Genetic Predisposition to Breast Cancer and Its Management

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Breast cancer incidence is rapidly increasing throughout the world. It may have a familial background or might be associated with certain mutations in genes related to either cellular proliferation, apoptosis or other pathways responsible for mitosis of cells.

Breast cancer is considered familial when it occurs in one or more members of the family, first degree or second-degree relative(s).

However in this familial type, genetic testing does not reveal any mutations that are known to increase breast cancer risk, such as the high-penetrant BRCA1 or BRCA2, p53, PTEN, CDH1 or PALB2 genes [1]. If a genetic mutation is found, the breast cancer is classified as a hereditary breast cancer.

About 5 to 10% of all patients with breast cancer carry a hereditary predisposition, which may influence management decisions.[1]

The public awareness about the genetic risk of cancer in general and BRCA in particular increased through the lay press and social media reporting of the decision of a Hollywood actress, Ms. Angelina Jolie, to undergo bilateral prophylactic mastectomy, when she discovered that she carried a pathogenic BRCA mutation(i.e. the ‘Angelina Jolie effect’) [2]. The identification of BRCA1 gene on chromosome 17 and BRCA2 gene on chromosome 13 is a major breakthrough in the modern field of oncology practice.

There are three major risk factors for the development of breast cancer: age, the gender and the genetic factors. Breast cancer is largely a disease of the elderly population. The risk of developing breast cancer increases dramatically with age. Moreover, breast cancer risk is 100 times greater amongst women than men. Even amongst women who carry a highly penetrant genetic mutation, there are external factors, namely, obesity and other lifestyle factors that may modify the actual risk of developing breast cancer. Out of all the cases of hereditary breast cancer, nearly half are associated with BRCA1 and BRCA2 gene mutations. BRCA 1 mutation carriers have a lifetime risk of developing breast cancer ranging from 75 to 80% [3]. Amongst BRCA2 mutation carriers, the lifetime risk of developing breast cancer ranges from 45 to 69% [4]. The risk of ovarian cancer ranges from 39 to 44% of women who inherit a harmful *BRCA1* variant and 11–17% of women who inherit a harmful *BRCA2* variant by 70 to 80 years of age [4].

Note that men may also inherit these genetic mutations and may be predisposed to development of prostate cancer and breast cancer and sometimes pancreatic cancer. However, in men, the breast cancer risk is substantially lower than that for women (i.e. about a 6% lifetime risk of breast cancer in male BRCA 2 mutation carriers).

There are other high penetrance genetic mutations responsible for increasing the risk for breast cancer. These include PTEN related Cowden’s syndrome, p53 related Li Fraumeni syndrome, CDH1 related diffuse hereditary gastric cancer syndrome, PALB 2 (partner and localizer of BRCA2 gene) related breast cancer [5].

Besides an increased risk of breast cancer, these mutations are associated with other cancers, namely, Cowden syndrome is associated with increased risk of thyroid carcinoma, renal cell carcinoma and endometrial carcinoma. Women with p 53 mutation carry an increased risk of brain tumours, bone tumours, bowel, soft tissue and skin tumours and leukaemia. Persons with STK11 mutation Peutz-Jegher’s syndrome have an increased risk of developing gastrointestinal polyps and typical brown pigmentation around the lips.

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Genetic Counselling and Genetic Testing

Persons presenting with the following conditions should be offered genetic counselling [6]:

Sporadic early-onset breast cancer below age 45 years or a triple-negative breast cancer below age 60 years.

- Male breast cancer at any age
- Early-onset colon, ovarian, uterine, pancreatic, diffuse gastric or renal cancer below age 50 years.
- Medullary thyroid cancer or adreno-cortical carcinoma at any age.
- Multiple primary cancers in one individual e.g. bilateral breast cancer; breast/ovarian; colon/uterine; uterine/renal/thyroid or multiple primary melanomas.
- Individual with multiple and/or early-onset gastrointestinal polyps, >15 gastro-intestinal polyps or >5 hamartomatous or juvenile polyps.
- Hereditary cancer syndrome
- Hereditary family-specific mutation identified
- Family history of any cancer

Based on the genetic counsellor's assessment, genetic testing by taking a sample of saliva or blood should be arranged [6].

Preventive Strategy

Various options available for women carrying a higher than usual risk of developing breast cancer are as follows:

Risk-reducing plan comprising prophylactic surgery with or without chemo-prevention and surveillance for likely cancers, according to the genetic mutation found.

The benefits and harms of each option should be explained to the patient and family. There is a need to evaluate long-term outcomes of these options, especially the risk-reducing surgery to better elucidate the benefits accrued from various surgical options such as nipple and skin-sparing mastectomy and bilateral salpingo-oophorectomy.

The risk of breast and ovarian cancer amongst these genetic mutation carriers is sufficiently high to necessitate the administration of some preventive measures in the form of either risk-reducing surgery of the breast and ovaries or in the form of breast cancer chemo-prevention with tamoxifen, exemestane, anastrozole or Raloxifene. Of these drugs, only tamoxifen is an available option for premenopausal women. The risk-reducing mastectomy is shown to reduce the risk of breast cancer in about 90% women. However, 10% ladies may still get breast

cancer from the residual milk ducts on the undersurface of nipple or at the periphery of the breast left during the 'risk-reducing nipple and skin-sparing mastectomy' [1, 7]. If a person carrying this genetic mutation is young and has not had family, we can offer surveillance measure in the form of high-resolution digital mammography and MRI scan of the breast at intervals of 6 months. For example, MRI with contrast is arranged every January and Digital mammography is performed every July starting at age 20 or about 10 years before the index case in the family, so that breasts are scanned at six-monthly intervals by a highly sensitive imaging reducing the chances of missing the interval cancers (interval cancers are defined as tumours arising between screen examinations). Any suspicious BIRADS 4 or 5 lesions picked up in the surveillance imaging is biopsied by stereotactic technique. A lesion with biopsy positive for malignancy or atypia is then excised by wire guidance.

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