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Moving towards population-based genetic risk prediction for ovarian cancer

Belinda Rahman, Lucy Side, Sahra Gibbon, Susanne F Meisel, Lindsay Fraser, Sue Gessler, Jane Wardle* and Anne Lanceley

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Author affiliations
Belinda Rahman
Institute for Women's Health, University College London, UK

Lucy Side
Institute for Women's Health, University College London, UK and North East Thames Regional Genetics Service, London, UK

Sahra Gibbon
Department of Anthropology, University College London, UK

Susanne F Meisel
Health Behaviour Research Centre, University College London, UK

Lindsay Fraser
Institute for Women's Health, University College London, UK

Sue Gessler
Institute for Women's Health, University College London, UK

Anne Lanceley
Institute for Women's Health, University College London, UK

* Jane Wardle passed away in October 2015

Corresponding author
Anne Lanceley
Institute for Women's Health, University College London, UK
Room 237c Medical School Building
74 Huntley Street
London WC1E 6AU
United Kingdom
Email: a.lanceley@ucl.ac.uk
Tel: +44 (0)20 7679 6807
Fax: +44 (0)20 7380 6929

Ovarian cancer is the fifth most common cancer in UK women, and the leading cause of gynaecological cancer death. Five-year survival rates, of around 40%, have shown little improvement despite recent advances in cancer treatment. Mutations in the cancer susceptibility genes BRCA1 and BRCA2 confer lifetime risks of breast and ovarian cancer of up to 80% and 40% respectively.[1] The traditional approach of using cancer family history to select patients for genetic testing is being challenged; up to 44% of BRCA mutation carriers do not have a significant family history.[2] Recent research has shown that offering BRCA testing to all women with high grade non-mucinous ovarian cancer is an effective approach to identifying more BRCA carriers.[3, 4] Furthermore, there is an opportunity to prevent ovarian cancer if women at increased risk can be identified before developing the disease.

Progress in technology means it is faster and cheaper to conduct large-scale genetic testing, making the introduction of population-based genetic testing for cancer risk prediction viable. Although genetic information has not yet been incorporated into cancer screening programmes, researchers are exploring population-based genetic risk estimation for women's cancers.[5, 6] This has the potential to reduce ovarian cancer morbidity and mortality by stratifying screening and preventive interventions on the basis of prior risk. Here we consider recent social and scientific advances that suggest population-based genetic testing could be implemented, and the challenges that remain.

Ongoing research in ovarian cancer has led to increased knowledge about genetics, risk factors, pathogenesis and early symptoms. Ovarian cancer is not a single disease; distinct histological types have different epidemiological and gene expression profiles which may influence treatment and prognosis. High grade serous (HGS) ovarian cancer is the most common subtype. Recent evidence indicates HGS ovarian cancers may arise from the fallopian tube and not the epithelial surface, with the identification of serous tubal intraepithelial carcinoma (STIC) lesions in up to 40% of advanced or symptomatic cases.[7] Endometrioid and clear cell carcinomas appear to develop from ectopic endometrium, whilst invasive mucinous cancers are metastases to the ovary from other solid tumours.[8]

There has been a shift in our understanding of ovarian cancer genetics. To date there are at least 16 genes and more than 10 single nucleotide polymorphisms (SNPs) associated with increased ovarian cancer risk. The best understood are the high penetrance BRCA1, BRCA2 and Lynch syndrome genes which confer lifetime risks from 7-40% for ovarian cancer.[1, 9] Increasingly, moderate penetrance genes such as BRIP1, RAD51C and RAD51D

with lifetime risks of 6-13%[10] are being used in multi-gene panels for clinical genetic testing. The residual genetic risk may be explained by common low penetrance susceptibility genes. Population-based genome wide association studies (GWAS) have identified SNPs with relative risks of around 1%.[11] SNPs are not currently used in clinical testing, although they may also play a role in moderating risk in BRCA carriers and are increasingly incorporated in risk models for ovarian cancer.[12]

[TABLE 1 here]

Although the prognosis for women with advanced ovarian cancer is poor, disease confined to the ovary has a five-year survival rate of more than 90%. Early detection has the potential to significantly improve ovarian cancer outcomes. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), showed that more early stage cancers were identified by multimodal screening; 38% (107/283) of invasive epithelial ovarian and tubal cancers were identified at stage I or II in the multimodal arm, compared to 23% (58/249) with ultrasound or 24% (136/559) no screening.[13] By using a risk algorithm with serial CA-125 biomarker measurement rather than the typical fixed threshold, the number of screen-detected ovarian cancers was doubled.[14] When prevalent cases and primary peritoneal cancers were excluded from the analysis, mortality was significantly reduced by 20%. There are however, wide confidence limits around this estimate, and an additional two to three years of follow-up will be required to determine the actual reduction of mortality. A large prospective study of screening in women at high risk, the UK Familial Ovarian Cancer Screening Study (UKFOCSS), used 4-monthly CA-125 biomarker and risk algorithm interpretation. Early data from the Phase II trial indicated encouraging sensitivity and specificity, although final results are yet to be reported.[15] CA-125 has typically been 'the gold standard' biomarker in ovarian cancer; research is ongoing to identify biomarkers with superior sensitivity and specificity. Human epididymis protein 4 (HE4) has comparable performance to CA-125 and when used in combination have demonstrated improved diagnostic performance; other candidate biomarkers also show promise.[16]

Counselling frameworks and risk reducing interventions are well defined for BRCA and Lynch syndrome carriers. Bilateral salpingo-oophorectomy (BSO) remains the most effective measure to reduce the risk of ovarian cancer, but is currently only recommended for women with a lifetime risk of >10%. However BSO may be considered for women at lower risks associated with moderate penetrance genes, given the current lack of mortality benefit from ovarian cancer screening.[10] Furthermore BSO has been shown to be cost-effective at ≥4% lifetime risk of ovarian cancer.[17] Developments in our understanding of the pathogenesis of ovarian cancer may provide other options for prevention. Bilateral salpingectomy followed by

delayed oophorectomy is being considered as an alternative to BSO. This approach could avoid premature menopause, but more research is needed to evaluate the impact of salpingectomy on reducing ovarian cancer risk.

Genetic tests are already used in a number of population-based screening programmes. Community carrier testing programmes for Tay Sachs disease within the Ashkenazi Jewish population have been in place since the 1970s. Within the UK, the largest population screening program for genetic conditions is the NHS Newborn Blood Spot Screening Programme which tests for diseases including sickle cell disease, cystic fibrosis and metabolic disorders.

Population-based genetic testing for breast and ovarian cancer susceptibility has been studied in the unaffected UK Ashkenazi Jewish population, demonstrating the feasibility of this approach. Data from the Genetic Cancer Prediction through Population Screening (GCaPPS) study showed that 56% more BRCA carriers were identified by population screening compared to selection based on family history, with no adverse short-term psychological outcomes. [18] This provides a paradigm for broader population genetic screening.

Although BRCA gene mutations are associated with both hereditary breast and ovarian cancer (HBOC), the link with ovarian cancer is less well recognised. Reflecting its moniker of an 'invisible disease', ovarian cancer has had a low profile in terms of public awareness. With a growing number of ovarian cancer charities, a Cancer Research UK 'Be Clear on Cancer' campaign and an ovarian cancer awareness month, this is beginning to change. The most recent event to bring breast and ovarian cancer genetics into the spotlight is the 'Angelina effect'. Actor and filmmaker Angelina Jolie disclosed her BRCA1 mutation status and decision to have risk-reducing bilateral mastectomy in 2013 and BSO in 2015. From the public interest that followed, referral rates to familial cancer clinics increased significantly.[19] Her story raised public awareness of breast and ovarian cancer risk and the management options available, as well as the role of genetic testing in preventing cancer.

With increasing interest in incorporating genetic testing into routine clinical care, researchers are studying the public's response to learning whether they have a genetic susceptibility to certain diseases, including cancer. Overall, attitudes to genetic testing for cancer risk have been positive and interest in testing is high.[20] When examining this in the context of ovarian cancer and subsequent risk-stratified screening, women felt genetic testing would be 'indisputably beneficial' and knowledge of this risk could be 'empowering'.[6] Similarly, from a

survey of 930 women, more than 80% would have genetic testing to learn their risk of ovarian cancer and more than 90% would participate in risk-stratified screening.[21] These findings are encouraging and convey enthusiasm for genetic risk stratification from the general public. However, most of our experience of 'real' genetic testing for cancer susceptibility is in high-risk groups, such as individuals with a strong family history of cancer. In families with a mutation predisposing to cancer, interest in genetic testing is high although actual uptake varies from 25% to 96%.[22] Given the gap between intention and actual uptake of genetic testing in high-risk patient groups, caution is needed when considering how women from the general population might respond to genetic risk stratification for ovarian cancer. Research into public attitudes towards genetic testing for cancer susceptibility has been promising, but is limited because it has only studied hypothetical intent to take part in such a programme.

Despite the encouraging progress in ovarian cancer genetics and aetiology, screening and risk management, as well as public attitudes and awareness, there remain challenges to the introduction of a population-based genetic testing programme for this disease. Existing population-based BRCA genetic testing programs in the UK and the United States have focused on Ashkenazi Jewish groups, where carrier frequencies are high and known founder mutations facilitate testing. Similarly, cost-benefit analyses of population-based BRCA genetic testing have only been undertaken for Ashkenazi Jewish groups. Advances in genetic testing mean that it is increasingly affordable to simultaneously test multiple genes; further research is needed to look at the cost effectiveness of such testing in terms of cancer prevention in the general population.

Women participating in a screening programme need to be fully informed of its risks and benefits. Furthermore, genetic testing can have implications for their relatives. To date, face-to-face genetic counselling has been an integral part of clinical genetic testing. Providing genetic testing to a large population requires new ways of information provision and counselling. Novel approaches, such as using online tools and decision aids, will be essential.

Genetic testing is relatively non-invasive, typically involving collection of a blood or saliva sample. However, there may be psychological costs, such as a short term increase in distress after receiving adverse test results.[23] Additionally, receiving a normal genetic test result could provide false reassurance, as women deemed to be at 'low risk' could still develop ovarian cancer due to other genetic and environmental factors. Variants of unknown significance (VUS) are genetic alterations where the pathogenicity is uncertain. These

uninformative results can be confusing to both patients and clinicians and careful consideration should be given as to how, or indeed whether, they should be reported. Management strategies for women at increased genetic risk of ovarian cancer will be key, with appropriate interventions and follow-up care required.

In conclusion, incorporating genetic testing into cancer screening programmes allows early detection and risk-reducing measures to be targeted to those at greatest risk. Importantly, this risk-stratification approach may also minimise screening and medical interventions in low risk individuals. Current cancer screening programmes in the UK are stratified by age and gender only. Given the recent debate about overdiagnosis in breast cancer screening,[24] stratifying risk using factors such as breast density or genetic predisposition may be beneficial.

Advanced ovarian cancer is a disease with a poor prognosis. If women at increased genetic risk can be identified, an effective strategy for disease prevention exists through risk-reducing BSO. The risk association with BRCA1/2 mutations and other ovarian cancer susceptibility genes is increasingly well understood. Ovarian cancer screening by CA-125 serial biomarker measurements shows some potential for early detection. Ovarian cancer biology, including genetics, remains an area of intense research. There is greater awareness of ovarian cancer, increasing public interest in genetic testing, and novel risk management options. Innovative approaches, such as looking at epigenetic biomarkers to detect early stage disease, are showing promise.[25] Public health policy is beginning to embrace the concept of genetic risk prediction for disease stratification. A recent public enquiry by the UK House of Commons Science and Technology Committee into national health screening '…welcomes the current, ongoing research that aims to improve the targeting of screening programmes towards those in higher risk groups'.[26]

Despite the challenges associated with implementing such a programme, with further research these may be addressed. The potential for reducing the burden of ovarian cancer through population-based genetic testing warrants further investigation.

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Table 1. Genetic basis of ovarian cancer

Genetic susceptibility associated with ovarian cancer		
High penetrance	Associated with HBOC and Lynch syndrome	BRCA1, BRCA2, MSH2, MSH6, MLH1, PMS2 and EPCAM
Moderate penetrance	Susceptibility genes	BRIP1, RAD51C and RAD51D
Low penetrance	Common variant susceptibility loci	9p22, 2q31, 8q24, 3q25,19p13, 17q21, 1p36, 4q26, 9q34.2, 17q11.2