Risk-reducing surgery for women at high risk of epithelial ovarian cancer

Eve Maria Geraldine Gaughan BSc MB BCh BAO MRCOG MRCPI,a,* Thomas Anthony Walsh BSc MB BCh BAO MRCOG MRCPIb

aClinical Fellow in Gynaecology Oncology, Mater Misericordiae Hospital, Eccles Street, Dublin 1, Ireland
bConsultant Gynaecologist Oncologist with special interest in gynaecology oncology, Mater Misericordiae Hospital, Eccles Street, Dublin 1, Ireland
*Correspondence: Eve Maria Geraldine Gaughan. Email: evegaughan@yahoo.co.uk

Accepted on 25 February 2014

Key content
• The lifetime risk of ovarian cancer in the general population is 1.4% but women with hereditary ovarian cancer syndromes have a lifetime probability as high as 25–60% for developing epithelial ovarian cancer.
• Screening has not been found to be associated with a statistically significant reduction in mortality from ovarian cancer and cannot be routinely recommended even for women at high risk. Serum CA125 levels are only elevated in 50–60% of stage I ovarian cancers and interval cancers may develop between screening visits.
• Studies show a 4–20% risk of finding an occult malignancy at the time of risk-reducing bilateral salpingo-oophorectomy.
• Studies support the efficacy of risk-reducing bilateral salpingo-oophorectomy in significantly reducing the risk of gynaecological and breast cancer in women who carry BRCA1 or BRCA2 mutations.
• Women undergoing risk-reduction bilateral salpingo-oophorectomy should be counselled about the effects of early menopause and the available management options including hormone replacement therapy.

Learning objectives
• To be able to identify those women at increased risk of ovarian cancer.
• To be able to appropriately counsel those at high risk of ovarian cancer regarding modifiable risk factors, screening and the role of risk-reducing surgery, including prophylactic bilateral salpingo-oophorectomy and its alternatives such as tubal ligation and salpingectomy.
• To understand the limitations of current screening modalities for the reduction of ovarian cancer risk.

Ethical issues
• Ethical concerns exist pertaining to the performance of screening modalities, which have not been found to significantly reduce mortality from ovarian cancer and can cause harm in terms of psychological and surgical morbidity from false-positive results.
• For those with a positive family history of ovarian cancer but no genetic cancer syndrome, the discussion to perform risk-reducing surgery should be balanced against the risk of surgical morbidity and early menopause. Individual patient risk factors must be considered in the decision-making process.

Keywords: bilateral salpingo-oophorectomy / BRCA gene / cancer / epithelial ovarian cancer / risk-reducing surgery

Introduction
Ovarian cancer is the second most common gynaecological malignancy and the most common cause of gynaecological cancer death. The majority of ovarian tumours (90%) arise from epithelial cells and the remainder are derived from other ovarian cell types (germ cell and sex cord stromal tumours).

The lifetime risk of ovarian cancer in the general population is 1.4%. The median age at diagnosis is 57.1 Despite the good prognosis associated with early-stage disease, overall 5-year survival is less than 45%. This poor survival rate is largely due to the spread of cancer beyond the ovary at time of diagnosis in 75% of patients.2

Risk factors
The strongest known risk factor is a family history of the disease, which is present in about 10–15% of women with ovarian cancer.3 The risk of ovarian cancer is increased when the family history suggests a sporadic case but is substantially greater when there is a hereditary cancer syndrome. Women with a single family member affected by epithelial ovarian cancer have a 4–5% risk, while those with two affected
relatives have a 7% risk of developing the disease. In contrast, women with hereditary ovarian cancer syndromes defined as having at least two first-degree relatives with epithelial ovarian cancer, have a lifetime probability as high as 13–50% for developing epithelial ovarian cancer.³

**Breast ovarian cancer syndrome**

Women with *BRCA* gene mutations have a greatly increased risk of ovarian and breast cancer. The estimated risk of ovarian cancer is 35–46% for *BRCA1* mutation carriers and 13–23% for *BRCA2* mutation carriers.⁴ *BRCA* mutations may account for up to 90% of hereditary ovarian cancers.

Tumours in *BRCA* carriers are more likely to be invasive serous adenocarcinomas when compared with non-*BRCA* age-matched controls (odds ratio [OR] 1.84, 95% confidence interval [CI] 1.21–2.79) and unlikely to be borderline or mucinous.⁴

The stage at presentation of ovarian cancer is similar for *BRCA* carriers and the general population – approximately 70% of patients present with stage III/IV disease.⁵ Ovarian cancers in *BRCA* mutation carriers are more likely to be of higher grade than ovarian cancers in age-matched controls.⁴ However, *BRCA* mutation carriers, particularly *BRCA2* carriers, have a better prognosis than non-carriers. Studies have shown that stage, grade and histology-adjusted 5-year all-cause mortality was 45% in *BRCA1* carriers versus 47% in non-carriers (hazard ratio [HR] 0.73, 95% CI 0.64–0.84) and 36% versus 47% for *BRCA2* carriers versus non-carriers (HR 0.49, 95% CI 0.39–0.61).⁶

**Other high-risk genetic syndromes**

Lynch syndrome, also called hereditary nonpolyposis colorectal cancer (HNPCC), is associated with cancer diagnosis at an early age and the development of multiple cancer types, particularly colon and endometrial cancer. Women with Lynch syndrome have a 3–14% lifetime risk of ovarian cancer.⁷ HNPCC carriers account for 1% of ovarian cancers.⁸ Peutz–Jeghers syndrome is associated with a 20% risk of developing ovarian cancer but many of these are non-epithelial sex cord stromal tumours.

**Other risk factors**

The risk of ovarian cancer appears to be decreased in women with a history of pregnancy, use of the oral contraceptive pill (OCP), breastfeeding, tubal ligation and hysterectomy.

A history of ever using the OCP is associated with a significant reduction in risk of developing ovarian cancer (risk reduction [RR] 0.73, 95% CI 0.70–0.76).⁹ Larger reductions in ovarian cancer risk occurred with increasing duration of OCP use; RR decreased by about 20% for each 5 years of use; by 15 years the risk of ovarian cancer was halved. Importantly, the protective effect persisted for 30 years after cessation of OCP use although the effect attenuated over time. For women with 5 years’ use of OCP the risk reduction in ovarian cancer within 10 years of discontinuing OCPs versus 20–29 years after discontinuing OCPs was 29% and 15%, respectively.⁹

Hysterectomy was associated with a 34% reduction in the risk of ovarian cancer in a meta-analysis of 12 case–control studies.¹⁰

Women who had undergone tubal ligation had a 34% reduction in ovarian cancer risk in a meta-analysis of 13 case–control studies.¹¹ In addition, a case–control study by the Hereditary Ovarian Cancer Clinical Study Group¹² found that tubal ligation lowered the rate of ovarian cancer among *BRCA1* carriers by 60%, after adjustment for oral contraception use, parity, history of breast cancer and ethnic group. A history of both OCP use and tubal ligation was even more protective, with 72% risk reduction. The mechanism for this reduction is unknown but may coincide with research that suggests that tubal neoplasia is a precursor for serous ovarian cancer.¹³

Breastfeeding for a cumulative duration of more than 12 months compared with never breastfeeding is associated with a statistically significant decrease in the risk of epithelial ovarian cancer (OR 0.72, 95% CI 0.54–0.97).¹⁴

Current available data suggest that an association between ovulation induction and ovarian cancer does not indicate necessarily a causal effect. Infertility alone is an independent risk factor. Nulliparous women may harbour a higher risk of ovarian cancer irrespective of their use of fertility drugs. A 2013 Cochrane review by Rizzuto et al.¹⁵ concluded that there was no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with in vitro fertilisation.

The risk of ovarian cancer is slightly increased in women with a history of endometriosis. The risk of malignant transformation of ovarian endometriosis was estimated at 2.5%.¹⁶ Endometriosis-associated ovarian cancer appears to occur in younger and nulliparous patients. These tumours are well-differentiated low-stage carcinomas that have a higher survival rate.

There is a small increased risk associated with polycystic ovary syndrome (OR 2.52, 95% CI 1.08–5.89).¹⁷

Obesity appears to increase the ovarian cancer risk. A systematic review reported a small, but statistically significant, association between obesity and ovarian cancer (OR 1.3, 95% CI 1.1–1.5).¹⁸

**Screening**

Screening for ovarian cancer with CA125 or ultrasound is not recommended for premenopausal and postmenopausal
women without a family history of ovarian cancer. The predictive value of either test alone (less than 3%) yields an unacceptably high rate of false-positive results and attendant morbidity and costs. The combination of annual CA125 testing with ultrasound did not decrease mortality at 13-year follow-up in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial and screening caused harm related to adverse effects from surgery for false positive findings. The continuing United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKC-TOCS) involves 202,638 low-risk postmenopausal women and is due to report in 2015.

The potential of screening for any cancer is limited by the clinical biology of the particular disease. At diagnosis, the majority of patients with advanced ovarian cancer have multiple nodules of cancer involving different peritoneal sites. While it has generally been assumed that each peritoneal nodule represents a metastasis from a primary ovarian cancer, the disease might, in fact, be multifocal. Hereditary ovarian cancer is frequently multifocal rather than clonal. Anecdotal cases indicate that widespread disease can be diagnosed 3 months after a negative transvaginal ultrasound and normal serum CA125 values have been obtained. As screening has not been associated with a statistically significant reduction in mortality from ovarian cancer, its use cannot be routinely recommended even in women deemed at high risk. Interval cancers can develop between screening visits and are often advanced at presentation. Serum CA125 levels are only elevated in 50–60% of stage I ovarian cancers. For these reasons it is not appropriate to use screening to reassure high-risk women and it should only be offered in women declining risk-reducing surgery, in the absence of a better alternative.

**Women at increased risk**

It is important to differentiate those with a possible rare familial cancer syndrome and those with the more common presentation of an isolated family member with ovarian cancer, without evidence of a hereditary pattern.

**Lower-risk family history**

Women with a family history but without evidence of a hereditary pattern should be counselled about their individual risk – considering age, parity and history of oral contraceptive pill use – about the limited evidence for effectiveness of screening and about the potential adverse effects of screening. There is no evidence to support screening in this group and decisions regarding screening and risk-reducing surgery should be based on individualised considerations involving the patient and clinician.

**High-risk family history**

Women with a suspected hereditary ovarian cancer syndrome should be referred to a genetic counsellor for consideration of testing for BRCA mutations or HNPCC if appropriate.

The United Kingdom Familial Ovarian Screening Study (UK FOCCS) study, looking at the effectiveness of screening in high-risk populations is due to report in 2015. Even though evidence for screening effectiveness has not been demonstrated to date, the decision to screen this patient population is based on their very high lifetime risk of ovarian cancer and is usually undertaken in women who decline risk-reducing surgery.

For women declining risk-reducing surgery, some expert groups have recommended screening with transvaginal ultrasound plus CA125 assays every 6 months, starting at the age of 35 years or 5–10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family. While this may be a reasonable option, the evidence indicates limited effectiveness of screening in this population, and clinicians and patients should not be falsely reassured by negative screening results. Most groups advise risk-reducing surgery for this group by age 35–40 or when childbearing is complete. See Table 1 for guidance on the management for those at increased risk of ovarian cancer.

**Chemoprevention**

The combined oral contraceptive pill (COCP) has been found to reduce the ovarian cancer risk in BRCA carriers. A history of ever using the COCP in these women was associated with significantly reduced risk of ovarian cancer (RR 0.50, 95% CI 0.33–0.75). The protective effect increased with longer duration of use. There has been concern that COCP may increase the risk of breast cancer in mutation carriers. Studies have shown an increased risk of breast cancer with oral contraceptive formulations used before 1975. However, studies have not shown a significantly increased risk of breast cancer in users overall, or in the first 10 years after cessation of use of recent oral contraceptive formulations. Given the available data, it has been suggested that women with a hereditary ovarian cancer syndrome who have not elected for risk-reducing surgery and who are not trying to conceive should consider COCP use.

**Risk-reducing surgery**

Lack of efficacy of ovarian cancer screening has prompted many clinicians to recommend risk-reducing bilateral salpingo-oophorectomy (rrBSO) at the completion of childbearing rather than intensified screening for ovarian cancer. Studies support the efficacy of rrBSO in significantly reducing the risk of gynaecological and breast cancer in
women who carry BRCA1 or BRCA2 mutations. BSO in premenopausal women with BRCA mutations has the additional benefit of significantly reducing the risk of breast cancer by 30 to 75%. As an example, in one study the relative risk of ovarian/fallopian tube/peritoneal cancer after rrBSO was 0.04% (95% CI 0.01–0.16) and in another study the relative risk of breast/ovarian/fallopian tube/peritoneal cancer was 0.25% (95% CI 0.08–0.74).

Data regarding the finding of occult fallopian tube cancers in women who have undergone rrBSO suggest that at least some apparent ovarian cancers were initiated in the tubes. The possibility that the fallopian tubes are the primary site of carcinogenesis in ovarian cancer has led to some experts advocating salpingectomy at the time of hysterectomy in the general population to reduce ovarian cancer risk.

Removal of healthy ovaries does not add significantly to the operating time or immediate surgical complications of hysterectomy, but may have significant implications for short- and long-term health.

Lack of evidence from high-quality randomised clinical trials limits the ability of surgeons and patients to make an informed decision about the relative merits of ovarian removal or conservation in those who are not at increased inherited risk of ovarian cancer.

The postmenopausal ovaries are physiologically active and continue to produce estradiol (at low levels) and testosterone. The relative risks and benefits of oophorectomy at the time of hysterectomy can be difficult to estimate on an individualised basis.

An observational study of nearly 30 000 women enrolled in the Nurse’s Health study, (median follow-up of 24 years), concluded that, ‘compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy for benign disease is associated with a decreased risk of breast and ovarian cancer but an increased risk of all-cause mortality, and fatal and nonfatal coronary heart disease’. At no age was oophorectomy associated with increased survival, but equally, it was not associated with a decreased survival in women over the age of 55 at the time of hysterectomy and oophorectomy.

A further prospective cohort study of over 24 000 women, with a shorter duration of follow-up (median 7.6 years), concluded that, whilst oophorectomy at the time of hysterectomy decreased the risk of ovarian cancer compared to hysterectomy alone, it was not associated with an increased risk of coronary heart disease, hip fracture or death.

Clearly there is conflicting evidence and therefore the decision for oophorectomy must consider the individual consequences for each woman with regard to her baseline risk for developing breast and ovarian cancers, coronary artery disease, osteoporosis, non-compliance and/or poor clinical response to HRT. In postmenopausal women, there is no consensus about whether ovaries should be removed or retained and decisions should be made following patient consultation on an individualised basis.

In view of the literature on ovarian carcinogenesis, Leblanc et al. have proposed radical fimbriectomy for ovarian...
cancer risk reduction, for women who wish to retain their fertility and ovarian function. Radical fimbriectomy consists of removing all of the fallopian tube and the fimbrio-ovarian junction. The safety and effectiveness of radical fimbriectomy for reducing ovarian carcinoma in the BRCA population has not been assessed in clinical trials. Leblanc et al. proposed this option for women who wish to retain their ovarian function and fertility in preference to having no prophylactic surgery at all.

It is important to remember that rrBSO is not completely protective and BRCA carriers still have a risk of developing primary peritoneal cancer (approximately 2% risk).35

Timing of surgery
This can be a difficult decision involving balancing the procedure-related consequences of sterility and premature menopause against the risk of ovarian and tubal cancer. BRCA1 carriers develop ovarian cancer at a younger age than BRCA2 carriers. Of women with a BRCA1 mutation and ovarian cancer, 54% are diagnosed before the age of 50 years. Diagnosis before the age of 40 is uncommon (2–3%) and under the age of 30 is rare.36,37 Given that the age of onset is usually over 40 it is appropriate to consider rrBSO for BRCA1 carriers after the age of 35 once childbearing is completed. BRCA2 carriers reach a 2–3% incidence a decade later, by age 50 years and the average age at diagnosis is 60 years – similar to the general population. Based on this difference in the likely age of onset of ovarian cancer, BRCA2 carriers may wish to delay their risk-reducing surgery but by doing this they would not benefit from the reduction in breast cancer afforded by salpingo-oophorectomy.38

Women considering rrBSO who have not completed childbearing should be counselled about alternative reproductive options including embryo cryopreservation. Preservation of ovarian tissue is under investigation. Surrogacy is an option for those undergoing concurrent hysterectomy.

Preoperative evaluation
There is a 4–8% chance of detecting an occult malignancy at the time of rrBSO. Over the age of 45 the risk rises to approximately 20%.35,39–41 Pelvic ultrasound and CA125 level to evaluate for the presence of an ovarian malignancy should therefore be performed prior to surgery. An intraoperative finding of malignancy necessitates full surgical staging and patients should be appropriately counselled and consented about the possible need for additional surgery.

Surgical procedure
The laparoscopic route is preferable to the open approach as it is associated with less morbidity. The minimum surgery required for risk reduction is bilateral salpingo-oophorectomy. All ovarian tissue should be removed. All ovarian adhesions should be removed in their entirety to ensure no residual ovarian cells remain.35 The ovarian artery and vein should be clamped at least 2 cm proximal to the ovary, and preferably at the pelvic brim to avoid leaving any ovarian tissue behind.41 The surgeon should remove as much of the fallopian tube as possible but cornual resection does not appear to be necessary. Although the intramural portion of the fallopian tube is typically left behind after BSO, there have been no reports of malignant transformation in the tubal remnant after this type of surgery.42

Concurrent hysterectomy
Hysterectomy may be performed at the same time as BSO when there are other gynaecological indications. This increases the associated morbidity and length of hospital stay. Risk-reduction hysterectomy is beneficial in some groups, for example women with Lynch syndrome who are at increased risk of endometrial cancer (40–60% lifetime risk).43

Some BRCA carriers wish to take tamoxifen for chemoprophylaxis of breast cancer. Tamoxifen use is associated with an increased risk of endometrial pathology and therefore these women may consider risk-reduction hysterectomy at the time of BSO.

Women who wish to take unopposed estrogen therapy may consider concurrent hysterectomy. Combined estrogen and progestin therapy for those who require hormone replacement therapy (HRT) is associated with a significantly increased risk of breast cancer in postmenopausal women, whereas no such association has been noted with unopposed estrogen in this group.44,45 The ability to generalise these data to premenopausal women who undergo rrBSO is unclear.

Premature menopause
Women undergoing rrBSO should be counselled about the effects of premature menopause and the available management options. Menopausal effects include menopausal symptoms such as hot flushes, sleep disturbance, mood change and hair and skin changes. Sexual-health-related effects include dyspareunia secondary to vaginal atrophy and decreased libido. Long-term health effects include osteoporosis, cardiovascular disease and effects on cognitive and psychological function.

Surgical menopause differs from natural menopause in that hormone levels drop abruptly and hormone production ceases completely, as opposed to a gradual decline in hormone level and continued production of androgens as occurs with natural menopause. Women who undergo rrBSO are typically younger than the average age of menopause of 51 and are therefore exposed to the detrimental effects of hypoestrogenism for longer.
Risk-reducing surgery for women at high risk of epithelial ovarian cancer

The Scottish Intercollegiate Guidelines Network’s guidelines on ovarian cancer have recommended giving HRT after rrBSO up to the age of 50 as there is no decrease in the benefit in terms of breast cancer risk reduction. Although there is a small increase in the rate of breast cancer in women on HRT, they are usually of a lower grade and HRT has no impact on breast cancer mortality.47

The type of BRCA mutation may impact on HRT breast cancer risk. Breast cancers in BRCA1 carriers are typically negative for estrogen and progestin receptors, and thus are potentially less likely to be influenced by hormones than the breast cancers that develop in BRCA2 carriers which are usually positive for these receptors.48

A shared decision-making process regarding the management of menopausal symptoms and effects should include discussion about non-hormonal options and the lack of population-specific data for the use of HRT in BRCA carriers after rrBSO. Factors that could possibly lower the potential increased risk of breast cancer with HRT use include limiting the duration of use until the age of 51 (the average age of natural menopause), concurrent hysterectomy to enable the use of unopposed estrogen and prophylactic mastectomy.

Traditionally, a personal history of breast cancer has been considered a contraindication to the use of HRT. However, management of menopausal symptoms is an important clinical problem. While most observational studies have reported no increase in the risk of recurrence with estrogen therapy, randomised clinical trial data suggest that estrogen therapy may be associated with excessive risk.49

Women who undergo rrBSO are at increased risk of osteoporosis and should be counselled about osteoporosis prevention, treatment and screening.

Vaginal atrophy can be treated with vaginal estrogen preparations. Low-dose vaginal estrogens typically do not raise the serum estrogen concentration above natural menopausal levels. Studies of the use of vaginal estrogen in women with a history of breast cancer have not shown an increase in recurrence rates but data are limited.50 Non-hormonal preparations can be used as firstline treatment but if these prove inadequate, vaginal estrogen is a reasonable option.

Conclusion

Screening has not been found to be associated with a statistically significant reduction in mortality from ovarian cancer and cannot be routinely recommended even for women at high risk. Studies support the efficacy of risk-reducing bilateral salpingo-oophorectomy in significantly reducing the risk of gynaecological and breast cancer in women who carry BRCA1 or BRCA2 mutations. Decisions regarding screening and risk-reducing surgery should be based on individualised considerations involving the patient and clinician.

Disclosure of interests

The authors of this article have no conflict of interest to disclose.

Contribution to authorship

TW came up with the idea to review the subject. EG performed the literature search on the subject and compiled the review with TW as supervisor. Both authors approved the final version of this article.

References
