

ORAL CONTRACEPTIVES AND ENDOMETRIAL CANCER: DO OTHER RISK FACTORS MODIFY THE ASSOCIATION?

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The joint effect of use of combination-type oral contraceptives and other exposure factors on risk of endometrial cancer was examined in data from a multicenter case-control study conducted in 5 areas of the United States. Cases were 405 women with histologically confirmed invasive epithelial endometrial cancer first treated at one of 7 participating hospitals. A total of 297 population-based controls of similar age, race, and geographic area were selected as a comparison group. Information on exposure factors was derived from in-person interviews. Combination-type oral contraceptive (COC) use was associated with a significant reduction in risk of endometrial cancer, with an adjusted odds ratio (OR) of 0.4 (95% confidence interval 0.3 to 0.7) for ever compared to never use. Long-term (≥ 10 years) users experienced a markedly lower risk (OR = 0.2). Women who discontinued COC use ≥ 20 years earlier remained at reduced risk (OR = 0.7) compared with non-users. The negative association with COC use was apparent regardless of the presence or level of several other risk factors for endometrial cancer, including age, menopausal status, parity, obesity, ever-use of menopausal estrogens, smoking history, or history of infertility. The magnitude of the negative association observed in COC users, however, was considerably diminished in women with no full-term births and in women who subsequently used replacement estrogens for 3 or more years. These results provide new evidence that the protective effect of COC use lasts for 20 or more years after use is discontinued, and highlight several sub-groups of users in whom the level of protection is attenuated by the presence of other risk factors for this disease.
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The use of combination-type oral contraceptives, which contain both an estrogen and a progestin, confers protection against the development of epithelial endometrial cancer, particularly if these agents are used for extended periods of time. Fifteen (Horwitz and Feinstein, 1979; Weiss and Sayvetz, 1980; Kaufman *et al.*, 1980; Ramcharan *et al.*, 1981; Kelsey *et al.*, 1982; Hulka *et al.*, 1982; Henderson *et al.*, 1983; La Vecchia *et al.*, 1986; Pettersson *et al.*, 1986; CASH, 1987; WHO, 1988; Beral *et al.*, 1988; Koumantaki *et al.*, 1989; Shu *et al.*, 1991; Levi *et al.*, 1991) of 16 (Trapido, 1983) published studies on oral contraceptives and endometrial cancer reported relative risk estimates of less than one in users as compared with non-users, with long-term users experiencing about a 50% reduction in risk (Schlesselman, 1991). Although the epidemiologic data are remarkably consistent, several questions concerning this association remain unanswered.

Earlier published studies included only small numbers of post-menopausal women who had an opportunity to use COCs during reproductive years. For this reason, it is unclear whether the beneficial effect of COC use lasts throughout menopausal years, the time when women are at highest risk of developing endometrial cancer. Prior investigations also have suggested that the reduced risk associated with COC use may be offset by the presence of other exposure factors linked to endometrial cancer. For example, some studies have reported less of a protective effect of COC use in women with 3 or more live births (Henderson *et al.*, 1983; CASH, 1987), in obese

women (Henderson *et al.*, 1983), and in women who used menopausal estrogens (Weiss and Sayvetz, 1980; Kaufman *et al.*, 1980), although the data are not consistent (WHO, 1988; Levi *et al.*, 1991; Hulka *et al.*, 1982).

In this report, we examine the association between use of combination-type oral contraceptives and epithelial endometrial cancer, with special attention to the questions of how long the effect of COC use lasts once a woman stops taking the pills, and whether or not other characteristics of women alter the effect of COC use.

MATERIAL AND METHODS

The design of the U.S. multicenter collaborative study that provided data for this report is presented in detail elsewhere (Brinton *et al.*, 1992). Briefly, cases were accrued from 7 hospitals in 5 geographic areas: Chicago, IL; Hershey, PA; Irvine and Long Beach, CA; Minneapolis, MN; and, Winston-Salem, NC. All women newly diagnosed with pathologically confirmed endometrial cancer between June 1, 1987, and May 15, 1990, who were aged 20 to 74, who were residents of defined geographic catchment areas, and who had not received a first course of treatment prior to admission to the participating hospitals, were eligible for the study. Eligible patients included only those women diagnosed with stages I to IV invasive disease.

A total of 498 eligible cases were identified for the study, and 434 agreed to interview, for a case-response rate of 87.1%. Reasons for non-participation included doctor refusals (2.0%), patient refusals (4.8%), illness (1.0%), communication problems (3.6%), location problems (0.2%), other problems (0.2%), and death (1.0%). For the present analyses, 29 cases with non-epithelial tumors also were excluded.

Controls were selected to approximate the distribution of cases according to age (same 5-year group), race, and area of residence. Random digit dialing procedures (Waksberg, 1978) were utilized to select controls under age 65, with residential matching based on the case's telephone exchange. Household census information that enumerated eligible control women was obtained for 86% of the working residential numbers. Controls over age 65 were randomly selected from current Health Care Financing Administration computer tapes, with residential matching on the case's zip code. A brief telephone questionnaire was administered initially to determine whether the woman had an intact uterus; if not, she was replaced with another eligible subject.

A total of 477 eligible controls were identified for the study. Three hundred and thirteen of these women completed study

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interviews for a control response rate of 65.6%. The primary reasons for non-response included refusals (21.8%), illness (2.3%), communication problems (2.5%), location problems (3.1%), other problems (3.6%), and death (1.0%).

Exposure information was obtained by an in-person interview conducted by trained personnel, usually in the study subject's home. Standardized questionnaires elicited detailed information on social and demographic factors, menstrual and reproductive history, use of contraceptive methods, use of exogenous hormones, nutritional status including body height and weight, diet and alcohol intake, smoking habits, certain medical conditions, and family history of cancer. For each episode of contraceptive and non-contraceptive hormone use, the beginning and ending dates, total duration of use, brand, and regimen of use were ascertained. A life-events calendar and color photographs of hormone preparations marketed in the US were used to assist accurate recall.

The association between endometrial cancer and COC use was evaluated by calculating odds ratios (OR) and 95% confidence intervals (CI). Unconditional logistic regression models were used to control for confounding variables and to evaluate potential effect modification (Breslow and Day, 1980). A number of established and suspected risk factors for endometrial cancer were evaluated as possible confounders, and included race, education, income, study center, marital status, ages at menarche and menopause, menstrual status, reproductive history (infertility, gravidity, abortion, parity, lactation), height, recent weight, body-mass index [wt(Kg)/ht(m)²], hormone-replacement therapy (estrogen and progestin use), smoking and alcohol use, and history of diabetes or hypertension. In addition to age, the following exposure factors changed the odds ratio estimates by more than 5% and have been controlled for in the analysis: education, parity, weight, and duration of use of menopausal estrogens. Assessment of interaction was performed by calculating a likelihood ratio test for heterogeneity from logistic regression models excluding and including the appropriate interaction term. For these analyses of combination-type oral contraceptive use, 6 women (3 cases, 3 controls) who were exclusive users of progestin-only or sequential-type oral contraceptives (or who were matched to such users) have been excluded.

RESULTS

Selected characteristics of the study population are shown in Table I. Cases were on average 2 years older than controls, the mean ages being 59.6 and 57.3 respectively. Compared with controls, a higher proportion of cases had completed 16 or more years of education, had never been pregnant, had fewer than 3 full-term births, had undergone natural menopause, reported a recent weight of ≥ 200 pounds, had used menopausal estrogens, and had a history of infertility or diabetes. Cases and controls had similar histories of hypertension and prior alcohol use, but cases were less likely than control subjects to report a history of cigarette smoking.

Ever-use of combination-type oral contraceptives was reported by 20.2% of cases and 36.4% of controls, resulting in a 66% reduction in the risk of endometrial cancer after adjustment for confounding factors (Table II). As shown, users were at lower risk than non-users, independent of age. Of particular interest is that COC use by women ages 65 and older was associated with about a 50% decrease in the relative odds of endometrial cancer.

A duration-related effect was noted for COC use (trend test $p = 0.03$), although there was not a direct linear decrease in risk estimates with increasing years of use (Table III). Women in the longest (≥ 10 years) duration-of-use category were at markedly reduced risk (OR = 0.2, 95% CI 0.1 to 0.5) compared with non-users. Analysis of recency and latency of use

TABLE I - DISTRIBUTION OF SELECTED CHARACTERISTICS OF EPITHELIAL ENDOMETRIAL CANCER CASES AND CONTROLS

Characteristic	Cases (N = 405)	Controls (N = 297)
Age, years		
< 45	9.6	13.1
45-54	19.8	23.9
55-64	37.3	36.7
≥ 65	33.3	26.3
Mean age	59.6	57.3
Race		
White	91.4	93.6
Black	5.7	5.4
Other	1.7	1.0
Unknown	1.2	—
Education, years		
< 12	20.7	25.6
12	30.4	30.6
13-15	23.0	27.9
≥ 16	24.2	14.8
Other	0.2	1.0
Unknown	1.5	—
Parity ¹		
0-1	24.4	13.9
2	27.1	31.5
3	21.3	21.3
4	14.0	11.7
≥ 5	13.2	21.6
Menopausal status		
Pre-menopausal	23.7	28.0
Natural menopause	74.1	69.7
Other	0.7	2.3
Unknown	1.5	—
Weight, pounds		
< 125	15.3	18.9
125-149	25.2	33.0
150-174	15.6	26.3
175-199	13.8	12.4
≥ 200	28.9	9.1
Unknown	1.2	0.3
History		
Menopausal estrogen use	23.0	13.1
Infertility	17.0	11.8
Diabetes	14.3	7.1
Hypertension	38.0	34.0
Cigarette smoking	34.1	44.8
Alcohol use	75.6	79.5

¹Excludes never-pregnant women (77 cases, 24 controls).

showed that the low-risk estimates observed in COC users were attenuated both with increasing years since last exposure (trend test $p = 0.001$) and with increasing years since initial exposure (trend test $p = 0.009$). However, even COC use that had been discontinued 20 or more years earlier was associated with a 33% reduction in risk compared with non-users. Risk estimates did not vary substantially according to age at first use.

In an attempt to examine separately the correlated effects of duration of use by recency and latency of use, we cross-tabulated these exposures (Table IV). The reduced odds ratios seen in COC users were somewhat diminished with increasing time since last use, regardless of total duration of use. However, risk estimates remained less than one for women who had discontinued their use of COCs 20 or more years earlier, with odds ratios of 0.6 and 0.8 in short- and long-duration users, respectively. The reduced risk estimates associated with COC use were apparent in all categories of duration stratified by time since initial use, except for short-term users who had first taken COCs 25 or more years previously (OR = 2.0; 95% CI 0.7 to 6.2).

The remaining analyses focus on the possible role of other risk factors in modifying the effect of COC use (Table V). As shown, among women who reported one or more full-term

TABLE II - ODDS RATIOS (OR) FOR EPITHELIAL ENDOMETRIAL CANCER IN RELATION TO COMBINATION-TYPE ORAL CONTRACEPTIVE (COC) USE, BY AGE

Age	Number of study subjects		Percent COC users		OR ¹	OR ²	95% CI ³
	Cases	Controls	Cases	Controls			
<45	38	38	68.4	81.6	0.49	0.49	(0.2,1.6)
45-54	70	63	28.6	61.9	0.25	0.27	(0.1,0.6)
55-64	139	109	20.1	27.5	0.67	0.55	(0.3,1.1)
≥65	155	84	4.5	8.3	0.54	0.49	(0.1,1.7)
Total	402	294	20.2	36.4	0.47	0.44 ⁴	(0.3,0.7)

¹Adjusted for age. Referent group is women who never used COCs in each age stratum.-
²Adjusted for age, education, parity, weight, and use of estrogen-replacement therapy.-³95% confidence interval for the multivariate adjusted OR.-⁴p value of the likelihood ratio test for heterogeneity = 0.72.

births, COC users were at lower risk than non-users. In women who reported no full-term births, however, COC use was associated with only a slight reduction in risk of endometrial cancer.

Weight was a strong risk factor for endometrial cancer in these data, and non-users who reported a recent weight of ≥200 pounds were at high risk (OR = 6.8) compared with non-users who weighed less than 150 pounds. However, in every weight category, COC users were at lower risk than non-users.

Estrogen-replacement therapy (ERT) also was associated with an elevated risk of endometrial cancer in these data. In post-menopausal women, both those who ever and those who never used ERT, COC users were at lower risk than non-users, but the negative association with COC use was not evident in long-term (≥3 years) ERT users.

A number of other possible risk factors for endometrial

cancer also were examined by duration of COC use. As shown, the reduced risk associated with COC use was obvious regardless of menopausal status, history of infertility, or smoking status. A history of cigarette smoking was associated with reduced risk of endometrial cancer in our data, and when COC use and smoking history were considered jointly, there was some suggestion that smoking slightly lessened the negative association with long-term COC use.

DISCUSSION

Our results are consistent with previous studies that reported a relatively low risk of developing endometrial cancer in COC users. Overall, our data show that any use of combination-type oral contraceptives reduces the risk of endometrial cancer by about 50%, and long-term use confers about an 80% reduction in risk. The reduced risk associated with COC use appears to last for at least 20 years after a woman stops taking

TABLE III - ODDS RATIOS (OR) FOR EPITHELIAL ENDOMETRIAL CANCER IN RELATION TO SELECTED MEASURES OF COMBINATION-TYPE ORAL CONTRACEPTIVE (COC) USE

	Number of subjects		OR ¹	OR ²	95% CI ³
	Cases (N = 402)	Controls (N = 294)			
Years of COC use ⁴					
<1	27	21	0.78	0.68	(0.3,1.4)
1-2	16	33	0.30	0.29	(0.1,0.6)
3-4	12	16	0.46	0.32	(0.1,0.8)
5-9	14	15	0.56	0.66	(0.3,1.6)
≥10	7	19	0.22	0.17	(0.1,0.5)
Trend test ⁵				p = 0.03	
Years since last COC use ⁶					
<10	6	18	0.19	0.10	(0.0,0.3)
10-14	15	27	0.32	0.32	(0.1,0.7)
15-19	24	32	0.44	0.40	(0.2,0.8)
≥20	33	27	0.71	0.67	(0.4,1.3)
Trend test ⁵				p = 0.001	
Years since first COC use ⁷					
<15	5	15	0.20	0.12	(0.0,0.4)
15-19	17	19	0.52	0.37	(0.2,0.9)
20-24	27	47	0.34	0.30	(0.2,0.6)
≥25	29	24	0.71	0.74	(0.4,1.4)
Trend test ⁵				p = 0.009	
Age at first COC use ⁸					
<25	33	44	0.49	0.49	(0.2,1.0)
25-29	12	20	0.38	0.49	(0.2,1.1)
30-34	15	18	0.51	0.48	(0.2,1.1)
≥35	18	23	0.46	0.28	(0.1,0.6)
Trend test ⁵				p = 0.18	

¹Adjusted for age. Referent group is women who never used COCs (321 cases, 187 controls).-
²Adjusted for age, education, parity, weight, and use of estrogen-replacement therapy.-³95% confidence interval for the multivariate adjusted OR.-⁴Excludes women with unknown years of use (5 cases, 3 controls).-⁵Trend test based on data for exposed subjects only.-⁶Excludes women with unknown years since last use (3 cases, 3 controls).-⁷Excludes women with unknown years since first use (3 cases, 2 controls).-⁸Excludes women with unknown age at first use (3 cases, 2 controls).

TABLE IV - ODDS RATIO (OR)¹ FOR EPITHELIAL ENDOMETRIAL CANCER IN RELATION TO DURATION OF COMBINATION-TYPE ORAL CONTRACEPTIVE (COC) USE AND INTERVALS SINCE LAST AND FIRST USE

Years of COC use	Years since last COC use		
	<15	15-19	≥20
<3	0.21 (0.1,0.6) ² [7, 15] ³	0.32 (0.1,0.8) [10, 16]	0.64 (0.3,1.3) [26, 23]
≥3	0.22 (0.1,0.5) [14, 30]	0.42 (0.2,1.0) [12, 16]	0.82 (0.2,3.3) [7, 4]

Years of COC use	Years since first COC use		
	<20	20-24	≥25
<3	0.26 (0.1,0.7) [13, 24]	0.30 (0.1,0.6) [15, 25]	2.0 (0.7,6.2) [15, 5]
≥3	0.28 (0.1,0.9) [9, 10]	0.30 (0.1,0.7) [10, 21]	0.42 (0.2,1.0) [14, 19]

¹Odds relative to women who never used COCs (321 cases, 187 controls), adjusted for age, education, parity, weight, and use of estrogen-replacement therapy. ²95% confidence interval. ³Number of cases, number of controls.

the pills. There appear to be, however, several high-risk sub-groups in whom COCs are not associated with this low incidence of endometrial cancer.

Recognized exposure factors that may have confounded the association between endometrial cancer and use of COCs were controlled for in the analyses. A number of other potential biases, however, should be considered in the interpretation of our study results. One concern is the low level of participation among eligible controls. If refusing controls were less likely than consenting controls to be COC users, we may have over-estimated the beneficial effect of oral contraceptives. No

information on COC use is available for non-respondents who were eligible for our study, but other studies have found no significant difference in the frequency of oral contraceptive use between interviewed and non-interviewed controls (UK National Case-Control Study Group, 1989; Jick *et al.*, 1989). The fact that our results on oral contraceptive use, as well as other established risk factors for endometrial cancer (Brinton *et al.*, 1992), are similar to those of most published studies provides some assurance that our control group was a representative sample.

Referral bias is another concern in studies that ascertain patients from referral institutions. In addition to physicians' referral patterns, patient characteristics such as income and education may influence who is admitted to a referral hospital. To the extent that these factors are positively associated both with COC use and with the likelihood of being admitted to one of the participating institutions, we may have under-estimated the true magnitude of the negative association between prior COC use and endometrial cancer. Among our cancer patients, those in the highest as compared with the lowest categories of income or education were more likely to have ever taken COCs.

Another concern in any study of endometrial cancer is possible misclassification of disease status, particularly if women with atypical endometrial hyperplasia are included. Although there was no formal pathology review component in the study, to be eligible for our study patients had to be diagnosed with pathologically confirmed, stages I to IV invasive disease. For this reason, our case series includes a higher proportion of women with more advanced stage tumors, reflecting referral patterns to the participating hospitals, and is less likely to include women with only precursor lesions. A total of 314 (78%) of the patients were classified as having

TABLE V - ODDS RATIOS (OR) FOR EPITHELIAL ENDOMETRIAL CANCER IN RELATION TO DURATION OF COMBINATION-TYPE ORAL CONTRACEPTIVE (COC) USE, BY SELECTED CHARACTERISTICS

Characteristics	Years of COC use ¹			p value ²
	0	<3	≥3	
Number of full-term births ³				
0	2.08 (1.1,3.8)	1.44 (0.1,19.0)	1.93 (0.3,11.3)	
1-2	1.00 ⁴	0.38 (0.2,0.8)	0.41 (0.2,1.0)	
3-4	1.05 (0.7,1.7) ⁵	0.59 (0.3,1.4)	0.27 (0.1,0.7)	
≥5	0.53 (0.3,1.0)	0.22 (0.0,0.8)	0.15 (0.0,0.6)	0.86
Weight (pounds) ⁶				
<150	1.00 ⁴	0.57 (0.3,1.2)	0.44 (0.2,0.9)	
150-174	0.96 (0.6,1.6)	0.49 (0.2,1.4)	0.09 (0.0,0.7)	
175-199	1.85 (1.0,3.4)	0.66 (0.2,2.2)	0.80 (0.2,3.8)	0.76
≥200	6.84 (3.6,13.0)	2.39 (0.9,6.5)	2.66 (0.8,8.5)	
Estrogen replacement therapy ⁷				
Never	1.00 ⁴	0.50 (0.2,1.2)	0.20 (0.1,0.6)	
Ever	1.95 (1.1,3.4)	0.97 (0.2,4.9)	1.35 (0.4,4.1)	0.30
<3 years	1.05 (0.5,2.2)	0.00 (0.0,3.8)	0.76 (0.2,3.2)	
≥3 years	4.20 (1.8,9.8)	3.16 (0.3,31.1)	4.10 (0.4,38.5)	
Menopausal status ⁸				
Premenopausal	1.00 ⁴	0.36 (0.2,0.8)	0.30 (0.1,0.7)	
Natural Postmenopausal	0.88 (0.5,1.6)	0.34 (0.1,0.9)	0.26 (0.1,0.7)	0.99
History of infertility ⁹				
No	1.00 ⁴	0.51 (0.3,0.9)	0.36 (0.2,0.7)	
Yes	1.32 (0.7,2.4)	0.62 (0.1,2.7)	0.65 (0.2,2.6)	0.92
Smoking status ⁹				
Never	1.00 ⁴	0.50 (0.2,1.0)	0.24 (0.2,0.5)	
Ever	0.60 (0.4,0.9)	0.32 (0.2,0.7)	0.39 (0.2,0.8)	0.20

¹Analysis excludes subjects with unknown duration of COC use (5 cases, 3 controls). ²Likelihood ratio test for heterogeneity. ³Adjusted for age, education, weight, and use of estrogen-replacement therapy. ⁴Referent group. ⁵95% confidence interval. ⁶Adjusted for age, education, parity, and use of estrogen-replacement therapy. ⁷Analysis limited to subjects who experienced natural menopause (287 cases, 202 controls); adjusted for age, education, parity, and weight. ⁸Analysis excludes subjects with unknown or other type of menopause (7 cases, 9 controls); adjusted for age, education, parity, weight, and use of estrogen-replacement therapy. ⁹Adjusted for age, education, parity, weight, and use of estrogen-replacement therapy.

early-stage tumors, 85 (21%) as late-stage tumors, and 3 (1%) could not be classified.

Our results are consistent with all 13 prior case-control investigations of endometrial cancer in relation to oral contraceptives that reported a lower frequency of contraceptive-pill use in cases as compared with controls (Horwitz and Feinstein, 1979; Weiss and Sayvetz, 1980; Kaufman *et al.*, 1980; Kelsey *et al.*, 1982; Hulka *et al.*, 1982; Henderson *et al.*, 1983; La Vecchia *et al.*, 1986; Pettersson *et al.*, 1986; CASH, 1987; WHO, 1988; Koumantaki *et al.*, 1989; Shu *et al.*, 1991; Levi *et al.*, 1991). In addition, 2 (Ramcharan *et al.*, 1981; Beral *et al.*, 1988) of 3 (Trapido, 1983) cohort studies found a lower incidence of endometrial cancer in oral contraceptive users than in non-users. Most earlier studies have found that long-term users experience about half the risk of non-users (Schlesselman, 1991). Few of these previous studies, however, included post-menopausal women who would have had an opportunity to use oral contraceptives during reproductive years. Thus, although a number of studies have suggested that the reduced risk attributed to oral contraceptive use lasts for 10 or more years following discontinuation of usage, the question of whether the protective effect persists throughout the post-menopausal period has remained unanswered.

In our data, the reduced risk estimates observed in COC users were slightly diminished with increasing time since last use, but users who had last taken COCs 20 or more years earlier remained at 33% lower risk than non-users. Two prior studies have reported relative-risk estimates in relation to oral contraceptive use that was discontinued 10 or more years earlier (CASH, 1987; Levi *et al.*, 1991), and the largest study was limited to women under age 55 (CASH, 1987). In the Cancer and Steroid Hormone Study (CASH, 1987), women who had stopped using oral contraceptives for ≥ 15 years had a risk estimate of 0.3 (95% CI 0.2 to 0.6). In the smaller study of Levi *et al.* (1991), risk estimates in women who had last used oral contraceptives 10 to 19 years and > 19 years earlier were 0.4 and 0.8 respectively. Although the latter study included women over age 55, the overall prevalence of oral contraceptive use was low (14% of cases, 27% of controls reported ever use).

Despite limited epidemiologic evidence on the risk of endometrial cancer in relation to latency of oral contraceptive use, Key and Pike (1988) predicted that 5 years of combined oral contraceptive use would result in about a 60% decrease in a woman's lifetime risk of endometrial cancer. Our data show that prior use of COCs is associated with about a 50% reduction in risk in women aged 55 and older (Table II), suggesting that users remain at lower risk than non-users during post-menopausal years. In addition, our data show that even though the reduced risk estimates of endometrial cancer in relation to COC use appear to weaken with the passage of time since last use, women who stopped using COCs 20 or more years earlier retain a lower risk than women who never used these agents. Further, this effect did not seem to be explained by duration of COC use.

Several prior studies have examined whether other risk factors for endometrial cancer offset the protective effect of oral contraceptive use. In a study of women under age 46, Henderson *et al.* (1983) reported that the protective effect of oral contraceptive use was limited to women who were of lower parity (≤ 3 live births) and those who weighed less than 170 pounds. The CASH Study (1987) also reported that the strongest protective effect was among nulliparous women. In contrast, 2 studies found lower risk estimates in users of higher gravidity (WHO, 1988) or in parous as compared with nulliparous women (Levi *et al.*, 1991). None of the above studies, however, reported relative risk estimates by duration of oral contraceptive use.

Three prior studies have examined risk of endometrial

cancer in relation to oral contraceptive use and weight. As noted above, Henderson *et al.* (1983) reported a stronger protective effect of oral contraceptive use in women who weighed less than 170 pounds. However, even among obese (≥ 170 pounds) women in that study, risk estimates associated with oral contraceptive use decreased directly with increasing duration of use (RR = 3.5 for < 2 years use, RR = 1.7 for 2 to 3 years use, and RR = 1.0 for ≥ 4 years use, as compared with obese, non-users). Thus, their data suggest that 2 or more years of oral contraceptive use confer some protection in obese women. In contrast, the 2 other published studies reported either no difference in the effect of oral contraceptives according to categories of adiposity (CASH, 1987), or a stronger protective effect associated with use for women in the highest category of body-mass index (Levi *et al.*, 1991). Our results indicate that COC use diminishes some of the excess risk of endometrial cancer associated with obesity.

Menopausal estrogen use is clearly associated with an enhanced risk of endometrial cancer, and 5 earlier investigations have examined the joint effect of estrogen-replacement therapy (ERT) and oral contraceptive use. Weiss and Sayvetz (1980) first reported that no protective effect of oral contraceptive use was apparent in women who subsequently used menopausal estrogens for 3 or more years. In the CASH Study (Rubin *et al.*, 1990), long-term (≥ 2 years) users of ERT who had never used oral contraceptives were at higher risk (RR = 3.5) than those who had previously used oral contraceptives (RR = 1.2). Discrepant results have been reported from several other investigations (Kaufman *et al.*, 1980; Hulka *et al.*, 1982; Levi *et al.*, 1991), which noted that the protective effect of oral contraceptives was not altered by ERT use. Our data are consistent with the study by Weiss and Sayvetz (1980), and provide further evidence that the negative association with oral contraceptive use is modified in women who subsequently use replacement estrogens for 3 or more years. It should be noted that the use of combination-type hormone-replacement therapy, which incorporates a progestin in addition to estrogen, was reported by only 3% of cases and 4% of controls in our study. Thus, our results on menopausal hormones reflect predominantly exposure to unopposed estrogens.

We also examined the risk of endometrial cancer in relation to COC use by the presence or level of several other risk factors for this disease. Overall, the negative association with COC use was apparent regardless of age, menopausal status, history of infertility, or smoking history. This is in agreement with 2 other studies that reported no differences in oral contraceptive effects in sub-groups defined by age, menstrual status or smoking status (CASH, 1987; Levi *et al.*, 1991). It is worth noting that long-term COC use in our data was associated with a stronger decrease in risk in non-smokers than in smokers.

There is clinical and epidemiologic evidence to support the observed protective effect of COCs, which contain estrogen plus progestin. In post-menopausal women, unopposed estrogen therapy has been shown to induce endometrial proliferation and enhance risk of endometrial cancer, whereas the addition of a progestin to the estrogen regimen has been shown to counteract the estrogen-stimulated endometrial hyperplasia (Whitehead *et al.*, 1981), and to reduce the incidence of endometrial cancer (Gambrell, 1986; Persson *et al.*, 1989; Voigt *et al.*, 1991). In pre-menopausal women, long-term (≥ 5 years) use of oral contraceptives has also been associated with decreased risk of endometrial hyperplasia (Kreiger *et al.*, 1986), considered a precursor lesion for endometrial cancer.

As reviewed above, most epidemiologic studies have shown a reduced risk of endometrial cancer in relation to oral contraceptive use, and the protective effect of COCs appears to be mediated through the progestin component of the pills

(Weiss and Sayvetz, 1980; Hulka *et al.*, 1982; Rosenblatt *et al.*, 1991). Additional evidence that progestins are important in the etiology of endometrial cancer is derived from the substantial reduction in risk of endometrial cancer that has been reported in women who have used the injectable contraceptive depot-medroxyprogesterone acetate (OR = 0.2), which is a potent progestational agent (WHO, 1991), and in women who have used progestin-only oral contraceptives (OR = 0.6) (CASH, 1987). In contrast, Weiss and Sayvetz (1980) observed a substantial elevation in risk of endometrial cancer in users of Oracon (RR = 7.3), a sequential-type oral contraceptive that contained a weak progestin and a high dose of estrogen.

In summary, our findings support earlier reports that use of COCs protects against the development of endometrial can-

cer. The reduction in risk among users appears to last for 20 or more years after a woman stops taking these agents. Although none of the statistical tests for the joint effects of COC use and other risk factors were significant, several sub-groups of users in whom the protective effect was diminished were identified. In particular, COC use was not protective in women who had never had a full-term birth or in women who subsequently took estrogen-replacement therapy for 3 or more years.

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