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The Epidemiology of Ovarian Cancer in Greece: a Case-control Study*

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Abstract—*One hundred and fifty women with common malignant epithelial tumors of the ovary (cases) and* 250 *comparison women hospitalized for various orthopedic conditions were interviewed regarding demographic, reproductive, socio-economic and biomedical characteristics, including their use of coffee, tobacco, alcohol, drugs and exogenous estrogens. The data were analyzed with standard* χ^2 *procedures and by modelling relative risk* (r) *through multiple logistic regression. The main results are as follows: women with ovarian cancer had fewer liveborn children (one-tailed,* $P \simeq 0.13$, *for women with* 4+ *children,* $r = 0.6$) *and later menarche* ($P \simeq 0.02$, *for women with age at menarche* 15+, $r = 1.9$) *and menopause* ($P \simeq 0.07$, *for women with age at menopause* 50+, $r = 1.5$); *they were slightly taller and heavier* ($P \simeq 0.15$ *and* 0.30 *respectively*); *they belonged to smaller sibships* ($P \simeq 0.05$); *they reported more frequently than controls familial occurrence of ovarian, endometrial and breast cancer* ($P < 0.05$ *in each instance*); *they were regular consumers of alcoholic beverages more frequently than controls, and the excess was both statistically significant* ($P \simeq 0.02$) *and dose-related; they were regular users of coffee slightly more frequently than controls* ($r = 1.2$) *but the excess was small and it was neither statistically significant nor dose-related* ($P \simeq 0.27$); *and they reported less frequently than controls the use of oral contraceptives (relative risk for users,* 0.4; 95% *confidence interval,* 0.1–1.1).

INTRODUCTION

IN THE developed countries of the world ovarian cancer ranks fourth among cancers as a cause of death in females. It has been estimated [1] that about one woman out of every 80 will develop ovarian cancer at some time during her life, and that of those who develop the disease about ⅔ will die from it. More than ten case-control studies have been undertaken (reviewed by Weiss [2] and Kelsey and Hildreth [1]) and several risk factors have been identified, including parity, use of oral contraceptives and some demographic variables and gynecologic conditions. However, most of these studies were done in Northern Europe and North America, where the incidence of the disease is uniformly high. The investigation of a disease under variable ecologic and environmental conditions is necessary for the realization of the epidemiologic spectrum and, conceivably, the identification of important causal factors or events. With this rationale we decided to undertake a case-control study of ovarian cancer in Athens, Greece, where the incidence of the disease, although increasing, is only one half of the corresponding incidence in Northern Europe [3].

MATERIALS AND METHODS

During 1980 and 1981 all accessible women who were operated on for ovarian cancer in any of ten large hospitals of the Greater Athens area were interviewed by two of us (MP or MS). A total of 182 women with histologically confirmed primary ovarian cancer were interviewed, but only 150 women with common epithelial tumors

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of the ovary were included in the analysis (the remaining having mainly granulosa cell tumors).

Comparison patients were women hospitalized during the same time period in the Athens Hospital for Orthopedic Disorders. About ten times during the period of the study the same physicians who interviewed the cases visited the Hospital for Orthopedic Disorders and interviewed a total of 250 comparison women randomly chosen among those hospitalized for the first time for their current disease. There were no refusals or exclusions; among the 250 control women, 136 had traumatic fractures, 20 other traumatic conditions, 68 rheumatoid arthritis, osteoarthrosis or related disorders, 24 other orthopedic conditions and only two had pathological (non-traumatic, spontaneous) fractures.

The questionnaires covered demographic, socio-economic and biosocial characteristics, as well as information concerning personal habits and clinical histories. Consumption of alcoholic beverages, tobacco and coffee was evaluated by questions probing the type, amount and duration of consumption prior to the onset of the present illness.

Statistical analysis was done by χ^2 techniques [4] and multiple logistic regression procedures [5] using the GLIM statistical package [6].

RESULTS

Table 1 shows the distribution of cases and controls by age at diagnosis. The two distributions are very similar, so that controlling for age has little or no effect on the various estimates of relative risk which follow. Among cases 52% were born in urban areas and the average duration of residence in such areas was 47 yr, whereas among controls the corresponding figures were 45% and 46 yr; neither of these differences was statistically significant. There was also no evidence for a difference in socio-economic status between cases and controls: 17% of cases and 19% of controls had finished high school and similar results were obtained with other socio-economic indicators (ownership of telephone, etc.).

Table 2 shows the distribution of cases and controls by number of liveborn, stillborn, spontaneous abortions and induced abortions. There is no significant difference between cases and controls with respect to any of the above or any of the other recorded reproductive variables (age at first pregnancy, age at first birth, age of the

Table 1. Distribution of age at diagnosis (cases) or at interview (controls) among 150 cases of ovarian cancer and 250 controls

Group	Age (yr) ⩽34	35–44	45–54	55–64	⩾65	Total
Cases	8	16	46	41	39	150
(%)	(5.3)	(10.7)	(30.7)	(27.3)	(26.0)	(100.0)
Controls	18	31	53	76	72	250
(%)	(7.2)	(12.4)	(21.2)	(30.4)	(28.8)	(100.0)

χ^2 for trend with one degree of freedom, 0.05; $P = 0.8$.

Table 2. Distribution of selected reproductive variables among 150 cases of ovarian cancer and 250 controls

Reproductive variables	Cases*	Controls*	Relative risk (95% confidence limits)	χ^2 for trend (on 1 d.f.)
Liveborn children				
0	35	49	1.0	
1–3	97	160	0.8 (0.5–1.4)	$\chi^2 = 1.3$
⩾4	18	41	0.6 (0.3–1.3)	$P = 0.25$
Stillborn children				
0	137	232	1.0	$\chi^2 = 0.01$
⩾1	11	18	1.0 (0.4–2.4)	$P = 0.91$
Spontaneous abortions				
0	113	173	1.0	$\chi^2 = 1.84$
⩾1	35	76	0.7 (0.4–1.2)	$P = 0.17$
Induced abortions				
0	100	176	1.0	$\chi^2 = 0.20$
⩾1	47	73	1.1 (0.7–1.8)	$P = 0.66$

*Cases and controls do not always add up to 150 and 250, respectively, because of occasional missing values.

mothers of the study subjects at the time of the subjects' birth). The observed trend for numbers of liveborn children, though non-significant, is similar in magnitude to previous observations [1]; furthermore, if the analysis is restricted to women aged under 45 yr, as suggested by Franceschi *et al.* [7], the linear trend becomes significant and the relative risk for parous women (vs nulliparous) is decreased to 0.2.

Cases and controls are compared in Table 3 with respect to age at menarche and menopausal status and age at diagnosis. Cases appear to have both a later menarche and a later menopause; both trends are unlikely to be explained by chance ($P = 0.02$ and $P = 0.07$ respectively) and both are unconfounded by age and by each other. In no case but in five controls was the menopause artificial. The difference was not statistically significant ($P \simeq 0.20$) and these women are included in Table 3.

Table 4 shows the distribution of cases and controls by height and weight. There is no significant difference between the two series with respect to either of the two variables; however, there appears to be an excess of tall and heavy women among cases with ovarian cancer. Ponderal index (weight/height^2) did not discriminate cases and controls any more effectively than either weight or height alone.

Cases of ovarian cancer belong to smaller sibships than control women, and they are first-born more frequently than expected (Table 5). However, sibship size and birth order are highly correlated and potentially confounded. Controlling for sibship size (by the Mantel extension procedure [4]) with both birth order and sibship size categorized as finely as possible eliminates the appearance of a birth order effect, whereas controlling for birth order brings the sibship size association to the borderline of significance (Mantel extension, $\chi^2 = 3.8$, $P \simeq 0.05$).

There was no significant difference between

Table 3. Distribution of age at menarche and menopausal status among 150 cases of ovarian cancer and 250 controls

Menarche and menopause	Cases*	Controls*	Relative risk (95% confidence limits)	χ^2 for trend (on 1 d.f.)
Age at menarche (yr)				
≤12	43	95	1.0	
13	24	46	1.2 (0.6–2.2)	
14	32	46	1.5 (0.8–2.9)	$\chi^2 = 5.3$
≥15	37	44	1.9 (1.0–3.4)	$P = 0.02$
Menopausal status:				
still menstruating	38	62		
Age at menopause				
≤39	8	17	1.0	
40–44	18	52	0.7 (0.2–2.2)	
45–49	44	60	1.6 (0.6–4.4)	$\chi^2 = 3.2$
≥50	38	55	1.5 (0.5–4.2)	$P = 0.07$

*Cases and controls do not always add up to 150 and 250, respectively, because of occasional missing values.

Table 4. Distribution of height and weight among 150 cases of ovarian cancer and 250 controls

Somatic variables	Cases*	Controls*	Relative risk (95% confidence limits)	χ^2 for trend (on 1 d.f.)
Height (cm)				
≤154	18	32	1.0	
155–159	40	63	1.1 (0.5–2.4)	
160–164	31	63	0.9 (0.4–1.9)	$\chi^2 = 2.0$
≥165	41	41	1.8 (0.8–3.9)	$P = 0.16$
Weight (kg)				
≤54	20	39	1.0	
55–59	16	38	0.8 (0.3–2.0)	
60–64	21	38	1.1 (0.5–2.5)	
65–69	21	37	1.1 (0.5–2.5)	
70–74	19	27	1.4 (0.6–3.3)	$\chi^2 = 1.0$
≥75	28	45	1.2 (0.6–2.6)	$P = 0.31$

*Cases and controls do not always add up to 150 and 250, respectively, because of occasional missing values.

Table 5. Distribution of sibship size and birth order among 150 cases of ovarian cancer and 250 controls

Birth order		Sibship size 1	2	3	4	5	6	7	⩾8	Total
1	Cases	5	17	4	9	1	3	1	3	43
	Controls	8	12	10	5	7	4	4	4	54
2	Cases		3	6	4	7	0	0	0	20
	Controls		7	8	12	9	8	2	4	50
3	Cases			3	8	4	4	2	5	26
	Controls			9	12	7	3	7	9	47
4	Cases				6	6	2	2	3	19
	Controls				10	12	11	6	7	46
5	Cases					5	5	5	0	15
	Controls					4	0	3	8	15
6	Cases						5	1	2	8
	Controls						9	2	3	14
7	Cases							3	5	8
	Controls							5	3	8
⩾8	Cases								11	11
	Controls								15	15
Total	Cases	5	20	13	27	23	19	14	29	150
	Controls	8	19	27	39	39	35	29	53	249

For birth order: crude χ^2 for trend = 0.3; adjusted for sibship = 2.4.
For sibship size: crude χ^2 for trend = 1.4; adjusted for birth order = 3.8.

cases and controls with respect to frequency of the following conditions or procedures in their medical histories: malaria, tonsillectomy, adenoidectomy, appendectomy, hepatitis, cholelithiasis, jaundice (unspecified), tuberculosis, diabetes mellitus and hypertension. In all these instances χ^2 with one degree of freedom was smaller than 1.5, corresponding to $P > 0.20$. On the other hand, cases reported cervical polyps significantly more frequently than controls (9.7 vs 2.8%, $P < 0.01$). Finally, and unexpectedly, women with ovarian cancer reported significantly more frequently than controls a past measles attack (89 vs 74%, $P + 0.05$), whereas reporting of mumps was equally frequent among women in the two groups (53 vs 50%, $P > 0.60$).

In Table 6 the data are examined for evidence of familial clustering between ovarian cancer and cancer at other sites. It appears that there is a tendency for aggregation between cancer of the ovary on the one hand and cancers of the ovary, breast and endometrium on the other, although memory bias may complicate the interpretation of these associations.

Table 7 shows the distribution of cases and controls according to their self-characterization as drinkers or non-drinkers and, for drinkers, according to their estimation of the duration of alcohol consumption. There is an excess of drinkers among cases of ovarian cancer, but it is neither significant nor dose-related. However, the association becomes significant when duration of alcohol consumption is evaluated as a trend variable, even when several potential confounders (including age, parity, age at menopause and use of exogenous estrogens) are controlled for by

Table 6. Number of cases of ovarian cancer and controls* reporting affliction of their mother or any of their sisters by any of a number of selected cancers*

Cancer in mother or any sister	Ovary		Breast		Cancer Digestive		Endometrium		Other	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Reporting	9	0	7	2	7	7	6	1	7	3
(%)	(6.2)	(0.0)	(4.8)	(0.8)	(4.8)	(2.9)	(4.2)	(0.4)	(4.8)	(1.2)
Total	146	243	146	243	146	243	144	243	146	243
χ^2	12.7		4.72		0.49		5.21		3.29	
P	0.0004		0.03		0.48		0.02		0.07	

*Cases and controls do not always add up to 150 and 250, respectively, because of occasional missing values.

Table 7. Distribution of alcohol consumption (drinkers, non-drinkers) and duration (yr) among cases of ovarian cancer and controls

	Alcohol		Duration of alcohol consumption (yr)				
	Non-drinkers	Drinkers	Non-drinkers	Drinkers ≤9	10–19	20–29	≥30
Cases	102	48	102	5	11	14	17
Controls	191	59	191	13	11	9	19
RR	1.0	1.5	1.0	0.7	1.9	2.9	1.7
(95% C.L.)		(0.9–2.5)		(0.2–2.2)	(0.7–4.8)	(1.1–7.6)	(0.8–3.5)
Crude χ^2	3.4		6.2 (trend on 1 d.f.)				
Adjusted* χ^2	5.4		5.9 (trend on 1 d.f.)				

*Adjusted for age, parity, age at menopause and use of exogenous estrogens via the multiple logistic regression model.

Table 8. Distribution of tobacco smoking (current smokers, by amount) among cases of ovarian cancer and controls

	Non-smokers	Smokers (less than half pack/day)	Smokers (more than half pack/day)
Cases	132	8	10
Controls	217	12	21
RR	1.0	1.1	0.8
Crude χ^2	0.2 (trend on 1 d.f.)		
Adjusted* χ^2	0.1 (trend on 1 d.f.)		

*Adjusted for age, parity, age at menopause and use of exogenous estrogens via the multiple logistic regression model.

Table 9. Distribution of coffee consumption (amount in cups per day, and duration in years) among cases of ovarian cancer and controls

		Amount of coffee (cups/day)			
	Non-drinkers	0.5–1	1.5–2.0	2.5–3.0	≥3.5
Cases	26	36	60	16	11
Controls	50	72	78	33	17
RR	1.0	1.0	1.5	0.9	1.2
Crude χ^2	0.5 (trend on 1 d.f.)				
RR	1.0	0.9	1.6	0.9	1.5
Adjusted* χ^2	1.2 (trend on 1 d.f.)				

*Adjusted for age, parity, age at menopause and use of exogenous estrogens via the multiple logistic regression model.

means of the logistic regression. Controlling for tobacco smoking and coffee drinking had virtually no effect.

In Table 8 cases and controls are compared with respect to current smoking habits. There is no indication of any significant trend in either direction, either before or after adjustment for the potential confounders previously considered. Controlling for alcohol and coffee drinking had virtually no effect.

Coffee consumption as a risk factor for ovarian cancer is examined in Table 9. There is little in these data to support the notion that coffee consumption increases the risk for ovarian cancer. After adjustment for age, parity, menopausal status, age at menopause, use of exogenous estrogens, smoking of tobacco and consumption of alcoholic beverages the χ^2 for trend in coffee consumption is 1.15, corresponding to a one-tailed P of 0.14; at no level of coffee consumption does the relative risk differ significantly from the value of 1.00.

Table 10 shows the distribution of cases and controls by the reported use of oral contraceptives.

The crude χ^2 is marginally significant and remains so after adjustment for age, parity, menopausal status, age at menopause and consumption of alcoholic beverages (one-tailed, $P = 0.014$). The estimated relative risk for ovarian cancer among users of oral contraceptives is 0.4, with 95% confidence limits 0.1–1.1. It should be noted that the association of oral contraceptives as well as the other reported associations of reproductive and biometric factors are independent and do not introduce mutual confounding to any noticeable degree.

In Table 11 the etiologic significance of menopausal status and of the use of replacement (menopausal) estrogens is explored. There is no significant evidence of any association; the adjusted χ^2 for the contrast between postmenopausal use and non-users is 0.2 corresponding to a one-tailed P of 0.33.

Among 150 cases of ovarian cancer eight reported frequent use of psychotropic drugs (four for depression, two for neurosis, one for hyperthyroidism and one for artificial stimulation–night shift), whereas among 250 controls only two reported frequent use of such drugs (one for depression and one for neurosis). The difference is statistically significant ($P < 0.05$) and would indicate an almost seven-fold increase in risk for ovarian cancer among frequent users of such drugs. By contrast, there was no evidence of any association between regular use of hair dyes and probability of development of ovarian cancer.

Table 10. Distribution of reported use of oral contraceptives among cases of ovarian cancer and controls

	Use of oral contraceptives	
	No	Yes
Cases	146	4
Controls	232	18
RR	1.0	0.4
(95% C.L.)		(0.1–1.1)
Crude χ^2	3.7 (1 d.f.)	
Adjusted* χ^2	3.2 (1 d.f.)	

*Adjusted for age, parity, age at menopause and use of exogenous estrogens in the multiple logistic regression model.

DISCUSSION

The present study is a typical hospital-based case-control investigation; as such, it has many of the strengths and limitations of the gender, described in standard epidemiologic textbooks. In addition, the present study shares with other similar epidemiologic investigations a limitation generated by the histological heterogeneity of ovarian cancer; if histological heterogeneity reflects etiologic heterogeneity, as some recent findings appear to indicate [8, 9], then much larger series would be required for the demonstration of empirical associations.

One theory of ovarian carcinogenesis postulates that 'incessant ovulation' increases the risk of ovarian cancer. Two studies have tested this hypothesis by constructing a crude index of ovulatory age [10, 11] and many others [1, 2, 7, 12] have confirmed that at least one dimension of ovulatory age, i.e. low parity, increases the risk of ovarian cancer. Our findings, although not significant, are supportive of the view that low parity (and increased ovulatory age) is conducive to the development of ovarian cancer.

At least seven case-control studies have examined the association between prior use of oral contraceptives and subsequent risk of ovarian cancer [1, 2, 13, 14], and their converging results indicate that women who have used oral contraceptives have a relative risk for ovarian cancer of about 0.5. Our finding contributes to the establishment of the negative association between use of oral contraceptives and risk of ovarian cancer, of particular interest since it is derived from a population different from those on which most of the previous results were based.

Table 11. Distribution of menopausal status and reported use of replacement estrogens among cases of ovarian cancer and controls

	Still menstruating	Post-menopausal	Use of replacement estrogens among post-menopausal women	
			Non-users	Users
Cases	38	112	100	12
Controls	62	188	175	13
RR	1.0	1.0	1.0	1.6
Crude χ^2	0.0 (1 d.f.)		0.9 (1 d.f.)	
Adjusted* χ^2	0.1 (1 d.f.)		0.2 (1 d.f.)	

*Adjusted for age, parity, age at menopause and use of exogenous estrogens via the multiple logistic regression model.

Most studies have indicated that menopausal estrogens do not alter the risk for ovarian cancer [1, 2]. However, Hoover *et al.* [15] found a slightly increased risk among women who have taken both conjugated estrogen and diethylstilbestrol. In our study we did not have information concerning the type of replacement estrogens, and the moderate size of the relative risk associated with their use can only contribute to the perpetuation of the uncertainty.

In the present larger study we were unable to confirm our preliminary observation that coffee intake increases the risk of ovarian cancer [16]. Although the association remains slightly positive and, perhaps, suggestive, it is neither significant nor dose-related. Nevertheless, it is too early to dismiss the likelihood of an association, particularly since Hartge *et al.* [17] have also found a slightly positive but statistically insignificant and descriptively irregular association.

We did not find an association, in either direction, between tobacco smoking and ovarian cancer. Our results are based on few heavy smokers, but are in agreement with those of most other investigators who have studied this association [18, 19]. It should be noted, however, that in the most recent follow-up of female British doctors an excess of ovarian cancer was found among smokers [20]. On the other hand, a marginally significant association between alcohol and ovarian cancer was present in our data. There was no dose-response with respect to quantity of consumption, but there was such a trend in reply to the question "for how many years did you consume alcoholic beverages regularly?". To the extent that this question may elicit a more accurate reply than a question focusing on quantity of alcohol intake, the time association may be thought of as credible. Therefore the possible link between alcohol and ovarian cancer needs further evaluation, perhaps in conjunction with dietary data.

Conflicting results have been reported in the literature with respect to age at menarche and age at menopause; they are reviewed by Kelsey and Hildreth [1]. The confusing picture is difficult to explain but is very unfortunate, given the importance of both menarche and menopause as biological markers of critical endocrine events. The appropriateness of our control series may be questioned in this respect, since early menopause predisposes to osteoporosis and bone fractures; however, only two of 138 women with fractures were likely to have had them because of underlying osteoporosis. Conflicting results have also been reported with respect to height, weight and obesity [1]. Our results do not reach statistical significance but are compatible with those of Casagrande *et al.* [10], who found that obesity is an important risk factor, particularly in young women (in our data there was no significant interaction of age by weight).

Among the miscellaneous associations reported in the literature, several were not supported by our findings. Thus we did not find an association between ovarian cancer and mumps [21, 22], cholelithiasis [10] and hypertension [9]. On the other hand, we did confirm the familial clustering [1] of ovarian cancer with cancers of the ovary, endometrium and breast (although memory bias is a serious problem here and may represent a common denominator), as well as the association within individuals with cervical polyps [10] (for the explanation of which memory bias must also be considered).

Our finding of a positive association of ovarian cancer with frequent use of psychotropic drugs cannot be thought of as anything more than an interesting observation that deserves further evaluation. It should be noted, however, that similar associations have been reported (with prochlorperazine and triamcinoline) [23]. Finally, the association of ovarian cancer with a smaller sibship size may explain the increased frequency of reporting of measles, since a smaller size of sibship may be accompanied by a delay in the age of occurrence of measles and other contagious diseases (a later attack is more easily remembered). However, the possible association, if any, between measles and other viral infections on the one hand and ovarian cancer on the other is open to speculation [1].

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