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Review Article

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Genetic Basis of Gynaecological Cancers

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Abstract

There has been an enormous progress in understanding of the molecular basis of disease, process of carcinogenesis & their impact on gynaecological cancers. This fundamental understanding is achieved; using molecular technology which provides opportunities for the prevention, early detection and adequate management of cancer. It is understood that cancer patients with same histological tumour variety and stage may have a different clinical outcome. Because there is biological diversity of tumours, which cannot be explained by microscopic type alone. So, the current focus of describing tumours is the analysis of gene expression using new DNA microarray technology.

Gynaecological cancers are examples of a number of contrasting mechanisms of carcinogenesis. It is known that, ovarian and endometrial cancer can occur as components of familial cancer syndromes (familial breast/ovarian cancer and Lynch II syndrome) due to germline inheritance of genetic abnormalities. However, most ovarian cancers are not considered to be due to inherited genetic alterations, but occur due to somatic mutations occurring in ovarian cells with an initially normal genome. These somatic mutations are considered to be secondary to environmental factors that increase the opportunity for spontaneous mutation in a number of susceptible genes. For example the genetic alterations that lead to cervical cancer is caused by an environmental factor, Human Papilloma Virus (HPV), and in some endometrial cancers, unopposed oestrogen exposure or hyperinsulinism that leads to carcinogenesis. This proposes that vulval and cervical carcinomas are not similar aetiologically, and that factors other than HPV infection are more important in vulval carcinogenesis. Various genetic events occur between HPV-positive and -negative vulval cancers, with a larger number of molecular alterations in HPV-negative vulval cancers compared with HPV-positive tumours [1].

As a result, HPV-positive vulval cancers are more frequently found in younger patients. Whereas, vulval cancers in older patients are more often HPV negative, and more often show allelic loss of the TP53 gene. Approximately 5% of endometrial cancers and 10% of ovarian cancers are attributed to an inherited predisposition [2,3]. Given the current incidence of these diseases in the United States, hereditary cancer syndromes will lead to approximately 2200 new cases of ovarian cancer and 2300 new cases of endometrial cancer in 2011 [4].

HBOC Syndrome

HBOC syndrome is caused by mutations in the BRCA1 or BRCA2 genes. These genes were initially identified and cloned in the early 1990s [5,6]. The prevalence of mutations in BRCA1 and BRCA2 among the general population has been estimated to be 1 in 400 [7].

BRCA mutation carriers are also at risk of many other cancers. The other rare cancers reported to be associated with BRCA mutations are male breast, pancreatic, melanoma Biliary cancer and prostate cancers, although lifetime risk of these cancers is low compared with female breast and ovarian cancer. The melanoma and biliary cancers, have also been reported to occur in BRCA carriers [8-12].

It is being noted that 5% of endometrial carcinomas and 20% of epithelial ovarian cancers are hereditary [13-15]. These are autosomal dominant disorders, Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (formerly referred to as Hereditary Nonpolyposis Colorectal Carcinoma, HNPCC) causes the majority of this inherited susceptibility [16]. The other rare syndromes such as Cowden, Peutz-Jeghers and Li-Fraumeni can also manifest with gynaecological malignancies. Besides, recent Genome-Wide Association Studies (GWAS) have highlighted the role of lower-penetrance variants in gynaecological cancer. It is important to identify those at increased risk in order to ensure that optimal preventive and treatment strategies are offered to women and their families [17].

Hereditary Breast and Ovarian Cancer

The BRCA1 and BRCA2 genes were first identified and cloned in the early 1990s [18, 19]. Women with a BRCA1 mutation have a lifetime risk of ovarian cancer of 63% and of breast cancer of up to 85%. Lifetime risks of ovarian and breast cancers in women among BRCA2 carriers are reported to be up to 27% and 84% respectively [20,21].

Lynch Syndrome

The Lynch syndrome is caused by mutations in the DNA Mismatch Repair (MMR) genes (MSH2, MLH1, MSH6, and PMS2) [22-25]. This condition causes an increased risk of early-onset cancer of multiple types, including colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, and brain, ureteric and renal pelvic cancers [26]. The lifetime risk for endometrial cancer is 40-60% whereas there is a risk of 3% in the general population. However, this risk may exceed the risk of colorectal cancer for women with Lynch syndrome, especially those that carry an MSH6 mutation [27]. Whereas, for ovarian carcinoma, the risk is 10-12% compared with the general population risk of 1.4% [28].

Cowden syndrome

Cowden syndrome is caused by germline mutations in the tumour suppressor gene PTEN and causes PTEN Hamartoma Tumour Syndrome (PHTS), encompasses the autosomal dominant conditions Cowden Syndrome (CS), in adulthood, and Bannayan-Riley-Ruvalcaba syndrome in children. CS is a cancer predisposition syndrome characterised by macrocephaly, multiple hamartomas and an increased risk of breast, thyroid and endometrial cancers, as well as colorectal, melanoma and renal cell carcinoma [29]. Though the penetrance of this condition is high, there is significant variability in its manifestation among families.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is caused by germline mutations in the STK11 gene. It is an autosomal dominant gastrointestinal polyposis disorder with an increased risk of breast, gastrointestinal and gynaecological tumours. The women have high characteristic pigmented lesions on the lips and buccal mucosa. Women with PJS have risk of developing sex cord stromal tumours with annular tubules of the ovary and adenoma malignum of the cervix.

Li-Fraumeni syndrome

Li-Fraumeni Syndrome (LFS) is caused by germline TP53 mutations. The important features of this condition are young-onset sarcomas, breast cancer, adrenocortical carcinoma and childhood tumours [30]. Gynaecological malignancies are not common. Though the most commonly diagnosed condition is epithelial ovarian carcinoma.

Management of Familial Gynaecological Cancer

Risk assessment

At present, risk assessment is based largely upon information derived from a detailed family history tree. Important information includes the number of cases of cancer relative to the number of people at risk, the pattern of cancers of different types, and the age at diagnosis of cancer.

It is difficult to define the minimum family history necessary to satisfy the description of a familial cancer syndrome involving a gynaecological cancer.

- Families in which two first-degree relatives have proven ovarian cancer;
- Families in which first-degree relatives have breast cancer at less than 50 years of age and ovarian cancer; and
- Families in which two first-degree relatives have breast cancer at less than 60 years of age and a third relative has ovarian cancer.

The high frequency of cancer in such families is due to an inherited predisposition rather than a chance event and the likelihood is in excess of 60%. Families in which at least one relative

has ovarian or endometrial cancer and two or more first-degree relatives have cancer of the colon/rectum with at least one relative having cancer at less than 50 years of age, can be classified as HNPCC families.

Prevention of familial cancer

Use of the oral contraceptive pill may be suggested for HNPCC and breast/ovarian cancer family members which indicate a protective effect against ovarian & endometrial cancer. Furthermore, there is concern in breast/ovarian cancer families that a reduction in risk of ovarian cancer may be offset by an increased risk of breast cancer.

Prophylactic salpingo-oophorectomy and hysterectomy as a primary procedure is justifiable in women from breast/ovarian cancer and HNPCC families after completion of their family and after thorough counselling. There is convincing evidence that salpingo-oophorectomy is an effective method of prevention of cancer of the ovary, fallopian tube and breast. Women undergoing prophylactic surgery should be counselled that the procedure will prevent ovarian and tubal cancer, but that they may still be at risk of primary peritoneal cancer for which complete peritonectomy is required.

Summary

Although the majority of gynaecological cancers are sporadic, it is important that those cancers caused by an inherited predisposition are identified. Clinicians should be alert to the possibility of a hereditary condition when managing women with gynaecological cancer.

This ensures that patients and family members have information about chemoprevention, surveillance, risk-reducing surgery and psychological support and are referred appropriately. Notably, this involves a multidisciplinary team that enables women to have tailored management based on their individual medical history and preferences.

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