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Genetics of gynaecological cancers

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Gynaecological cancers accounted for 16.3% of all cancers and 13.9% of all cancer deaths in women globally in 2012. Cancer of the cervix is the most common gynaecological cancer, followed by cancers of the uterus and the ovary. Although cervical cancer is almost exclusively triggered by human papilloma virus infection, approximately 5% of all uterine cancers and 20% of all ovarian cancers are caused by germline mutations in cancer predisposition genes. A number of genetic syndromes are associated with rarer gynaecological tumours. This review focuses on the epidemiology and pathology of inherited gynaecological cancer predisposition syndromes arising because of germline mutations.

Introduction

Families with a strong history of gynaecological cancer have classically been evaluated in the genetic clinic, with genetic testing for monogenic cancer predisposition syndromes reserved for families fitting strict diagnostic and family history criteria. With the advent of next-generation DNA sequencing, testing has become faster, cheaper and widely available. Indications for testing have been broadened on the basis of evidence from large cohorts and datasets with long-term follow-ups. Genetic testing is now increasingly initiated at the time of diagnosis by the gynaecologist or oncologist as it becomes more relevant to clinical management involving tailored treatments. A familiarity with common and rarer inherited gynaecological cancer predisposition syndromes is therefore essential. This review focuses on the investigation and management of affected and at-risk families and individuals.

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Ovarian cancer

Background

Ovarian cancer is the seventh most common cancer in women globally [1]. Incidence rates are higher in more developed countries. In the UK in 2013, ovarian cancer was the sixth most common cancer among women, accounting for approximately 4% of all cancers in women with a median 5-year age-range of onset of 65–70 years and a lifetime risk of 2% [2]. Around 90% of ovarian cancers arise from the germinal epithelium covering the outer cortex and are termed epithelial ovarian cancer (EOC). The remaining 10% are non-EOCs, including carcinosarcomas, sex cord tumours, germ cell tumours and other rarer forms. The predominant subtype of EOC is serous adenocarcinoma, accounting for 30–70% of all EOCs, followed by endometrioid (10–20%), mucinous (5-20%), clear-cell (3–10%) and undifferentiated (1%) [3]. Family history is a significant risk factor with ovarian cancer being three times more likely in an individual with an affected first-degree relative and six times more likely where there are two affected first-degree relatives [4]. In families with an inherited predisposition, ovarian cancer often presents at a younger age than average and in association with other cancers within the family, including breast cancer, as in hereditary breast ovarian cancer syndrome (HBOC) or with colorectal cancer and endometrial cancer in Lynch syndrome (LS).

Hereditary breast and ovarian cancer syndrome

HBOC is an autosomal dominantly inherited predisposition to breast and ovarian cancer. It is caused by mutations in the *BRCA1* and *BRCA2* tumour suppressor genes, which encode proteins that are important in the repair of double-stranded breaks in DNA [5]. HBOC is frequently referred to as being autosomal dominant at the organism level but autosomal recessive at the cellular level, following Knudson's two-hit hypothesis [6]. The population carrier frequency for germline mutations in *BRCA1* and *BRCA2* is at least 1 in 400, although this varies depending on ethnic and racial background [7]. For example, the combined carrier frequency of three founder mutations in the Ashkenazi Jewish population is 1 in 40 [8]. Founder mutations and carrier frequencies in many other populations have been documented [9]. In addition to ovarian cancer, *BRCA1* and *BRCA2* mutations are associated with an increased lifetime risk of breast cancer (observed to be as high as 80%) prostate cancer (up to 30% lifetime risk in *BRCA2* mutation carriers) and, to a lesser degree, pancreatic cancer [10,11].

Prevalence

In a recent systematic review of 5897 unselected cases of EOC from nine studies, a mean prevalence of 12.7% for mutation in either *BRCA1* or *BRCA2* was recorded [12]. Other recent studies of unselected EOC cases have reported similar mutation frequencies, with *BRCA1* mutations approximately twice as frequent as *BRCA2* [13]. Family history of breast or ovarian cancer appears to be associated with an increased prevalence of mutations in *BRCA1* and *BRCA2* [14]. In a large study of families in Germany, selected according to a panel of established clinical criteria mainly focusing on family history, 31.6% of families affected by breast and ovarian cancer harboured a mutation in *BRCA1* and 10.2% in *BRCA2* [14]. For families affected by ovarian cancer only, the mutation rates were similar: 29.6% for *BRCA1* and 13.1% for *BRCA2*. Lower age-of-onset of EOC is also associated with an increased mutation rate.

Histopathology

The histological subtype of EOC in germline *BRCA1* and *BRCA2* carriers is skewed towards serous adenocarcinoma, present in 60-100% of cases; high-grade serous EOC is much more strongly associated with germline mutation in *BRCA1* and *BRCA2* than low-grade tumours [15]. Endometrioid and clear-cell tumours are seen infrequently, whereas mucinous adenocarcinomas and borderline ovarian tumours do not appear to be associated with germline *BRCA1* or *BRCA2* mutations. Histopathological examination of specimens from mutation carriers undergoing prophylactic bilateral salpingo-oopherectomy (BSO) has revealed interesting insights into their pathogenesis. Changes have been identified in the fallopian tubes of mutation carriers in the form of serous tubal intra-epithelial tumours, atypical tubal hyperplasia and dysplasia, and invasive serous carcinoma [16]. These appear to be present in at least

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