Comparison of symptoms and presentation of women with benign, low malignant potential and invasive ovarian tumors

C.M. Olsen[1, 2], J. Cnossen[3], A.C. Green[1], P.M. Webb[1]

[1]*Cancer and Population Studies Group, Queensland Institute of Medical Research, Brisbane*
[2]*School of Population Health, University of Queensland, Brisbane (Australia)*
[3]*Department of Gynecology and Obstetrics, University Medical Center, Groningen (The Netherlands)*

Summary

Objectives: To describe symptoms, delay in presentation and reasons for non-presentation among women diagnosed with benign, low malignant potential and malignant ovarian tumors. *Methods:* Study participants included 457 women who underwent surgery for an ovarian tumor in Queensland, Australia, between July 1999 and February 2002 (244 with invasive cancer, 62 with low malignant potential tumors, and 151 with benign ovarian tumors). Women were contacted a minimum of three months post-diagnosis. Information concerning symptoms and presentation history was obtained via interview. *Results:* Overall, only 8% of the women were asymptomatic at the time of their diagnosis. Women with invasive cancer reported a greater number of symptoms (3.1 and 3.6 for Stages I-II and III-IV, respectively) than women with benign or low malignant potential tumors (2.8 and 2.2 respectively; $p < 0.0001$). Women with invasive disease were more likely to experience weight loss or gain, general malaise, chest/respiratory pain, abdominal swelling and bowel symptoms than women with benign ovarian tumors, however the symptom pattern for early- and late-stage invasive ovarian cancer could not be clearly differentiated. There was no suggestion that women with advanced stage disease had delayed longer before presenting to their doctor. The most common reasons given for not telling their doctor about specific symptoms were the woman's perception that the symptom was not serious enough, it was mild or intermittent, or was related to normal physical changes associated with age or menopause. *Conclusions:* We found only marginal differences in the symptom patterns of early and advanced stage invasive cancer. Delay in presentation was not associated with more advanced disease suggesting that earlier diagnosis may not increase the proportion of cancers diagnosed at an early stage.

Key words: Ovarian neoplasm; Signs and symptoms; Diagnosis.

Introduction

Ovarian cancer is the sixth most common cancer in women [1]. The low incidence of the disease in the population (12.6/100,000 in Australia [1]; 14.2/100,000 in the United States [2]) makes successful screening difficult and, although research using serum proteomic methods to find new markers of early-stage disease is ongoing [3-6], current screening modalities of CA-125 and transvaginal ultrasonography have not been shown to reduce mortality in unselected populations [6, 7].

While most women diagnosed with ovarian cancer have one or more symptoms [8-12], these are often subtle and non-specific (e.g. abdominal discomfort, bloating, gastrointestinal symptoms or back pain) [11, 13, 14], and can be easily attributed to other common illnesses, such as irritable bowel disease, or other more common gynecologic conditions, leading women to delay seeking medical attention [8, 14-17], or to delays in diagnosis [16-20]. As a result, around 75% of women with surgically staged ovarian cancer have advanced disease at diagnosis [21], and five-year survival rates for women with advanced disease range from 10-30% compared with 60-80% for women with early-stage disease [22].

In order to make advances in the early detection of ovarian cancer, there must be earlier recognition of possible symptoms of the disease among medical practitioners and women themselves. Although in recent years there has been an increase in research focussing on symptoms experienced prior to diagnosis of ovarian cancer [8-12, 15, 17, 20, 23-26], very few have examined delays in presentation [15, 20, 27], or reasons for non-presentation [15]. This study describes the symptoms experienced by women with benign, low malignant potential and invasive ovarian tumors. We also report on the symptoms which prompted women to go to their doctor, the timeliness of this first presentation and of the diagnosis, and women's reasons for not reporting symptoms to their doctor.

Methods

Women who underwent surgery for an ovarian tumor in Queensland, Australia, between July 1999 and February 2002 were identified via the Queensland Centre for Gynecological Cancer (QCGC). Permission to contact each woman was obtained from her treating physician. Women were eligible if aged between 18-79 years of age, able to give informed consent, and able to speak English. A total of 685 eligible women were identified, 612 (89%) were able to be contacted, and 457 of these (75%) participated in the study.

The study was approved by the Human Research Ethics Committees at the Queensland Institute of Medical Research, the University of Queensland, and participating hospitals.

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Data Collection

Women were contacted a minimum of three months post-diagnosis (median 12 months). Information was collected using a standard questionnaire in a face-to-face or telephone interview with a trained interviewer. Women were presented with a list of 11 symptoms and asked which symptoms they had experienced, when they started, whether they reported the symptom to their doctor and when, and if not, the reasons for this. Women were also able to report symptoms experienced that were not listed.

Statistical Analysis

Women were grouped according to their diagnosis: benign, low malignant potential, early (FIGO Stage I-II) or advanced (FIGO Stage III-V) invasive cancer. Continuous variables were compared using independent t-tests for two groups and analysis of variance for more than two, categorical variables were compared using chi-squared tests. Analyses were conducted using SAS (SAS Institute, Cary, NC, USA).

Table 1. — *Symptoms reported by 421 women with benign and malignant ovarian tumors.*

Symptom	Benign (n = 129) %	LMP (n = 57) %	Stage I/II (n = 85) %	Stage III/IV (n = 150) %	Total %	p value
No symptoms	14.6	8.1	4.5	3.2	7.9	0.002
Abdominal symptoms:						
Lump	11.9	19.4	19.1	14.8	15.3	0.37
Swelling	30.5	48.4	42.7	60.0	45.3	< 0.0001
Pain/Pressure	54.3	56.5	56.2	58.1	56.2	0.93
Gynecological symptoms:						
Abnormal bleeding	17.9	14.5	22.5	11.6	16.2	0.14
Pain on intercourse	6.6	6.5	7.9	6.5	6.8	0.06
Urinary symptoms	25.2	25.8	24.7	27.1	25.8	0.99
Gastrointestinal symptoms:						
Gas/Nausea/Indigestion	23.8	27.4	33.7	43.9	33.0	0.002
Bowel symptoms	13.9	11.3	23.6	32.3	21.7	0.0002
Chest/Respiratory symptoms	4.6	3.2	7.9	20.0	10.3	< 0.0001
General symptoms:						
Weight loss	2.0	3.2	5.6	13.6	6.8	0.0004
Weight gain	15.9	35.5	23.6	26.5	23.6	0.01
Lower back pain	9.3	6.5	9.0	5.8	7.7	0.65
General malaise	4.6	12.9	18.0	21.9	14.2	0.0002
Other	4.0	6.5	13.5	13.6	9.4	0.01
Any symptom	85.4	91.9	95.5	96.8	92.1	0.002

*X^2 test for homogeneity.

Results

The final study group included 151 women with benign ovarian tumors, 62 with low malignant potential tumors and 244 with invasive ovarian cancer (89 Stage I-II and 155 Stage III-IV). Mean age at diagnosis was significantly higher for women with Stage III-IV cancer (58.1 years), compared with women diagnosed with Stage I-II cancer (53.3 years), benign ovarian tumors (53.7 years, respectively), and low malignant potential tumors (49.1 years) ($p < 0.0001$). There was no difference between the groups in marital status, ethnicity, income or education level (data not shown). Some 107 women (25%) reported having a family history of breast cancer, 17 (4%) of ovarian cancer, and 14 (3%) of both breast and ovarian cancer. Twenty-one women reported a previous diagnosis of breast, uterine or cervical cancer; these women were equally distributed across the study groups.

Types and frequency of symptoms

A total of 421 women reported having experienced symptoms prior to their diagnosis; 85% of those with benign tumors, 92% with low malignant potential tumors, 96% with early-stage cancer and 97% with advanced cancer ($p = 0.002$) (Table 1). Overall, abdominal pain/pressure (56%) or swelling (45%) were the symptoms reported most frequently, followed by gas/nausea/indigestion (33%) and urinary symptoms (26%). While abdominal pain/pressure and urinary symptoms were equally common in all patient groups, the prevalence of both abdominal swelling and gas/nausea and indigestion increased significantly with increasing extent of disease. The prevalence of other non-specific symptoms including bowel symptoms, weight loss/gain, chest/ respiratory symptoms also increased significantly with increasing severity of disease. Gynecological symptoms such as amenorrhoea or dysmenorrhoea (16%) and pain on intercourse (7%) were less commonly reported by women overall. Among women with advanced disease (Stage III-IV) the most commonly reported symptoms were abdominal swelling (60%) and abdominal pain/pressure (58%); however these were also the most commonly reported symptoms by women with early-stage cancer, low malignant potential or benign disease.

Women with invasive cancer reported a greater number of symptoms on average (3.1 and 3.6 for Stages I-II and III-IV, respectively) than women with low malignant potential tumors or benign disease (2.8 and 2.2, respectively; $p < 0.0001$). After controlling for age at diagnosis, the following symptoms were all significantly associated with a diagnosis of invasive disease: weight loss ($p = 0.004$) or gain ($p = 0.02$), general malaise ($p = 0.0001$), chest/respiratory pain ($p = 0.001$) abdominal swelling ($p < 0.0001$), and bowel symptoms ($p = 0.0002$). Among women with invasive disease, abdominal swelling ($p = 0.004$) and chest/respiratory pain ($p = 0.009$) were significantly more common among women with Stage III-IV disease than those with Stage I-II cancers.

Symptom onset, duration, and presentation to a medical practitioner

The symptoms most likely to be reported to doctors were lower back pain (83%), abnormal bleeding (76%), general malaise (74%) and abdominal pain/pressure or an abdominal lump (70%). The symptoms least likely to be reported to a doctor were unexplained changes in weight.

The symptoms that women were most likely to report to their doctor within one week of onset were chest/respiratory pain (51%), abnormal bleeding (43%), and abdominal pain or pressure (41%) (Table 2). An abdominal lump, abdominal pain/pressure, abnormal bleeding, chest or respiratory symptoms, lower back pain and general malaise were also commonly reported within three months.

Table 2. — *Time delay from symptom onset to presentation.*

	Percentage of women reporting sympton within:				
	< 1 week	1 week - < 3 months	3-6 months	> 6 months	Never*
Abdominal symptoms:					
Lump	37.2	23.8	6.0	3.0	30.0
Swelling	26.6	20.6	5.9	4.9	42.0
Pain/Pressure	41.4	21.1	4.0	3.6	30.0
Gynecological symptoms:					
Abnormal bleeding	42.7	20.7	1.4	11.0	24.3
Pain on intercourse	19.4	19.4	3.3	9.7	48.4
Urinary symptoms	27.4	18.3	6.4	6.4	41.5
Gastrointestinal symptoms:					
Gas/Nausea/Indigestion	27.6	18.6	4.8	6.9	43.0
Bowel symptoms	29.9	16.0	5.3	3.2	45.4
Chest/Respiratory symptoms	51.1	12.8	0.0	2.1	34.0
General symptoms:					
Weight loss	9.7	9.7	6.4	3.2	71.0
Weight gain	13.7	5.9	10.8	2.0	67.6
Lower back pain	33.7	24.5	6.1	18.4	17.1
General malaise	37.7	19.7	6.6	9.8	26.1
Other	39.1	19.5	5.6	5.6	30.2

* Includes a small proportion of women who could not recall whether they had reported the symptom to their doctor.

Table 3. — *Reasons given by 103 women who experienced at least one symptom in the 12 months prior to diagnosis but did not report the symptom to their doctor.*

Reason for non-presentation	n (%)
Nature/degree of symptoms (mild/intermittent, single episode)	29 (28.2%)
Symptoms not considered significant/serious	29 (28.2%)
Symptoms attributed to normal physical changes (e.g., age, menopause)	21 (20.4%)
Symptoms attributed to emotional state (e.g., stress)	9 (8.7%)
Symptoms attributed to existing medical condition (e.g., IBD, IBS)	8 (7.8%)
Reluctance to visit doctor (fear, embarrassment)	3 (2.9%)
Preferred practitioner not available	2 (1.9%)
Patient travelling at time of symptom occurrence	2 (1.9%)

IBD = irritable bowel disease
IBS = irritable bowel syndrome

Time delay from symptom onset to presentation to a doctor was not associated with level of education, income or family history of either breast or ovarian cancer. Older women did not wait as long as younger women to report either abdominal swelling ($p = 0.03$) or lower back pain ($p = 0.04$), but there was no significant age difference in the time delay from symptom onset to presentation for any other symptom. There was no suggestion that women with advanced disease had delayed longer before presenting to their doctor. Instead, women diagnosed with Stage III-IV invasive cancer had reported both bowel symptoms ($p = 0.002$) and abdominal swelling ($p = 0.004$) after a significantly shorter duration than women in the other groups. The time interval from onset of the first symptom to diagnosis ($p = 0.16$) and from first presentation to a medical practitioner to diagnosis ($p = 0.50$) were also not associated with stage of disease at diagnosis.

Reasons for non-presentation

A significant proportion of women (36%) reported having at least one symptom that they did not report to a doctor. Table 3 shows that the main reasons women did not report their symptom to their doctor were because they did not consider it significant or serious enough (28%), because the symptom was mild and/or intermittent (28%), or because they had attributed the symptom to normal physical changes associated with age or menopause (20%). There was no significant association between stage of disease at diagnosis and reasons given for nonpresentation ($p = 0.16$).

Incidental diagnosis

For 94 women (21%), their ovarian tumor was not diagnosed based on the presence of symptoms but during a routine doctor visit or other surgery. Women with benign ovarian tumors were more likely to be diagnosed through routine examination (31%) than women with either low malignant potential tumors (12%) or invasive cancers (11% of Stage I-II, and 18% of Stage III-IV) ($p = 0.003$). Thirty-six of these women reported experiencing no symptoms, but it is important to note that 58 (62%) reported experiencing one or more symptoms in the 12 months prior to their diagnosis and 31 (53%) (11 invasive, 2 low malignant potential and 18 benign) of these women had reported at least one symptom to their doctor in that time period.

Discussion

The proportion of asymptomatic women in this study was 8.0%, which is comparable with the results of a recent meta-analysis (7.2%) [9]. Our finding that a lower proportion of women with invasive cancers were asymptomatic than those with low malignant potential cancers is also consistent with other research comparing these groups of women [12, 24, 28]. The proportion of women who were diagnosed through routine examination (21%) is higher than has been reported elsewhere (Vine *et al.*, 12% [10], Yawn *et al.*, 15% [17]), however more than half of these women reported experiencing symptoms in the year prior to their diagnosis, and 53% of these women had reported at least one symptom to their medical practitioner in that time period.

The most frequently reported symptoms were those that can be attributed to mass effect in the abdomen (abdominal pain/pressure or swelling, gas/nausea/indigestion, urinary and bowel symptoms). The symptoms most strongly associated with invasive cancer were those common to many cancers (and ill-health in general) including weight loss and general malaise, followed by chest/respiratory pain, abdominal swelling, and bowel symptoms. This compares with a similar study using controls with benign disease which found that bloating, urinary urgency and constipation were the symptoms most strongly associated with invasive cancer [8]. It is important to note that the associations would probably be even stronger if a disease-free control group was used for comparison. Of the women diagnosed with invasive disease, the only symptoms significantly and specifically associated with late-stage disease were abdominal swelling and chest/respiratory pain, both most likely associated with ascites and/or metastatic disease [29].

Of clinical importance is the finding that women with malignant ovarian tumors were more likely to report a greater number of symptoms than women with benign ovarian tumors or those with low malignant potential tumors. In a previous study, Goff *et al.* [8] also found that the median number of symptoms experienced by women with ovarian cancer was higher than for women with benign ovarian tumors.

The symptoms most likely to be reported by women to their doctor quickly included chest/respiratory pain, abdominal pain/pressure, abnormal bleeding, an abdominal lump and general malaise. It may be that these symptoms are associated with some medical urgency (e.g., difficulty breathing, severe pain), or alternatively they may be obvious as being atypical for the woman (e.g., abdominal lump). Symptoms that were most likely not to be reported quickly included weight loss and pain on intercourse. Weight loss can be attributed to numerous causes, and thus may not be recognized as clinically relevant. Pain on intercourse may be less likely to be reported quickly because of the personal nature of the symptom. In contrast to the finding of Goff *et al.* [18], we did not find that women with advanced disease were more likely to have delayed reporting symptoms to their doctor. The most common reasons given for not telling their doctor about specific symptoms were the woman's perception that the symptom was not serious enough, it was mild or intermittent, or was related to normal physical changes associated with age or menopause.

The strengths of this study include its size, population-based design, and relatively high participation rate (75%). The study did not rely on medical record review. All participants were interviewed in-person with a standardized questionnaire, and were systematically asked a series of detailed symptom questions. All women were asked about specific symptoms rather than broad categories of symptoms, enabling distinction between onset and duration of specific symptoms. The study may be limited due to its retrospective design. There is potential for recall bias since women were interviewed up to three years post-diagnosis, and the ability to accurately recall symptoms experienced before diagnosis is likely to decrease with time [30], however, the average time duration between diagnosis and interview was not significantly different for the different diagnosis groups and thus the effect of such as bias would be non-differential. It is also possible that women with a diagnosis of ovarian cancer may be more likely to over-report symptoms as a result of their diagnosis. However, since all women in the study were reporting symptoms associated with a diagnosis of an ovarian tumor, such a bias, if any, is likely to be small.

We were unable to differentiate early-stage disease on either the presence or absence of any particular symptom; the most common symptoms for early-stage disease (abdominal pain/pressure or swelling) were also the most common symptoms reported for women with benign or low malignant potential tumors as well as in advanced-stage disease. One feature that may help to distinguish women with ovarian cancer from other women is symptom severity [8]. Although we did not record the severity of symptoms in this study, we found that women with advanced disease were more likely to report symptoms including abdominal pain/pressure and bowel symptoms quickly, suggesting a greater severity of these symptoms.

In terms of the natural history of ovarian cancer, clinical studies of women who had normal-appearing ovaries at hysterectomy and who subsequently developed ovarian cancer have shown that advanced disease can develop within 13-24 months [31, 32], and it would seem plausible that women would develop symptoms during this time period. The different subtypes of ovarian cancer may, however, develop via different pathways and at different rates. For example, Singer *et al.* [33] and Jordan *et al.* [34] have postulated that low and high-grade serous cancers represent two distinct entities: one a slow-growing cancer that progresses from a benign or low malignant potential tumor, and the other an aggressive cancer that progresses rapidly. If this is the case, then the spectrum of symptoms and their timing may differ according to the subtype of cancer. Women with low-grade serous or mucinous carcinoma might be expected to develop symptoms over time as the disease progresses slowly, while those with the most commonly encountered high-grade serous carcinomas may develop symptoms of greater severity in a shorter time-frame in parallel with the rapid advancement of disease. With such a scenario, the fact that most women are diagnosed with advanced disease may be a consequence of aggressive tumor growth rather than delays in detection.

Regardless, better symptom recognition and awareness by women is essential if improvements are to be made in the timeliness of presentation. Women should be encouraged to seek early consultation for symptoms, including those that are general or non-specific, mild or intermittent, particularly if they are experiencing more than one symptom. Women who are experiencing persistent, recurrent or unexplained abdominal symptoms together with more general symptoms of ill-health including general malaise should be promptly investigated for ovarian cancer. It remains unclear, however, whether earlier diagnosis will result in greater detection of early-stage disease since there appear to be only marginal differences in the symptom pattern of early- and advanced-stage disease, and delay in diagnosis was not associated with stage of disease at diagnosis. It may, however, allow the performance of an optimal cytoreduction which is the most important predictor of long-term survival [29, 35].

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Address reprint requests to:
C.M. OLSEN, PhD
Cancer and Population Studies Group
The Queensland Institute of Medical Research
PO Royal Brisbane Hospital
Herston QLD 4029 (Australia)