Hereditary and familial cancer

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Abstract

Advances in both access to and the technology underpinning next-generation sequencing have provided a formidable basis for the evaluation of individuals and families recognized as having a potential hereditary cancer. This article focuses on the most clinically relevant hereditary cancer predisposition syndromes such as hereditary breast and ovarian cancer syndromes and hereditary colorectal cancer. It also reviews current best practice in both surveillance for affected individuals as well as an providing an overview of the available risk-reduction strategies for affected individuals.

Keywords Breast neoplasms; colorectal neoplasms; genetic predisposition to disease

Introduction

The majority of solid organ malignancies are sporadic in nature. Yet there are a number of recognized familial cancer predisposition syndromes and the timely recognition of these has important implications not only for treatment, but also for enhanced surveillance and the use of preventative or risk-reduction interventions for affected individuals and family members.

A multitude of genes have been implicated in inherited cancer susceptibility ranging from high penetrance cancer syndromes such as hereditary breast and ovarian cancer, to other genes that confer more moderate increases in personal risk. Increased numbers of specialist genetic clinics coupled with reduced cost and wider availability of access to next generation sequencing technologies has resulted in more cancer patients undergoing some form of genomic sequencing. The implications for clinical practice for surgeons who deal with oncology include the recognition of a potentially relevant family history, identifying when genetic testing or referral to a specialist genetic clinic may be required and the appropriate management of patients with an identified genetic mutation.

This article aims to outline the known genetic contributions to the major subtypes of inherited solid organ malignancies and in addition to the pathogenesis review recommendations for treatment and prevention in affected individuals.

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Breast cancer

BRCA1 and BRCA2 mutations

Mutations in BRCA1 and BRCA2 are the most common genes associated with a high risk for the development of breast cancer and are responsible for 20% of familial breast cancer cases.[1] Both genes encode for a tumour suppressor protein and are inherited in an autosomal dominant pattern. To date hundreds of distinct germline mutations in BRCA1 and BRCA2 have been described that vary in frequency. Most breast cancers that arise in BRCA1 mutation carriers are negative for expression of the estrogen, progesterone and HER2 receptors (triple negative subtype). The subtype of breast cancers that arise in BRCA2 mutation carriers reflects those of sporadic breast cancer in the general population with over 70% estrogen receptor positive. In addition to conferring a risk of breast and ovarian cancer, mutations in BRCA2 also confer an increased risk of prostate cancer, melanoma and pancreatic cancer.

Cumulative risks for breast and ovarian cancer in BRCA1/2 mutation carriers: Most estimates of cumulative breast and ovarian cancer risk for BRCA1/2 mutation carriers have been derived from retrospective cohorts. Variations in the estimated risks are accounted for by differences in the populations studied, sampling methods and additional risk factors. Risk estimates from the largest prospective cohort study to date have just been published.[2] For BRCA1 mutation carriers the risk of developing breast cancer by age 80 was 68% and the risk of ovarian cancer was 44%. Cumulative risk at age 80 for BRCA2 carriers was 63% for breast cancer and 17% for ovarian cancer. These figures are consistent with estimates from previous meta-analyses. Kaplan–Meier cumulative risk curves demonstrate that incidence of breast cancer increases rapidly with age in early adult life followed by a more stable, constant increase through remaining life years (see Figure 2 in Ref. 2) (see Table 1).

Guidelines for assessment of familial risk and threshold for referral for genetic testing: In patients being evaluated in primary and secondary care, a family history assessment should include a two generation family history including the paternal side. A variety of risk algorithms are available that evaluate an individual's lifetime risk of breast cancer such as the Tyrer-Cuzick model[5] [download free from http://www.ems-trials.org/riskevaluator/]. These include assessment of non-genetic contributors to risk such as parity and body mass index. Assessment in secondary care should also determine whether the patient requires referral to a tertiary cancer genetics service, namely those deemed high risk or patients with a greater than 10% risk of harbouring a BRCA1/2 mutation. This can be assessed using either the Manchester score[6] or the BOADICEA computer algorithm. Prior to testing, patients must be assessed by a trained genetic counsellor with most units consulting with an individual on two occasions.

Management of known BRCA1/2 mutation carriers

Surveillance – Guidelines recommend enhanced surveillance for BRCA1 and BRCA2 mutation carriers who have not undergone risk-reducing surgery. Most surveillance strategies employ both MRI and mammography as the screening modality. Current

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UK guidelines recommend annual MRI from age 30–49 years with the use of annual mammography from age 40–69 years. In high-risk women, MRI is considerably more sensitive than mammography.

Surgical management of breast cancer in BRCA1/2 mutation carriers – In BRCA1/2 mutation carriers who have been diagnosed with breast cancer it is now unequivocally acknowledged that the risk of contralateral breast cancer is high.[2] Overall estimates of risk of contralateral cancer are in the order of 2.3% per year with risks at 10 years of 27% for BRCA1 and 19% for BRCA2.[4] The risk of contralateral cancer increases with a younger age at diagnosis of the index cancer. There is emerging evidence of a survival advantage for patients with BRCA1/2 mutations who are treated with bilateral as opposed to unilateral mastectomy for stage I or II breast cancer.[7] While individual patient or tumour characteristics may dictate the choice of and timing of surgery for the index cancer, patients should be counselled as to the risk of contralateral cancer with bilateral mastectomy as the definitive surgical management.

In BRCA1/2 mutation carriers risk-reducing bilateral salpingo-oophorectomy is advisable from age 38–40 for BRCA1 carriers and age 40–45 for BRCA2 carriers. Postoperatively, the use of hormone replacement therapy until the age of anticipated menopause is recommended.

Risk-reducing surgery – Bilateral risk-reducing mastectomy is currently the most effective means of reduction of personal risk of breast cancer for BRCA1/2 mutation carriers. Reductions in risk in excess of 90% have consistently been reported in cohort studies with follow up of patients with who have undergone risk-reducing mastectomy compared to those who have not. The decision to proceed with such surgery mandates careful consideration and counselling as regards timing of surgery and the type of procedure with a variety of options for immediate breast reconstruction that can be tailored to the individual. Skin-sparing mastectomy and nipple-sparing mastectomy techniques are now routinely employed for these patients and allow for an improved aesthetic outcome following reconstruction. Data confirming the oncological safety of these approaches continues to accrue. Women should be cautioned that these procedures do not eliminate all risk and that preservation of the nipple–areola complex does retain a small additional volume of breast tissue when compared to a nipple sacrificing mastectomy. No studies have reached sufficient maturity to provide a reliable lifetime estimate of the risk of malignancy in the preserved nipple in patients who undergo nipple sparing mastectomy.

In women who have tested negative for a BRCA mutation or do not meet the threshold for testing but have an elevated lifetime risk of breast cancer, the options for risk reduction include chemoprevention and risk-reducing surgery. The use of both tamoxifen, suitable for pre- and post-menopausal women, and the aromatase inhibitor anastrazole in post-menopausal women has demonstrated a relative risk reduction of 38–53% in the incidence of breast cancer.[8] Despite proven efficacy, the uptake of chemoprevention among women at moderate and high risk remains low. Chemoprevention is not as effective in BRCA1 mutation carriers as the reduction in risk is mediated through a reduction in estrogen receptor positive cancers. For women who are not a BRCA gene carrier but have a validated high predicted lifetime risk for the development of breast cancer, our unit currently sets a threshold of greater than 25% estimated lifetime risk and these patients undergo a number of consultations including clinical psychology and dedicated multidisciplinary case discussion before a decision is made to proceed to risk-reducing surgery.

Li-Fraumeni syndrome

This cancer predisposition syndrome is due to abnormalities in the tumour protein p53 gene and is inherited in an autosomal dominant fashion. The syndrome is characterized by the development of multiple malignancies in affected individuals. Women have high lifetime risk for the development of breast cancer, particularly prior to menopause. Guidelines for screening of patients with a known TP53 mutation reflect this and recommend annual MRI for women aged 20–49 years. In addition to breast cancer, a wide variety of cancers have been described in patients with Li-Fraumeni syndrome such as sarcomas (both soft tissue sarcomas and osteosarcomas), brain tumours and adrenocortical carcinoma.[9]

Moderate penetrance genes

Outside of BRCA1/2, attention has more recently focused on a group of moderate penetrance genes that confer a more modest increased risk of breast cancer. To date, the main three genes with a relevance to breast cancer are PALB2, ATM and CHEK2. The odds ratio for the development of breast for these genes are PALB2: 5.3, ATM: 2.8, CHEK2: 3.0. To date there is insufficient data to recommend risk-reducing surgery or even contralateral prophylactic mastectomy for patients with breast cancer, identified with a mutation in one of these genes. Enrolment of these patients into increased surveillance programmes is recommended and most would advocate the commencement of MRI screening from age 40.

Hereditary colorectal cancer syndromes

The majority of colorectal cancers develop as a repercussion of sporadic genetic events but, analogous to breast cancer, a small fraction of cases (approximately 5%) are due to germline mutations. The responsible hereditary syndromes can be grouped into non-polyposis and polyposis syndromes based on phenotype (Table 2).

Assessment of familial risk for hereditary colorectal cancer syndrome

A comprehensive family history assessment in all first and second degree relatives is equally as relevant in colorectal cancer as it is in breast cancer. A range of factors including variability in gene penetrance, means that a considerable proportion of carriers of important germline mutations may not meet classic diagnostic criteria and as an entity, hereditary colorectal cancer syndromes remain under recognized.

A range of family history criteria are available and used to assess in particular for the risk of Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC), the most well-known of which is the Amsterdam criteria.[10] The Amsterdam criteria are summarized to the '3-2-1 rule' that requires a family history of three colorectal cancers involving two successive generations with one member affected at a young age (under 50). The lack of sensitivity that has been demonstrated with the use of the

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