

## LETTERS TO THE EDITOR

To the Editor:

In continuation of the discussion concerning the endodermal sinus tumor of the ovary, I would like to agree in general with statements of Dr. Talerman from the University of Chicago [1]. Unfortunately, in his list of references Dr. Talerman missed our publication describing two cases of EST, one of them occurring in a woman after the age of 45 [2]. Thus, we may state that at least three cases of EST in women after menopause have been reported in the literature.

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To the Editor:

Most epidemiologic investigations of epithelial ovarian cancer have not divided cases into the different histologic subtypes, partly because they are hard to classify and may include mixed cell types [1,2]. The most common subtypes of epithelial ovarian cancer using the WHO classification are serous, endometrioid, clear cell, mucinous, mixed epithelial, and undifferentiated [3]. Szamborski *et al.* [4], in the only case-control investigation to date that has focused entirely on histology-specific risk factors, found that obesity and hypertension were associated with increased risk of endometrioid but not serous cancers. Moreover, in their investigation, the serous subgroup failed to show as strong a protective effect of increasing parity as the endometrioid subgroup. Cramer *et al.* [5] also reported a greater degree of nulliparity in

women with endometrioid and clear cell tumors (grouped together) than in women with serous tumors, though the difference was not statistically significant. Only a few other analytic investigations of ovarian cancer have reported any histology-specific findings [6-9] and none has presented data regarding parity, obesity, or hypertension.

To address the hypotheses of Szamborski *et al.*, we have estimated the relative risks of the major types of ovarian cancer for parity, obesity, and hypertension, using data from a hospital-based case-control study of epithelial ovarian cancer in the Washington, D.C., metropolitan area [10]. Study details, as well as histology-specific findings regarding menstrual factors have been presented previously [10]. Eligible cases were all women aged 20-79 residing in the Washington, D.C., metropolitan area who were first diagnosed by operation with microscopically confirmed primary epithelial ovarian cancer during the period August 1978 to June 1981. Case ascertainment was virtually complete at the study hospitals. Careful clinical and pathologic review were priorities of the study. For all cases, we obtained pertinent medical records and the microscopic slides made from the tumors. One of us (H.J.N.) reviewed all of the slides, another reviewed the records (L.M.). Thirty women were excluded from study after this review, as they were found not to have definite primary ovarian cancer of the epithelial type by clinical or microscopic evaluation. Several of these had been classified as mucinous ovarian cancer, but were found to be of colorectal origin.

We identified 400 cases aged 20-79 and successfully recruited 296 (74%). As shown in Table 1, serous and endometrioid types predominated, a distribution similar to that seen in Szamborski *et al.* and in a large ( $n = 990$ ) Norwegian case series [11]. For undetermined reasons, other investigators have tended to report relatively fewer endometrioid and more mucinous cases [6,9,12-14].

For this analysis, we included the histologic categories with adequate numbers to yield stable estimates ( $n \geq 25$ ). We excluded all patients with low malignant potential tumors, since these distinct lesions tend to occur in younger women and are disproportionately serous, thus their inclusion could bias the intertype comparison. We also excluded the few non-whites in the series, since

TABLE 1  
Histologic Subtypes of Epithelial Ovarian Cancer in 7 Case-Control Studies

Source	<i>n</i>	% Serous	% Mucinous	% Endometrioid	% Other
Demopoulos <i>et al.</i> [12]	327 <sup>a</sup>	59	18	5	19
Annegers <i>et al.</i> [13]	138 <sup>b</sup>	36	12	20	22
Szamborski <i>et al.</i> [4]	309 <sup>b</sup>	46 <sup>d</sup>	11 <sup>d</sup>	42 <sup>d</sup>	Excluded
Weiss <i>et al.</i> [6]	205 <sup>c</sup>	35	16	8	41
La Vecchia <i>et al.</i> [14]	455 <sup>b</sup>	84	5	3	8
CDC/NICHHD [9]	324 <sup>a</sup>	44	14	27	15
Present investigation	296 <sup>a</sup>	34	7	31	27

<sup>a</sup> Low malignant potential lesions excluded.

<sup>b</sup> Unclear whether low malignant potential lesions included.

<sup>c</sup> Low malignant potential lesions included.

<sup>d</sup> Percentages in a selected series including only serous, mucinous, and endometrioid tumors.

their small numbers would not permit statistical adjustment for race. The resultant histologic categories for analysis were serous ( $n = 75$ ), endometrioid ( $n = 70$ ), mixed epithelial ( $n = 21$ ), and undifferentiated ( $n = 28$ ).

Controls were identified from hospital discharge lists and were matched to cases according to hospital of discharge, age, and race. A woman was not eligible to be a control if her discharge diagnosis was psychiatric or potentially related to the major exposures of interest. Discharge diagnoses so excluded were breast disease, myocardial infarction, stroke, thromboembolism, gall bladder disease, osteoporosis, gynecological complaints, melanoma, and colon cancer. For this analysis we excluded non-whites, leaving 295 controls. The discharge diagnoses

in the control group varied widely; musculoskeletal diseases constituted the most frequent single category, contributing 22% of the control group.

We estimated the rate ratios (RR) by fitting polychotomous logistic regression models, simultaneously comparing the four histologic subtypes to the control group [15,16]. This procedure allows correct estimation of the variance of the subgroup-specific RR parameters and direct statistical significance testing of differences between the RR estimates for the four histologic groups. We fitted each risk factor singly in a model that also included a dichotomous age term based on the median age of the controls ( $\leq 57$ ,  $> 57$ ).

The four case groups and one control group were similar

TABLE 2  
Estimated Relative Risks (and 95% Confidence Intervals) for Selected Risk Factors, for Four Histologic Types of Epithelial Ovarian Cancer

Risk Factor	Histologic type <sup>a</sup>								<i>P</i>
	Serous ( $n = 75$ )		Endometrioid ( $n = 70$ )		Mixed ( $n = 21$ )		Undifferentiated ( $n = 18$ )		
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	
Ever had a livebirth									
No	1.0		1.0		1.0		1.0		0.37
Yes	1.4	(0.7-2.5)	0.8	(0.5-1.5)	0.6	(0.2-1.4)	1.0	(0.4-2.6)	
Quetelet index <sup>b</sup>									
Lowest three quartiles (<25.56)	1.0		1.0		1.0		1.0		0.03
Uppermost quartile ( $\geq 25.56$ )	0.5	(0.2-1.0)	1.6	(0.9-2.8)	0.9	(0.3-2.8)	0.5	(0.1-1.6)	
History of hypertension									
No	1.0		1.0		1.0		1.0		0.83
Yes	0.9	(0.5-1.6)	0.7	(0.4-1.2)	1.0	(0.4-2.7)	0.7	(0.3-1.6)	

<sup>a</sup> Case groups compared, by polychotomous logistic regression, with single control group ( $n = 295$ ).

<sup>b</sup> Quetelet index: (weight in kilograms divided by height in centimeters squared)  $\times 10,000$ .

with regard to age. The median ages were 57 for controls, 56 for serous cancer cases, 58 for endometrioid, 59 for mixed epithelial, and 59 for undifferentiated cancer cases. As shown in Table 2, parity appeared to decrease risk of the endometrioid, mixed, and undifferentiated cancers, but not the serous subtype. This qualitative difference persisted when number of livebirths was considered as a trichotomous (0, 1-2, 3+) or a continuous variable. The slightly elevated risk ratio in the serous subgroup showed no trend with increasing number of livebirths (RR = 1.4 for both 1-2 and 3+ births). For the endometrioid, mixed, and undifferentiated subtypes, risk decreased with increasing parity (RRs = 0.8, 0.3, and 0.7, respectively, for 3+ births). The upper quartile of Quetelet index (a proxy for obesity) was associated with an increased risk of endometrioid cancer alone. The test for differences among the types was statistically significant for this variable ( $P = 0.03$ ). A history of hypertension was slightly protective in the endometrioid and undifferentiated categories, but no striking type-specific differences were seen.

Our results support two observations reported by Szamborski *et al.* We observed as they did that increasing parity may be more protective against endometrioid than serous ovarian cancer. The strong protective effect of increasing parity is one of the best etiologic clues regarding ovarian cancer, so an attempt should be made to confirm this histology-specific finding. We also observed, as did Szamborski *et al.*, that obesity was a risk factor particularly for the endometrioid subtype. Perhaps, as suggested by those authors and others [17], endometrioid ovarian cancers may relate etiologically to uterine body adenocarcinomas, sharing some of the same risk factors. However, in contrast to Szamborski *et al.*'s data, our results did not implicate hypertension as a risk factor for the endometrioid subtype.

Our findings overall suggest that histology-specific analyses hold promise, especially for clarifying how parity and obesity affect ovarian cancer risk. A major possible drawback of such analyses is the generation of false leads by the random effects of dividing the cases into subgroups. It will be important to select topics cautiously for histology-specific analyses, relying on a priori hypotheses and biological plausibility to minimize this problem.

The few histology-specific findings presented or mentioned in this report represent much of the published literature on the topic. Further progress on the epidemiology of the histologic subtypes will require very large studies or pooled data sets, to obtain adequate statistical power. In either case, the reproducibility of histologic categories will be important. It will be necessary when pooling or comparing data sets to consider whether the varying proportions of different histologic types, dem-

onstrated in Table 1, represent true biologic variability or just interpathologist variability. At present, it would be worthwhile to use existing data to confirm the lack of a protective effect of parity for serous ovarian cancers and the association of obesity with endometrioid cancers. If these findings persist, further histology-specific analyses will be justified.

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