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Family History And Risk Of Breast Cancer: A Case-Control Study In Thailand

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ABSTRACT

Data from Western populations indicated approximately two-fold increased risk of breast cancer in women with a family history. Such data are limited for Asian populations where the incidence rates are low. This case-control study investigated the association in Thai women. Subjects were 405 newly-diagnosed and pathologically-confirmed breast cancer cases and 811 control patients matched for age and residential area, during 1999-2000. Information on family history was collected using a structured questionnaire. Approximately 3.5% of cases and 1.6 percent of controls reported having a history of breast cancer in their mother or sister. Women with a family history of breast cancer had an increased risk of developing breast cancer (OR = 2.20: 95%CI= 1.02-4.72) in age-adjusted model and, OR= 1.93 (95%CI, 0.88-4.23) in multivariate model. The relationship was stronger in postmenopausal women and also in women who had a history of breast cancer in sister. Despite the low incidence rates and small proportion of family history of breast cancer in this population, the relationships was similar to those from Western and other Asian populations. Accordingly the attributable risk of breast cancer due to family history in this population is estimated to be small.

Keyword : breast neoplasm / case-control study / Thailand / family history /genetics

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Abbreviations :
CI, confidence interval; OR, odds ratio;

INTRODUCTION

Family history has long been established as a risk factor of breast cancer with an effect of increased risk of approximately two-fold (1, 2). Most of these studies have been based on European or the US populations where incidence rates of breast cancer have been high. In Asia however where the incidence rates are low, data on the effect of family history have been limited.

This report presents a case-control study investigating the association between breast cancer and history of breast cancer in a first degree relative in Thailand, a country in South-east Asia, where these data are limited.

MATERIALS AND METHODS

This case-control study collected data from patients aged 70 years or less, living in the north-east region of Thailand, who were admitted to one of the seven largest hospitals in the region, during 1999-2000. This study was approved by ethic committees at the Faculty of Medicine, Khon Kaen University and the Ministry of Public Health. The case group comprised 405 pathologically confirmed breast cancer patients diagnosed from November 1998 to April 2000. Randomly selected individual control patients were matched to indicator cases by age (± 5 years), residential area (province) and hospital of admission. Patients with the following conditions were excluded from the control group: pregnancy related conditions; illnesses requiring respiratory supports and intensive care; mental disorder; severe brain disease; and malignant tumour.

A single set of one case and two matched controls was interviewed by the same interviewer using structured questionnaires which contained questions for information on demography, reproductive factors and history of all cancer sites in parents and siblings with information of age at onset. Body composition including weight and height were directly measured.

Unconditional logistic regression using SPSS for Windows (Version 9.0, SPSS Incorporated) was used to estimate adjusted odd ratios, 95% confidence intervals and test for trend, if applicable, for the relations between breast cancer and exposures. Odds ratios were adjusted for age, family income, parity, lactation and BMI. Tests for trend were calculated across categories.

RESULTS

Selected characteristics of 405 breast cancer cases and 811 controls were shown in Table 1. The majority of breast cancer patients were below 50 years of age (60%) and at pre-menopause (56%). Other characteristics of this population were low affluence, late age at menarche, high parity and prolonged breast-feeding duration. Among 220 breast cancer patients with information available on staging, just over 50 percent of the patients had stage III or more advanced stage disease. Approximately 90 percent of the case subjects were ductal carcinoma. Controls were selected from all hospital departments (general, cardiothoracic and plastic surgery, urology, internal medicine, gynaecology, ophthalmology, ENT and orthopaedics). Approximately 60 percent of cases and controls were employed in agricultural sectors and 94 percent of subjects were Thai ethnicity.

Approximately 1.6 percent of control patients reported having history of breast cancer in mother or sister. None of the subjects, neither cases or control, had more than one relative diagnosed with breast cancer. The relationship between breast cancer and history of breast cancer in mother or sister was OR = 2.20 (95%CI, 02-4.72) in age-adjusted model and, OR= 1.93 (95%CI, 0.88-4.23) in multivariate model see Table 2. The analysis restricted to history of breast cancer in sister yielded a stronger association because of small numbers. The data, however, were limited for examining the effect of the history of breast cancer in mother. In Table 3, the analysis stratified by age at diagnosis of women showed a larger effect in women diagnosed with breast cancer at the age of 50 years or older. The examination of the effect of age at onset of breast cancer in first degree relatives was limited by the lack of data on the age at onset see Table 4. The available data suggested that younger age at onset of breast cancer in mother or sister was associated with higher risk of breast cancer.

In the analysis of history of cancers in other sites see Table 5, history of cancer of liver and bile tract was the most common and significantly associated with breast cancer in this population.

Table 1. Demographic characteristics of subjects.

Variables	Categories	Cases		Controls	
		No.	(%)	No.	(%)
Age groups	< 30 years	9	(2)	28	(4)
	30-39 years	76	(19)	152	(19)
	40-49 years	157	(39)	290	(36)
	50-59 years	106	(26)	216	(27)
	60 -70 years	57	(14)	125	(15)
Menopausal status	Pre-menopause	227	(56)	421	(52)
	Post-menopause	178	(44)	390	(48)
Total annual income (Baht)	1,000-16,700	110	(28)	185	(24)
	16,701-36,000	115	(29)	214	(27)
	36, 001-97,200	85	(21)	181	(23)
	97,200-552,600	87	(22)	207	(26)
Highest education	Pre-primary school	38	(9)	71	(9)
	Primary school	271	(67)	497	(61)
	Secondary school	38	(9)	110	(14)
	College or higher	56	(14)	132	(16)
Occupations	Public sectors	37	(9)	95	(12)
	Retail, personal & household goods	61	(15)	115	(14)
	Agriculture, hunting and forestry	242	(60)	496	(61)
	Other occupational groups	64	(19)	105	(13)

Table 2. Association between breast cancer and history of breast cancer in mother or sister.

Having affected relative	Cases		Controls		Age adjusted model		Multivariate model*	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Mother or sister								
No	391	96.5	798	98.4				
Yes	14	3.5	13	1.6	2.20	(1.02-4.72)	1.93	(0.88-4.23)
Mother								
No	403	99.5	805	99.3				1.00
Yes	2	0.5	6	0.7	0.66	(0.13-3.29)	0.62	(0.12-3.18)
Sister								
No	393	97.0	804	99.1				1.00
Yes	12	3.0	7	0.9	3.52	(1.37-9.01)	3.01	(1.15-7.89)

*Adjusted odds ratios were made for age (continuous variables), number of pregnancy, duration of breast-feedings, household income, and body mass index

Table 3. Associations between breast cancer and history of breast cancer in mother or sister stratified by age at diagnosis of subjects.

Age at diagnosis in subjects	Cases		Controls		Age adjusted model		Multivariate model*	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Age below 50								
FH (-)	235	97.1	460	97.9	1.00		1.00	
FH (+)	7	2.9	10	2.1	1.34	(0.50-3.58)	1.28	(0.47-3.51)
Age 50 or older								
FH (-)	156	95.7	338	99.1	1.00	1.00	1.00	
FH (+)	7	4.3	3	0.9	5.00	(1.27-19.6)	5.22	(1.25-21.75)

*Adjusted odds ratios were made for age (continuous variables), number of pregnancy, duration of breast-feedings, household income, and body mass index
FH, status of having family history in mother or sister; (+), yes; (-), no.

Table 4. Associations between breast cancer and age at diagnosis of breast cancer in mother or sister.

Onset in affected relative	Cases		Controls		Age adjusted model		Multivariate model*	
	No.	%	No.	%	OR	95% CI	OR	95% CI
No history	391	96.5	798	98.4	1.00		1.00	
Onset < 50	8	2.0	4	0.5	4.06	(1.22-13.58)	3.06	(0.89-10.54)
Onset ≥ 50	2	0.5	8	1.0	0.51	(0.11-2.42)	0.47	(0.10-2.27)
Unknown onset	4	1.0	1	0.1	8.19	(0.91-73.57)	9.25	(1.00-85.46)

*Adjusted odds ratios were made for age (continuous variables), number of pregnancy, duration of breast-feedings, household income, and body mass index

Table 5. Associations between breast cancer and history of specific cancers in parents or siblings.

History of cancers in parents or siblings θ	Cases, N=405		Controls, N=811		Age adjusted model		Multivariate model*	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Kidney & adrenal gland	1	0.2	1	0.1	2.01	(0.13-32.13)	3.08	(0.18-52.21)
Uterus & cervix	16	4.0	17	2.1	1.92	(0.96-3.84)	1.82	(0.87-3.78)
Stomach & intestine	8	2.0	11	1.4	1.47	(0.58-3.67)	1.19	(0.45-3.16)
Lip & oral cavity	1	0.2	5	0.6	0.40	(0.05-3.43)	0.25	(0.03-2.26)
Blood & lymph system	3	0.7	3	0.4	2.01	(0.41-10.00)	2.43	(0.47-12.68)
Skin	3	0.7	1	0.1	6.05	(0.63-58.30)	7.58	(0.76-76.04)
Prostate	1	0.2	2	0.2	1.00	(0.09-11.07)	1.06	(0.09-13.00)
Bone & extremities	6	1.5	7	0.9	1.73	(0.58-5.17)	1.98	(0.64-6.13)
Lung	7	1.7	11	1.4	1.28	(0.49-3.32)	1.60	(0.59-4.32)
Liver & bile tract	34	8.4	45	5.5	1.56	(0.98-2.48)	1.65	(1.01-2.69)
Neck & thyroid	4	1.0	4	0.5	2.01	(0.50-8.09)	1.85	(0.45-7.62)
All sites	88	21.7	109	13.4	1.79	(1.31-2.44)	1.84	(1.32-2.57)

θ compared to no family history in particular cancer sites.
*Adjusted odds ratios were made for age (continuous variables), number of pregnancy, duration of breast feedings, household income, and body mass index

DISCUSSION

This case-control study showed that proportion of women who had history of breast cancer in first degree relatives in this population is small. In addition, those women with family history were associated with approximately two-fold increased risk of breast cancer. Despite limited data, the increased risk was shown to be stronger in women i) whose affected relative was sister; ii) whose first degree relative was diagnosed at young age; and iii) who were diagnosed with breast cancer at an older age. History of cancer at liver and bile tract was related with elevated risk of breast cancer.

Proportion of women with family history

The proportion of women with positive family history in this population was relatively small compared to data from Western populations. According to the pooled analysis by Collaborative Group on Hormonal Factors in Breast Cancer (2001), approximately 7% of controls had at least one first-degree relative diagnosed with breast cancer. The proportion in this study however was similar to the figure from the pooled analysis estimated for developing countries (2%) and from other

studies in Asian populations as presented in Table 6. For example, the proportions varied from study to study, 2.1-4.5% from Japan, 1.0-2.4% from China, 1.8% from Taiwan and 4% from Singapore (3-6). Among these studies, the proportions estimated from investigations using self-administered questionnaire tended to derive higher proportions than interviews. Two reports from Thailand found 4.0% (7) and 1.9% (8) from 50 and 160 control subjects respectively identified through hospitals in Bangkok. In comparison to these two studies and other Asian studies, the present study observed only slightly lower percent of women with family history. These proportions were substantially less than those from Western populations.

The relationship between breast cancer and family history

The present study found a magnitude of about two-fold increased risk, which was similar to previous reports from Western and Asian populations. The pooled analysis from Western populations found an increased risk of OR =1.8 (95%CI: 1.7-1.9) for women who had one first-degree relative diagnosed with breast cancer (9). Among Asian studies, two large case-control studies with more than 1,000 cases from Japan (5, 10) reported the association of OR = 1.8 (95%CI: 1.4-2.4) and OR = 2.1(95%CI: 1.7-2.7) respectively. Recently, one large study from China (11) found the positive association of OR = 1.56 (95%CI: 1.02-2.39). In a small study from Singapore (6), OR for the association was 1.81(95%CI: 0.9-3.5). Two case-control studies, however, reported unusually high estimates of the associations of 4.66 (2.07-11.40) from Taiwan (12) and 4.33(95%CI: 1.39-13.46) from China (13) but the confidence intervals of the estimates were wide. Data from Thailand observed the effect of OR = 1.68 (95%CI: 0.95-2.05) (8) and 2.14(95%CI: 0.31-11.97) (7).

Limitations of these studies are that they compared only positive and negative family history in first-degree relatives and did not investigate the effect of having more than one affected relative. In addition, the investigation of the effect of family history was not always the primary hypothesis. Moreover, sample sizes in certain studies were small and since proportions of women with family history of breast cancer in Asian populations are low, some studies will therefore, have lacked power. However, these studies from Asian population derived similar findings and comparable to our findings. A study from Japan (3) found a stronger association for women with two affected relative (OR = 1.80, 95%CI: 0.76-4.31) than one affected relatives (OR = 1.49; 95%CI: 1.10-2.03); the effect sizes in this study however were lower than most other studies.

Collectively, data from the present study, other Asian studies and the collaborative reanalysis (the largest dataset investigating the effect of family history) have similarly reported the relationship between breast cancer and the family history of breast cancer in a first-degree relative to have an odds ratio of approximately 1.8-2.0.

The role of types of first-degree relatives

This study found a larger effect of history of breast cancer in a sister. This result was similar to other studies in that the relationship between breast cancer and family history were found to be stronger in women with an affected sister than mother (14-17). The possible explanation might be that the major breast cancer genes, *BRCA1* and *BRCA2*, are associated with early onset of breast cancer (18, 19).

Age at diagnosis breast cancer in subjects

In the examination on the effect of age at onset of breast cancer in subjects, the findings did not show the higher risk in early onset breast cancer but instead in women diagnosed at 50 year or after. These results were different from the accepted notion that early onset breast cancer has higher risk ratio than late onset (18, 19). Nonetheless, according to the pooled analysis of Western studies, case-control studies using hospital controls derived risk ratio for women at 50 or older of OR=2.2 which was higher than women before 50 years with OR=1.86 (9). Therefore, the effects of age at diagnosis in women in this study may be influenced by using hospital controls. Since hospitalised patients were older than the general population, this group of women may be less likely to know whether they had a family history of breast cancer than their counterparts in the community because registration of cancer would have been poorer. This study found that the percentage of those with a family history in the control group was not increased with age, 2.1% in younger women and 0.9% for older women, and this observation differed from the collaborative reanalysis. However the proportions

Table 6. Associations between breast cancer and history of the cancer in mother or sister, according to studies in Asian women.

References	No. Cases	Family history [Π] (%in controls)	Odds ratios
From Japan: combined OR[#]			**1.75(1.53-2.00)**
(Hirohata et al., 1985)	212	-	0.96(0.65-1.42)
(Kato et al., 1992) [π]	908	4.5%	1.52(1.14-2.03)
(Land et al., 1994)	196	2.1%[ϕ]	1.16(0.36-3.16)
(Hirose et al., 1999) [π]	1359	3.6%	2.15(1.73-2.67)
(Tung et al., 1999) [π]	376	3.5%	2.68(1.44-5.00)
(Yoo et al., 2001)	1154	-	1.82(1-38-2.38)
From China: combined OR[#]			**1.93(1.37-2.72)**
(Tao et al., 1988) [π]	495	1.4%	2.17(0.81-5.78)
(Yuan et al., 1988)	534	1.1%	2.83(1.09-7.32)
(Zheng et al., 2000)	404	1.0%[γ]	4.33(1.39-13.46)
(Shu et al., 2001)	1459	2.4%	1.56(1.02-2.39)
From Taiwan			
(Yang et al., 1997)	694	1.8%	4.66(2.07-11.4)
From Singapore			
(Ng et al., 1997) [π]	204	4%[Ψ]	1.81(0.93-3.51)
From Thailand: combined OR[#]			**1.72(1.00-2.96)**
(Suvankereekhun, 1993)	50	4%	2.14(0.31-11.97)
(Sipiyarak, 1996)	160	1.9%	1.68(0.95-2.97)
Overall combined OR [#]			**1.80 (1.60-2.03)**
OR of the present study			**1.93 (0.88-4.23)**

[Π] first degree relatives, [π] using self-administered questionnaire, [Ψ] among mother, sister, daughter, grandmother, and aunt., [ϕ] among mother, sister, daughter [γ] not specified relatives
[#] Odds ratios were combined using the variance-based method (Greenland, 1987).

patients with family history in the case group were higher in older women than younger women. Apart from the effect of using hospital controls, the low proportion of breast cancer in older controls might be due to the exclusion of cancers in other sites from being control subjects because breast cancer genes such as *BRCA1* and *BRCA2* are also associated with increased risk in some other cancers.

Onset of breast cancer in first-degree relatives

In this population, a stronger odds ratio was found in the group of women who had history of early onset breast cancer in first-degree relatives than late onset of the cancer and this finding was similar to previous studies (14, 20). However, the results for women with a family history of late onset breast cancer did not show positive association as expected. This might be due to the large proportion of missing data on age at diagnosis in relatives as shown in table 4; 4 out of 14 in cases and 1 out of 13 in controls did not report the age at onset of breast cancer in their relatives.

History of other cancers in first degree relatives

These data show a marginally significant positive relationship between breast cancer risk and history of liver and bile tract cancer. This type of cancer is the most common cancer in men and women in this region of the country (21) and the proportion of the cancer in family history from the data also reflect this fact. There are two common types of liver cancer,

cholangiocarcinoma (87% of all histological types) and hepatocellular carcinoma (7%) and they are associated with infections of liver fluke and hepatitis B virus respectively. It is possible that these infections might transmit among family; however, the proportion of the family history should not be different between cases and controls unless there was differential recall bias. Genetically, there are possible explanations. Firstly oestrogens were suggested to be related to carcinogenesis of breast cancer and hepatocellular carcinoma (22) and heriditary abnormality in oestrogen metabolism, such as genetic polymorphism, might link the cancer in a family. Secondly, certain genes are suggested to play a role in both cancers. Carriers of *BRCA2* mutation were found to have a significantly increased risk of cancers of gall bladder and bile duct, pancreas, stomach and skin (23). Similarly, mutations of *p53* gene were associated with cancers of both breast and liver/bile (24-28). For other cancers, percentage of family history was too small to derive a precise estimate.

Overall

This study found a similar proportion of family history of breast cancer to that in Asian populations but it was substantially lower than Western populations. The relationship between breast cancer and family history of breast cancer in mother or sister was 1.93 (95%CI: 0.88-4.23) which is similar to most studies. A history of an affected sister was associated with a stronger risk but not for the history of an affected mother. Young age at diagnosis of subjects (less than 50 years) was not found to be associated with a higher increased risk, while family history of breast cancer in a mother or sister diagnosed at age less than 50 years was related to a stronger risk. Overall, the results of family history of breast cancer in this study were similar to previous data.

Although the strength of the relationships was fairly similar in most reports, attributable risk was different according to the prevalence of family history of breast cancer. The attributable risk estimated from this study using case fraction (29) was 1.7% (95%CI: - 0.5 -2.7%). In other words, only about 2% of breast cancer in this population was attributable to family history of breast cancer mother or sister. Family history is therefore accountable for a small proportion of breast cancer in the population, compared to Western population where the estimates are about 5-10%, and the small proportion in this population infers lower influence of the major high penetrance genes.

The limitation of the present study in the investigation of the relationship with family history was the limited number of subjects. In the situation where proportion of family history was 1.6% and the odds ratio was 1.8, this study would require 1600 cases to achieve a power of 80%. Another possible disadvantage is that differential recall bias cannot be ruled out. That is, cases might be more likely to report their family history of cancer than controls. If this consideration was correct, it might explain the slightly low percentage of women reporting positive history of breast cancer in a family. In addition, four cases and one control were not able to report age at diagnosis of breast cancer in their relatives. Interviews were used for data collection and questions were asked systematically for history of cancers and the age at onset in parents, sisters and brothers. The structured questions facilitated subjects to recall their family history of cancers.

Due to insufficient data, this study was not able to investigate family history of other cancers that were suggested to be related to breast cancer such as ovary and prostate cancer as these two cancer were shown to be associated with mutation of the genes *BRCA1* and *BRCA2* (30-32). There have been however no reports of the percentage of *BRCA1* and *BRCA2* mutations among Thai women.

In conclusion, the proportion of women in the control population was about 1.6%, which is only slightly lower than those estimated from other studies (2-3%). Despite the low risk of breast cancer in this population, the relationships with history of breast cancer in first-degree relatives was similar to those from Western and other Asian populations. The increased risk was nearly two fold compared to women without family history of breast cancer. Family history of breast cancer in first-degree relatives accounts for a relatively small proportion (approximately 1.7%) of breast cancer in this population. Although effects of age at diagnosis in women and their first-degree relatives were not sufficiently evaluated due to limited number of subjects this study supports the hypothesis that women with relatives with early onset of breast cancer tended to have higher risk. In this study, risk of early age at diagnosis in subject women was not higher than women with late onset, a finding that has consistently been found in other case-control studies using hospital controls. In the comparison between more and less developed countries, the

combined analysis shows that women from less developed countries had a substantially lower proportion of history of breast cancer in first-degree relatives, namely 2% compared with 8% in more developed countries. As incidence rates in less developed countries are much lower generally than the developed countries; the absolute risk according to family history in this population would thus be considerably lower.

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