

Symptoms of ovarian cancer in young patients 2 years before diagnosis, a case–control study

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Ovarian cancer is usually diagnosed after it has spread and is difficult to cure. Most of attempts to identify early symptoms have lacked control group or have been based on interviews. We examined early symptoms of ovarian cancer in young women and compared with a matched control group. Symptoms recorded in medical files of 100 women aged 15–35 years with ovarian cancer who were referred to Vali-Asr hospital between 1995 and 2005. Symptoms of cases were compared with 100 matched controls during 2 years before diagnosis. More cases (95%) than controls (28%) complained of at least one symptom up to 2 years before diagnosis, most of these symptoms were abdominal. Others included urinary symptoms, infertility and abnormal vaginal bleeding. The most common symptoms among cases were: unusual abdominal or lower back pain 52%, unusual bloating, fullness and pressure in the abdomen 37%, gastro-intestinal problems 36%. In total, 11%, 3% and 12% of controls reported these symptoms respectively, resulting in odds ratios of 8.7, 18.9 and 4.1 respectively for these symptoms. Unusual abdominal or lower back pain, fullness and pressure, gastrointestinal, urinary problems and infertility should make women and physicians more aware of changes associated with ovarian cancer.

Keywords: ovarian cancer, early symptom, young women.

INTRODUCTION

Ovarian cancer continues to be one of the main causes of cancer death among women. The annual incidence rate varies between 9 and 17 cases per 100 000 women, being higher in those in developed countries (Benedet *et al.* 2000).

Most women with ovarian cancer are diagnosed when the disease is advanced and difficult to cure (Ozols *et al.*

2001; Friedman *et al.* 2005). Most of the epithelial ovarian carcinomas are diagnosed in post menopause women, the average age at diagnosis is 51 years. Only 10% of tumours are detected in patients younger than 40 years and around 3% of them in those younger than 30 years old (FIGO 2006; Sardi *et al.* 2005).

Non-epithelial ovarian cancer forms dominate in young girls before the age of puberty (Harlaps 1993). In a population including all ages, 3–5% of the ovarian malignancies are sex cord-stromal tumours and about 6% are germ cell tumours (Saigo 1993).

Thus, efforts have been made to identify early symptoms of ovarian cancer in the hope that women experiencing them will seek medical care promptly and care providers, in turn, will have a high index of suspicions when patients report them. It has been suggested that if

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the percentage of detection in stage I could be increased from 25% to 75%, mortality would be reduced by 50% (Van Nagell 1991).

Most of the studies to date have identified symptoms experienced by women at all ages and after diagnosis of ovarian cancer.

Previous publications have not ascertained symptom in control groups of women without ovarian cancer (Pearse & Behrman 1954; Ranney & Ahmad 1979; Flam *et al.* 1988; Wikborn *et al.* 1993).

Other studies have been based on interviews or self-administered questionnaires completed by patients or their families (Smith & Anderson 1985; Goff *et al.* 2000, 2004; Olson *et al.* 2001; Koldjeski *et al.* 2003; Webb *et al.* 2004). Only two of these included control groups (Olson *et al.* 2001; Goff *et al.* 2004). Since recall bias, meaning that cases are more apt to remember symptoms than controls, is a major pitfall in these studies.

In this study, we evaluated the early symptoms of ovarian cancer in young women and compared these symptoms with age-matched healthy controls.

MATERIALS AND METHODS

Our ovarian cancer cases were among women aged 15–35 years who were originally evaluated in different clinics, primary care units and hospitals related to Tehran University of Medical Sciences (TUMS) and were referred for further evaluation to Vali-Asr gynecology oncology clinic of Imam Khomeini hospital, which is the main hospital of TUMS, between 1995 and 2005. Women with ovarian cancer were eligible if they were aged between 15 and 35 and resided in Iran. The Institutional review board of Imam Khomeini hospital approved this study and informed consent was obtained from all cases and controls. We found 100 cases of ovarian cancer. About 41% were diagnosed with disease confined to the ovaries (stage I) and 56% with some evidence of metastases or progression beyond the ovary (stages II, III, IV). Three patients suspicious to ovarian cancer did not accept the operation according to their desire even though they were informed of the risk of progression of their cancer.

Controls were among all females who were under supervision of TUMS healthcare system in primary healthcare units of Tehran for preventive care such as vaccination, contraception but not because of abdominal or gynecological symptoms and were then matched for year of birth, length of self referral to the clinic, and medical facility used based on location of residence. Then a control subject was randomly selected from them for each case.

A structured interview was carried out by two medical record analysts. The period covered for cases were 2 years before the date of they were informed of the diagnosis. Symptoms often reported in the outpatient setting including visits, with emphasis on abdominal, gastrointestinal, lower back, urinary and pelvic or coital symptoms.

The list was expanded as the analysts initially recorded all symptoms that they found in the charts. It was clear that much effort was being spent on recording symptoms and conditions unlikely to be related to ovarian cancer, such as upper respiratory tract infections. The list from 62 symptoms was then reduced to 41 symptoms. An evaluation was performed for the most common symptoms, which were more prevalent in cases than controls, before designing the final analysis for individual common symptoms. We report here only the symptoms which are statistically different in cases in comparison with controls; other symptoms like hot flushes, lower and upper paresthesia, numbness, burning, tingling, rectal pain, unintentional weight loss, headache, shortness of breath, anxiety and panic attacks were excluded since they were not statistically different between cases and controls. Our analysis consisted of comparing the number and percentage of cases and controls reporting each symptom, looking at the entire period 2 years before diagnosis of cases to cut-off date.

We selected women 15–35 years because incidence of ovarian cancer in this age group is low and finding cancer in lower stages and in younger women may mean them more than older age groups. Besides, in our Medline search from January 1970 to July 2006, there was only one study (Flam *et al.* 1988) restricted to young women with ovarian cancer and we found this topic a new one which requires more studies. Furthermore, in our centre's 20-year experience in surgery of ovarian cancer, the proportion of our young patients is increasing. We included all subtypes of ovarian cancer because the number of cases through 11 years was small in this age group.

We used spss (version 13) to analyse data and present odds ratios (OR) and 95% confidence intervals (CI) based on the chi-squared test and Fisher's exact test to describe differences between cases and controls.

RESULTS

Of 100 young women with ovarian cancer, 42 (42%) were epithelial (including 10 borderline tumours), 41 (41%) were germ-cell, 14 (14%) were stromal and sex-cord, two (2%) were malignant lymphoma and one (1%) was metastasis to ovary in origin (Table 1). Stage distribution of the cases at diagnosis, according to FIGO stage distribution, is shown in Table 1.

Table 1. Stage distribution of different types of ovarian cancer in young women (under 35 at diagnosis)

Cancer type	Epithelial	Germ-cell	Sex cord-stromal	Others	Total
Stage					
IA	5	7	5	1	18
IB	2	1	0	0	3
IC	11	7	2	0	20
IIA	1	3	1	1	6
IIB	1	0	1	0	2
IIC	5	5	0	0	10
IIIA	3	1	1	0	5
IIIB	0	4	0	0	4
IIIC	12	7	3	0	22
IV	2	3	1	1	7
Total	42	38*	14	3	97

*Three patients were not operated due to their desire.

Table 2. Symptoms experienced by young cases with ovarian cancer and matched controls, 2 years before diagnosis, significant at $P < 0.05$ *

Symptoms	Cases ($n = 100$) n	Controls ($n = 100$) n	P -value	OR (95% CI)
Any symptom	95	28	0.000	48.8 (17.9, 132.7)
Unusual bloating, fullness and pressure in the abdomen or pelvis	37	3	0.000	18.9 (5.6, 64.2)
Unusual abdominal or lower back pain	52	11	0.000	8.7 (4.1, 18.3)
Gastrointestinal problems				
Diarrhea	11	2	0.01	6 (1.3, 28)
Constipation	10	3	0.45	3.5 (0.9, 13.4)
Nausea	19	9	0.42	2.3 (1, 5.5)
Vomiting	9	2	0.03	4.8 (1, 23)
Intestinal gas	12	7	NS	–
Food intolerance	3	2	NS	–
Gastroenteritis	9	7	NS	–
Total number of patients with gastrointestinal problems	36	12	0.000	4.1 (1.9, 8.5)
Unusual lack of energy	22	7	0.003	3.7 (1.5, 9.2)
Infertility	10	3	0.045	3.5 (0.9, 13.4)
Frequent urination, urgency or burning	21	9	0.017	2.6 (1.1, 6.2)
Abnormal menses and abnormal vaginal bleeding	19	9	0.042	2.3 (1.0, 5.5)
Irritable bowel syndrome	11	3	0.027	3.9 (1, 14.7)

*Symptoms which had $P > 0.05$ are not mentioned in this table.
NS, not significant.

The age range was 15–35 years in cases and controls. In both cases and control groups, the mean, median and standard deviation of age at diagnosis were respectively 24.8, 24, 5.8 years.

Nearly all the cases (95%) complained of at least one symptom, compared with 28% of the controls. Of all 41 symptoms in all subjects, nine were reported by equal numbers of cases and controls so the analysis was applied to the 32 symptoms with case–control differences. As shown in Table 2 in details, the most common symptom among the cases was Unusual abdominal or lower back pain mentioned by 52% of cases and 11% of controls (OR = 8.7, 95% CI 4.1, 18.3).

Unusual bloating, fullness and pressure in the abdomen or pelvis were also common symptoms mentioned by 37% of cases and 3% of controls (OR = 18.9, 95% CI 5.6, 64.2).

Gastro-intestinal problems, including nausea, vomiting, gastroenteritis, food intolerance, diarrhea, constipation and intestinal gas (shown in Table 2 in details), were common symptoms, mentioned by 36% of cases and 12% of controls (OR = 4.1, 95% CI 1.9, 8.5). Unusual lack of energy was noted by 22% of cases and 7% of controls (OR = 3.7, 95% CI 1.5, 9.2).

Other symptoms were less common; frequent urination, urgency or burning 21%, abnormal menses and abnormal vaginal bleeding 19%, infertility 10% and irritable bowel syndrome (IBS) 11%. Other symptoms that are not mentioned here are not statistically different between cases and controls ($P > 0.05$).

Among the patients with ovarian cancer, there were 59 with earlier stages (I or II) and 38 with later stages (III or IV). For three patients, staging was incomplete or was not

Table 3. Presenting symptoms as related to FIGO stages

Description	Stage I + II n (%)	Stage III + IV n (%)
Any symptom	57 (96.6)	37 (97.3)
Unusual bloating, fullness and pressure in the abdomen or pelvis	20 (33.9)	17 (44.7)
Unusual abdominal or lower back pain	30 (50.8)	21 (55.2)
Gastrointestinal problems	20 (33.9)	13 (34.2)
Unusual lack of energy	10 (16.9)	12 (31.5)
Infertility	5 (8.5)	5 (13.1)
Frequent urination, urgency or burning	15 (25.4)	6 (15.8)
Abnormal menses and abnormal vaginal bleeding	11 (18.6)	8 (21)
Irritable bowel syndrome	6 (10.1)	5 (13.15)

accessible. There were few differences between those with early and late stage in reported system.

In total, 96.6% of patients with early stage disease reported one or more symptoms, whereas 97.3% of patients with late stage disease reported one or more symptoms. Unusual lack of energy was reported more frequently by women with later stage disease (Table 3).

DISCUSSION

We compared early symptoms of ovarian cancer in two young groups of patients and matched control group. The symptoms that showed up in this young case-control comparison are very similar to those that have been reported previously from different settings in all age groups (Pearse & Behrman 1954; Ranney & Ahmad 1979; Smith & Anderson 1985; Flam *et al.* 1988; Wikborn *et al.* 1993; Goff *et al.* 2000, 2004; Olson *et al.* 2001; Koldjeski *et al.* 2003; Webb *et al.* 2004). Our finding that a high proportion of women with ovarian cancer noted some symptoms in the months before diagnosis is consistent with reports of case series (Pearse & Behrman 1954; Flam *et al.* 1988; Luesley 1991; Goff *et al.* 2000), which found that nearly all patients had symptoms (Flam *et al.* 1988) estimated that only 2% of patients of all ages with ovarian cancer are asymptomatic. In Medline search from January 1970 to July 2006, there was only one study (Nelson *et al.* 1999) restricted to young women with ovarian cancer where they found 152 cases of ovarian cancer, during the 3 years study with only one patient without symptoms. The most common symptom in their study was abdominal or back pain in 49 patients. These studies suggest that diagnosis of ovarian cancer is unlikely in young healthy women lacking subjective symptoms. Our findings among cases are in general agreement with reports based on case

series that unusual abdominal or lower back pain, unusual bloating, fullness and pressure in the abdomen are the most prominent symptoms, followed by gastrointestinal problems (Pearse & Behrman 1954; Davis *et al.* 1956; Timm 1973; Smith & Anderson 1985; Luesley 1991; Petignat *et al.* 1997; Goff *et al.* 2000). We also confirmed that some pelvic, urinary, menstrual abnormalities, abnormal vaginal bleedings, infertility and irritable bowel syndrome, predate the diagnosis of ovarian cancer.

Abdominal and gastrointestinal symptoms have generally been the most frequently mentioned.

This study offered the advantages of a matched control group of young women and objective ascertainment of symptoms with limited the recall bias.

We viewed the analysis of each symptom as independent since some had been reported previously and elected not to make statistical adjustments for multiple comparisons (Rothman & Greenland 1995).

An important difference between studies that ascertain symptoms by questionnaire and those that review medical records is that the former would seem more relevant to patient education alerting of what they should notice and report to their providers, the latter would be of more help to providers in evaluating patients.

Possibly because of small numbers of patients in stages III, IV, we could not find significant differences of symptoms between this group and the early stage group. The question remains as to whether any of these symptoms occurred when the disease was sufficiently localized to permit complete surgical removal. Symptoms of ovarian cancer are often described as non-specific, but the prevalence of these symptoms among healthy young women has not been studied previously. Our results indicate that although the symptoms we investigated are fairly common, the prevalence of some symptoms was much higher among the cases.

In our study, a large majority of women with early stage disease also reported symptoms in the months before diagnosis. In contrast to our findings, some oncology texts state that the disease is asymptomatic in its early stages (Devita *et al.* 1993; Knapp & Berkowitz 1993). Other studies (Flam *et al.* 1988; Petignat *et al.* 1997; Goff *et al.* 2000) have also shown that women diagnosed at early stages are very likely to have symptoms.

Because manual medical record review is so costly and time-consuming, it is not a practical way for the timely identification of women in the clinical setting, even if such combinations of symptoms could be found possibly with the addition of laboratory data.

Hope for rapid screening comes with the increasing substitution of computer for paper medical records. This

could be useful in rapidly identifying women with relevant combinations of findings and raising the index of suspicion of healthcare providers.

We propose that caregivers at least consider the possibility that ovarian cancer may be present when women complain of abdominal pain and pressure symptoms.

As noted by Daly and Ozols (2004), good patient-physician communication is important and 'early detection of ovarian cancer will continue to challenge both the artistic skill of astute clinicians as well as their accumulated scientific acumen'.

This statement is more valid when we try to find ovarian cancer in a young woman.

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