Cancer biology: Familial cancers and genetic testing

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Epidemiology

Inherited cancer syndromes are rare, explaining less than 5-10% of cancers. However, they are associated with high penetrance, resulting in significantly increased risks of specific cancers or groups of cancers. Most syndromes are autosomal dominant, caused by a single germline mutation in a tumour suppressor gene, particularly a DNA repair gene, or an oncogene. The sex-specific distribution of certain cancers can give the impression of a X-linked inherited pattern (e.g. the preponderance of females of affected with breast and/or ovarian cancer compared to males with breast or prostate cancer, in BRCA1 or BRCA2 mutation carriers.)

Risk factors

Family history is the single biggest risk factor. However, for some highly penetrant syndromes associated with childhood cancers, up to 50% of mutation occur de novo (e.g. familial adenomatous polyposis (FAP), Li Fraumeni and Multiple Endocrine Neoplasia (MEN) 2B). Ethnicity is important in some syndromes (e.g. Ashkenazi Jewish heritage and specific BRCA1 and BRCA2 mutations) due to founder effects.

Cancer biology

Cancers in inherited cancer syndromes may be more aggressive, disseminate early and be associated with poor prognosis (e.g. medullary thyroid cancer in MEN2B). They also may contain targetable mutations or be more sensitive to standard therapy providing better prognosis (e.g. ovarian cancer in BRCA1 or BRCA2 mutation carriers) or indistinguishable from non-heritable cancers.

Clinical presentation

While some inherited cancer syndromes are associated with a specific phenotype (e.g. macrocephaly in Cowden syndrome or mucosal freckling in Peutz Jegher syndrome), many are not. Presentations suggestive of a germline mutation include the 3:2:1 rule (3 relatives, in 2 generations where 1 is was diagnosed under 50), cancer diagnosed at a young age; and multiple cancers in a patient or family. Tumour characteristics include bilateral or multifocal tumours, rare tumours or uncommon types of common cancers (e.g. triple negative breast cancer).

Diagnosis

Diagnosing an inherited cancer syndrome usually relies on family history. Risk calculators that examine family and personal history (e.g. Manchester score or BOADICEA in breast cancer) are often used to determine the pre-test likelihood of a germline mutation.

Tumour testing is also used to determine the likelihood of a germline cause. For example, universal testing of bowel cancers, looking for loss of IHC staining of the proteins associated with the mismatch repair genes that cause Lynch syndrome, is a cost effective screening test and guides which gene to test first. Genetic testing of tumours to demonstrate biallelic loss of a particular gene is also used, for example in Von Hippel Lindau (VHL) as well as retinoblastoma.

Principles of management

For example: Surgery, medical, radiation, palliative care, allied health

The key to good management is to maintain a high degree of suspicion of inherited cancer syndromes and refer patients for assessment and/or testing in a timely manner. Alternate treatments may be offered if a specific mutation is identified (e.g. choosing mastectomy over lumpectomy to avoid unnecessary radiation in Li Fraumeni syndrome, which is associated with a germline TP53 mutation).

Genetic testing should only occur after effective counselling and informed consent. This includes discussing the limitations of genetic testing, the impact on relatives, risk reducing strategies and the psychosocial issues that may go beyond those encountered in general oncology practice.

Follow-up and survivorship

After the initial diagnosis, follow-up may occur via screening clinics or at specific times, such as when a family is planned, a child reaches an appropriate age for testing, risk reducing surgery is contemplated, or the family history changes.

Screening and prevention

Oncology patients with germline mutations may be at risk of other malignancies. Screening usually starts earlier and incorporates more sensitive modalities (e.g. breast MRI from age 30 in BRCA1, BRCA2 or TP53 mutation carriers or colonoscopy in Lynch syndrome). Where screening is ineffective, surgery, if feasible, is recommended (e.g. risk-reducing salpingo-oophorectomy in BRCA1 at age 40, colectomy around age 21 in APC mutation carriers). Screening may be performed in high-risk or multidisciplinary specialist clinics (e.g. VHL).

Prevention applies to relatives and offspring as well. After the initial mutation is identified, cascade testing involves informing at-risk relatives and offering counselling and genetic testing. Testing is not performed in minors, unless there is a clinical need to do so (e.g. genetic testing in infancy in MEN2 to offer to offer lifesaving thyroidectomy). IVF and pre-implantation genetic diagnosis can be used to prevent the family mutation being inherited by future generations, although expense and toxicity limit its application within adult-onset cancer conditions.

Case studies

Case study 1. (Young onset breast cancer)

Rachel, age 37, has just had a wide local excision and sentinel node biopsy for a right sided, invasive duct carcinoma. The pathology report states that it is 15mm, grade 3, ER-/PR-/HER2-, no nodes are involved.

She denies any cancers on her mother's side. What else do you need to know?

- Paternal history
- Any Ashkenazi Jewish heritage
- Size of family and age at which relatives died
- Any phenotypic characteristics that would suggest other inherited cancer syndromes associated with an increased risk of breast cancer (see eviQ referral guidelines)

Her paternal grandmother had some sort of gynaecological cancer at 71 and her paternal uncle had prostate cancer at 48. Does she meet criteria for genetic testing? If so, for what gene(s)?

- Yes: BRCA1 and BRCA2 mutation search
  - Genetic testing for BRCA mutations offered to all triple negative breast cancer <40yrs, even if no family history
  - Manchester score >16 (>10% pre test likelihood) if gynaecological cancer was a high-grade, epithelial non-mucinous ovarian cancer. Pathology and/or death certificate required.
- Other inherited cancer syndromes unlikely: no phenotypic features of Cowden or Peutz Jegher syndrome and no strong history of Li Fraumeni related cancers

She undergoes a BRCA mutation search after informed consent is obtained and a mutation in BRCA1 is identified. Describe alternate treatment plans (if any), other management options and implications for the family?

- Contralateral breast cancer risk high – offer bilateral mastectomy as alternate to WLE + RTx
- Standard chemotherapy regimen
- Risk reducing salpingo-oophorectomy (RRSO) should be strongly recommend at age 40
- Cascade testing, starting with parents and adult siblings (at 50% risk due autosomal dominant inheritance and very low rate of de novo mutations)

Case study 2. (Young onset bowel cancer)

James, age 29, presented with PR bleeding. Colonoscopy demonstrated obstructing lesion in sigmoid colon. Biopsy demonstrated an adenocarcinoma. What other workup is required at/after surgery?

- Staging of tumour and tumour testing (IHC for MMR proteins +/- MSI)
- Family history
- Completion colonoscopy and types of polyp(s) (if any found)
- Phenotypic characteristics that would suggest other inherited cancer syndromes associated with an increased risk of bowel cancer (see eviQ referral guidelines)

Tumour invades through muscularis, 3/25 nodes involved. Normal staining for MMR proteins and MSI-low. Family history reveals no history of bowel, uterine, ovarian, other GI or other cancers in his family. Completion colonoscopy demonstrated 9 polyps (mainly adenomas but no hamartomatous or juvenile polyps). What germline conditions should be considered? Does the lack of family history change your thinking?

- Not Lynch syndrome – very unlikely in presence of normal IHC staining
    - Incomplete penetrance means family history may be absent even though de novo mutation rate is very low
- May be Attenuated Familial Adenomatous Polyposis (AFAP) associated with mutations in the APC gene (oncogene) or MUTYH Associated Polyposis (MAP) associated with mutations in the MUTYH gene (a base excision repair tumour suppressor gene).
    - FAP associated with a high de novo mutation rate, so family history may be absent
    - Attenuated FAP more likely than FAP as polyp load in FAP usually much higher at this age
    - MAP inherited in autosomal recessive manner with no significant increase in risk for heterozygotes, so parents usually unaffected

What information would help to determine which gene, APC or MUTYH to test first?

- APC gene mutations causes FAP and AFAP which are associated with a phenotype that includes
  - Congenital hypertrophy of the retinal pigment epithelium (CHRPE) in >70% and is usually present at birth
  - Supernumary teeth
  - Osteoma of the jaw
  - Epidermal cysts
- MUTYH gene mutation associated with MAP which is an autosomal recessive condition so increased likelihood if consanguinity, parents close relations or specific ethnic group

No evidence of CHRPE or other FAP phenotypic features. Parents are from England and are distantly related. Decide to perform MUTYH first. Homozygous mutations are identified in MUTYH. Describe alternate treatment plans (if any), other management options and implications for family.

- Repeat colonoscopy and polpectomy or proceed to colectomy if polyp load too great
- Standard chemotherapy regimen
- Upper endoscopy (see eviQ MUTYH management guidelines)
- Cascade testing, starting adult siblings (at 25% risk due autosomal recessive inheritance). No significant increased risk for heterozygotes

Further reading and links

- Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)
- Cancer Genetics section of eviQ for information on risk management, referral guidelines, germline genetic testing and family cancer clinics: www.eviQ.org.au
  - Manchester score (requires login)
- Evans DGR, Lalloo F, Cramer A, Jones EA, Knox F, Amir E, et al. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. J Med Genet 2009 May 12 [cited 2014 Jun 5];46:811-817 [Abstract available at http://jmg.bmj.com/content/46/12/811.abstract].
- Hodgson SV, Foulkes WD, Eng C, Maher ER. A practical guide to human cancer genetics, 4th edition. London: Springer; 2007 [cited 2014 Jun 5] Available from: http://link.springer.com/book/10.1007/978-1-4471-2375-0.
- Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong C, et al. GeneReviews®. [homepage on the internet] Seattle: Seattle (WA): University of Washington; 32202 Jan 1 [cited 2014 Jun 5; updated 2014 Jan 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1116/.
  - BRCA1 and BRCA2

- FAP
- Li-Fraumeni Syndrome
- Multiple Endocrine Neoplasia (MEN) Type 2
- Cowden Syndrome
- Peutz-Jegher Syndrome
- Von Hippel-Lindau Disease
- Retinoblastoma
- MUTYH-Associated Polyposis (MAP)

- Tobias ES, Connor M, Ferguson-Smith M. Essential medical genetics, 6th edition. Australia: Wiley-Blackwell; 2011 [cited 2014 Jun 5] Available from: http://au.wiley.com/WileyCDA/WileyTitle/productCd-EHEP002300.html.