

I. OVARIAN CANCER IN AUSTRALIAN WOMEN

INTRODUCTION

Routine statistics do not separate epithelial, germ cell and sex cord-stromal tumours. However, as the great majority of ovarian cancers are epithelial (>90%), rates of epithelial tumours are closely approximated by ovarian cancer rates overall. The only exception is at young ages (below the age of 40) where epithelial tumours are rare and germ-cell tumours relatively more common. The data reported in this chapter will refer to all types of ovarian cancer unless indicated otherwise.

Ovarian cancer in Australian women in 1999¹

- 1,173 women diagnosed with ovarian cancer
- 731 women died from ovarian cancer
- 5,948 years of life lost under the age of 75
- relative survival nationally of 42% at five years after diagnosis in 1992-1997
- the most common cause of death from gynaecological malignancy

In 1999, cancer of the ovary was the eighth most common cancer (the seventh most common cancer excluding cancers of unknown site) and the sixth most common cause of death from cancer (the fifth most common cause of death excluding cancers of unknown site) in Australian women.¹ The ranking of the most frequently occurring cancers based on the number of new cases and deaths in Australian women is shown in Figures 1 and 2.

Figure 1 Most frequently occurring cancers. Numbers of new cases in Australian women, 1999. (NHL refers to Non-Hodgkin's lymphoma)

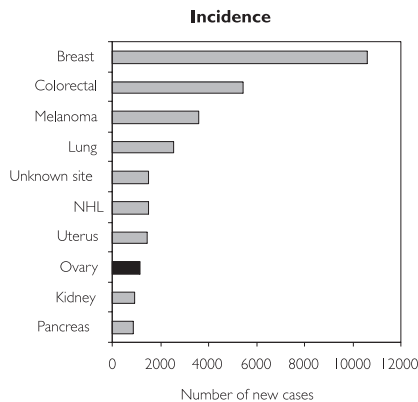
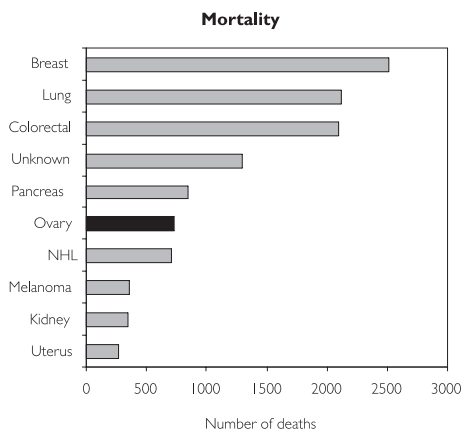


Figure 2 Most frequently occurring cancers. Numbers of deaths in Australian women, 1999. (NHL refers to Non-Hodgkin's lymphoma)



INTERNATIONAL COMPARISONS

Ovarian cancer incidence varies more than two fold around the world. Countries with a high incidence include the Scandinavian countries, the United Kingdom and the United States. Asian countries have relatively low rates of ovarian cancer, although there is evidence that rates have increased over recent years. Rates in Australia tend to be lower than those in the UK, USA and Northern Europe but higher than those in Southern Europe and Asia. Incidence rates probably reflect differences in diagnostic and registration accuracy in different populations as well as differences in the distribution of risk factors for ovarian cancer, particularly fertility patterns.

Examples of ovarian cancer incidence and mortality rates in different regions are shown in Figures 3 and 4.

Figure 3 Age standardised incidence of ovarian cancer per 100,000 in selected countries.²

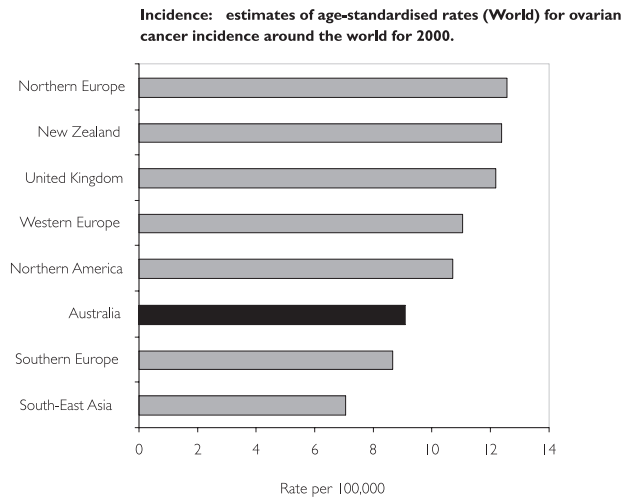
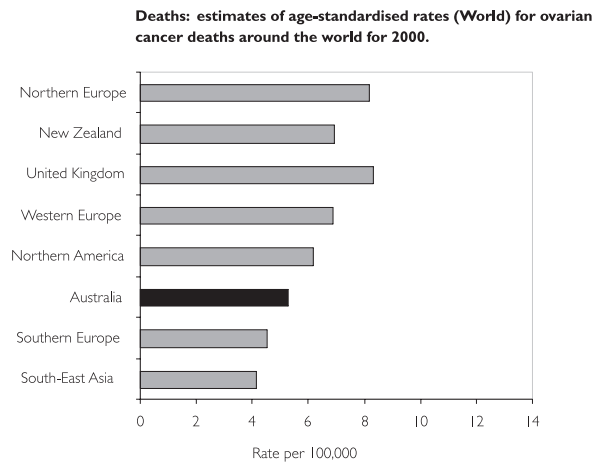


Figure 4 Age standardised mortality rates of ovarian cancer per 100,000 in selected countries.²

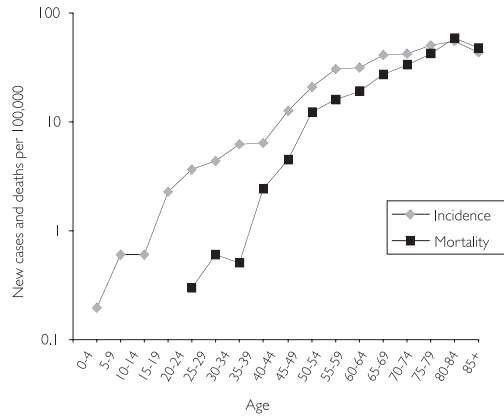


Note: the data from each country in Figures 3 and 4 are estimated for the middle of 2000 from the most recent data available, generally 3-5 years earlier.

AGE-SPECIFIC INCIDENCE AND MORTALITY RATES

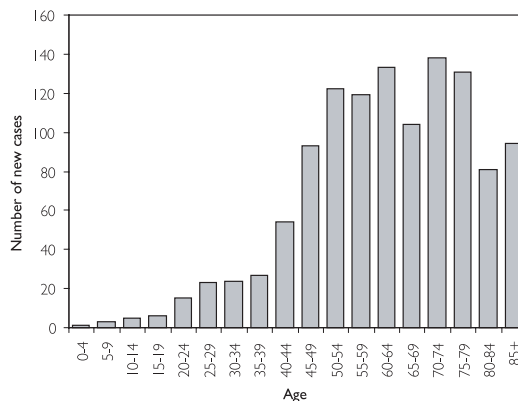
Ovarian cancer incidence and mortality rates increase with age as shown in Figure 5. Incidence increases steeply to 50 years of age and continues to increase, although more slowly, in women at older ages.

Figure 5 Age-specific incidence and mortality rates for ovarian cancer in Australian women 1999



The age distribution of women diagnosed with ovarian cancer in 1999 is shown in Figure 6. The distribution is skewed towards later life. The median age at diagnosis was 63 years. Overall, 87% of cancers are diagnosed among women over the age of 45 years and, as noted above, the majority of tumours in women under 40 years are germ-cell tumours and not epithelial cancers. For a detailed review of population and clinical cancer statistics, see the report *Ovarian Cancer in Australian Women*.³

Figure 6 Age distribution of new ovarian cancer cases, Australia, 1999

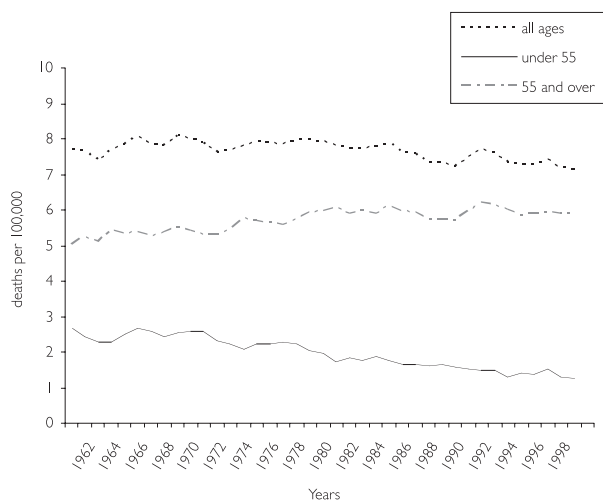


TRENDS IN OVARIAN CANCER INCIDENCE AND MORTALITY

In 1999 the age-standardised incidence rate was 10.6 per 100,000 female population and the lifetime risk to age 74 was 1 in 107; the age-standardised mortality rate was 6.3 per 100,000 women.¹

National cancer incidence data only became available in 1983 and since then the incidence of ovarian cancer has remained stable. In contrast, national mortality data have been available since 1921. Over the last 40 years there has been a decline in ovarian cancer mortality, most notably in women under the age of 55 (Figure 7). Similar trends have been seen in some other countries.^{4,5} Possible explanations for the trend include differences in the histological types and prognosis of tumours occurring in younger age groups, protective effects of oral contraceptive use and improvements in treatment.

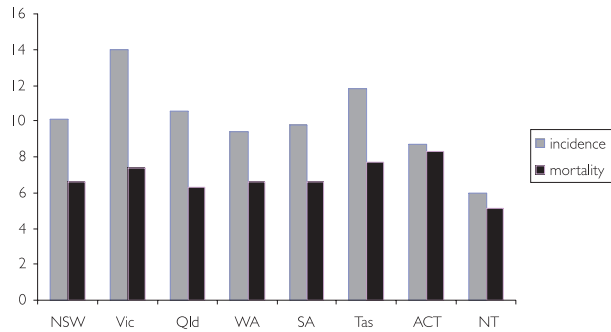
Figure 7 National trends in age-standardised mortality rates for ovarian cancer, 1958-98. (3-year leading averages)



DIFFERENCES IN STATE AND TERRITORY CANCER INCIDENCE AND MORTALITY RATES

In 1994-1998, incidence of ovarian cancer was highest in Victoria and Tasmania and mortality was highest in Victoria, Tasmania and the Australian Capital Territory (ACT). In general, differences in State and Territory cancer incidence rates may be explained by normal incidence rate fluctuations, the availability and utilisation of diagnostic procedures, and reporting and coding inconsistencies. It is also possible, however, that the differences could be due to geographic variations in the prevalence of risk factors for ovarian cancer.

Figure 8 Average annual incidence and mortality rates by State and Territory, Australia, 1995-1999

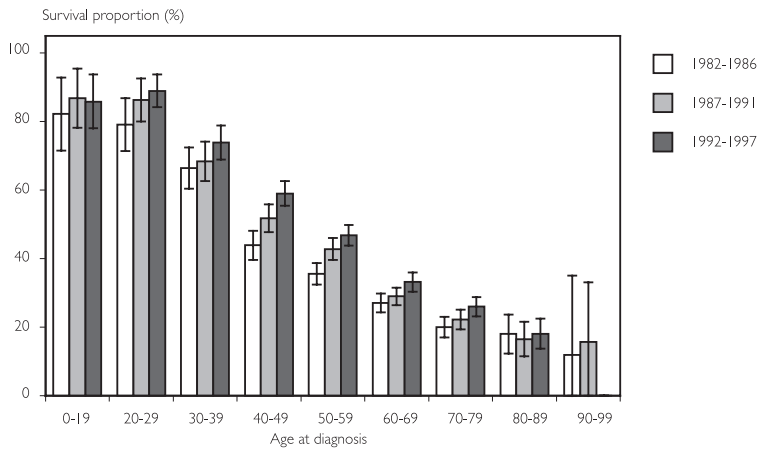


SURVIVAL FROM OVARIAN CANCER

Five-year relative survival for Australian women of all ages with ovarian cancer was 42% in 1992-1997. The data in Figure 9 show that five-year relative survival after a diagnosis of ovarian cancer increased between 1982-1986 and 1992-1997. Survival was highest in the younger age groups.

Note: 95% confidence intervals are shown for each age group.

Figure 9 Cancer of the ovary. Five-year relative survival proportions: age at diagnosis by period of diagnosis, Australia.⁶



Evidence of improved survival of women with ovarian cancer comes from relative survival analysis of national ovarian cancer data.⁶ Relative survival analysis compares the survival of persons diagnosed with cancer (observed) with that experienced by the general age and sex-matched population to which they belong (expected).⁶ Expressed as a percentage, it is the proportion of cancer patients that survives a specific number of years after the diagnosis of cancer divided by the general population that survives the same number of years. A survival rate of less than 100% indicates that the survival of women with ovarian cancer is less than expected for women in the general population of the same age.

Key points:

- Five-year relative survival after a diagnosis of ovarian cancer is highest in younger women and decreases with age.
- Five-year relative survival increased significantly between 1982-1986 and 1992-1997.

Increased survival from cancer may arise for a range of reasons. For ovarian cancer, these may include more effective and more widely available treatment, more effective investigation, diagnosis and staging of disease, and increased speed of referral. Clinical cancer registry data have made possible some comparisons of survival by clinical characteristics.

Information about tumour stage and grade is not available at the national level. Registries in South Australian teaching hospitals have, however, collected data about Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stage and tumour grade. Data from the South Australian Hospital-based Cancer Registries are used as an indication of the situation in the whole of Australia.

After adjusting for these characteristics and for age, women diagnosed between 1992-98 had a 21% lower risk of dying (Relative risk = 0.79; 95% Confidence interval 0.66 to 0.95) than women diagnosed between 1984-91.⁷ This was indicative of treatment gains. The registries also showed that five-year survival fell from 86% for women with FIGO stage IA tumours to 7% for women with stage IV tumours, and from 70% for low-grade tumours to 25% for high-grade tumours.⁷ Age at diagnosis was also an important predictor of outcome, with the five-year survival rates ranging from 74% for cases under 40 years at diagnosis to 18% for those aged 75 years or more. (In this instance, the survival proportions were not calculated as relative survival.) Similar figures have been reported by a study of ovarian cancer conducted in Queensland, New South Wales and Victoria between 1990 and 1993. Five year survival fell from 88% for stage 1 tumours to 12% for stage IV cancers; from 79% for low grade tumours to 30% for high grade tumours and from 67% for women diagnosed below the age of 40 to 29% among women diagnosed at age 70-79 years.⁸

Table 1 Five year survival rates for ovarian cancer in Australia by age at diagnosis, FIGO stage and tumour grade

	South Australia, 1984-1998 ⁷	Queensland, NSW & Victoria, 1992-1994 ⁸
Age		
Younger	74% (age <40)	67% (age < 40)
Older	18% (age 75+)	29% (age 70-79)
FIGO stage		
I	86% (IA)	88%
II		65%
III		27%
IV	7%	12%
Tumour grade		
Well-differentiated	70%	79%
Moderately differentiated		41%
Poorly differentiated		39%
Undifferentiated	25%	30%

Key points:

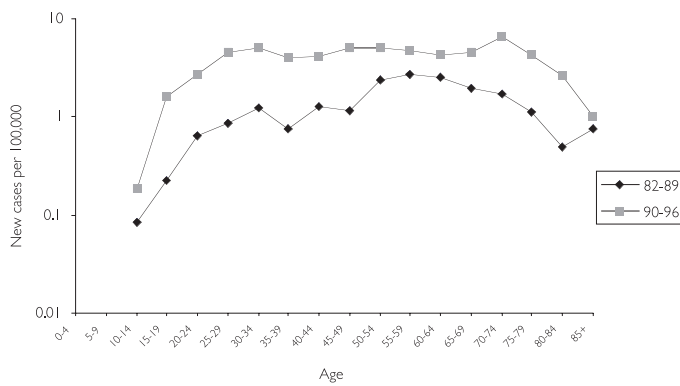
- Stage and grade of tumour at diagnosis are important predictors of five-year survival; FIGO stage 1A and low grade tumours have the highest survival rates.

BORDERLINE OVARIAN TUMOURS

One group of epithelial cancers, not as aggressive as others, are described as ‘borderline’ (or low malignant potential) ovarian cancers. They generally occur at younger ages and with a more favourable stage distribution than other ovarian cancers. (*See chapters on Risk factors for ovarian cancer, Chapter 3; The biology and pathology of ovarian tumours, Chapter 5; and Management of borderline ovarian tumours, Chapter 9*)

There are no national cancer registry data on borderline ovarian tumours. Few cancer registries in Australia enter data on borderline ovarian tumours into their registry databases (eg they are not registered in the NSW Central Cancer Registry). Data are available from the Victorian Cancer Registry although they are influenced by changes in coding as well as reporting and registration practices. Prior to 1995, borderline ovarian tumours were coded as International Classification of Disease (ICD) 236.2, neoplasms of uncertain behaviour - ovary. Since 1995, under ICD-O2 rules, borderline ovarian tumours are coded as malignant under ICD 183 and distinguished by separate morphology codes. Data presented in Figure 10 are from Victoria from 1982 to 1996.

Figure 10 Age specific incidence rates for borderline ovarian tumours, Victoria 1982-1996



Borderline ovarian tumours are less common than invasive ovarian cancers. The age-specific incidence of borderline ovarian tumours shows a different pattern from that of invasive ovarian tumours (see Figure 5). Incidence of borderline ovarian tumours increases to age 30 and then flattens with a fall in incidence from age 75. Incidence rates in 1990-1996 were higher than in 1982-89, reflecting both increased reporting and registration of borderline ovarian tumours, though the pattern of incidence with age was similar.

In a report from the USA, 10-years survival for 2818 women with borderline tumours was 95%⁹ although this figure fell from 97% among women with stage I tumours (82% of all borderline tumours) to 69% among the small group (3%) with stage IV tumours. Data from Switzerland¹⁰ and Norway¹¹ have also shown overall survival to be more than 90% after five years. A recent Australian study reported only two deaths during an average of seven years follow-up of 145 women with borderline epithelial ovarian tumours.⁸

Key point:

- Reliable national data on the incidence of borderline ovarian tumours and on the incidence of ovarian tumours by major histopathological type are not currently available and would be of value in monitoring trends and outcomes.

TECHNICAL GUIDE

CANCER REGISTRATION

Cancer registration is a legal requirement in all Australian States and Territories. Population-based data are collected by each State and Territory cancer registry to monitor cancer trends, increase understanding of the causes of cancer, and assist prevention efforts and treatment decisions. Population-based registries normally collect a limited range of data items only.^{12,13} Priority is placed on case ascertainment, rather than on collecting a broad range of data items. The data show the burden of cancer on the total population, and its component sub-groups, as indicated by incidence, mortality and survival data.¹²

Hospital-based registries can play an important role in collecting the clinical data that hospitals require for purposes such as monitoring care and survival by stage and other clinical characteristics to assess concordance with recommended protocols and expectations from the scientific literature. Data can be used for research purposes and to assess caseloads for planning and resource negotiation.⁷

NATIONAL POPULATION-BASED CANCER STATISTICS

Established in 1987, the National Cancer Statistics Clearing House (NCSCCH) compiles data produced by State and Territory registries and produces national cancer statistics.¹⁴ The Australian Institute of Health and Welfare (AIHW) operates the NCSCCH under the supervision of the Australasian Association of Cancer Registries. Although some State and Territory cancer registries have been operating for more than 20 years, registration was not universal in Australia until 1982.

National data on cancer deaths have been available for many years based on information provided to the Registrar of Births, Deaths and Marriages in each State and Territory.

The statistics presented here for ovarian cancer in Australia are derived from data collected by the NCSCCH and reported by the Australian Institute of Health and Welfare. Data are from 1999 except where numbers of cancers in particular sub-groups are small and data from several years are pooled. Incidence rates for borderline ovarian tumours come from the Victorian cancer registry.

HOSPITAL-BASED CANCER STATISTICS

Although there are currently no national clinical data collections on ovarian cancer, the National Cancer Control Initiative has released recommended minimum data sets for hospital and other clinical cancer registries.¹⁵ A standardised approach to the collection of clinical data would enable national patterns of cancer survival by stage at diagnosis and patterns of cancer care to be assessed.

Hospital-based cancer registries have a long history in the USA. In Australia, hospital-

based cancer registry data have been collected from South Australian teaching hospitals with specialist gynaecological oncology services. The data have been used for a broad range of purposes including monitoring clinical practice and outcomes and for planning health services.

DEFINITIONS

Rates are presented per 100,000 female population. Age-standardised rates have been calculated by the direct method using the 1991 Australian standard population.¹⁴ For international comparisons, the world standard population has been used.

CODING

Australian data for ovarian cancer in 1999 are presented for “malignant neoplasms of the ovary” (International Classification of Diseases revision 10, ICD-10 code C56). Prior to this date cancers were coded to ICD-9 and data are presented for “malignant neoplasms of the ovary and other uterine adnexa” as classified to the single three-digit code 183.¹⁶ The majority of neoplasms with this code are malignant neoplasms of the ovary. Coding at the four digit level of 183.0 to 183.9 distinguishes between different sites as follows: 183.0 ovary; 183.2 fallopian tube; 183.3 broad ligament; 183.4 parametrium; 183.5 round ligament; 183.8 other; 183.9 uterine adnexa, unspecified.

Cancers of the ovary comprised 97.3% of all cancers coded as ICD-9 183 malignant neoplasms of the ovary and uterine adnexa in 1992-1996. Malignant neoplasms of the broad ligament (ICD 183.3), parametrium (ICD 183.4) and round ligament (ICD 183.5) were very rare with fewer than ten cases in total diagnosed in the five-year period. The number of new cases and the age standardised incidence rates are shown in Table 2 for sites with more than five cases.

Table 2 Malignant neoplasms of the ovary and uterine adnexa in Australia 1992-1996 by site. (National Cancer Statistics Clearing House and Australian Institute of Health and Welfare: Personal Communication)

	Ovary 183.0	Fallopian tube 183.2	Other 183.8	Uterine adnexa, unspecified 183.9
Number of new cases	5,408	104	26	14
Age-standardised incidence rate per 100,000	11.1	0.2	0.1	<0.1

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2. RISK FACTORS FOR OVARIAN CANCER

Established risk factors for ovarian cancer have been identified in well-designed studies from multiple research groups around the world and observed in the pooled re-analysis of data from several studies. They include the increase in risk with age and a family history of ovarian cancer. Evidence for other risk factors has been less consistent. Important protective factors are parity and use of the oral contraceptive pill.

As a comprehensive review of recent research literature on risk factors for ovarian cancer has been commissioned by the National Breast Cancer Centre and detailed reviews of the epidemiology of ovarian cancer can be found elsewhere,^{1,2,3} these guidelines will provide a general overview.

The epidemiology of specific ovarian tumour types has not been well described and risk factors may differ. Some studies have focussed on the epidemiology of epithelial ovarian tumours while others have grouped together a broad range of histological types. There have been relatively few studies of the epidemiology of borderline ovarian tumours. Evidence to date suggests a similar pattern of risk factors to invasive ovarian tumours. Possible exceptions include weaker protection from oral contraceptive use, a stronger association with infertility and fertility drug use and a weaker association with family history.^{4,5}

AGE

Invasive ovarian cancer is rare among young women; the majority of cases are diagnosed in women over the age of 50. The pattern for borderline ovarian tumours is different (*see chapter 1 on Ovarian cancer in Australian women, Figure 10*).

FAMILY HISTORY

Familial clusters of ovarian cancer have been recognised for many years and family history has been identified as a risk factor in most epidemiological studies that have investigated its role.⁶ Between 5% and 10% of cases of ovarian cancer are believed to be attributable to hereditary factors.⁷ The proportion is higher in women of Ashkenazi Jewish descent - about 30%. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as important. Although particular gene mutations, such as these, confer a high risk, the majority of ovarian cancers occur in women who do not have a family history of the disease (*see chapter 4 on Familial aspects of ovarian cancer*).

REPRODUCTIVE HISTORY

Infertility

The relationship between infertility and ovarian cancer risk is not well understood. Studies have had difficulty in separating the effects of low parity, infertility and its treatment with fertility drugs; few have distinguished between anovulatory infertility and infertility due to other causes.

Findings about ovarian cancer risk in women who have been treated with fertility drugs have been inconsistent.⁸ Follow-up of a large Australian cohort of In Vitro Fertilisation patients treated with fertility drugs to induce superovulation has, to date, shown no increase in ovarian cancer incidence.⁹ A recent pooled reanalysis of 8 case-control studies of ovarian cancer showed no increased risk of invasive ovarian cancer in women with a history of fertility drug use¹⁰ When the different histologic subtypes were considered separately an odds ratio of 2.4 (CI 1.0-5.9) for borderline serous ovarian tumours was seen among treated women who had never had children. However, this association could have been due to chance.

One study suggests a possible association between ovarian epithelial dysplasia and ovulation induction therapy, in accord with previous results of increased risk of ovarian cancer in women with a history of fertility treatment. The higher dysplasia score could be attributable to the drugs used to induce ovulation or to a genetic susceptibility of ovarian cancer.¹¹

Pregnancy

Evidence for the protective effect of pregnancy on ovarian cancer risk comes from analyses of population fertility rates and ovarian cancer mortality¹² and more recently from case-control studies, including a large Australian study.¹³ The combined analyses of 12 US case-control studies⁴ and 3 European case-control studies^{14,15} confirmed the protective effect of parity with a risk reduction of up to 50% depending on the study design and number of births women had experienced. One study notes that compared with women who have never had children (Relative Risk of 1.0), women with a single pregnancy have a lower relative risk (CI 0.6 to 0.8). Each additional pregnancy lowers risk by about 10 to 15 percent.¹⁶ The effect may be greatest for non-mucinous tumours.¹⁷ Increasing parity has also been shown to reduce the risk of borderline ovarian tumours in women aged 50-74.¹⁴

Greater age at first birth^{18,19} and greater age at last birth^{18,20,21} have both been associated with a reduced risk of ovarian cancer in some but not all studies. Multiple pregnancies may also confer increased protection compared to singleton births, particularly for non-mucinous tumours.²²

There has been some suggestion that incomplete pregnancies reduce ovarian cancer risk but the effect appears to be less than for complete pregnancies.^{3,4}

Hysterectomy and tubal ligation

Many studies have observed protective effects of hysterectomy (with bilateral ovarian conservation) and tubal ligation on ovarian cancer risk. Risk reductions of 35% - 40% were found in one case-control study.²³ The explanation for this finding is not clear, but it has been suggested that protection may result from reduced passage of carcinogens to the upper genital tract. Hormonal and circulatory sequelae of hysterectomy and tubal ligation have also been proposed as possible explanations.²⁴

OTHER REPRODUCTIVE FACTORS

There are other reproductive factors in determining ovarian cancer risk which are uncertain. Studies have reported no association with age at menarche^{18,13} and earlier age at natural menopause has been associated with both decreased¹⁸ and increased²⁵ risk. Among women with early onset disease, there is little evidence to suggest that early menopause is related to ovarian cancer.²⁵

Breastfeeding may, however, reduce the risk of ovarian cancer slightly.^{4,26} It has also been shown to reduce the risk of borderline ovarian tumours in women aged 50-74.¹⁴

EXOGENOUS HORMONES

The effect of hormone replacement therapy (HRT) on ovarian cancer risk has been controversial with some studies showing a significant increase in risk¹⁸ while others show no association or only a non-significant increase in risk.²⁷ A recent study of long term users of menopausal HRT by Lacey *et al.* showed an association between oestrogen only HRT and ovarian cancer, with Relative Risks, for 10-19 years of use and 20 or more years of use, of 1.8 and 3.2 respectively. There was no increased risk found for short-term use of combined progestin/oestrogen HRT.²⁸ However, in a study published shortly after this by Sit *et al.*, there was no association overall between any use of HRT and epithelial ovarian carcinoma.²⁹

Unopposed oestrogen replacement has been associated with a significant increase in relative risk of endometrioid and clear cell epithelial ovarian cancer (OR 2.56, CI 1.32 to 4.94).³⁰ This finding is consistent with the well-known association between oestrogen therapy and risk of endometrial cancer. A second study reported the greatest increase in risk for serous cancers.¹⁸ The association between HRT and risk of the different histologic subtypes of ovarian cancer needs to be investigated in larger studies.

Key point:

- Further studies are needed to establish whether there are associations between different types of hormone replacement therapy and different histological types of ovarian cancer.

ORAL CONTRACEPTIVE PILL

There has been consistent evidence of a protective effect of the combined oral contraceptive pill on ovarian cancer risk. Women who had ever used the oral contraceptive pill had a 50% reduction in risk compared to women who had never used the Pill in the Australian case-control study.¹³ Although there is evidence that the protective effect persists for up to 15 years,^{4,31} it may diminish in the longer term.³²

One study compared oral contraceptive oestrogen and progestin content for cases and controls, adjusted for current age, number of pregnancies, race and family history of ovarian cancer. Use of low-oestrogen/low-progestin pills afforded an estimated risk-reduction that was identical to that for high-oestrogen/high-progestin pills.³³

Suppression of ovulation has been believed to be the most likely explanation for the protective effect of oral contraceptives. However, there is increasing recognition of the role of hormones in the aetiology of ovarian cancer³⁴ and evidence that oral contraceptives are protective even after adjusting for the number of ovulatory cycles a woman has experienced.³⁵ Whether or not changes to the formulations of oral contraceptives in recent years has affected the degree of protection remains to be seen.

A recent Swedish case control study confirmed a long-lasting protective effect of oral contraceptive use against ovarian cancer, but noted some differences in odds ratio by histologic type, with no protective effect seen for mucinous carcinoma.¹⁸ Others have, however, reported similar benefits for both mucinous and non-mucinous cancers.¹⁷

A single study of borderline tumours reported no protective effect for oral contraceptive use¹⁴ but others have found similar protection for invasive and borderline tumours.⁴

OTHER FACTORS

It has been suggested that inflammation may play a part in ovarian cancer risk and that ovarian cysts and hyperthyroidism may be associated with inflammatory responses of the ovarian epithelium.³⁶ Endometriosis has been associated with an increased risk of ovarian cancer in a large Swedish cohort study³⁷ and in a pooled analysis of seven case-control studies,¹⁰ but has yet to be confirmed in other well-designed cohort studies. There is also clinical evidence indicating that deposits of endometriosis on the ovary may develop into epithelial ovarian cancer, and in particular the endometrioid and clear cell subtypes.^{38,39} The question of whether a history of benign ovarian cysts increases the risk of ovarian cancer has been addressed in only a small number of studies and there is currently little evidence to support an association.^{40,41}

BODY SIZE

Some data suggest that increasing body weight may confer a protection against cancer⁴² but taken together, the evidence is in favour of a small to moderate positive relation between high Body Mass Index (BMI) and occurrence of ovarian cancer.⁴³

LIFESTYLE FACTORS

Diet

While retrospective studies of dietary intake are notoriously difficult, the influence of dietary factors on ovarian cancer risk has been studied as a possible explanation for differences in incidence between countries and ethnic groups. Increased risks have been associated with the consumption of meat, whole milk⁴⁴ and animal fat in some studies; others have found no such associations.² It has been suggested that intake of low fat milk, calcium or lactose may reduce the risk of ovarian cancer.⁴⁵ Overall, results suggest no association between intake of any type of fat and ovarian cancer.⁴⁶ There has been more limited research on the effects of alcohol and coffee consumption with no consistent evidence of an increased risk.⁴⁷

Smoking

Some studies have shown an association between smoking and ovarian cancer.^{13,48,49} One study showed that women who had ever smoked were more likely to develop ovarian cancer than those who had never smoked.⁵⁰ The level of risk may vary according to the histologic type of tumour, with higher risk for borderline and mucinous ovarian cancer but not for non-mucinous tumours.^{50,49} A case-control study by Marchbanks *et al.* showed that the risk for mucinous epithelial ovarian cancer was more than doubled for women who had ever smoked and for current smokers. This elevated risk was regardless of years since the first cigarette or age at which women first smoked.⁴⁸

Physical activity

Overall results provide only limited support for an inverse association between recreational physical activity and risk of ovarian cancer.⁵¹

Use of talcum powder

An association between the use of talcum powder in the perineal area has been suggested in some studies,^{13,23} but not found in others.^{52,53}

Key points:

- Level III-2 evidence indicates that important risk factors for ovarian cancer include the increase in risk with age^{1,2} and a family history of ovarian cancer.⁶ Evidence for other risk factors has been less consistent.
- Protective factors include increasing parity and oral contraceptive use.
- The epidemiology of specific ovarian tumour types has not been well described and risk factors may differ.
- At present, the risk factors for ovarian cancer are not readily modifiable and have not been translated into primary prevention strategies.

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3. SCREENING FOR OVARIAN CANCER

INTEREST IN OVARIAN CANCER SCREENING

There is great interest in the feasibility and benefits of early detection of ovarian cancer through screening, defined as the investigation of asymptomatic women. In this chapter the focus will be on women at average or population risk. The management of women at high risk will be covered in chapter 4, *Familial aspects of ovarian cancer*.

The poor prognosis for women diagnosed with ovarian cancer is related to the fact that the disease is usually diagnosed at an advanced stage. By the time that the patient is investigated for often generalised symptoms, the disease has usually progressed and chances of a cure are reduced. Early stage disease, where the disease is confined to the ovaries, is associated with a 5-year survival rate of over 80%.¹

ISSUES FOR OVARIAN CANCER SCREENING

- No true precursor lesion has been identified (*see chapter 5 on The biology and pathology of ovarian tumours*)
- Any screening for ovarian cancer should ideally detect early, pre-clinical, asymptomatic disease to reduce morbidity and mortality
- To date there is no evidence to indicate a decrease in mortality as a consequence of ovarian cancer screening, although survival advantage has been found in two trials^{2,3}
- Any screening test will need to have an appropriate sensitivity (the ability to determine the presence of the disease in those who have it) and specificity (the ability to exclude the disease in those who do not)
- The benefits of any screening test should outweigh any chance of physical or psychological harm

(For the World Health Organization (WHO) criteria for screening, *see Appendix 3 - Principles of screening*).

TECHNIQUES FOR SCREENING FOR OVARIAN CANCER

BI-MANUAL PELVIC EXAMINATION

When used alone, bimanual pelvic examination lacks both the sensitivity and specificity to be effective and is not recommended as a screening method.⁴

ULTRASOUND

Transabdominal ultrasound

Transabdominal ultrasound has been used to detect changes in the ovaries which may be suggestive of the presence of a tumour, such as enlargement. Transabdominal ultrasound was used to screen over 7000 asymptomatic women or post menopausal women and showed a specificity ranging from 94% to 98%, with a positive predictive value ranging from 1.5% to 7.7%.^{5,6,7,8}

Transvaginal ultrasound (TVUS)

Transvaginal ultrasound provides increased proximity to the ovaries and allows for better visualisation of morphological changes than transabdominal ultrasound. While it does have the ability to detect the presence of ovarian disease, it gives rise to a large number of false positives, due to its inability to distinguish between benign and malignant masses.^{9,10} Studies with asymptomatic women showed that for those who had a positive ultrasound test, the proportion who correctly had ovarian cancer predicted was only between 6% and 9%.^{11,12,13,14}

Combination of transabdominal and transvaginal ultrasound

Studies that used a combination of transabdominal and transvaginal ultrasound in women with a family history of ovarian cancer have achieved a positive predictive value of between 7% and 9.8%.^{15,16}

Sonography may best be used as a secondary test due to its low positive predictive value, and its inability to accurately differentiate between benign and malignant disease (giving rise to false positives).

Doppler ultrasound

Colour Doppler ultrasound has been used singly or in conjunction with other techniques, to improve differentiation between benign and malignant disease through imaging of the blood flow characteristics. Results have been mixed and it has not been shown that this technique is a better differential test than transvaginal ultrasound or CA125.^{17,18,19,20}

CA125

CA125 is an ovarian cancer antigen which can be detected in blood serum. The levels present in the blood can be affected by a number of factors such as prior cancer diagnosis, regular smoking, caffeine consumption, age, and age at menarche, age at menopause and history of previous ovarian cyst.²¹ Elevated levels may also be associated with other malignancies or benign conditions. It is most often raised in serous and less frequently in mucinous cancer and is found in over 80% of non-mucinous epithelial ovarian cancers.²²

As a screening test, a cut-off value of 30U/ml-35U/ml is usually used. CA125 is elevated in 76% of women with FIGO stage II disease, over 90% of women with FIGO stage III and IV disease but only 49% of women with FIGO stage I disease.²³ As a stand-alone screening tool it lacks the specificity and sensitivity required.

Key point:

- Less than 50% of women presenting with FIGO stage 1 ovarian cancer have elevated levels of CA125.

Using CA125 in combination with other modalities such as ultrasound, as a serial measure or with complementary tumour markers, such as inhibin,²⁴ has been investigated in an attempt to increase its specificity and sensitivity.

FUTURE DIRECTIONS

Genomic and proteomic technologies²⁵ have the potential to identify specific genes and novel cancer-specific markers for ovarian cancer. The development of molecular profiles for ovarian cancer and a better understanding of the genetic and molecular origins of ovarian cancer may also be used for early detection.

RECOMMENDATIONS ABOUT SCREENING FOR OVARIAN CANCER

There is currently no national or international study which recommends routine screening for women in general. (For the management of women with a family history of ovarian cancer or with a hereditary cancer syndrome, *see chapter 4 on Familial aspects of ovarian cancer*).

FUTURE PROSPECTS IN OVARIAN CANCER SCREENING

Three large multi-centre, population-based randomised trials are in progress.

- St Bartholomew's trial (UK) commenced in 1995, plans to recruit 200,000 post-menopausal women over seven years, randomised to screening with CA125 followed by ultrasound, ultrasound only or a control group.
- Prostate, lung, colon-rectum and ovary trial (PLCO - USA) commenced around 1993 and has enrolled 37,000 women in each arm. The protocol involves a combination of transvaginal ultrasound, CA125 and pelvic examination conducted annually.
- European Organisation for Research and Treatment of Cancer trial (EORTC-UK and Europe) commenced in 1995 and the trial has 30,000 in each arm and 60,000 in the control arm. The protocol involves transvaginal ultrasound at either 18 or 36 month intervals, with repeat scans performed based on criteria which may indicate carcinoma.

The results of these trials will be used to frame a decision on the type of population screening test and the optimal screening interval.

Key points:

- None of the currently available screening tests, either singly or in combination, have been shown to be effective in reducing mortality from ovarian cancer.
- Population-based screening for ovarian cancer cannot be recommended at this time due to the absence of evidence for a reduction in morbidity or mortality.

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4. FAMILIAL ASPECTS OF OVARIAN CANCER

Up to 10% of all cases of epithelial ovarian cancer are thought to be due to the autosomal dominant inheritance of mutations in one of a small number of ovarian cancer-related genes (see Table 3).² Carriers of mutations in such genes have an increased risk of epithelial ovarian cancer of at least 10 fold. Some of these genes are also associated with an increased risk of female breast cancer, while others are associated with an increased risk of other cancers, such as male breast cancer and cancer involving other organs.³

These genetic factors are the strongest known risks for ovarian cancer, although they are rare and do not inevitably lead to disease.

Table 3 - Known genes responsible for hereditary ovarian cancer

Syndrome	Gene	Chromosome	Risk of other cancers
Hereditary breast/ovarian cancer	BRCA1	17q	Female breast, prostate, fallopian tube, primary peritoneal
	BRCA2	13q	Female breast, male breast, prostate, pancreas fallopian tube, primary peritoneal and other
Hereditary non-polyposis colorectal cancer	DNA mismatch repair genes (HNPCC)	Various	Colorectal, other gastrointestinal, endometrial, renal tract, ovarian

Two main hereditary ovarian cancer syndromes have been identified (*see Table 3*). These two syndromes account for about ten percent of all cases of ovarian cancer. They are:

- hereditary breast/ovarian cancer syndrome, which is characterised by susceptibility to both breast and ovarian cancer, cancer of the fallopian tube, primary peritoneal cancer, male breast, prostate and pancreatic cancer.
- hereditary non-polyposis colorectal cancer syndrome (HNPCC), which includes early onset colorectal cancer, other gastrointestinal cancers and cancer of the renal tract and an increased risk of extracolonic cancers, including endometrial and ovarian.

GENES ASSOCIATED WITH OVARIAN CANCER

Constitutive (germline) mutations in specific genes are associated, in carriers, with an increased risk of ovarian cancer. The degree of risk depends on the gene involved, and there is evidence that different mutations in the same gene may be associated with different risks of certain cancers.

The BRCA1 and BRCA2 breast/ovarian cancer susceptibility genes have been well studied because of their major role in the genetic predisposition to breast cancer. Carriers of a germline mutation in either BRCA1 or BRCA2 are also at increased risk of ovarian cancer.^{4,5} The risk of developing ovarian cancer by age 70 for female carriers of a mutation in BRCA1 or BRCA2 has been estimated to be between 15% and 66%,^{4,6,7} although the risk for BRCA2 mutation carriers is, on average, at a later age and less than for BRCA1 mutation carriers.^{4,5} The age at diagnosis of ovarian cancer in women with a BRCA1 mutation tends to be earlier than for women in the general population, with a median age at diagnosis of 48 years, while the average age at diagnosis of BRCA2-related ovarian cancer is similar to that for women without a genetic predisposition⁸ and usually in the late 50s or early 60s.

Key points:

- Female carriers of germline mutations in BRCA1 have a lifetime risk of ovarian cancer that may be as high as 60%,¹⁰ and in BRCA2 as high as 40%.⁵
- For women with a BRCA1 mutation, who develop ovarian cancer, the average age at diagnosis is earlier than for women in the general population.⁸

Neither BRCA1 nor BRCA2 appear to be associated with very early ovarian cancer (i.e. diagnosed before the age of 30 years). There is some evidence that some mutations in the BRCA2 gene are associated with a higher risk of ovarian cancer and a lower risk of breast cancer.⁹ There is ongoing Australian and international research investigating the frequency of BRCA1 and BRCA2 mutations in the population, their associated risks of different cancers (penetrances) and phenotypes, such as tumour morphology, and the effect on disease risk due to genes and/or environmental risk factors.

Between 1 in 500 and 1 in 1000 unaffected women carry a germline mutation in one of these genes. The founder mutations 185 del AG and 5382 ins C in BRCA1, and 6174 del T in BRCA2, are carried by about 2% of individuals of Ashkenazi Jewish ancestry. For this reason, a higher proportion of ovarian cancer cases in Ashkenazi Jewish women are due to germline mutations in these genes (estimated to be 40-60%).¹¹ Each of these mutations is associated with an increased risk of ovarian cancer.⁶ BRCA-associated invasive epithelial ovarian malignancy tends to be of the non-mucinous, mostly serous, subtype, as is the case for most ovarian cancers in the general population.¹² Cancers of the fallopian tube¹³ and primary peritoneal cancers are also associated with germline mutations in BRCA1 and BRCA2, though to a lesser extent.

In families with HNPCC due to a germline mutation in one of the DNA mismatch repair genes, mutation carriers have a 70-90% lifetime risk of developing any cancer.

There is a higher risk of colorectal cancer for men compared to women from HNPCC families. Women who carry a mismatch repair gene mutation have a lifetime risk of up to 40% for endometrial cancer and a lifetime risk for ovarian cancer of up to 10%.¹⁴ In a retrospective review of HNPCC-associated ovarian cancers, the mean age at diagnosis was relatively young at 42.7 years.¹⁵ There is a tendency for these cancers to be of lower grade and earlier stage, and synchronous ovarian/endometrial cancers may occur.

All the above risks for carriers of deleterious mutations in ovarian cancer-related genes are estimates, and have large confidence intervals. They are mostly derived from selected families with extensive family histories, and in which case the penetrance of the gene mutation may be particularly high. Increasingly, though, risk evidence is accumulating from families unselected for a strong family history.⁸

Finally, there may be many other genes, as yet undiscovered, which are associated with an increased risk of ovarian cancer.¹⁶

MUTATION TESTING FOR GENES ASSOCIATED WITH OVARIAN CANCER

Familial Cancer Clinics make a thorough assessment of the family's cancer history and determine the likelihood that a germline mutation in an ovarian cancer-related gene may be present. Genetic testing should only be offered with pre and post-test counselling, conducted in conjunction with a specialist genetics service for breast/ovarian cancer. The potential harms, benefits and limitations of genetic testing need to be considered.

The process of genetic testing usually begins with the analysis of ovarian cancer-related genes by taking a blood sample from an affected family member. Although it is technically possible to detect constitutive alterations in ovarian cancer-associated genes, genetic testing requires specialised laboratory techniques and the 'mutation search' is expensive and time consuming. It is possible that some disease-related genetic mutations may not be detected using current technology. Detection of a genetic mutation in an affected family member allows for further predictive genetic testing of adult, unaffected relatives. Some family cancer clinics are also involved in ongoing risk management.

Key point:

- The potential harms, benefits and limitations of genetic testing need to be considered. Genetic testing (mutation searching and predictive testing) should only be offered with pre- and post-test counselling, conducted in conjunction with a specialist genetics service for breast/ovarian cancer.

FAMILY HISTORY

Having a family history of ovarian cancer is an important risk factor for ovarian cancer.¹⁷ Similarly, having a family history of breast cancer, or of cancers associated with HNPCC, may be associated with an increased risk of ovarian cancer.

Epidemiological data (case-control studies) have found a 2-to-20-fold increase in risk of ovarian cancer associated with a family history of ovarian cancer.^{17,18} The risk increases with the number of affected first degree relatives. The lifetime risk of ovarian cancer for women with a single first degree relative with ovarian cancer may approach 3% (a 3 fold increase compared to the general population), while for a woman with a single first degree relative with breast cancer, it is less than 2%, (compared to the population risk of around 1%).¹⁹ The lifetime risk for women with two first degree relatives with ovarian cancer has been estimated to range between 7% and 20%.²⁰ It should be noted that estimates of risk for women with various combinations of multiple affected relatives on the same side of the family are often based on small numbers, and should be interpreted with caution.

For any woman of Ashkenazi Jewish origin with a family history of breast or ovarian cancer, her Jewish background should be considered as an additional risk factor.⁶

In estimating risk of ovarian cancer based on family history, it is essential to take an accurate family history, and update it regularly. Taking a family history involves asking about all cancers for all first and second-degree relatives, both male and female, on both the maternal and paternal sides of the family. Attempts should be made to verify all cancer reports.

Key points:

- A comprehensive cancer family history is essential to be able to estimate risk of ovarian cancer.
- Any Ashkenazi Jewish woman with a family history of breast or ovarian cancer should have her ancestry considered as an additional risk factor.

PREDICTING RISK BASED ON CANCER FAMILY HISTORY

The National Breast Cancer Centre has previously published guidelines for health professionals to assist in assessment of risk based on family history.²¹ The information about familial aspects of ovarian cancer has now been updated (*see Appendix 1*), and the changes are included in the section below. For the purpose of advising women about their risk of ovarian cancer, it is useful to divide women into TWO broad categories.

Category 1: This covers more than 99% of the female population and includes women with no family history of epithelial ovarian cancer, or a limited family history, who are at or at most moderately above average risk.

Category 2: This covers less than 1% of the female population and includes women at a potentially high risk of ovarian cancer. (*See Risk classification for women at potentially high risk of epithelial ovarian cancer p.36*)

Being in Category 2 suggests that there may be, within the family, a dominantly inherited mutation in a gene such as BRCA1 or BRCA2, which confers a high risk of breast cancer and an increased risk of ovarian cancer, or a dominantly inherited mutation in the mismatch repair genes involved in HNPCC. Women from families in which the presence of an ovarian cancer-associated gene mutation has been established also belong to this category, since they are at potentially high risk.

Generally, it would be appropriate to commence testing for a causative germline mutation in any affected individual (or obligate carrier) in a family that meets the criteria for Category 2 (potentially high risk). In an Ashkenazi Jewish family, if the family meets the criteria, but an affected family member is not available, germline testing may be offered to an unaffected individual, in order to test for any of the three founder mutations in BRCA1 and BRCA2 that are associated with familial breast/ovarian cancer in that particular background.

Key point:

- Women who are proven to carry an ovarian cancer-associated gene mutation should be considered at potentially high risk.

Note:

To make these risk categorisations the family history of ovarian cancer must not be considered in isolation. A family history of breast cancer, and of some other types of cancer, should also be taken into account. Ashkenazi Jewish background is also important. If these additional features are present, referral to a specialist cancer genetics service may be appropriate. Women should be encouraged to seek medical advice promptly if they develop symptoms or signs that could be related to any cancers. Women found to have a pelvic mass at any age should be referred for specialist opinion.

Key point:

- A family history of breast cancer and of some other types of cancer should be taken into account, to ensure that a family history of ovarian cancer is not considered in isolation. Ashkenazi Jewish background is also important.

RISK CLASSIFICATION FOR WOMEN AT POTENTIALLY HIGH RISK OF EPITHELIAL OVARIAN CANCER

(See Category 2 above)

The following women should be advised that they have a potentially high risk of developing ovarian cancer and perhaps other cancers. This group includes less than 1% of the population, and comprises women who have:

- One first degree relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry;
- Two first or second-degree relatives on the *same side* of the family diagnosed with breast or ovarian cancer, especially if one or more of the following features occurs on the same side of the family:
 - breast cancer diagnosed before the age of 40;
 - bilateral breast cancer;
 - breast **and** ovarian cancer in the same woman;
 - breast cancer in a male relative;

OR

- Three or more first or second degree relatives on the same side of the family diagnosed with any of the cancers associated with hereditary non-polyposis colorectal cancer (HNPCC): colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract;
- A member of a family in which the presence of a high risk ovarian cancer mutation in a gene such as BRCA1, BRCA2 or one of the DNA mismatch repair genes, has been demonstrated.

Women in this group should be advised that, although potentially at high risk for ovarian cancer, the majority of women in this group will not develop ovarian cancer. For a woman who has had genetic testing, the identification of a germline mutation in one of the ovarian cancer susceptibility genes, however, is associated with a high risk of ovarian cancer, and perhaps other cancers, depending on the gene.

Key point:

- For a woman who has had genetic testing, the identification of a germline mutation in one of the ovarian cancer susceptibility genes is associated with her having a high risk of ovarian cancer.

ISSUES TO CONSIDER IN THE MANAGEMENT OF WOMEN AT KNOWN OR POTENTIALLY HIGH RISK OF EPITHELIAL OVARIAN CANCER

There are limited data on which to base the management of women at known or potentially high risk of ovarian cancer, so precise protocols remain controversial.

Women from families with the breast/ovarian cancer syndrome should be considered at increased risk of breast cancer. Bilateral prophylactic (risk reducing) mastectomy, with or without reconstruction, should be considered as an option in the context of risk counselling and management. Women from families with suspected HNPCC may require screening for gastrointestinal and endometrial cancers, as well as screening for ovarian cancer.

Two observational studies of the effect of the oral contraceptive pill (OCP) on women with a mutation in BRCA1 or BRCA2 are conflicting; one study showed a protective effect,²² but there was no evidence for such an effect in a second study.²³ In addition, there is some evidence that the use of the OCP may increase the risk of breast cancer in mutation carriers.²⁴ To date this has only been demonstrated from a study of BRCA1 mutation carriers.²⁴ Although the increased risk for BRCA1 mutation carriers who used the OCP, compared to those who did not, was only 1.3-fold for OCP use for 5 or more years in BRCA1 carriers, the higher baseline risk of breast cancer in BRCA1 carriers means that even such small increases in risk may translate into substantial increases in absolute risk. Given these conflicting data, it is not possible to recommend the use of the OCP as a chemoprevention against ovarian cancer in women with a mutation in BRCA1 or BRCA2. Tubal ligation has been reported to reduce the risk of ovarian cancer in BRCA1 (but not BRCA2) mutation carriers²⁵ and could be considered as a means of contraception after childbearing had been completed.

In women who carry a germline mutation in BRCA1 or BRCA2, bilateral salpingo-oophorectomy (with or without hysterectomy) reduces the risk of epithelial ovarian cancer by at least 90%.^{26,27,28} It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. In addition, bilateral risk reducing salpingo-oophorectomy has been reported to be associated with at least a 50% reduction of risk of breast cancer in BRCA1 or BRCA2 mutation carriers.^{26,27,28}

Guideline - Risk reducing surgery	Level of Evidence	Refs
Bilateral risk reducing salpingo-oophorectomy in carriers of BRCA1 and BRCA2 mutations reduces the risk of epithelial ovarian cancer by at least 90%. It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. It may also halve the risk of breast cancer in mutation carriers. Ideally, risk reducing surgery should always be discussed with women at potentially high risk of ovarian cancer.	III-2	26,27,28

These findings support the practice of offering bilateral risk reducing salpingo-oophorectomy to carriers of a mutation in BRCA1 or BRCA2 after their childbearing is completed. The current practice, based on risk figures derived from mutation-carrying families, is to offer such surgery from about the age of 35–40 years in BRCA1 carriers and 40–45 years in BRCA2 mutation carriers. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member.

Women with germline HNPCC or women from HNPCC families (where definitive predictive testing is not possible) may also consider prophylactic (risk reducing) total hysterectomy once their child-bearing has been completed, from the age of 30–35 years. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member.

There are no data about the safety of combined short term hormone replacement therapy (HRT) or tibolone use for women at increase genetic risk. When making a decision about risk reducing salpingo-oophorectomy, either with or without hysterectomy, issues related to other health sequale need to be taken into account. For example, hormone replacement (HRT) issues such as the possible need for relief of symptoms such as hot flushes, as well as the prevention of osteoporosis, may be considered for pre-menopausal women.¹⁶ If the uterus remains intact, therapies other than HRT should be tried in the first instance, but if unsuccessful in controlling symptoms, combined (oestrogen/progesterone) HRT or tibolone might be offered in the short term for relief. The type of therapy recommended will depend on each woman's situation and the effect on her quality of life of menopausal symptoms, so it is appropriate that this is discussed on a case-by-case basis. Longer term use of combined hormone replacement therapy is associated with an increased risk of breast cancer in the general population,²⁹ although no specific data are available for women at high genetic risk. Recently, the use of tibolone has also been associated with an increased risk of breast cancer in women in the general population in a single large observational study that had several important methodological limitations.³⁰

Monitoring of bone density may also be appropriate, with treatment for reduced bone density, if required. If a total hysterectomy is performed (which removes also the small intramural uterine portion of the fallopian tube), then unopposed oestrogen might be considered for relief of menopausal symptoms, if required. Several studies have suggested that, in women in the general population, unopposed oestrogen results in a smaller risk for breast cancer compared to combined oestrogen and progesterone HRT. Thus the consequences of hysterectomy need to be weighed against the advantages of removal of the entire fallopian tube and the ability to use short-term unopposed oestrogen as HRT, if required.

In deciding whether women who have already had breast cancer should use post-operative HRT, the details of the breast cancer history and treatment should be considered. For those women who do not have a past history of breast cancer, details of any prophylactic breast surgery may also be relevant if considering HRT use.

The complexities associated with the decision to have bilateral risk reducing salpingo-oophorectomy (with or without hysterectomy) and the post-operative care decisions mean that this is best done in a multi-disciplinary environment.

Key points:

- Decisions about timing of risk reducing surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member, and other possible health sequelae of this surgery.
- The decision to have risk-reducing gynaecological surgery is complex and best made in a multi-disciplinary environment.

MANAGEMENT OF WOMEN AT POTENTIALLY HIGH RISK WHOSE OVARIAN CANCER-ASSOCIATED GENE STATUS IS UNKNOWN

The first step for women at potentially high risk, but whose ovarian cancer-associated gene status is not known, must be to exclude cancer. Thereafter early detection should be emphasised. While surveillance of women at increased risk may be appropriate, women should be made aware of the current limitations of such surveillance. It should be emphasised that there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality from ovarian cancer in women at risk.³¹ Furthermore, women should be informed that unnecessary intervention can sometimes result after a false positive test, and that interval cancers can develop between tests.

Women in this group should be advised:

- that an appropriate surveillance program may include transvaginal ultrasonography, preferably with colour flow Doppler, although the age at which this could commence may depend on details of the family history and CA125 measurement
- bilateral salpingo-oophorectomy has been proven to reduce the risk of ovarian and breast cancers in women who carry a BRCA1 or BRCA2 mutation.^{32,33}

(See chapter 3 on Screening for ovarian cancer)

MANAGEMENT IN WOMEN WHO HAVE BEEN SHOWN BY GENETIC TESTING TO CARRY A HIGH RISK MUTATION IN A GENE WHICH PREDISPOSES TO OVARIAN CANCER

The first step for women in this group must be to exclude cancer. Following that, consideration should be given to advising women:

- that an appropriate surveillance program may include transvaginal ultrasonography, preferably with colour flow Doppler, although the age at which this could commence may depend on details of the family history and CA125 measurement.
- that because early detection may be important and risk reducing surgery (bilateral salpingo-oophorectomy) has been proven to reduce the risk of ovarian and breast cancer in women with a mutation in BRCA1 or BRCA2,^{32,33} she should see a gynaecological oncologist. The age at which risk reducing surgery may be considered depends on the details of her family history, but would generally be from about age 35-40 years and when her child-bearing has been completed in BRCA1 carriers. In BRCA2 carriers, whose risk of ovarian cancer rises later in life, this decision might be deferred until age 40-45 years, and when child-bearing has been completed. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member. Primary peritoneal carcinoma may occur despite prophylactic oophorectomy.³⁴
- that women in HNPCC families may also consider prophylactic total hysterectomy when their child-bearing has been completed, from the age of 30-35 years. Decisions about the timing of such surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member.
- to consider participation in a relevant approved clinical trial.

(See chapter 3 on Screening for ovarian cancer)

Key points:

- Decisions about timing of risk reducing surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member.
- Primary peritoneal carcinoma may occur despite risk reducing oophorectomy³⁴ but is uncommon.

CONCLUSION

The state of knowledge and technology as it applies to genetic and familial aspects of ovarian cancer are changing rapidly. The need for updating information, collection of relevant Australian data and links to new research are as important to this field as they are to breast cancer.

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