

RESEARCH ARTICLE

Relationship between Breast Cancer and Oral Contraceptive Use among Thai Premenopausal Women: a Case-Control Study**Wisit Chaveepojnkamjorn^{1*}, Natchaporn Pichainarong², Rungsinoppadol Thotong³, Pratana Sativipawee⁴, Supachai Pitikultang⁵****Abstract**

Background: Breast cancer (BC) is an important issue both in medicine and public health as it is the leading malignancy with high incidence and mortality among women worldwide. The objective of this research was to determine the associations of BC with oral contraceptive (OC) use among Thai premenopausal women (TPW). **Materials and Methods:** A case-control study was conducted among TPW attending the National Cancer Institute, with 257 cases and 257 controls in 2013-2014. Cases and controls were matched by age (± 5 years), residential area and duration of attendance. Data were collected with a questionnaire that comprised 2 sections: part 1 socio-demographic characteristics, and part 2 health risk behavior and reproductive factors. The obtained data were analyzed using descriptive and analytic statistics with a computerized statistical package. **Results:** The study participants were mainly 40-44 years old (60 %) with an average age of 39 years. The major BC type was invasive ductal carcinoma (91.8%). Multiple unconditional logistic regression analysis, controlling for possible confounding factors, revealed that TPW with OC use increased the risk of BC by a factor of over 3 times (OR_{adj}=3.39, 95%CI=1.99-5.75). In addition, the greater the duration of OC, the greater the risk (OR_{adj} 6-10 yrs=3.91, 95%CI = 1.99-7.64, OR_{adj} >10 yrs=4.23, 95%CI = 2.05-8.71). **Conclusions:** From our findings, a surveillance system of cancer risk with OC use should be conducted, accompanied by an exercise promotion campaign among risk groups, providing information and counseling for physical exercise and physical activities, weight control and basic adjustment for a healthy lifestyle to reduce BC.

Keywords: Breast cancer- oral contraceptive use, Thai premenopausal women

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Introduction

Cancers are the top leading cause of death. According to estimates of The World Health Organization (WHO), approximately 8.2 million cancer deaths occurred in 2014 and mortality mainly occurred in developing countries. Of these, 3.4 million are male and female 3.3 million. Almost 70 % of all cancers was seen in underdeveloped and developing countries (Siegel et al., 2015). At present, it is well established that BC is the most commonly diagnosed invasive cancer and the leading cause of cancer death among women worldwide including in Thailand (Siegel et al., 2015; National Cancer Control Committee, 2013; Bureau of Policy and Strategies, 2011; Bureau of Policy and Strategies, 2015). Causes of being BC are likely to be multifactorial. Some studies found that OC use is one of the risk factors of BC (Soroush et al., 2016; Rosenberg et al., 2009). The association between OC use and BC risk has been examined in numerous studies, mainly in western countries. In Thailand, there are quite very few studies of this association among premenopausal women.

The present study was carried out to assess the association between OC use and BC occurrence among TPW.

Materials and Methods*Study Design, Sample Size and Sampling Technique*

A hospital based case-control study (1:1) was performed at the National Cancer Institute in Bangkok during November 2013 - December 2014 to determine the effect of OC use and BC risk among TPW. A total of 257 BC cases and 257 controls were included in the study. The cases were newly diagnosed with breast cancer by pathologists. The controls were healthy TPW who had annual health check-up. Cases and controls were matched (1:1) by age (± 5 years), residential area and duration of attending. Of the 514 women were both premenopausal and aged <45 years at the time of study. Cases and controls used the same questionnaire to obtain data collection.

The sample size was calculated by the formula (Lwanga and Lemeshows, 1991). Where P_o = proportion of exposure in controls = 0.32 (Umpan, 2004); P_1 = proportion of

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exposure in cases = 0.68 (Umpan, 2004); $Z\alpha/2 = 1.96$ at $\alpha = 0.05$; $Z\beta = 0.84$ at $\beta = 0.20$; and $P = 0.5$. The calculated sample size in each group was at least 256.

Tool and Measurements

Data collection was obtained by interviewing the study subjects by researcher and trained research assistants. The questionnaire comprised socio-demographic factors, health risk behaviors, reproductive factors, obesity and cancer status. While BC information was collected by laboratory and pathological results, namely, TNM classification, stage of disease, hormone receptor test, and date of diagnosis with BC.

Variable definitions

Premenopausal women were defined as those still having menstrual cycles at the time of study.

Ethical Considerations

The study was reviewed and approved by the Ethics Committee for research of National Cancer Institute, Ministry of Public Health (148/2556) and the Ethics Committee for Research in Human Subjects of the Faculty of Public Health, Mahidol University (Ref No. MuPH 2014-090) and agreed with the Helsinki declaration. All participants participated in this study are on a voluntary basis. Informed consent to participate in the study was obtained from participants after providing sufficient information. Information was collected by a self-administered questionnaire with the help and supervision of research assistants. Confidentiality was well kept throughout the study using anonymous technique (respondents were identified by code numbers to ensure confidentiality and the results were analyzed as a whole).

Statistical Analyses

The data were analyzed with SPSS version 18 (IBM, NY, USA). Categorical variables were given as a frequency and percentage, crude odds ratio, 95 % Confidence Interval (CI) of OR and p-value. The numerical variables were expressed as mean, minimum and maximum, and standard deviation (SD). Univariate analysis was performed using the chi-square test to differentiate proportional exposures between BC patents and controls for categorical variables. Adjusted odds ratio and the 95 % CI of OR were calculated from multiple unconditional logistic regression to examine associations between BC occurrence and BMI, adjusted for potential confounding factors of reproductive factors and health risk behaviors. A p-value of < 0.05 was considered to be statistically significant.

Results

Demographic Characteristics of Cases and Controls

A total of 514 TPW participated in the case-control study (1:1). The average age of subjects was 39 years. Table 1 outlines the socio-demographic characteristics of them. To summarize majority of them were aged 40-44 years (59.9%, 61.1%), married (61.8%, 60.7%), higher education (39.7%, 51.4%), buddhism (96.5%, 96.1%), living in central region (68.5%), office employee (35.8%,

Table 1. General Characteristics of Cases and Controls

Characteristics	Cases No.	%	Controls No.	%	p value ^a
Age gr. (yrs)					0.981
≤ 29	10	3.9	11	4.3	
30-34	30	11.7	28	10.9	
35-39	63	24.5	61	23.7	
40-44	154	59.9	157	61.1	
Mean (SD)	39.20 (4.39)		39.30 (4.41)		
Min-Max	25-44		25-44		
Marital status					0.07
Single	68	26.5	84	32.7	
Married	159	61.8	156	60.7	
Widowed/ Divorced	30	11.7	17	6.6	
Education					0.068
No formal education	10	3.9	8	3.1	
Primary school	67	26.1	52	20.2	
Secondary school	78	30.3	65	25.3	
Higher education	102	39.7	132	51.4	
Religion					0.689
Buddhism	248	96.5	247	96.1	
Islam	7	2.7	6	2.3	
Christianity	2	0.8	4	1.6	
Residence					1
North	1	0.4	1	0.4	
Northeast	11	4.3	11	4.3	
Central	176	68.5	176	68.5	
East	16	6.2	16	6.2	
West	48	18.7	48	18.7	
South	5	1.9	5	1.9	
Occupation					0.668
Office employee	92	35.8	87	33.8	
Entrepreneur	77	30	85	33.1	
Government officer	73	28.4	75	29.2	
Agriculture	15	5.8	10	3.9	
Monthly family income (baht)					0.066
< 10,000	38	14.8	34	13.2	
10,000-15,000	52	20.2	48	18.7	
15,001-30,000	138	53.7	124	48.2	
>30,000	29	11.3	51	19.9	
Mean(SD)	22,740.08 (9,311.92)		24,174.32 (13,541.38)		
Min-Max	7,000- 70,000		7,800- 95,000		

^a, chi-square test

33.8%), and had monthly family income of 15,000-30,000 baht (53.7%, 48.2%). There was no significant difference regarding demographics among cases and controls (p>0.05).

Table 2. Crude Analysis of Characteristics associated with BC among TPW

Characteristics	Cases No.	%	Controls No.	%	ORc	95%CI	p-value ^a
Family history of BC							
No	211	82.1	249	96.9	1.00		
Yes	46	17.9	8	3.1	6.79	3.13-14.69	< 0.001*
History of benign breast tumor							
No	209	81.3	235	91.3	1.00		
Yes	48	18.7	22	8.6	2.45	1.43-4.20	0.001*
Age at menarche (yrs)							
≥14	83	32.3	140	54.5	1.00		
<14	174	67.7	117	45.5	2.51	1.75-3.59	< 0.001*
Parity							
No	193	75.1	172	66.9	1.00		
Yes	64	24.9	85	33.1	0.67	0.45-0.99	0.041*
Miscarriage							
No	186	72.4	214	83.3	1.00		
Yes	71	27.6	43	16.7	1.90	1.21-2.98	0.003*
OC use							
No	90	35	162	63.0	1.00		
Yes	167	65	95	37.0	3.16	2.21-4.54	< 0.001*
Duration of OC use (yrs)							
0	90	35	162	63.0	1.00		
1-5	42	16.3	44	17.1	1.72	1.01-2.90	0.031*
6-10	70	27.2	30	11.7	4.2	2.48-7.17	< 0.001*
>10	55	21.5	21	8.2	4.71	2.59-8.72	< 0.001*
Active smoking							
No	248	96.5	251	97.7	1.00		
Yes	9	3.5	6	2.3	1.52	0.53-4.33	0.432
Passive smoking							
No	153	59.5	198	77.1	1.00		
Yes	104	40.5	59	22.9	2.28	1.53-3.41	< 0.001*
Alcohol consumption							
No	251	97.7	252	98.1	1.00		
Yes	6	2.3	5	1.9	1.20	0.32-4.61	0.761
Multivitamin use							
No	227	88.3	168	65.4	1		
Yes	30	11.7	89	34.6	0.25	0.15-0.40	< 0.001*
Body mass index (kg/m ²)							
18.5-22.9	89	34.7	122	47.4	1.00		
23.0-24.9	44	17.1	54	21.0	1.12	0.67-1.86	0.629
25.0-29.9	88	34.2	41	16.0	2.94	1.81-4.79	< 0.001*
≥30.0	26	10.1	10	3.9	3.56	1.55-8.38	< 0.001*
<18.5	10	3.9	30	11.7	0.46	0.20-1.05	0.056

^a, chi-square test, ORc= crude odds ratio, CI= confidence interval; *, significant at p-value <0.05.

BC and Risk Factors

Using a univariate analysis, we found that risk factors of developing BC among TPW were family history of BC, history of benign breast tumor, younger age at menarche, parity, miscarriage, OC use, passive smoking, multivitamin use and BMI (p<0.05) as shown in Table 2. Using a multiple unconditional logistic regression analysis, OC use showed the association with BC

occurrence after controlling for possible confounding factors (family history of BC, history of benign breast tumor, younger age at menarche, parity, miscarriage, BMI, passive smoking, and multivitamin use). Risk of developing BC with OC use was 3.39 and times (OR_{adj} = 3.39, 95%CI=1.99-5.75). When considering the duration of OC use, the more exposed, the more being BC (OR_{adj} 6-10 yrs=3.91, 95%CI = 1.99-7.64, OR_{adj} >10 yrs=4.23,

Table 3. Multivariable Logistic Regression Analysis of OC use associated with BC among TPW

Variables	OR _c	95%CI	OR _{adj}	95%CI	p-value
OC use					
No	1		1		
Yes	3.16	2.21-4.54	3.39	1.99-5.75	<0.001*
Duration of OC use (yrs)					
0	1		1		
1-5	1.72	1.01-2.90	1.72	0.90-3.25	0.099
6-10	4.2	2.48-7.17	3.91	1.99-7.64	<0.001*
>10	4.71	2.59-8.72	4.23	2.05-8.71	<0.001*

OR_c, crude OR; OR_{adj}, adjusted OR for family history of BC; history of benign breast tumor, age at menarche, parity, miscarriage, passive smoking, multivitamin use and BMI; *, significant at p-value <0.05

95%CI = 2.05-8.71) as shown in Table 3.

BC Patients' Characteristics

Cases were newly patients with BC diagnosed by pathological confirmation and laboratory testing during November 2013-December 2014. Majority of them were 55-64 kg (40.5%) and 150-159 cm (65.7%). Focusing on body size, 60.7% showed obesity and overweight. Location of BC, mostly in both sides (52.2%). Most of study cases were IDC-NOS (91.8%), stage II (45.5%). For OC use group, duration for OC use, mostly 6-10 yr. (41.9%).

Discussion

Study participants were the TPW, mostly aged 40-44 years (60%). Socio-demographic characteristics of cases and controls were quite alike. When controlled by health risk behaviors and reproductive factors, found that TPW with OC use was being BC risks. Our findings indicated that women with OC use were about 3 times risk to develop BC. It was consistent with the previous studies (Soroush et al., 2016; Rosenberg et al., 2009; Nyante et al., 2008; Kahlenborn et al., 2006; Newcomer et al., 2003; Hemminki et al., 2002; Grabrick et al., 2000), meanwhile some studies showed the contrary results (Haile et al., 2006; Silvera et al., 2005; Mine et al., 2005; Jernstrom et al., 2005; Tessaro et al., 2001; Van Hoften et al., 2000).

The reason to support the association owing to estrogen hormone in OC pills, therefore it will have a cohesion with specific receptor on cancer cell's surface and then it will send the biochemical signals and activate cell multiplication (Howlader et al., 2016). The association had no evidence in OC use with only progesterone (McNaught et al., 2006). In addition, the present studies revealed the risk of BC had increased according to duration of OC use and it's consistent with some studies (Howlader et al., 2016; Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Therefore, birth control with BC patients should be namely, contraceptive pills with progesterone, depot medroxyprogesterone acetate injection, intrauterine device (IUD) with progesterone, and so on (Kabos and Borges, 2011). In addition, breast

self examination is very necessary, so women should be done correctly (Smith et al., 2003). For women ≥ 40 years should be checked up with mammogram annually (Smith et al., 2003; American College of Radiology, 2013). There are a lot of tools for BC risk evaluation, such as the Gail Model, the Claus Model, the Tyree-Cuzick Model and the BRCAPRO model (Santen et al., 2007; Hollingsworth et al., 2004). For Thais, campaign of women aged ≥ 20 years to examine by themselves, they should be aware of advantages and limitations of this technique, support breast feeding after give birth 6 months, reduce alcohol consumption and reduce obesity (National Cancer Control Committee, 2013). Therefore, the surveillance of cancer risk and contraceptive use is the crucial measure to reduce BC risks.

Advantages and limitation of the Study

There are some advantages of this case-control study. First, the National Cancer Institute is the specialized hospital for cancer patients. Second, they are easily identified, and provide sufficient numbers. Finally, cases are newly BC patients diagnosed and confirmed by pathologists, which lead to the reduction in classification bias. Some limitations of this study should be noted. First, the study was a hospital based case-control study, therefore, the representative of target population couldn't be mentioned. Second, it was very difficult to select the suitable controls. However, we matched cases and controls by age, residence and duration of attending. In summary, it should be the surveillance system of cancer risks and OC use and campaign of cancer prevention such as proper exercise, healthy diet, weight control and basic methods for health lifestyle among risk groups (National Cancer Control Committee, 2013), it will minimize and reduce risks of developing BC.

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