

Canstat



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Canstat: A digest of facts and
figures on cancer

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Ovarian cancer

Contents

- 2–3 Overview
 - Types of ovarian cancer
- 4–7 Incidence and mortality
- 8–9 Survival
- 10–11 Comparative incidence
 - International incidence
 - Incidence in migrants
- 12–16 Management of ovarian cancer
 - Invasive epithelial cancer
 - Borderline tumours
- 17–21 Epidemiology
 - Risk, lifestyle and protective factors
 - Proposed hypotheses for ovarian cancer aetiology
- 22–23 Screening
- 24–27 References
- 28 Cancer Epidemiology Centre Publications

Ovarian cancer was the seventh most common cancer in Victorian women in 2004

Overview

In 2004, 324 Victorian women were diagnosed with invasive ovarian cancer and 106 were diagnosed with a borderline ovarian tumour. In the same year 232 women died from ovarian cancer. Ovarian cancer was the seventh most common cancer and fifth most common cause of cancer death after breast, lung, bowel and pancreas¹ (Figure 1).

Table 1 and Figure 2 show the distribution of ovarian cancer in Victoria by histological type. The most common form is epithelial, derived from the pluripotent cells of the coelomic epithelium. The three major subtypes of epithelial cancer are serous, mucinous and endometrioid².

'Borderline' epithelial tumours (also known as 'atypically proliferating

tumours', 'tumours of low malignant potential' or 'tumours of borderline malignancy') are a subgroup of epithelial tumours which have a high degree of cellular proliferation without stromal invasion. They are histologically distinguished from benign tumours by having at least two of the following in any one area of the tumour – 'budding' architectural pattern, multi-layering, at least mild atypia and increased mitoses.

Non-epithelial tumours include sex-cord stromal tumours and germ-cell tumours.

References:

1. Giles G, Thursfield V, Farrugia H 2006. Cancer in Victoria 2004. Canstat No.42. Cancer Council of Victoria. Melbourne 2006.
2. Cotran R, Kumar V and Collins T, 1999. Robbins Pathologic Basis of Disease. 6th ed. Pennsylvania: W.B. Saunders.

Table 1: Distribution of ovarian cancer by histological type, Victoria 1982–2004

Table shows the average new cases per year (and percentage of total cases for invasive cancers) for the common histological types of invasive ovarian cancer diagnosed in Victoria from 1982 to 2004.

Histological type	Cases per year	% of total
Invasive ovarian cancer	279	100.0
Epithelial tumours	232	83.2
<i>Serous adenocarcinoma</i>	94	33.7
<i>Mucinous adenocarcinoma</i>	26	9.3
<i>Endometrioid adenocarcinoma</i>	24	8.6
<i>Clear cell adenocarcinoma</i>	16	5.7
<i>Other & unspecified adenocarcinoma</i>	58	20.8
<i>Anaplastic/undifferentiated carcinoma</i>	3	1.0
<i>Squamous cell carcinoma</i>	<1	<1.0
<i>Transitional cell carcinoma</i>	<1	<1.0
<i>Other & unspecified types</i>	11	4.9
Sex-cord stromal tumours	3	1.1
Germ cell tumours	7	2.5
Other tumours*	9	3.2
Type not specified (no histological diagnosis)	28	8.2

*includes soft tissue tumours, sarcomas, fibromatous and myxomatous neoplasms, complex mixed and stromal neoplasms.

Figure 1: Leading sites of cancer in Victorian women 2004

Figure shows the new cases and deaths for the fifteen most common sites of new cancer in Victorian women in 2004¹.

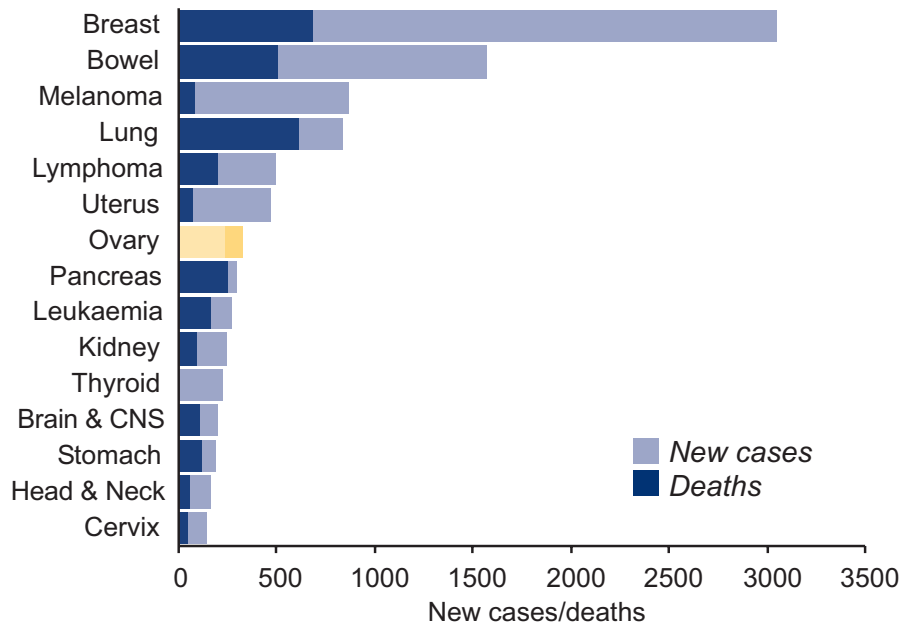
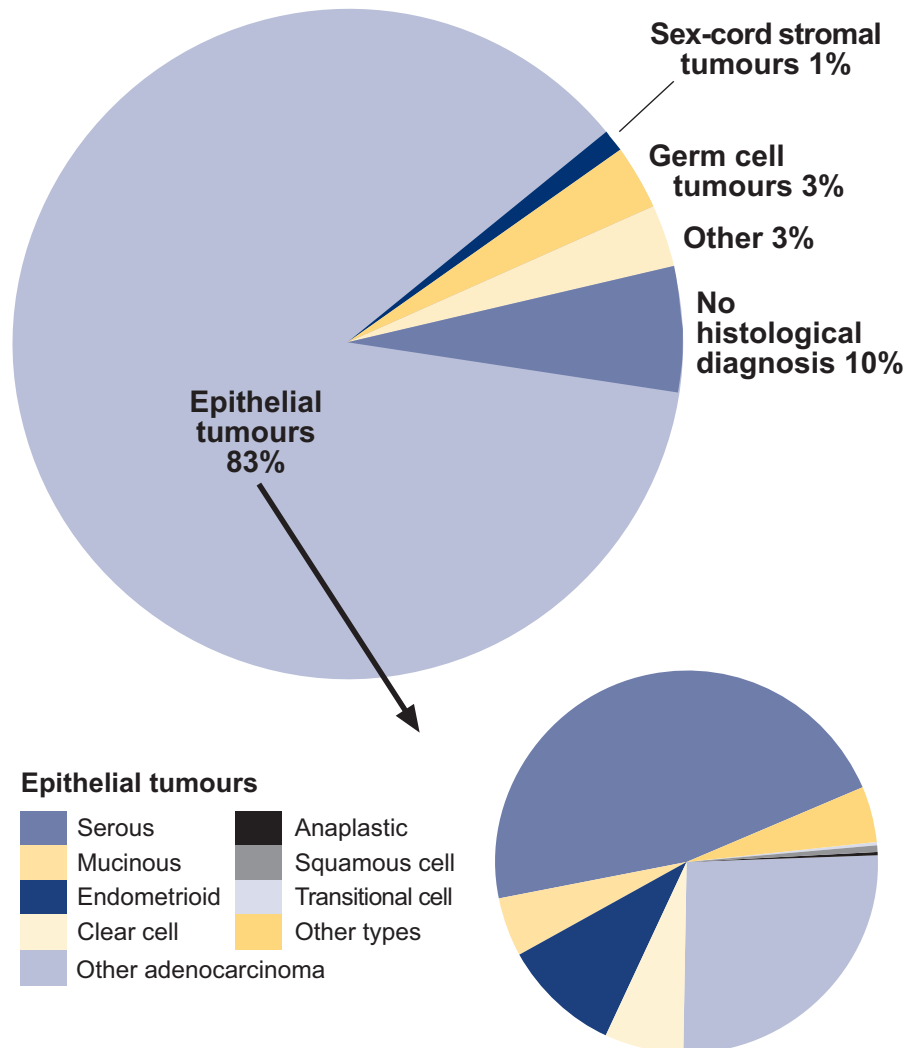


Figure 2: Distribution of ovarian cancer by histological type, Victoria 1982–2004

Figure shows the proportion of new cases for the common histological types of invasive ovarian cancer and the types of epithelial cancers diagnosed in Victoria from 1982 to 2004.



Incidence and mortality

Overview

Ovarian cancer incidence and mortality rates both decreased by about 1% per year during the last decade. The trends in Figure 3 show the random fluctuations expected with relatively small numbers of cases but the overall trend is clearly downwards with mortality closely following incidence rates.

Table 2 summarises incidence and mortality for ovarian cancer in 1984, 1994 and 2004. The figures show that, whilst rates are falling, the actual number of cases and deaths is rising. This reflects the greater number of women at risk due to the increasing size and age of the Victorian population. The median age at diagnosis has risen over the past twenty years from 63 to 65 years.

Age-specific rates

Figure 4 shows the age-specific incidence of ovarian cancer in Victorian women. Malignant ovarian cancer is diagnosed predominantly in older women with the median age at diagnosis in Victorian women in 2004 being 65 years. It is rare before the age of 40 (<10% of cases) with rates rising thereafter with increasing age and more rapidly in post-menopausal women.

Borderline epithelial tumours show a different age-distribution with incidence increasing slowly from puberty to menopause and then decreasing with increasing age in women aged over 50 years.

Table 2: Invasive ovarian cancer in Victoria – the size of the problem 1984, 1994 and 2004

Summary statistics for incidence¹ and mortality² for ovarian cancer in Victoria for the three years 1984, 1994 and 2004.

References:

- 1 Victorian Cancer Registry (2007) unpublished material.
- 2 Australian Institute of Health and Welfare (AIHW) 2005. State & Territories GRIM (General Record of Incidence of Mortality) Books. AIHW., Canberra.

	Year of diagnosis/death		
	1984	1994	2004
Incidence: All malignant cancer			
New cases	240	299	324
Rate	9.1	9.7	8.1
Annual change (to 2004)	-0.6%	-1.0%	
Median age	63	65	65
Lifetime risk	1 in 92	1 in 86	1 in 109
Incidence: Malignant epithelial cancer			
New cases	204	267	260
Rate	7.8	8.7	6.6
Annual change (to 2004)	-0.5%	-1.3%	
Median age	63	64	65
Lifetime risk	1 in 109	1 in 92	1 in 126
Mortality			
Deaths	169	204	237
Rate	5.9	5.8	5.0
Annual change (to 2004)	-0.6%	-1.2%	
Median age	66	68	71
Lifetime risk	1 in 140	1 in 141	1 in 170
PYLL	1,813	1,740	1,643

Notes:

Rate per 100,000 women is age-standardised to the World Standard Population (Segi)

Annual change is the average annual rate of change (%) in age-standardised rates over the periods 1984–2004 or 1995–2004 calculated using a geometric formula from the fitted linear line of best fit through observed rates.

Median age is median age at diagnosis/death in whole years

Lifetime risk is cumulative risk of diagnosis/death from age 0 to 75 years

PYLL is the aggregated number of years of life lost between age at death, as a result of ovarian cancer, and 75 years.

Figure 3: Incidence and mortality trends in invasive ovarian cancer

Incidence (for all invasive ovarian cancer and for malignant epithelial cancers) and mortality trends for Victoria 1982–2004. The graph shows age-standardised rates (Segi World Standard Population) per 100,000 Victorian women.

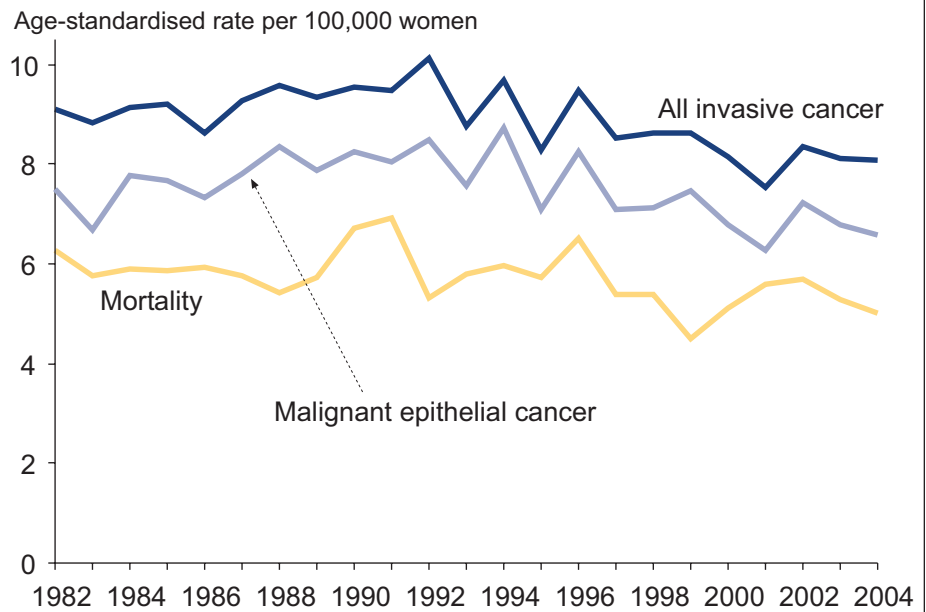
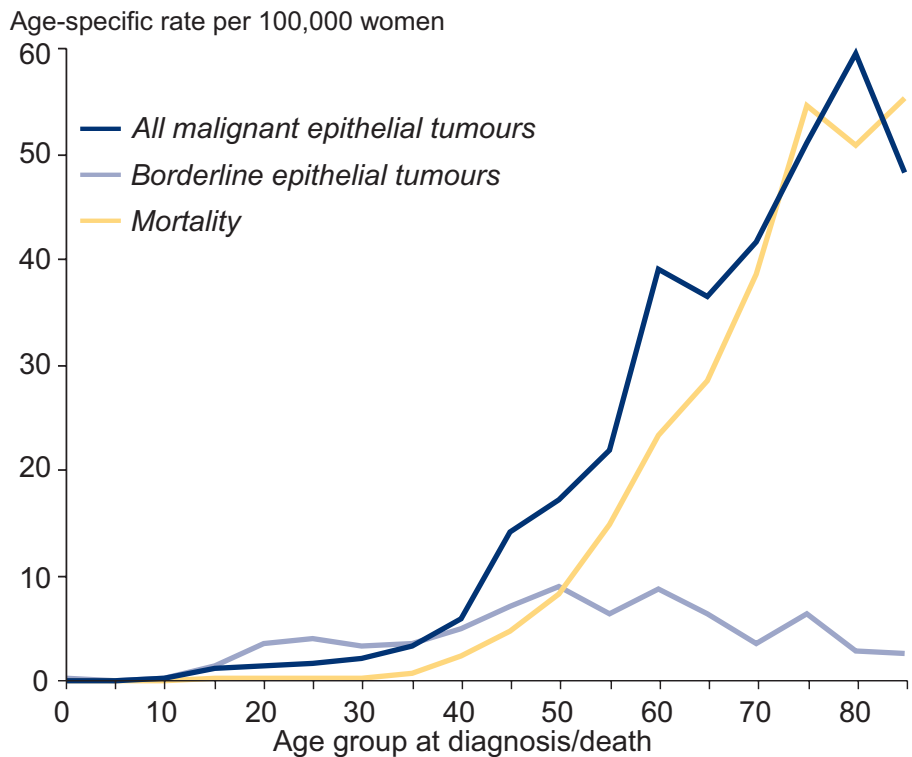


Figure 4: Age-specific incidence and mortality rates for ovarian cancer

Incidence (for malignant and borderline epithelial tumours) and mortality rates by age group for Victoria 2002–2004.



References:

1. Australian Institute of Health and Welfare (AIHW) 2005. *State & Territories GRIM (General Record of Incidence of Mortality) Books*. AIHW, Canberra.
2. Grossi M, Quinn M, Thursfield V et al. 2002. *Ovarian cancer: patterns of care in Victoria during 1993–1995*. *MJA* 177: 11–16.

Mortality

In 2004, 237 Victorian women died from ovarian cancer. Deaths are rare before the age of 40 years (1% of deaths) and more than 80% of deaths occurred in women aged over 60 years. As with incidence, the median age at death from ovarian cancer is increasing, and rose from 66 years in 1984 to 71 years in 2004. The pattern of age-specific mortality is similar to that for incidence though the lines converge with increasing age reflecting poorer survival with increasing age at diagnosis.

Ovarian cancer accounts for around 5% of all cancer deaths in Victorian women and this proportion has remained very constant over the past two decades. In 2005 ovarian cancer was the fourth ranking cancer cause of death and has remained in this position (apart from occasional years in which pancreatic cancer deaths were slightly higher) for many years, behind cancers of the breast, lung and bowel.

Figure 5 compares the trends in ovarian cancer mortality for Victorian women since 1968 with mortality from other gynaecological cancers¹. Over this period ovarian cancer mortality decreased by 0.6% per year which is attributable to falling incidence and increasing survival. Since 1968, mortality for other gynaecological cancers has also been decreasing with the largest fall in cervical cancer (-4.7% per annum) and smaller falls in uterine (-1.6% per annum), and other female genital cancers (-1.3% per annum.). During the same period mortality from breast cancer, the most common cancer in Victorian women, decreased by 0.7% per annum.

In the case of both breast and cervical cancer, effective screening tests are available and population-based screening programs were introduced during this period of

analysis. There is currently no sufficiently effective screening test available for the early detection of ovarian cancer (see pages 22–23) and no means of primary prevention.

Figure 6 shows the trends in ovarian cancer mortality in age cohorts by median year of birth. This clearly demonstrates that the decreasing rates of overall mortality in Figure 5 are not reflected in women of all ages. Mortality rates are decreasing in all age groups under 50 years but stable or increasing in older women. This may reflect relatively smaller benefits in older women from the advances in treatment due to factors influencing treatment choices and outcomes such as age and comorbidity.

In a patterns of care survey of Victorian women diagnosed with ovarian cancer from 1993–1995², older women were less likely to undergo surgery than younger women and, amongst those women who had surgery as their primary treatment, older women (aged over 50 years) were significantly more likely to have advanced disease (63% in older women compared to 47% in women aged under 50 years $p < 0.0001$). Thus, later stage at presentation may also be a contributing factor in the continuing increase in mortality rates in older women and decreasing mortality in younger age groups. It is encouraging to note, however, that even though mortality rates are increasing in women aged over 70 years, the rate of increase is slowing.

Figure 5: Mortality trends for ovarian and other gynaecological cancers

Graph shows the trends in mortality rates (age-standardised per 100,000 women) for Victoria 1968–2005 for cancers of the ovary, cervix, uterus and other female genital organs¹.

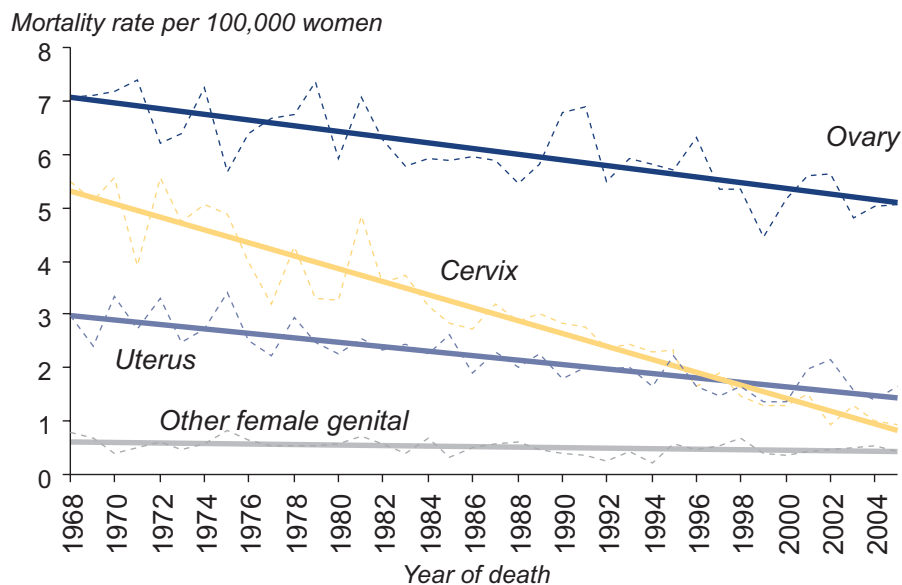
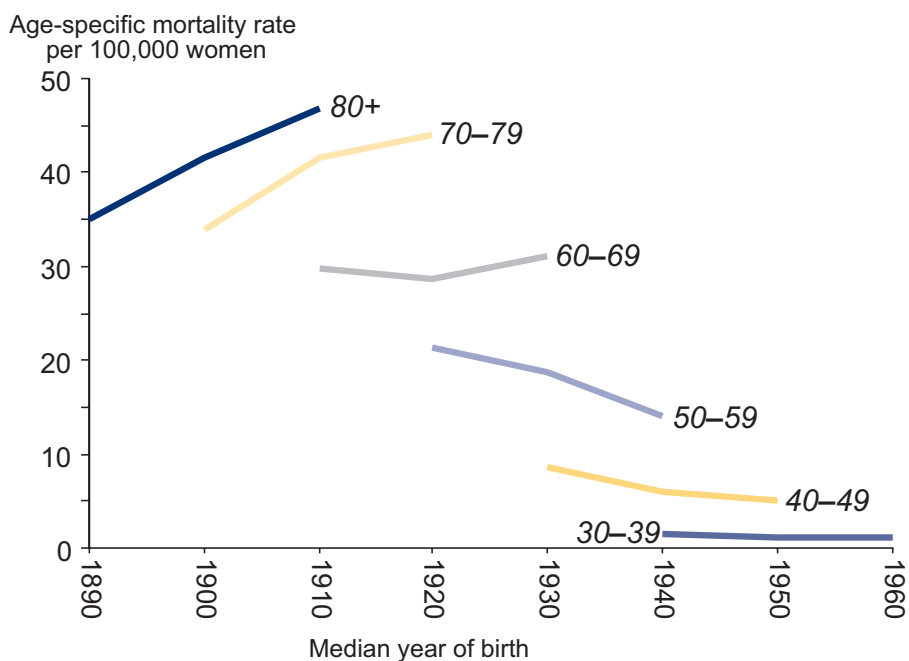


Figure 6: Age-specific ovarian cancer mortality in Victorian women 1968–2005 by median year of birth

Each curve shows the mortality trends in Victorian women in a specific age group by their median year of birth¹.



Survival

References:

1. English D, Farrugia H, Thursfield V, Chang P, Giles G 2007. *Cancer Survival Victoria 2007: Estimates of survival in 2004 (and comparisons with earlier periods)*. The Cancer Council Victoria Melbourne
2. Grossi M, Quinn M, Thursfield V et al. 2002. *Ovarian cancer: patterns of care in Victoria during 1993–1995*. MJA 177: 11–16.
3. Ries LAG, Harkins D, Krapcho M, Mariotto A, Miller BA et al. (eds) 2006. *SEER Cancer Statistics Review, 1975–2003*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to the SEER web site, 2006

Five-year survival from ovarian cancer increased from 35% in 1990 to 41% in 2004 in Victorian women¹ (Figure 7). Older age at diagnosis was strongly associated with poorer survival with estimates of 74% in women aged under 45 and 16% in women aged over 75 (Figure 8).

There was wide variation in survival between different types of ovarian cancer. The highest five-year survival was in women with endometrioid adenocarcinomas (86%) with poorer prognosis in those with papillary & serous adenocarcinomas (36%), mucinous adenocarcinomas (60%) and the less common tumour types. Not surprisingly, the poorest survival (11%) was observed in women with tumours lacking histological confirmation, who usually presented with advanced disease or other factors making them unsuitable for surgical treatment (Figure 9). Victorian survival in 2004 is shown in Table 3.

Five-year relative survival was analysed in a retrospective cohort study of the management of patients with ovarian cancer diagnosed in Victoria in 1993–1995². In the 23% of women who did not undergo surgery due to advanced disease stage, inoperable disease, age, comorbidities, refusal, or death, survival was only 5%, whilst in women who underwent surgery as

their primary treatment survival was 46%. Multivariate analyses of the latter group showed age, stage, grade and ascites to be independent prognostic factors for survival with the risk of death increasing significantly with older age, later stage at diagnosis, higher tumour grade and the presence of clinical ascites. Histological type, use of chemotherapy or hormonal therapy and speciality of the treating doctor did not significantly influence survival. In the subgroup of 156 women with early stage cancer, significant predictors of poorer survival were higher grade, inadequate staging surgery and treatment by a general surgeon rather than a gynaecological specialist. In 251 women with advanced disease, absence of clinical ascites and use of hormonal therapy predicted better survival. Chemotherapy and younger age had a more marginal effect.

The USA SEER (Surveillance, Epidemiology and End Results program) registries reported five-year relative survival proportion of 44.9% for all females diagnosed with ovarian cancer from 1996–2002 (44.6% for white females and 38.9% for black females)². This was an increase from 37.0% reported 5-year survival for the period 1975–1978.

Table 3: Survival for Victorian women with ovarian cancer

New cases and deaths and five-year relative survival (with 95% confidence interval) by age group and tumour morphology for Victorian women with ovarian cancer in 2004¹.

95% CI=95% confidence interval for 5-year survival.

	Cases	Deaths	5-year survival	95% CI
All women	324	232	41%	37–46
Age at diagnosis (<i>p</i> -value <0.01)				
0–44	35	6	74%	62–89
45–54	49	15	59%	48–70
55–64	73	49	50%	41–60
65–74	70	57	37%	28–46
75+	105	97	16%	10–22
Tumour morphology (<i>p</i> -value <0.01)				
Adenocarcinomas:				
Papillary/serous	131		36%	29–42
Endometrioid	24		86%	75–97
Mucinous	17		60%	41–78
Clear cell	16		67%	50–85
Other & unspecified	72		30%	21–40
Other tumour types	28		61%	45–77
No histological confirmation	36		11%	3–19

Figure 7: Survival from ovarian cancer in Victorian women 1990–2004

Relative survival in the ten years from diagnosis by year of diagnosis¹.

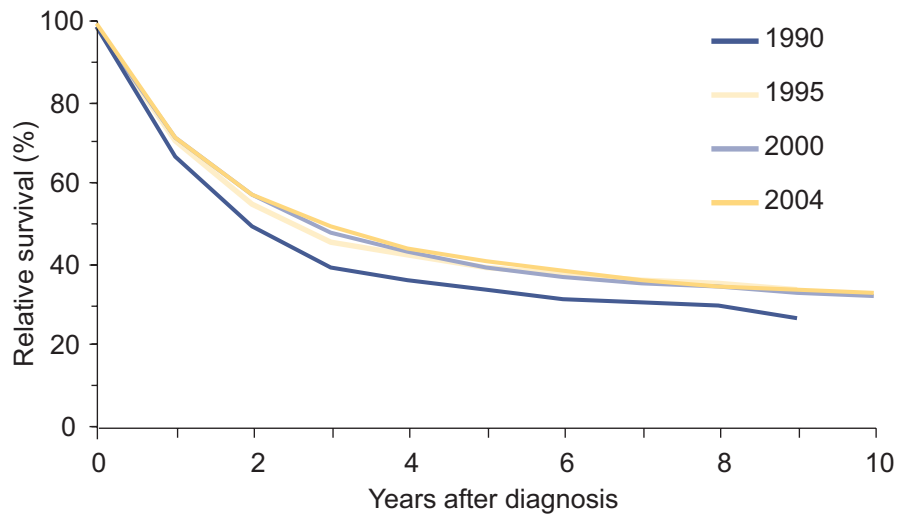


Figure 8: Ovarian cancer survival in Victorian women 2004 by age group at diagnosis

Relative survival in the five years from diagnosis by age group¹.

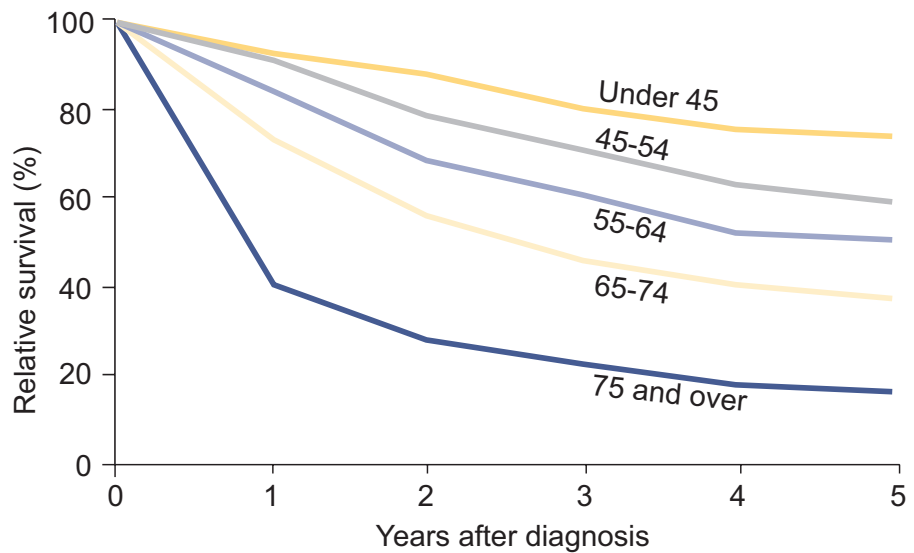
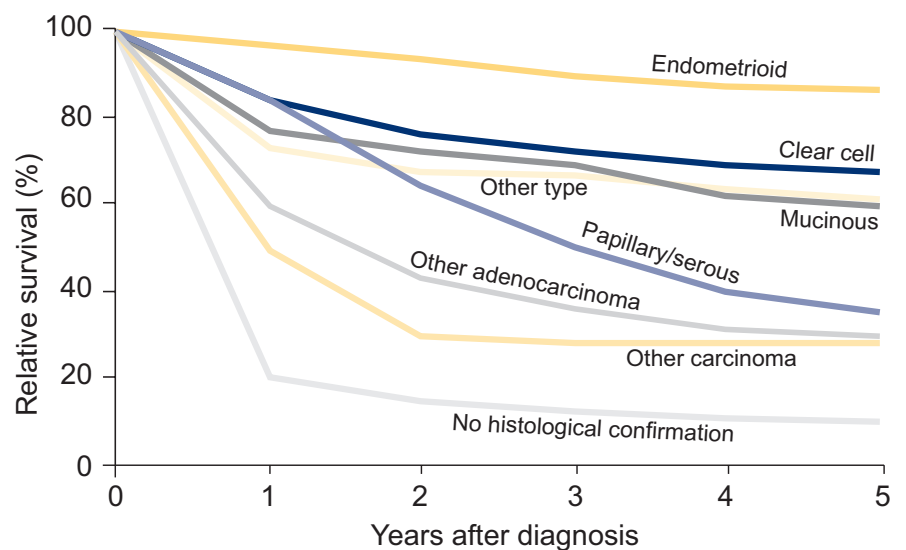


Figure 9: Ovarian cancer survival in Victorian women 2004 by tumour type

Relative survival in the five years from diagnosis by morphology of tumour¹.



Population variation

References:

1. Ferlay J, Bray F, Pisani P, Parkin D 2004. *Globocan 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0. Lyon.*
2. Holschneider CH and Berek JS 2000. *Ovarian Cancer: Epidemiology, Biology, and Prognostic Factors. Semin Surg Oncol 19: 3–10.*
3. Daly M and Oram S 1998. *Epidemiology and risk assessment for ovarian cancer. Semin Oncol 25: 255–64.*

International rates

There is a seventeen-fold variation in worldwide incidence rates for ovarian cancer¹. The highest estimated rates in the world are in Northern Europe (annual age-standardised rate of 13.3 new cases per 100,000 women) with Iceland (17.0) and Lithuania (16.6) having the highest rates for individual countries within this region. Australia's incidence rate (8.9) is similar to those observed in Southern European countries such as Greece (8.7) and Italy (9.3) and slightly lower than rates in the USA (10.6) and Canada (11.6). The lowest rates in the world are observed in Asia (3.2 in China), the Middle East (excluding Israel (8.6) and Bahrain (9.1)), Africa, the Caribbean, and the Pacific Islands. Mortality rates followed a very similar distribution to incidence. Figure 10 shows incidence and mortality rates for 2002 for a selection of countries from Globocan¹.

Migrants to Australia

Within Victoria, population sub-groups experience different risks of ovarian cancer. Figure 11 compares the age-standardised ovarian cancer incidence rates for various migrant groups with women who were born in Australia. Those from Asia and Southern Europe tended to have lower incidence rates compared to Australian-born women whilst rates in migrants from northern and western Europe were higher. Incidence rates in women from Italy, Malta and Vietnam were significantly lower than those for Australian-born women whilst rates in migrants from the UK and Ireland, Netherlands, Poland and the Philippines were significantly higher. Individual countries were included in the figure if their migrants contribute at least 0.5% of the total Victorian population – it should be noted that for some of these countries the numbers of

cancers were extremely small and likely to fluctuate between time periods.

Both ethnic and environmental factors may be important, as it has been observed that the descendents of women who migrate from low-risk countries to high-risk countries experience a gradual increase in ovarian cancer incidence towards the rates of native-born women^{2,3}.

Regional variation

Within Victoria there were slight differences in incidence rates between the eight Department of Human Service Integrated Cancer Services (ICS) regions with rates for women residing in the Gippsland and Grampians ICS regions being lower than in those from the three metropolitan and the Loddon-Mallee, Barwon and Hume ICS regions. The only statistically significant differences were between the lowest rates in Gippsland RICS (5.7 per 100,000 women) and the highest rates in North-Eastern (8.4) and Southern (8.2) Metropolitan ICS regions.

Similar small, but generally not statistically significant, differences were observed between the Australian states and Territories.

Figure 10: International ovarian cancer incidence and mortality

Estimates of incidence and mortality in 2002 for selected countries worldwide from Globocan. Countries are grouped into regions according to the highest incidence rate reported for each region. Rates are age-standardised rates per 100,000 women standardised to the World Standard Population¹.

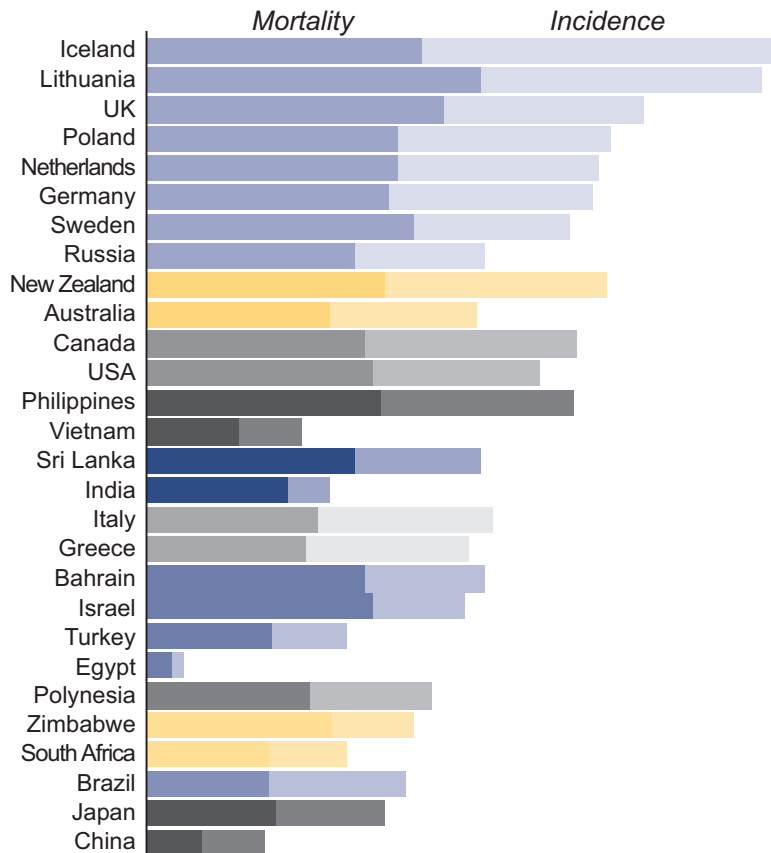
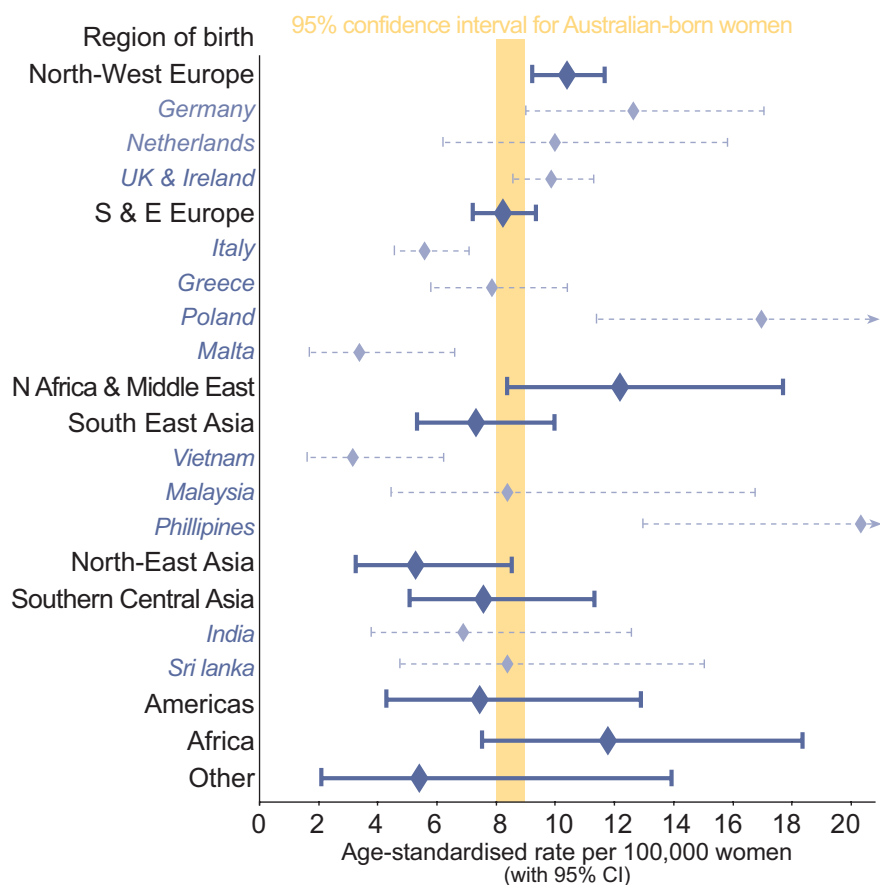


Figure 11: Ovarian cancer incidence in Victorian women by region of birth

Malignant ovarian cancers diagnosed in Victorian women 1999–2004 by region of birth and selected individual countries. Data from the Victorian Cancer Registry 2007 (unpublished).

Graph shows the age-standardised incidence rate per 100,000 with 95% confidence interval (CI) for women born in each region. The yellow band indicates the 95% CI for the rate in Australian-born women. If the CI for a migrant group overlaps this Australian-born band, the rates do not differ significantly.



Initial management

INVASIVE EPITHELIAL CANCER

Primary cytoreductive surgery

Primary cytoreductive surgery is the initial treatment of choice for most women, and involves a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and resection of metastases from the peritoneum or bowel⁴⁷.

The goals of initial surgery are to establish the diagnosis, accurately stage disease, and achieve optimal cytoreduction^{47, 108} (generally to leave no residual tumour or residual tumour masses of less than 1–2 cm in greatest diameter¹⁰⁹). The benefits of cytoreduction include improvement of disease-related symptoms such as abdominal pain, abdominal distension, dyspnoea and early satiety; optimisation of response to adjuvant systemic chemotherapy by

minimising disease burden, and possibly improvement of patient immunocompetence by reducing the amount of immunosuppressive cytokines which have been found to be produced by ovarian cancers, e.g. IL-10, VEGF¹¹⁰⁻¹¹². Recent studies and meta-analyses of optimal cytoreductive surgery in advanced ovarian cancer have shown an improvement in the duration of median survival¹¹³⁻¹¹⁹.

Staging

Management of ovarian cancer is primarily determined by the surgical staging (extent of disease) at the time of diagnosis.

The guidelines for staging, established by FIGO (Federation Internationale de Gynecologie et d'Obstetrique)¹²⁰, are shown below.

FIGO staging system for ovarian cancer

Stage I: Tumour confined to the ovaries

- IA: Tumour limited to one ovary. No tumour on ovarian surface, and capsule intact. No malignant cells in ascites or peritoneal washings.
- IB: Tumour limited to both ovaries. No tumour on ovarian surface, and capsules intact. No malignant cells in ascites or peritoneal washings.
- IC: Tumour limited to one or both ovaries, and any of – tumour on ovarian surface, ruptured capsule, or positive for malignant cells in ascites or peritoneal washings.

Stage II: Tumour involves one or both ovaries with pelvic extension

- IIA: Extension and/or implants in uterus and/or tubes, but no malignant cells in ascites or peritoneal washings.
- IIB: Extension to other pelvic organs, but no malignant cells in ascites or peritoneal washings.
- IIC: IIA/IIB and positive for malignant cells in ascites or peritoneal washings.

Stage III: Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis. Includes liver capsule metastases.

- IIIA: Microscopic peritoneal metastasis beyond the pelvis; no regional lymph node involvement.
- IIIB: Macroscopic peritoneal metastasis beyond the pelvis, ≤2cm in greatest dimension; no regional lymph node involvement.
- IIIC: Peritoneal metastasis beyond the pelvis, >2cm in greatest dimension, and/or regional lymph nodes.

Stage IV: Distant metastasis beyond the peritoneal cavity

If pleural effusion is present, this must have positive cytology to be classified as Stage IV; includes liver parenchymal metastases.

Chemotherapy

Early epithelial ovarian cancer: Only 25% of women present with Stage I or Stage II ovarian cancer¹²¹. There is NHMRC Level II evidence^{47, 122} that those patients with good prognosis early ovarian cancer (those with Stage IA or Stage IB and with well- or moderately well-differentiated tumours) do not require adjuvant chemotherapy¹²³. This subset of patients have an overall and disease-free survival rate of over 90%^{123, 124}.

Those patients with Stage IC and Stage II disease, clear cell histology¹²⁵, and high grade tumours¹²⁶ have a poorer prognosis^{124, 127}, and platinum-based adjuvant chemotherapy is recommended with Level II evidence^{128–130} for this group.

Advanced epithelial ovarian cancer: Approximately 75% of women present with Stage III or Stage IV ovarian cancer¹²¹; this may be due to the frequently vague and non-specific symptoms of early stage disease.

For women with advanced epithelial ovarian cancer, optimal cytoreductive surgery followed by systemic chemotherapy is standard care.

The results of two recent meta-analyses^{131, 132} favoured a survival benefit with the use of platinum-based chemotherapy compared to non-platinum based chemotherapy. The most recent meta-analysis by the Advanced Ovarian Cancer Trialists Group¹³² analysed individual-patient data from 49 trials involving 8,763 women on an intention-to-treat basis. The survival hazard ratio (HR) for non-platinum regimens compared with the same regimen plus cisplatin was 0.88 (95% CI 0.79–0.98), indicating some benefit. The survival HR for single non-platinum compared to platinum combination chemotherapy was 0.93 (95% CI 0.83–1.05), and for single platinum compared with platinum combination

chemotherapy was 0.91 (95% CI 0.79–1.05); the confidence limits for the latter two comparisons indicate inconclusive results. Note, however, that in most of the randomised trials, women were offered platinum salvage therapy upon relapse which may have masked a possible survival difference, and some drugs were administered at a dose and schedule not consistent with today's standards¹³².

Multiple randomised controlled trials and one meta-analysis¹³¹ have shown that there is no therapeutic benefit of cisplatin over carboplatin, both alone and in combination with paclitaxel^{133–135}. Moreover, carboplatin has a favourable toxicity profile compared to cisplatin, which has more neurotoxicity, nephrotoxicity, ototoxicity, and gastrointestinal toxicity, but less myelosuppression¹²¹.

Two recent randomised controlled trials (GOG 111 and OV-10) demonstrated a survival benefit for cisplatin and paclitaxel compared to cisplatin and cyclophosphamide^{136, 137}.

The SCOTROC trial¹³⁸ compared the benefits of carboplatin with paclitaxel compared to carboplatin and another taxane, docetaxel. At a median follow-up of 23 months, survival benefits appeared similar. Whilst those in the docetaxel arm reported less overall and grade 2 or higher neurologic toxicity, and less arthralgias, myalgias, and extremity weakness, this regimen was associated with more grade 3 to 4 vomiting, diarrhea, hypersensitivity reactions and grade 3 to 4 neutropenia and its consequences. Further data on the latter approach are required before it can be considered standard¹²¹.

Hence, current practice guidelines recommend combination chemotherapy with carboplatin and paclitaxel as standard first-line chemotherapy⁴⁷.

When patients are not suitable for combination chemotherapy due to medical comorbidities, poor performance status, or patient preference, there is Level II evidence that use of single agent carboplatin is an acceptable treatment⁴⁷. This is supported by some trials which have shown comparable results from treatment with single-agent carboplatin and platinum-based combination chemotherapy^{139, 140}.

Intraperitoneal chemotherapy

As the bulk of disease in ovarian cancer is found within the peritoneal cavity, the use of intraperitoneal (IP) chemotherapy has been investigated. Higher intraperitoneal drug concentrations have been achieved with IP therapy compared to systemic chemotherapy¹⁴¹, possibly strengthening the rationale for using this route of administration.

A recent systematic review and meta-analysis¹⁴² of eight randomised controlled trials examined whether administration of a component of the adjuvant chemotherapy regime via the IP route improved disease-free survival and overall survival, or reduced toxicity in women with newly diagnosed primary epithelial ovarian cancer of any FIGO stage following primary cytoreductive surgery. Six of the eight trials studied patients with Stage III disease¹⁴³⁻¹⁴⁸; the two remaining trials included participants with Stage II to IV and Stage IIc to IV disease^{149, 150}. Seven of the trials were included in the meta-analysis of time to death^{143-145, 147-150}, which showed a benefit in favour of the IP arm (HR 0.79, 95% CI 0.70–0.90). Four of the trials were included in the meta-analysis of time to recurrence^{144, 145, 149, 150}, which also showed a benefit in favour of the IP arm (HR 0.79, 95% CI 0.69-0.90).

However, due to methodological issues in some of the included trials, it is not clear if the benefits seen in the IP arm can be solely attributed to having some IP administration of chemotherapy or if other factors have contributed. For example,

some trials compared different chemotherapeutic agents in the intravenous and IP arms^{145, 150}, investigated different total doses of the drugs^{144, 147} or a different number of cycles of chemotherapy in the two arms¹⁴⁵. Moreover, none of the trials included the current standard of treatment, carboplatin with paclitaxel, in both arms.

Catheter-related complications which can lead to discontinuation of IP chemotherapy, such as pain, obstruction, leakage, infection, diarrhea, bowel perforation and fistula formation are another important issue. In the three trials which demonstrated a benefit in the IP arm^{144, 145, 149}, only 42% to 71% of the patients were able to complete all six planned cycles of IP chemotherapy. In the GOG 172 trial¹⁴⁴, 39% of patients discontinued IP therapy due to catheter complications. This raises the question of the feasibility of IP chemotherapy and indicates that IP chemotherapy would need to be given only in cancer centres with expertise in this method of administration.

After the publication of the GOG 172 trial, the US National Institute of Cancer released a clinical announcement on 5 January 2006, encouraging the use of IP cisplatin (this was the chemotherapy delivered in the three largest trials with the greatest survival advantage in the aforementioned meta-analysis) in addition to intravenous chemotherapy after primary cytoreductive surgery in primary epithelial ovarian cancer¹⁵¹.

However, there is a role for further clinical trials as the optimal drugs, dosages, combination, number of courses, and timing of administration of IP chemotherapy are all currently unknown. Further randomised trials could also have greater homogeneity of the chemotherapeutic agents and doses administered in the two arms. There is insufficient information

regarding the differences made to quality of life and the histological subtypes for which there may be more or less benefit.

Radiotherapy

Radiotherapy using Whole Abdominal Radiation Therapy (WART) and intraperitoneal isotopes has been previously used in adjuvant therapy for those with Stage I to III disease without residual tumour after primary cytoreductive surgery, and also to consolidate chemotherapy in those with advanced disease and minimal residual tumour at second-look laparotomy¹⁵².

Three previous trials demonstrated greater toxicity and no increased benefit with using intraperitoneal P-32¹⁵³⁻¹⁵⁵. No well-designed prospective randomised controlled study has been performed to compare adjuvant chemotherapy to adjuvant WART⁴⁷.

A major limitation of WART lies in the total dosage of radiotherapy required, as the whole abdomen is considered at risk¹⁵⁶. There is a substantial risk of complications, especially bowel obstruction¹⁵⁷.

The benefit of WART for women with poor prognosis early-stage ovarian cancer is controversial¹⁵⁸. There is Level II NHMRC evidence⁴⁷ for consideration of WART in women with Stage III ovarian cancer who have complete surgical and pathologic remission at second-look laparotomy¹⁵⁹.

BORDERLINE EPITHELIAL OVARIAN CANCER

Generally, borderline epithelial ovarian cancers have an excellent prognosis. The majority of borderline tumours are serous¹⁶⁰, and most are Stage I¹²⁶.

A meta-analysis by Seidman¹⁶¹ showed an overall disease-specific survival rate of 99.5% for those with Stage I disease at a mean of 6.7 years follow-up. The survival of those with non-invasive peritoneal

implants was 95.3%, compared to 66% for those with invasive implants, at 7.4 years of follow-up.

A study of women in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, who had been diagnosed with borderline tumours from 1978–1997¹⁶², using age- and sex- matched US Census data for comparison, demonstrated a 10-year relative survival of 99%, 98%, 96% and 77% for Stage I, II, III and IV borderline ovarian cancer.

Fertility-conserving surgery may be performed for those with low grade borderline tumours⁴⁷.

Those with mucinous histology should undergo abdominal exploration and appendicectomy¹⁶⁰, as the mucinous tumour may not be in fact be borderline, but may be associated with pseudomyxoma peritonei and originate from the appendix¹⁶³.

Where conservation of fertility is not required, total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of obvious disease is the treatment of choice⁴⁷.

A review of four consecutive randomised trials in Norway¹⁶⁴ reported no survival advantage with adjuvant chemotherapy for Stage I tumours.

Abbreviations:

FIGO	Federation Internationale de Gynecologie et d'Obstetrique
NHMRC	National Health and Medical Research Council
HR	Hazard ratio
95% CI	95% confidence interval
IP	Intraperitoneal
WART	Whole abdomen radiation therapy
SEER	Surveillance, Epidemiology and End Results

Follow-up management

Those who undergo fertility-conserving surgery are at continued risk of progressive or persistent disease.

In a prospective study by Zanetta¹⁶⁵, all women with borderline tumours who were undergoing primary surgery were followed up with procedures including pelvic examination, diagnostic imaging and measurement of CA125, CA 19-9 or both every 3 months for the first 2 years and every 6 months thereafter. Of 164 women with borderline tumours who were treated conservatively, 12.1% (20 women) experienced a recurrence of borderline tumour (median time to recurrence of 45 months and 39 months for contralateral (11 women) and ipsilateral (9 women) tumours, respectively). All these women were salvaged by surgery and remained disease-free at a median follow-up of 70 months. Five women experienced progression to carcinoma at 9, 40, 41, 43 and 54 months following primary surgery; all were salvaged by surgery. Three women experienced diffuse recurrence in the peritoneal cavity, with one fatality at 5 months after recurrence, despite chemotherapy. CA125 was elevated in 8/28 cases of recurrence, and transvaginal ultrasound was diagnostic for an adnexal mass in 23/28.

The authors found that transvaginal ultrasound was an optimal mode of follow-up, given the indolent behaviour of the recurrences. A recent review by Tinelli¹⁶⁶ has suggested that combined use of pelvic examination, CA125 and transvaginal ultrasound may be a good approach.

Performance of total hysterectomy and bilateral salpingo-oophorectomy when child-bearing is complete is controversial^{47, 160}.

Epidemiology of epithelial ovarian cancer

Risk factors

Age: An established risk factor for ovarian cancer is increasing age. The median age at diagnosis for Victorian women is 66 years.

Family history of ovarian cancer: In the general population, a woman's lifetime risk of developing ovarian cancer is 1.6%. Having a first-degree relative with ovarian cancer increases this risk to 5%; having two first-degree relatives with ovarian cancer increases the risk to 7%^{1, 2}.

Hereditary ovarian cancer: No gene has yet been found which confers an increased risk of ovarian cancer alone³.

Mutations of the tumour suppressor genes BRCA1 and BRCA2, located on chromosomes 17q21 and 13q12-13 respectively, are associated with increased susceptibility to breast and ovarian cancer³. Meta-analyses of ovarian cancer studies⁴ indicate that in general, 5.7% and 3.8% of all ovarian cancers are associated with germline mutations of BRCA1 and BRCA2, respectively. An estimated 29–41% of Ashkenazi Jewish women with ovarian cancer have one of three BRCA founder mutations (BRCA1*185delAG, BRCA1*5382insC or BRCA2*6174delT). Founder mutations are gene mutations which were present in the founder or ancestor who gave rise to most of the individuals in a restricted population, and are thus prevalent at an increased frequency in that population⁵.

Mutations in the BRCA1 and BRCA2 genes are thought to confer lifetime risks for ovarian cancer of between 40–50% and 20–30%, respectively⁴. In addition to breast and ovarian cancer, mutations in BRCA1 lead to an increased risk of prostate and colon cancers^{6, 7}, and mutations in BRCA2 lead to an increased

risk of malignant melanoma and prostate, stomach, pancreatic, gall bladder and bile duct cancers⁷.

Mutations in DNA mismatch repair genes are responsible for hereditary non-polyposis colorectal cancer (HNPCC)⁸. People carrying a mutation in one of these mismatch repair genes have a cumulative lifetime risk of ovarian cancer of over 12%⁹, in addition to an increased risk of colorectal, endometrial, stomach, small bowel, pancreas, hepatobiliary tract, brain and upper uroepithelial tract malignancies¹⁰.

Lifestyle factors

Diet: Possible associations between diet and ovarian cancer were initially proposed when international differences in incidence were observed in ecological studies⁸⁴.

Whilst some studies have found an increased risk of ovarian cancer with higher consumptions of saturated fat⁸⁵ and animal fat^{86, 87}, others have shown no association⁸⁸⁻⁹¹.

A recent meta-analysis by Genkinger⁹² of twelve prospective cohort studies found no significant associations between specific dairy foods or calcium and ovarian cancer risk. However, higher lactose intakes of ≥ 30 g per day as compared with <10 g per day were associated with an elevated risk. This requires further examination.

Alcohol: There have been conflicting results from studies examining the role of alcohol, some reporting a positive⁹³, null^{83, 94, 95} or inverse^{91, 96} association. A pooled analysis of ten prospective cohort studies by Genkinger⁹⁷ showed no association between total alcohol intake and ovarian cancer risk, or wine, beer or spirits intake and ovarian cancer risk.

Smoking: Multiple studies of smoking and ovarian cancer have also shown conflicting results. Some show no association^{20,83}, whilst others show a positive association^{98,99}, in particular with mucinous tumours. A meta-analysis by Jordan¹⁰⁰ which investigated the relationship between smoking and risk of different histological subtypes of epithelial ovarian cancer, found a doubling of risk of mucinous cancer in current smokers compared to those who had never smoked, no increased risk for serous or endometrioid cancers, and a reduced risk for clear cell cancers.

Physical activity: The effect of physical activity on risk of ovarian cancer is also unclear. Whilst three cohort studies have found a positive association between increased physical activity and ovarian cancer¹⁰¹⁻¹⁰³, two other studies have found no association^{104, 105}, and two have found a negative association^{106, 107}.

Protective factors

Parity: A collaborative analysis of 12 US case-control studies¹¹ and a combined analysis of three European case-control studies¹² showed a protective effect of parity; in addition, the risk decreased with increasing parity.

There are conflicting results from studies regarding the risk associated with greater age at first birth^{11, 13-21}. The role of incomplete pregnancies on risk is also not clear; in most of the studies which show a risk reduction, the effect has been weak²².

Oral contraceptive pill: There is consistent evidence that the combined oral contraceptive pill has a protective effect, which increases with longer duration of use²².

In a meta-analysis by Hankinson²³, ever-use compared to never-use of the oral contraceptive pill was

associated with a relative risk of 0.64 (95%CI 0.57–0.73). There was a 10–12% decrease in ovarian cancer risk with 1 year of use, and an approximately 50% reduction in risk with 5 years of use. This risk reduction occurred in both parous and nulliparous women, and lasted for at least 10 years after cessation of use. However, results of a study by Gnagy²⁴ indicate that the relative decrease in ovarian cancer incidence rates due to the protective effect of oral contraceptive use declines in the long term.

There have been concerns that earlier studies of older oral contraceptive pills investigated the effects of doses of oestrogen and progestin which were higher than the concentrations present in modern formulations. To this end, Ness²⁵ performed a study specifically examining the effect of doses of oral contraceptive pill on the risk ovarian cancer. Their results demonstrated that use of low-oestrogen/low-progestin pills achieved the same risk reduction (OR 0.5, 95%CI 0.3–0.6) as high-oestrogen/high-progestin pills (OR 0.5, 95%CI 0.3–0.7).

Studies give conflicting results as to whether the protective effect that the oral contraceptive pill confers is equal for all histological subtypes of ovarian cancer, in particular mucinous compared to non-mucinous tumours^{13, 26–28}.

Hysterectomy and tubal ligation: Hysterectomy and tubal ligation have both been associated with reduced risk of ovarian cancer^{29–37}. It has been hypothesised that these procedures may protect against cancer by interrupting the pathway of potential pro-inflammatory environmental carcinogens from the lower to the upper genital tract^{38,39}. Alternatively, inspection at the time of surgery provides an opportunity to remove abnormal appearing ovaries, which may lead to a

reduced risk of ovarian cancer, akin to the 'healthy screenee effect'^{29,30}. There is conflicting evidence about the temporal relationship of these procedures to their protective effect. In some studies, the protective effect has waned after a period of 5–20 years^{29–31} and in others the effect has been more prolonged^{32, 38}.

Proposed hypotheses for ovarian cancer aetiology

Two general hypotheses have been proposed to explain the aetiology of epithelial ovarian cancer.

Incessant ovulation hypothesis: this hypothesis asserts that ovarian epithelial cells experience recurrent minor trauma from the proliferation and repair that occurs after every ovulation⁴⁰. The greater the number of ovulatory cycles in a woman's life, the greater the chance of the ovarian cells undergoing an aberrant repair process that may lead to malignancy.

Pituitary gonadotropin hormone hypothesis: this hypothesis asserts that high levels of circulating gonadotropins (follicle-stimulating hormone and luteinising hormone) stimulate oestrogen or oestrogen precursors, which in turn stimulates ovarian surface epithelium which is entrapped in inclusion cysts, leading to excessive proliferation and possibly malignant transformation⁴¹.

These two hypotheses are supported by the protective effect of both parity and use of the oral contraceptive pill. During pregnancy, high levels of oestrogen and progesterone suppress LH and FSH, preventing ovulation⁴². The oral contraceptive pill stabilises oestrogen and progesterone levels, which inhibits the gonadotrophins and their stimulation of ovulation⁴².

However, several issues challenge these hypotheses.

Under the **incessant ovulation**

hypothesis one would expect that different causes of ovulation cessation lead to a similar change in the risk of ovarian cancer. However, Whittemore's analysis of 12 US case-control studies⁴³ showed that a year of early menopause and a year of delayed menarche were associated with lesser risk reductions than one year of pregnancy, breast feeding or oral contraceptive pill use. This may be explained by the fact that the age at menarche and age at menopause do not reflect the initiation and cessation of menses as accurately as pregnancy or oral contraceptive use reflects cessation of ovulation⁴⁴.

Even so, Ness⁴² argued that if the incessant ovulation hypothesis were true, one full-term pregnancy would be expected to reduce ovarian cancer risk by 5% if we assumed that ovulations occur over at least 20 years, whereas the risk reduction observed in Whittemore's study was approximately 14% for each additional pregnancy after the first⁴³. Moreover, in an Australian study by Siskind⁴⁵, even after adjusting for a woman's ovulatory life (factoring in pregnancy, post-partum amenorrhoea and other causes of amenorrhoea), one year of oral contraceptive use reduced ovarian cancer risk by 7%.

These examples suggest that different or additional factors to anovulation or gonadotropin suppression are at play.

If the incessant ovulation hypothesis was correct, those with ovulatory infertility would have a decreased risk of ovarian cancer. The association between ovulatory infertility and ovarian cancer has been difficult to ascertain, as it is often difficult to obtain accurate information regarding the cause of infertility^{42, 46}, and also to separate the effects of infertility, treatment with infertility drugs and low

parity⁴⁷. Two retrospective studies which have specifically examined different causes of fertility^{46, 48} did not find a decreased risk of ovarian cancer with anovulatory infertility.

Finally, women with multiple births have higher levels of gonadotropins when fertile⁴⁹ and have a higher incidence of double ovulation in the menstrual cycle⁵⁰. They would thus be expected to have an increased risk of ovarian cancer. However, there is evidence that multiple births are associated with the same⁵¹ or a lower risk^{17, 52, 53} of ovarian cancer.

Under the **pituitary gonadotropin hormone hypothesis**, low- and high-dose oral contraceptive pills would be expected to provide different levels of protection against ovarian cancer, as they differentially affect gonadotropin levels. However, the results of Ness²⁵ study indicate the contrary.

We would also expect hormone replacement therapy, which reduces gonadotropin levels, to be protective. The results of epidemiological studies on HRT have been inconsistent. A meta-analysis by Garg⁵⁴ found that ever-use of HRT was associated with an increased risk of ovarian cancer (OR 1.15, 95% CI 1.05–1.27). A recent prospective study by Lacey⁵⁵ demonstrated an OR for ever-users compared to never-users of oestrogen-only HRT of 1.6 (95% CI 1.2–2.0), with an increasing risk of ovarian cancer associated with increasing duration of oestrogen-only use (increase in RR of 7%, 95% CI 2–13%, per year of use). Combined oestrogen–progestin use was not associated with an increased risk; however, these results were based on only a small number of women on oestrogen–progestin therapy who developed ovarian cancer. A subsequent case-

control study by Sit⁵⁶, conversely, found no overall association between HRT and epithelial ovarian cancer.

Helzlsouer's prospective study which found that higher serum gonadotropin levels were actually associated with a lower risk of developing ovarian cancer, especially among post-menopausal women, also contradicts this hypothesis⁵⁷.

Lactation suppresses gonadotropin secretion and leads to anovulation, especially in the early post-partum period²². Under the incessant ovulation and pituitary gonadotropin hormone hypotheses, lactation would be expected to reduce the risk of ovarian cancer. Whilst most studies have demonstrated a decreased risk^{11, 16, 58, 59}, some have shown no association^{17, 41}.

In light of these observations which do not completely fit the two older hypotheses, some newer hypotheses have been generated⁶⁰:

The androgen/progesterone hypothesis: Risch⁶¹ proposed that androgens may be implicated in the pathogenesis of ovarian cancer. Biologically, ovarian epithelial cells are exposed to appreciable amounts of androgens⁶¹, and androgen receptors are found on normal ovaries⁶². Post-menopausally, when the incidence of ovarian cancer is increased, the ovary is relatively androgenic⁶³.

Evidence supporting the role of androgens includes studies showing that oral contraceptives suppress ovarian testosterone production^{64, 65}, and Helzlsouer's study⁵⁷, which also demonstrated higher serum androstenedione levels in cases with ovarian cancer than controls.

A recent Australian case-control study and systematic review⁶⁶ concluded that, taking all of the evidence into consideration, there is likely to be a small to moderate positive association between a high BMI and risk of ovarian cancer. In addition to ovulatory infertility⁶⁶, obesity may increase the risk of ovarian cancer through polycystic ovary syndrome – which is associated with elevated androgen levels⁶⁷⁻⁶⁹ – or by hyperandrogenemia alone⁷⁰. Previous studies of the association of PCOS with ovarian cancer have given conflicting results^{71, 72}.

Evidence for the protective role of progesterone includes the observation of increased progesterone levels during both pregnancy⁷³ and with oral contraceptive use⁷⁴. Additionally, a case-control study by Rosenberg⁷⁵ found that the progestin-only oral contraceptive pill was as effective in reducing ovarian cancer risk as combined oestrogen-progestin pills. However, this study was limited by the difficulties in recollection of type of pill used and the small number of long-term users of the progestin-only pill included in the study.

The inflammation hypothesis:

Another hypothesis is that epithelial inflammation is involved in ovarian carcinogenesis⁴². This is supported by the association of hysterectomy and tubal ligation with a decreased risk of ovarian cancer, as described above.

Endometriosis, which is associated with an inflammatory response in the endometrial tissue⁴², has been shown to increase the risk of ovarian cancer in two large Swedish registry-based studies^{76, 77} and a pooled analysis of eight case-control studies⁷⁸.

Associations with non-steroidal anti-inflammatory drugs (NSAIDs)

and talc, an inflammatory agent, have also been investigated. A recent meta-analysis including six case-control and four cohort studies⁷⁹ did not support a protective effect of NSAIDs, although unpublished or original data were not included, and heterogeneity in study design and exposure measurements in the included studies were acknowledged. The use of talcum powder has been associated with ovarian cancer in some studies^{80, 81} but not others^{82, 83}.

Abbreviations:

<i>OR</i>	<i>Odds ratio</i>
<i>95% CI</i>	<i>95% confidence interval for odds ratio</i>
<i>RR</i>	<i>relative risk</i>
<i>HNPCC</i>	<i>hereditary non-polyposis colorectal cancer</i>
<i>FSH</i>	<i>follicle-stimulating hormone</i>
<i>LH</i>	<i>lutensising hormone</i>
<i>HRT</i>	<i>hormone replacement therapy</i>
<i>BMI</i>	<i>body mass index</i>
<i>PCOS</i>	<i>polycystic ovary syndrome</i>
<i>NSAIDs</i>	<i>non-steroidal anti-inflammatory drugs</i>

Screening

Introduction

A screening test for disease is one which can be applied rapidly and which investigates for unidentified disease in an asymptomatic person¹⁶⁷.

The WHO (World Health Organization) principles for a screening program for a disease are listed below¹⁶⁸:

1. *The condition should be an important health problem*
2. *The natural history of the disease should be well understood*
3. *There should be a recognisable latent or early asymptomatic stage*
4. *Treatment at an early stage should be of more benefit than treatment started at a later stage*
5. *There should be a suitable test or examination*
6. *The test should be acceptable to the population*
7. *Facilities should be available for the diagnosis and treatment*
8. *Screening should be repeated at intervals determined by the natural history of the disease*
9. *The chance of physical or psychological harm to those screened should be less than the chance of benefit*
10. *The cost of a screening program should be balanced against the benefit it provides*

Issues in screening

Potential benefits of screening for ovarian cancer include diagnosis at an early and potentially curable stage, which may lead to reduced mortality from the disease. Two large multi-centre population-based trials currently in progress (UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), UK and Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO), USA) aim to determine whether these benefits exist, and the optimum timing and type of screening tests.

The most obvious risks are the consequences of false-positive results – which would lead to surgery and its attendant physical and financial morbidity, as well as potential psychological harm. There is a lack of studies showing sufficient specificity and sensitivity of available screening tests.

Screening tests

Bimanual examination alone lacks the required sensitivity and specificity for a screening test¹⁶⁹.

Serum CA125 concentration: The CA125 antigen is a glycoprotein which has 90% sensitivity in Stage II disease¹⁷⁰, but a lower sensitivity (49%) in Stage I disease¹⁷⁰.

Unfortunately, it has limited specificity, as it is also raised in other malignancies including endometrial, breast, lung and pancreatic cancer¹⁷¹, and benign conditions, including endometriosis¹⁷². A high CA125 level is associated with the presence of serosal fluid and serosal involvement (pleural or peritoneal) from various causes¹⁷³.

CA125 levels are also increased in 1% of healthy persons¹⁷⁴, and have been shown to be subject to variation in healthy post-menopausal women¹⁷⁵.

A Swedish population-based study¹⁷⁶ demonstrated specificity ranging from 97.0–98.5% for CA125 levels ≥ 30 U/mL and ≥ 35 U/mL respectively, in women aged over 50 years old.

Alone, CA125 does not have the sensitivity or specificity required for a screening test⁴⁷.

Ultrasound: Transvaginal ultrasound (TVUS) provides better visualisation of the ovaries than a transabdominal ultrasound⁴⁷, however it is still difficult to distinguish between benign and malignant disease with this technique¹⁷⁷.

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In a study of 14,469 asymptomatic women ≥ 50 years old by van Najell Jr¹⁷⁷, use of annual TVUS had a sensitivity of 81% and specificity of 98.9%. In comparison to the advanced disease present at diagnosis of ovarian cancer in most women, in this trial 72% of patients receiving annual screening were detected with stage I or II cancer. However, a major limitation was that TVUS was not effective in detecting ovarian cancer in which ovarian volume was normal. Three of four patients who developed ovarian cancer within 12 months of their negative screens had an elevated CA125 level, and it was suggested that adding serum CA125 to TVUS in a screening program could help decrease the false-negative rate in those with normal-sized ovaries.

Combination of tests: In a prospective study by Jacobs¹⁷⁸, serum CA125 concentrations were measured annually in 22,000 asymptomatic post-menopausal women aged ≥ 45 years old. Abdominal ultrasonography was performed in those with CA125 concentrations ≥ 30 U/mL, and surgery was performed if the ultrasound was abnormal. Sequential use of CA125 and abdominal ultrasonography achieved a specificity of 99.9% and sensitivity of 78.6% at 1-year follow-up.

Skates¹⁷⁹ subsequently retrospectively analysed results of serial CA125 concentrations from the latter trial using longitudinal statistical models, and concluded that use of serial CA125 levels improves pre-clinical detection compared with a fixed cut-off for CA125 measurement – the sensitivity increased to 86%, whilst maintaining a specificity of 98%.

Incorporating both a multimodal screening strategy and a "risk of cancer" (ROC) algorithm using serial CA125 levels, the ongoing UKCTOCS trial¹⁸⁰ has recruited 202,638 non-high risk post-

menopausal women aged 50–74 years old¹⁸¹. It is comparing annual transvaginal ultrasound (TVUS) to a multi-modal arm in which a CA125 level is followed by annual screening, repeat CA125 or transvaginal ultrasound as determined by a ROC algorithm, and to a control (no screening) group. In addition to the primary endpoint of ovarian cancer mortality, it plans to evaluate cost, morbidity, compliance and participant acceptability of the screening tests. Preliminary results show that compliance with 2-year screening was 89% in the TVUS arm and 92% for the multi-modal arm¹⁸¹. The percentage of participants who had surgery in the multi-modal arm following an abnormal ROC algorithm and TVUS was 0.16%, and in the US arm following an abnormal TVUS was 1.01%. Specificities in these arms were 99.8% and 99.0%, respectively¹⁸¹.

The Prostate, Lung, Colorectal and Ovarian (PLCO) trial¹⁸² is another large multimodality trial in progress, which has randomised over 74,000 women to receive screening with CA125 and transvaginal ultrasound or usual care.

Other modalities: There are multiple ongoing studies which are evaluating combinations of tumour markers which may be more sensitive than individual tumour markers in screening for ovarian cancer^{47, 183}.

Newer technologies, including the use of **proteomic analysis**¹⁸⁴, have also been investigated for potential as a screening method for ovarian cancer.

Recommendations

Currently, no national or international studies recommend routine screening for ovarian cancer in asymptomatic women without a hereditary cancer syndrome⁴⁷.

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