Title Page

Title of article

Genetic Testing for Gynaecological Cancer

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Abstract

The traditional family-history approach to genetic testing involves taking a detailed three generation family-history from both sides of the family, ethnicity, type of cancer, age of onset and death. Testing for *BRCA1/BRCA2* mutations is offered at a ≥10% combined *BRCA1/BRCA2* probability. Risk models such as the Manchester scoring system, BOADICEA, BRCAPRO can be used to calculate *BRCA1/BRCA2* probability. High-risk women identified should be referred to a regional genetics service for genetic counselling and testing. The Amsterdam-Criteria-2 have been traditionally used to identify Lynch Syndrome (caused by a mismatch repair gene (*MLH1/MSH2/MSH6/PMS2*) mutation). Molecular (immunohistochemistry and Microsatellite instability) analysis of tumour tissue is now established as an initial step, with genetic testing undertaken for protein deficient or MSI unstable tumours. This is offered for those fulfilling Bethesda criteria and recently for all colorectal cancer cases <60 years. *BRCA1/BRCA2* testing is recommended for all non-mucinous invasive epithelial ovarian cancers irrespective of family-history (10-20% have a *BRCA1/BRCA2* mutation). This is being undertaken by non-genetics clinicians. A population-based approach to genetic testing identifies 50% more carriers at risk. It has been extensively investigated in the Ashkenazi-Jewish population and found to be extremely cost-effective in this community. This is expected to lead to change in guidelines in the future.

Keywords

BRCA, genetic testing, risk prediction, ovarian cancer, breast cancer, endometrial cancer, Lynch Syndrome, high risk

Genetic Testing for Gynaecological Cancer

Introduction

The traditional approach to genetic testing for high penetrance gynaecological cancer gene mutations has been driven by family history (FH). This involves testing affected individuals from high-risk families through specialist cancer genetics clinics following intensive face-to-face genetic counselling. It requires both the individual patient as well as the clinical practitioner to be aware of the FH, appreciate the risk/significance of the FH and to act on it. The usually encountered hereditary gynaecological cancer syndromes include hereditary breast and/or ovarian cancer syndrome, Lynch Syndrome (or Hereditary Non-Polyposis Colorectal Cancer – HNPCC), Cowden's Syndrome and Peutz–Jeghers syndrome.

Hereditary breast and/or ovarian cancer

Autosomal dominant mutations in the *BRCA1/BRCA2* genes account for most of the known hereditary risk of ovarian cancer. Women carrying *BRCA1/BRCA2* genes have an 18-40% risk of ovarian cancer and 45-65% risk of breast cancer (higher risk estimates are obtained from data analysed from cancer genetics clinics which are uncorrected for ascertainment). Additionally, newer moderate penetrance genes (ovarian cancer risks 5%-9%) like the *RAD51C*, *RAD51D* and *BRIP1* have been recently identified and validated risk estimates published. In the general population- around 1:300 – 1:400 individuals carry a *BRCA1/BRCA2* mutation. In certain populations called founder populations (such as Ashkenazi Jews), *BRCA1/BRCA2* mutations occur more frequently. 1:40 Ashkenazi Jewish individuals carry one of the three common *BRCA1/BRCA2* mutations called founder mutations.

Over the years, a number of risk assessment models have been developed and modified. Models vary widely with respect to the data used to derive them, the study design, level of detail of FH, risk factors and the specifics of genetic transmission patterns included. Hence, each model has strengths and weaknesses dependent upon population characteristics, methodology, underlying assumptions and the statistical tools used to create them. Models are generally two types: Empiricial and Mendelian. Descriptive FH variables are used to develop Empirical models, typically using logistic regression. These models are more straightforward to implement/use and can readily incorporate other non-genetic risk factors. A widely used example is the Manchester Scoring System (MSS). A major drawback is that they cannot adequately deal with complex family histories and MSS cannot be used for Ashkenazi Jewish families.

Mendelian models use pedigree analysis and Mendelian rules of genetic inheritance to develop a genetic model for disease, usually based on Bayesian and other likelihood ratio analyses. They are able to account for complex family histories and provide individualised probabilities of carrying a mutation. BOADICEA (Cambridge, UK) and BRCAPRO (Bayes-Mendel, USA) are commonly used examples. The National Institute of Health and Care Excellence (NICE) recommend that *BRCA1/BRCA2* testing be offered to those who have a 10% combined *BRCA1/BRCA2* probability. This threshold of offering genetic testing in the UK was earlier 20% and was lowered to 10% in 2013.

Models commonly used in the UK to estimate *BRCA1/BRCA2* probability are – MSS, BOADICEA, Tyrer Cuzick (UK), BRCAPRO. MSS is an easy to use table which provides scores for BRCA1 and BRCA2 mutations based on female/male breast cancers, ovarian cancers,

prostate and pancreatic cancers on the same side of the family. With the MSS, a combined score of 16 corresponds to the 10% testing threshold and a score of 20 to the 20% threshold. Table-1 provides easy to read risk criteria which have been adapted from criteria widely used to identify high risk women in the UKFOCSS national ovarian cancer screening trial and the London Cancer familial gynaecological cancer MDT (Barts Hosptial, UCLH). Different FH testing criteria exist for Jewish and the non-Jewish general population given the significantly different *BRCA1/BRCA2* prevalence estimates (criteria being more lax in the latter). Thus taking a detailed FH is critical to risk assessment for considering genetic testing. This should include history from both maternal and paternal sides of the family, spanning at least 3 generations (first and second degree relatives), ethnicity, age of onset of cancer, type of cancer and age of death. Both affected and unaffected relatives should be noted. High-risk women identified should be referred to a regional genetics service for genetic counselling and testing.

Lynch Syndrome (LS)

LS is an autosomal dominant syndrome, the tumour spectrum of which comprises colorectal (60% risk), endometrial (40-60% risk) and ovarian (approximate 10% (4-20%) risk) cancers. Additionally it also includes gastric, small bowel, hepato-biliary, brain, ureteric and renal pelvic (upper urologic tract) cancers. It is caused by a mutation in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*. The Amsterdam criteria-2 (AC-2) have been traditionally used to identify LS. AC-2 includes at least 3 relatives in the family with one of the LS cancers, all of whom should be related by a first degree relationship, the LS cancers should span at least 2 generations and one should be <50 years. The AC-2 criteria miss a number of mutation carriers. Hence more lax criteria called Revised Bethesda criteria have

been used to improve ascertainment by identifying colorectal cancer cases for molecular analysis (immunohistochemistry (IHC) and Microsatellite instability (MSI)) as an initial step, with genetic testing undertaken for IHC protein deficient or MSI unstable tumours. IHC/MSI testing for all colorectal cancer cases <60 years is now recommended as an unselected approach increases carrier deification and is cost-effective. IHC & MSI analysis for 'all' EC cases is more effective at identifying MMR carriers/LS than Bethesda/AC-2 criteria alone, which miss 12-30%/ 55-70% of carriers respectively. Although IHC and MSI testing for endometrial cancer cases have been recommended by some guidelines to better ascertain individuals for genetic testing for MMR mutations, this is not yet common practice in the UK. However, this is likely to change going forward. Such an approach of unselected testing if implemented for epithelial ovarian cancers would also be able to identify 1-2% additional LS carriers. However, this is not yet part of routine practice and the cost-effectiveness of this approach has not been evaluated.

Systematic Epithelial Ovarian Cancer Case Series BRCA1/BRCA2 Testing

Around 10%-20% of non-mucinous epithelial ovarian cancers have mutations in the *BRCA1/BRCA2* genes. Around half of these would not be identified by the traditional FH based testing. NHS England and NICE guidelines now recommend *BRCA1/BRCA2* testing for all women with non-mucinous high grade invasive epithelial ovarian cancer. This is gradually being implemented across the UK. In addition to predictive testing of unaffected family members, an added advantage is access to PARP inhibitors for those who develop Platinum sensitive relapsed ovarian cancer. Different models of pre-test counselling have been followed for this: (a) traditional approach of face-to-face counselling by the genetics clinician/genetic counsellor in a specialist genetics clinic; (b) telephone counselling by the

genetics clinician/genetic counsellor in a specialist genetics clinic; (c) Mainstreaming – non genetics clinician performing pre-test counselling after online training and post-test counselling undertaken by the regional genetics service; (d) GTEOC Cambridge model: genetics co-ordinated testing through local non-genetics clinicians.

***RAD51C*, *RAD51D* and *BRIP1* mutations:**

Genetic testing for these ovarian cancer gene mutations is not yet routine practice. However, a recent paper showed it would be cost-effective to offer risk reducing surgery at the levels of risk associated with these gene mutations. This provides clinical utility for genetic testing at these levels of risk, and suggests guidelines need changing in this respect.

Cowden's Syndrome

Autosomal dominant condition caused by *PTEN* gene mutations. It is associated with a 10-28% risk of endometrial cancer, 50% risk of breast cancer and 3-10% risk of thyroid cancer.

Peutz-Jeghers Syndrome-

This is caused by a mutation in the *STK11/LKB1* gene. The condition is associated with an increased risk of cervical cancer (adenoma malignum), sex cord stromal ovarian tumours and breast cancer.

Population based testing-

FH based prediction models are only moderately effective at predicting the presence of a *BRCA1/BRCA2* mutation and have a poor ability for predicting their absence. A large proportion (approximately 50%) of mutation carriers do not give a strong FH of cancer and

will not be detected by current clinical means. Given the significant benefits of screening/ prevention available to mutation carriers, this questions the efficacy of the current FH based approach. These limitations can be overcome using a population-based approach to genetic testing.

A population testing approach for *BRCA1/BRCA2* mutations has been extensively investigated in the Ashkenazi Jewish population and shown to identify 50% more people at risk, not detrimentally affect psychological health and can be highly cost-effective for the NHS, saving both lives and money. While there is strong evidence to suggest need for changing the clinical paradigm in this population to population based *BRCA1/BRCA2* testing, this is yet to be implemented and is a matter of ongoing discourse.

Table-1. Criteria to identify high risk families (London Cancer MDT)

Volunteer/Proband should either have been affected by cancer or be a FDR of an affected family member
Families with ovarian* or ovarian* and breast cancer
1) >2 individuals with ovarian cancer (any age) who are first degree relatives (FDR). 2) 1 ovarian cancer (any age) and 1 breast cancer <50 who are FDR. 3) 1 ovarian cancer (any age) and 2 breast cancers <60 who are FDR. 4) Breast cancer in volunteer/proband (<45 years) and mother with both breast and ovarian cancer (in the same person). 5) Breast cancer in volunteer/proband (<40 years) and sister with both breast and ovarian cancer (in the same person). 6) Criteria 1, 2 and 3 can be modified where paternal transmission is ocuring i.e. families where affected relatives are related by second through an unaffected intervening male relative and there is an affected sister eligible. ** History of tubal/primary peritoneal cancers may be considered equivalent to ovarian cancer.*
Families with a known gene mutation
7) The family contains an affected individual with a mutation in 1 of the known ovarian / endometrial cancer predisposing genes e.g. BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, PTEN, STK11/LKB1
Lynch Syndrome / HNPCC Families
8) The family contains 3 or more individuals with a LS or HNPCC related cancer*, who are FDR and >1 case is diagnosed before 50 years and the cancers affect >1 generation. **LS or HNPCC related cancers include: colorectal, endometrial, small bowel, ureteric and renal pelvic cancers.*
Families with only breast cancer
9) ≥4 breast cancers in the family (any ages) 10) 3 breast cancers related by FDR: i) 1 <3O years or ii) All <4O years or iii) 1 male breast cancer (MBC) and 1 bilateral breast cancer. 11) Breast cancer in volunteer/proband (<50 years) and: i) Breast cancer in mother (age of onset being <30 in one and <50 years in the other) or ii) Bilateral breast cancer in mother (<40 years onset) or iii) 1 MBC and 1 bilateral breast cancer. 12) 2 MBC (1 <40 years) in the family and proband is a FDR of 1 of them.
Families with Ashkenai Jewish (AJ) ancestory
13) Breast cancer (<40 years) or bilateral breast cancer (first cancer <50 years) in volunteer/proband irrespective of family history of cancer. 14) Breast cancer in volunteer/proband (<50 years) and 1 FDR with breast cancer (<50 years) or ovarian cancer (any age) or MBC (any age). 15) Breast cancer in volunteer/proband (<60 years) and 1 FDR with breast cancer (<40 years) or ovarian cancer (any age) or MBC (any age). 16) 1 FDR with ovarian cancer (<50 years). 17) FDR with breast and ovarian cancer in the same woman (any age). 18) 2 FDR with breast cancer (<40 years). 19) 2 MBC (<60 years) in the family and proband is a FDR of 1 of them. 20) Breast Cancer in self <50 years or Ovarian cancer in self at any age
Women with non-mucinous invasive epithelial ovarian cancer (EOC)

21) Women with invasive non mucinous EOC regardless of family history/ethnicity.
Women with triple negative (TN) Breast Cancer <50 years
22) Women with TN Breast Cancer <50 years

Further reading

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