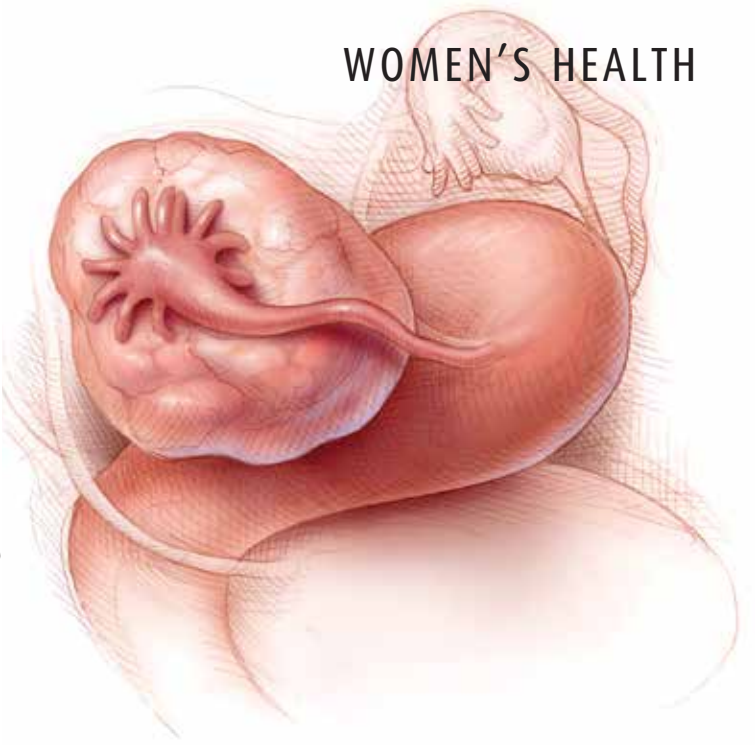
Ovarian cancer

Where are we now?



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As there are no proven screening tests for ovarian cancer and initial symptoms are nonspecific, diagnosis requires a high index of suspicion. Women with unexplained suggestive symptoms should be assessed with measurement of cancer antigen 125 (CA-125), a pelvic ultrasound examination and calculation of the risk of malignancy index.

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In Australia, ovarian cancer is the ninth most common cancer among women and the sixth most common cause of cancer death; it has the worst incidence to mortality ratio of all women's cancers. Every year, about 1300 Australian women are diagnosed with ovarian cancer, one every seven hours, and 800 women die of this disease, one every 12 hours. These poor outcomes stem from the lack of any effective screening test and the fact that the initial symptoms are so nonspecific. Hence, most women are diagnosed in the advanced stages of the disease, with inherently poor survival outcomes.

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Ovarian cancer is a loosely used diagnostic category that includes ovarian cancer, primary peritoneal cancer and many (probably far more than we realise) advanced stage fallopian tube cancers. Primary peritoneal carcinomas arise from the peritoneum, a serosal surface, and are serous or serous papillary carcinomas. They are histologically indistinguishable from serous carcinomas of the ovary, as are primary fallopian tube cancers.

It is possible to differentiate a primary peritoneal cancer from an ovarian cancer only if the ovaries have been previously removed or, if present, are clinically and histologically normal apart from surface metastases. Recent evidence from prophylactic surgery suggests that many apparently advanced ovarian cancers as well as peritoneal cancers arise in the fimbriae of the fallopian tube.[1-3] Nevertheless, this article will follow convention and discuss the entire group as ovarian cancers, as they have similar presentations, treatments and survival rates.

RISK FACTORS FOR OVARIAN CANCER

Although the causes of ovarian cancer are generally not known in any individual woman, some features are epidemiologically more common in women with ovarian cancer. These known risk factors include:

- age, especially being postmenopausal. However, ovarian cancer can occur at almost any age; the youngest patient with advanced epithelial ovarian cancer seen at the Queensland Centre for Gynaecological Cancer was 17 years of age
- a strong family history of ovarian, breast, endometrial and/or colon cancer. Over time it has become apparent that more patients have a genetic predisposition than was initially believed. At least 10% of ovarian cancers may be due to an inherited genetic mutation
- smoking

1. SYMPTOMS COMMONLY REPORTED BY WOMEN WITH OVARIAN CANCER[4,5]

- Abdominal bloating
- Abdominal or pelvic discomfort or pain
- Satiety – feeling full after eating a small amount
- Indigestion or heartburn
- Anorexia
- Persisting urinary frequency in the absence of urinary tract infection
- Difficulty emptying the bowel although not constipated
- Unexplained weight gain or loss
- Fatigue

- long-term use of oestrogen-only hormone replacement therapy
- obesity
- endometriosis
- nulliparity or infertility.

There are also known protective epidemiological factors, which include:

- previous hysterectomy with adnexal conservation
- tubal ligation
- bilateral salpingo-oophorectomy
- multiparity
- use of oral contraceptives.

SYMPTOMS

Ovarian cancer is often referred to as the 'silent killer'. Some argue that this is not correct, because most women experience at least one symptom of the disease in the year before diagnosis.[4] However, although symptoms may be retrospectively teased out with questioning, in practice they are frequently nonspecific and are generally ignored. Further, early-stage ovarian cancer is generally asymptomatic and often an incidental finding. Remember that although most ovarian cancers occur in women over 50 years of age and symptoms are frequently dismissed as part of life at this age, ovarian cancer can occur at any age.

The symptoms most commonly reported by patients with ovarian cancer are shown in Box 1.[4,5] These symptoms are of particular importance when they are new, unexplained and persistent. In this situation, ovarian cancer needs to be excluded. It needs to be remembered that 'if you don't think about it, you'll never diagnose it'. If you think 'could this be ovarian cancer?' then you need to exclude it.

DIAGNOSIS

If a patient presents with one or more of the symptoms in Box 1, and the symptoms persist for more than a couple of weeks with no sound explanation, then the diagnosis of ovarian cancer needs to be excluded. The following assessments are needed.

Physical examination

Physical examination should include an abdominal examination and/or a pelvic examination. If you are not experienced at pelvic examination then it may not help with diagnosis. Many women with ovarian cancer have a palpable mass in their lower abdomen or shifting dullness caused by ascites.

Pap smear

A Pap smear should be performed as part of a general gynaecological assessment unless the patient has had a negative smear result in the previous two years, as per NHMRC guidelines. However, Pap smears are not used to diagnose ovarian cancer.

Blood tests

A blood test for the biomarker cancer antigen 125 (CA-125) should be ordered. An increased level, especially if in the 100s or 1000s IU/mL, suggests the possibility of ovarian cancer. However, measurement of CA-125 alone or in combination with other tests is not appropriate as a screening test for ovarian cancer (see below).

Pelvic ultrasound examination

Ultrasound is the least expensive of the diagnostic imaging tests that should be performed. It is also preferable to a CT scan when looking for pelvic pathology. The finding of a pelvic mass, especially if it is complex (partially cystic and partially solid), raises the index of suspicion for ovarian cancer. Furthermore, if there is also either excessive pelvic or intraperitoneal fluid (ascites) then the index of suspicion becomes extremely high.

RISK OF MALIGNANCY INDEX

From the above investigations it is possible to calculate the patient's risk of malignancy index (RMI), as described in Box 2. Patients with an RMI score greater than 200 have a substantial risk of ovarian malignancy and should be referred to a certified gynaecological oncologist (accredited by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists). The overall sensitivity of the RMI for diagnosing borderline and invasive ovarian cancers and primary peritoneal cancers is about 87%, and the positive predictive value is about 87%.[6]

In addition, if the patient has any ovarian tumour (lump) and is postmenopausal then she needs to be referred to a specialist gynaecologist. This is because ovarian tumours are either functional (a part of normal ovarian function, such as a corpus luteum cyst) or pathological. As the ovary has no function after the menopause, any ovarian cyst or tumour in a postmenopausal woman is by definition a pathological tumour and needs to be removed for pathology examination.

OVARIAN CANCER SCREENING

There are no screening tests for ovarian cancer. This is a position statement supported by the Australian Society of Gynaecological Oncologists, Cancer Council of Australia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Royal Australian College of General Practitioners, Royal College of Pathologists of Australasia and the

2. RISK OF MALIGNANCY INDEX FOR OVARIAN CANCER

Risk of malignancy index (RMI)
= U x M x CA-125 level, where

- U is the ultrasound score (1 or 3) based on the presence or absence of the following five ultrasound features:
  - multiloculations
  - solid elements
  - bilateral lesions
  - ascites
  - evidence of metastases.

  U = 1 if none or only one of the above features are present
  U = 3 if two or more of the above features are present
- M is a score for menopausal status.
  M = 1 if the patient is premenopausal or, if she has had a hysterectomy, is aged under 50 years
  M = 3 if the patient is postmenopausal or, if she has had a hysterectomy, is aged 50 years or older
- CA-125 level is measured in IU/mL.

An RMI score greater than 200 indicates a substantial risk of ovarian malignancy.

Screening Subcommittee of the Department of Health.[7]

The position statement states the following.

- There is currently no evidence that any test, including pelvic examination, measurement of CA-125 or other biomarkers or ultrasound (including transvaginal ultrasound), or combination of tests results in reduced mortality from ovarian cancer.
- There is no evidence to support the use of any test, including pelvic examination, measurement of CA-125 or other biomarkers or ultrasound (including transvaginal ultrasound), or combination of tests for routine population- based screening for ovarian cancer.[7]

For a test to be useful as a screening test it must be both sensitive and specific, and CA-125 measurement is neither. Although the CA-125 level is elevated in most patients with ovarian cancer, about 75 to 80% of these have advanced disease. In most women with stage I ovarian cancer, CA-125 levels are normal. They are elevated in more than 90% of women with advanced disease.

In terms of specificity, CA-125 measurement also performs poorly. The CA-125 level is elevated in many diseases that have nothing to do with ovarian cancer, including:

- pelvic inflammatory disease
- fibroids
- endometriosis
- benign ovarian tumours
- liver disease
- chronic lung disease
- many other malignancies, especially if they have metastasised to the peritoneal cavity.

Similarly, ultrasound examination, including transvaginal ultrasound examination, has significant limitations in distinguishing between benign and malignant masses. The high rate of false-positive results leads to considerable unnecessary surgery.[8]

The combination of measurement of CA-125 levels and ultrasound examination was investigated in the UK Collaborative Trial of Ovarian Cancer Screening and also shown to be ineffective as a screening approach.[9] The use of this combination of tests specifically in high-risk patients is under investigation, and results are anxiously awaited. However, at this stage no effect on disease mortality would be seen.

CONCLUSION

There are no proven screening tests for ovarian cancer. Requests for screening CA-125 tests should not be fulfilled, as a normal result does not exclude the disease and may lull doctor and patient into a false sense of security.[7]

Diagnosis of ovarian cancer requires a high index of suspicion. Any women with appropriate unexplained symptoms, as outlined above, should be assessed with CA-125 measurement and a pelvic ultrasound examination. Early-stage diagnosis is associated with good survival results. MT

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