-control study (1991) (71)	Italy	2569 cases, 5155 controls	Cruciferous vegetables[b]	Controls: 0.7 servings/week	OR: 1.0 (0.9, 1.1)	
Population-based case-control study (1990) (83)	US	568 cases, 1451 controls	Cruciferous vegetables[b]	Servings/week: <1.4: 261/671 1.4-2.0: 74/215 2.1-3.4: 132/296 >3.4: 101/269	OR: 0.95 (0.7, 1.3)	
Population-based case-control study (1993) (70)	Sweden	2832 cases, 2650 controls[d]	Brassica vegetables[e]	Median, servings/day Q1, 0.1: 661/580 Q2, 0.2: 715/634 Q3, 0.5: 675/635 Q4, 1.1: 627/643	OR: 0.88 (0.72, 1.07)[f] 0.76 (0.62, 0.93)	0.01
Population-based case-control study (2001) (82)	US	441 cases, 370 controls	Cruciferous vegetables[b]	Range, servings/day Q1, <0.07: 109/99 Q2, <0.14: 113/87 Q3, <0.29: 122/95 Q4, >0.29: 95/89	OR: 0.91 (0.61, 1.38)	0.69
Population-based case-control study (1989) (97)	China	378 cases, 1070 controls	Total vegetables, including crucifers[g]	Servings/day ≤1.5: 118/268 <2: 80/265 <2.6: 74/269 ≥2.6: 106/268	OR: 0.60 (0.38, 0.94)	0.03
Shanghai Breast Cancer Study (1996) (67)	China	3035 cases, 3037 controls	Bok choy, cabbage, Chinese cabbage, cauliflower, and turnip	Q1: 722/695 Q2: 681/694 Q3: 700/695 Q4: 69//696 Q5: 650/694	0.92 (0.79, 1.07)	0.388
Cohort studies						
Black Women's Health Study (1995) (64)	US	1268 cases, 51928 women	Broccoli, collard/mustard greens, and cabbage/coleslaw	Servings/month: < 1: 202 1-3: 526 4-8: 350	IRR: 0.80 (0.65, 0.99)	0.06

				≥9: 190		
Women's Healthy Eating and Living (1995) (65)	US	487 recurrences, 2940 survivors	Cruciferous vegetables[b]	Comparison group: 0.36 ± 0.11 ser/day Intervention group: 0.56 ± 0.02 ser/day	HR: 0.65 (0.47, 0.89)	
Japan Public Health Center-based Prospective Study (1990) (66)	Japan	452 cases, 140420 women	Cruciferous vegetables[b]	Q1: 25 g/day Q2: 48 g/day Q3: 73 g/day Q4: 120 g/day	RR: 0.91 (0.70, 1.19)	0.18
After Breast Cancer Pooling Project (80)	US, China	1421 recurrences, 1725 deaths, 11390 survivors	Cruciferous vegetables[b]	g/day: <39: 738/934/5447 39-78: 341/378/2806 ≥78: 342/413/3137	HR: 1.10 (0.95, 1.28)[h] 0.99 (0.86, 1.13)[j]	0.34[b] 0.84[c]
EPIC (72)	Europe	3658 cases, 285526 women	Cabbage	Q1: 761/306346 Q2: 649/2587278 Q3: 678/268073 Q4: 749/282510 Q5: 666/278529	HR: 1.09 (0.95, 1.25)[k] 1.18 (1.01, 1.38)	0.11
BCDDP (68)	US	1868 cases, 40559 women	Cabbage, coleslaw, and sauerkraut	Never eat: 176 T1: 285 T2: 305 T3: 325	HR: 0.80 (0.66, 0.97)	0.02
Pooling Project (73)	Multiple countries[l]	7377 incident cases, 351825 women	Broccoli, brussels sprouts, and cabbage	NA	RR: 0.96 (0.87, 1.06)	NA

Note: All the cutoff points of quantiles were defined in the control group. For case-control study, values of intake frequency are given as number of cases/number of controls. For cohort study, values of intake frequency are given as: BWHS: number of cases; WHEL: mean ± standard error; JPHCPS: intake amount; ABCPP: recurrence/death/survivors; EPIC: number of cases/person-years; BCDDP: cases.
Abbreviations: CI, confidence interval; OR, odds ratio; HR, relative hazard; RR, relative risk; IRR, incidence rate ratio: wk, week; ser, servings; mo, month; US, United States; EPIC, European Prospective Investigation into Cancer and Nutrition study.
[a]For quantiles/tertiles (Q/T), only the measurement of association between the last quantile/tertile (Q/T) and the reference quantile/tertile (Q/T) was presented.
[b]No subtypes specified in the original literature.
[c]Included cabbage, brussel sprouts, kale, cauliflower, broccoli, kohl-rabi, turnips and rutabaga (100).
[d]Included postmenopausal women only.
[e]Included bok choy, cabbage, Chinese cabbage, watercress, broccoli, Chinese broccoli, cauliflower, radish, and turnips.
[f]Included cabbage, red cabbage, Chines cabbage, kale, broccoli, cauliflower, and brussels sprouts.
[g]The OR by comparing the third quartile to the lowest quartile.
[h]Recurrence.
[j]Death.
[k]The HR by comparing the fourth quintile to the lowest quintile.
[l]Included United States, Canada, Netherlands, and Sweden.

Table 3. Sample questions from the baseline questionnaires, including food frequency questionnaire (FFQ), BOSS Cohort Study, 2005-2013.

Question number	Question text
Q55	What is the frequency did you consume broccoli, brussel sprouts, cabbage, and cauliflower during the past year? • Not at all • Less than once per week • 1-2 per week • 3-6 per week • 1 per day • More than once per day
Q57	What is the frequency did you consume mustard during the past year? • Not at all • Less than once per week • 1-2 per week • 3-6 per week • 1 per day • More than once per day
Q58	During the past year, how did you change your consumption of mustard? • Not at all • Unchanged • Increased • Decreased

Table 4. Baseline characteristics of cases and controls from the BOSS Cohort Study, 2005-2013.

	Cases (N=200)	Controls (N=200)	*P*
Age at baseline[a], y	49.2 (10.9)	49.2 (11.0)	0.98
Enrollment year[a], y	2008 (2.4)	2008 (2.3)	0.32
BMI category			0.13
Normal (18.5-24.9 kg/m^2)	112 (56.0)	92 (46.0)	
Overweight (25-29.9 kg/m^2)	55 (27.5)	70 (35.0)	
Obese (> 30 kg/m^2)	33 (16.5)	38 (19.0)	
Smokers			0.49
Non-smoker	123 (61.5)	114 (57.0)	
Former smoker	69 (34.5)	80 (40.0)	
Current smoker	8 (4.0)	6 (3.0)	
Education			0.44
Less than college	44 (22.0)	55 (27.5)	
College graduate	76 (38.0)	69 (34.5)	
Post-college graduate	80 (40.0)	75 (37.5)	
Missing	0 (0.0)	1 (0.5)	
Physical activity			0.03
Light activity (<3 METs)	32 (16.0)	37 (18.5)	
Moderate activity (3-6 METs)	20 (10.0)	7 (3.5)	
Vigorous activity (≥ 6 METs)	148 (74.0)	156 (78.0)	
Age at menarche[a], y	12.4 (1.4)	12.7 (1.7)	0.03
Age at menarche			0.001
< 12 years	28 (14.0)	57 (28.5)	
12 – 13 years	71 (35.5)	51 (25.5)	
> 13 years	101 (50.5)	92 (46.0)	
Parity and Age at first birth			0.33
Nulliparous	28 (14.0)	28 (14.0)	
≤ 25 years	65 (32.5)	52 (26.0)	
> 25 years	107 (53.5)	120 (60.0)	
Menopausal status at baseline			0.005
Premenopausal	112 (56.0)	84 (42.0)	
Postmenopausal	88 (44.0)	116 (58.0)	
Age at menopausal[a,b], y	47.7 (5.5)	47.9 (7.54)	0.85
Hormone replacement therapy			0.24
Never	157 (78.5)	148 (74.0)	
Estrogen only	15 (7.5)	20 (10.0)	
Progesterone only	7 (3.5)	5 (2.5)	
Combination	14 (7.0)	24 (12.0)	
Missing	7 (3.5)	3 (1.5)	
Oral contraceptive use			0.003
Never used	35 (17.5)	37 (18.5)	
Former user	161 (80.5)	141 (70.5)	
Current user	4 (2.0)	19 (9.5)	
Missing	0 (0.0)	3 (1.5)	
Flame broiled food[c], servings/day	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.81
Family history of cancer[d]			<0.001
No family history	54 (27.0)	5 (2.5)	
Second-degree only	107 (53.5)	134 (67.3)	
First-degree and second-degree	39 (19.5)	60 (30.2)	
BRCA status[e]			0.16

No mutation	128 (75.7)	61 (64.9)	
BRCA 1 mutation	19 (11.2)	17 (18.1)	
BRCA 2 mutation	22 (13.0)	16 (17.0)	
Age at breast cancer diagnosis[f], y	48.43 (10.84)	-	-
Time from diagnosis to baseline[f], y	0.78 (0.77)	-	-
Estrogen receptor status[f]			-
Positive	151 (77.44)	-	
Negative	44 (22.56)	-	
Progesterone receptor status[f]			-
Positive	132 (68.04)	-	
Negative	62 (31.96)	-	

Note: For categorical/binary variables, values were presented as number (proportion, %), and *P-value* was calculated through Pearson's chi-square test. For normally distributed continuous variables, values were presented as mean (standard deviation), and *P-value* was calculated through t-test. For skewed continuous variables, values presented as median (IQR), and *P*-value was calculated through Wilcoxon rank-sum test.
Abbreviation: BMI, body mass index; METs, metabolic equivalents.
[a]Normally distribution.
[b]Among postmenopausal women without missing data, *N* = 196.
[c]Skewed distribution, including flame broiled meat, fish and chicken.
[d]Including women relatives with breast cancer and/or ovarian cancer.
[e]Among women who were tested, *N* = 267.
[f]Among invasive cases only, *N* = 200.

Table 5. Baseline characteristics of participants stratified by consumption of cruciferous vegetable, BOSS Cohort Study, 2005-2013.

	Categories of total quantified cruciferous vegetables consumption				*P*
	I (N=114)	**II (N=82)**	**III (N=102)**	**IV (N=102)**	
Total intake of subtypes, servings/day	< 0.5	(0.5, 1.0)	(1.0, 1.5)	≥ 1.5	
Breast cancer					0.44
Cases	54 (47.4)	38 (46.3)	50 (49.0)	58 (56.9)	
Controls	60 (52.6)	44 (53.7)	52 (51.0)	44 (43.1)	
Age at baseline[a], y	48.6 (11.0)	50.5 (11.0)	49.1 (11.7)	48.9 (10.1)	0.64
Enrollment year[a], y	2008.8 (2.2)	2008.1 (2.2)	2008.7 (2.4)	2008.9 (2.5)	0.065
BMI category					0.32
Normal (18.5-24.9 kg/m^2)	59 (51.8)	38 (46.3)	50 (49.0)	57 (55.9)	
Overweight (25-29.9 kg/m^2)	36 (31.6)	32 (39.0)	27 (26.5)	30 (29.4)	
Obese (> 30 kg/m^2)	19 (16.7)	12 (14.6)	25 (24.5)	15 (14.7)	
Age at menarche[a], y	12.4 (1.3)	12.5 (1.5)	12.6 (1.4)	12.7 (1.9)	0.56
Age at menarche					0.65
< 12 years	29 (25.4)	19 (23.2)	18 (17.6)	19 (18.6)	
12 – 13 years	29 (25.4)	28 (34.1)	33 (32.4)	32 (31.4)	
> 13 years	56 (49.1)	35 (42.7)	51 (50.0)	51 (50.0)	
Smokers					0.31
Non-smokers	71 (62.3)	44 (53.7)	59 (57.8)	63 (61.8)	
Former smokers	42 (36.8)	33 (40.2)	37 (36.3)	37 (36.3)	
Current smokers	1 (0.9)	5 (6.1)	6 (5.9)	2 (2.0)	
Parity and Age at first birth					0.82
Nulliparous	15 (13.2)	11 (13.4)	14 (13.7)	16 (15.7)	
≤ 25 years	36 (31.6)	23 (28.0)	34 (33.3)	24 (23.5)	
> 25 years	63 (55.3)	48 (58.5)	54 (52.9)	62 (60.8)	
Oral contraceptive use					0.61
Never used	20 (17.5)	17 (20.7)	17 (16.7)	18 (17.6)	

Former user	87 (76.3)	62 (75.6)	80 (78.4)	73 (71.6)	
Current user	7 (6.1)	3 (3.7)	4 (3.9)	9 (8.8)	
Missing	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	
Menopausal status					0.95
Premenopausal	56 (49.1)	40 (48.8)	53 (52.0)	53 (52.0)	
Postmenopausal	58 (50.9)	42 (51.2)	49 (48.0)	49 (48.0)	
Hormone replacement therapy					0.76
Never	90 (78.9)	63 (76.8)	78 (76.5)	74 (72.5)	
Estrogen only	8 (7.0)	7 (8.5)	10 (9.8)	10 (9.8)	
Progesterone only	1 (0.9)	2 (2.4)	4 (3.9)	5 (4.9)	
Combination	11 (9.6)	10 (12.2)	7 (6.9)	10 (9.8)	
Missing	4 (3.5)	0 (0.0)	3 (2.9)	3 (2.9)	
Education					0.36
Less than college	33 (28.9)	23 (28.0)	25 (24.5)	18 (17.6)	
College graduate	45 (39.5)	25 (30.5)	36 (35.3)	39 (38.2)	
Post-college graduate	35 (30.7)	34 (41.5)	41 (40.2)	45 (44.1)	
Missing	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Physical activity					0.009
Light activity (<3 METs)	19 (16.7)	20 (24.4)	18 (17.6)	12 (11.8)	
Moderate activity (3-6 METs)	6 (5.3)	12 (14.6)	4 (3.9)	5 (4.9)	
Vigorous activity (≥ 6 METs)	89 (78.1)	50 (61.0)	80 (78.4)	85 (83.3)	
Flame broiled food[b], servings/day	0.6 (0.6, 0.9)	0.7 (0.6, 0.9)	0.7 (0.4, 0.9)	0.7 (0.6, 1.0)	0.39
Family history[c]					0.71
No family history	21 (18.4)	14 (17.1)	13 (12.7)	11 (10.9)	
Second-degree only	68 (59.6)	47 (57.3)	61 (59.8)	65 (64.4)	
First-degree and second-degree	25 (21.9)	21 (25.6)	28 (27.5)	25 (24.8)	
BRCA status[d]					0.45
No mutation	59 (73)	41 (80)	41 (69)	48 (67)	

BRCA 1 mutation	13 (16)	5 (10)	6 (10)	12 (17)	
BRCA 2 mutation	9 (11)	5 (10)	12 (20)	12 (17)	
Age at breast cancer diagnosis[e], y	46 (40, 54)	47.5 (41, 55)	50 (41, 58)	47 (41, 55)	0.64
Time from diagnosis to baseline[e], y	1 (0, 1)	1 (0, 1)	1 (0, 1)	1 (0, 1)	0.48
Estrogen receptor status[e]					0.52
Positive	15 (29)	6 (16)	11 (23)	12 (21)	
Negative	37 (71)	32 (84)	37 (77)	45 (79)	
Progesterone receptor status[e]					0.71
Positive	18 (35)	12 (32)	17 (35)	15 (26)	
Negative	33 (65)	26 (68)	31 (65)	42 (74)	

Note: For categorical/binary variables, values were presented as number (proportion, %), and *P-value* was calculated through Pearson's chi-square test. For normally distributed continuous variables, values were presented as mean (standard deviation), and *P-value* was calculated through t-test. For skewed continuous variables, values presented as median (IQR), and *P*-value was calculated through Wilcoxon rank-sum test.
Abbreviation: BMI, body mass index; METs, metabolic equivalents.
[a]Normally distribution.
[b]Skewed distribution, including flame broiled meat, fish and chicken.
[c]Including women relatives with breast cancer and/or ovarian cancer.
[d]Among women who were tested, *N* = 267.
[e]Among invasive cases only, *N* = 200.

Table 6. Adjusted matched odds ratios (ORs) and 95% confidence interval (95% CI) of breast cancer according to total and subtypes cruciferous vegetables consumption, BOSS Cohort Study, 2003-2015.

Cruciferous vegetables		Cases[a] (N=200)	Controls[a] (N=200)	aOR (95% CI)	a*P*
Subtype	**Frequency**				
Total intake of all cruciferous subtypes					
I, < 0.5 serving/day		32(16)	28(14)	1(ref)	
II, 0.5 - 1 serving/day		60(30)	76(38)	0.577(0.233,1.431)	0.236
III, 1 - 1.5 serving/day		50(25)	52(26)	1.381(0.557,3.423)	0.486
IV, ≥ 1.5 serving/day		58(29)	44(22)	1.362(0.548,3.386)	0.506
				P_{trend}	0.066
Total intake of four selected subtypes					
I, < 2 servings/week		39(19.5)	49(24.5)	1(ref)	
II, 2-3 servings/week		60(30.0)	60(30.0)	1.409(0.675,2.942)	0.361
III, > 3 servings/week		91(45.5)	101(50.5)	1.836(0.894,3.771)	0.098
				P_{trend}	0.098
Intake of cruciferous subtypes					
Broccoli	No	4 (2.00)	9 (4.50)	1(ref)	
	< 1 serving/week	57(28.50)	62(31.00)		
	≥ 1 serving/week	139(69.50)	129(64.50)	1.765(0.961,3.243)	0.067
Arugula	No	104(52.26)	111(55.78)	1(ref)	
	Yes	95(47.74)	88(44.22)	1.238(0.712,2.154)	0.450
Bok choy	No	140(70.00)	138(69.00)	1(ref)	
	Yes	60(30.00)	62(31.00)	1.107(0.596,2.059)	0.747
Broccoli raab	No	156(78.39)	152(77.16)	1(ref)	
	Yes	43(21.61)	45(22.84)	0.927(0.468,1.834)	0.827
Broccoli sprouts	No	126(63.32)	122(61.00)	1(ref)	
	Yes	73(36.68)	78(39.00)	1.164(0.652,2.078)	0.608
Broccolini	No	155(78.68)	145(74.36)	1(ref)	

	Yes	42(21.32)	50(25.64)	**0.505(0.251,1.014)**	**0.055**
Brussel sprouts	No	86(43.00)	110(55.28)	1(ref)	
	Yes	114(57.00)	89(44.72)	1.619(0.935,2.802)	0.085
Cabbage	No	47(23.74)	51(25.50)	1(ref)	
	Yes	151(76.26)	149(74.50)	1.422(0.741,2.730)	0.290
Cauliflower	No	45(22.50)	38(19.00)	1(ref)	
	Yes	155(77.50)	162(81.00)	0.933(0.496,1.756)	0.830
Chinese cabbage	No	130(65.33)	144(72.36)	1(ref)	
	Yes	69(34.67)	55(27.64)	1.581(0.828,3.019)	0.165
Collard greens	No	142(71.36)	149(74.50)	1(ref)	
	Yes	57(28.64)	51(25.50)	1.253(0.683,2.298)	0.466
Cress/watercress	No	150(75.38)	142(71.36)	1(ref)	
	Yes	49(24.62)	57(28.64)	1.084(0.606,1.937)	0.786
Honey mustard	No	98(49.25)	82(41.00)	1(ref)	
	Yes	101(50.75)	118(59.00)	0.672(0.383,1.178)	0.165
Horseradish	No	101(50.75)	99(50.00)	1(ref)	
	Yes	98(49.25)	99(50.00)	1.125(0.654,1.936)	0.671
Kale	No	125(62.81)	139(69.50)	1(ref)	
	Yes	74(37.19)	61(30.50)	1.597(0.847,3.012)	0.148
Mustard	No	86(43.43)	75(37.88)	1(ref)	
	Yes	112(56.57)	123(62.12)	0.783(0.428,1.433)	0.428
Radish	No	112(56.57)	127(65.13)	1(ref)	
	Yes	86(43.43)	68(34.87)	1.326(0.748,2.349)	0.334
Turnips	No	143(72.96)	158(79.00)	1(ref)	
	Yes	53(27.04)	42(21.00)	1.749(0.901,3.397)	0.099
Wasabi	No	126(63.32)	133(66.50)	1(ref)	
	Yes	73(36.68)	67(33.50)	1.302(0.712,2.379)	0.392

Note: Univariate and multivariate conditional logistic regression models were used to calculate unadjusted and adjusted ORs, respectively. Multivariate model was adjusted for age at baseline (continuous, y), enrollment year (continuous, y), body mass index (continuous), oral contraceptive therapy (never

use, current user, and former user), age at menarche (less than 12 years, 12-13 years, and more than 13 years), hormone replacement therapy (never used, estrogen, progesterone, and combination) , menopausal status (premenopausal and postmenopausal), physical activity (light, moderate, and rigorous), family history (no family history, second-degree relatives only, and both of first-degree and second-degree relatives), and flamed broiled consumption (combination of flame broiled meat, fish, and chicken). Only individuals without missing data in each subtype were included in the analyses.
[a]n (proportion, %).

Table 7. Adjusted odds ratios (ORs) and 95% confidence interval (95% CI) of breast cancer according to total and subtypes cruciferous vegetables consumption, stratified by women menopausal status, BOSS Cohort Study, 2003-2015.

		Premenopausal				Postmenopausal				
Cruciferous	**Frequency**	**Cases[a]**	**Controls[a]**	**aOR (95% CI)**	**a*P***	**Cases[a]**	**Controls[a]**	**aOR (95% CI)**	**a*P***	***P*[b]**
Total cruciferous vegetables[c]	< 1 ser/d[d]	40(47.62)	54(48.21)	1(ref)		52(44.83)	50(56.82)	1(ref)		
	≥ 1 ser/d[d]	44(52.38)	58(51.79)	1.404(0.678,2.909)	0.361	64(55.17)	38(43.18)	**1.951(0.994,3.826)**	**0.052**	0.316
Broccoli	< 1 ser/wk[e]	30(33.33)	39(34.82)	1(ref)		31(28.18)	32(36.36)	1(ref)		
	≥ 1 ser/wk[e]	60(66.67)	73(65.18)	1.327(0.612,2.976)	0.480	79(71.82)	56(63.64)	1.152(0.573,2.309)	0.690	0.672
Arugula	No	44(48.89)	61(54.95)	1(ref)		60(55.05)	50(56.82)	1(ref)		
	Yes	46(51.11)	50(45.05)	1.607(0.76,3.452)	0.217	49(44.95)	38(43.18)	1.189(0.595,2.392)	0.624	0.749
Bok choy	No	62(68.89)	72(64.29)	1(ref)		78(70.91)	66(75.00)	1(ref)		
	Yes	28(31.11)	40(35.71)	0.957(0.434,2.079)	0.913	32(29.09)	22(25.00)	1.337(0.645,2.818)	0.438	0.368
Broccoli raab	No	68(75.56)	81(74.31)	1(ref)		88(80.73)	71(80.68)	1(ref)		
	Yes	22(24.44)	28(25.69)	1.108(0.461,2.604)	0.816	21(19.27)	17(19.32)	0.902(0.394,2.082)	0.808	0.905
Broccoli sprouts	No	60(66.67)	67(59.82)	1(ref)		66(60.55)	55(62.50)	1(ref)		
	Yes	30(33.33)	45(40.18)	0.713(0.325,1.535)	0.392	43(39.45)	33(37.50)	1.550(0.791,3.083)	0.205	0.096
Broccolini	No	69(76.67)	75(68.18)	1(ref)		86(80.37)	70(82.35)	1(ref)		
	Yes	21(23.33)	35(31.82)	0.448(0.177,1.047)	0.074	21(19.63)	15(17.65)	1.065(0.460,2.506)	0.884	0.075
Brussel sprouts	No	49(54.44)	67(60.36)	1(ref)		37(33.64)	43(48.86)	1(ref)		
	Yes	41(45.56)	44(39.64)	1.500(0.726,3.120)	0.274	73(66.36)	45(51.14)	**2.040(1.043,4.052)**	**0.039**	0.400
Cabbage	No	25(27.78)	36(32.14)	1(ref)		22(20.37)	15(17.05)	1(ref)		
	Yes	65(72.22)	76(67.86)	1.684(0.739,4.007)	0.224	86(79.63)	73(82.95)	1.308(0.540,3.153)	0.548	0.692
Cauliflower	No	22(24.44)	20(17.86)	1(ref)		23(20.91)	18(20.45)	1(ref)		
	Yes	68(75.56)	92(82.14)	0.651(0.265,1.616)	0.350	87(79.09)	70(79.55)	1.151(0.495,2.652)	0.741	0.289
Chinese cabbage	No	56(62.22)	81(72.32)	1(ref)		74(67.89)	63(72.41)	1(ref)		
	Yes	34(37.78)	31(27.68)	1.793(0.828,3.902)	0.138	35(32.11)	24(27.59)	1.272(0.622,2.624)	0.510	0.634
Collard greens	No	67(74.44)	79(70.54)	1(ref)		75(68.81)	70(79.55)	1(ref)		
	Yes	23(25.56)	33(29.46)	0.837(0.360,1.883)	0.671	34(31.19)	18(20.45)	**2.297(1.060,5.192)**	**0.039**	0.089

Cress/watercress	No	63(70.00)	78(69.64)	1(ref)		87(79.82)	64(73.56)	1(ref)		
	Yes	27(30.00)	34(30.36)	0.959(0.433,2.078)	0.916	22(20.18)	23(26.44)	0.917(0.411,2.069)	0.832	0.972
Honey mustard	No	44(48.89)	44(39.29)	1(ref)		54(49.54)	38(43.18)	1(ref)		
	Yes	46(51.11)	68(60.71)	0.738(0.345,1.576)	0.432	55(50.46)	50(56.82)	0.772(0.399,1.481)	0.438	0.974
Horseradish	No	46(51.11)	61(54.46)	1(ref)		55(50.46)	38(44.19)	1(ref)		
	Yes	44(48.89)	51(45.54)	1.619(0.762,3.501)	0.213	54(49.54)	48(55.81)	0.762(0.394,1.466)	0.416	0.086
Kale	No	59(65.56)	74(66.07)	1(ref)		66(60.55)	65(73.86)	1(ref)		
	Yes	31(34.44)	38(33.93)	1.198(0.559,2.557)	0.639	43(39.45)	23(26.14)	1.998(0.984,4.172)	0.059	0.224
Mustard	No	35(39.33)	40(36.36)	1(ref)		51(46.79)	35(39.77)	1(ref)		
	Yes	54(60.67)	70(63.64)	0.844(0.380,1.882)	0.675	58(53.21)	53(60.23)	0.747(0.377,1.466)	0.399	0.969
Radish	No	47(52.22)	79(71.82)	1(ref)		65(60.19)	48(56.47)	1(ref)		
	Yes	43(47.78)	31(28.18)	**3.218(1.526,6.986)**	**0.002**	43(39.81)	37(43.53)	1.009(0.524,1.955)	0.978	**0.047**
Turnips	No	64(71.91)	94(83.93)	1(ref)		79(73.83)	64(72.73)	1(ref)		
	Yes	25(28.09)	18(16.07)	**2.778(1.127,6.969)**	**0.027**	28(26.17)	24(27.27)	1.460(0.682,3.192)	0.335	0.396
Wasabi	No	53(58.89)	68(60.71)	1(ref)		73(66.97)	65(73.86)	1(ref)		
	Yes	37(41.11)	44(39.29)	1.194(0.558,2.554)	0.646	36(33.03)	23(26.14)	1.254(0.596,2.672)	0.552	0.827

Note: Multivariate unconditional logistic regression models were used to calculate adjusted ORs. Multivariate model was adjusted for age at baseline (continuous, y), enrollment year (continuous, y), body mass index (continuous), oral contraceptive therapy (never use, current user, and former user), age at menarche (less than 12 years, 12-13 years, and more than 13 years), hormone replacement therapy (never used, estrogen, progesterone, and combination) , physical activity (light, moderate, and rigorous) , family history (no family history, second-degree relatives only, and both of first-degree and second-degree relatives), and flamed broiled consumption (combination of flame broiled meat, fish, and chicken). Only individuals without missing data in each subtype were included in the analyses.

[a]n (proportion, %).

[b]*P* value for interaction term, menopausal status*frequency of subtype intake.

[c]Binary variable was calculated by the total amount of all subtypes.

[d]Short for servings/day.

[e]Short for servings/week.

Table 8. Adjusted odds ratios (ORs) and 95% confidence interval (95% CI) of breast cancer according to total and subtypes cruciferous vegetables consumption, stratified by women BMI category, BOSS Cohort Study, 2003-2015.

		BMI < 25 kg/m²				BMI ≥ 25 kg/m²				
Cruciferous	**Frequency**	**Cases[a]**	**Controls[a]**	**aOR (95% CI)**	**a*P***	**Cases[a]**	**Controls[a]**	**aOR (95% CI)**	**a*P***	***P*[b]**
Total cruciferous vegetables[c]	< 1 ser/d[d]	55(49.11)	42(45.65)	1(ref)		37(42.05)	62(57.94)	1(ref)		
	≥ 1 ser/d[d]	57(50.89)	50(54.35)	0.999(0.521,1.916)	0.997	51(57.95)	45(42.06)	**4.098(1.806,9.298)**	**0.001**	**0.015**
Broccoli	< 1 ser/wk[e]	33(29.46)	26(28.26)	1(ref)		28(31.82)	45(42.06)	1(ref)		
	≥ 1 ser/wk[e]	79(70.54)	66(71.74)	1.115(0.554,2.250)	0.759	60(68.18)	62(57.94)	1.640(0.764,3.613)	0.210	0.239
Arugula	No	53(47.32)	49(53.26)	1(ref)		51(58.62)	62(58.49)	1(ref)		
	Yes	59(52.68)	43(46.74)	1.588(0.816,3.134)	0.176	36(41.38)	44(41.51)	1.266(0.593,2.724)	0.542	0.631
Bok choy	No	78(69.64)	64(69.57)	1(ref)		62(70.45)	73(68.22)	1(ref)		
	Yes	34(30.36)	28(30.43)	0.906(0.430,1.904)	0.793	26(29.55)	34(31.78)	1.054(0.472,2.343)	0.897	0.561
Broccoli raab	No	90(81.08)	67(74.44)	1(ref)		66(75.00)	85(80.19)	1(ref)		
	Yes	21(18.92)	23(25.56)	0.606(0.265,1.355)	0.226	22(25.00)	21(19.81)	1.710(0.697,4.257)	0.242	0.191
Broccoli sprouts	No	72(64.29)	50(54.35)	1(ref)		54(62.07)	72(67.29)	1(ref)		
	Yes	40(35.71)	42(45.65)	0.771(0.397,1.483)	0.437	33(37.93)	35(32.71)	1.781(0.832,3.885)	0.140	0.164
Broccolini	No	87(79.82)	61(69.32)	1(ref)		68(77.27)	83(78.30)	1(ref)		
	Yes	22(20.18)	27(30.68)	0.480(0.213,1.050)	0.070	20(22.73)	23(21.70)	0.982(0.394,2.413)	0.969	0.146
Brussel sprouts	No	48(42.86)	47(51.65)	1(ref)		38(43.18)	63(58.88)	1(ref)		
	Yes	64(57.14)	44(48.35)	1.317(0.673,2.582)	0.421	50(56.82)	44(41.12)	**2.285(1.078,4.959)**	**0.033**	0.536
Cabbage	No	32(29.09)	29(31.52)	1(ref)		15(17.05)	22(20.56)	1(ref)		
	Yes	78(70.91)	63(68.48)	1.104(0.536,2.275)	0.788	73(82.95)	85(79.44)	1.762(0.640,5.273)	0.287	0.418
Cauliflower	No	27(24.11)	15(16.3)	1(ref)		18(20.45)	23(21.5)	1(ref)		
	Yes	85(75.89)	77(83.7)	0.708(0.308,1.593)	0.408	70(79.55)	84(78.5)	1.485(0.591,3.868)	0.406	0.088
Chinese cabbage	No	74(66.07)	66(71.74)	1(ref)		56(64.37)	77(72.64)	1(ref)		
	Yes	38(33.93)	26(28.26)	1.368(0.684,2.760)	0.376	31(35.63)	29(27.36)	1.528(0.673,3.479)	0.309	0.317
Collard greens	No	79(70.54)	69(75)	1(ref)		63(72.41)	79(73.83)	1(ref)		

Cress/watercress	Yes	33(29.46)	23(25)	1.305(0.636,2.708)	0.470	24(27.59)	28(26.17)	1.322(0.573,3.067)	0.512	0.836
	No	79(70.54)	62(68.13)	1(ref)		71(81.61)	79(73.83)	1(ref)		
Honey mustard	Yes	33(29.46)	29(31.87)	0.909(0.452,1.826)	0.788	16(18.39)	28(26.17)	0.807(0.316,2.004)	0.647	0.935
	No	60(53.57)	42(45.65)	1(ref)		38(43.68)	40(37.38)	1(ref)		
Horseradish	Yes	52(46.43)	50(54.35)	0.699(0.366,1.329)	0.276	49(56.32)	67(62.62)	1.058(0.502,2.256)	0.882	0.296
	No	61(54.46)	46(50.55)	1(ref)		40(45.98)	53(50)	1(ref)		
Kale	Yes	51(45.54)	45(49.45)	0.849(0.437,1.640)	0.626	47(54.02)	53(50)	1.980(0.950,4.256)	0.073	0.104
	No	71(63.39)	64(69.57)	1(ref)		54(62.07)	74(69.16)	1(ref)		
Mustard	Yes	41(36.61)	28(30.43)	1.499(0.767,2.966)	0.239	33(37.93)	33(30.84)	1.642(0.739,3.695)	0.225	0.435
	No	48(43.24)	37(40.66)	1(ref)		38(43.68)	38(35.85)	1(ref)		
Radish	Yes	63(56.76)	54(59.34)	0.771(0.395,1.489)	0.440	49(56.32)	68(64.15)	0.779(0.363,1.665)	0.518	0.503
	No	67(59.82)	56(60.87)	1(ref)		45(52.33)	70(68.63)	1(ref)		
Turnips	Yes	45(40.18)	36(39.13)	1.181(0.602,2.326)	0.628	41(47.67)	32(31.37)	**2.351(1.122,5.046)**	**0.025**	0.326
	No	82(74.55)	74(80.43)	1(ref)		61(70.93)	84(78.5)	1(ref)		
Wasabi	Yes	28(25.45)	18(19.57)	1.771(0.816,3.925)	0.152	25(29.07)	23(21.5)	2.199(0.933,5.309)	0.074	0.913
	No	72(64.29)	52(56.52)	1(ref)		54(62.07)	80(74.77)	1(ref)		
	Yes	40(35.71)	40(43.48)	0.688(0.346,1.356)	0.281	33(37.93)	27(25.23)	**3.204(1.376,7.836)**	**0.008**	**0.027**

Note: Multivariate unconditional logistic regression models were used to calculate adjusted ORs. Multivariate model was adjusted for age at baseline (continuous, y), enrollment year (continuous, y), oral contraceptive therapy (never use, current user, and former user), age at menarche (less than 12 years, 12-13 years, and more than 13 years), hormone replacement therapy (never used, estrogen, progesterone, and combination) , physical activity (light, moderate, and rigorous) , menopausal status (premenopausal and postmenopausal), family history (no family history, second-degree relatives only, and both of first-degree and second-degree relatives), and flamed broiled consumption (combination of flame broiled meat, fish, and chicken). Only individuals without missing data in each subtype were included in the analyses.

[a]n (proportion, %).

[b]*P* value for interaction term, menopausal status*frequency of subtype intake.

[c]Binary variable was calculated by the total amount of all subtypes.

[d]Short for servings/day.

[e]Short for servings/week.

Table 9. Adjusted odds ratios (ORs) and 95% confidence interval (95% CI) of breast cancer according to total and subtypes cruciferous vegetables consumption, stratified by molecular features of breast cancer, BOSS Cohort Study, 2003-2015.

			ER+			ER-		
Subtypes	**Frequency**	**Control (N=200)**	**Cases (N=150)**	**aOR (95% CI)**	**a*P***	**Cases (N=44)**	**aOR (95% CI)**	**a*P***
Total crucifers	< 1 serving/day	112	78(41.1)	1(ref)		21(47.7)	1(ref)	
	≥ 1 serving/day	86	72(45.6)	**1.72(1.05,2.81)**	**0.03**	23(52.3)	2.02(0.89,4.61)	0.10
Broccoli	< 1 serving/week	71	46(30.5)	1(ref)		13(29.5)	1(ref)	
	≥ 1 serving/week	127	105(69.5)	1.24(0.73,2.13)	0.42	31(70.5)	1.32(0.53,3.48)	0.55
Arugula	No	111	74(49.3)	1(ref)		27(61.4)	1(ref)	
	Yes	86	76(50.7)	**1.69(1.02,2.83)**	**0.04**	17(38.6)	0.91(0.37,2.22)	0.84
Bok Choy	No	136	102(67.5)	1(ref)		34(77.3)	1(ref)	
	Yes	62	49(32.5)	1.35(0.80,2.28)	0.26	10(22.7)	0.78(0.27,2.11)	0.64
Broccoli raab	No	151	114(76)	1(ref)		37(84.1)	1(ref)	
	Yes	44	36(24)	1.20(0.66,2.15)	0.55	7(15.9)	0.75(0.21,2.37)	0.64
Broccoli sprouts	No	122	86(57.3)	1(ref)		36(81.8)	1(ref)	
	Yes	76	64(42.7)	1.28(0.78,2.12)	0.33	8(18.2)	0.80(0.29,2.11)	0.65
Broccolini	No	143	115(77.2)	1(ref)		35(81.4)	1(ref)	
	Yes	50	34(22.8)	0.73(0.39,1.31)	0.29	8(18.6)	0.59(0.18,1.74)	0.36
Brussel sprouts	No	109	67(44.4)	1(ref)		18(40.9)	1(ref)	
	Yes	88	84(55.6)	1.55(0.94,2.57)	0.09	26(59.1)	**3.29(1.31,9.05)**	**0.01**
Cabbage	No	50	36(24.2)	1(ref)		11(25)	1(ref)	
	Yes	148	113(75.8)	1.42(0.78,2.61)	0.26	33(75)	1.74(0.61,5.40)	0.31
Cauliflower	No	38	35(23.2)	1(ref)		9(20.5)	1(ref)	
	Yes	160	116(76.8)	0.94(0.51,1.74)	0.84	35(79.5)	1.64(0.56,5.29)	0.38
Chinese cabbage	No	143	94(62.7)	1(ref)		32(72.7)	1(ref)	
	Yes	54	56(37.3)	**1.82(1.08,3.08)**	**0.03**	12(27.3)	1.25(0.43,3.50)	0.67
Collard greens	No	147	103(68.7)	1(ref)		34(77.3)	1(ref)	
	Yes	51	47(31.3)	1.44(0.84,2.48)	0.19	10(22.7)	1.42(0.49,3.92)	0.50
Cress/watercress	No	140	110(73.3)	1(ref)		36(81.8)	1(ref)	
	Yes	57	40(26.7)	1.02(0.59,1.78)	0.93	8(18.2)	0.86(0.27,2.48)	0.79
Honey mustard	No	81	70(46.7)	1(ref)		26(59.1)	1(ref)	

	Yes	117	80(53.3)	0.88(0.54,1.44)	0.62	18(40.9)	0.53(0.21,1.30)	0.17
Horseradish	No	98	73(48.7)	1(ref)		27(61.4)	1(ref)	
	Yes	98	77(51.3)	1.27(0.78,2.08)	0.34	17(38.6)	0.64(0.26,1.55)	0.33
Kale	No	137	93(62.0)	1(ref)		29(65.9)	1(ref)	
	Yes	61	57(38.0)	1.64(0.97,2.76)	0.06	15(34.1)	1.47(0.57,3.72)	0.42
Mustard	No	75	68(45.6)	1(ref)		18(40.9)	1(ref)	
	Yes	121	81(54.4)	0.78(0.46,1.29)	0.33	26(59.1)	0.68(0.26,1.73)	0.42
Radish	No	126	83(55.7)	1(ref)		25(56.8)	1(ref)	
	Yes	67	66(44.3)	**1.80(1.09,2.97)**	**0.02**	19(43.2)	1.46(0.61,3.55)	0.39
Turnips	No	157	103(70.1)	1(ref)		35(79.5)	1(ref)	
	Yes	41	44(29.9)	**2.03(1.15,3.62)**	**0.01**	9(20.5)	2.19(0.72,6.56)	0.16
Wasabi	No	131	90(60.0)	1(ref)		32(72.7)	1(ref)	
	Yes	67	60(40.0)	1.57(0.93,2.66)	0.09	12(27.3)	0.60(0.21,1.60)	0.32

Note: Multivariate unconditional logistic regression models were used to calculate adjusted ORs. Multivariate model was adjusted for age at baseline (continuous, y), enrollment year (continuous, y), body mass index (continuous), oral contraceptive therapy (never use, current user, and former user), age at menarche (less than 12 years, 12-13 years, and more than 13 years), hormone replacement therapy (never used, estrogen, progesterone, and combination) , physical activity (light, moderate, and rigorous) , menopausal status (premenopausal and postmenopausal), family history (no family history, second-degree relatives only, and both of first-degree and second-degree relatives), and flamed broiled consumption (combination of flame broiled meat, fish, and chicken).
Abbreviation: PR, progesterone receptor; ER, estrogen receptive.
[a]n (proportion, %).

Table 10. Agreement of responses in food frequency questionnaire of selected subtypes of cruciferous vegetables, BOSS Cohort Study, 2003-2015.

	Responses in question 57[a]		Agreement[b]	Kappa statistic
	No	Yes		
Responses in question 58[c]				
Broccoli			98.50%	0.74
No	9	2		
Yes	4	385		
Brussel sprouts			82.50%	0.65
No	139	13		
Yes	57	191		
Mustard			78.50%	0.52
No	84	9		
Yes	77	230		

[a]The frequency of subtypes consumption answered in the frequency questions.
[b]Agreement (%) was calculated by the total counts of answers which were agreed to the total population.
[c]The frequency of subtypes consumption answered in the pattern change questions.
[d]The frequency of total consumption which was answered directly in the baseline questions.

Table 11. Pattern of changes in selected cruciferous vegetables consumptions by cases status and baseline consumption category, respectively, BOSS Cohort Study, 2003-2015.

Subtypes, pattern of change	Cases status			Baseline consumption category		
	Cases[a] (N=200)	Controls[a] (N=200)	*P*[b]	I[c]	II[c]	*P*[b]
Broccoli			0.260			0.141
Not used	3 (1.5)	8 (4.0)		11 (8.33)	0 (0)	
Unchanged	134 (67.0)	133 (66.5)		83 (62.88)	184 (68.66)	
Increased	57 (28.5)	47 (23.5)		24 (18.18)	80 (29.85)	
Decreased	4 (2.0)	8 (4.0)		8 (6.06)	4 (1.49)	
Missing	2 (1.0)	4 (2.0)		6 (4.55)	0 (0)	
Brussel sprouts			0.036			< 0.001
Not used	63 (31.5)	89 (44.5)		139 (70.92)	13 (6.37)	
Unchanged	105 (52.5)	92 (46.0)		51 (26.02)	146 (71.57)	
Increased	28 (14.0)	14 (7.0)		4 (2.04)	38 (18.63)	
Decreased	3 (1.5)	3 (1.5)		2 (1.02)	4 (1.96)	
Missing	1 (0.5)	2 (1.0)				
Mustard			0.720			0.058
Not used	49 (24.5)	44 (22.0)		84 (52.17)	9 (3.77)	
Unchanged	140 (70.0)	138 (69.0)		68 (42.24)	210 (87.87)	
Increased	5 (2.5)	9 (4.5)		5 (3.11)	9 (3.77)	
Decreased	5 (2.5)	7 (3.5)		4 (2.48)	8 (3.35)	
Missing	1 (0.5)	2 (1.0)		0 (0)	3 (1.26)	

[a]n (proportion, %).
[b]Fisher exact test was used to calculate the *P*-value. “Not used” and “unchanged” groups were collapsed and “increased” and “decreased” groups were collapsed when calculated the *P*-value.
[c]For broccoli, category I denotes frequency < 1 servings/week and category II denotes frequency ≥ 1 servings/week. For Brussel sprouts and mustard, category I denotes frequency = 0 serving/week and category II denotes frequency > 0 servings/week.

Table 12. Sensitivity analysis of the association of breast cancer risk according to the sum or subtypes of cruciferous vegetables consumption, BOSS Cohort Study, 2003-2015.

Subtypes	Frequency	Cases[a]	Controls[a]	aOR (95% CI)	a*P*-value
Each selected subtype, excluded women changed dietary pattern[b]					
Broccoli (*N* = 281)	< 1 serving/week	45(32.37)	55(37.93)	1(ref)	
	≥ 1 serving/week	94(67.63)	90(62.07)	1.483(0.831,2.677)	0.186
Mustard (*N* = 363)	No	83(44.15)	69(37.91)	1(ref)	
	Yes	105(55.85)	113(62.09)	0.792(0.481,1.300)	0.357
Brussel sprouts (*N* = 346)	No	81(47.93)	109(59.89)	1(ref)	
	Yes	88(52.07)	73(40.11)	1.633(0.987,2.717)	0.057
All subtypes, excluded women diagnosed beyond one year before enrollment[c]					
I, < 0.5 serving/day		29(16.85)	28(14.00)	1(ref)	
II, 0.5-1.0 serving/day		53(30.81)	76(38.00)	0.562(0.216,1.465)	0.239
III, 1.0 -1.5 servings/day		42(24.42)	52(26.00)	1.610(0.581,4.466)	0.360
IV, ≥ 1.5 servings/day		48(27.91)	44(22.00)	1.395(0.539,3.613)	0.493
				P_{trend}	0.087
Each subtype, excluded women diagnosed beyond one year before enrollment[c]					
Broccoli	< 1 serving/week	54(31.4)	71(35.5)	1(ref)	
	≥ 1 serving/week	118(68.6)	129(64.5)	1.670(0.867,3.216)	0.125
Arugula	No	88(51.46)	111(55.78)	1(ref)	
	Yes	83(48.54)	88(44.22)	1.221(0.661,2.257)	0.524
Bok Choy	No	121(70.35)	138(69)	1(ref)	
	Yes	51(29.65)	62(31)	1.460(0.736,2.895)	0.279
Broccoli raab	No	136(79.53)	152(77.16)	1(ref)	
	Yes	35(20.47)	45(22.84)	0.895(0.412,1.945)	0.780
Broccoli sprouts	No	108(63.16)	122(61)	1(ref)	
	Yes	63(36.84)	78(39)	1.174(0.629,2.190)	0.614
Broccolini	No	134(79.29)	145(74.36)	1(ref)	
	Yes	35(20.71)	50(25.64)	**0.435(0.201,0.944)**	**0.035**

Brussel sprouts	No	76(44.19)	110(55.28)	1(ref)	
	Yes	96(55.81)	89(44.72)	1.699(0.940,3.071)	0.079
Cabbage	No	44(25.88)	51(25.5)	1(ref)	
	Yes	126(74.12)	149(74.5)	1.331(0.685,2.585)	0.398
Cauliflower	No	39(22.67)	38(19)	1(ref)	
	Yes	133(77.33)	162(81)	1.024(0.525,1.997)	0.945
Chinese cabbage	No	110(64.33)	144(72.36)	1(ref)	
	Yes	61(35.67)	55(27.64)	**2.229(1.062,4.680)**	**0.034**
Collard greens	No	124(72.51)	149(74.5)	1(ref)	
	Yes	47(27.49)	51(25.5)	1.182(0.610,2.289)	0.620
Cress/watercress	No	129(75)	142(71.36)	1(ref)	
	Yes	43(25)	57(28.64)	1.072(0.580,1.980)	0.825
Honey mustard	No	82(47.95)	82(41)	1(ref)	
	Yes	89(52.05)	118(59)	0.576(0.307,1.083)	0.087
Horseradish	No	85(49.71)	99(50)	1(ref)	
	Yes	86(50.29)	99(50)	1.370(0.734,2.557)	0.323
Kale	No	110(64.33)	139(69.5)	1(ref)	
	Yes	61(35.67)	61(30.5)	1.475(0.731,2.978)	0.278
Mustard	No	75(44.12)	75(37.88)	1(ref)	
	Yes	95(55.88)	123(62.12)	0.722(0.370,1.409)	0.340
Radish	No	97(57.06)	127(65.13)	1(ref)	
	Yes	73(42.94)	68(34.87)	1.454(0.793,2.668)	0.226
Turnips	No	125(74.4)	158(79)	1(ref)	
	Yes	43(25.6)	42(21)	1.832(0.877,3.827)	0.107
Wasabi	No	106(61.99)	133(66.5)	1(ref)	
	Yes	65(38.01)	67(33.5)	1.430(0.736,2.781)	0.292

Note: Multivariate conditional logistic regression models were used to calculate the adjusted ORs, respectively. Multivariate model was adjusted for age at baseline (continuous, y), enrollment year (continuous, y), body mass index (continuous), oral contraceptive therapy (never use, current user, and former user), age at menarche (less than 12 years, 12-13 years, and more than 13 years), hormone replacement

therapy (never used, estrogen, progesterone, and combination) , physical activity (light, moderate, and rigorous) , menopausal status (premenopausal and postmenopausal), family history (no family history, second-degree relatives only, and both of first-degree and second-degree relatives), and flamed broiled consumption (combination of flame broiled meat, fish, and chicken).

[a]n (proportion, %).

[b]Among women with unchanged intake of each subtype of cruciferous vegetables.

[c]Included all controls and cases who were diagnosed within one year before enrollment, *N* = 344.

FIGURES

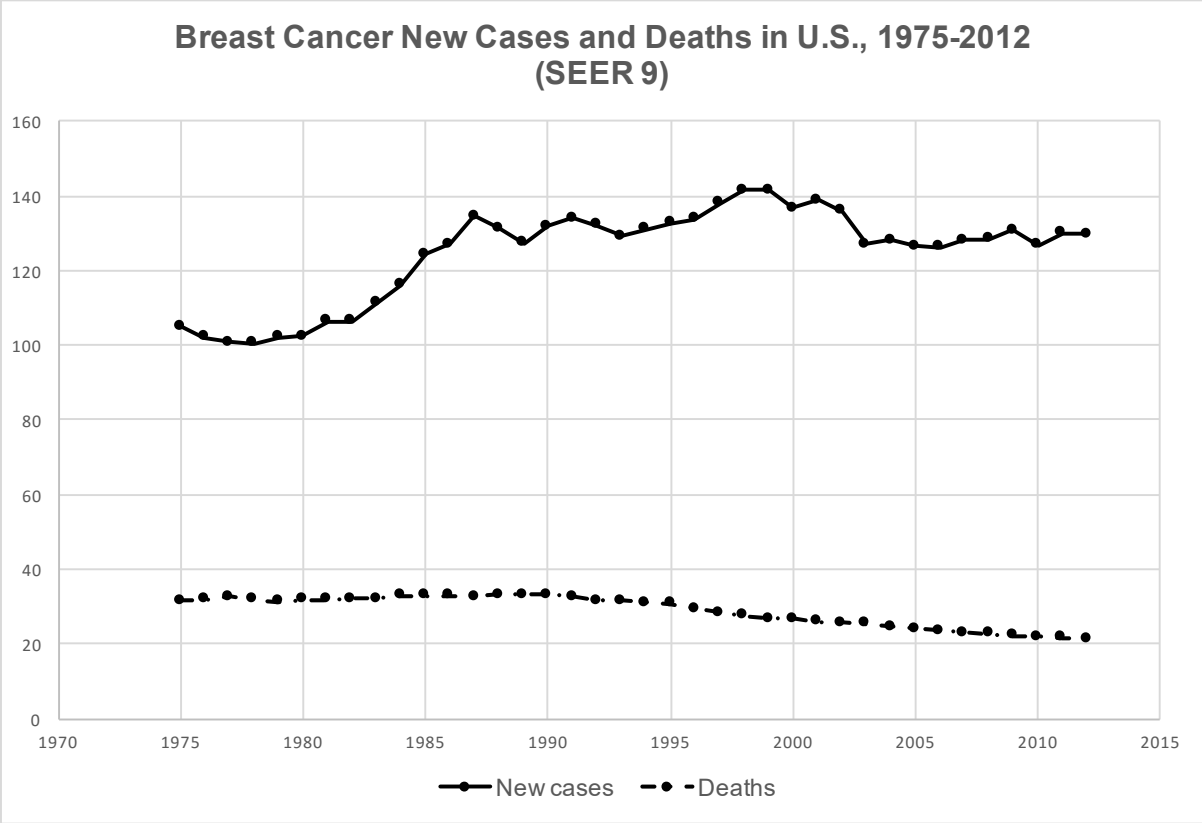

Figure 1. Age-adjusted number of new cases and deaths per 100,000 persons (all races, females) in US during 1975-2012 (1).
*** SEER 9 registries include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah.**

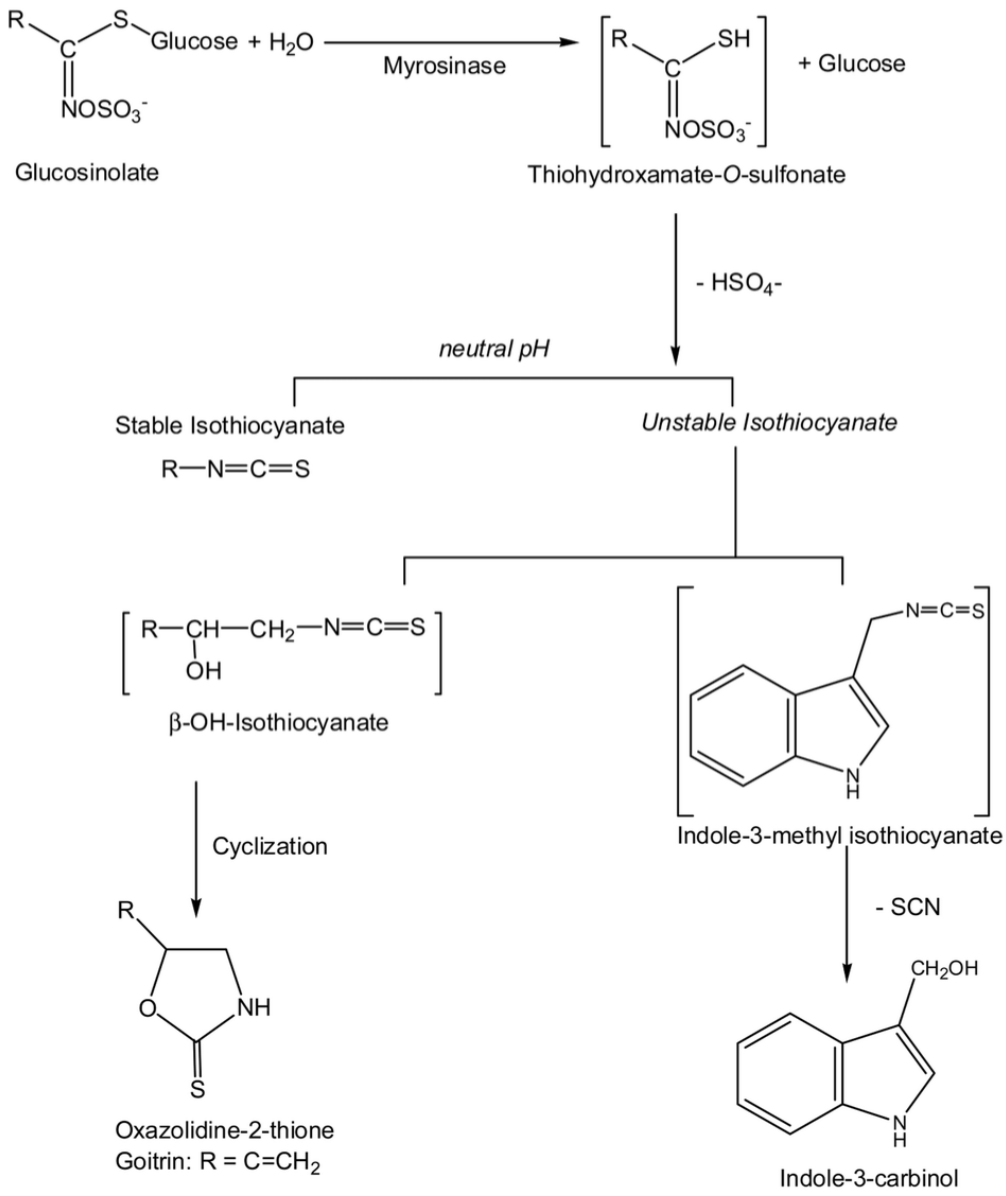

Figure 2. Glucosinolates hydrolysis and the formation of the I3C and ITC (42, 44).

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PROFILE

Master of Science candidate in Cancer Epidemiology with a clinical medicine training background. Research interests in cancer genetic epidemiology, particularly gene-environment interactions and risk prediction. Research experience in cancer and genetic epidemiology. Planning to pursue a doctoral degree to further develop expertise in genetic epidemiology and statistical methods applied to cancer with the long-term goal of doing research, teaching and service to improve public health.

EDUCATION

08/2014 – 05/2016 **Master of Science of Cancer Epidemiology** — Johns Hopkins University (Baltimore, MD)

GPA: 3.95/4.00 (major GPA: 4.00/4.00, up to current term)

Thesis: *"Association between cruciferous vegetables consumption and breast cancer risk: a case-control study among women with familial risk"*

Advisor: Dr. Kala Visvanathan

Courses: Principles of Genetic Epidemiology series, Epidemiologic Methods series, Biostatistics Methods series, Etiology, Prevention, and Control of Cancer, Causal Inference, Survival Analysis, etc.

The Trudy Bush Fund at Johns Hopkins Bloomberg School of Public Health — 2016

Nutramax Award at Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital — 2016

Master's Tuition Scholarship at Johns Hopkins Bloomberg School of Public Health — 2015

09/2009 – 07/2014 **Bachelor of Medicine** — Peking University (Beijing, China)

GPA: 3.74/4.00 (major GPA: 3.84/4.00)

Thesis: *"Interferon regulatory factor 6 gene and non-syndromic cleft lip with/without palate in Chinese population"*

1st prize scholarship at Peking University *(university-wide, top 5%)* — 2013, 2012, 2011

Merit Student at Peking University *(university-wide, top 5%)* — 2012, 2011

RESEARCH EXPERIENCE

05/2015 – 05/2016 **Research Assistant,** Supervisor: Dr. Terri H. Beaty

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

COPDGene, International Consortium to Identify Genes & Interactions Controlling Oral Clefts

- Reviewed the literature to identify the COPD phenotypes for the analysis
- Performed single variant analysis and gene-based analysis on *COPDGene* exome chip data to test the association between COPD

phenotypes and SNPs among African-American and Non-Hispanic Whites
- Discovered the association between gene *MYLIP* and smoking habits and summarized the methods and results for the manuscript *"Exome Array Analysis of smoking behavior related phenotypes"*

11/2013 – 06/2014 **Undergraduate Thesis,** Advisor: Dr. Tao Wu / PI: Dr. Terri H. Beaty
Peking University School of Public Health, Beijing, China
International Consortium to Identify Genes & Interactions Controlling Oral Clefts
- Conducted literature review on NSCL/P and explanatory data analysis on SNPs of *IRF6* and *MTHFR* gene
- Performed transmission disequilibrium tests (TDT) to test for the association between gene *IRF6* and *MTHFR* and non-syndromic cleft lip with/without the palate (NSCL/P), considering marginal and interaction effects with genes and maternal exposures in 806 Chinese case-parent trios
- Reported the results and composed the undergraduate thesis

12/2012 – 06/2014 **Research Assistant,** Supervisors: Dr. Liming Li, Dr. Jun Lv and Dr. Siyan Zhan
Peking University School of Public Health, Beijing, China
Twin Study, China Kadoorie Biobank, etc.
- Recruited and interviewed participants to collect the information of demographic, family history, medical history, behavior and lifestyles, physical examination, etc.
- Participated in the compilation of the book: *"Techniques Appropriate for Mega- and Prospective Cohort Study".* Responsible for drafting the medication and female health history chapter on methodology for survey in prospective cohort study: including survey design, questionnaire construction and interviewing
- Screened eligible articles from 800+ publications for a network meta-analysis on the difference surgical treatments for displaced fractures of the femoral neck in elderly population

09/2010 – 12/2012 **Research Assistant,** Supervisor: Dr. Xiaochuan Pan
Peking University School of Public Health, Beijing, China
- Extracted respiratory system related symptoms and medical information from ER patients' medical records to investigate the effect of air pollution on the ER admission related respiratory system disease
- Replicated time-series analysis to detect the impact of air pollution during the extreme-temperature days on the mortality in Guangzhou city, China and scripted an original research entitled *"The impact of ambient particle pollution during extreme-temperature days in Guangzhou city, China"*

TEACHING EXPERIENCE

07/2015 – 05/2016 **Teaching Assistant,** Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

INTERNSHIPS AND EXTRACURRICULAR ACTIVITIES

09/2015 – Present **Mentor,** Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

07/2015 – 08/2015 **Reader Volunteers,** SOURCE, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

03/2015 – Present **Volunteers,** Susan G. Komen Breast Association, Baltimore, MD

01/2015 – Present **Volunteers,** Chinese Forum of Public Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

01/2014 – 07/2014 **Research Assistant/Intern**, *Breast Cancer Awareness Education and Training Promotion Pilot Programs in China* (Project coordinated by Harvard T.H. Chan School of Public Health & Peking Union Medical College)

09/2013 – 10/2013 **CDC Intern***,* Nanshan Center of Disease Control and Prevention, Shenzhen, Guangdong, China

07/2013 – 08/2013 **Junior Research Assistant**, Chinese University of Hong Kong, Hong Kong

07/2012 – 08/2012 **International Medical Volunteer,** *We Women Clinic*, Kathmandu, Nepal

03/2012 – 12/2012 **Project Manager**, *"Cross-sectional investigation of polychlorinated biphenyls pollution in Ziyang, China"*

01/2012 – 01/2013 **Clinical Intern,** Beijing Shijitan Hospital, Beijing, China

04/2011 – 10/2011 **Project Manager, "***Cross-sectional Investigation of Rural Sanitary Facility Status in Beijing"* , China CDC

PUBLICATIONS

1. Lutz S, Frederiksen B, Begum F, Cho MH, Parker MM, **Jiang L**, Hobbs B, McDonald ML, DeMeo DL, Ehringer MA, Foreman MG, Kinney GL, Make BJ, Lomas DA, Bakke P, Gulsvik A, Lange C, Crapo JD, Silverman EK, Beaty TH, Hokanson JE, the ECLIPSE and COPDGene Investigators. Common and rare variants analysis of smoking related traits among current and former smokers of European and African ancestry. *(Ready to submit)*
2. Li G, **Jiang L**, Zhang Y, Cai Y, Pan X, Zhou M. The impact of ambient particle pollution during extreme-temperature days in Guangzhou city, China. Asia Pac J Public Health. 2014 Nov;26(6):614-21.
3. **Jiang L**, Wen L, Lv J. The association between gastric cancer and spicy food: a review. Chinese Journal of Prevention and Control of Chronic Diseases. 2014, 03:363-4.
4. **Jiang L**, Wang L, Pan X. Public Latrine Status in Beijing Rural District. Journal of Environment and Health, 2012, 29(8).

COMPUTER SKILLS

R (with programming skill), STATA (with programming skill), Latex, SAS, SPSS, Microsoft Office products, Photoshop