Relationship between selenium and breast cancer: a case-control study in the Klang Valley

Suzana S, Cham B G, Ahmad Rohi G, Mohd Rizal R, Fairulnizal M N, Normah H, Fatimah A

ABSTRACT

Introduction: The purpose of this study was to assess the relationship between selenium status and intake among breast cancer patients from the Klang Valley.

Methods: 64 cases and 127 controls were matched for age (range 30–65 years) and ethnicity, with an 80 percent study power. Subjects were interviewed to obtain information on their habitual dietary intakes, demographic data and medical history. Selenium status was determined from toenail and hair analysis using an inductively coupled plasma mass spectrometer.

Results: The nutrient analysis showed that total energy and protein intake was significantly higher among controls (1,403 +/− 367 kcal/day, 75.6 +/− 33.2 g/day) as compared to cases (1,273 +/− 295 kcal/day, 60.9 +/− 19.1 g/day) (p-value is less than 0.05). The selenium intake among cases (78.47 +/− 25.34 µg/day) was significantly lower than the controls (89.34 +/− 36.85 µg/day) (p-value is less than 0.05). Breast cancer risk decreased with the increasing quartiles of selenium intake, with odds ratios (95 percent confidence interval) of 2.95 (1.22–7.12), 2.17 (1.13–4.19) and 1.71 (0.84–3.52), respectively. However, the association diminished after adjustment for confounding factors. Selenium in hair did not differ among cases and controls, but selenium status in the nails of controls was significantly higher as compared to cases (p-value is less than 0.05). Breast cancer risk decreased with the increasing quartiles of toenail selenium status as measured in the toenail and hair.

Conclusion: Selenium intake and status was associated with breast cancer risk. Thus, it is essential for Malaysian women to achieve a good selenium status by consuming good food sources of selenium as a chemopreventive agent.

Keywords: selenium, breast cancer, cancer risk factors, case-control studies, chemopreventive agent, selenium intake

Singapore Med J 2009;50(3):265-269

INTRODUCTION

Breast cancer is the third most common cancer worldwide and the most common cancer among women.[1] In Malaysia, there were 3,738 female breast cancer cases reported in the year 2003, making it the most commonly-diagnosed cancer among women from all ethnic and age groups from the age of 15 years. The Chinese had the highest incidence, with an age-standardised incidence rate (ASR) of 59.7 per 100,000 population, followed by Indian women with an ASR of 55.8 per 100,000 population and Malay women with an ASR of 33.9 per 100,000 population.[2] Antioxidants, including selenium, protect cells from DNA oxidative damage by scavenging free radicals in epithelial cells of the breast that can cause cancer.[3,4] The relationship between selenium status and risk of cancer such as of the prostate, intestines, lung and liver has been documented in Western countries. However, its association with breast cancer remains a controversial issue. An earlier prospective study reported no association between selenium levels in toenails with breast cancer;[5] however, a contradictory finding was reported in another study which found that low selenium status increased breast cancer risk by 1.24 times.[6] Case-control studies have reported that selenium status as assessed via toenails is not associated with breast cancer,[7,8] but significant findings were found in plasma levels and dietary selenium intake.[4] Thus, investigations on the role of selenium in breast cancer are important in constructing chemopreventive strategies. Thus the aim of this study is to identify the relationship between selenium status and breast cancer among women in the Klang Valley using a case-control approach. This study obtained ethical approval from the Ministry of Health of Malaysia and informed consent was obtained from subjects.

METHODS

The estimated sample size of 180 was calculated at 95%

Department of Nutrition and Dietetics, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur 50300, Malaysia

Suzana S, BSc, MMedSci, PhD
Lecturer

Cham BG, BSc
Research Student

Normah H, BSc, MSc
Postgraduate Student

Department of Biomedical Sciences

Ahmad Rohi G, BSc, MSc, PhD
Lecturer

Mohd Rizal R, BSc
Research Student

Toxicology and Pharmacology Unit, Herbal Medicine Research Centre, Institute for Medical Research, Jalan Pahang, Kuala Lumpur 50588, Malaysia

Fairulnizal MN, BSc, MSc, PhD
Research Officer

Department of Nutrition and Dietetics, International Medical University, Plaza Komanwel, Bukit Jalil, Kuala Lumpur 57000, Malaysia

Fatimah A, BSc, MSc, PhD
Lecturer

Correspondence to:
Dr Suzana Shahar
Tel: (60) 3 4040 5335
Fax: (60) 3 2694 7621
Email: suzanas@medic.ukm.my

Table I. Demographic profiles of cases and controls.

Demographic profile	No. (%) of cases (n = 64)	No. (%) of controls (n = 127)
Age group (years)		
30–35	5 (7.8)	8 (6.3)
36–40	3 (4.7)	18 (14.2)
41–45	15 (23.4)	26 (20.5)
46–50	24 (37.5)	34 (26.8)
> 50	17 (26.6)	41 (32.3)
Mean ± SD age (years)	46.7 ± 6.4	47.2 ± 7.4
Ethnicity		
Malay	39 (60.9)	63 (49.6)
Chinese	15 (23.4)	44 (34.6)
India	10 (15.6)	20 (15.7)

SD: standard deviation

Table II. Macronutrient and selenium intake of cases and controls.

	Mean ± SD of cases (n = 64)	Mean ± SD of controls (n = 127)
Energy (kcal)	1,273 ± 295	1,403 ± 367*
Protein (g)	60.86 ± 19.04	75.64 ± 33.17*
Fat (g)	38.93 ± 14.39	43.39 ±16.94
Selenium (μg)	78.46 ± 25.34	89.34 ± 36.85*

*$p < 0.05$, significant difference at two-tail independent *t*-test,
SD: standard deviation

confidence interval (CI) (two-tail) and 80% study power with an odds ratio (OR) of 2.5 using the recommended formula.[9] In order to meet the ratio of 1:2, approximately 60 cases and 120 controls were needed. Finally, the study managed to successfully recruit 64 cases and 127 controls. However, only 12 cases and 36 controls were willing to give their hair and toenail samples. Cases were selected among breast cancer patients at Kuala Lumpur Hospital, Hospital Universiti Kebangsaan Malaysia and Hospital Selayang. The inclusion criteria for cases were newly-diagnosed breast cancer patients (limited to stages I, II and III) and not being on any therapy or medication for cancer, except for painkillers. Controls were healthy women without a history of any cancer, recruited from government agencies and household residences in the Klang Valley. Cases and controls were matched by ethnicity and age (± five years). Pregnant and lactating women were excluded.

Subjects were asked for their demographical and socioeconomic information, past medical history, family history and reproductive data, including menstrual cycle, menopausal status, pregnancy and lactating history, consumption of oral contraceptive pill and hormone replacement therapy. Body weight (kg) was measured using the digital scale SECA (SECA, Germany) while height (m) was measured using SECA bodymeter (SECA, Germany). A measurement tape was used to measure the waist and hip circumference (cm). Body mass index (BMI) and waist: hip ratio (W:H) were derived from the measurements. All measurements were carried out according to the standard procedure.[10] Food intake including selenium was assessed through a face-to-face interview using a validated Diet History Questionnaire (DHQ), and supplemented by a semiquantitative Food Frequency Questionnaire (FFQ).[11] Cases were requested to report their eating habits before diagnosis. The interview included details for every meal or snack through the use of open-structured questions. A set of household measures was shown to the subjects to help in portion size estimation. In completing the FFQ, subjects were required to report the frequency of taking each food in the form of frequency per week.

Toenail and fingernail samples were collected from the subjects. Hair was cut randomly at different locations on the head. All samples were stored in sealed plastic bags at room temperature. Nail and hair selenium was measured using an Inductively Coupled Plasma Mass Spectrometer (ICP-MS) (model ELAN 6000, Perkin Elmer, Norwalk, USA), at the Institute for Medical Research, Kuala Lumpur. The preparation and analysis of samples were carried out by the Inductively Coupled Plasma-Atomic Emission Spectrometer, ICP-MS method.[12] Hair and toenail samples were prepared by appropriate nitric (Aristar, BDH Laboratory, Poole, England) – perchloric (Merck, Darmstadt, Germany) acid digestion procedure.[13] The basis of the method was the measurement of atomic emission by an optical spectroscopic technique. Samples were nebulised and the aerosol that was produced was transported to the plasma torch where excitation occurred.

Characteristic atomic-line emission spectra were produced by a radiofrequency inductively coupled plasma. The spectra were dispersed by a grating spectrometer and the intensities of the lines were monitored by photomultiplier tubes. The photocurrents from the photomultiplier tubes were processed and controlled by a computer system. A selenium standard (Merck, Darmstadt, Germany) was also run and a background correction technique was also required to compensate for variable background contribution to the determination of the trace elements. An American food database, i.e. Nutritionist Pro, was used to perform the diet analysis,[14] because Nutrient Composition of Malaysian Food does not contain selenium. The nutrient intake that was analysed included energy, fat, protein and selenium. The Statistical Package for Social Sciences version 12.0 (SPSS Inc, Chicago, IL, USA) was used to analyse the data. A significance level of $p < 0.05$ was adopted for hypothetical testing.

Table III. Quartile and odds ratios for selenium intake and selenium levels in nail and hair with the risk of breast cancer.

	Quartile		
	25th	50th	75th
Selenium intake (µg/day)	57.2	70.8	92.5
OR (95% CI)	2.95 (1.22–7.12)	2.17 (1.13–4.19)*	1.71 (0.84–3.52)*
Toenail selenium (µg/day)	0.04	0.11	0.13
OR (95% CI)	16.0 (3.27–78.28)*	3.75 (0.869–16.19)	1.92 (0.357–10.36)
Hair selenium (µg/day)	0.03	0.11	0.19
OR (95% CI)	2.96 (0.72–12.17)	1 (0.27–3.69)	0.2 (0.05–0.837)*

OR: odds ratio; CI: confidence interval
*p < 0.05, significant difference using chi-square test.

Table IV. Selenium levels in the nail and hair for the different ethnic groups and between the cases and controls.

Variable	No.	Selenium in nail (µg/g)	Selenium in hair (µg/g)
Race			
Malay	24	0.109 ± 0.064	0.119 ± 0.103
Chinese	11	0.132 ± 0.136	0.128 ± 0.078
Indian	13	0.063 ± 0.068	0.115 ± 0.134
Group			
Case	12	0.056 ± 0.088	0.136 ± 0.152
Control	36	0.114 ± 0.085*	0.114 ± 0.084

Data is expressed as mean ± standard deviation
For race, data is not significant, using the Kruskal-Wallis test.
*p < 0.05, significant difference at two-tail independent sample *t*-test for case and control groups

Table V. Correlation between selenium levels in nail and hair with dietary intake and age.

Correlation	Nail (r)	Hair (r)
Energy intake	0.21	0.034
Protein intake	0.435*	0.008
Fat intake	0.269	–0.103
Selenium intake	0.487*	0.017
Age	–0.057	0.026

*p < 0.05, Pearson's correlation test

RESULTS

A total of 191 women, 64 cases and 127 controls participated in the study. Toenail and hair samples were obtained from a subsample of 12 cases and 36 controls.

Cases comprised 39 (60.9%) Malays, 15 (23.4%) Chinese and 10 (15.6%) Indians, while controls comprised 63 (49.6%) Malays, 44 (34.6%) Chinese and 20 (15.7%) Indians. The mean age for cases (46.7 ± 6.4 years) and controls (47.2 ± 7.4 years) did not differ significantly (Table I). Table II shows the intakes of selenium, energy and protein, which were significantly higher among controls than cases ($p < 0.05$). The mean energy intake in both cases and controls did not meet the Malaysian Recommended Nutrient Intakes (RNI), i.e. energy: 2,180 kcal/day for women aged 35–59 years and 1,780 kcal/day for those aged ≥ 59 years. Only 3.9% of controls achieved these recommendations. The estimated selenium intake of cases and controls were 313.9 ± 101.4% and 357.3 ± 147.4% of the RNI at 25 µg/day, respectively.[15]

The ORs for breast cancer risk decrease with the increasing quartile of selenium intake, with significant association was found at the 50th (2.17 [1.13–4.19]) and 75th quartile (1.71[0.84–3.52]) (Table III). After adjustment for confounding factors including education, working status, family history, lactation and waist circumference, the risk of breast cancer was reduced and was not significant. For example, the adjusted OR (CI) of breast cancer risk at the 50th percentile was reduced to 1.56 (0.72–3.39). Selenium intake significantly differed among different ethnic groups, where Chinese subjects (94.3 ± 39.7 µg/day) had the highest intake, followed by Malays (83.4 ± 28.9 µg/day) and Indians (76.5 ± 33.9µg/day) ($p < 0.05$). However, the selenium status did not differ significantly among ethnic groups. Nevertheless, the level of selenium in the nail and hair remained high in Chinese as compared to the Malays and Indians. The mean selenium level in nails was higher in controls ($p < 0.05$) (Table IV). The OR for breast cancer risks decreased by increasing quartile of selenium status, as measured in the toenail and hair samples (Table III). Significant association was noted for toenail selenium at 25th percentile and hair selenium at 75th percentile. However, the adjusted OR for selenium status was not calculated due to the small sample size. Selenium in the nail was positively correlated to protein (r 0.435, $p < 0.005$) and selenium intake (r 0.487, $p < 0.001$) (Table V).

DISCUSSION

The energy intake of both cases and controls was below the Malaysian RNI, with controls reporting a higher intake. This could be due to the high percentages of under-reporters, especially among cases, i.e. 82.8% in cases and 67.7% in controls. They were not able to recall the food intake before being diagnosed with cancer or the disease process might have influenced the memory. The energy intake pattern found in this study goes against the findings of some local studies, where energy intake was found to be higher among cases as compared to controls.[16,17] One cohort study (Nurses' Health Study), which began in the United States in 1976, did not show any correlation between energy intake and breast cancer in postmenopausal and premenopausal women.[18] Another case-control study among breast cancer women in Montreal also showed similar findings.[19] The control subjects have a higher protein intake perhaps due to their higher energy consumption.

The selenium intake of cases (78.46 ± 25.34 µg/day) was lower than that of controls (89.34 ± 36.85 µg/day) ($p < 0.05$). In one local study that involved cancer patients at Hospital Kuala Lumpur, the mean selenium intake for cases (90.93 ± 71.25 µg/day) and controls (74.84 ± 44.94 µg/day) did not show any significant difference.[15] The values of selenium intake in the present study and another local study[15] were comparable to those reported among Americans, i.e. 80–120 µg/day.[20] This is because the US food database was used in these studies. Selenium intake for subjects in this study was much higher than those reported in New Zealand (28–30 µg/day),[21] East Croatia, (24.8 µg/day)[22] and Andean Highland (36.6 ± 13 µg/day),[23] but slightly lower than in South California (90–168 µg/day).[24] Women from seleniferous areas, such as South Dakota and Wyoming, have a selenium intake of 128 ± 58 µg/day.[25] Subjects in this study appeared to have moderate selenium intake as compared to other places. However, it should be borne in mind that the US Food Composition Table was used to analyse the selenium intake, and there might be some under- or over-reporting.

The risk of breast cancer decreased with the increasing quartile of selenium intake, with significant association noted at the 50th and 75th percentiles; however, the associations were not significant after adjustment for confounding factors. The opposite trend was found in one study, where the OR of breast cancer increased at the lowest and highest quartiles.[26] Women in this study consumed selenium at higher levels than in the US RDA[16] and RNI Malaysia,[11] but lower than the recommended upper tolerable level, 400 µg/day.[16] Only one subject (from the case group) had a low intake of below the Malaysian RNI of 25 µg/day. In this study, the Chinese had the highest selenium intake and status, followed by the Malays and Indians. This is because the Chinese consume pork, and among selenium-rich meat, pork has a higher level of selenium,[23] followed by meat and fish.[27] Pork consumption is prohibited by Malays or Muslims, whereas beef is not eaten among Indians. According to the USDA,[28-30] the selenium level in pork is the highest, followed by beef, then lamb. It is important for non-pork eaters to increase their selenium intake by consuming good sources of selenium, such as wholegrain products, legumes, milk, seafood, fish and meat.

Selenium levels in the nail and hair of subjects in this study were quite low compared to previous studies.[31,32] In one intervention study among 12 healthy men, a low selenium diet had lowered their hair selenium level from 0.56 ± 0.14 µg/g to 0.32 ± 0.02 µg/g, while a high selenium diet successfully increased hair selenium levels from 0.79 ± 0.46 µg/g to 0.90 ± 0.12 µg/g and remained constant at a certain level.[33] Hair selenium level in this study was almost similar to the level caused by a low selenium diet, although the selenium intake levels of all the subjects were quite high. Inappropriate amounts of hair and nail samples or contamination might have caused the undetected concentration. In addition, the selenium intake estimated from the US Food Composition Table might be overestimated, as the level in American food might be higher than in Malaysian food. When the selenium intake is high until it is metabolically saturated, excessive selenium will accumulate in the nail.[33,34] In this study, subjects had a selenium intake higher than the Malaysian RNI[11] and USRDA,[16] but nail selenium levels were lower than in other studies.

There are a few possibilities for what led to these findings. it might either be due to the high metabolic requirement of subjects or the fact that the RNI Malaysia was too low for this group. As a result, although their selenium intake was 300% higher than the RNI, there was no excessive selenium accumulation in their nails. Subjects in this study ate more cereal compared to seafood, and the bioavailability of selenium in plants is lower.[23,35] This might be the cause of the low levels of selenium in the nail and hair. In addition, the chemical form of selenium in the diet plays an important role in affecting one's selenium level because the bioavailability of selenium depends on the chemical form.[36] However, no information about the chemical form of selenium in local food was available and therefore this factor could not be investigated in this study.

Selenium status was found to increase with selenium and protein intake, indicating the importance of dietary factors in obtaining a good selenium status. Another study also found a moderate correlation (r 0.53, $p < 0.001$) between the selenium level in nails and selenium intake.[21] In conclusion, selenium intake and status are related to breast cancer risk. Therefore, selenium intake through the diet should be emphasised as a chemopreventive agent in reducing the risk of breast cancer. There is an urgent need to analyse the selenium content in Malaysian foods.

ACKNOWLEDGEMENTS

We are grateful to all the subjects, fieldworkers, Institute for Medical Research, hospitals and others involved during the data collection. This study has been funded by the National Cancer Board (MAKNA).

REFERENCES

1. Management of breast cancer. In: Clinical Practice Guidelines, Ministry of Health Malaysia. Kuala Lumpur: Academy of Medicine Malaysia; 2002. Report no: MOH/P/PAK/57.02 (GU).
2. National Cancer Registry Malaysia. The Second Report of the National Cancer Registry-Cancer Incidence in Malaysia 2003. Ministry of Health Malaysia, 2004.
3. Borek C. Dietary antioxidants and human cancer. Integr Cancer Ther 2004; 3:333-41.
4. Key TJ, Allen NE, Spencer EA, Travis RC. Nutrition and breast cancer. Breast 2003; 12:412-6.
5. Hunter DJ, Morris JS, Stampfer MJ, et al. A prospective study of selenium status and breast cancer risk. JAMA 1990; 264:1128-31. Comment in: JAMA 1991; 265:28.
6. Garland M, Morris JS, Stampfer MJ, et al. Prospective study of toenail selenium levels and cancer among women. J Natl Cancer Inst 1995; 87:497-505.
7. van't Veer P, van der Wielen RP, Kok FJ, Hermus RJ, Sturmans F. Selenium in diet, blood and toenails in relation to breast cancer: a case-control study. Am J Epidemiol 1990; 131:987-94.
8. Männistö S, Alfthan G, Virtanen M, et al. Toenail selenium and breast cancer: a case-control study in Finland. Eur J Clin Nutr 2000; 54:98-103.
9. Lwanga SK, Lemeshow S. Sample size determination in health studies: a practical manual. Geneva:World Health Organization, 1991.
10. Fidanza F. Nutritional status assessment: manual for population studies. London: Chapman & Hall, 1991.
11. Suzana S, Azhar Y, Fatimah A. Association between dietary fibre and cancer: a case-control study in Malaysia. Malay J Nutr 2004; 10:173-82.
12. Maxfield R, Minak B. EPA Method Study 27, Method 200. 7 Trace Metals by ICP. National Technical Information Service, 1983. Order no: PB 85-248-656.
13. Ming Y, Bing L. Determination of rare earth elements in human hair and wheat flour reference material by inductively coupled plasma mass spectrometry with dry ashing and microwave digestion. Spectrochim Acta Part B 1998; 53:1447-54.
14. USDA. United States Department of Agriculture. Agricultural Research Service. Available at: www.ars.usda.gov. Accessed December 8, 2007.
15. Recommended Nutrient Intakes for Malaysia, National Coordinating Committee on Food and Nutrition, Ministry of Health Malaysia, Putrajaya: NCCFN; 2005. ISBN 983-42438-0-4.
16. Tan EP. The effect of carcinogen on cancer occurrence. BSc Thesis. Kuala Lumpur: Universiti Kebangsaan Malaysia; 2002. Unpublished.
17. Yee LH. A case control study on the association between dietary antioxidant intake and cancer. BSc Thesis. Kuala Lumpur: Universiti Kebangsaan Malaysia; 2002. Unpublished.
18. Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999; 281:914-20.
19. Ghadirian P, Lacroix A, Perret C, et al. Breast cancer risk and nutrient intake among French Canadians in Montreal: a case-control study. Breast 1998; 7:108-13.
20. Institute of Medicine. DRI dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington DC: National Academies Press, 2000.
21. Thomson CD, Robinson MF. Selenium in human health and disease with emphasis on those aspects peculiar to New Zealand. Am J Clin Nutr 1980; 33:303-23.
22. Klapec T, Mandić ML, Grgić J, et al. Daily dietary intake of selenium in eastern Croatia. Sci Total Environ 1998; 217:127-36.
23. Imai H, Kashiwazaki H, Rivera J, et al. Selenium intake status in an Andean highland population. Nutr Res 1997; 17:599-602.
24. Schrauzer GN, White DA. Selenium in human nutrition: dietary intakes and effects of supplementation. Bioinorg Chem 1978; 8:303-18.
25. Swanson CA, Longnecker MP, Veillon C, et al. Selenium intake, age, gender, and smoking in relation to indices of selenium status of adults residing in a seleniferous area. Am J Clin Nutr 1990; 52:858-62.
26. van't Veer P, van der Wielen RP, Kok FJ, Hermus RJ, Sturmans F. Selenium in diet, blood, and toenails in relation to breast cancer: a case-control study. Am J Epidemiol 1990; 131:987-94.
27. Murphy J, Cashman KD. Selenium content of a range of Irish foods. Food Chem 2001; 74:493-8.
28. Human Nutrition Information Service. Composition of foods: lamb, veal, and game products. Washington DC: USDA, 1989.
29. Human Nutrition Information Service. Composition of foods: beef products. Washington DC: USDA, 1990.
30. Human Nutrition Information Service. Composition of foods: pork products. Washington DC: USDA, 1992.
31. Hunter DJ, Morris JS, Chute CG, et al. Predictors of selenium concentration in human toenails. Am J Epidemiol 1990; 132:114-22.
32. van den Brandt PA, Goldbohm RA, van't Veer P, et al. Toenail selenium levels and the risk of breast cancer. Am J Epidemiol 1994; 140:20-6.

34. Alfthan G, Aro A, Arvilommi H, Huttunen JK. Selenium metabolism and platelet glutathione peroxidase activity in healthy Finnish men: effects of selenium yeast, selenite, and selenate. Am J Clin Nutr 1991; 53:120-5.
35. Levander OA, Alfthan G., Arvilommi H, et al. Bioavailability of selenium to Finnish men as assessed by platelet glutathione peroxidase activity and other blood parameters. Am J Clin Nutr 1983; 37:887-97.
36. Young VR, Nahapetian A, Janghorbani M. Selenium bioavailability with reference to human nutrition. Am J Clin Nutr 1982; 35:1076-88.