

Trends and outcomes for women diagnosed with ovarian cancer in Australia

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BACKGROUND Cancer of the ovary is the sixth most common cancer in women and the leading cause of death from a gynaecological malignancy. Early disease is asymptomatic and often results in a late diagnosis with approximately two-thirds of all cases presenting at an advanced stage.

OBJECTIVE To provide an overview of ovarian cancer trends and disease management, and the implications of these for general practice.

DISCUSSION There has been little change in the incidence and mortality of ovarian cancer in the past two decades, despite an increase in the proportion of women receiving surgical treatment to manage the disease. The aetiology of ovarian cancer remains obscure. There is an urgent need for new techniques to be developed that will allow diagnosis to occur at an early stage in the disease process if real improvements in morbidity and mortality outcomes are to be achieved. The general practitioner has an important role in the initial diagnosis of ovarian cancer by assessing female patients' risk of the disease and by making the appropriate referral to a gynaecological oncologist.

Incidence and mortality

The leading cancers diagnosed in Australian women today are breast, colorectal, melanoma, and lung, which account for 59% of all registrable cancers in women.¹ Ovarian cancer is the sixth most common cancer in Australian women, with approximately 1200 women diagnosed each year.¹ It is also the leading cause of death from a gynaecological malignancy with approximately 750 women dying from the disease annually (Figure 1).¹

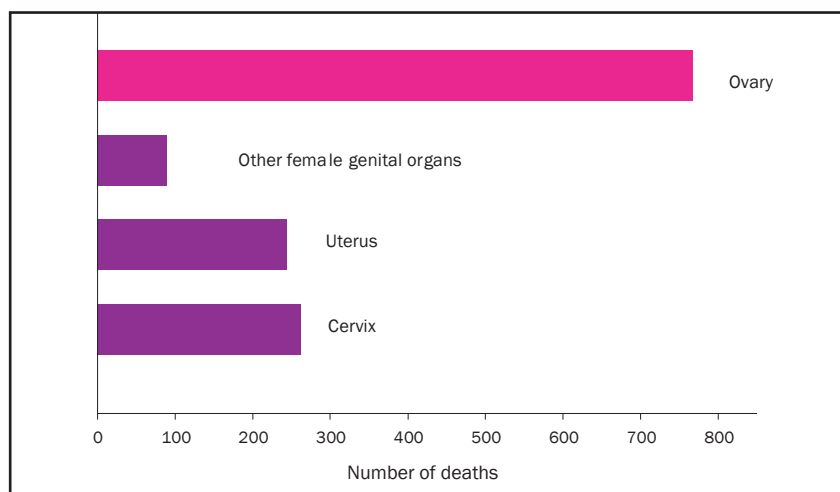


Figure 1. Mortality from gynaecological cancers, 1998 Australian data¹

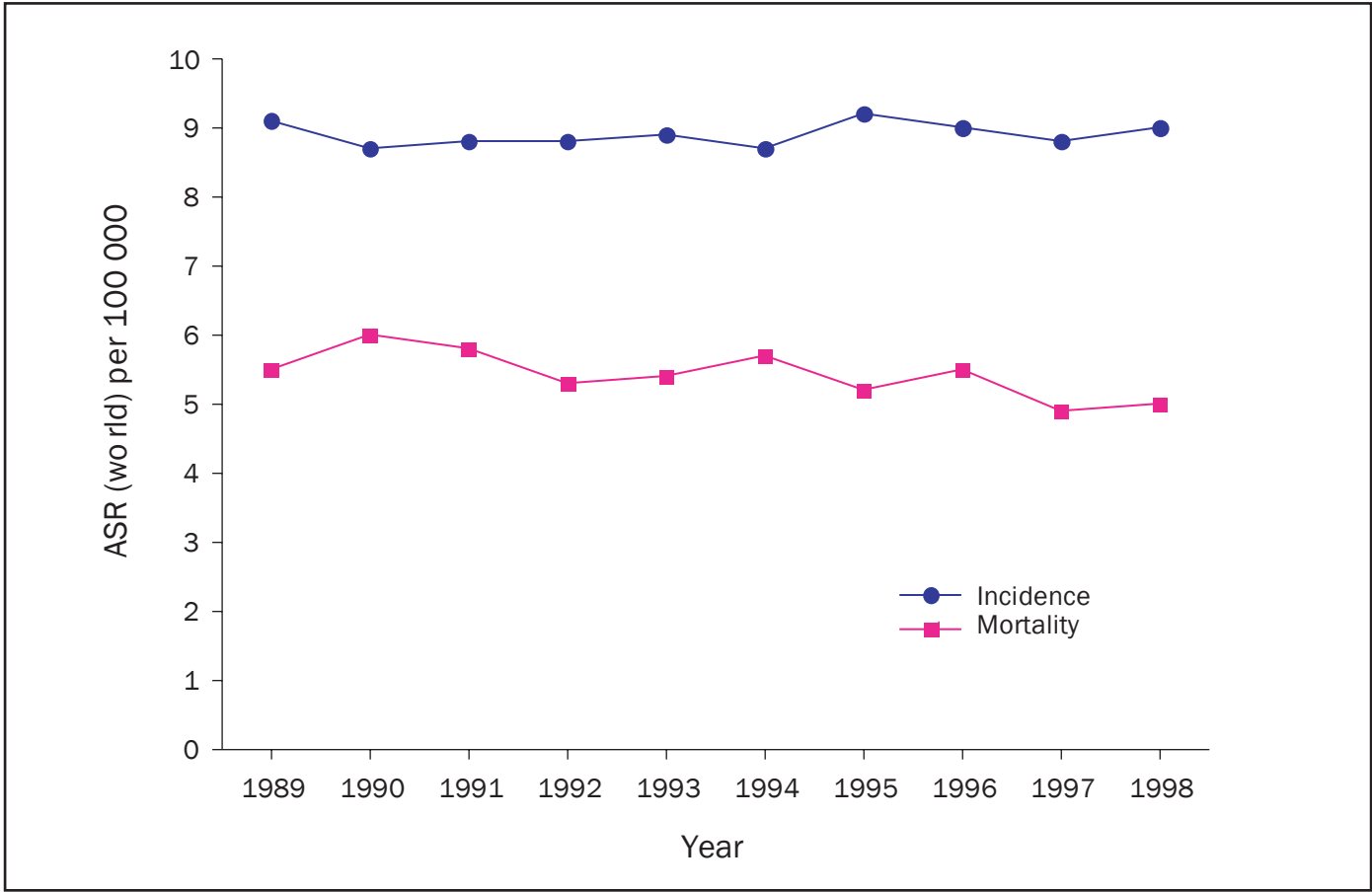


Figure 2. Annual incidence and mortality rates for ovarian cancer in Australia, 1989-1998^{4,6}

Age standardised incidence and mortality rates in Australia have changed little since 1983, although the mortality rate between 1993-1998 decreased by 1.4% per annum (Figure 2).¹⁻⁶ The incidence and mortality trends in most Australian states reflect the national trend; however, the mortality rate in New South Wales was reported to have decreased by 13% between 1990 and 2002, for reasons which were not stated.⁷

Aetiology

The cause of ovarian cancer is only partially understood and most studies focus on epithelial tumours as a whole, despite differences in the origin of serous, mucinous, endometrioid and clear cell tumours. Several factors, including advanced age,⁸ nulliparity⁹ and a family history of ovarian cancer^{8,10} have been associated with an increased risk of

epithelial ovarian cancer. Five to ten percent of all ovarian cancer cases result from a hereditary predisposition.^{11,12} The lifetime risk of ovarian cancer is:

- 1.4% if there is no family history
- 5-7% if a primary or secondary relative has had the disease, and
- 40% if the woman is found to have a hereditary ovarian cancer syndrome.¹²

A decreased risk of ovarian cancer has been found in women who use oral contraceptives^{13,14} or who have undergone a tubal ligation and hysterectomy.^{13,15}

Genetic factors

Less than 5% of all malignancies are estimated to be due to gene mutations, however, those women found to have a

Table 1. Ovarian cancer symptoms ¹⁷	
Early disease symptoms	Advanced disease symptoms
Irregular menses (premenopausal women)	Irregular or heavy menses (premenopausal women)
Urinary frequency	Vaginal bleeding (postmenopausal women)
Constipation	Constipation
Lower abdominal distention, pressure or pain	Abdominal distention and bloating
	Nausea
	Anorexia or early satiety

gene mutation are at an increased risk of ovarian cancer.¹⁶ Carriers of the BRCA1 mutation are shown to have a 60% cumulative risk of ovarian cancer, whereas BRCA2 mutations are shown to have a 10% cumulative risk by the age of 70 years.¹²

Diagnostic/screening tests

There has been little progress in identifying an acceptable screening test that can be used in the general population to identify early, asymptomatic disease. Methods that have been used to diagnose ovarian cancer include the cancer antigen 125 (CA-125) test, transvaginal ultrasound and vaginal examination, the limitations of these methods of screening have been described by Quinn.¹⁶ At present, only women at higher risk of developing the disease are currently recommended to have annual transvaginal ultrasounds and CA-125 estimations in Australia.¹⁶ Had a suitable screening test for ovarian cancer been introduced in Australia in the past 20 years we would have likely seen a dramatic rise in the incidence rate, such as that seen for prostate cancer between 1990 and 1994 when prostate specific antigen (PSA) testing was introduced.¹

Research groups are working hard to identify new and potential diagnostic tests for ovarian cancer. Inhibin has been examined as a biomarker for granulosa cell tumours of the ovary, which account for 1-2% of all ovarian tumours.¹⁷ Inhibin is a dimeric glycoprotein that is produced by normal ovarian granulosa cells for the purpose of regulating the secretion of pituitary follicle stimulating hormone (FSH).¹⁸ After menopause inhibin decreases to non-detectable levels.¹⁹ A number of studies have shown that inhibin levels are elevated among postmenopausal women with granulosa cell tumours of the ovary.^{18,20,21} The actual biological and molecular basis for elevated inhibin levels associated with these ovarian tumours is unclear and it is questionable whether inhibin would be suitable as a screening test given the low incidence of these tumours. Until further research is undertaken to address these

Table 2. FIGO stage distribution of ovarian cancer^{22,25}

FIGO stage	South Australia, 1984-1998 n = 889		International stage distribution 1990-1992 n = 2854	
1	180	20.2%	743	26%
2	98	11%	292	10%
3	422	47.5%	1459	51%
4	163	18.3%	360	13%
Unknown	26	2.9%		

issues, an inhibin assay may only be useful in detecting granulosa cell tumours among women at increased risk of ovarian cancer and for the purpose of monitoring the recurrence of disease.

Symptoms and diagnosis

Most women with epithelial ovarian cancer have no symptoms for long periods. When symptoms do develop they are not disease specific. Women with early disease may report irregular menses if they are premenopausal or report urinary frequency and constipation if a pelvic mass is compressing the bladder or rectum (Table 1). Among women with advanced disease, symptoms are most often related to the presence of ascites, omental metastases or bowel metastases. Symptoms can include abdominal

Table 3. Surgical procedures for ovarian cancer²⁵⁻²⁷

Standard procedures

- Bilateral salpingo-oophorectomy
- Infracolic omentectomy
- Total abdominal hysterectomy
- Pelvic-/para-aortic lymphadenectomy

Additional procedures for advanced disease

- Small bowel resection
- Large bowel resection
- Resection of the rectum



Figure 3. Advanced ovarian cancer resulting in an en bloc resection

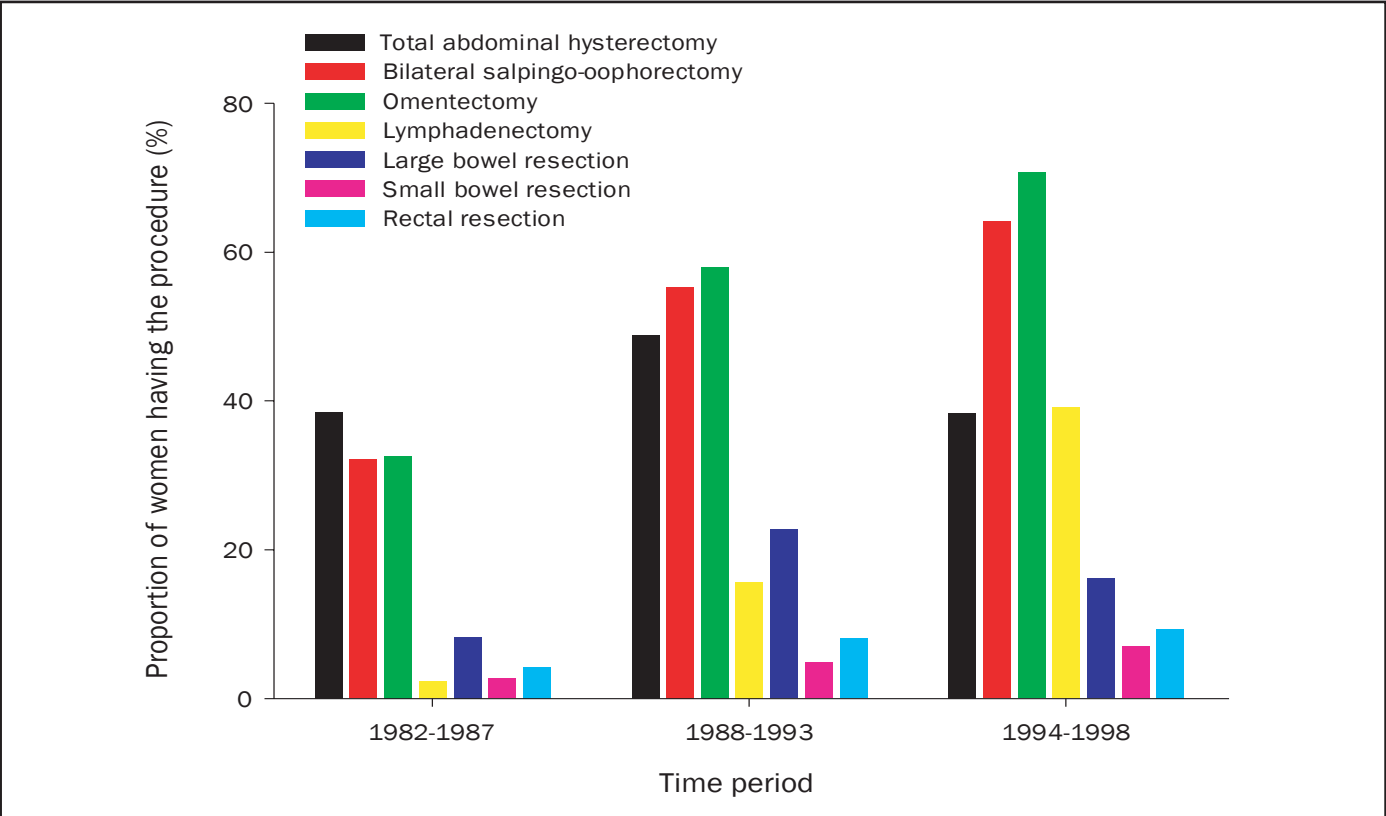


Figure 4. Proportion of women receiving specific surgical procedures for ovarian cancer in Western Australia during the periods 1982-1987, 1988-1993 and 1994-1998

Table 4. Equation for assigning the Ovarian Tumour Index ³⁶	
Feature	Value
Patient age	+ (years)
Ovarian volume	+ (mL)
Morphology scale	+ (0-15)
Pulsatility index (PI)	+ (-10 x PI)
Vessel location	
• peripheral	-10
• central/septal	+10
Intense echoes	-10
Ovarian tumour index	Total

distention and bloating or constipation. A definitive diagnosis of ovarian cancer requires an exploratory laparotomy.¹⁷

Without a means to detect early, asymptomatic disease most women are still diagnosed with advanced disease (Table 2). It is estimated that two-thirds of ovarian tumours are first diagnosed at an advanced stage.¹² South Australia reported that 66% of cases diagnosed in 1984-1998 were International Federation for Gynecology and Obstetrics (FIGO) stage 3 or 4 at presentation.²² At King Edward Memorial Hospital (Perth, Western Australia) it was found that 60% (102/169) of the hospital's ovarian cancer cases were FIGO stage 3 or 4 in 1995-1998.²³

Management

Surgery is common in the primary management of ovarian cancer. The aim of surgery is to remove as much of the diseased tissue as possible, referred to as debulking or cytoreduction of the tumour.⁸ The theoretical benefits of primary cytoreduction have been summarised by Griffiths.²⁴ In theory, cytoreductive surgery

should improve blood supply to the affected area and enable chemotherapy to be administered more effectively. The standard surgical procedures used in the primary management of ovarian cancer are summarised in Table 3.²⁵⁻²⁷ Women with metastatic disease at primary surgery may also require gastrointestinal surgery.^{28,29} Figure 3 depicts an en bloc resection from a patient with advanced ovarian cancer.

A population based study in Western Australia, showed that 77% of cases diagnosed in 1982-1998 were surgically treated and there has been a steady increase in the proportion of women who receive standard surgical procedures, such as bilateral salpingo-oophorectomy, omentectomy and lymphadenectomy (Figure 4).²³ The same trend was found for resection of the rectum, small bowel and large bowel. The increase in the proportion of women undergoing these procedures over the study period, relative to the incidence rate, suggests two things: an increase in the proportion of women with

advanced disease, and an increase in the surgical aggressiveness by surgeons.

The literature suggests that a woman's survival is better when there is less than 2 cm of residual disease after primary surgery.^{30,31} At King Edward Memorial Hospital, the gynaecological oncologists achieved less than 2 cm residual disease in 86% (145/169) of women surgically treated in 1995-1998.²³ Gynaecological oncologists are more likely to achieve optimal cytoreduction than general surgeons and gynaecologists, as they have the training necessary to manage ovarian tumours that have spread beyond the true pelvis to surrounding tissue.³²⁻³⁴ The ability of these subspecialists to achieve optimal cytoreduction in most patients has likely impacted on their patients' survival.

The Australian Cancer Network and the National Health and Medical Research Council are currently developing guidelines for the management of epithelial ovarian cancer. Once completed the clinical guidelines can be obtained from the following website:

http://www.cancer.org.au/clinical_guidelines.html.

Prognosis

The prognosis of women diagnosed with ovarian cancer is generally poor due to the late presentation of disease. Relative survival was an estimated 42% at five years in Australia during the period 1992-1997.³⁵ Overall, survival has improved in Australia over the past 20 years. Compared to the period 1982-1986, five year relative survival in 1992-1997 significantly increased by 7.6%.³⁵ The improvement in relative survival is very encouraging, however, overall survival is still below 50% at five years. We also need to take into account the FIGO stage when reporting survival as it decreases dramatically with increasing FIGO stage at diagnosis. The South Australian Cancer Registry reported that five year survival for the period 1984-1998 was 79% for women diagnosed with FIGO stage 1, 66% for stage 2, 20% for stage 3 and 7% for stage 4.²²

Role of the GP: 'so you have detected a mass'

General practitioners can play a key role in the early detection of ovarian cancer. Female patients should be encouraged to undergo a vaginal examination, in addition to a Pap smear, at the time of their annual or biannual check up. This is of paramount importance for women who are identified as being at an increased risk of the disease. Women with a family history, especially those with gene mutations, should also undergo annual transvaginal ultrasounds and CA-125 estimations.¹⁶ As the GP may be the first health professional to encounter a suspected adnexal mass in a female patient, he or she must assess their patient's condition and determine the appropriate referral. The Ovarian Tumour Index can be used to estimate the probability of the mass being malignant by combining the patient's age with specific ultrasonographic markers.³⁶ The equation used for the assignment of the Ovarian Tumour

Index is provided in Table 4. To simplify the calculation of the Ovarian Tumour Index the following website was developed: <http://www.utsouthwestern.edu/oti>. Female patients with a suspected malignant mass should be referred to a specialist in the field of gynaecological oncology.

Conclusion

Ovarian cancer continues to present late in the disease process, which limits treatment options for cure, and will continue to do so until techniques are established to improve the early detection of the disease. Nationally we have observed little change in incidence and mortality rates. A greater proportion of women diagnosed with ovarian cancer are being treated surgically. In Western Australia, more women are undergoing surgery today than 20 years ago. Surgical techniques have improved, as have the gynaecological oncologists' ability to achieve optimal cytoreduction in their patients with ovarian cancer. The GP plays

a vital role in the initial diagnosis of ovarian cancer. The GP should be aware of their female patients' family history of disease and take note of any nonspecific symptoms presented to them. If a malignant mass is suspected then a referral to a gynaecologist oncologist should be made without delay.

Conflict of interest: none declared.

Funding body: NH&MRC.

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