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ORAL CONTRACEPTIVES AND BREAST CANCER RISK IN TAIWAN, A COUNTRY OF LOW INCIDENCE OF BREAST CANCER AND LOW USE OF ORAL CONTRACEPTIVES

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One hundred and seventy four (81% of all) pathologically confirmed new incident cases of female breast cancer identified from a medical center in Taipei from February, 1993 to June, 1994 were selected as the case group. Four hundred and fifty three inpatient controls who were without obstetric-gynecological, breast, or malignant diseases were individually matched for each case by age and date of admission. Information was obtained through direct interview and review of medical records. Conditional logistic regression was used to estimate the effects of each risk factor. After adjusting for education level, body mass index, age at menarche and first full-term pregnancy, parity, menopausal status and age at menopause, lifetime lactation, use of lactation inhibition hormones, and family history of breast cancer, breast cancer risk significantly elevated in use of OC before 25 years old and before 1971. In stratified analysis, significantly higher risk were found in OC use before 25 years old and in duration of use less than one year among post-menopausal subjects. Our results support the notion that OC use in early life for younger women and in early calendar years increase breast cancer risk. ***Int. J. Cancer*** **77:219–223, 1998.**
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The effects of oral contraceptives (OC) on the risk of developing breast cancer have been widely studied in Caucasian women but the results are inconclusive (Malone *et al.,* 1993; Brinton and Shairer, 1993). In the review of Malone *et al.* (1993) there is no evidence of an increased risk of breast cancer in women who have ever used OC, except for the use in young age and long duration. In a meta-analysis, recency was the most important predictor (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Results of single studies on Caucasian women have been reported from the United States (Wingo *et al.,* 1993) Canada (Rosensberg *et al.,* 1992), South America (Gomes *et al.,* 1995) and Europe (Lipworth *et al.,* 1995; Tavani *et al.,* 1993; Rookus and van Leeuwen, 1994; Chilvers *et al.,* 1994). For Asian countries, a worldwide review of epidemiologic studies (Thomas, 1991) and reports of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1990), and Stalsberg *et al.* (1989) have detected a small increase in risk of breast cancer in OC users in Asian low-incidence countries, as well as a trend of increasing risk along with longer duration of use and shorter recency. There have been very limited reports from single Asian countries. A case-control in Shanghai (Yuan *et al.,* 1988) showed an elevated risk for longer duration and older age of use. Another case-control study in Indonesia (Bustan *et al.,* 1993) found an elevated risk of breast cancer in ever users, especially for longer and recent use, as well as use in younger age.

Taiwan has had a very successful experience of birth control. The social and economic development further accelerated the declining of birth rate. The total fertility declined from 6.5 children per woman during the mid-1950s to 2 during the mid-1980s (Feeney, 1994). Contraception rate has been around 80% for more than 10 years since 1983 (Department of Health, 1993). Contraceptive methods were introduced first by non-government organizations, then supplied and promoted by the government with strong political commitment and policy supports since 1965. However, unlike Western countries, the use of OC was much lower than other contraceptive methods. The aim of our study was thus to assess the effects of OC use on the risk of breast cancer in a country of both low incidence of breast cancer and low use of OC. We report here the results of a hospital-based case-control study conducted in Taipei.

MATERIAL AND METHODS

The ''cases'' in our study constituted a total of 174 (81% of all according to the Cancer Registry) consecutive pathologically confirmed new incident cases of female breast cancer in a teaching hospital (National Taiwan University Hospital) from February 1993 to June 1994. Pathological reports and medical records of these subjects were reviewed to rule out misclassification. Of the 19% cases not included, most were due to a random information delay after admission. Only 2 eligible cases refused the interview. For each case, we selected 1 to 3 female inpatients from medical, surgical, orthopedic, urological, ophthalmic, ENT and dentistry wards, as the ''controls'' who were free from obstetric-gynecological, breast, or malignant diseases according to the daily computer record of the Division of Admission of the same hospital. The controls were aged-matched (within 3 years) and time-matched (within 1 week admission) to the case. If more than 3 were eligible, the 3 with closest matching conditions were chosen as controls. A total of 453 controls were selected. Medical records were reviewed to ensure the eligibility of control status. All cases and controls were interviewed at hospital, using a pre-designed questionnaire by trained interviewers under the permission of the subjects themselves and their surgeons or physicians. Periodical meeting, medical record checking and telephone re-interview were used to improved the quality of data. Health education pamphlets were kept from the study subjects until the end of the interview. The interviewers were instructed not to read news and articles about breast cancer risk before all data were collected. Medical records were reviewed to verify the medical history, height and weight of the subjects.

Risk factors studied were OC use, including age and calendar year at first use, temporal relation of OC use and age at first full-term pregnancy, total duration of OC use. Recency of OC use was not studied because we only included the time of first use and duration of use but not the time of last use and the pattern of use.

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Education level, body mass index, age at menarche, age at first full-term pregnancy, parity, menopausal status and age at menopause (defined as the age of last menstruation after 1 year free of menstrual cycles), duration of life-time lactation, family history of breast cancer, use of female sex hormones other than OC and lactation suppression hormones, found in our previous studies (Chie *et al.,* 1996*a*,*b,* 1997*a*,*b,* 1998), were considered as potential confounders for the effect of OC use. Alcohol was not adjusted for since women in Taiwan seldom drink alcohol to the same extent as Western women. Neither was history of benign breast disease because it might be an intermediate variable. Conditional multiple logistic regression (proc phreg of the SAS package, SAS Institute, 1991) was used to estimate the effects of all risk factors with all potential confounders being adjusted. In further stratification into pre- and post-menopausal groups, only risk sets in which both the case and at least one control belonged to the same group, were analyzed.

RESULTS

Cases and controls are comparable in age. Means and standard deviations of the 2 groups are 47.7 ± 10.4 years *vs.* 47.5 ± 10.4 years. Table I shows the distribution of education level and major reproductive risk factors of cases and controls. Table II presents the effect of OC use for all subjects. After adjusting for education level, body mass index, ages at menarche and first full-term pregnancy, parity, menopausal status and age at menopause, lifetime lactation, family history of breast cancer, use of female sex hormones other than OC and lactation suppression hormones, the adjusted odds ratio (OR) for OC use was 1.7 (95% CI = 0.9–3.2). The adjusted OR for OC use before 25 years old *vs.* never use was 3.4 (95% CI = 1.2–9.7); *p* for trend was 0.019. The adjusted OR for OC use before 1971 *vs.* never use was 3.2 (95% CI = 1.2–8.9); *p* for trend was 0.014. Table III presents the effects of OC use on breast cancer risk in pre-menopausal subjects. The adjusted OR for age at first use <25 years *vs.* never use was 5.8 (95% CI = 1.5–22.1); *p* for trend = 0.04, for duration ≥5 years *vs.* never use was 3.5 (95% CI = 0.9–14.3). Table IV presents the effect of OC use for post-menopausal subjects. The adjusted OR of duration less than one year *vs.* never use was 7.5 (95% CI = 1.1–50.1). We also examined the relation between calendar year at first use, age at first use, duration, and relation to age at first full-term pregnancy by cross tabulation and chi-square test. The calendar year at first use was not related to age at first use, and duration. More subjects who used OC later in calendar year started OC use before age at first full-term pregnancy. (Table V).

TABLE I – EDUCATION LEVEL AND MAJOR REPRODUCTIVE RISK FACTORS FOR BREAST CANCER IN ALL SUBJECTS

Factors	Cases (N)	*n* = 174 (%)	Controls (N)	*n* = 453 (%)
Education level				
Illiterate	19	10.9	72	15.9
Elementary school	52	29.9	155	34.2
High school	57	32.8	131	28.9
College	46	26.4	96	21.2
Age at menarche				
≤12	23	13.2	36	7.9
13–14	68	39.1	176	38.9
15–16	58	33.3	178	39.3
≥17	25	14.4	61	13.5
Unknown	0	0.0	2	0.4
Age at menopause				
Not yet	103	59.2	267	58.9
Before 50 years	26	14.9	94	20.8
After 50 years	40	23.0	84	18.5
Age unknown	5	2.8	8	1.8
Parity				
0	17	9.7	37	8.2
1	24	14.0	37	8.2
2	50	28.7	111	24.5
3	45	25.9	115	25.4
4	22	12.6	77	17.0
≥5	16	9.2	76	16.8
Age at first FTP[1]				
<20 years	9	5.2	51	11.3
20–24 years	65	37.4	187	41.3
25–29 years	60	34.5	147	32.5
30–34 years	16	9.2	28	6.2
≥35 years	7	4.0	3	0.6
Nulliparous	17	9.8	37	8.2

[1]FTP: full-term pregnancy.

DISCUSSION

We have found a moderate but not statistically significant increased risk of breast cancer in OC users. Previous studies conducted elsewhere in Asia (Thomas, 1991; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Stalsberg *et al.,* 1989; Bustan *et al.,* 1993), Brazil (Gomes *et al.,* 1995), and Italy (Tavani *et al.,* 1993) but not those in Greece (Lipworth *et al.,* 1995) and China (Yuan *et al.,* 1988) also found a moderately elevated risk. Explanation by Stalsberg *et al.* (1989) that OC may release a latent growth potential of lobular cells not previously influenced by nutrition or other factors may be applicable in Taiwan, since its pattern of breast cancer (Department of Health, 1994) is similar to those of other low-risk countries. Laboratory experiments, however, did not find elevated cell proliferation (Going *et al.,* 1988) or estrogen conversion (Soderqvist *et al.,* 1994) in OC users.

The elevated risk for of early life and longer use especially in young (pre-menopausal in our study) subjects are consistent with the present conclusions (Malone *et al.,* 1993; Brinton and Shairer, 1993; Collaborative Group on Hormonal Factors in Breast Cancer, 1996) and recent studies in the United States (Wingo *et al.,* 1993), Canada (Rosenberg *et al.,* 1992), The Netherlands (Rookus and van Leeuwen, 1994), and the United Kingdom (Chilvers *et al.,* 1994), but not with several other studies conducted in China (Yuan *et al.,* 1988) and southern Europe (Lipworth *et al.,* 1995; Tavani *et al.,* 1993; Primic-Zabelj *et al.,* 1995). The negative result of the temporal relation with age at first full-term pregnancy was different from that of a study in Italy (Tavani *et al.,* 1993). Age of exposure is more critical than the temporal relation with important reproductive events in breast cancer risk in Taiwan. Only one study performed in Greece (Lipworth *et al.,* 1995) exhibited finding similar to ours of an increased risk with very short duration of OC use in the post-menopausal group. Other previous studies showed an increased (Rookus and van Leeuwen, 1994) or no change (Wingo *et al.,* 1993) of risk for longer duration of use in older ages. The explanation is unclear. It is possible that the post-menopausal subjects who had a very short duration of OC use might have had health conditions which caused both a stop of use and an elevation of risk of breast cancer.

The most interesting and unique finding of our study is the elevated breast cancer risk in users of earlier calendar years (before 1971). This has never been reported in previous studies either in Western or Asian countries. The use of OC is not common in Taiwan. Women in Taiwan seldom know the brand, content and dosage of OC they are using. However, because almost all the OC were provided by the Provincial Institute of Family Planning and Centers of Family Planning of Taipei and Kaoshiung, and the dose of estrogen and progestin decreased by calendar years, we can use calendar year as a surrogate of dosage. This result suggested that earlier brands of higher dosage of estrogen and progestin may increase breast cancer risk. Since calendar year of first use was not

TABLE II – ODDS RATIOS FOR ORAL CONTRACEPTIVE USE FOR BREAST CANCER RISK IN ALL SUBJECTS

Factors	Cases (N)	$n = 174$ (%)	Controls (N)	$n = 453$ (%)	Unadjusted odds ratios (95% CI)[1]	Adjusted odds ratios (95% CI)[2]
OC use						
No	149	85.6	406	89.6	1	1
Yes	25	14.4	47	10.4	1.5 (0.8–2.5)	1.7 (0.9–3.2)
Age at first use						
Never use	149	85.6	406	89.6	1	1
<25 years	9	5.2	12	2.7	2.3 (0.9–5.7)	3.5 (1.2–9.7)
25–29 years	11	6.3	21	4.6	1.5 (0.7–3.3)	1.7 (0.7–4.1)
≥30 years	5	2.9	14	3.1	0.8 (0.3–2.3)	0.7 (0.2–2.4)
p for trend[3]					0.068	0.019
Calendar year						
Never use	149	85.6	406	89.6	1	1
Before 1971	12	6.9	12	2.7	2.8 (1.1–6.7)	3.2 (1.2–8.9)
1971–1980	10	5.8	19	4.2	1.5 (0.7–3.3)	2.2 (0.9–5.5)
After 1980	3	1.7	16	3.5	0.5 (0.1–1.7)	0.4 (0.1–1.7)
p for trend[3]					0.038	0.014
Relation to FTP[4]						
Never use	149	85.6	406	89.6	1	1
Before	3	1.7	5	1.1	1.8 (0.4–7.4)	1.3 (0.3–6.0)
After	22	12.6	42	9.3	1.4 (0.8–2.5)	1.8 (0.9–3.5)
Duration						
Never use	149	85.6	406	89.6	1	1
<1 year	11	6.3	18	4.0	1.7 (0.8–3.8)	2.0 (0.8–4.7)
1–4 years	5	2.9	14	3.1	1.0 (0.4–2.9)	0.9 (0.3–3.0)
≥5 years	9	5.2	15	3.3	1.5 (0.6–3.6)	2.1 (0.8–5.6)
p for trend					0.276	0.118

[1]CI, confidence interval.–[2]Adjusted for education level, body mass index, ages at menarche and first full-term pregnancy, parity, menopausal status and age at menopause, lifetime lactation, and family history of breast cancer, hormone use other than OC, and lactation suppression hormones.–[3]Reversed trend.–[4]Full-term pregnancy.

TABLE III – ODDS RATIOS FOR ORAL CONTRACEPTIVE, FOR BREAST CANCER RISK IN PREMENOPAUSAL SUBJECTS

Factors	Cases (N)	$n = 97$ (%)	Controls (N)	$n = 237$ (%)	Unadjusted odds ratios (95% CI)[1]	Adjusted odds ratios (95% CI)[2]
OC use						
No	84	86.6	211	89.0	1	1
Yes	13	13.4	26	11.0	1.3 (0.6–2.7)	1.6 (0.7–3.8)
Age at first use						
Never use	84	86.6	211	89.0	1	1
<25 years	8	8.3	7	3.0	3.3 (1.1–10.5)	5.8 (1.5–22.1)
25–27 years	2	2.1	8	3.4	0.8 (0.2–3.6)	1.0 (0.2–5.7)
≥27 years	3	3.1	11	4.6	0.5 (0.1–2.4)	0.4 (0.06–2.5)
p for trend[3]					0.140	0.040
Calendar year						
Never use	84	86.6	211	89.0	1	1
Before 1971	2	2.1	1	0.4	3.7 (0.3–43.9)	6.4 (0.4–104.6)
1971–1980	8	8.3	11	4.6	1.9 (0.7–4.9)	3.5 (1.1–11.1)
After 1980	3	3.1	14	5.9	0.6 (0.1–2.2)	0.4 (0.09–1.9)
p for trend[3]					0.220	0.064
Relation to FTP[4]						
Never use	84	86.6	211	89.0	1	1
Before	3	3.1	5	2.1	1.7 (0.4–7.3)	1.1 (0.2–5.5)
After	10	10.3	21	8.9	1.2 (0.5–2.8)	1.8 (0.7–5.1)
Duration						
Never use	84	86.6	211	89.0	1	1
<1 year	5	5.2	12	5.1	1.0 (0.3–3.0)	1.0 (0.3–4.1)
1–4 years	3	3.1	8	3.4	1.0 (0.2–3.8)	1.0 (0.2–4.9)
≥5 years	5	5.2	6	2.5	2.3 (0.7–8.3)	3.5 (0.9–14.3)
p for trend					0.313	0.145

[1]CI, confidence interval.–[2]Adjusted for education level, body mass index, ages at menarche and first full-term pregnancy, parity, lifetime lactation, and family history of breast cancer, the use of female sex hormones other OC, and lactation suppression hormone.–[3]Reverse trend.–[4]Full-term pregnancy.

associated with age of first use and duration of use, their effects on breast cancer could not be explained by the effects of each other.

We did not assess the effect of latency or recency because of lack of data for the time of last use and the pattern of use (continuing or intermittent). If we take the time of first use plus duration of use as the time of last use, since the duration of use of most subjects was relatively short (only 3.5% of the controls used OC over 5 years), the recency might be close to the true time of last use, but its effect will be confounded by the calendar year of first use and thus not be able to offer correct information for risk assessment.

TABLE IV – ODDS RATIOS FOR ORAL CONTRACEPTIVE USE, FOR BREAST CANCER RISK IN POSTMENOPAUSAL SUBJECTS

Factors	Cases (N)	$n = 66$ (%)	Controls (N)	$n = 146$ (%)	Unadjusted odds ratios (95% CI)[1]	Adjusted odds ratios (95% CI)[2]
OC use						
No	54	81.8	133	91.1	1	1
Yes	12	18.2	13	8.9	2.2 (0.9–5.3)	2.3 (0.8–6.6)
Age at first use						
Never use	54	81.8	133	91.1	1	1
<27 years	2	3.0	5	3.4	0.8 (0.1–4.3)	1.5 (0.2–9.2)
27–29 years	6	9.1	2	1.4	7.7 (1.5–39.6)	6.2 (0.9–40.7)
≥30 years	4	6.1	6	4.1	1.7 (0.4–7.4)	1.6 (0.3–9.6)
p for trend[3]					0.176	0.146
Calendar year						
Never use	54	81.8	133	91.1	1	1
Before 1971	10	15.2	10	6.9	2.3 (0.9–6.0)	2.7 (0.8–8.5)
After 1971	2	3.0	3	2.1	1.4 (0.2–11.9)	1.1 (0.1–14.5)
p for trend[3]					0.083	0.107
Duration						
Never use	54	81.8	133	91.1	1	1
<1 year	6	9.1	3	2.1	6.3 (1.2–32.4)	7.5 (1.1–50.1)
1–4 years	2	3.0	4	2.7	1.3 (0.2–7.8)	1.5 (0.1–15.9)
≥5 years	4	6.1	6	4.1	1.3 (0.3–4.7)	1.1 (0.2–5.0)
p for trend					0.361	0.414

[1]CI, confidence interval.–[2]Adjusted for education level, body mass index, ages at menarche and first full-term pregnancy, parity, age at menopause, lifetime lactation, and family history of breast cancer, the use of female sex hormones other OC, and lactation suppression hormone.–[3]Reverse trend.

TABLE V – CROSS TABLE OF CALENDAR YEAR OF FIRST USE, AGE AT FIRST USE, DURATION, AND RELATION TO FIRST FTP OF OC USERS ($n = 72$)

	Before 1971		1971–1980		After 1980		Chi-square and *p*
	N	%	N	%	N	%	
Age at first use							
<25 years	7	29.7	10	34.5	4	21.1	$\chi^2 = 1.32$
25–29 years	11	45.8	11	37.9	10	52.6	$p = 0.86$
≥30 years	6	25.0	8	27.6	8	26.3	(d.f.[1] = 4)
Duration							
<1 year	11	45.8	10	34.5	8	42.1	$\chi^2 = 0.80$
1–4 years	6	25.0	8	27.6	5	26.3	$p = 0.94$
≥5 years	7	29.2	11	37.9	6	31.6	(d.f.[1] = 4)
Relation to FTP[3]							
Before	0	0.0	3	4.2	5	26.3	$\chi^2 = 7.47$[2]
After	24	100.0	26	89.7	14	73.7	$p = 0.02$
							(d.f.[1] = 2)

[1]Degree of freedom.–[2]Should be interpreted with caution because no subjects used OC before 1971 and before first full-term pregnancy.–[3]Full-term pregnancy.

Our study involves a small sample size and has a limited power of test especially in further stratification into pre- and post-menopausal groups. It is a common limitation of single studies in low-incidence countries. Moreover, most of the trends were not significant. Without a dose-response relationship, we should interpret our isolated elevation of risk with caution. Regarding selection bias, although we used hospital controls, the study might not be affected too much by selection bias. The major reason is that both the use of OC and the contra-indications for OC use such as cardiovascular diseases, are low in Taiwan as compared with Western countries. In the past, most OC were supplied by health stations without physician evaluation and prescription with a strict concern of contra-indications. In addition, women in Taiwan seldom perform breast self-examination or undergo mammography (Chie *et al.*, 1993; Chie and Chang, 1994). Physicians might not be able to know patients' detailed OC history, either. Screening bias might be unlikely to happen. Therefore, controls (even hospital controls) in Taiwan might be more representative of the population at risk, while those of Western countries are over-selected as a lower risk group because of their previous knowledge of breast cancer and contra-indications of OC use. Since women in Taiwan were not given clear information about OC and risk of breast cancer, information bias is less likely to have happened. Regarding confounding, we had adjusted all possible potential confounders and their effects should not be a problem.

In conclusion, the risk of breast cancer appears moderately elevated in OC users starting use before 25 years of age, especially in the pre-menopausal group, and early calendar years (before 1971), as well as very short duration (≤1 year) in the post-menopausal group, in a population of low incidence of breast cancer and low OC use.

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