Published in final edited form as:
Cancer Causes Control. 2009 February ; 20(1): 27–34. doi:10.1007/s10552-008-9213-y.

Oral Contraceptives and the Risk of All Cancers Combined and Site-Specific Cancers in Shanghai

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Abstract

From 1998 to 1991, an in-person baseline interview was administered to approximately 267,400 female textile workers in Shanghai, China.. The cohort was followed until July, 2000 for incident cancer cases. Incidence rate ratios (RR) for 12 types of cancer in users of oral contraceptives (OCs) were calculated using Cox Proportional Hazards analysis. There was a reduced risk of uterine corpus cancer for women who had ever used OCs (RR=0.68, 95% CI=0.45–1.04) and a trend of decreasing risk with increasing duration of use (p=0.015). There was an increased risk of colon cancer in women who had used OCs for 10 years or more (RR=1.56, 95% CI=1.01–2.40) and an increased risk of rectal cancer in women who had ever used OCs (RR=1.31, 95% CI=0.98–1.75), with a trend of increasing risk with increasing duration of use (p=0.017), but these associations may have been due to uncontrolled confounding by physical activity or other non-causal factors. No associations were observed between OCs and the risk of all cancers combined or for any of the 9 other cancers. It is unlikely that the use of OCs has contributed to the temporal trends in cancer incidence in China in recent decades.

Keywords

neoplasms; oral contraceptives; cohort studies; China

Introduction

Combined oral contraceptives (OCs) have been associated with a reduced risk of ovarian and endometrial cancers, an increased risk of cervical cancer and liver cancers, and an increased risk of breast cancer among recent users [1].

Pill No. 1, the main OC used in China, consisted of 0.625 mg. of norethisterone and 0.035 mg. ethinyl estrdiol until 1974 and 0.3 mg. norethisterone and 0.03 mg. ethinyl estradiol after 1974 [2]. Few women used other formulations, providing the opportunity to investigate the possible influence of a single product (albeit in two doses) on the risk of cancer. Virtually all prior studies have been of multiple formulations, and their possible associations with various neoplasms were only assessed in the aggregate.

Most prior studies of OCs and cancer have been conducted in developed countries with relatively high rates of many of the cancers of interest, including those of the breast, ovary, and endometrium. The relatively few studies in developing countries, with different patterns of cancer occurrence than in western countries, have been case-control studies [3]. The cohort design, which we used in our study and which is less subject to potential reporting biases than case-control studies, has rarely been used in developing countries, and to our knowledge has not previously been used to investigate the relationship between oral contraceptives and cancer in China.

The purpose of this study was to assess the possible relationship between use of OCs and the risk of all cancers combined, and the risk of twelve site-specific cancers, in a cohort of approximately 267,400 Chinese women.

Methods

Study Design

The methods used in this study have been described previously [4]. Between October 1989 and October 1991, approximately 267,400 current and retired employees of the Shanghai Textile Industry Bureau (STIB), who were born between 1925 and 1958, and who worked in one of 519 factories of the STIB, were enrolled in a randomized trial of breast self-examination (BSE) [5]. After receiving training from study workers, approximately 500 factory clinic medical workers orally administered a four-page optically-scanned questionnaire to all eligible women to ascertain information on menstrual and reproductive history, use of alcohol and tobacco, and contraceptive use. The questions on oral contraceptives ascertained whether they were used (current and previous use) and the duration of use (less than 1 year, at least 1 year but less than 2 years, at least 2 years but less than 5 years, at least 5 years but less than 10 years, at least 10 years but less than 15 years, or 15 years or more), and type of oral contraceptive used (Pill No. 1, other, or both).

Comparisons between the baseline questionnaire (administered between 1989 and 1991) and a more detailed questionnaire subsequently administered to women enrolled in a case-control study of breast cancer nested in the cohort (data collection stopped in 1999) [6] showed a 97.5% agreement for ever/never having been pregnant, and, among women who had ever been pregnant, a 99.8% agreement of ever/never having a live birth. The data on oral contraceptives showed a 90.1% agreement for ever/never use (unpublished data, not shown).

Women in the cohort initially consulted medical workers in their factory when they became ill and were referred to one of several hospitals associated with the textile industry if cancer was suspected. Surveillance for breast cancer was accomplished as part of the BSE trial through active reporting by the medical workers in each factory. For other cancers, case finding was through a Tumor and Death Registry operated by the STIB, which received annual reports from each factory, of all cases of cancer and deaths that had occurred in the cohort members during the previous year. This information was supplemented by periodic reviews of the records of the Shanghai Cancer Registry, which meets the standards for inclusion of data in Cancer Incidence in Five Continents [7].

Diagnoses of cancers that were detected through December 31, 1998 were confirmed by computer matching to the Shanghai Cancer Registry, and by review of medical records if the diagnosis differed from that in the STIB Tumor and Death Registry or if the cancer could not be found in the Shanghai Cancer Registry. Hospital records were also reviewed for tumors coded as “uterine cancer, unspecified” and “intestinal cancer, unspecified”. The percentage of initially reported diagnoses that were corrected was 5.4% for all cancers combined, and varied from 0.3% (for breast cancer) to 13.5% (for gallbladder cancer). Because we were not able to

validate the diagnoses from January 1, 1999 onward, the cancer site as reported by the STIB registry was used for cancers that were identified from that date to the end of follow-up on July 31, 2000. Cancers selected for specific analyses included those that may have a hormonal etiology (breast, colon, gallbladder, liver, ovary, thyroid, uterine cervix, and uterine corpus) and those that occurred commonly in this population (lung, pancreas, rectum, and stomach). Information on censored observations was obtained from personnel records (i.e. whether the woman left the STIB) and from the STIB Tumor and Death Registry (i.e. deaths). Only 7.5% of the subjects transferred out of the STIB and were lost to follow-up [5].

Statistical Analyses

Cox Proportional Hazards models [8] were used to calculate cumulative risk ratios with the number of months of follow-up being the time scale variable. All models were controlled for the potentially confounding effects of age (using linear splines with knots at 5-year periods) and parity. Splines allow for a change in slope of the age-cancer risk relationship at five year intervals and provide better adjustment for age than traditional age adjustment techniques [9]. Age at first live birth, duration of breastfeeding, the use of various contraceptive methods (injectable contraceptives and intrauterine devices), spontaneous abortions, induced abortions, use of injections during pregnancy, tobacco use, and alcohol drinking were considered as potential confounders. Variables that altered the rate ratio (RR) of cancer in relation to ever having used OCs by more than 5% were retained as confounding variables in the model in addition to age and parity. The joint effects of OC use and injectable contraceptive use were evaluated by using likelihood ratio tests.

Analyses were restricted to those subjects who were at risk for newly diagnosed cancer and therefore, women who had had a previous mastectomy were excluded from the breast cancer analysis, women who had had a previous bilateral oophorectomy were excluded from the ovarian cancer analysis, and women who had had a previous hysterectomy were excluded from the uterine cervix and uterine corpus analyses.

This study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center, the University of Illinois at Urbana-Champaign, and the Station for Prevention and Treatment of Cancer of the STIB in accordance with an assurance filed with the Office for the Protection from Research Risks (OPRR) of the National Institutes of Health.

Results

Included in this analysis were the 258,956 women who answered the question on ever use of oral contraceptives and had at least one month of follow-up time. Of these women, 37,319 of them had ever used oral contraceptives. There were 2,410,072 person years of follow-up in this cohort, with 352,695 person years being contributed by oral contraceptive users.

Of women in the cohort who did not develop cancer, 1.1% were current users of OCs at the time the baseline questionnaire was administered, and 13.4% had used them in the past. The median length of time women who did not develop cancer used OCs was 27.2 months. In women without cancer who had used OCs, 87.6% had used Pill No. 1, 9.4% had used other oral contraceptives, and 2.6% had used both (see introduction). There was a reduced risk of all cancers combined, of borderline statistical significance, in women who ever used OCs.

There was no relationship between ever use of OCs and cancers of the breast, colon gall bladder, liver, lung, ovary, pancreas, stomach, or thyroid (Table 1). There was a reduction in risk of uterine cervix and uterine corpus cancers, of borderline statistical significance, associated with ever use of OCs, although there were few uterine cervix cases in the cohort. There was a borderline elevation in risk of rectal cancer associated with ever using OCs.

There was no trend in the risk of all cancers combined, or in the risk of cancers of the breast, colon, liver, lung, ovary, pancreas, stomach or thyroid with duration of use (Table 2). There was an elevation in risk of colon cancer in women who used OCs for 10 or more years that was of borderline statistical significance. A significant increasing trend in risk with increasing duration of use was seen for rectal cancer. There was a reduced risk of uterine corpus cancer in women who used OCs for more than one year, and a decreasing trend in risk with increasing duration of use of OCs, both of which were statistically significant. There were too few women with other cancers who had used OCs to assess risk of those neoplasms in relation to duration of use.

In addition to controlling for use of injectable contraceptives, the joint effects of oral and injectable contraceptives on risks of all cancers combined, and on cancers of the breast, colon, rectum, ovary, and corpus uteri were investigated. No statistically significant interaction (in multiplicative models – not shown) were observed, although the number of women that used both products was small, and the power to detect such interactions was low.

Discussion

Our study did not detect an increased risk of all cancers combined or of breast, colon, gall bladder, liver, lung, ovarian, pancreatic, rectal, stomach, thyroid, or cervical cancers in women who had used OCs. We detected a significant reduction in risk of cancer of the uterine corpus in users of OCs and there was a trend of decreasing risk with increasing duration of use.

The reduction in risk of cancers of the uterine corpus associated with OC use has been noted in a previous analysis of a subset of our study data [10]. The reduced risk of uterine corpus cancer, which can be assumed to consist largely of endometrial cancer, is similar to conclusions from an International Agency for Research on Cancer Monograph Working Group[1]. The Working Group concluded that the reduction in risk in oral contraceptive users may occur through promotion of “atrophic and antiproliferative effects” on the endometrium. The Working Group also noted that the level of reduction in risk of endometrial cancer increased with duration of use of oral contraceptives and this was confirmed in our study.

We found no association with ever having used OCs and risk of colon cancer. There was an increased risk in users of over 10 years duration, but it was only of borderline statistical significance. A previous study in China [11] observed a reduction in risk of colon cancer in OC users, but this was also not statistically significant. Studies conducted elsewhere have found either no association with OC use, or a reduction in risk [1,12,13]; a meta-analysis published in 2001 [13] found significant heterogeneity of results among studies.

Although we observed a statistically significant increasing trend in risk of rectal cancer with duration of OC use, the trend was not monotonic and our findings differ from previous observations of a negative or no association in China [11] and elsewhere [12,13].

The associations between OC use and the risks of cancers of the colon and rectum may be explained, at least in part, by uncontrolled confounding by physical activity. We found increased physical activity to be associated with decreased use of OCs (analyses not shown) in controls selected for a case-control study of benign and malignant breast diseases in our cohort [14] and we were unable to control for physical activity in our present study (since we did not collect this information on all cohort members). In this group of controls, we were also able to investigate whether body mass index (BMI) and various nutrient levels from diet were associated with OC use. They were not, and therefore, uncontrolled confounding by these variables is not a likely explanation for our findings. Given the potential for confounding by physical activity and the inconsistent results of other studies, it seems unlikely that the use of OCs alters the risk of cancers of the colon and rectum.

We observed no association between use of OCs and risk of breast cancer. A large pooled analysis [15] also found no overall increase in risk with OC use, nor did two prior studies in China [16,17]. The pooled analysis did show a small increase in risk in recent OC users [15]. The prospective nature of our study, with no collection of exposure data after baseline, precluded assessment of risk in recent users in our investigation.

We observed no association between OC use and gallbladder cancer and this finding is consistent with previous studies [18]. We also did not observe an increased risk of liver cancer associated with OC use. This is consistent with results of a meta-analysis [19], which found no increased risk in hepatitis B endemic areas like China.

We observed no association between OC use and lung cancer. Although Kreuzer et al. [20] detected a decreased risk of lung cancer in women who ever used OCs, there was no relationship with duration of use in that study. Elliott and Hannaford [21] and Vessey et al. [22] did not detect an association with OC use and lung cancer, nor did a study by Wu-Williams et al. [23] in China.

We observed no association between OC use and the risk of ovarian cancer. This differs from the results of most other studies [1,12,24], that consistently show a reduced risk in users of OCs. However, our findings are similar to those of two previous case-control studies in China [25,26]. Since use of OCs in China is generally of short duration, findings from a large pooled analysis [27] suggesting a lack of a negative association with short duration of use may explain ours and other Chinese findings.

There was no increased risk of pancreatic cancer associated with OC use in our study. This observation is consistent with the results of two studies in the United States [28,29], although the results of both of these studies and ours differ from those of Kreiger et al. [30], who found a reduced risk in OC users. Only one study, a case-control study in China [31], observed an increased risk. Since this finding was not confirmed by our prospective study in the same country, or by any other study, it seems unlikely that use of OCs increases the risk of pancreatic cancer.

We observed no association between OC use and stomach cancer. Studies in Canada [32] and Italy [33] had similar results.

Although an earlier case-control study in Shanghai [34] found an increased risk of thyroid cancer in OC users, this was not confirmed by our cohort study in the same city or by other studies [35] or the results of a pooled analysis [36].

Our study is limited by the small percentage of OC users in our cohort, the relatively short duration of use, and the lack of data on use after the baseline questionnaire was administered. These features limited our ability to study the possible carcinogenic effects of long term and recent use of oral contraceptives. The prospective nature of this study eliminated the possible influence of differential recall of OC use by cases and controls on our results. Additional advantages of our study are that it included large numbers of subjects and provided the opportunity to investigate the possible effects of largely a single formulation of OCs on risks of all cancers combined and of twelve different sites of cancer. Even so, for some of the rarer cancers in this population (e.g. cervix and gallbladder), we did not have sufficiently large enough numbers of cancers to determine whether there was a trend in risk with duration of use.

Another limitation of the present study is the inability to control for the potentially confounding effects of some risk factors associated with some of the site-specific cancers. Most of the risk factors ascertained in the baseline questionnaire were for breast cancer. However, many of these factors are also risk factors for ovarian, endometrial, and some other cancers. We also

had information on alcohol and tobacco use. The prevalence of tobacco use (2.8% ever use) and alcohol drinking (4.2% once a week or more) was infrequent, making them unlikely to be confounders. As mentioned previously, we did not observe an association between dietary intake or BMI and OC use in a sample of the cohort, and it is therefore unlikely that confounding by these factors are an explanation for any of our findings. Although we also did not acertain information on family history of cancers other than those of the breast, there is no reason to suspect that such a family history or most other missing risk factors would be related to having used OCs in China. It is therefore unlikely that confounding by other unmeasured risk factors obscured true relationships between OCs contraceptives and the risk of any specific cancer. The potential bias associated with not obtaining information on physical activity was discussed previously with respect to the colon and rectal cancer results.

It is reassuring that we observed no increased risk for all cancers combined in users of OCs contraceptives, and no trend of increasing risk with increasing duration of use. This suggests that OCs, as they have been used in China, have not contributed to the temporal trends in cancer incidence occurring in that country in recent decades [37].

Acknowledgements

Karin Rosenblatt, PhD, Department of Kinesiology and Community Health, 127 Huff Hall, University of Illinois at Urbana Champaign, 1206 S. Fourth St., Champaign IL 61820. This work was supported by National Cancer Institute grants R03-CA80637, R01-CA46823, and R01-CA80180.

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Table 1

Ever Use of Oral Contraceptives and Cancer in the Shanghai Cohort

Cancer Site	Ever Use	Number of Cases	Number of Person-Years	RR[a]	95% CI
All Cancers Combined	No	6,669	2,048,373	1.00	
	Yes	979	352,699	0.94	0.88, 1.01
Breast	No	1,496	2,032,357	1.00	
	Yes	253	350,741	0.90	0.78, 1.03
Colon	No	563	2,045,338	1.00	
	Yes	92	352,851	1.09	0.86, 1.37
Gall bladder	No	121	2,045,817	1.00	
	Yes	10	353,015	0.73	0.38, 1.42
Liver	No	420	1,173,637	1.00	
	Yes	48	1,226,787	0.82[b]	0.60, 1.13
Lung	No	746	2,048,263	1.00	
	Yes	82	353,284	0.87	0.69, 1.10
Ovary	No	254	2,008,845	1.00	
	Yes	53	349,539	1.17	0.86, 1.60
Pancreas	No	208	2,046,309	1.00	
	Yes	30	353,106	1.11	0.74, 1.66
Rectal	No	306	2,045,266	1.00	
	Yes	62	352,877	1.31	0.98, 1.75
Stomach	No	721	2,046,890	1.00	
	Yes	103	353,051	1.02	0.82, 1.27
Thyroid	No	141	2,044,687	1.00	
	Yes	20	352,876	0.75[b]	0.46, 1.23
Uterine Cervix	No	62	1,983,158	1.00	
	Yes	1	345,909	0.13	0.02, 0.96
Uterine Corpus	No	236	1,982,639	1.00	
	Yes	27	345,869	0.68[b]	0.45, 1.04

[a] Adjusted for parity and age using linear splines unless otherwise noted

[b] Adjusted additionally forever having had a tubal ligation

[c] Adjusted additionally for number of induced abortions

Table 2

Length of Use of Oral Contraceptives and Cancer in the Shanghai Cohort

Cancer Site	Number of Months of Use	Number of Cases	Number of Person-Years	RR [a]	95% CI
All Cancers Combined	None	6,669	2,048,373	1.00	
	1–11	296	133,981	0.88	0.78, 0.99
	12–59	384	133,176	0.95	0.85, 1.05
	60–119	143	42,602	1.04	0.88, 1.23
	120+	156	42,447	0.99	0.84, 1.16
					p = 0.70
Breast	None	1,496	2,032,357	1.00	
	1–11	73	133,492	0.71	0.56, 0.90
	12–59	112	132,404	1.04	0.86, 1.27
	60–119	34	42,318	0.97	0.69, 1.36
	120+	34	42,033	0.94	0.66, 1.32
					p = 0.53
Colon	None	563	2,045,338	1.00	
	1–11	25	134,048	0.97	0.64, 1.47
	12–59	32	133,308	0.96	0.67, 1.38
	60–119	13	42,625	1.13	0.65, 1.97
	120+	22	42,378	1.56	1.01, 2.40
					p = 0.16
Liver	None	420	2,047,302	1.00 [b]	
	1–11	14	134,154	0.86	0.50, 1.48
	12–59	16	133,451	0.68	0.41, 1.14
	60–119	11	42,639	1.34	0.73, 2.45
	120+	7	42,406	0.67	0.32, 1.44
					p = 0.30
Lung	None	746	2,048,263	1.00	
	1–11	25	134,223	0.96	0.64, 1.45
	12–59	29	133,484	0.77	0.53, 1.12
	60–119	14	42,667	1.05	0.62, 1.79
	120+	14	42,417	0.83	0.49, 1.41
					p = 0.29
Ovary	None	254	2,008,845	1.00	
	1–11	22	132,754	1.36	0.87, 2.13
	12–59	14	131,891	0.82	0.47, 1.41
	60+	17	84,400	1.44	0.87, 2.39
					p = 0.36
Pancreas	None	208	2,046,309	1.00	
	1–11	7	134,161	0.94	0.44, 2.04
	12–59	16	133,439	1.46	0.87, 2.46
	60+	7	85,013	0.81	0.37, 1.74
					p=0.74
Rectal	None	306	2,045,266	1.00	
	1–11	11	134,064	0.71	0.37, 1.34
	12–59	29	133,351	1.54	1.04, 2.29
	60–119	12	42,594	1.93	1.08, 3.46
	120+	10	42,373	1.34	0.71, 2.52
					p = 0.017
Stomach	None	721	2,046,890	1.00	
	1–11	30	134,167	0.94	0.65, 1.37
	12–59	38	133,390	0.96	0.69, 1.33
	60–119	14	42,610	1.04	0.61, 1.77
	120+	21	42,390	1.32	0.85, 2.05
					p = 0.49

Cancer Site	Number of Months of Use	Number of Cases	Number of Person-Years	RR [a]	95% CI
Thyroid	None	141	2,044,687	1.00	
	1–11	5	134,094	0.52	0.21, 1.27
	12+	15	218,289	0.99	0.57, 1.72
					p = 0.65
Uterine Corpus	None	236	1,982,639	1.00[c]	
	1–11	14	131,423	1.15	0.65, 2.01
	12+	13	213,962	0.48	0.27, 0.85
					p = 0.015

[a] Adjusted for parity and age using linear splines unless otherwise noted

[b] Adjusted additionally forever having had a tubal ligation

[c] Adjusted additionally for number of induced abortions