Effect of Oral Contraceptives on Risk of Cervical Cancer

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Objective: *To assess the risk of oral contraceptives on the occurrence of cervical cancer.*
Material and Method: *A hospital-based case-control study was conducted. Sixty women patients with histologically confirmed invasive cervical cancer and 180 healthy women as the control group who attended the King Chulalongkorn Memorial Hospital, Bangkok, Thailand were recruited. Information about the use of oral contraceptives and other cervical cancer risk factors were obtained from personal interviews. The risk factors were evaluated by using odds ratio (OR).*
Results: *60 women with invasive cervical cancer and 180 healthy controls were interviewed by the investigator.s Compared with non-users, patients who had ever used or currently used oral contraceptive had an increased risk of cervical cancer (OR 1.45; 95% CI 0.79-2.64). However, the risk was not statistically significant. Considering the duration of use, patients who had used oral contraceptives for 3 years or less did not have an increased risk of cervical cancer (OR 0.78; 95% CI 0.39-1.77). Nevertheless, the odds ratio of oral contraceptive pill use for more than 3 years was 2.57 (95% CI 1.22-5.49) which was statistically significant.*
Conclusion: *Long-term use of oral contraceptive might be a cofactor that increases the risk of cervical carcinoma. Further investigations should be conducted to confirm this risk. However, Pap smear has to be done routinely in long-term oral pill users.*

Keywords: *Oral contraceptives, Cervical cancer*

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Since the use of exogenous steroid hormones became more widespread in the 1960s, concern has been raised about the safety of such treatment in patients with neoplastic diseases. Association between use of oral contraceptives and the occurrence of cervical cancer have been raised in many epidemiological studies[1]. Human papillomavirus (HPV) has an important role in causation of cervical cancer, and is probably a prerequisite for development of the disease[2,3]. Exogenous female hormones such as those used in combined oral contraceptives have been proposed as cofactors[4].

The incidence of cervical cancer in Thailand in 2004 was 20.9 per 100,000 population or 6,583 new cases per year and 3,791 deaths per year (50%)[5].

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The objective of the present study was to evaluate the association between oral contraceptives and cervical cancer.

Between July 2006 - February 2007, a case-control, hospital-based study of association between invasive cervical cancer and the use of oral pills at King Chulalongkorn Memorial Hospital (KCMH) was performed.

Material and Method

Data collection

The present study included women between the ages of 30 and 70 years old who were diagnosed with invasive cervical cancer (either squamous cell carcinoma or adenocarcinoma) at KCMH. Institutional review boards at KCMH approved the present study, and written informed consent was obtained from all subjects. All eligible cases had histologically confirmed disease and had agreed to participate in the present

study. Hospital-based controls were the female patients who came to the hospital for other problems that were not associated with anogenital tract cancer.

All consenting and eligible participants completed personal risk factor interviews. To minimize the effect of diagnosis on exposures and to exclude a recent Pap smear test that led to the diagnosis of cervical cancer, case-group reported exposures that occurred before a reference date, which was 12 months before their diagnosis. Controls were assigned the same range reference date. A calendar approach captured recency (time since last use), current use, and duration of OC use which related to the reference date.

The sample size was calculated by the formula:

$$n/group = \frac{\{Z_{\alpha/2}2PQ + Z_{\beta}\sqrt{(P_1Q_1+P_0Q_0)}\}^2}{(P_1-P_0)^2}$$

$\alpha = 0.05$ $\beta = 0.20$

$Z_{\alpha/2} = 1.96$ $Z_{\beta} = 0.84$

P_0 = Case at risk = 28.4% = 0.284

R = 2.5 (from reviewed of literature)

$$P_1 = \frac{P_0R}{1+P_0(R-1)}$$

$$P = \frac{P_1+P_0}{2}$$

Q = 1-P

The proportion of case:control = 1:3
If case:control is not 1:1, further calculation as below

$$N = \frac{c + 1 \times n_e}{2c}$$

n_e = case if 1:1

c = proportion of case:control = 3

Questionnaire

Women were interviewed face-to-face by trained staff (first investigator, obs-gyn resident) that used a structured questionnaire. Proxy interviews were not accepted. The authors tabulated information about life-long use of oral contraceptives from a lifetime calendar. The age at starting and stopping point was recorded. From these tables, the authors computed ever use, onset of use, duration of use and time since last use.

Statistical analysis

Summary odds-ratio and their corresponding 95% confidence interval (95% CI) were calculated. Mean, standard deviation and percentage were used for numerical data. Student t-test was used for comparison between groups.

Results

Sixty patients with invasive cervical cancer and 180 controls were included in the present study. Seventy five percent of cases were squamous cell carcinoma, 21.7% were adenocarcinoma and 3.3% were adenosquamous carcinoma. Mean age of women in the present study were 49.95 years in the case-group and 50.78 years in the control-group. Gravidity and parity had statistically significant difference between groups (3.22 ± 1.56 versus 1.9 ± 1.15; - $p < 0.05$ and 2.51 ± 1.51 versus 1.69 ± 1.1; $p < 0.05$ respectively). Fifty-five (91.7%) cases and 122 (67.8%) controls had graduated from primary school to college. Twenty-three (38.3%) cases and 11 (6.1%) controls had never had a Papanicolaou smear. Fourteen (23.3%) patients compared with 75 (31.7%) controls had five times or more of Papanicolaou smears. Thirty-eight (91.7%) patients and 98 (54.4%) controls had ever used or currently use oral contraceptives (Table 1, 2).

Women who had ever used or currently use oral contraceptives were almost 1.5 times more likely to develop cervical cancer than controls (OR 1.45; 95% CI 0.79,2.64) but was not statistically significant.

Average duration of use of oral contraceptives among users was 98 months in the case-group and 26.65 months in the control-group. Considering the duration of oral pill use, it was shown that there was no increase in risk of cervical neoplasia for duration of oral contraceptive use for up to 3 years (OR 0.78; 95% CI 0.33,1.77). However, the use of oral contraceptives for longer than 3 years was significantly associated with cervical cancer (OR 2.57; 95% CI 1.22, 5.49). Women who had used oral contraceptives for longer than 3 years had 2.5 times increase in risk of developing invasive cervical cancer (Table 3).

The mean age on set of oral pill use in the case group was 14.1 years and control group was 16.08 years. There were not statistically significantly differently in both groups ($p > 0.05$). Women who had started oral contraceptives before age 20 were almost 12 times more likely to develop cervical cancer than those who started after 20 years old (OR 11.9; 95% CI 4.37-35.09). The detail is demonstrated in Table 3.

However, if it was compared with never users, analysis unadjusted for duration of use was shown that women starting oral contraceptives at age 20 or before were eight times more likely to develop cervical

Table 1. Characteristics of cases and controls

Characteristics	Case (n = 60)	Control (n = 180)
Age (year)	49.95 ± 7.74	50.78 ± 9.19
BMI (kg/m^2)	25.05 ± 4.99	23.71 ± 3.94
Gravidity*	3.22 ± 1.56	1.90 ± 1.15
Parity*	2.51 ± 1.51	1.69 ± 1.1
Age at first pregnancy (year)	22.38 ± 7.11	22.35 ± 9.7
Duration of OCs use (month)	56.98 ± 77.68	26.65 ± 46.06

Data were presented as mean ± SD
* Significance different between groups ($p < 0.05$)

Table 2. Risk factors of cervical cancer

Risk factor	Cases (n = 60) (%)	Control (n = 180) (%)	OR (95% CI)
Age			
< 40 years	5	76	8.04 (3.07, 21.0)
≥ 40 years	55	104	
Income/month (Baht)			
10000 and below	42 (76.0)	113 (62.8)	1.38 (0.74, 2.6)
10001 and above	18	67	
History of pregnancy			
Yes	58 (96.7)	159 (88.3)	3.83 (0.87, 16.8)
No	2	21	
Age at 1st pregnancy			
≤ 20 years	28 (46.7)	31 (17.2)	3.85 (2.02, 7.36)
> 20 years	30	128	
Prior Pap smear			
No	23 (38.3)	11 (6.1)	0.15 (0.04, 0.23)
Yes	37	169	
Last Pap smear			
≥ 2 years	6 (16.2)	126 (74.6)	15.14 (5.63, 46.72)
< 2 years	31	43	
OCs use			
Ever/current	38 (91.7)	98 (54.4)	1.45 (0.79, 2.64)
Never	22	82	
Duration of use (if duration > 0)	n = 38	n = 98	
More than 3 years	25 (65.7)	36 (36.7)	3.31 (1.5, 7.3)
3 years and less	13	62	
Onset of OCs			
> 20 years	17 (44.7)	89 (90.8)	11.90 (4.37, 35.09)
≤ 20 years	21	9	
Time since last use			
≤ 10 years	14 (36.8)	66 (67.3)	3.50 (1.51, 8.39)
> 10 years	24	32	
Smoking			
Ever/current	4 (6.7)	3 (1.7)	4.21 (0.9, 19.4)
Never	56	177	
Family history of cancer			
Yes	13 (2.7)	20 (11.1)	2.21 (1.02, 4.78)
No	47	160	

Table 3. OCs use among cases and controls

	Case (n = 60)	Control (n = 180)	OR (95% CI)
Never used OCs	22	82	1
Ever or current use	38	98	1.45 (0.79-2.64)
Duration of use			
3 years or less	13	62	0.78 (0.33-1.77)
More than 3 years	25	36	2.57 (1.22-5.49)
Onset OCs use			
> 20 years	17	89	0.71 (0.33-1.52)
≤ 20 years	21	9	8.52 (3.22-24.39)
Time since last use			
≤ 10 years	14	66	0.79 (0.35-1.76)
> 10 years	24	32	2.78 (1.26-6.02)

cancer than controls. Moreover, the risk was not significantly increased in those who first used oral contraceptives older than 20 years (Table 3).

Women who had used oral contraceptives within the past 10 years were three times more likely to develop cervical cancer than those who had used oral contraceptives for more than 10 years (OR 3.5; 95% CI 1.51-8.39).

Prior Pap smear test was a protective factor for developing cervical cancer (OR 0.15, 95% CI 0.04-0.23). However, if the last time of performing a Pap smear test was 2 years or longer, the risk increased about 15 times more than women who had the last Pap smear less than 2 years. Age at first pregnancy was associated with an increased risk of developing cervical cancer. Age at first pregnancy was 20 years or below increased risk nearly four times when compared with age at first pregnancy older than 20 years (OR 3.85; 95% CI 2.02-7.36) (Table 2).

Smoking also increased the risk of developing cervical cancer about four times when compared with non-smokers (OR 4.21; 95% CI 0.9-19.5) (Table 2).

Discussion

The authors' analysis suggests that risk of invasive squamous cervical cancer is increased almost three-fold if they have used oral contraceptives for more than 3 years. The increase in risk for women who had used oral contraceptives for more than 3 years was more consistent than that for ever or currently used. Among patients who had used oral contraceptives, risk of development of cervical cancer was substantially changed by time since last use, or by age at first use.

Results of several studies of oral contraceptive use and squamous-cell ICC (invasive cervical carcinoma) showed a small increase in the risk ratio associated with long duration of use[4]. However, many studies had a wide range of confident interval and were not significant[4]. In a meta-analysis of 51 studies, risk ratios associated with ever use of oral contraceptives were 1.5 (95% CI 1.3-1.8) for ISC (in situ carcinoma) and 1.2 (1.1-1.4) for ICC [1]. Results of cohort studies generally have higher risk ratios than case-control studies, and both types of study showed a clear dose-response effect of increasing risk with increased duration of use.

In a 25-year follow-up study of 46,000 British women, mortality from cervical cancer was increased 2.5-fold (1.1-6.1) in women who either were presently using, or had recently used oral contraceptives after adjustment for parity, social class, and smoking[6]. The conclusion of these studies is similar to the present study. Nevertheless, the strong effect of HPV was not taken into account fully. In some of these studies, biases associated with sexual behavior, screening, and, most notably, HPV infection, could not be ruled out[7]. There were few studies in Thailand about oral contraceptives and cervical cancer and had some results similar to the present study[8,9].

The present study had many constraints. The case-control study has limitation to elaborate the effect of risk factors. There are some confounders and effect modifiers in the study of hormonal contraceptives and cervical cancer. Due to the case-control design, the present study was not able to perform HPV testing. This was also the limitation in the present study. HPV infection is the major cause of squamous cell carcinoma of the cervix.

In conclusion, the present study demonstrated the risk factors of cervical cancer focusing on hormonal

contraceptive use. Even though there were many limitations of the present study, the results suggested the risk of long-term hormonal contraceptive use and occurrence of cervical cancer. The women who have risk of cervical cancer such as persistent HPV infection should consider the risk and benefit of long-term use of hormonal contraceptives. However, a further study should be conducted to confirm this association. Nevertheless, it was suggested that Pap smear has to be done routinely in women who use hormonal contraceptives. Long-term users of hormonal contraceptive are recommended to do a cervical cancer-screening test annually. A cervical cancer-screening program has to be implemented in a family planning clinic to ensure the quality of health care for women who use hormonal contraceptives.

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ผลของการใช้ยาเม็ดคุมกำเนิดกับการเกิดโรคมะเร็งปากมดลูก

ณัฐกานต์ วนการโกวิท, สุรศักดิ์ ฐานีพานิชสกุล

วัตถุประสงค์*: เพื่อศึกษาความสัมพันธ์ของการเกิดโรคมะเร็งปากมดลูกและการใช้ยาเม็ดคุมกำเนิดในสตรีที่มารับบริการในคลินิกนรีเวชกรรม โรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการ*: เป็นการศึกษาแบบ case-control โดยการสัมภาษณ์สตรีที่เป็นโรคมะเร็งปากมดลูกที่มารับการรักษาและตรวจติดตามที่โรงพยาบาลจุฬาลงกรณ์ จำนวน 60 คน และสัมภาษณ์สตรีกลุ่มควบคุม จำนวน 180 คน ทำการสัมภาษณ์เกี่ยวกับการใช้ยาเม็ดคุมกำเนิด ประวัติการตั้งครรภ์และการมีบุตร และปัจจัยเสี่ยงอื่น ๆ ที่เกี่ยวข้องกับการเกิดโรคมะเร็งปากมดลูก*

ผลการศึกษา*: เมื่อเปรียบเทียบกับสตรีที่ไม่ได้ใช้ยาเม็ดคุมกำเนิด พบว่า สตรีที่เคยใช้ยาเม็ดคุมกำเนิด มีแนวโน้มที่จะมีความเสี่ยงของการเกิดโรคมะเร็งปากมดลูกเพิ่มขึ้นประมาณ 1.5 เท่า (OR 1.45; 95% CI 0.79-2.64) และเมื่อเปรียบเทียบในกลุ่มสตรีที่ใช้ยาเม็ดคุมกำเนิดติดต่อกันนานกว่า 3 ปี พบว่าจะเพิ่มความเสี่ยงการเกิดโรคมะเร็งปากมดลูกประมาณ 2.5 เท่า (OR 2.57; 95% CI 1.22-5.49)*

สรุป*: การใช้ยาเม็ดคุมกำเนิดติดต่อกันในระยะเวลานาน อาจเป็นปัจจัยส่งเสริมการเกิดโรคมะเร็งปากมดลูก และควรแนะนำให้มีการตรวจคัดกรองมะเร็งปากมดลูกเป็นประจำในสตรีที่ใช้ยาเม็ดคุมกำเนิด*