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SURGICAL SYMPOSIUM CONTRIBUTION

Global Disparities in Breast Cancer Genetics Testing, Counselling and Management

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Abstract Hereditary breast cancers, mainly due to *BRCA1* and *BRCA2* mutations, account for only 5–10% of this disease. The threshold for genetic testing is a 10% likelihood of detecting a mutation, as determined by validated models such as BOADICEA and Manchester Scoring System. A 90–95% reduction in breast cancer risk can be achieved with bilateral risk-reducing mastectomy in unaffected BRCA mutation carriers. In patients with BRCA-associated breast cancer, there is a 40% risk of contralateral breast cancer and hence risk-reducing contralateral mastectomy is recommended, which can be performed simultaneously with surgery for unilateral breast cancer. Other options for risk management include surveillance by mammogram and breast magnetic resonance imaging, and chemoprevention with hormonal agents. With the advent of next-generation sequencing and development of multigene panel testing, the cost and time taken for genetic testing have reduced, making it possible for treatment-focused genetic testing. There are also drugs such as the PARP inhibitors that specifically target the *BRCA* mutation. Risk management multidisciplinary clinics are designed to quantify risk, and offer advice on preventative strategies. However, such services are only possible in high-income settings. In low-resource settings, the prohibitive cost of testing and the lack of genetic counsellors are major barriers to setting up a breast cancer genetics service. Family history is often not well documented because of the stigma associated with cancer. Breast cancer genetics services remain an unmet need in low- and middle-income countries, where the priority is to optimise access to quality treatment.

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Introduction

Breast cancer is the commonest cancer worldwide. There is at least a tenfold variation in the incidence rates around the world, largely due to variations in reproductive, hormonal and dietary factors. The increased incidence in migrants from low-income to high-income countries provides solid evidence that environmental rather than genetic determinants of risk are responsible for most of the geographic and inter-ethnic differences in breast cancer incidence [1]. Genetic mutations only account for about 5–10% of breast cancers, and for this small group of women, the risk of breast cancer can certainly be significantly reduced by prophylactic breast and/or ovarian surgery. A study had shown that the prevalence of *BRCA1*/*BRCA2* pathogenic variants (the commonest breast cancer genetic mutations) is comparable among breast cancer patients of African, Asian, White and Hispanic descent. However, between racial/ethnic groups, there are important differences in the spectrum of *BRCA1* compared with *BRCA2*, in *BRCA1/2* variants of uncertain significance (VUS) and in the accuracy of clinical models that predict *BRCA1/2* mutation carriage. [2]

Breast cancer genetics services are well developed in high-income countries, with published guidelines on genetic counselling and testing, and for management of mutation carriers. However, in low- and middle-income countries, resources for such services are lacking. A workshop on breast cancer genetics was held as a pre-conference workshop at the World Congress of Surgery in Basel, Switzerland, on 13th August 2017, with a focus on breast cancer genetics around the world. This review is based on lectures and panel discussions during this workshop.

Genetic contribution to breast cancer

The most common genetic alteration related to hereditary breast and ovarian cancer syndrome (HBOC) is due to mutations in the *BRCA1* and *BRCA2* genes. In the context of breast cancer, it confers a 45–85% lifetime risk of developing breast cancer by the age of 70, which is much higher compared to the general population ($\sim$ 12.5%) [3]. Prevalence and risk management of *BRCA1*/*BRCA2* mutations in breast cancer patients and asymptomatic carriers have been much studied, resulting in recommendations for screening and risk-reduction interventions for *BRCA1*/*BRCA2* mutation carriers and their family members, such as the NCCN guidelines [4]. Advances in technology provide an alternate option for high-throughput approaches to handle more patients with fewer resources. The increased use of next-generation sequencing (NGS) has allowed the investigation of multiple genes at a lower cost [5]. To date, more than 25 breast cancer-associated susceptibility genes have been identified, including genes with high penetrance (*TP53, CDH1, PTEN, STK11* and *PALB2)*, moderate penetrance (*NF1, CHEK2, ATM, NBN* and related genes) and low penetrance (*MLH1, MSH2, MSH6, PMS2* and *MEN1*). These gene mutations are comparatively rare, and hence the knowledge of risk management in individuals and families who carry some of these gene mutations is still limited [6, 7]. Management of such individuals and their families requires a multidisciplinary team, with genetic counsellors and geneticists playing an important role to avoid misinterpretation of results.

Who do we test?

Until recently, the only two genes routinely tested for inherited breast cancer were *BRCA1* and *BRCA2*. These genes are associated with high lifetime risks of breast and ovarian cancer, and so early detection and prevention strategies are recommended for individuals with mutations in these genes.

The threshold for offering *BRCA1/2* testing in many countries has been a 10% likelihood of detecting a mutation in the individual tested [8]. However, even with falling costs from NGS, many developing countries would have to limit testing to a 20% or higher threshold. The use of validated models to assess likelihood is recommended, such as BOADICEA [9] or the Manchester Scoring system that has recently been updated to include a further iteration of pathology adjustment [10]. Testing should usually starts with an affected individual in the family to provide an informative test to relatives and to allow informed decision-making regarding future preventive measures for that individual. However, many countries are now offering testing to unaffected at-risk individuals in families where there is no available affected person to test [8].

Multigene panel testing

The recent innovation of testing of panels of genes, many of which have no established validated relative risks of breast cancer [6], has increasingly changed how many health services undertake testing. Some of these genes tested are not specific to breast cancer alone, e.g. *PALB2* is also linked to pancreatic cancer, *CDH1* predisposes to hereditary diffuse stomach cancer, while *CHEK2* has been associated with colon cancer. Genetic predisposition can be due to the synergistic action of several genes.

In a study of over 35,000 women with breast cancer tested with a 25-gene panel, the most frequent mutations were seen in *BRCA1* and *2, CHEK2, ATM* and *PALB2*. [11]. One of the challenges faced by multigene panel testing is the possibility of misinterpretation leading to inappropriate interventions [12]. There may also be mutations in genes which do not have any clinical guidelines at the present time as well as unexpected findings, such as pathogenic mutations without a family history [13]. The NCCN Guidelines 2017 state that multi-gene testing may be indicated if more than one gene can explain an inherited cancer syndrome, as it will be more efficient and cost-effective, especially in patients with suggestive family history tested negative for a single syndrome. The guidelines also assert that tests should include moderate-risk genes whose penetrance is influenced by other genes and that multi-gene testing be offered with professional genetic expertise. A recent study on a decision-analytic model comparing lifetime costs and effects of criteria-based *BRCA1/BRCA2* testing, criteria-based panel testing (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2*) and population-based panel testing concluded that population-based panel testing was the most cost-effective strategy as it was able to prevent 657/655 ovarian cancers and 2420/2386 breast cancer cases per million in the UK/US population, respectively. [14]

Risk management

Risk-reducing mastectomy (RRM)

Bilateral risk-reducing mastectomy (BRRM) for hereditary breast cancer has become an important issue in recent years. Although observational studies show that BRRM can achieve a 90–95% reduction in breast cancer risk, and a subsequent improvement in survival of *BRCA1/2* mutation carriers without breast cancer, more rigorous prospective studies are needed [15]. The reported cumulative risks of development of contralateral breast cancer 20 years after the first diagnosis of breast cancer were 40% for *BRCA1* carriers and 26% for *BRCA2* carriers [16]. Contralateral risk-reducing mastectomy (CRRM) has been shown to reduce the incidence of contralateral breast cancer; however, there is insufficient evidence that it improves survival, because of the continuing risk of recurrence and death from the first breast cancer [15].

Risk-reducing mastectomy is well suited in combination with immediate breast reconstruction, and the preferred technique is nipple-sparing mastectomy. Breast size and shape will determine type of skin incisions, need of removing skin excess and depending on whether reconstruction is performed concurrently. Surgery to remove the mammary ducts behind the nipple–areola complex should be as radical as possible by coring-out the nipple, and the tissue thus removed must be biopsied to ensure that an occult DCIS is not left behind. To preserve vascularity of the nipple, saline can be injected into the subcutaneous layer [17]. The reconstruction is then performed using implants (frequently combined with acellular dermal matrix) or autologous tissue.

Complications are less common in experienced hands but cannot be completely avoided. The most frequent complications are skin flap necrosis (4–5%), nipple necrosis (3–4%), implant loss (2–4%), infection (2–3%), hematoma (2%) and seroma (2%). The risk factors for complications include smoking, flap thickness <3 mm, and periareolar incision [18].

Risk-reducing bilateral salpingo-oophorectomy

Risk-reducing bilateral salpingo-oophorectomy is recommended for carriers of the *BRCA1* and *BRCA2* mutations, in order to reduce the risk of ovarian cancer. However, whether oophorectomy reduces the risk of breast cancer is debatable. A large prospective study on 3722 women with *BRCA* mutation over a mean follow-up period of 5.6 years concluded that oophorectomy reduces the risk of pre-menopausal *BRCA*2-associated breast cancer (HR 0.18) but not of *BRCA*1-associated breast cancer (HR 0.79) [19].

Surveillance

Women under the age of 50 years who do not qualify for National Breast Screening Programmes but who have a significant family history of breast cancer have frequently been referred for regular mammography as an early detection measure. Such women may have incidence of the disease equal to or even greater than the population risk of women in their fifties. A study to evaluate annual mammography in women aged 40–49 [20] shows a likely survival advantage to screening, with lower stage, lymph node status and size than equivalent control groups. No evaluation has yet been published in women aged 35–39 although the results of FH02 are expected imminently [21]. Magnetic resonance imaging (MRI) is now standard of care for carriers of high-risk mutations such as *BRCA1, BRCA2 and TP53* due to the greater sensitivity for those aged <50 years [22], and a survival advantage is seen in MRI screened group compared to no intensive screening [23]. The starting age for MRI screening is usually between 20 and 30 years. Most centres offer annual screening with mammography to women judged to have a 17% risk of developing breast cancer at 80 years age, starting at 35–40 years of age. Tumour detection rates appear to range from 4 to 9/1000 examinations, which is comparable to the

mammographic detection rate for unselected women >50 years in the general population in the Western world. Interval cancers with mammography alone are still nonetheless common even with annual screening of women <50 years of age [20, 24]. Countries with poorer health infrastructure and resources can perhaps aim to offer annual mammography in 40–49-year age-group and additional screening thereafter to those at high risk (lifetime risk >30%).

Chemoprevention

Chemoprevention is an attractive option based on the 35–50% reduction in breast cancer incidence with raloxifene, tamoxifen or anastrozole (ordered in increasing efficacy) [8]. Tamoxifen is currently the only available drug in premenopausal women. It is also somewhat more effective than raloxifene in postmenopausal women but has more side effects (endometrial cancer and thromboembolic events are increased slightly) [25, 26]. The international trial IBIS 2 has provided good-quality evidence of benefit of aromatase inhibitors, showing a 50% reduction in risk, with less side effects than tamoxifen [27]. Both tamoxifen and raloxifene are licensed for primary prevention of breast cancer in North America and have been recommended by a NICE guideline for their use in the UK, with the latest iteration of NICE guidelines (2017) now recommending anastrozole over the others in postmenopausal women. Studies of uptake of chemoprevention have generally been disappointing with only around 16% usually partaking [28]. However, uptake varies hugely by context, with high-risk surgical clinics having the highest levels of 29–42% followed by trials 11.5–27% and evaluation in healthcare systems as low as 0.5%. Chemoprevention is inexpensive at around £15 ($20) annually for anastrozole and £25 ($33) for tamoxifen and has been found by NICE to be cost saving [8]. As such the targeted use of chemoprevention to those at moderate/high risk of breast cancer offers advantages to all health care systems globally.

Treatment-focused genetic testing

With increasing evidence that a positive *BRCA1/2* status can impact treatment decisions [29], there has been an impetus to appropriately counsel women who have a strong family history of breast cancer or other risk factors that would make them eligible for treatment-focused genetic testing (TFGT). The main surgical treatment decision that needs to be made in this case is the decision between breast-conserving surgery and bilateral risk-reducing mastectomy. BRCA carriers need to also consider risk-reducing bilateral salpingo-oophorectomy in order to significantly reduce the risk of ovarian cancer [30]. In addition, identification of BRCA mutations will influence the choice of chemotherapeutic agents, such as platinum-based chemotherapy [31]. Use of PARP inhibitors has shown benefit in BRCA-related ovarian cancers and is likely to also benefit BRCA-related breast cancer patients [32, 33].

Genetic testing is unique in that patient involvement—whether it can be giving consent or using results to make treatment decisions—is a lot greater than for other diagnostic testing. This places a greater burden on patients to bridge the information gap that is inherent in health care. Not only must patients adjust to their cancer diagnosis, but they must also be able to make sense of their genetic result and use it to base their treatment decisions. Meiser et al. interviewed 20 women with a diagnosis of invasive breast cancer or DCIS, who met eligibility criteria for TFGT in order to ascertain its impact on patients' psychological adjustment and to underline any unmet support needs [34]. They found that a patient's family history status greatly influenced the burden placed on them by their genetic result. BRCA carriers without a family history of breast cancer had more difficulties dealing with the psychological burden of their status as well as with making decisions regarding extent of surgery. Conversely, patients with a positive family history, but negative BRCA result reported feelings of shock, "lack of closure" and difficulties making treatment decisions. Despite the limitations of this small, qualitative study, it highlights the existence of unmet social support needs in patients regardless of their family history status. Even though adjustment to genetic testing results is sometimes difficult, patients view TFGT positively and agree that it is strongly relevant to their decision-making and should be offered around the time of diagnosis. Evidence also shows that most health care professionals have positive experiences with TFGT as well [35]. Therefore, it is paramount that genetic counselling targets the needs of individual patients as they differ depending on their personality and cancer history.

Setting up a risk management clinic

Risk management clinics are recognised as essential for the management of selected high-risk patients. In each jurisdiction, the resources, medical expertise and health funding will vary. Hereditary breast cancer clinics are designed to quantify risk, enhance surveillance and offer advice on preventative strategies. Typically, this will be a cohort of well, younger women, coming from a wide referral base but comprising a small target group. Greater efficiency and consistency of information are obtained by creating multidisciplinary teams. Key members of the team would be a

clinical geneticist, breast surgeon, gynaecological surgeon, specialist radiologist, psychologist and breast care nurse. Some clinics have a breast physician and other team members such as plastic surgeon, medical oncologist, endocrinologist and fertility specialists will also be important resource people that may be accessed intermittently.

Multidisciplinary care is about integrating services, establishing inter-specialty communication and developing agreed upon management plans. It is important that this be framed around evidence-based guidelines and the provision of common information. Participating specialists need to aim for "interdisciplinary" care, whereby they themselves develop a greater understanding of cross-specialty issues so that women and families have confidence in the consistency of information and develop familiarity with the point of care—a patient-centred approach. It is important that health administrators understand that organised multidisciplinary care is not only optimal for patient outcomes, but ultimately more efficient health delivery. Proper triaging of services and efficient use of health resources makes good economic sense.

What are the barriers to genetic testing in low- and middle-income countries?

Multiple barriers exist to providing basic breast cancer care in low- and middle-income counties (LMICs), where late presentation and inadequate access to optimal care result in poor survival. Familial and genetic breast cancers constitute a small proportion of all breast cancers. In LMICs, the precise prevalence of genetic breast cancers is not known, as there is no registry of such cancers. In such countries, genetic testing may not be seen as a necessity. For example, in South Africa, medical genetic services have been neglected in lieu of the HIV/AIDS pandemic [36]. Cancer genetics services are not widely available in the LMICs [37]. The cost of genetic testing is currently not covered by most healthcare funders or by insurance. Even in high-resource nations, subsidies are needed to improve testing rates [38]. Genetic testing done free through research is still associated with poor uptake of testing in unaffected family members [39]. Poor genetic literacy amongst healthcare providers and the community compounds this further [40].

Due to poor documentation of family history in oncology practice, follow-up of breast cancer patients has not incorporated referral to genetics services [41, 42]. Poor understanding of genetic results by surgeons has been reported even in high-resource settings [2]. Uptake of BRRM and risk-reducing bilateral salpingo-oophorectomy is low in low-resource settings, where lack of reconstructive surgery services in the public sector is an important barrier. Most of the studies on preventive strategies are from high-resource settings, with a dearth of studies from LMICs resulting in poor confidence in the minds of the treating doctors for referring patients to genetic counselling and testing.

Although health care providers have an obligation to the person being tested, not to share the results of genetic testing with other family members without the permission of the person tested, duty to disclose is important as results of a genetic test may have implications for a patient's family members. In most LMICs, no legal framework exists to protect medical practitioners who choose to divulge genetic results without permission of the person tested, unlike in Australia where family members are contacted by the genetics services once a family member has been shown to carry a genetic mutation. Genetic test results could affect a person's insurance coverage or employment. While the USA has a Genetic Information Non-Discriminatory Act (GINA) prohibiting genetic discrimination, this legislation is not available worldwide and is an important barrier to testing [39].

There are no widely accepted or used published guidelines on genetic counselling and testing, or for the management of BRCA mutation carriers and asymptomatic family members of a known genetic/familial breast cancer patient in LMICs. Furthermore, genetic testing options have become exceedingly complex in recent years, with commercial laboratories offering a variety of genetic tests, including the *BRCA1/2* testing packaged in a variety of ways. Healthcare professionals face numerous and considerable challenges integrating genetic testing into the clinical protocols owing to these complexities.

The GenTEE project, which is an initiative of an international consortium of academic and medical centres, aims at documenting and comparing current practices and the state of genetic service provision, including those relating to cancer genetics services, in eight emerging economies, namely—Argentina, Brazil, China, Egypt, India, Oman, Philippines and South Africa. The objective of the project is to identify current knowledge gaps and unmet service needs and to promote international collaboration for capacity building in genetic testing and services. Based on a questionnaire-type survey that seeks to map the current state of genetic services in the participating countries and to identify current drivers, barriers and opportunities for genetic services development, it was concluded that the lack of equitable access to genetic services in all 8 countries was primarily due to financial barriers. In these countries, the health care public services are underfunded and fragmented, and the majority of patients need to pay out-of-pocket for genetic counselling and testing services. Other issues identified by this project include geographical

and logistic barriers, as the services are concentrated in bigger cities and rural patients have difficulty in accessing these services. Many private laboratories and hospitals have developed genetic services and testing facilities, which are opportunistic and mostly technology and market driven. Such facilities lack standard operating procedures and well-accepted quality assessment processes for new technologies, resulting in questionable quality of genetic services being provided to the few patients who can afford to access them [43].

In such countries, priority should be to develop programmes on early detection and optimal access to treatment, rather than on developing a breast cancer genetics service, which is unlikely to improve breast cancer outcomes. Once treatment facilities are available, genetic services can be incorporated into clinical practice, with training of genetic counsellors, medical geneticists and provision of preventive strategies.

Conclusion

At the present time, only a small proportion of breast cancers can be attributed to a genetic mutation, the commonest of which are the *BRCA1* and *BRCA2* mutations. Risk management of *BRCA* mutation carriers are risk-reducing surgery (contralateral risk-reducing mastectomy for affected carriers, bilateral risk-reducing mastectomy for unaffected carriers, and bilateral risk-reducing salpingo-oophorectomy), chemoprevention with hormonal therapy, and surveillance with mammogram and breast MRI. While genetic services are well developed in high-income countries, very few services are available in LMICs, where the priority is to develop early detection programmes and to optimise access to quality management.

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