Published in final edited form as:
Int J Cancer. 2013 August 1; 133(3): 680–686. doi:10.1002/ijc.28027.

Calcium intake is not related to breast cancer risk among Singapore Chinese women

Jingmei Li[1], **Woon-Puay Koh**[2,3], **Ai-Zhen Jin**[4], **Jian-Min Yuan**[5,6], **Mimi C. Yu**[7], and **Lesley M. Butler**[5,6]

[1]Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore

[2]Duke-NUS Graduate Medical School, Singapore 169857, Singapore

[3]Saw Swee Hock School of Public Health, National University of Singapore, Singapore 117597, Singapore

[4]National Registry of Diseases Office, Health Promotion Board, 3 Second Hospital Avenue, Singapore 168937, Singapore

[5]University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, 15232, USA

[6]University of Pittsburgh Graduate School of Public Health, Department of Epidemiology, Pittsburgh, Pennsylvania, 15261, USA

[7]retired from the Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California 90089, USA

Abstract

There is experimental evidence that calcium protects against breast cancer development. Prospective epidemiologic studies supporting a protective effect of calcium on breast cancer risk have mainly been limited to Western populations. We examined the association between calcium intake and breast cancer risk in the Singapore Chinese Health Study, a large population-based prospective cohort. Calcium intake and supplement use was assessed by in-person interviewer using a validated food frequency questionnaire. After a mean follow-up of 14.2±3.5 years, 823 cohort participants developed invasive breast cancer. Multivariate proportional hazards regression models were fitted to examine the associations between calcium intake and breast cancer risk. Vegetables were the primary food source of calcium in this study population, followed by dairy products, grains and soy foods. Calcium intake was not associated with breast cancer risk, comparing highest quartile (>345.6 mg/1000 kcal/day) to lowest quartile (<204.5mg/1000 kcal/day) of intake. There was no evidence of effect modification by menopausal status, body mass index, dietary vitamin D or stage of disease at diagnosis. Our findings do not support a hypothesis for calcium in breast cancer chemoprevention, contrary to findings from previous studies among Western populations with higher calcium intake primarily from dairy products and supplements.

Keywords

calcium intake; breast cancer; Asian; Chinese; cohort studies

Correspondence to: Lesley Butler, University of Pittsburgh Cancer Institute, 5150 Centre Avenue, Pittsburgh, PA 15232, USA; butlerl3@upmc.edu.

Introduction

Calcium may play a protective role in breast carcinogenesis because of its importance in regulating cell proliferation, differentiation, and apoptosis[1–2]. Calcium has anti-proliferative and pro-differentiation effects on mammary cells[3] and can inhibit the development of mammary tumors in mice[3]. Although much of the evidence suggesting that calcium protects against cancer relies on its interrelation with vitamin D, experimental evidence from several model systems suggests that an increased level of calcium alone is a sufficient signal to induce apoptosis[4].

Epidemiologic studies conducted mostly among Western populations support an inverse association between calcium intake and breast cancer risk. A meta-analysis by Chen et al.[5] using results from six prospective cohort and nine case-control studies on calcium intake and breast cancer risk reported a statistically significant 19% reduction in breast cancer risk when comparing those in the group with highest (>1000 mg/day) versus lowest (<500–600mg/day) calcium intake. With the exception of one case-control study conducted in Shangahi[6], all of the studies in the meta-analysis were conducted among US or European populations. These findings are further supported by prospective results from a study of serum calcium levels and breast cancer risk among premenopausal women[7]. In Western populations, dairy products are the main dietary source of calcium, and the prevalence of calcium supplement use is higher than in Asian populations[8–11]. In addition, dairy products in many Western populations are fortified with vitamin D, thus making it difficult to establish whether the observed inverse associations between calcium and breast cancer in these populations are independent of vitamin D intake[12–13].

Asian populations have historically had among the lowest incidence of breast cancer worldwide until recently[14–17] and also consume diets relatively low in calcium[18]. Heretofore, no prospective studies in Asian populations have evaluated calcium-breast cancer associations. Of the three case-control studies conducted to date among Asians[6, 19–20], two studies supported statistically significant protective effects of overall calcium on breast cancer risk[19–20]. These prior studies were limited by the retrospective design and hospital-based controls[19–20], thus increasing the potential for spurious associations due in part to differential recall and selection bias. In order to address these limitations, we used a prospective database with detailed dietary and vitamin supplement information among a Chinese population in Singapore, to test the hypothesis that calcium intake is associated with a decreased risk of breast cancer.

Methods

Study population

The Singapore Chinese Health Study is a population-based prospective study initiated between 1993 and 1998, previously described in detail[21]. Briefly, the cohort consisted of 27,959 men and 35,298 women aged 45–74 years during the period of recruitment who were either permanent residents or citizens of Singapore and residing in government-built housing estates (86% of the population resided in such facilities during the recruitment period). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore: the Hokkiens and the Cantonese. Of those who were eligible, 85% agreed to participate. For the analyses in this study, 34,028 women were eligible after exclusion of subjects with a previous diagnosis of invasive cancer at baseline. The study was approved by the Institutional Review Boards at the National University of Singapore and the University of Pittsburgh.

Identification of incident breast cancer cases and deaths among cohort members was accomplished by record linkage of the cohort database with respective databases from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The linkage was performed using a unique national identification number given to all Singaporeans. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases[22]. There were 823 incident cases of invasive breast cancer diagnosed on or before December 31, 2010. To date, only 47 cohort participants were lost to follow-up due to migration out of Singapore.

Baseline questionnaire and assessment of calcium intake

At recruitment, a face-to-face interview was conducted in the subject's home by a trained interviewer who used a structured questionnaire. Information was collected on demographics, height, weight, lifetime use of tobacco, usual physical activity, menstrual and reproductive history, medical history, and familial history of cancer. The questionnaire included a validated dietary component (including questions about coffee, tea, and alcoholic beverages) that assessed current intake patterns[23]. Each subject was asked to estimate her usual intake frequencies and portion sizes for 165 food and beverage items during the past 12 months. Study participants were also asked about supplement use with the following question, "Did you take any vitamins or minerals at least once each week during the last year?" If the participant responded "Yes," then the interviewer asked to view the supplement bottle(s) in order to record the dose of each vitamin and/or mineral.

Average daily intake of roughly 100 nutrient and non-nutrient compounds, including calcium, were computed for each study subject based on the Singapore Food Composition Database[23]. Our calculation of the food sources as percentages of dietary calcium in the study population was based on a series of 24-hour dietary recall interviews, as previously described[23]. Specifically, as part of the FFQ validation study, 24-hour diet recall data were collected from 1,022 (425 men and 597 women) randomly chosen cohort subjects[23]. For calcium intake, the correlation coefficients between 24-hour recalls and FFQ responses were between 0.51 and 0.61 for the four gender-dialect subgroups. The percentage of contribution of calcium from a specified food item or food group was calculated as the ratio of A_i/B, where A_i = dietary calcium from a single food (i) summed across all subjects who consumed that food, and B = total dietary calcium summed across the 1,022 subjects.

Statistical methods

Person-years of follow-up time were calculated from the date of study recruitment until the date of breast cancer diagnosis, death, migration out of Singapore, or end of follow-up (December 31, 2010), whichever occurred first. As of December 31, 2010, only 47 subjects from this cohort were known to be lost to follow-up due to migration out of Singapore or for other reasons. After testing the validity of the proportional hazards assumption, Cox proportional hazards regression models[24] were fitted to examine the associations between calcium intake (mg per 1,000 kcal per day) in quartiles and breast cancer risk. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using the SAS PROC PHREG procedure[25]. The following covariates were included in the final models to adjust for potential confounding: age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/or higher), family history of breast cancer (yes/no first degree relative), age when menstrual period became regular (<13, 13–14, 15–16, ≥17 years, never regular), number of live births (0, 1–2, 3–4, ≥5), and body mass index (BMI, kg/m^2). These variables were included as covariates in the adjusted models because they were either associated with calcium intake or with breast cancer risk in our data. To adjust for energy intake, all nutrient variables were expressed in weight unit per 1000 kcal or percentage of total energy. There were no important differences between the hazard ratios and 95% confidence intervals for calcium and breast cancer risk that were calculated from models adjusted only for age at interview and those calculated from models adjusted for all covariates, so we only present results for the covariate-adjusted models. *P* values for linear trend tests for calcium–breast cancer associations were obtained by treating quartiles of calcium intake as an ordinal variable (0, 1, 2 and 3).

In addition, we used stratified analyses to examine whether the association between calcium and breast cancer risk varied by disease stage (early or advanced), menopausal status at baseline, BMI (below or above median, 23.2 kg/m^2) and dietary intake of vitamin D (below or above median, 83.2 IU/day). All analyses were conducted using SAS version 9.1 (SAS Institute Inc.). All reported *P* values were two-sided and considered statistically significant if less than 0.05.

Results

Table 1 shows the distributions of baseline characteristics of 34,028 eligible female participants by quartiles of total calcium intake. Compared to women with low calcium intake, women with increasing calcium intake were younger, more educated, more likely to use dietary supplements and had higher daily energy intake. Overall, the frequency of calcium supplement use was 4.3% for any weekly use. The median daily intakes of the major food sources of calcium increased with increasing quartile of total calcium intake. The major food source of calcium in our study population was vegetables, especially green leafy vegetables, followed by dairy products, grains and soy foods (Table 2).

During an average follow-up of 14.2±3.5 years (484,303 person-years), 823 cohort participants without a prior cancer diagnosis developed invasive breast cancer. Calcium intake was not associated with breast cancer risk among Singaporean Chinese women (Table 3). Regardless of sources (food-only or food and dietary supplement), there remained a null association with greater intake and breast cancer risk. No association between calcium and breast cancer risk was seen either in subgroups of women stratified by menopausal status, median BMI, or median vitamin D intake (Table 4). Additional analysis for subgroups of women stratified by tertile or quartile of vitamin D intake did not alter the null association between calcium and breast cancer risk (data not shown). A null association persisted for both localized and advanced stages of breast cancer (data not shown).

Discussion

In these prospective analyses we did not provide evidence for a protective effect of calcium intake on breast cancer risk among Chinese women in Singapore. There was no association with breast cancer risk regardless of whether we evaluated calcium intake from food and supplement sources or from food sources alone. The lack of an association between calcium intake and breast cancer risk persisted after stratifying the data by menopausal status, BMI or vitamin D intake. Our finding does not support experimental evidence or recent findings from a meta-analysis with studies mostly from Western populations suggesting that calcium may protect against the development of breast cancer. The recommended daily allowance for calcium intake for adults over age 50 is 1000 mg/day in Singapore[26] and 1200 mg/day in the United States[27]. It is possible that the absence of association between total calcium intake and overall breast cancer risk in our study may be due to the relatively low calcium intake in the Singaporean Chinese population, where 72% of the population had total calcium intake below 500 mg/day (median 353 mg/day). In a recent meta-analysis, a linear dose-response relationship between increasing calcium intake and lower breast cancer risk was reported, with the lowest risk observed for intake around 600 mg/day[28]. It has been suggested that the actual amount of calcium intake needed to observe beneficial health effects may be greater in populations with diets high in sodium and/or animal protein[29]. High levels of calcium intake are typical in Western populations, and a protective effect against breast cancer development was observed for calcium intake levels of at least 800 and 1366 mg/day in the Nurses' Health Study[12] and Women's Health Study[30], respectively. The daily consumption of calcium among Singapore Chinese women was relatively low compared with other female Asian populations with median intakes around 500 mg/day[6, 19–20]. Thus, it is possible that the levels of calcium intake among Chinese women in Singapore were too low to exert a protective effect on breast cancer risk.

We considered whether our study population lacked a wide enough range of calcium intake in order for us to have the statistical power to observe an association with breast cancer risk. However, in our study, the daily median calcium intake in the highest quartile was 2.5 fold that of the lowest quartile, and this was similar to the range reported for two prospective studies in the US. For example, the range of calcium intake was approximately 2.5 and 2.2 fold in the Nurses' Health Study[12] and Women's Health Study[30], respectively.

It is also possible that differences in the dominant dietary patterns between Asian and Western populations may have contributed to the contrasting findings for our study compared with previous prospective studies in the US[12, 31] and Western Europe[1, 32–33]. For example, perhaps the observed protective effect of calcium on breast cancer risk is actually driven by certain calcium food sources. More than one study has reported that only calcium intake from dairy products was found to be inversely associated with breast cancer risk[12–13]. We did not observe an association between greater intake of dairy products and breast cancer risk (HR=0.98; 95% CI: 0.80, 1.19), comparing fourth to first quartiles. Contributing more than two-thirds of the daily total calcium intake requirement[34], dairy products are the major food source of calcium in Western populations, among which most previous epidemiologic studies were conducted. In contrast, dairy products constituted only 17.3% of the total calcium intake among Singaporean Chinese women. Consumption of dairy products in our cohort was low, and only 29% of the cohort reported drinking a glass of milk (250 mL) at least once a week.

The previous reports of an inverse association between dairy intake and breast cancer risk may have been confounded by vitamin D, a factor previously shown to be protective for breast cancer in other studies[35], but not in our data (HR=0.92; 95% CI = 0.75–1.12, comparing fourth versus first quartile of dietary vitamin D). The milk consumed in our population is not likely to contain vitamin D. While vitamin D-fortified products are sold in Singapore, the most popular brand of milk is not fortified. However, in the two previous studies that reported inverse associations with dairy intake, one was conducted among a US population[12], where a vitamin D-fortification policy exists, while the other was among a Norwegian population[13], where no policy exists.

Our results of a null association between calcium and breast cancer risk are in contrast to those reported from the three previous case-controls studies among Asian populations. Kawase et al.[20] reported a statistically significant trend (P=0.022) of increasing quartiles of calcium intake and decreasing breast cancer risk among Japanese women, where highest versus lowest intake was associated with a 17% decrease in risk. Among women in Shanghai, China, a statistically non-significant inverse association was reported comparing highest to lowest deciles of total calcium intake (OR= 0.74; 95% CI = 0.46–1.20)[6]. In the Guangdong, China study, Zhang et al.[19] observed a statistically significant inverse association between dietary calcium intake and breast cancer risk, with an adjusted OR (95% CI) of 0.35 (0.22–0.56) for the highest (≥531 mg/day) versus the lowest quartile (<274mg/day).

The equivocal reports on the associations between calcium intake and breast cancer risk among Asians could be due in part due to the different study designs used. All three other studies performed to date on Asian populations were retrospective case-control studies. When the analysis was stratified by study design in Chen et al.'s meta-analysis on calcium intake and breast cancer risk[5], the inverse association was most evident among case-control studies. The pooled estimates comparing the highest to the lowest quantiles of calcium intake in the nine case-control studies was 0.75 (95% CI = 0.63–0.88) under the random-effects model, as opposed to the weaker, statistically non-significant pooled estimate (HR=0.87; 95% CI = 0.75–1.00) based on six prospective cohort studies. Given that the prospective results are not influenced by differential recall or selection bias, the prospective results are likely to be more closely aligned with the true underlying association.

Together, calcium and vitamin D are hypothesized to have synergistic, metabolically interrelated effects that protect against the development of breast cancer[18]. Calcium has been reported to at least partially exert its anticarcinogenic effects through vitamin D. For example, calcium is one of the key mediators of apoptosis induced by vitamin D compounds in breast cancer cells[36]. In addition, an interaction between calcium and vitamin D has been observed in the prevention of cancers of the colon and rectum in some studies[37–40]. However, observational studies, including ours, do not support any effect modification by vitamin D on the possible inverse association between calcium and breast cancer risk[20, 41–43]. The lack of an interaction between calcium and vitamin D was also reported in a four-year, population-based intervention trial in which subjects were randomly assigned to receive 1400–1500 mg/day supplemental calcium only, supplemental calcium plus 1100 IU vitamin D3 per day, or placebo[44]. Thus, the totality of human data suggest that if there is a protective effect of calcium on breast cancer development, it is likely to be independent of vitamin D intake. Nonetheless, in spite of the plentiful sunshine in the equatorial region that includes Singapore, vitamin D deficiency is widespread in part due to sociocultural factors[45–46], and the inadequacy of this mineral in the general population could potentially obscure a relationship between calcium and breast cancer.

We hypothesized that calcium would be most strongly associated with lower breast cancer risk among those with a lower BMI, because there is evidence that smaller sized individuals have greater net absorption of calcium[47–49]. We have previously reported a 2-fold increase in prostate cancer risk comparing the highest versus the lowest quartiles of total calcium intake in the same cohort among men with less than median BMI[50]. However, in the current analyses, stratification by median BMI did not reveal a protective effect of calcium intake on breast cancer risk. It is possible that gender is also a relevant characteristic for differences in calcium absorption by body size, but this has not yet been evaluated.

To our knowledge this is the first prospective study assessing the association between total calcium intake and breast cancer risk in an Asian population. The strengths of this study include the high participant response rate, small (<1%) loss to follow-up, data obtained through a detailed face-to-face interview that included a validated 165-item food frequency questionnaire that was developed for this study population and captured both food and supplement sources of calcium intake. Limitations of our analyses included the relatively low intake of calcium in our study population. Another limitation was our inability to account for changes in dietary intake that may have occurred during follow up, because that dietary information was collected only at baseline. In stratified analyses by duration of follow-up, there remained no association between calcium intake and breast cancer risk, suggesting that greater misclassification of calcium intake with longer follow-up is not a likely explanation for our null finding.

In summary, we did not observe a reduction in breast cancer risk with increasing total calcium intake among Chinese women in Singapore. Our finding for a null association between calcium and breast cancer risk persisted in stratified analyses by menopausal status, BMI or vitamin D intake. It remains a possibility that calcium may protect against breast cancer, but that the level of intake needed is higher than that present in populations with low dairy intake and low supplement use.

Acknowledgments

This study was supported by the National Institutes of Health, USA (NCI RO1 CA55069, R35 CA53890, R01 CA80205, and R01 CA144034). JL was supported by the Agency for Science, Technology and Research (A*STAR). We thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study, and Kazuko Arakawa and Renwei Wang for the development and management of the cohort study database. We also thank the Ministry of Health in Singapore for assistance with the identification of breast cancer cases and mortality via database linkages.

References

1. Larsson SC, Bergkvist L, Wolk A. Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. Am J Clin Nutr. 2009; 89:277–282. [PubMed: 19056569]
2. Lipkin M, Newmark HL. Vitamin D, calcium and prevention of breast cancer: a review. J Am Coll Nutr. 1999; 18:392S–397S. [PubMed: 10511319]
3. Jacobson EA, James KA, Newmark HL, Carroll KK. Effects of dietary fat, calcium, and vitamin D on growth and mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene in female Sprague-Dawley rats. Cancer Res. 1989; 49:6300–6303. [PubMed: 2509066]
4. Kumar B, Kumar A, Ghosh S, Pandey BN, Mishra KP, Hazra B. Diospyrin derivative, an anticancer quinonoid, regulates apoptosis at endoplasmic reticulum as well as mitochondria by modulating cytosolic calcium in human breast carcinoma cells. Biochem Biophys Res Commun. 2011
5. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat. 2010; 121:469–477. [PubMed: 19851861]
6. Boyapati SM, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Dietary calcium intake and breast cancer risk among Chinese women in Shanghai. Nutr Cancer. 2003; 46:38–43. [PubMed: 12925302]
7. Almquist M, Manjer J, Bondeson L, Bondeson AG. Serum calcium and breast cancer risk: results from a prospective cohort study of 7,847 women. Cancer Causes Control. 2007; 18:595–602. [PubMed: 17410477]
8. Miller GD, Jarvis JK, McBean LD. The importance of meeting calcium needs with foods. J Am Coll Nutr. 2001; 20:168S–185S. [PubMed: 11349940]
9. Yu YH, Farmer A, Mager DR, Willows ND. Dairy foods are an important source of calcium and vitamin D among Canadian-born and Asian-born Chinese in Edmonton, Alberta. Nutr Res. 2012; 32:177–184. [PubMed: 22464804]
10. Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer JT, Moshfegh AJ, Sempos CT, Picciano MF. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr. 2010; 140:817–822. [PubMed: 20181782]
11. Chen SY, Lin JR, Chen TH, Guo SG, Kao MD, Pan WH. Dietary supplements usage among elderly Taiwanese during 2005–2008. Asia Pac J Clin Nutr. 2011; 20:327–336. [PubMed: 21669602]
12. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin d and risk of breast cancer. J Natl Cancer Inst. 2002; 94:1301–1311. [PubMed: 12208895]
13. Hjartaker A, Thoresen M, Engeset D, Lund E. Dairy consumption and calcium intake and risk of breast cancer in a prospective cohort: the Norwegian Women and Cancer study. Cancer Causes Control. 2010; 21:1875–1885. [PubMed: 20658314]
14. Porter PL. Global trends in breast cancer incidence and mortality. Salud Publica Mex. 2009; 51(Suppl 2):s141–s146. [PubMed: 19967268]

15. Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, Sandelin K, Derossis A, Cody H, Foulkes WD. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010; 34:2308–2324. [PubMed: 20607258]
16. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973–1997. Int J Epidemiol. 2005; 34:405–412. [PubMed: 15737977]
17. Shin HR, Joubert C, Boniol M, Hery C, Ahn SH, Won YJ, Nishino Y, Sobue T, Chen CJ, You SL, Mirasol-Lumague MR, Law SC, et al. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. Cancer Causes Control. 2010; 21:1777–1785. [PubMed: 20559704]
18. Peterlik M, Grant WB, Cross HS. Calcium, vitamin D and cancer. Anticancer Res. 2009; 29:3687–3698. [PubMed: 19667166]
19. Zhang CX, Ho SC, Fu JH, Cheng SZ, Chen YM, Lin FY. Dairy products, calcium intake, and breast cancer risk: a case-control study in China. Nutr Cancer. 2011; 63:12–20. [PubMed: 21128178]
20. Kawase T, Matsuo K, Suzuki T, Hirose K, Hosono S, Watanabe M, Inagaki M, Iwata H, Tanaka H, Tajima K. Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. Cancer Sci. 2010; 101:1234–1240. [PubMed: 20151981]
21. Yuan JM, Stram DO, Arakawa K, Lee HP, Yu MC. Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev. 2003; 12:890–898. [PubMed: 14504200]
22. Parkin, D.; Whelan, S.; Ferlay, J.; Teppo, L.; De, T. Cancer incidence in five continentsed. Lyon: International Agency for Research on Cancer; 2003.
23. Hankin JH, Stram DO, Arakawa K, Park S, Low SH, Lee HP, Yu MC. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer. 2001; 39:187–195. [PubMed: 11759279]
24. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B (Methodological). 1972; 34:187–220.
25. SAS/STAT User's Guide. 8 ed. Cary, NC: SAS Institute Inc; 1999.
26. Peloso GM, Lunetta KL. Choice of population structure informative principal components for adjustment in a case-control study. BMC Genet. 2011; 12:64. [PubMed: 21771328]
27. Robinson L, Jewell N. Some Surprising Results about Covariate Adjustment in Logistic Regression Models. International Statistical Review. 1991; 59:227–240.
28. Hong Z, Tian C, Zhang X. Dietary calcium intake, vitamin D levels, and breast cancer risk: a dose-response analysis of observational studies. Breast Cancer Res Treat. 2012; 136:309–312. [PubMed: 22872547]
29. Nordin BC. Calcium requirement is a sliding scale. Am J Clin Nutr. 2000; 71:1381–1383. [PubMed: 10837273]
30. Lin YC, Lyle RM, McCabe LD, McCabe GP, Weaver CM, Teegarden D. Dairy calcium is related to changes in body composition during a two-year exercise intervention in young women. J Am Coll Nutr. 2000; 19:754–760. [PubMed: 11194528]
31. Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM. Intakes of calcium and vitamin D and breast cancer risk in women. Arch Intern Med. 2007; 167:1050–1059. [PubMed: 17533208]
32. Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: results of the French SU.VI.MAX prospective study. Ann Nutr Metab. 2007; 51:139–145. [PubMed: 17536191]
33. Knekt P, Jarvinen R, Seppanen R, Pukkala E, Aromaa A. Intake of dairy products and the risk of breast cancer. Br J Cancer. 1996; 73:687–691. [PubMed: 8605108]
34. Fleming KH, Heimbach JT. Consumption of calcium in the U.S.: food sources and intake levels. J Nutr. 1994; 124:1426S–1430S. [PubMed: 8064396]
35. Chlebowski RT. Vitamin D and breast cancer: interpreting current evidence. Breast Cancer Res. 2011; 13:217. [PubMed: 21884640]

36. Mathiasen IS, Sergeev IN, Bastholm L, Elling F, Norman AW, Jaattela M. Calcium and calpain as key mediators of apoptosis-like death induced by vitamin D compounds in breast cancer cells. J Biol Chem. 2002; 277:30738–30745. [PubMed: 12072431]
37. Grau MV, Baron JA, Sandler RS, Haile RW, Beach ML, Church TR, Heber D. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J Natl Cancer Inst. 2003; 95:1765–1771. [PubMed: 14652238]
38. Peters U, McGlynn KA, Chatterjee N, Gunter E, Garcia-Closas M, Rothman N, Sinha R. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiol Biomarkers Prev. 2001; 10:1267–1274. [PubMed: 11751444]
39. Zheng W, Anderson KE, Kushi LH, Sellers TA, Greenstein J, Hong CP, Cerhan JR, Bostick RM, Folsom AR. A prospective cohort study of intake of calcium, vitamin D, other micronutrients in relation to incidence of rectal cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 1998; 7:221–225. [PubMed: 9521437]
40. Levine AJ, Harper JM, Ervin CM, Chen YH, Harmon E, Xue S, Lee ER, Frankel HD, Haile RW. Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. Nutr Cancer. 2001; 39:35–41. [PubMed: 11588900]
41. Anderson LN, Cotterchio M, Vieth R, Knight JA. Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. Am J Clin Nutr. 2010; 91:1699–1707. [PubMed: 20392891]
42. Abbas S, Linseisen J, Chang-Claude J. Dietary vitamin D and calcium intake and premenopausal breast cancer risk in a German case-control study. Nutr Cancer. 2007; 59:54–61. [PubMed: 17927502]
43. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA, Shikany JM, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst. 2008; 100:1581–1591. [PubMed: 19001601]
44. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007; 85:1586–1591. [PubMed: 17556697]
45. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, Ragi-Eis S, Chandler J. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med. 2006; 260:245–254. [PubMed: 16918822]
46. Lips P. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Mol Biol. 2007; 103:620–625. [PubMed: 17287117]
47. Barger-Lux MJ, Heaney RP. Calcium absorptive efficiency is positively related to body size. J Clin Endocrinol Metab. 2005; 90:5118–5120. [PubMed: 15998768]
48. Davies KM, Rafferty K, Heaney RP. Determinants of endogenous calcium entry into the gut. Am J Clin Nutr. 2004; 80:919–923. [PubMed: 15447899]
49. Heaney RP, Recker RR. Determinants of endogenous fecal calcium in healthy women. J Bone Miner Res. 1994; 9:1621–1627. [PubMed: 7817809]
50. Butler LM, Wong AS, Koh WP, Wang R, Yuan JM, Yu MC. Calcium intake increases risk of prostate cancer among Singapore Chinese. Cancer Res. 2010; 70:4941–4948. [PubMed: 20516117]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Novelty: There is evidence linking calcium intake to a reduced risk of breast cancer. However, prospective studies have mainly been limited to Western populations. We examined the association between calcium intake and breast cancer risk in the Singapore Chinese Health Study, a large population-based prospective cohort. To our knowledge this is the first prospective study assessing the association between calcium intake and breast cancer risk in an Asian population.

Impact: Novel prospective analyses among an Asian population do not support a protective effect of calcium intake on breast cancer risk.

Table 1

Distribution of study population characteristics by quartiles (Q) of total calcium intake

	Calcium intake (mg/day) by quartiles *			
	Q1	Q2	Q3	Q4
Person-years	120,718	122,279	121,273	120,034
Median age (IQR)†, year	58 (14)	55 (13)	54 (12)	54 (12)
% with none or primary education only	88.34	81.43	77.23	70.12
Median BMI (IQR), kg/m2	23.3 (3.1)	23.3 (3.3)	23.2 (3.5)	23.1 (3.6)
% premenopausal	22.3	29.0	31.2	30.2
% nulliparous	6.3	6.2	7.2	8.4
% weekly any supplement use‡	1.7	3.4	5.8	18.8
% weekly calcium supplement use	0.2	1.0	2.2	14.1
Median (IQR)† daily energy intake (kcal)	984.6 (323.2)	1270.2 (334.5)	1486.6 (466.4)	1706.2 (652.4)
Median (IQR)† daily intake§				
Calcium from food only (mg/1,000 kcal)	183.9 (57.4)	232.0 (61.1)	281.7 (93.3)	389.7 (145.2)
Calcium from food and supplements (mg/1,000 kcal)	184.0 (57.4)	232.8 (61.8)	283.5 (94.5)	411.7 (158.5)
Total vegetables (g)	64.3 (38.5)	94.8 (49.2)	116.1 (68.7)	133.7 (94.3)
Dairy products (g)	2.4 (11.5)	15.1 (25.4)	37.5 (81.4)	252.8 (185.1)
Total grain products (g)	397.4 (188.9)	459.1 (200.9)	478.6 (214.4)	499.7 (236.3)
Soy foods (g)	46.5 (43.5)	81.5 (62.9)	113.6 (99.5)	134.1 (137.7)

*Calcium intake from combined food and supplement sources.

†Interquartile range, IQR

‡Supplement use was defined by Yes/No responses to the question, “Did you take any vitamins or minerals at least once each week during the last year?”

§Intake was based on food sources only, unless otherwise noted.

Table 2

Daily intake, calcium concentration, and percent contribution to total calcium for selected food groups

Food item/group	Median daily intake (g)*	Median mg calcium per g food group*	Percent contribution of each food group to total calcium intake†
Total vegetables	97.2	3.5	19.3
Cruciferous vegetables	36.9	9.3	9.3
Dairy products	20.4	15.0	17.3
All grain products	459.4	0.8	14.7
Bread	25.5	14.3	5.3
Noodles	38.5	9.3	4.7
Rice	335.4	1.1	3.0
All soyfoods	85.5	4.0	11.8
Total fruit	158.7	2.3	7.3
All fish and shellfish	47.8	7.5	6.2

*These values were derived from intake among all female cohort subjects.

†The percent contribution to total calcium intake was calculated using 24-hour dietary recalls among a randomly selected subset of cohort subjects (see Methods).

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) for quartiles of calcium intake (mg/1000kcal/day) and breast cancer risk

	Total cases, n	Person-years	Adjusted HR†	95% CI
Total calcium (from food and supplements)				
<204.5	186	122,220	1.00	Reference
204.5–257.0	234	122,721	1.21	1.00–1.47
257.1–345.6	196	120,980	1.00	0.82–1.22
>345.6	207	118,382	1.04	0.85–1.27
P for trend				0.73
Calcium from food only				
<203.2	185	121,996	1.00	Reference
203.2–254.4	237	122,511	1.24	1.02–1.50
254.5–334.3	202	120,985	1.03	0.84–1.26
>334.3	199	118,811	1.01	0.82–1.24
P for trend				0.57

†Adjusted models included variables for: age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/or higher), family history of breast cancer (yes/no first degree relative), age when period became regular (<13, 13–14, 15–16, ≥17 years, never regular), number of live births (0, 1–2, 3–4, ≥5), and body mass index (kg/m^2).

Table 4

Hazard ratios (HR) and 95% confidence intervals (CI) for calcium intake (mg/1000kcal/day) and breast cancer risk stratified by selected covariates

	Total calcium				P trend
	Q1	**Q2**	**Q3**	**Q4**	
Premenopausal					
Cases, n	52	74	75	54	
Person-years	32,040	37,561	40,195	32,432	
HR (95% CI)*	1.00 (ref)	1.15 (0.81–1.64)	1.07 (0.75–1.53)	0.87 (0.59–1.28)	0.40
Postmenopausal					
Cases, n	134	160	121	153	
Person-years	90,163	85,128	80,753	85,932	
HR (95% CI)*	1.00 (ref)	1.23 (0.98–1.55)	0.96 (0.75–1.23)	1.09 (0.86–1.38)	0.99
BMI (<23.2 kg/m^2)					
Cases, n	84	104	89	104	
Person-years	54,289	57,001	57,116	62,919	
HR (95% CI)*	1.00 (ref)	1.12 (0.84–1.50)	0.92 (0.68–1.24)	0.93 (0.69–1.24)	0.33
BMI (≥23.2 kg/m^2)					
Cases, n	102	130	107	103	
Person-years	67,931	65,720	63,864	55,463	
HR (95% CI)*	1.00 (ref)	1.29 (0.99–1.67)	1.07 (0.81–1.40)	1.14 (0.86–1.50)	0.69
Vitamin D (<83.2 IU/day)					
Cases, n	175	202	151	43	
Person-years	112,816	106,252	90,024	25,692	
HR (95% CI)†	1.00 (ref)	1.17 (0.95–1.43)	0.99 (0.79–1.23)	0.91 (0.65–1.28)	0.58
Vitamin D (≥83.2 IU/day)					
Cases, n	11	32	45	164	
Person-years	9,404	16,469	30,956	92,690	
HR (95% CI)†	1.00 (ref)	1.64 (0.83–3.26)	1.22 (0.63–2.37)	1.45 (0.78–2.67)	0.51

*Adjusted models included variables for: age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/or higher), family history of breast cancer (yes/no first degree relative), age when period became regular (<13,13–14,15–16,≥17 years, never regular) and number of live births (0,1–2,3–4, ≥5).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

†Models were additionally adjusted for body mass index (kg/m^2).

‡All P for interaction values were >0.05.