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

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

*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*

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

*Symptoms which had P > 0.05 are not mentioned in this table.
NS, not significant.
cases are in general agreement with reports based on case
women lacking subjective symptoms. Our findings among
diagnosis of ovarian cancer is unlikely in young healthy
nal or back pain in 49 patients. These studies suggest that
The most common symptom in their study was abdomi-
3 years study with only one patient without symptoms.
1999) restricted to young women with ovarian cancer
1970 to July 2006, there was only one study (Nelson
symptoms in the months before diagnosis is consistent
higher among the cases. In contrast to our findings, some oncology texts
disease also reported symptoms in the months before diag-
disease is asymptomatic in its early stages.
Arousal of computer for paper medical records. This
such combinations of symptoms could be found possibly
identification of women in the clinical setting, even if
time-consuming, it is not a practical way for the timely
stages are very likely to have symptoms.
We compared early symptoms of ovarian cancer in two
younger 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; 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 gener-
ally 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 compari-
sions (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 symp-
toms 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 preva-
ence 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 diag-
nosis. 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 sub-
stitution of computer for paper medical records. This

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

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
younger 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 abdomi-
nal 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;
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with the addition of laboratory data.
Hope for rapid screening comes with the increasing sub-
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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.

Acknowledgement

The authors would like to thank Dr Marc Steben who commented on the final revision.

REFERENCES


