

Ovarian Cancer: The Neglected Diagnosis

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OBJECTIVE: To investigate presenting signs and symptoms of ovarian cancer and stage of tumor in a community cohort of women with the diagnosis of ovarian cancer.

PATIENTS AND METHODS: We reviewed retrospectively the medical records of all women who sought primary and specialty care in Olmsted County, Minnesota, between January 1, 1985, and December 31, 1997, to evaluate presenting symptoms, time from first symptom to diagnosis of ovarian cancer, and stage of tumor at diagnosis.

RESULTS: Of 107 women with a diagnosis of ovarian cancer, the most commonly documented presenting symptom was crampy abdominal pain. Urinary symptoms and abdominal pain were the most commonly documented presenting symptom in patients with stage I and II ovarian cancers, whereas abdominal pain and increased abdominal girth were the most commonly documented symptoms in patients with stage III and IV cancer. Approximately 15% of tumors (n=15) were found during routine evaluations or during a procedure for another problem. Less than 25% of presenting symptoms (n=24 women) related directly to the pelvis or were more traditional gynecologic symptoms. Delays in women seeking medical care, health care system issues, competing medical conditions, physicians' failure to follow up, and women not returning for follow-up were associated with longer time to diagnosis.

CONCLUSION: Both stage I and II cancer are associated with symptoms, but few symptoms are directly related to the reproductive pelvic organs or unique to ovarian cancer. A longer interval from first sign or symptom to diagnosis of ovarian cancer is associated with both patient and health care system factors.

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Ovarian cancer is the fifth most common cause of cancer-related deaths in US women after lung, breast, colon, and pancreatic cancer. Rates of diagnosed ovarian cancer vary from less than 15 per 100,000 women younger than 40 years to more than 50 per 100,000 women older than 70 years¹⁻⁴; thus, ovarian cancer is an uncommon condition in generalists' practices. Most women (60%-75%)³⁻⁵ have stage III or IV tumors at diagnosis, with 5-year survival rates of 30% or less.^{2,5,6}

The advanced stage of ovarian cancer at diagnosis has been attributed to 2 factors: the lack of a sufficiently reliable and cost-effective screening test⁷⁻¹⁰ and the presump-

tion that ovarian cancer is asymptomatic in the early stages, resulting in diagnostic delays.¹¹⁻¹⁵ Both self-report¹⁶⁻¹⁸ and medical records^{11,13,19} studies of women with ovarian cancer suggest that women may have symptoms for weeks to months before the initial diagnosis of ovarian cancer. Unfortunately, the symptoms noted in these studies are common symptoms in the general population²⁰ and are not directly associated with ovarian cancer.

The types of symptoms present in women with different delays in diagnosis have not been assessed, and the conflicting results of medical record and self-report data have not been addressed.^{18,21} The current study evaluated a population-based cohort of women diagnosed with ovarian cancer between 1985 and 1997 to identify presenting signs and symptoms, assess time between first recognition of signs or symptoms and diagnosis, and evaluate factors associated with periods of 2 months or longer between recognition of signs or symptoms and diagnosis.

PATIENTS AND METHODS

We reviewed retrospectively the medical records of all primary, specialty, and tertiary care provided to a population-based cohort of women with the diagnosis of primary ovarian cancer in Olmsted County, Minnesota, between January 1, 1985, and December 31, 1997. Capture of more than 98% of all medical care provided to these women is possible through the use of the Rochester Epidemiology Project (REP) that links a diagnostic database and the medical records of all medical care providers (outpatient, emergency, and inpatient) for all residents of the county.^{22,23} Thus, it is possible to identify all women with a physician diagnosis of ovarian cancer (including at autopsy) and to link these women with all the health care services they received in the 2-year period before their first diagnosis of ovarian cancer.

SETTING

Olmsted County is a standard metropolitan statistical area in southeast Minnesota. It is served by a large tertiary care multispecialty group (the Mayo Clinic), a 120-clinician primary care multispecialty group (the Olmsted Medical Center), and a 2-clinician family practice clinic (the Rochester Family Care Clinic). Previous studies have shown that these 3 groups provide more than 98% of the care delivered to Olmsted County residents.²³ The population of

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TABLE 1. Factors Associated With Delayed Diagnosis of Ovarian Cancer*

Time from signs or symptoms to diagnosis (mo)	Health care-seeking behavior		Health care system issues			
	Delayed presentation for care	Did not return for follow-up care	Diagnosis other than ovarian cancer	Delayed pelvic focus	Extended or delayed work-up	Competing conditions
2.1-4.0	5	0	2†	3	4	2‡
4.1-6.0	5	2	3§	2	5	2//
>6	0	7	0	1	6	0

*Values are number of women.

†Diverticulitis, pseudomyxoma peritonei.

‡Severe mitral stenosis, class IV congestive heart failure.

§Irritable bowel syndrome (n=2), diverticulitis, depression.

//New breast cancer, metastatic lung cancer plus active alcoholism with liver failure and unstable angina.

Olmsted County is approximately 120,000, and 90% of the residents are white non-Hispanic.

SUBJECT IDENTIFICATION

We searched the diagnostic database of the REP^{22,23} for all women who sought medical care for ovarian cancer, including those listed as having “primary peritoneal” cancer, between January 1, 1985, and December 31, 1997. In addition, the local Survey, Epidemiology, and End Results System registry was searched for all women residing in Olmsted County during the period of interest who had been diagnosed as having ovarian cancer. All diagnoses were reviewed in the medical records to confirm that they were new diagnoses during the study period and that they were diagnoses of primary ovarian cancer.

DATA COLLECTION

The REP database was used to identify and link each woman in the cohort with all medical records from any site at which she received medical care in Olmsted County. Beginning with the date of the first diagnosis of ovarian cancer at any site, information was abstracted for the period 2 years before the first diagnosis. Information collected included all visits; reasons for visits; all complaints of abdominal symptoms, fatigue, weight loss, pain, or discomfort; general feelings of being unwell; and the tests and referrals used to evaluate those complaints. The duration of symptoms before the first physician visit was abstracted if documented in the medical record. Special attention was given to collecting information on symptoms potentially linked to ovarian cancer that have been identified previously in the medical literature.^{2,11,13,16-18} If the record of evaluations led back more than 2 years, data were collected from the first visit that identified that specific complaint, as far back as the woman’s first visit to any Olmsted County medical facility. These data were merged with demographic information and mortality data from a previous study of this same population.²⁴

In addition to the usual recording of data, the nurse abstractors, who were familiar with the topic of ovarian cancer and with the records of Olmsted County medical facilities, constructed a short summary of each woman’s course of symptoms and care before the first diagnosis. This summary was used to ensure that the abstracted information provided a complete picture of the prediagnostic course of symptoms and care from the medical community’s perspective, capturing transitions across specialties and medical care sites and systems.

Data analysis included simple descriptive statistics, tabulation of symptoms, timing of testing and referrals, non-ovarian cancer diagnoses used to explain symptoms, time from onset of symptoms (as recorded in the medical record) to first visit, and time from first visit to diagnosis of ovarian cancer. Patients were divided into 2 groups: those with less than a 2-month period and those with a 2-month or longer period from the first documentation of a symptom or physical finding that was later associated with ovarian cancer to the diagnosis of cancer. Information from the nurse-constructed case summaries and the abstracted data were used to place all women with a 2-month or longer period between first symptom and diagnosis into categories describing factors associated with the diagnostic “course.” The choice of 2 months to complete a more in-depth study of the diagnostic course was arbitrary but consistent with previous studies.^{18,21}

Six categories were developed to describe the factors associated with the diagnostic course: 2 categories describe the women’s health care-seeking behavior and 4 categories describe issues related to the health care systems (Table 1). Each case with 2 months or longer from first symptom or sign to diagnosis of ovarian cancer was assigned to a category. This process is similar to qualitative analysis used to develop “theme” or “domains” from “field” notes. The nurses’ case summaries were used as field notes and reviewed by a team of 1 physician (B.P.Y.) and 3 nurses with

TABLE 2. Sign or Symptom, Stage at Diagnosis, and Time From Sign or Symptom Appearance to Diagnosis (N=107)*

Sign or symptom	Stage at diagnosis†			Time from first symptom to diagnosis‡ (mo)		
	Total§	I and II (n=42)	III and IV (n=62)	<2 (n=58)	2-6 (n=33)	>6 (n=14§)
Abdominal pain	38 (35)	9 (22)	22 (35)	21 (36)§	15 (45)§	2 (14)§
Bloating, increased abdominal girth	14 (13)	2 (5)∥	12 (19)∥	10 (17)§	3 (9)§	1 (7)§
Urinary symptoms	14 (13)	8 (19)§	6 (10)§	9 (15)	3 (9)	2 (14)
Mass noted by woman	8 (7)	2 (5)	6 (10)	4 (7)	4 (12)	0 (0)
Vaginal bleeding	10 (9)	4 (10)	6 (10)	7 (12)	3 (9)	0 (0)
Weight loss	5 (5)	0 (0)§	5 (8)§	3 (5)	1 (3)	1 (7)
Bowel changes	7 (6)	1 (2)§	6 (10)§	3 (5)	3 (9)	1 (7)
Fatigue	2 (2)	1 (2)	1 (2)	2 (3)	0 (0)	0 (0)
None	16 (15)	12 (28)∥	4 (6)∥	7 (12)∥	2 (6)∥	7 (50)∥
Other	8 (7)	3 (7)	5 (8)	2 (3)	5 (15)§	1 (7)

*Values are number (percentage).

†Does not include the 2 women in whom diagnosis was made at autopsy and the 1 woman who refused to undergo staging surgery.

‡Does not include the 2 women in whom diagnosis was made at autopsy.

§ $P \geq .05$.

∥ $P < .01$.

experience in immersion/crystallization analysis of qualitative data. The field notes were read, discussed, and reread until consensus was reached regarding the diagnostic course domains and the placement of cases within these domains. All cases with times of 2 months or longer were reviewed by a second physician (B.A.B.).

RESULTS

A total of 107 women were identified with incident cases of ovarian cancer. The age-adjusted incidence rate (adapted to the 1990 US white population) was 20.2 per 100,000 woman-years. At the time of diagnosis, the women ranged in age from 30.5 to 98.1 years, with a mean age of 64.7 years (SD, 23.8 years). All women were white non-Hispanic, and 20% were nulliparous.

Most of the tumors (n=98 [92%]) were classified as simple epithelial ovarian cancers. Five tumors were listed as primary peritoneal, 3 were listed as mixed mesodermal, and 1 was not specified. Sixty percent of the cancers (n=62) were stage III or IV (in 3 patients, stage of tumor was not known), and about 60% were grade 3 or 4. The 2-year survival rate varied from 96% for women with stage I and II tumors to 22% for those with stage III and IV cancers. The 5-year survival rate was 88% for women with stage I and II tumors and 17% for women with stage III and IV tumors.

The most common presenting symptoms recorded from visits close to the diagnosis of ovarian cancer were abdominal pain (often cramping pain); increased abdominal girth or bloating; urinary frequency, urgency, or incontinence; a mass noted by the woman; or no symptoms (Table 2). Other symptoms were documented less frequently, and

some symptoms, such as weight loss, were almost always accompanied by abdominal pain. Of the 16 women with no symptoms, 9 had a pelvic mass or "fullness" noted on a pelvic examination performed at a scheduled visit for some other problem; 1 was noted to have a pelvic mass when she presented to the emergency department with a transient ischemic attack; 5 had ovarian cancer diagnosed during an abdominal hysterectomy for other indications (3 for stress incontinence, 1 for early cervical dysplasia [cIN1], and 1 for metrorrhagia); and 1 was noted to have an externally visible pelvic mass during anesthesia induction for mitral valve replacement surgery (patient's body mass index, >40 kg/m²).

The initial symptoms varied by the stage of the tumor (Table 2). Patients with earlier-stage tumors (I and II) were about equally likely to present with abdominal pain and urinary symptoms, or the tumors were found during routine evaluation of "asymptomatic" women. Women with later-stage tumors (III and IV) were more likely to present with bloating or weight loss, symptoms that occur when the disease spreads beyond the pelvis.

The time from first recognized sign or symptom to the diagnosis of ovarian cancer ranged from 3 days to 18 months. Table 2 lists the first symptom(s) for all women, stratified by the time from first documented symptom or sign recognized by the woman or physician to diagnosis. The 2 women in whom ovarian cancer was diagnosed at autopsy were not included in the calculations. Of 105 women, the time from onset of symptoms or recognition of the first sign potentially associated with their ovarian cancer to the diagnosis of ovarian cancer was less than 2 months for 58 (55%), 2 to 6 months for 33 (31%), and more than 6 months for 14 (13%).

Abdominal pain and nonabdominal symptoms such as shortness of breath or pleurisy, symptoms that are not directly related to pelvic disease, were associated with a longer time between first symptoms and diagnosis. Symptoms with a strong link to gynecologic tumors, such as severe bloating or increased abdominal girth, were associated with a shorter time between symptom recognition and diagnosis.

Of women whose time from first symptom to diagnosis was difficult to determine, there were 5 in whom ovarian cancer was an unanticipated discovery at pelvic surgery: 2 hysterectomies for stress incontinence, 1 revision of an earlier vaginal hysterectomy with anteroposterior repair, 1 hysterectomy for uncontrolled menorrhagia, and 1 hysterectomy for treatment of early cervical dysplasia (cIN1). In all these women, tumors were 10 cm or smaller and limited to the pelvis (stage I or II). Whether any of these women had symptoms associated with their tumors or the other pelvic problems that resulted in surgery is unclear.

In 2 women, ovarian cancer was diagnosed at autopsy. Both diagnoses were anticipated, and the women died of other malignancies before surgical biopsy of the ovary or metastatic lesions could be completed.

Factors associated with periods of 2 months or longer between symptom recognition and diagnosis were grouped into those that appeared to be related to the woman's health care-seeking behavior (delayed presentation for medical care or lack of completion of recommended tests) and those related to the health care system (later inclusion of pelvic evaluation in the diagnostic process, establishing other diagnoses to explain symptoms, >1-month delay in scheduling of tests or referral appointments, and need to evaluate or treat competing medical problems). A greater than 1-month period in completing a referral process or an ordered test and reporting the results to the woman was the most common health care system issue (Table 1). For example, longer periods elapsed when a pelvic mass was noted on an ultrasound study or in a physical examination summary, but no documentation recommending follow-up care was found in the medical records. At least 4 women presented within 8 to 12 weeks of the initial examination with additional findings that triggered further evaluation and the diagnosis of ovarian cancer.

Nineteen women (18%) delayed seeking health care. Ten women had symptoms (recurrent abdominal pain, weight loss, pelvic mass, or increased abdominal girth) documented to have begun 3 to 6 months before their first symptom-related visit. Another 9 women did not appear to return for follow-up care that was documented in the medical record as "scheduled." These 9 women had either physical findings of a newly enlarged uterus (n=6) or pelvic ultrasonographic findings consistent with a "probably benign" ovarian cyst (n=3; 2 simple and 1 loculated cyst, all <8 cm). One of these

women eventually returned for follow-up ultrasonography but refused to undergo exploratory surgery.

In 5 women, a diagnosis other than ovarian cancer was established for presenting symptoms (abdominal pain [n=4], pelvic pressure [n=1]) that in retrospect appeared to be associated with ovarian cancer. The alternative diagnoses are listed in Table 1. The women diagnosed as having irritable bowel syndrome and depression had multiple prior medical visits, including visits more than a year previously, for recurrent symptoms that could be consistent with the initial diagnosis.

Six women presented with symptoms that led to evaluation of other organs in the abdomen, to a mental health evaluation, or to evaluation of the thorax. The presenting symptoms in these women included pleurisy, pleural effusion, "vague" abdominal pain (n=2), fatigue, and recurrent bouts of diarrhea. Besides the initial evaluation, these women often had multiple visits to subspecialists with no pelvic evaluation being performed. For example, 1 ovarian cancer was found by a gastroenterologist during sigmoidoscopy.

Four women had other major conditions diagnosed simultaneously with the first visit for possible ovarian cancer (Table 1). In each of these women, specific diagnostic testing of the possible ovarian disease was delayed until the other competing condition could be evaluated (breast mass [cancer]) or treated (severe mitral stenosis, unstable angina, liver failure, and class III congestive heart failure).

DISCUSSION

Most women in this cohort had symptoms or signs for weeks to months before ovarian cancer was diagnosed. Those with earlier stages of tumors presented with urinary symptoms or vague abdominal pain, or an enlarged ovary was found on routine examination or during surgery for another gynecologic problem. Rapid diagnoses were associated with women presenting with bloating or increased abdominal girth. Unfortunately, these rapid diagnoses due to symptoms of ascites were for stage III and IV tumors.

For most women, the initial documented symptoms were not specifically related to the pelvis or commonly considered gynecologic problems. Nelson et al¹¹ and Wikborn et al¹³ found similar results in their data from the Swedish Health Care System, in which gastrointestinal symptoms, either abdominal pain or bowel changes, were documented most frequently as the presenting symptoms in women with ovarian cancer. The distribution of presenting symptoms was similar in both the Swedish studies and the current study of women in Olmsted County.

However, the frequency and distribution of symptoms in medical records studies are different from information in studies that ask women to self-report prediagnostic symptoms 1 to 4 months after initiation of chemotherapy.^{15,16,19,25}

Self-reported data show a much higher percentage of women relating the prediagnostic presence of abdominal swelling and fatigue but lower rates of abdominal pain and urinary symptoms. When given a list of possible symptoms and asked to check all that were present, women marked substantially more symptoms and indicated that all occurred with greater frequency than documented in their medical records.

The differences in self-reported data and symptoms documented in the medical record are not surprising. Recall bias of self-reported symptoms collected after a serious event or diagnosis has been described previously.²⁶⁻²⁸ Although activities documented in the medical record have been shown to be an adequate proxy for those that occur during a medical visit,²⁹⁻³⁰ this may not be true for recording all symptoms mentioned during the visit. Also, it is likely that during a medical visit women do not report all the symptoms they experience, especially if they do not associate them with their current problem.²⁵ Medical record documentation is dependent on the information that the physician or nurse selects to record. This selection may be based on the physician's ability to elicit information from the patient, the perceived importance and need to document each piece of information, and the competing time demands of medical practice.³¹ Therefore, symptoms may not be elicited, heard, linked to the working differential diagnosis, or recorded. This documentation bias may be as important as women's recall bias in explaining discrepancies in information in self-reported¹⁸ and medical records studies.

Most women with ovarian cancer have symptoms for weeks or months before the cancer is diagnosed. The majority of these symptoms are related to the entire abdomen and are not specific to the pelvis. The prior probability that isolated or even chronic crampy abdominal pain or urinary stress incontinence is associated with ovarian cancer is extremely low. For example, irritable bowel syndrome is estimated to affect 5% to 15% of the population,⁴ whereas ovarian cancer affects less than 0.1%.^{3,24} Therefore, generalists appropriately look first for common explanations and may not include ovarian cancer in the initial differential diagnosis. However, a pelvic examination should be included in the evaluation of abdominal problems in women of any age. In addition, although it is appropriate to consider common causes of symptoms first, persistent symptoms unresponsive to therapy require more comprehensive differential diagnoses, including uncommon conditions such as ovarian cancer in a woman with unresolved abdominal pain or urinary urgency. Symptoms such as an increased abdominal girth or weight loss have higher prior probabilities for malignancies and are evaluated more promptly for ovarian cancer but are usually associated with a higher stage of disease.^{12,32,33}

Articles in women's magazines encourage women to be evaluated for abdominal pain and urinary symptoms.³⁴ Al-

though this advice may be helpful to women who delay presentation for evaluation of abdominal masses, the effect on early diagnosis of ovarian cancer is less clear. In the current study, 10 women had a documented delay in seeking medical care of more than 1 month after they had first recognized a sign or symptom. Earlier presentation for evaluation may have hastened a diagnosis, but it is unclear whether the diagnosis would have been of an earlier stage of tumor.

For the health care systems, 2 issues of potential importance were noted. First, increased physician awareness that ovarian cancer is symptomatic in its early stages might lead to more complete explanations and documentation of reasons for testing (eg, to rule out ovarian cancer) that would facilitate patient follow-through and help consultants provide better interpretation of results. Increased awareness and more complete documentation of the differential diagnosis might also result in more aggressive recall of women who failed to return for recommended testing and evaluation (10% of the women in our study). In our study, 4 women with early symptoms were lost to follow-up, and late-stage disease was diagnosed months later.

Second, health care systems' mechanics for completion of referral or ordered testing may be an appropriate area for continuous quality improvement. Most of the interrupted testing or referral processes seen in our study group of women appeared to result in periods of diagnostic uncertainty of no more than 2 to 3 months and may have had no effect on the stage of disease at diagnosis. However, this type of system lapse is unacceptable and can serve as a marker for quality improvement opportunities.

On the basis of these data and information from other studies, it remains unclear how we can effectively increase early diagnosis of most ovarian cancers. Although mass screening has the potential to improve early recognition based on rapid technological advances in the analysis of tumor/serum markers, it remains a challenge given the rarity of ovarian cancer diagnoses in the general population and the resulting high false-positive rates of screening tests.^{35,36} Ovarian cancer screening in a high-risk population increases the prior probability of disease and positive predictive value of the tests. However, such testing is still in the early stages of evaluation.^{7,9,10,37} In fact, despite high expectations of ultrasound screening in high-risk populations, Schwartz et al³⁸ described the limited value of the role of ultrasonography as an independent modality to detect early-stage ovarian carcinoma.

Our study has several limitations. As with most rare conditions, our sample size is small, and our study is limited to white non-Hispanic women. Therefore, the data may not be generalizable to the US nonwhite or Hispanic population. Using medical records limits information to that in the medical record. Women may have discussed other

symptoms that physicians did not record, and physicians may have considered ovarian cancer a possibility but failed to document this suspicion or its evaluation with a pelvic examination. Failure to document a pelvic examination is unlikely according to previous, direct observation of primary care studies and would appear to be uncommon in the current climate of excessive medical litigation claims.

Because we evaluated only women in whom ovarian cancer was diagnosed, it is not possible to discuss the prior probability of ovarian cancer in women presenting with recurrent abdominal pain or other commonly reported symptoms. However, we assumed that the prior probability of ovarian cancer is low in women presenting with these symptoms and did not suggest immediate evaluation for ovarian cancer but rather evaluations of common problems first and then continued evaluation for more rare problems if the symptoms persisted for unknown reasons or if treatment of the diagnosed conditions failed. Finally, this study did not include women who may have had undiagnosed ovarian cancer.

CONCLUSION

Symptoms of early ovarian cancer, such as urinary symptoms and crampy abdominal pain, are often associated with other more common medical conditions. However, when recurrent, unresolved, or unexplained, these symptoms require exclusion of ovarian cancer as an etiology. By ruling out this diagnosis in a timely manner, we will reduce the interval between first sign or symptom and treatment and possibly improve the survival of our patients.

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