

# Types and Duration of Symptoms Prior to Diagnosis of Invasive or Borderline Ovarian Tumor

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**Objective.** The objective was to describe and compare types and duration of symptoms among women with invasive versus borderline ovarian tumors.

**Methods.** Cases were women, ages 20–69 years, diagnosed with invasive (616) and borderline (151) epithelial ovarian tumors from 1994 to 1998. Symptoms were obtained using a standardized in-person interview. Differences in types and duration of symptoms, time to diagnosis after consulting a physician, and primary reason for diagnosis by invasive/borderline status and histologic type were determined using bivariate and regression analyses controlling for age.

**Results.** Borderline and invasive cases reported similar types of symptoms. However, borderline cases were twice as likely to report not having had symptoms as invasive cases (16 vs 8%,  $P = 0.005$ ). Prediagnostic symptom duration was longer among borderline versus invasive cases (median: 6 vs 4 months,  $P < 0.001$ ). The median time from first consultation with a physician to diagnosis (1 month) did not differ by invasive/borderline status. Borderline cases were twice as likely to be diagnosed through routine examination as invasive cases (28 vs 16%,  $P = 0.001$ ). Invasive cases were more likely to be diagnosed because of symptoms (62 vs 48%,  $P = 0.002$ ).

**Conclusions.** Because most (90%) women with ovarian tumors have symptoms and median symptom duration is 4 months, greater awareness of symptoms by women and physicians is needed for the earlier detection of ovarian tumors. The lesser likelihood of being detected by routine examination and the shorter symptom duration for invasive versus borderline cases underscores the need for effective screening and preventive strategies. © 2001 Academic Press

**Key Words:** ovarian cancer; symptoms; invasive; borderline; diagnosis.

## INTRODUCTION

There are several significant obstacles to the early detection of ovarian cancer, the most lethal cancer of the female repro-

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ductive system. Because the ovaries are located deep within the body, physical examination has not been effective in detecting localized disease. Development of more technological screening strategies has been hampered by the lack of a recognizable premalignant lesion in the ovary. Current proposed screening techniques, such as tumor markers in blood (e.g., CA125 blood test) and transvaginal ultrasound, are considered too costly and inaccurate for population application. False positive results lead to many unnecessary surgeries for benign disease [1] and the sensitivity of tumor markers can vary substantially by histologic type [2–4]. Evidence that current screening techniques reduce ovarian cancer mortality is lacking [1].

Therefore, symptom recognition is important in the detection of ovarian cancer. While the vast majority of women diagnosed with ovarian cancer have had at least one symptom [5–10], the disease most often reaches advanced stages before it is detected, hindering effective treatment. The overall survival rate for all stages is about 50%, but if caught and treated early, the 5-year survival can be as high as 95%. However, only 25% of cases are diagnosed while still localized [11]. Better recognition and characterization of symptoms might lead to earlier detection of ovarian cancer in some cases, thus improving chances for survival.

Symptoms of ovarian cancer can be subtle, such as abdominal discomfort, increased urinary urgency or frequency, and irregular menstrual bleeding. They often resemble symptoms of less serious and more common diseases, for example, irritable bowel syndrome or other benign gynecologic problems. As a result, women may delay seeking medical attention and health care providers may not consider the possibility that symptoms may be attributable to ovarian cancer.

Little systematic research has been undertaken to characterize symptoms of ovarian cancer or to assess delays in diagnosis [5–10, 12–15]. Unlike the current study where women were interviewed with a structured questionnaire, many prior studies have involved retrospective record review [5, 8, 9, 13–15]. Few studies have been large enough to examine differences in

symptoms according to histologic type or whether the ovarian tumor was borderline or invasive.

Borderline tumors, characterized by lack of stromal invasion, have an earlier age at diagnosis and are more likely to be diagnosed in stages I or II than invasive tumors which are more likely to present in stages III or IV. Survival is also better for all stages of borderline tumors compared to invasive cancers [16]. However, women with invasive and borderline tumors are similar with respect to many epidemiologic characteristics such as age at menarche and menopause, pregnancy history, history of breastfeeding, race, education, income, history of hysterectomy or tubal surgery, and postmenopausal estrogen use [16, 17]. While there has been some debate about whether borderline ovarian tumors are precursors of invasive cancer or whether invasive cancer arises *de novo* through a separate disease process, more recent evidence suggests they arise separately [1, 18–22].

The primary aim of the current study is to describe and compare types and duration of ovarian cancer symptoms among women with invasive and borderline epithelial ovarian tumors by histologic type of tumor. Secondary goals are to determine whether the time from first consultation with a physician to diagnosis and primary reason for diagnosis are associated with borderline/invasive status, histologic type of tumor, or demographic factors.

## MATERIALS AND METHODS

### *Study Participants*

Data for this study come from a case–control study originally designed to investigate the association between oral contraceptive use and ovarian cancer risk. Ovarian cancer cases were women, 20–69 years of age, diagnosed with histologically confirmed primary epithelial invasive or borderline ovarian cancer between 1994 and 1998. Cases were identified from 39 hospitals around the Delaware Valley in contiguous counties in eastern Pennsylvania, southern New Jersey, and Delaware. A total of 1278 cases met age and location of residence criteria. Cases were excluded for the following reasons: did not speak English or were not mentally competent (25), diagnosis greater than 6 months prior to interview (296), critically ill or dead (69), or untraceable (15), leaving 873 women eligible for the study. Of these 873 cases, 14 were excluded because the physician did not give consent to contact and 92 refused to participate, resulting in 767 completed interviews.

Central pathologic review was conducted on 120 randomly sampled cases. The reference pathologist agreed with the original pathologic review for invasiveness in 95% of cases and for cell type in 82% of cases. Therefore, the original pathologic review was used for all cases. Tumor stage and size were not collected as part of this case–control study, nor was it possible to obtain this information for these analyses. This study was approved by the institutional review boards at the University of Pennsylvania and all other participating institutions.

### *Data Collection*

An in-person interview with a standardized questionnaire was conducted in the homes of study participants by trained interviewers. The symptom section of the questionnaire asked women to recall whether they had any of the following symptoms and, if so, for how many months prior to diagnosis: (1) pelvic or abdominal discomfort such as heaviness, fullness, pressure, or pain; (2) bowel irregularity such as diarrhea, constipation, gas, or bloating; (3) a need to urinate more often than usual; or (4) any other symptoms. Women were also asked the month and year they first consulted a physician about symptoms and the primary reason for the doctor visit that led to the discovery of their ovarian tumor. Primary reasons for the doctor visit included unrelated symptoms, routine examination, infertility evaluation, pregnancy, tumor symptoms, or some other reason. In addition, medical and reproductive history and demographic information were collected.

### *Statistical Analysis*

The chi-square test or the Fisher's exact test was used to assess differences between dichotomous variables by invasive/borderline status, histologic type of tumor, and histologic type within categories of invasive and borderline cancer separately. The Wilcoxon Rank Sum test was used to evaluate time from symptom onset to diagnosis and time from first consultation with a physician to diagnosis by invasive/borderline status.

Since borderline cases were younger, on average, than invasive cases, we repeated all comparisons between invasive and borderline disease controlling for age both as a dichotomous variable (20–49, 50–69 years) using the Mantel–Haenszel chi-square test [23] and as a continuous variable using nonparametric ANCOVA [24]. Because results using the two methods were similar, for simplicity, only *P* values calculated controlling for dichotomous age are presented.

## RESULTS

Table 1 presents demographic information and tumor characteristics for the 616 women with invasive cancer and 151 women with borderline tumors. Women with invasive cancers were significantly older (mean age: invasive, 53.0 years; borderline, 44.7 years,  $P < 0.0001$ , *t* test), but there was no difference between women with invasive and borderline tumors with respect to race, education, or household income. The distribution of histologic types of cancer were significantly different among women with invasive and borderline disease ( $P < 0.0001$ ), and this relationship remained after controlling for age (Table 1). Borderline tumors were more likely than invasive tumors to be mucinous (40 vs 8%) and less likely to be endometrioid (2 vs 22%). Because so few women with borderline tumors had histologic types other than serous or mucinous, all tumors were classified into three histologic types: serous, mucinous, and “other.” There were no differ-

**TABLE 1**  
**Comparison of Personal and Tumor Characteristics of Women Diagnosed with Invasive versus Borderline Epithelial Ovarian Tumors**

Characteristic	Invasive N = 616 No. (%)	Borderline N = 151 No. (%)	P value*
<b>Personal characteristics</b>			
Age <50 years	210 (34)	97 (64)	<0.0001
Race (white)	537 (87)	132 (87)	0.94
High school grad	549 (89)	137 (91)	0.57
Income <\$30,000	159 (31)	43 (31)	0.92
<b>Tumor characteristics</b>			
<b>Histologic type</b>			
Serous	278 (45)	79 (52)	<0.0001**
Mucinous	52 (8)	60 (40)	
Clear cell	58 (9)	3 (2)	
Endometrioid	136 (22)	3 (2)	
Mixed	34 (6)	5 (3)	
Un/poorly diff	55 (9)	1 (1)	
Other	3 (0)	0 (0)	

Note. 112 missing income (102 invasive; 10 borderline).

\* P values comparing frequencies of demographic factors by invasive and borderline status were calculated by chi-square tests.

\*\* P value was calculated controlling for age using Mantel-Haenszel test.

ences in the demographic factors by histologic type analyzed separately within invasive/borderline status.

The percentage of women with symptoms was significantly higher for women with invasive versus borderline disease (any symptoms: 92 versus 84%,  $P = 0.001$ ; pelvic discomfort: 71 vs 66%,  $P < 0.05$ ; bowel irregularity: 47 versus 35%,  $P < 0.005$ ; "other" symptoms: 53 versus 38%;  $P < 0.001$ ) (Table 2). Conversely, women with borderline tumors were more likely to report having had no symptoms than women with invasive cancer (16 versus 8%,  $P = 0.001$ ). These differences remained with or without controlling for age. Differences were also seen among women with the serous histologic type, and, although not statistically significant due to smaller sample sizes, the same trends were evident for mucinous and "other"

histologic types. (For comparison, preliminary results from an ongoing population-based case-control study of ovarian cancer in North Carolina, being conducted by several of the authors, show that the percentages of 133 control women, ages 20–69 years, reporting having had pelvic discomfort, bowel irregularity, and urinary frequency/urgency for at least 2 weeks were 14, 13, and 18%, respectively (unpublished data).) "Other" symptoms were obtained with an open-ended question. Women mentioned having had bowel pain, menstrual irregularities, vaginal bleeding or discharge, other urinary problems, weight loss or gain, pain during intercourse, fatigue, respiratory difficulties, back pain, loss of appetite, pain or swelling in legs, lump or mass, night sweats or hot flashes, and fever. While each "other" symptom was reported by less than 10% of women, because we did not ask about each symptom in a systematic fashion, it is difficult to know their true prevalence among the women in the study.

Analyses conducted to determine whether age, race, education, or income were associated with the reporting of symptoms revealed that among women with invasive cancer, younger age (20–49 versus 50–69 years) was associated with a small increase in the reporting of symptoms (95 vs 90%,  $P = 0.02$ ). Specifically, younger women with invasive cancer were more likely to report pelvic discomfort (78 vs 67%,  $P = 0.005$ ) and urinary frequency/urgency (45 vs 33%,  $P = 0.003$ ).

Table 3 presents the median duration of symptoms in months by histologic type among women with invasive and borderline tumors who reported symptoms. The median duration of any symptom for all cases was 4 months (mean: 10.9 months, indicating a skewed distribution). Women with borderline tumors reported having had symptoms longer than women with invasive cancer with or without controlling for age (median: 6 vs 4 months,  $P = 0.002$ ). Whereas 75% of women with borderline tumors reported the initiation of any symptom within 24 months and specific symptoms (pelvic discomfort, bowel irregularity, and urinary frequency/urgency) within 12 months of diagnosis, 75% of women with invasive cancer

**TABLE 2**  
**Percentage of Women with Symptoms by Invasive/Borderline and Histologic Type of Epithelial Ovarian Tumors**

Symptoms	Invasive				Borderline			
	Serous (N = 278)	Mucinous (N = 52)	Other (N = 286)	All (N = 616)	Serous (N = 79)	Mucinous (N = 60)	Other (N = 12)	All (N = 151)
Any symptom	94	85	91	92	82**	85	92	84**
Pelvic discomfort	75	60	70	71	66*	67	58	66*
Bowel irregularity	51	44	44	47	35**	33	42	35**
Urinary freq/urgency	36	42	37	37	42	33	8	36
Other symptoms	54	56	52	53	34**	43	33	38**
No symptoms	6	15	9	8	18	15	8	16**

\*  $P < 0.05$ ; \*\*  $P < 0.01$  for difference in percentage for invasive versus borderline tumors controlling for age.

TABLE 3

**Median and Range of Months from First Experience of Symptoms to Date of Diagnosis by Type of Epithelial Ovarian Tumor**

Histologic type	Type of epithelial ovarian tumor	
	Invasive	Borderline
Any symptom	4 (556)	6 (127)**
Range	1–99	1–99
Interquartile range	1–12	2–24
Pelvic discomfort	2 (434)	4 (99)**
Range	1–96	1–99
Interquartile range	1–6	2–12
Bowel irregularity	3 (287)	5 (53)**
Range	1–99	1–90
Interquartile range	1–6	2–12
Urinary freq/urgency	3 (222)	6 (54)*
Range	1–99	1–36
Interquartile range	2–8	3–12
Other symptoms	3 (325)	4 (57)
Range	1–99	1–90
Interquartile range	1–6	1–12

Note. Values in parentheses indicate number of cases with specific symptoms.

\*  $P < 0.05$ ; \*\*  $P < 0.01$  for difference in months of symptoms for invasive versus borderline cancer controlling for age.

reported initiation of any symptom within 12 months and specific symptoms within 6–8 months of diagnosis.

Differences in length of time with symptoms between women with invasive cancers and those with borderline tumors among all histologic types were statistically significant for pelvic discomfort ( $P < 0.001$ ), bowel irregularity ( $P = 0.002$ ), and urinary frequency/urgency ( $P = 0.011$ ). Statistically significant differences in duration of symptoms among women with borderline versus invasive tumors were also noted in the subset of cases with serous histology. Length of time with symptoms was not associated with histologic type of tumor analyzed separately within invasive/borderline status, nor with age, race, education, or income.

The median number of months from first consultation with a physician to diagnosis for women with either invasive or borderline tumors was 1 month (range: 0–122 months). However, 75% of invasive cases were diagnosed within 3 months and 75% of borderline cases were diagnosed within 4 months after consulting with a physician. Analyses of the distribution of months from first consultation with a physician about symptoms to diagnosis by each of the demographic factors suggested that women who were younger, those who were non-White, and those with a lower household income took longer to diagnose ( $P = 0.03$ ).

Among all cases, the majority of women reported that symptoms of the cancer were the primary reason for the doctor visit leading to the diagnosis. However, women with invasive tu-

mors were more likely than women with borderline disease to report symptoms as the primary reason (62 versus 48%,  $P = 0.002$ ). Women with borderline tumors were twice as likely as women with invasive tumors to report routine examination as the primary reason for the doctor visit that led to their diagnosis (borderline 28%, invasive 16%,  $P < 0.001$ ). There were no differences in the percentage of women reporting each reason for the doctor visit by histologic type of cancer analyzed separately within invasive/borderline status. Among women with invasive cancer, those who were less educated (had not graduated from high school) ( $P = 0.01$ ) and who had a lower household income (<\$30,000) ( $P = 0.052$ ) were more likely to be diagnosed because of symptoms than routine examination.

## DISCUSSION

Results of two small retrospective medical record review studies [5, 8] support our findings that women with borderline tumors are more likely than women with invasive tumors to report not having had symptoms. Ranney and Ahmad [5] found that 13% of women with tumors of low malignant potential (LMP) ( $n = 38$ ) reported no symptoms, while 2.5% of women with invasive cancer ( $n = 42$ ) reported having had no symptoms. Eltabbakh *et al.* [8] noted much higher percentages of women reporting no symptoms (31.8 and 18.0% for borderline ( $n = 22$ ) and invasive cancer ( $n = 50$ ), respectively) than Ranney and Ahmad [5] or us. Whereas 90% of the women in our study reported having had symptoms, only 78% of women in the study by Eltabbakh *et al.* [8] reported symptoms. The lower percentage of women with symptoms reported by Eltabbakh *et al.* [8] most likely reflects the fact that only women with stage I/II ovarian were included in the study. Goff *et al.* [10] and Nelson *et al.* [9] have noted that women with stage I/II cancer were more likely to report having had no symptoms than women with stage III/IV disease. Our study and that of Ranney and Ahmad [5] included women with any stage disease, the majority of which were most likely stage III/IV since 75% of women are diagnosed with late-stage disease [11]. As stage information was not available to us, we could not assess the reporting of symptoms by early and late stage disease. However, the fact that Eltabbakh *et al.* [8] included women with stages I/II only when comparing the occurrence of symptoms among women with borderline versus invasive cancers means that differences found in our study are not necessarily due to differences in stage between women with borderline and invasive disease.

As with our study, Eltabbakh *et al.* [8] also reported that women with borderline tumors were more likely to have had symptoms for a longer duration than women with invasive cancer. They found that the mean duration of symptoms for women with borderline and invasive cancers was 8.0 and 3.4 months ( $P = 0.03$ ), respectively. We found that duration of

symptoms was highly skewed and, therefore, reported median values (6 versus 4 months for borderline and invasive cancers). The relatively short median duration of symptoms among women with invasive (mostly late stage) cancers suggests that the disease progresses rapidly.

Symptom duration (onset to diagnosis) reflects patient, physician, and system-related delays in diagnosis. We cannot tease them apart in our data. While the overall duration of symptoms was greater for women with borderline than invasive disease, the distribution of months from the date of first consultation to diagnosis (median: 1 month) did not differ by invasive/borderline status after controlling for age.

The longer duration of symptoms among women with borderline tumors is consistent with the notion that borderline tumors may be slower growing than their invasive counterparts, allowing them to be detected more often through routine gynecologic examinations. On the other hand, it is possible that symptoms among women with borderline tumors may be milder than those of invasive cancer, as suggested by Eltabbakh *et al.* [8], leading women to delay seeking medical attention. Severity of symptoms was not collected in our study or in other studies comparing symptoms among women with invasive and borderline tumors [5, 8]. While increased surveillance among women with borderline disease, who are often younger than women with invasive disease, might explain why borderline tumors are more often detected through routine examination, one would expect increased surveillance to result in decreased not increased duration of symptoms.

Limitations of the study include the clustering of ovarian cancer symptoms into three main groups (pelvic, bowel, and urination problems), limiting our ability to distinguish onset and duration of more specific symptoms. The lack of availability of tumor stage and size prevented us from assessing the effect of these factors on the reporting and duration of symptoms as well as the delay in diagnosis. Recall bias could potentially have accounted for the fewer symptoms reported among borderline versus invasive cases. For example, women with the less severe/more curable borderline disease may have underreported the occurrence of milder symptoms of lesser duration. To reduce chances of recall bias, only cases interviewed within 6 months of diagnosis were included in the study. Multiple statistical comparisons by symptom, histologic type, invasive/borderline status, and demographic factors could have led to some positive findings, while small numbers of women with borderline disease may have hindered our ability to detect some significant associations. The fact that a large number of women with ovarian cancer were systematically asked about each of the symptom groupings was an improvement over some past studies that employed retrospective review of medical records, relying on women to remember to mention specific symptoms and medical personnel to accurately record them.

## CONCLUSIONS

Because most women with ovarian tumors (92% invasive cases and 84% borderline cases) have symptoms and median symptom duration prior to diagnosis is 4 months, greater awareness of symptoms by women and physicians is needed for the earlier detection of ovarian tumors. The lesser likelihood of being detected by routine examination and the shorter symptom duration for invasive versus borderline cases underscores the need for effective screening and preventive strategies.

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