



Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies

III. Epithelial Tumors of Low Malignant Potential in White Women

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Epithelial ovarian neoplasms of low malignant potential, also called borderline ovarian tumors, have various features of malignancy, but they do not invade the ovarian stroma. Women with these tumors usually are younger when diagnosed and have better prognoses than do women with invasive tumors. There have been few epidemiologic studies of borderline tumors, and it is unclear whether there are etiologic differences between the two types of tumor behavior. Combined data from nine case-control studies, conducted from 1974 to 1986 and representing 327 white women with tumors of low malignant potential and 4,144 white controls, were used to evaluate the relation between these tumors and personal characteristics related to invasive ovarian cancer. The risk profile for tumors of low malignant potential was found to be similar to that for invasive tumors, with two exceptions: Compared with that of invasive tumors, risk of borderline tumors was less clearly reduced among women who had used oral contraceptives and more clearly elevated among women with a history of infertility. *Am J Epidemiol* 1992;136:1204-11.

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Epithelial ovarian tumors of low malignant potential are established, specific histologic categories of ovarian tumors. These

tumors, also called borderline tumors, have various features of malignancy, including the capacity for metastasis, but they do not

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Abbreviations: CI, confidence interval; OR odds ratio.

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invade the ovarian stroma (1). Numerous studies have demonstrated that women with tumors of low malignant potential have better prognoses than do women with invasive tumors (2-4). Some have suggested that borderline tumors are precursors of invasive tumors (5). The more favorable prognosis of tumors of low malignant potential is seen, however, even among women with metastatic disease (2).

While there are differences in prognosis between invasive epithelial ovarian tumors and those of low malignant potential, it is unclear if there are etiologic differences. Several studies have found similarities between the two with respect to odds ratios associated with reproductive and personal characteristics (6-9). One consistent difference, besides prognosis, is that women with tumors of low malignant potential are younger than women with invasive tumors.

The paucity of epidemiologic investigations concerning ovarian tumors of low malignant potential is in part due to problems inherent to diagnosing and reporting these tumors: Their histologies are often omitted from pathology reports, they are classified according to various nonuniform coding schemes, and they are not usually included in cancer registries. Reports of the relative frequency of the two types of ovarian tumors usually have come from hospitals or pathology referral practices. A histopathologic review of all ovarian tumors reported to any Denver hospital between 1969 and 1979 showed that tumors of low malignant potential comprised 20 percent of all epithelial malignancies (10).

Here we report the results of a collaborative analysis of data from the nine studies that had included women with tumors of low malignant potential from among 12 United States case-control studies of ovarian cancer. The combined total of 327 white women with borderline tumors allows evaluation of etiologic differences between these tumors and those that are invasive. We focus on risks associated with reproductive and fertility history, use of exogenous estrogens, and body weight.

MATERIALS AND METHODS

The nine case-control studies providing data on tumors of low malignant potential were conducted in the United States between 1974 and 1986, and are described in table 1 of part I in this series (11). Four (12-15) of the studies used hospitalized controls and five (6, 16-19) used controls obtained from the general population. Part I (11) describes criteria used to select studies and subjects, procedures for merging the data and defining variables, and statistical analysis. The proportion of white women whose epithelial tumors were classified as borderline varied from 5 to 26 percent across the nine studies; the overall proportion was 13 percent.

This report describes two analyses. First, characteristics of women with tumors of low malignant potential were compared with those of controls, adjusting for joint categories of study and 2-year age group (<20, 20-21, . . . , ≥80 years). Second, characteristics of women with borderline tumors were compared directly with those of women with invasive tumors. This second "case-case" analysis was adjusted for joint categories of study and 5-year age group. These two analyses included 327 white women with an epithelial ovarian cancer of low malignant potential, 1,758 white women with an invasive epithelial ovarian cancer, and 4,144 white controls.

RESULTS

Table 1 shows odds ratios for epithelial ovarian tumors of low malignant potential according to reproductive characteristics that have been related to risk of invasive ovarian cancer. Parity was inversely related to risk of tumors of low malignant potential, with an odds ratio of 0.54 for a woman who had ever had a term pregnancy (95 percent confidence interval (CI) 0.41-0.72). Furthermore, risk decreased with increasing number of term pregnancies and with total months of pregnancy (data not shown). There was no evidence that odds ratios associated with parity differed between hospital and population studies.

TABLE 1. Odds ratio (OR) for epithelial ovarian tumors of low malignant potential according to selected reproductive characteristics

	Cases		Controls		OR†	95% CI‡	p value
	No.	%	No.	%			
No. of term pregnancies							
0	111	34	646	16	1.0		
1	69	21	499	12	0.84	0.59–1.2	
2	74	23	1,149	28	0.50	0.35–0.70*	
3	36	11	844	20	0.39	0.26–0.60*	
4	37	11	1,006	24	0.37	0.24–0.57*	
Trend per pregnancy					0.78		<0.001
Any term pregnancy	216	66	3,498	84	0.54	0.41–0.72*	
Age at first livebirth (years), parous only§							
<20	42	22	627	19	1.0		
20–24	84	44	1,507	46	0.94	0.61–1.4	
25–29	48	25	829	25	0.79	0.48–1.3	
≥30	18	9	322	10	0.65	0.34–1.3	
Trend per year					0.98		0.22
No. of failed pregnancies, gravid only§,							
0	155	65	2,215	63	1.0		
1	46	19	805	23	0.68	0.46–1.0	
2–3	26	11	287	8	1.1	0.65–1.7	
≥4	10	4	190	5	0.65	0.32–1.3	
Any failed pregnancy	82	35	1,282	37	0.80	0.59–1.1	
Diagnosed infertile¶, #							
No	180	81	2,779	89	1.0		
Yes	43	19	370	12	1.9	1.3–2.7*	
Fertility drug use††							
No infertility	69	78	657	87	1.0		
No, but infertile¶	15	17	86	11	1.6	0.83–3.1	
Yes	4	5	9	1	4.0	1.1–13.9*	
Months of breast feeding, parous only§							
0	101	52	1,598	49	1.0		
1–5	49	25	838	26	0.93	0.64–1.4	
6–11	21	11	374	11	0.80	0.48–1.3	
12–23	14	7	309	9	0.67	0.36–1.2	
≥24	8	4	166	5	0.92	0.42–2.0	
Trend per month					0.92		0.25
Ever breast-fed	93	43	1,687	50	0.86	0.63–1.2	

* $p < 0.001$.

† Adjusted for age, study, and parity.

‡ CI, confidence interval.

§ Adjusted for parity.

|| Abortions, miscarriages, ectopic pregnancies, and stillbirths.

¶ Physician-diagnosed infertility among ever-married women.

Based on studies 6, 8, 9, 11, and 12 (see part I, table 1 (11)).

†† Based on studies 6, 8, and 9.

Risk of a borderline ovarian tumor was inversely related to age at first livebirth, number of failed pregnancies, and, among parous women, history of breast feeding. However, none of these associations

achieved statistical significance (table 1).

Table 1 also shows odds ratios associated with history of fertility problems among ever-married women. Women who reported a previous physician-diagnosed fertility

TABLE 2. Odds ratios (OR) for epithelial ovarian tumors of low malignant potential according to use of exogenous hormones

	Cases		Controls		OR*	95% CI†	p value
	No.	%	No.	%			
Years of oral contraceptive use							
0	163	51	2,137	53	1.0		
<1	36	11	481	12	0.91	0.59–1.4	
2–3	52	16	451	11	1.0	0.69–1.6	
4–5	28	9	306	7	0.72	0.44–1.2	
>5	38	12	686	17	0.60	0.40–0.93	
Any use	156	49	1,970	48	0.80	0.59–1.1	
Trend per year‡					0.96		0.05
Years of use of ERT§							
<1	177	86	2,219	83	1.0		
1	9	4	140	5	1.3	0.60–2.7	
2–4	9	4	158	6	1.1	0.51–2.3	
5–9	6	3	84	3	1.3	0.51–3.2	
>10	4	2	76	3	0.87	0.29–2.6	
Any use	28	14	458	17	1.1	0.70–1.9	
Trend per year					1.00		0.99

* Adjusted for age, study, and parity.

† CI, confidence interval.

‡ Numbers for years of oral contraceptive use do not add to total for any use because of missing data.

§ ERT, estrogen replacement therapy, first used after age 40 years for at least 3 months.

problem that could not be attributed to the male partner had increased risk (odds ratio (OR) = 1.9, 95 percent CI 1.3–2.7) relative to women with no such history. The increase was greater among nulliparous women (OR = 3.8, 95 percent CI 1.3–10.8) than among parous women (OR = 1.4, 95 percent CI 0.87–2.2), although not significantly so. Data were too sparse to perform similar analyses among nulligravid women. Odds ratios for tumors of low malignant potential also varied with reported type of infertility. Although most women could not recall the reason for their infertility, those who reported ovarian dysfunction were at elevated risk (OR = 2.7, 95 percent CI 1.0–7.0); this odds ratio was 1.6 (95 percent CI 0.34–7.2) among parous women compared with 8.5 (95 percent CI 0.81–88.7) among nulliparous women. Risk among women who had used fertility drugs was significantly higher than that of women with no history of infertility (OR = 4.0, 95 percent CI 1.1–13.9), based on data from the three studies that had obtained this information.

Approximately 50 percent of both cases and controls reported ever using oral contra-

ceptives (table 2), resulting in a parity-adjusted odds ratio of 0.80 (95 percent CI 0.59–1.1). There was a trend of decreasing risk with increasing duration of use, with use for more than 5 years associated with an odds ratio of 0.60 (95 percent CI 0.40–0.93). Odds ratios associated with oral contraceptive use did not vary by parity and did not vary between hospital and population studies. No association was seen between risk for borderline tumors and use of estrogen replacement therapy (defined as use of at least 3 months duration starting after age 40 years), nor was there any trend of increased risk with increased duration of such hormone use.

Table 3 presents odds ratios for tumors of low malignant potential according to various catamenial and surgical experiences and body mass index. Neither age at menarche nor age at natural menopause was associated with risk of a borderline tumor. Women who had had a prior hysterectomy or tubal ligation were at decreased risk, although none of the odds ratios were statistically significant when adjusted for parity.

A trend of increasing risk with increasing

TABLE 3. Odds ratios (OR) for epithelial ovarian tumors of low malignant potential according to menstrual characteristics, pelvic surgeries, and body mass index

	Cases		Controls		OR*	95% CI†	p value
	No.	%	No.	%			
Age at menarche (years)							
<12	70	23	771	20	1.0		
12	65	21	945	25	0.70	0.49–1.0	
13–14	136	45	1,623	43	0.85	0.62–1.2	
≥15	33	11	437	12	0.85	0.54–1.3	
Trend per year					0.99		0.79
Age at menopause (years)‡							
<45	9	15	134	16	1.0		
45–49	16	27	228	27	0.85	0.35–2.1	
50–52	18	30	262	32	1.0	0.44–2.5	
≥53	17	28	206	25	1.3	0.56–3.2	
Trend per year of delayed menopause					1.03		0.25
Prior hysterectomy§							
No	293	90	4,785	84	1.0		
Yes	33	10	883	16	0.87	0.58–1.3	
Prior tubal ligation							
No	258	93	2,881	86	1.0		
Yes	18	7	451	14	0.69	0.41–1.1	
Usual body mass index							
<20	54	22	662	20	1.0		
20–22	61	25	1,004	30	0.92	0.61–1.4	
23–25	64	26	926	27	1.2	0.80–1.8	
26–28	31	13	387	12	1.2	0.92–2.5	
>28	36	15	399	12	2.0	1.2–3.2	
Overall trend per unit					1.05		0.02

* Adjusted for age, study, and parity.

† CI, confidence interval.

‡ Among naturally menopausal women aged ≥55 years at reference date.

§ At least 2 years prior to the reference date.

|| Weight (kg)/height (m)².

adiposity was observed for “usual” adult body mass index (weight (kg)/height (m)²), shown in table 3. The increased risk was confined primarily to the most obese category; women with a body mass index of greater than 28 had an odds ratio of 2.0 (95 percent CI 1.2–3.2), compared with women with an index of less than 20. Risk was also associated with heavier body mass indices during the teen years, but to a lesser extent (data not shown).

Table 4 compares odds ratios for epithelial tumors of low malignant potential with those for invasive epithelial tumors, obtained for the hospital and population studies, as described in part II (20). In general, there is close agreement among all three sets

of odds ratios. Two possible exceptions are the odds ratios for use of oral contraceptives and history of infertility. Oral contraceptive use was associated with an odds ratio of 0.80 (95 percent CI 0.59–1.1) for borderline tumors versus 0.70 (95 percent CI 0.52–0.94) and 0.66 (95 percent CI 0.55–0.78) for invasive ovarian cancer in hospital and population studies, respectively. A prior diagnosis of infertility was associated with an odds ratio of 1.9 (95 percent CI 1.3–2.7) for tumors of low malignant potential versus 1.0 (95 percent CI 0.76–1.2) for invasive ovarian cancer.

Some of the similarities in odds ratios in table 4 could reflect similarities in characteristics of the controls used in the two analyses,

TABLE 4. Odds ratios (OR) for epithelial ovarian tumors of low malignant potential and for invasive epithelial ovarian cancer

Characteristic	Low malignant potential			Invasive					
	OR*	95% CI†	p value	Hospital studies			Population studies		
				OR‡	95% CI	p value	OR‡	95% CI	p value
Ever parous	0.54	0.41–0.72		0.76	0.63–0.93		0.47	0.40–0.56	
Overall trend per term pregnancy	0.78		<0.001	0.87		<0.001	0.81		<0.001
Ever a failed pregnancy§	0.80	0.59–1.1		0.86	0.68–1.1		0.87	0.75–1.0	
Ever infertile	1.9	1.3–2.7					1.0	0.76–1.2	
Ever used fertility drugs¶	4.0	1.1–13.9					2.8	1.3–6.1	
Ever breast-fed, parous only	0.86	0.63–1.2		0.73	0.51–1.0		0.81	0.68–0.95	
Ever used oral contraceptives	0.80	0.59–1.1		0.70	0.52–0.94		0.66	0.55–0.78	
Overall trend per year of use	0.96		0.05	0.95		0.11	0.90		<0.001
Ever used estrogen replacement therapy#	1.1	0.70–1.9		0.93	0.69–1.3		1.1	0.89–1.4	
Prior hysterectomy	0.87	0.58–1.3		0.66	0.50–0.86		0.88	0.72–1.1	
Prior tubal ligation	0.69	0.41–1.1		0.59	0.38–0.93		0.87	0.62–1.2	

* Adjusted for age, study, and parity.

† CI, confidence interval.

‡ Adjusted for age, study, parity, and oral contraceptive use.

§ Gravid only.

|| Physician-diagnosed among ever-married women, based on studies 6, 8, 9, 11, and 12 (see part I, table 1 (11)).

¶ Based on studies 6, 9, and 12.

After age 40 years for at least 3 months.

since most controls provided data for both analyses. To avoid this problem and to provide direct formal comparison of the two tumor types, we also compared characteristics of the 327 women with borderline tumors with those of 1,758 women with invasive tumors. Women with borderline tumors were younger at diagnosis (mean age, 44 ± 14.6 years) than were women with invasive tumors (mean age, 52.9 ± 11.7 years); 43 percent of women with tumors of low malignant potential were less than age 40 years compared with 12 percent of women with invasive tumors. Moreover, the age-adjusted prevalence of parity differed between the two types of ovarian cancer. Among women less than age 60 years, those with borderline tumors were more likely than women with invasive tumors to have had at least one term pregnancy. In older women, this difference was not seen. There was, however, no difference between the tumor types in number of term pregnancies after the first.

Other characteristics that have been associated with epithelial ovarian cancer were compared between the two types of cases,

after adjustment for parity and age at diagnosis. There were no differences with respect to age at first pregnancy, number of failed pregnancies, history of breast feeding, age at menarche, age at menopause, or history of hysterectomy or tubal ligation. The case types also were similar with respect to use of postmenopausal estrogens and body mass indices. Women with borderline tumors, however, were more likely to have used oral contraceptives than were women with invasive tumors (51 vs. 25.6 percent) and had used this birth control method for longer periods. Women with borderline tumors also were more likely than women with invasive tumors to have been diagnosed infertile (19.3 vs. 14.8 percent). These differences persisted after adjustment for age.

DISCUSSION

These combined data from nine case-control studies provide an opportunity to examine the etiology of epithelial ovarian tumors of low malignant potential with greater statistical precision than has been

possible previously. However, several potential sources of bias, some of which are described in part I of this series (11), mandate caution in interpreting the results.

Overall, the findings support the conclusion that the etiology of tumors of low malignant potential is similar to that of invasive tumors, despite differences in age distribution and prognosis. Oral contraceptive use has been associated with reduced risk of invasive ovarian cancer, with strong trends of decreasing risk with increasing duration of use (20). Use of oral contraceptives was somewhat less strongly associated with decreased risk of tumors of low malignant potential than with risk of invasive tumors. This difference might be due to selection bias, i.e., the ovaries of oral contraceptive users might be screened more aggressively than those of nonusers, and such screening might uncover borderline tumors not otherwise detected. Alternatively, the difference could reflect differences in pill formulation, i.e., the more recent, lower potency formulations used by the relatively young women at risk of borderline tumors may be less protective than the earlier high-dose formulations used by the older women at risk for invasive tumors (20).

Conversely, use of fertility medications was more strongly associated with increased risk of tumors of low malignant potential than with risk of invasive tumors (20). The latter finding, if not due to chance or bias, could reflect a causal relation between fertility drugs and ovarian cancer. Alternatively, the findings could arise because of increased cancer risk among women with specific types of infertility that tend to be treated with such drugs. Interpretation is limited by the small number of women who used fertility medications and by the absence of information concerning the types of drugs used. These limitations suggest the need for further research to provide more precise exposure classification.

In conclusion, similarities between the present findings for epithelial ovarian tumors of low malignant potential and the findings of part II (20) for invasive epithelial cancers strengthen the inferences for both

and suggest that the two types of cancer have similar etiologies. Histology-specific analyses, while not feasible for the present data, may be useful in future comparisons.

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