



Royal College of
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Management of Women with a Genetic Predisposition to Gynaecological Cancers

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1. Introduction

Approximately 5% of endometrial carcinomas and 20% of epithelial ovarian carcinomas are hereditary.¹⁻³ The autosomal dominant disorders, hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (formerly referred to as hereditary nonpolyposis colorectal carcinoma, HNPCC) underlie the majority of this inherited susceptibility.⁴ However, rare syndromes such as Cowden, Peutz-Jeghers and Li-Fraumeni can also manifest with gynaecological malignancies. Furthermore, recent genome-wide association studies (GWAS) have highlighted the role of common lower-penetrance variants in gynaecological cancer predisposition.⁵

In this paper, we will discuss the management of women with hereditary gynaecological cancer with regard to current genetic testing, preventive and therapeutic options, focusing on Mendelian conditions known to increase the risk of gynaecological malignancies as the clinical utility of low-penetrance susceptibility variants identified through GWAS remains to be clarified. It is imperative that healthcare professionals identify those at increased risk in order to ensure that optimal management strategies are offered to women and their families.

2. Hereditary breast and ovarian cancer

The *BRCA1* and *BRCA2* genes were first identified and cloned in the early 1990s.^{6,7} Women with a *BRCA1* mutation have a lifetime risk of ovarian cancer by age 70 years of up to 63% and of breast cancer by age 70 years of up to 85%. Risks of ovarian and breast cancers in women by age 70 years among *BRCA2* carriers are reported to be up to 27% and 84% respectively.^{8,9}

2.1 Identification of high-risk families

In light of the substantial risk of cancer, it is important to identify high-risk families. Current guidance from the National Institute for Health and Care Excellence (NICE) uses an individual's family history of cancer to stratify women into categories of breast cancer risk. Women are then managed within primary care or referred to the secondary or tertiary setting as appropriate. Women with greater than a 30% lifetime risk of breast cancer from age 20 years are considered to be high risk and should be managed by a multidisciplinary tertiary team.¹⁰

Family history clinics and regional genetics centres use risk assessment tools to calculate a woman's chance of having a *BRCA1* or *BRCA2* gene mutation and hence their lifetime breast and ovarian cancer risk: for example, BOADICEA and the Manchester scoring system.¹⁰ Decisions regarding intensity of surveillance and risk-reducing surgery are then made according to the level of risk. It is therefore important that accurate information about the individual's personal and family history of cancer is obtained. Clinicians should ensure that there is histological confirmation of pertinent diagnoses before making a risk assessment. For example, the discovery that a family member has had a borderline or non-epithelial ovarian tumour, which are less likely to have a hereditary component, instead of epithelial ovarian carcinoma could substantially alter a woman's risk category. Notably, ovarian tumours that are associated with constitutional *BRCA1* or *BRCA2* mutations tend to be high-grade serous and endometrioid carcinomas that are typically aggressive and present in advanced stage. By contrast, mucinous ovarian carcinomas, which are characteristically more indolent, are much less likely to harbour perturbations of *BRCA1* or *BRCA2* expression.¹¹

2.2 Genetic testing

When considering genetic testing for constitutional mutations, it is important to appreciate the distinction between diagnostic and predictive testing. A diagnostic genetic test is a full screen of the gene normally undertaken in an individual affected with cancer. By contrast, a predictive test is a targeted test for a specific mutation, previously identified in another family member, and usually undertaken in an individual who has not had cancer. Recent technological advances in gene sequencing have led to cheaper, quicker testing. Together with the proven benefits of identifying families that carry a *BRCA1* or *BRCA2* germline mutation, the threshold for offering diagnostic *BRCA1* and *BRCA2* gene testing is now a combined *BRCA1* and *BRCA2* mutation carrier probability of 10% or more.¹⁰ Previously, the vast majority of women who were offered testing had been affected with either breast, ovarian or primary peritoneal carcinoma and it was exceptional to offer testing to unaffected women, unless they were of Jewish descent, which increases the probability of finding a *BRCA1* or *BRCA2* founder mutation. However, 2013 guidance from NICE suggests that women without a personal history of cancer but with a high-risk family history may also be eligible for diagnostic *BRCA1* and *BRCA2* genetic testing, if an affected relative is unavailable and the individual has a 10% or greater risk of being a *BRCA1/2* carrier.¹⁰

Historically, a woman with ovarian carcinoma would only be offered *BRCA1* and *BRCA2* gene testing if she or a close relative had also been diagnosed with breast or ovarian carcinoma. However, studies investigating the prevalence of *BRCA1* and *BRCA2* mutations in epithelial ovarian carcinoma patients unselected for family history or ethnicity have found pathological mutations in up to 17% of women,¹² suggesting that the present threshold for testing may be too high. As a result, it has been proposed that every woman with epithelial ovarian, fallopian tube and primary peritoneal carcinoma should be offered *BRCA1* and *BRCA2* gene testing, regardless of family history, the results of which could be used to inform treatment decisions and enable appropriate recruitment to clinical trials. Furthermore, identifying a *BRCA1* or *BRCA2* mutation would have significant implications for other family members who could be offered predictive genetic testing and risk-reducing options. A study of patients with epithelial ovarian cancer who underwent *BRCA1* and *BRCA2* gene testing found that one-third had not been referred for genetic counselling until they had recurrent disease. Given the poor prognosis of recurrent ovarian cancer, the investigators suggested referral for genetic counselling and testing at initial diagnosis.¹³ A Wellcome Trust-funded initiative is currently underway to investigate the feasibility and cost effectiveness of this approach within the National Health Service.¹⁴

2.3 Risk-reducing surgery

The mainstay of management for women who carry a constitutional *BRCA1* or *BRCA2* mutation is risk-reducing bilateral salpingo-oophorectomy (RRBSO) and risk-reducing breast surgery or breast screening. RRBSO in these women can usually be performed laparoscopically and should be undertaken in accordance with published protocols.¹⁵ Studies have reported an 80–96% decrease in ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers who underwent RRBSO.^{16–19} However, there remains a residual 1–6% risk of primary peritoneal cancer that appears to persist for up to 20 years after oophorectomy.^{19–21} Furthermore, there is evidence that RRBSO prolongs survival. Studies have found a 60–76% reduction in overall mortality in *BRCA1* and *BRCA2* mutation carriers who have undergone RRBSO compared with those who have not.^{22,23}

In light of these data, the option of RRBSO should be discussed with all *BRCA1* and *BRCA2* mutation carriers after conclusion of childbearing. A *BRCA1* mutation carrier's chance of developing ovarian cancer increases significantly during her 40s. As a result 35–40 years is deemed to be an appropriate age for women to consider surgery.²⁴ The risk for *BRCA2* mutation carriers does not appear to increase until later,⁹ so surgery may be delayed until 45 years of age. Notably, RRBSO in premenopausal *BRCA1* and *BRCA2* mutation carriers also affects their breast cancer risk.¹⁷ In *BRCA1* mutation carriers the risk may decrease by as much as 56% and for women with a *BRCA2* mutation by up to 46%, with the risk reduction being greatest if surgery is performed before 40 years of age.²⁵ It is therefore important that women are informed of this additional benefit.

However, early RRBSO is not without its complications and, in particular, the potential implications for cardiovascular, bone and psychosexual health^{26,27} should be explored with women so that they can make an informed decision regarding the timing of surgery. If RRBSO is undertaken premenopausally, *BRCA1* and *BRCA2* mutation carriers who do not have a personal history of breast cancer should be offered hormone replacement therapy (HRT) at least until the age of natural menopause, around 50 years, in order to abrogate the cardiovascular and bone complications.²⁸ For women with a history of breast cancer, the use of HRT is not usually recommended.²⁹

Notably, studies of pathological specimens from *BRCA1* and *BRCA2* mutation carriers who have undergone RRBSO have suggested that many *BRCA*-associated pelvic serous carcinomas originate in the fallopian tube, from a lesion called serous tubal intraepithelial carcinoma (STIC), and subsequently spread to the ovary and peritoneum. STICs are distinguishable from the normal fallopian tube and appear to shed malignant cells without invading the tube.³⁰ This may explain how patients diagnosed with ovarian or primary peritoneal carcinoma due to a significant bulk of tumour on the ovary and peritoneum have little tubal disease, despite the fact that their cancer originated in the fallopian tube. It is also a possible explanation for the residual risk of primary peritoneal cancer following RRBSO.¹⁹⁻²¹

As a result of these findings, it has been proposed that the tubal hypothesis of epithelial ovarian cancer pathogenesis offers an alternative surgical approach in younger women, comprising of risk-reducing bilateral salpingectomy while conserving their ovaries nearer to the age of natural menopause, when a delayed bilateral oophorectomy can be performed.³¹ However, this surgical option is currently of unproven benefit as the long-term effect on ovarian cancer incidence and mortality in this patient group remains unknown. A 2014 RCOG Scientific Impact Paper on high-grade serous carcinomas discusses this issue in greater depth.³²

2.4 Screening for ovarian cancer

For women at high risk of ovarian carcinoma who choose not to have RRBSO, the evidence for screening is yet to be established. In 13 studies evaluating ovarian cancer screening in high-risk women, it was noted that, of the 70 tumours discovered, 24% were early stage.³³ The incidence of early-stage disease in unscreened women in the general population is similar³⁴ and therefore it is unclear whether screening impacts on mortality.

Although to date there is no definitive evidence that current screening techniques for ovarian carcinoma in high-risk women prolong survival, final results from the UK Familial Ovarian Cancer Screening Study (UK FOCSS), which evaluated serial ultrasound and CA125 measurement in this group of patients, are awaited. However, until such a large prospective study provides conclusive evidence that screening can improve morbidity and mortality for this cohort, surveillance for ovarian carcinoma should not be offered as an alternative to RRBSO.

2.5 Therapeutic implications for BRCA-related ovarian cancer

The *BRCA1* and *BRCA2* proteins play a key role in a form of DNA repair called homologous recombination.³⁵ Cells with defective DNA repair mechanisms are prone to mutagenesis and more likely to progress to malignancy. On one hand this provides *BRCA*-defective cells with a survival advantage but, on the other hand, the defect can be exploited therapeutically. This selective targeting of tumour cells has been termed 'synthetic lethality' and is the basis for the development of poly (ADP-ribose) polymerase (PARP) inhibitors. Preclinical and clinical trials of PARP inhibition in both sporadic and inherited ovarian carcinomas are underway and the data from these studies are promising.³⁶ Use of PARP inhibitors in *BRCA*-related ovarian cancer may be considered as a step towards true personalised treatment in this disease.^{37,38}

2.6 Other genes associated with ovarian cancer

Previously it was thought that *BRCA1* and *BRCA2* gene mutations account for the majority of hereditary ovarian carcinomas, with a smaller proportion caused by inherited mismatch repair defects.¹² However, recent studies have identified new genes that confer an increased risk of ovarian carcinoma, including *RAD51C*³⁹ and *RAD51D*.⁴⁰ The penetrance for these gene mutations does not appear to be as high as for *BRCA1* and *BRCA2*. However, studies suggest that it is at least 10% and therefore unaffected women who harbour these mutations would be considered candidates for RRBSO.⁴⁰ Furthermore, like *BRCA1* and *BRCA2*, these genes encode proteins that are involved in the homologous recombination DNA repair pathway and therefore tumours with defects in *RAD51C* and *RAD51D* may also be susceptible to PARP inhibition.⁴⁰ At present, routine testing is not available for these genes and therefore the clinical utility of these findings is yet to be realised.

3. Lynch syndrome

Lynch syndrome is caused by germline mutations in the DNA mismatch repair (MMR) genes (*MSH2*, *MLH1*, *MSH6*, *PMS2*).^{41–44} The condition confers an increased risk of early-onset cancer of multiple types, including colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, brain, ureteric and renal pelvic cancers.⁴⁵ The lifetime risk for endometrial cancer is 40–60% compared with a risk of 3% in the general population. Notably this risk may exceed the risk of colorectal cancer for women with Lynch syndrome, particularly those that carry an *MSH6* mutation.⁴⁶ For ovarian carcinoma, the lifetime risk is 10–12% compared with the general population risk of 1.4%.⁴⁷ Unlike *BRCA*-associated ovarian cancers, which are usually high-grade serous tumours, Lynch-related ovarian carcinomas are often early stage and moderately or well differentiated. Women with Lynch syndrome also have a greater likelihood of synchronous endometrial cancer than other ovarian cancer patients.⁴⁸

3.1 Identification of at-risk families

Families with Lynch syndrome are identified clinically using the Amsterdam criteria⁴⁹ and the Bethesda Guidelines.⁵⁰ Immunohistochemistry and microsatellite instability testing is then performed on paraffin-embedded tumour tissue in order to identify those individuals with the greatest probability of carrying a germline MMR gene mutation.⁵¹ These pathological studies enable clinicians to simplify genetic testing by targeting specific genes in individuals with positive results. However, with the advent of next-generation sequencing it is now feasible to sequence all the MMR genes in one test, which may be more appropriate and cost-effective in certain cases.

Population-based studies suggest that MMR gene mutations are found in 2% of ovarian cancer cases unselected for age^{52,53} and 9% of endometrial cancer cases under the age of 50 years.⁵⁴ Women with endometrial cancer under 50 years of age and a first-degree relative (FDR) with another Lynch-related cancer have a 23% chance of carrying a MMR mutation,⁵⁵ and women from families with two or more FDRs with endometrial cancer and no family history of other cancers have an 8.7% chance.⁵⁶ These gynaecological cancers should therefore be considered 'sentinel cancers' for Lynch syndrome and it is important that clinicians refer at-risk women for genetic counselling and testing. Women with the condition and their family members can then be offered preventive measures for some of the cancers that they may be at risk for, such as colorectal cancer.

3.2 Risk-reducing surgery

The efficacy of endometrial cancer surveillance in Lynch syndrome is still unproven.⁵⁷ Gynaecological surveillance of the endometrium by transvaginal ultrasound and aspiration biopsy starting from age 35–40 years may lead to the detection of early cancer, but should be performed as part of a clinical trial given the lack of proven benefit.⁵⁷ The good prognosis and early presentation of this tumour type mean that it is difficult to know whether screening would result in a survival advantage for these women. Studies to date

have been inconsistent and in light of the proven benefits of risk-reducing surgery, most women are offered total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (TLHBSO), unless contraindicated, after completion of their families. One study of 315 women with Lynch syndrome found that no ovarian or endometrial cancer occurred in women who underwent risk-reducing surgery, whereas 33% of women who did not have surgery developed endometrial cancer and 5.5% developed ovarian cancer.⁵⁸

As with *BRCA1* and *BRCA2* mutation carriers, the risks of surgical menopause under the age of 45 years are significant and HRT should be recommended for women until at least 50 years of age.²⁸

3.3 Preventive therapy for Lynch syndrome-associated cancers

Recent studies have suggested that regular intake of low-dose aspirin (75 mg daily) may reduce the risk of colorectal cancer after 5 years of use.⁵⁹ Aspirin may also reduce the risk of developing the other cancers associated with Lynch syndrome.⁶⁰ A research study called CaPP3 (Cancer Prevention Programme 3) began to investigate the most effective dose of aspirin for people with Lynch syndrome to take in 2014 (www.capp3.org).

4. Other syndromes

Several other rare autosomal dominant genetic conditions are associated with malignant gynaecological tumours. These conditions have specific cardinal features that are recognisable and should prompt a clinical genetics referral.

4.1 Cowden syndrome

Germline mutations in the tumour suppressor gene *PTEN* cause *PTEN* hamartoma tumour syndrome (PHTS), an umbrella term that encompasses the autosomal dominant conditions Cowden syndrome (CS), presenting in adulthood, and Bannayan–Riley–Ruvalcaba syndrome in children. CS is a cancer predisposition syndrome characterised by macrocephaly, multiple hamartomas and an increased risk of several tumour types, in particular breast, thyroid and endometrial cancers, but also colorectal, melanoma and renal cell carcinoma.⁶¹ Although the penetrance of the condition is high, there is significant inter- and intrafamilial variability in its manifestation.

Recent data suggest that the lifetime risk of endometrial cancer in CS approaches 30%⁶¹ and, as a result, it is one of the key discriminatory features in identifying women with the condition.⁶² To date, there is no definitive evidence for endometrial screening in CS, although some have suggested annual endometrial biopsies. The option of risk-reducing hysterectomy may also be discussed with women, although data regarding efficacy are sparse.⁶³

4.2 Peutz-Jeghers syndrome

Germline mutations in the *STK11* gene cause Peutz-Jeghers syndrome (PJS), an autosomal dominant gastrointestinal polyposis disorder which confers an increased risk of breast, gastrointestinal and gynaecological tumours. Patients with the condition manifest characteristic pigmented lesions on the lips and buccal mucosa, which should prompt clinicians to consider the underlying diagnosis. Women with PJS are at risk of developing sex cord stromal tumours with annular tubules of the ovary and adenoma malignum of the cervix. Annual screening with Pap smear from age 18 years and transvaginal ultrasound and CA125 measurement starting from 25 years have therefore been suggested by some,⁶⁴ although definitive evidence for screening is lacking.

4.3 Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is caused by germline *TP53* mutations. The cardinal features of the condition are young-onset sarcomas, breast cancer, adrenocortical carcinoma and childhood tumours.⁶⁵

Gynaecological malignancies are unusual in LFS, the most commonly diagnosed being epithelial ovarian carcinoma, for which there are no definitive screening recommendations.

5. Summary

Although the majority of gynaecological cancer is sporadic, it is important that those cancers caused by an inherited predisposition are identified. In light of the prognostic implications for individuals and their families, clinicians should be alert to the possibility of a hereditary condition when managing women with gynaecological cancer. Therefore, any healthcare professional involved in the patient's diagnostic pathway – general practitioners (GPs), specialist nurses, trainee doctors, general gynaecologists and gynae-oncologists – should be familiar with the clinical criteria and national guidance used to identify these women.

At present most individuals present to their GP with concerns about their personal or family history and they are then referred for a genetic assessment. Alternatively, the oncologist or surgeon recognises that an individual has an unusual personal or family history and refers them for genetic testing. As a result, most genetic testing is being carried out through regional genetics services. This ensures that patients and family members have information about chemoprevention, surveillance, risk-reducing surgery and psychological support and are referred appropriately. Notably, this involves a multidisciplinary team that enables women to have tailored management based on their individual medical history and preferences. Furthermore, the implications of identifying a gene mutation are far-reaching and include not only the physical risk of cancer but also the psychological and financial impact that the knowledge can have on the whole family.

6. Opinion

The threshold for genetic testing is falling and identifying patients with a specific mutation as soon as possible is important to ensure that they get the most appropriate treatment. Rapid advances in sequencing technology and the development of novel targeted drug therapies, for example, PARP inhibitors, are leading to a shift in how cancer genetics services are delivered. It is likely that a new model of care will be adopted in the near future where all patients with cancer, irrespective of their family history, will be screened for relevant cancer predisposition genes at diagnosis. If an individual is subsequently found to carry a germline mutation, it is essential that they are then referred to the regional genetics service to ensure that they receive appropriate management and at-risk relatives are identified.

Crucially, for this model to work it will require close collaboration between commissioners, primary and secondary care clinicians and clinical genetics services. The funding for some genetic tests may need to move from regional genetics centres to mainstream services and commissioning arrangements would need to address this. There are different models of delivering this service but notably all should involve clinical geneticists and genetic counsellors working closely with oncology centres. The genetics services will continue to have a key role in educating healthcare professionals and supervising the provision of genetic testing within secondary care in order to ensure that all involved understand the importance of genetic testing for both the individual patient and the wider family. Furthermore, the interpretation of genetic test results, confidentiality and ethical issues associated with genetic testing for hereditary cancer are complex and require management by clinicians with the relevant expertise.

With the expanding array of novel technologies at our disposal, the repertoire of known cancer predisposition genes will undoubtedly continue to increase. The ability to search for mutations in numerous genes simultaneously will further expedite this process. However, the true challenge lies in translation of this knowledge into clinical practice, such that a definitive improvement in longevity and quality of life for patients and their families is realised. In order to achieve this goal, it is imperative that evidence-based strategies for the management of individuals at increased risk of cancer are implemented, a goal that will inevitably require multidisciplinary input across the patient pathway.

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Dr A Kulkarni, London and Dr AF Brady, London

and peer reviewed by:

Dr S Banerjee MBBS MA MRCP PhD, Consultant Medical Oncologist and Research Lead Gynaecological Cancers, The Royal Marsden NHS Foundation Trust, London; British Gynaecological Cancer Society; Mr AJ Drakeley FRCOG, Liverpool; Dr AJ Farthing FRCOG, London; Mr A Pal FRCOG, Southall, Middlesex; RCOG Ethics Committee; RCOG Women's Network.

The Scientific Advisory Committee lead reviewer was: Dr S Ghaem-Maghani MRCOG, London.

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