Risk of Breast Cancer in Post-Menopausal Women Using Hormone Replacement Therapy

ADUNE RATANAWICHITRASIN, M.D.*,
WORAMIN REANSUWAN, M.D.*,
SOMSRI RATANAWICHITRASIN, M.D.***
KRIS BHODHISUWAN, M.D.*,
SUPORNCHAI KONGPATANAKUL, M.D.**,

Abstracts

Objective : To study the relationship of hormone replacement therapy (HRT) in post-menopausal women and risk of breast cancer.

Patients and Method : The authors conducted a case-control study comparing the proportion of HRT used between breast cancer and non-breast-cancer women. Cases were breast cancer patients who had natural menopause (excluded hysterectomy) and aged ≥50-years-old from the Siriraj Breast Cancer database (1983-1996). Controls were post-menopausal volunteers aged 50 year or older who visited Siriraj Hospital for other purposes such as elderly clinics, health check, etc. After informed consent, well-trained surgeons examined the women in the control group to exclude any potential breast cancer. Patient characteristics and risk factors were collected.

Results : Of 1913 patients in the database, 623 were included as the cases. Data from 679 volunteers were collected for controls from May to December 1999. Among 1302 of the study population 58 women had ever used HRT (4.5%), which distributed to 3.2 per cent (20/623) in cases and 5.6 per cent (38/679) in controls. From univariate analysis, age, age at menopause, number of children, habitat, education, contraceptive pills, familial history of breast cancer and HRT usage were associated with breast cancer (p-value<0.05). After multivariate forward stepwise logistic regression analysis, there was no association between HRT use and breast cancer (adjusted odds ratio (OR) = 0.61, 95% CI = 0.31-1.20). In subgroups analysis, women who had older age, higher education level, history of taking contraceptive pills, or positive familial history of breast cancer in second degree relatives had a decreased risk of breast cancer, while those living outside Bangkok had an increased risk.

Conclusion : Hormonal replacement therapy in post-menopausal women was not associated with increased risk of breast cancer.

Key word : Breast Cancer, Hormone, Replacement, Post-menopausal, Risk

RATANAWICHITRASIN A, BHODHISUWAN K, REANSUWAN W, KONGPATANAKUL S, RATANAWICHITRASIN S
J Med Assoc Thai 2002; 85: 583-589

* Division of Head & Neck and Breast Surgery, Department of Surgery,
** Department of Pharmacology,
*** Division of Clinical Epidemiology, Department of Research Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Hormone replacement therapy (HRT) has been expected to increase survival, decrease the risk of cardiovascular disease[1-3], and prevent osteoporosis in post-menopausal women[4,5]. On the other hand, an increasing risk of endometrial cancer[6,7], breast cancer[8-10] and deep vein thrombosi[11] has been reported among HRT users.

The risk of breast cancer among HRT users is controversial, although many reports from meta-analysis showed prolonged HRT use (10-15 years) may increase the risk of breast cancer 1.3-2.5 times[10,12].

Currently, HRT is commonly used in Western countries and has increasingly been prescribed for Thais during the last 5-10 years. Promotion of HRT and menopausal clinics has commonly been organized countrywide, while the incidence of breast cancer tends to change to be the most common cancer among Thai women. Therefore, studying the risk of breast cancer among post-menopausal HRT users might be beneficial not only for medical knowledge but also from the consumer protection aspect.

PATIENTS AND METHOD

A case-control study was done comparing the proportions of HRT used between breast cancer patients from Siriraj Hospital Breast Cancer Database (Cases) and non-breast-cancer visitors at Siriraj Hospital, Mahidol University (Controls).

Cases selection

Women aged 50 year or more, who had breast cancer treated surgically during 1983 and 1996, were selected from Siriraj Hospital Breast Cancer database as the cases. Patients who had been hysterectomized were excluded from the study.

Controls selection

Healthy or non-breast-cancer volunteers, aged 50 year or more, who visited Siriraj Hospital during 1999 were included as controls in the study after giving informed consent. All women in the control group had to have no history of breast cancer and no suspected breast cancer lesion on physical exam performed by well-trained breast surgeons. To avoid selection bias, women who had been hysterectomized or the possibility of HRT used for medical purposes, such as women from the orthopedic clinic, post-menopausal clinic and screening mammogram were not eligible to be controls.

Outcome assessment

The authors studied the proportion, type, and duration of HRT used among cases and controls. Hormone replacement therapy was defined as hormones prescribed for peri- or post-menopausal women intended to prevent menopausal symptoms and health promotion, but not those prescribed for treating abnormal bleeding (DUB). Other factors of interest

were collected for analysis, for example, age, habitat, race, education, marital status, childbirth, breast-feeding, menstruation cycle, hormonal use and familial history of cancer or breast cancer.

Sample size calculations

Epi Info 6.04® statistical program was used to calculate the sample size needed. A total of 1,138 persons (569 persons each group) were calculated from the expectation of 2.0 per cent HRT use in the control group, an odds ratio of 2.5, α=0.05 (confidence level = 95%), β=0.30 (power = 70%), and case: control ratio equal 1:1.

Data collections and analysis

The data of breast cancer patients were interviewed by surgeons at the time of admission and processed in the database from 1983 to 1996. The control group was interviewed and information was recorded by trained nurse-assistants, medical students or physicians.

The data were validated and double entries using Epi Info 6.04®. Analysis was performed by SPSS 7.5® statistical program. In univariate analysis, chi-square test was used for categorical variables and *t*-test was used for continuous variables. Factors which were found to increase the risk of breast cancer (p-value<0.05) from univariate analysis would be included in the forward stepwise logistic regression model for multivariate analysis.

RESULTS

Of 1913 patients in the Siriraj Hospital Breast Cancer Database (1983-1996), 623 patients (33%) were selected to be cases. Breast cancer staging of the cases is presented in Table 1. The control-group included 679 volunteers who visited Siriraj Hospital from May to December 1999 as presented in Table 2. The proportion of case: control was close to 1:1 (623:679) in this 1302 study-population.

Table 1. Staging of 623 breast cancer patients in the case-group selected from Siriraj Hospital breast cancer database (1983-1996).

Pathological staging	N*	%
0	3	0.5
1	90	15.5
2	409	70.6
3	69	11.9
4	8	1.4
Total	579	100

* (missing 44 patients = 7%)

The characteristics between breast cancer patients and controls were compared and presented in Table 3. The authors found 4.5 per cent (58/1,302) of the total study population had used hormone replacement therapy, 3.2 per cent (20/623) in cases and 5.6 per cent (38/679) in controls. HRT was found to be associated with breast cancer (95% CI = 0.31-1.0, p-value=0.036) in univariate analysis. Other factors, such as: age, age at menopause, number of children, habitat, education, contraceptive pills and familial history of breast cancer, were also found, in univariate analysis, to have an association with breast cancer (p-value<0.05).

The factors of those found to have an association with breast cancer from the univariate analysis were put into a forward stepwise logistic regression model for the multivariate analysis. As presented in Table 4, there was no association between HRT use and the risk of having breast cancer (adjusted odds ratio (OR) = 0.61, 95% CI = 0.31-1.20, p-value=

Table 2. Source of women in the control-group who visited Siriraj Hospital from May to December 1999.

Source	N	%
Health check for the elderly project*	538	79.2
Elderly clinics and elderly health groups	53	7.8
Patients who visited OPD with other health problems	88	13.0
Total	679	100

* Health check for the elderly project to cerebrate the 72nd Anniversary of His Majesty the King.

Table 3. Comparison of characteristics between breast cancer patients and controls.

Variables	Case			Control			95% CI	P-value
	N	Mean	SD	N	Mean	SD		
Age	623	60.7	7.9	679	64.3	6.8	-4.4, -2.8	0.000*
Age at menarche	527	15.1	1.9	676	15.4	2.1	-0.5, -3.0	0.467
Age at natural menopause	623	48.8	4.0	671	49.3	4.5	-0.9, 2.2	0.029*
Number of children (included stillbirth)	487	4.4	2.6	481	4.2	2.4	-0.2, 0.5	0.021*
Age at birth of first child	480	25.2	5.6	550	24.7	5.3	-0.2, 1.2	0.202
Age at birth of last child	477	33.5	6.2	548	33.3	6.1	-0.5, 1.0	0.248

	N	%	N	%		
Habitat					1.4, 2.2	0.000*
Bangkok	324	52.0	442	65.2		
Others	299	48.0	236	34.8		
Race					0.8, 1.4	0.849
Thai	527	84.6	571	85.0		
Chinese & Thai-Chinese	96	15.4	101	15.0		
Education						0.021*+
No	127	20.5	99	14.7		
Primary school	332	53.5	396	58.8		
Secondary school or higher	162	26.1	178	26.4		
Marital status						0.135+
Single	87	14.0	97	14.3		
Married before 30 yrs	462	74.3	524	77.3		
Married after 30 yrs	73	11.7	57	8.4		
Contraceptive pills					0.4, 0.8	0.000*
Never	534	85.7	522	77.0		
Yes	89	14.3	156	23.0		
HRT					0.3, 1.0	0.036*
Never	603	96.8	641	94.4		
Yes	20	3.2	38	5.6		
Sex of first child					0.8, 1.3	0.821
Male	243	50.2	279	50.9		
Female	241	49.8	269	49.1		
Breast feeding					0.8, 1.3	0.962
No	169	27.1	185	27.2		
Yes	454	72.9	494	72.8		
Number of breast feeding (≥2 wks)						0.161+
Never	169	27.1	185	27.2		
1	57	9.1	51	7.5		
2	68	10.9	97	14.3		
3	69	11.1	90	13.3		
4 or higher	260	41.7	256	37.7		
Breast fed predominately					0.6, 1.4	0.646
Unequal	60	13.2	59	12.2		
Equal	394	86.8	424	87.8		
Family history of breast cancer						0.000*+
No	591	95.9	619	91.2		
First degree relative	21	3.4	31	4.6		
Second degree relative	4	0.6	29	4.3		

* p-value<0.05

\+ Chi-square for trends

Table 4. Factors associated with the risk of breast cancer from stepwise multivariate logistic regression model.

Variables	Adjusted odds ratio	95% CI	P-value
HRT	0.61	0.31, 1.20	0.151
Age	0.90	0.88, 0.92	0.000
Habitat	1.45	1.09, 1.92	0.011
Education (secondary school)	0.37	0.25, 0.55	0.000
Education (>secondary school)	0.47	0.30, 0.74	0.001
Contraceptive pills	0.36	0.25, 0.51	0.000
Family history of breast cancer (1st degree relatives)	0.69	0.33, 1.47	0.337
Family history of breast cancer (2nd degree relatives)	0.24	0.08, 0.75	0.014

HRT = hormone replacement therapy

0.151). Other potential factors, for instance, increasing age (OR = 0.90, 95% CI = 0.88-0.92), higher education level (OR = 0.47, 95% CI = 0.30-0.74), history of taking contraceptive pills (OR = 0.36, 95% CI = 0.25-0.51) and positive familial history of breast cancer in second degree relatives (OR = 0.24, 95% CI = 0.08-0.75) were found to decrease the risk of breast cancer, while those living outside Bangkok (OR = 1.45, 95% CI = 1.09-1.92) had an increased risk of breast cancer. Age at natural menopause and number of children were found to have no association with breast cancer from the multivariate analysis (p-value=0.070 and 0.081 respectively).

DISCUSSIONS

There was no association found between HRT use and risk of having breast cancer in this study but a slightly decreased risk (not statistically significant) was observed in the non-HRT group. The risk of breast cancer in HRT users from previous studies varied depending on the method of study; from meta-analysis data, some studies found an increased risk but others found a decreased risk (12,13). Among studies designed in case-control setting, Steinberg KK, et al noticed that studies which selected a hospital based control had a tendency of no increase risk of breast cancer, while studies which selected a population based control tended to find association between HRT and breast cancer(14).

In the present study, association between HRT and breast cancer that was shown in univariate analysis was lost after multivariate analysis. This may be the effect of potential confounder or the interaction between factors, as there was a wide range of differences between cases and controls among the other factors such as age, habitat, education level, contraceptive and familial history of cancer. Although the authors tried to minimize the difference between case and control by limiting the scope of control selection, for instance, selecting only women aged 50 years or older, excluded hysterectomized women and did not include women from some special clinics which tended to prescribe HRT, variation of factors between case and control still existed.

The finding that post-menopausal women who had taken HRT did not have an increased risk of breast cancer and were probably protected from breast cancer (odds = 0.61) may be effected by the time frame of data collection. Not only was data of cases and controls collected in a different period of time, data in the case group were also collected from a period of many years (length bias)(15). The authors' cases were retrieved from the database which included patients who visited Siriraj Hospital 5-18 years ago when HRT use was uncommon, therefore, the proportion of HRT use in this group was only 3.2 per cent. Widespread use of HRT has only begun recently, as can be shown from the data that half of patients who used HRT were found in the latest 4 years (1993 to 1996). HRT use was introduced and became common in Thailand during the last decade, so the control group who gave their information in the year 1999 would have a higher chance of taking HRT. Furthermore, half of the HRT-users in the control group were younger than the age of 60 while the mean age of the controls was 64.

The time frame of data collection is one of the limitations of this study due to the limited budget and the ability to include breast cancer patients. The authors could not get enough breast cancer patients

for the study during the period of one year. A multi-institute setting would be needed to collect the data of cases and controls at the same period of time, which would require a larger budget.

Another possible explanation for this negative finding might be the bias in the control group. Women who used her HRT in the control-group might have more health concern than women in the case-group and seek many health providers to assure their health status.

Subgroup analysis could not be done to distinguish the type and duration of HRT used because of the small amount of HRT used and most of the users could not remember the product name. The majority of drugs used were estrogen while only around 15 per cent used progestrogen or a combination drug.

Other factors related to breast cancer such as contraceptives, habitat, education level and familial history of breast cancer had a trend of decreased risk in the present study. The results were different from other reports that women who have a familial history of breast cancer, higher education level and living in a big city have a higher risk of breast cancer[8-10]. This finding may be interpreted as a limitation of the study, or that breast cancer patients in Thailand have a different genetic background and characteristics which would be interesting for further study.

From the present study, HRT use was only 4.5 per cent that is not the same as Western countries but has had an increasing trend over the last decade. Information from this study might benefit consumer protection and might be a reference for further study in Thailand.

SUMMARY

There was no association between HRT use in post-menopausal women and the risk of breast cancer. However, using HRT should be closely monitored by medical specialist. Further study may be needed to establish the effect between HRT and breast cancer.

ACKNOWLEDGEMENT

The authors wish to thank Ms. Chamiporn Satiraleela and the nursing team who helped to organize and collect data in the control group. We also wish to thank FDA Thailand who supported the grant for this study.

(Received for publication on November 18, 2001)

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ความเสี่ยงต่อการเกิดมะเร็งเต้านมในหญิงวัยหมดประจำเดือนที่ใช้การให้ฮอร์โมนเสริม

อดุลย์ รัตนวิจิตราศิลป์, พ.บ., กริช โพธิสุวรรณ, พ.บ.*, วรมินทร์ เหรียญสุวรรณ, พ.บ.*, สุพรชัย กองพัฒนากูล, พ.บ.**, สมศรี รัตนวิจิตราศิลป์, พ.บ.****

ทำการศึกษา แบบ Case-control เพื่อหาความสัมพันธ์ระหว่างการใช้ฮอร์โมนเสริม (HRT) กับ การเกิดมะเร็งเต้านมในหญิงวัยหมดประจำเดือน โดยเปรียบเทียบสัดส่วนการใช้ HRT ในกลุ่มผู้ป่วยมะเร็งเต้านม (Case) อายุมากกว่าหรือเท่ากับ 50 ปี และ หมดประจำเดือนตามธรรมชาติ 623 ราย จากฐานข้อมูลผู้ป่วยมะเร็งเต้านมของ โรงพยาบาลศิริราช (พ.ศ. 2526-2539) เทียบกับ กลุ่มเปรียบเทียบ (Control) 679 ราย ซึ่งสำรวจจากผู้มาใช้บริการที่ โรงพยาบาลศิริราช ด้วยเหตุอื่น เช่น ตรวจสุขภาพ ชมรมผู้สูงอายุ ฯลฯ โดยแพทย์จะตรวจร่างกายกลุ่มเปรียบเทียบทุกคน หากพบก้อน หรือลักษณะที่สงสัยว่าจะเป็นมะเร็งจะคัดออกจากการศึกษา เก็บข้อมูลส่วนตัว ปัจจัยเสี่ยง และ การใช้ฮอร์โมนเสริม (HRT)

พบผู้ใช้ฮอร์โมนเสริม 58 ราย จากประชากรศึกษา 1,302 ราย คิดเป็นร้อยละ 4.5 โดยเป็นกลุ่มมะเร็งเต้านม ร้อยละ 3.2 (20/623) และ กลุ่มเปรียบเทียบ ร้อยละ 5.6 (38/679) เมื่อศึกษาแบบ univariate พบว่า อายุ อายุเมื่อหมดประจำเดือน จำนวนบุตร ถิ่นที่อยู่อาศัย การศึกษา การใช้ยาคุมกำเนิด ประวัติมะเร็งเต้านมในครอบครัว และ การใช้ฮอร์โมนเสริม มีส่วนสัมพันธ์กับมะเร็งเต้านม (p-value < 0.05) แต่เมื่อวิเคราะห์แบบ multivariate ไม่พบความสัมพันธ์ระหว่างมะเร็งเต้านม กับ การใช้ฮอร์โมนเสริม (adjusted odds ratio (OR) = 0.61, 95% CI = 0.31-1.20) ส่วนปัจจัยอื่น ๆ พบว่า อายุที่เพิ่มขึ้น การศึกษาระดับสูง การใช้ยาคุมกำเนิดและการมีประวัติมะเร็งเต้านมในครอบครัวในกลุ่มญาติไม่ใกล้ชิด ลดความเสี่ยงต่อการเป็นมะเร็งเต้านม ขณะที่ผู้ที่มีถิ่นที่อยู่อาศัยอยู่นอกกรุงเทพ ฯ เพิ่มความเสี่ยง

การศึกษานี้ ไม่พบความสัมพันธ์ระหว่างการใช้ Hormone Replacement Therapy (HRT) ในหญิงวัยหมดประจำเดือน กับการเกิดมะเร็งเต้านม

คำสำคัญ : มะเร็งเต้านม, วัยหมดประจำเดือน, ฮอร์โมนเสริม, ความเสี่ยง

อดุลย์ รัตนวิจิตราศิลป์, กริช โพธิสุวรรณ, วรมินทร์ เหรียญสุวรรณ, สุพรชัย กองพัฒนากูล, สมศรี รัตนวิจิตราศิลป์
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 583-589

* ภาควิชาศัลยศาสตร์,
** ภาควิชาเภสัชวิทยา,
*** สถานส่งเสริมการวิจัย, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700