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Original Article

Serum Selenium Level and Other Risk Factors for Breast Cancer among Patients in a Malaysian Hospital

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Abstract

Objective: The aim of this study is to investigate the association between breast cancer and serum selenium level as well as other risk factors for breast cancer.

Methods: A matched case-control study was conducted in a hospital in Malaysia from July 2000 to January 2001 and from May 2001 to June 2001. Sixty-two newly diagnosed breast cancer patients were selected as the cases. Each control, selected from the same hospital population was matched to each case according to age, ethnic group, and menopausal status.

Results: The mean selenium concentration among the cases was significantly lower than that among the control. There was a significant association ($p<0.05$) between breast cancer and low selenium serum level, nulliparity (OR=5.5, 95% CI=1.22 to 24.81), exposure to cigarette smoke (OR=2.2, 95% CI=1.04 to 4.65) and use of oral contraceptives (OR=3.0, 95% CI=1.09 to 8.25) as determined by the McNemar test. Multivariate analysis showed that nulliparity (OR=10.08, 95% CI=1.48 to 68.52) and use of oral contraceptives (OR=3.66, 95% CI=1.36 to 9.87) were associated with increased breast cancer risk. An increased selenium concentration contributes to a reduced risk of breast cancer (OR=0.89, 95% CI=0.84 to 0.94).

Conclusion: The results suggest that use of oral contraceptive pills, being nulliparous, and a low serum selenium level are associated with breast cancer.

Key words: breast cancer, selenium, glutathione peroxides enzyme, oral contraceptives, nulliparity

Introduction

Despite the development of modern technology for diagnosis and treatment, cancer remains a major health burden. Breast cancer is the commonest cancer among women worldwide (1) and account for 18% of all female cancers (2). There are one million new cases of cancer diagnosed globally each year (2). Of all cases of cancer in Malaysia since 1991, breast cancer is the second most frequent cause of admission to hospitals after cervical cancer (3).

There are various studies of the relationship between selenium and cancer. Selenium is an essential mineral found in trace amounts in the body and works as an antioxidant. Selenium is important for the activity of glutathione peroxides, which may protect DNA and other cellular molecules against oxidative damage (4). At relatively high levels, selenium protects against the action of certain carcinogens in various animal models (5).

Serum selenium level in humans has been suggested to be inversely associated with the risk of certain types of cancer (6). In 1971, Shamberger and Willis reported that the rates of mortality caused by lymphomas and cancers of the gastrointestinal tract, peritoneum, lung, and breast are lower for men and women who lived in areas of the United States that have high selenium levels than those residing in areas with low selenium levels (7). Similar results were also reported by Xiu et al., which showed lower levels of serum selenium in breast cancer patients than in controls (8). Most studies based on prediagnostic serum selenium level support the hypothesis that there is an association between low levels of selenium and the risk of various cancers (6).

The level of selenium found in different foods depends on the level of selenium in the soil. Selenium deficiencies are common in certain parts of the world, for example, China (9). This mineral is destroyed when foods are refined or processed. Therefore, eating a variety of whole, unprocessed foods is the

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best way to obtain this nutrient. A low dietary intake of selenium has been proposed as a risk factor for breast cancer (10).

Other common risk factors for breast cancer include age, family history, reproductive and menstrual history, hormone therapy, lifestyle factors, diet, radiation history, and history of breast disease (11). The risk of breast cancer increases with age and most breast cancers occur after the age of 50 (2). Studies have shown that women with a family history of breast cancer in a first-degree relative have a higher risk of developing breast cancer than women without a family history of the disease (12, 13). Breast cancer risk increases with early menarche and late menopause, and is reduced by early first full-term pregnancy. In addition to this, the risk of developing breast cancer among women who attain menopause naturally after the age of 55 is twofold than that among women who experience menopause before the age of 45 (2).

It is also frequently reported that the use of contraception is associated with breast cancer. A meta-analysis of data from 54 studies showed a relative risk (RR) of 1.24 (95% CI=1.15–1.33) for current users; whereas there is no significantly increased risk of breast cancer 10 or more years following the cessation of intake of an oral contraceptive agent (RR=1.01; 95% CI=0.96–1.05) (14). The association between hormone replacement therapy (HRT) and breast cancer risk among women with a family history of breast cancer has not been consistent. Some studies suggested that risk is particularly high among women with a family history of breast cancer, whereas others have not found evidence for an increased risk in families with a history of breast cancer (15).

There are some lifestyle factors associated with breast cancer risk. These include obesity and a high fat intake. Being overweight is a risk factor for breast cancer, and overweight women are generally at an increased risk of postmenopausal breast cancer (2). A study in China found that there is an increased mean intake of total fat and calories in subjects with breast cancer compared with controls (8).

The hypothesis of this study is that serum selenium level in breast cancer patients is lower than that in subjects without breast cancer. Subjects who have well-recognized risk factors for breast cancer such as family history, reproductive and menstrual history, HRT, lifestyle factors, diet, radiation history, and history of breast disease have a higher risk of breast cancer than those without the risk factors mentioned above. The objective of this study is to examine the relationship of breast cancer with serum selenium level and other risk factors.

Materials and Methods

This study was a matched case-control study of 62 pairs of participants in a hospital in Malaysia from July 2000 to January 2001 and May 2001 to June 2001. Cases were defined as those who were newly diagnosed as having breast cancer by the Breast and Endocrinology Unit, Department of Surgery, Hospital Kuala Lumpur. Patients with non-carcinoma breast tumors were not included in this study. The exclusion criteria included the nonrecruitment of patient who were on follow-up for breast cancer and those who were on radiotherapy or chemotherapy because of the strong probability that their eating patterns had been altered. Patients who refused to participate in this study or could not be contacted were also excluded. Control subjects were randomly recruited from non-breast cancer female patients treated in the same hospital who agreed to participate in the study. Controls were matched to cases according to race, menopausal status and age range (±5 years compared to cases). Patients diagnosed with cancers other than breast cancer, were also excluded from this study. The Human Scientific Research and Ethics Committee of the Hospital Universiti Kebangsaan Malaysia as well as the director of the hospital approved the study protocol materials and informed consent was obtained from all participants.

All subjects were interviewed by the authors using a structured questionnaire to obtain detailed information on demographic factors, total fat intake per week and body mass index. The questionnaire comprised four parts. The first part consisted of sociodemographic data, which included age, race, marital status, educational level, and income of family. The second part included medical history and risk factors for breast cancer such as menarche, breastfeeding history, use of oral contraceptives, HRT, family history of breast cancer, and smoking history. The third part included height and weight, and the last section pertained to eating habits.

A venous blood sample was obtained from each participant by one of the researchers or the medical officer on duty using a 22G syringe. The minimum amount of blood per sample collected from each participant was 3 ml. Each collected blood sample was transferred into a plain tube and kept in an ice container before being transported to the laboratory. The blood samples were then centrifuged within 24 h. The serum obtained was transferred into plastic tubes with 5% nitric acid and kept at 4°C.

Assessment of fat intake

Using the dietary recall method, the subjects were interviewed regarding their average dietary pattern during the previous year. Attention was paid to the type, frequency and average intake of 13 food groups including grains and grain products, milk and dairy products, bread spread, potatoes, seafood, eggs, fast foods, processed foods, fruits, vegetables, malt drinks, and snacks. The average weekly intake of fat was calculated by first multiplying the frequency of consumption of each food item by its fat content, which was calculated on the basis of composition values reported from the Malaysian Food Composition Manual (16) and then summing the fat intake from all the food items.

Determination of the serum selenium level

In this study, serum selenium level was measured by the method described by Thomas (17) with modifications. The two main apparatus used in this technique were an atomic absorption spectrometer (AAS) (GBC, Scientific Instruments, Melbourne, Australia) and a Digital Dry Block Heater, Dataplate (PMC, San Diego, CA, USA).

The first step in analyzing serum selenium level was to obtain a standard calibration curve with the spectrometer using a standard solution containing a standardized concentration of selenium. This standard solution was diluted to 0, 12.5, 25, 50 and 100 μg/dl and the spectroscopic readings were plotted

accordingly to obtain a standard curve. The standard curve we obtained had a correlation value of 0.994. The next step was wet-sample digestion carried out to destroy organic matter. Nitric acid was added to a serum sample that was then heated using the digital dry block heater at 100±0.5°C for one hour, followed by the addition of sulfuric acid and perchloric acid, and further heating for another one hour. Blood samples were then placed in the atomic absorption spectrometer for analysis. For each sample, two measurements were taken and the mean selenium level reading was taken as the true serum selenium level.

Anthropometry

Body weight and height were measured during the interview. Participants wore light clothing with no shoes during the measurement. Weight was measured using a portable weighing scale to the nearest 0.1 kg. Height (m) was measured with a stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated. In this study, being overweight was defined as having a BMI of more than 25.

Statistical methods

Data were analyzed using SPSS version 10.0. Descriptive statistics were used for qualitative data to determine data. For both the cases and controls, the McNemar test was used to determine any association between breast cancer and variables such as work status, menarche before the age of 15, having less than two offspring, age 25 or later at first childbirth, breastfeeding status, use of oral contraceptive pills (OCP), family history of breast cancer, smoking status, BMI exceeding 25 and frequency of eating out per week.

The significance of differences in serum selenium level between the case and control groups was determined by Student's t-test. A probability level of 5% was considered statistically significant. A logistic regression model was used to predict the risk of developing breast cancer as contributed by the independent variables. The association between serum selenium level and the risk of breast cancer was expressed as an odds ratio (OR), with a 95% confidence interval (CI).

The independent variables of the study were as follows: reproductive history (menarche before the age of 15, nulliparity, age of first delivery ≥25 years, number of children, breastfeeding, use of OCP and use of HRT, family history, smoking, being overweight, and serum selenium level.

Results

There were 62 matched pairs of subjects in the study. The baseline characteristics of the case and control subjects are shown in Table 1. The majority of the respondents were Malay (38 pairs), followed by Chinese (14 pairs), and Indian (10 pairs). The mean age of the patient group was 49.85±11.19, whereas that of the control group was 49.34±10.80. Among the cases, 26 (41.9%) had primary school education, 21 (33.9%) secondary school education, and 10 (16.1%) tertiary school education. Among the controls, 11 (17.7%) had primary school education, 32 (51.6%) secondary school education, and 14 (22.6%) tertiary school education. For both groups of respondents, the majority of them were working women.

Table 2 shows the OR of breast cancer according to risk factors such as reproductive history, family history of breast cancer, smoking, and BMI as determined by the McNemar test. It was found that reproductive history such as nulliparity, not breastfeeding and OCP use, contributed significantly to the risk of breast cancer. Family history of breast cancer and BMI of more than 25 were not associated with breast cancer ($p>0.05$). Menarche before the age of 15 and having one or two children were not proven to reduce the risk of breast cancer. Smoking was not shown to contribute to an increased risk of breast cancer.

The mean serum selenium level was lower among the cases than among the controls ($p<0.001$) (Table 3).

The mean fat intake per week among the cases was 229.9± 105.1 g whereas that among the controls was 197.4±80.8 g. However, the difference was not statistically significant.

Logistic regression analysis indicated that being nulliparous and using OCP were among the significant predictors of breast cancer, where OR for nulliparity was 10.08 (95% CI=

Table 1 Demographic characteristics of study population

Variable	Case (%) N=62	Control (%) N=62
Ethnicity		
Malay	38 (61.3)	38 (61.3)
Chinese	14 (22.6)	14 (22.6)
Indian	10 (16.1)	10 (16.1)
Mean Age (years)		
	49.85±11.19	49.34±10.80
Educational Level		
No School	5 (8.1)	5 (8.1)
Primary School	26 (41.9)	11 (17.7)
Secondary School	21 (33.9)	32 (51.6)
Tertiary education	10 (16.1)	14 (22.6)
Working status		
Working	38 (61.8)	43 (69.4)
Not Working	24 (38.7)	19 (30.6)

Table 2 Odds ratio for breast cancer according to riskdetermined by McNemar test

Risk factors	OR	(95% CI)	P value
Reproductive History			
Menarchy before 15 years	0.71	(0.23–2.25)	0.774
Nulliparity	5.50	(1.22–24.81)	0.022*
Age at first delivery ≥25 years	1.80	(0.60–5.37)	0.424
Number of children 1–2	0.78	(0.29–2.09)	0.804
Breastfeeding	4.00	(1.34–11.96)	0.012*
Use of OCP	3.00	(1.09–8.25)	0.041*
Use of HRT	1.33	(0.30–5.96)	1.000
Family History	1.67	(0.61–4.59)	0.424
Smoking	2.20	(1.04–4.65)	0.050
BMI≥25	1.88	(0.79–4.42)	0.210

* Significant when $p<0.05$.

HRT=Hormonal Replacement Therapy; BMI=Body Mass Index; OCP= Oral Contraceptive Pills; OR=Odds ratios; 95% CI=95% confidence intervals.

Table 3 Mean level of serum selenium in cases and controls

Serum selenium (μg/dl)	Mean±SD	t value	P value
Case	16.24±8.21	5.09	0.001*
Control	23.85±9.80		

Statistical test used=Student's t-test.
* Significant when $p<0.05$.
SD=Standard Deviation.

Table 4 Logistic regression model for predicting breast cancer

Risk factors	Regression Coefficient	P value	OR	(95% CI)
Nulliparity	2.311	0.018*	10.08	(1.48–68.52)
Use of OCP	1.297	0.010*	3.66	(1.36–9.87)
Not breastfeeding	0.355	0.536	1.43	(0.46–4.87)
Serum selenium	–0.115	0.001*	0.89	(0.84–0.94)
Coefficient	1.583	0.010*		

* Significant when $p<0.05$.
OR=Odds ratio; OCP=Oral contraceptive pills; 95% CI=95% confidence intervals.

1.48 to 68.52) whereas that for OCP was 3.66 (95% CI=1.36 to 9.87) when compared with controls. An increase of 1 μg/dl in serum selenium level was found to reduce the risk of breast cancer by 0.89 (OR) (95% CI=0.84 to 0.94). From the factors studied here, women who did not breastfeed were not found to have a higher risk of developing breast cancer.

Discussion

The risk factors for breast cancer have been investigated in many studies (2, 8–11, 13, 18, 19). A possible genetic contribution to breast cancer risk is suggested by the increased incidence of breast cancer among women with a family history of breast cancer (12, 13). Factors such as age, reproductive history, and smoking increase the risk of breast cancer in women (2, 11, 19).

In this study, subjects with breast cancer had lower serum selenium concentration than the controls. There is an inverse association between serum selenium level and the risk of breast cancer. The biological mechanism by which selenium affects breast cancer is as yet unknown, but several mechanisms have been hypothesized. The mechanisms proposed for the anticarcinogenic effect of selenium include protection from oxidative damage from carcinogens, effects on carcinogen metabolism, and reduction in mutagenecity and toxicities of selenium metabolites to proliferating cells (20, 21). A case control study, which compared the mean serum selenium level in 244 breast cancer patients with that in controls, found that there is a significantly lower level of serum selenium among cancer subjects even after adjusting for confounding factors such as fat intake, total cholesterol level, and HDL level (8). Schrauzer et al. (22) whose study focused on Japanese women found that the serum selenium level among women without breast cancer is significantly higher than that among women who have been diagnosed with breast cancer or women having recurrent breast cancer. The findings of this study provide further support for the hypothesis that a relationship exists between a low serum selenium level and the occurrence of breast cancer.

In this study, it is also suggested that nulliparity is a risk factor for breast cancer. The OR for nulliparity was 10.08, as compared with that for multiparity. This is consistent with other research findings indicating that nulliparity is a risk factor for breast cancer (23). As stated by Helmrich et al. (24) and Lipnick et al. (25), an increase in parity has a protective effect against breast cancer. As for breastfeeding as a risk factor for breast cancer, this study showed that women who did not breastfeed had a higher odds ratio (4.0) than those who did breastfeed. However, according to our logistic regression model, this factor was not significant. In a study by Soini (26), there was no evidence for an association between the period of lactation and breast cancer.

This study did not prove that women with a BMI of more than 25 were at a higher risk of developing breast cancer. In a study by Lahmann et al. (27), BMI was not found to be a predictor of breast cancer risk. Contrary to this study, Zhu et al. (28) found that among African American women, BMI positively correlated with breast cancer; women with a BMI of 25 to 29.9 and 30 or higher, have OR of 1.75 and 2.32, respectively, compared with women having a BMI lower than 25. Discrepancy in the observed results may have been due to the fact that there is a lower prevalence of being overweight or obesity among Asian women than among women from other regions (29). Consequently, it is not possible to denote a BMI of more than 25 as a risk factor for breast cancer.

The total amount of fat intake was not associated with breast cancer. Hunter et al. (30) had proven from his study, that there was no evidence for a positive association between total dietary fat intake and risk of breast cancer and there was also no reduction in the risk even among women whose energy intake from fat was less than 20 percent of the total energy intake.

Another important predictor of breast cancer, as determined from this study is the use of contraception. It was found that OCP use contributes to a fourfold increase in the risk of breast cancer when compared with non-OCP use. Similar results have been obtained from a collaborative analysis of 54 epidemiological studies (31), in which the risk of breast cancer was reported to increase by 25% in current users of OCP.

Exposure to cigarette smoke was not shown to increase the risk of developing breast cancer. A clinical trial by McPherson (2) supports the hypothesis that smoking is not a significant risk factor for breast cancer development.

The lack of significant associations between breast cancer and the other variables studied was unexpected. For example, there were no statistically significant differences in family history of breast cancer, HRT use, age at delivery of the first baby, BMI and fat intake between those who had been diagnosed with breast cancer, and those without breast cancer. Nonetheless, considering this is a case-control study, further prospective studies and randomized trials of these relationships are needed to confirm or refute the findings.

Limitations of the present study includes those inherent to the case-control study design, i.e., cases' recall bias with respect to risk factors ascertained after the diagnosis of breast cancer, particularly information regarding fat intake and use of OCP. The data on patients collected retrospectively may be of

poor quality as they are based on the patient ability to recall the past. In addition, their ability to recall may be influenced by their known outcome.

The study was carried out on a population taken from a public hospital. This population may not be representative of the general population in Malaysia. For example, women in rural areas may choose a complementary medicine and women with a high socioeconomic background may seek treatment from private hospitals. Lastly, serum selenium level is influenced by dietary intake (32). Therefore, blood samples should be collected at the fasting status to avoid the effects of food intake. In addition, the measured serum selenium level may not reflect the average selenium level before the diagnosis of breast cancer among the cases. Although the results cannot be generalized, our findings suggest the association of breast cancer with a low serum selenium level, nulliparity, and contraceptive use, which are consistent with the findings in other studies.

Conclusion

In this study, we demonstrated that nulliparity, use of OCP, and serum selenium level are significantly associated with breast cancer. There was no evidence that factors such as early age at menarche, late age at the first birth, low number of deliveries, use of hormone replacement therapy, positive family history of cancer, exposure to cigarette smoke, being overweight, and a high fat intake are associated with breast cancer. Multivariate analysis showed that only serum selenium level, nulliparity and use of oral contraceptives are associated with an increased risk of breast cancer.

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