Family history of gynaecological cancers

Carol Gardiner

Abstract

Women are presenting to primary and secondary care with concerns about a family history of ovarian and breast cancer, or ovarian, endometrial and bowel cancer. Although most ovarian and endometrial cancer is sporadic, about 5–10% is due to mutations in genes which predispose to breast/ovarian cancers, *BRCA1* and *BRCA2*, and ovarian/endometrial and bowel cancer, the mismatch repair genes of hereditary non-polyposis colon cancer (HNPCC). This review considers different scenarios in women presenting with a family history of ovarian and endometrial cancer. It uses these family histories to illustrate the ways in which families at high risk of ovarian and endometrial cancer can be identified by pedigree analysis. There will be further discussion about these genes and the different management options available to families, including surveillance, chemoprevention and prophylactic surgery.

Keywords endometrial cancer; family history; gene mutations; ovarian cancer; prophylactic surgery; risk; surveillance

Introduction

Epithelial ovarian cancer is the sixth most common female malignancy, representing about 90% of all malignant ovarian neoplasms and approximately one quarter of all genital tract cancer in women. Survival rates have not improved dramatically over the past 30 years, which is thought to be related to the advanced stage of the disease at presentation. For a woman in the UK, the lifetime risk of ovarian cancer is 1.25%. Endometrial cancer is the most common gynaecological cancer, with a lifetime risk of 2.7% and an overall 5-year survival of 86% due to early disease presentation. Epidemiological studies have shown a significantly increased risk of several different cancers in first-degree relatives of women with ovarian cancer, indicating a possible genetic component in some women. This review gives four illustrative scenarios to enable the identification of women at higher risk of ovarian or ovarian and endometrial cancer based on pedigree analysis and will discuss the management options for this group of women, which will allow modification of their disease risk.

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Scenario 1: a single case of ovarian cancer

A 35-year-old woman presents to her GP clinic with concerns about her risk of developing ovarian cancer. Her mother has recently died from epithelial ovarian cancer at age 57 years. On taking a family history to include all first-degree relatives (parents, children and siblings), second-degree relatives (grandparents, grandchildren, aunts and uncles) and third-degree relatives (cousins), no other people with cancer are identified (Figure 1).

When taking a family history, it is important to take the history from the paternal as well as the maternal side as genes that predispose to ovarian cancer are just as likely to be inherited from the paternal side of the family.

After controlling for age, the most important risk factor for ovarian cancer is a family history of ovarian cancer. Estimates of the proportion of ovarian cancers due to inherited genes vary from 5% to 10%. For women with a family history of ovarian cancer in a first-degree relative compared to those with no family history the odds ratio is 1.9 – 2.7, which for a woman of 35 equates to a lifetime risk of 5%. This risk falls as the women get older without developing ovarian cancer so that by the age of 70 the risk has fallen to 1%. The risk appears greater for sisters and daughters of the affected individual rather than the mother for reasons that are not clear but which may include the effects of parity.

This family history, with just one case of ovarian cancer and no other related cancers, would fall into the low-risk category and ovarian surveillance is not recommended in this situation. A family history of isolated ovarian cancer becomes high risk if there are two or more cases of ovarian cancer in women who are first-degree relatives of each other, or two women with ovarian cancer on the same side of the family separated by a male intervening relative. The relative risk of ovarian cancer in first-degree relatives rises to 7.18, corresponding to a lifetime risk of 11% by age 70. Families with this family history would fulfil the clinical high-risk category and current guidelines for ovarian surveillance.

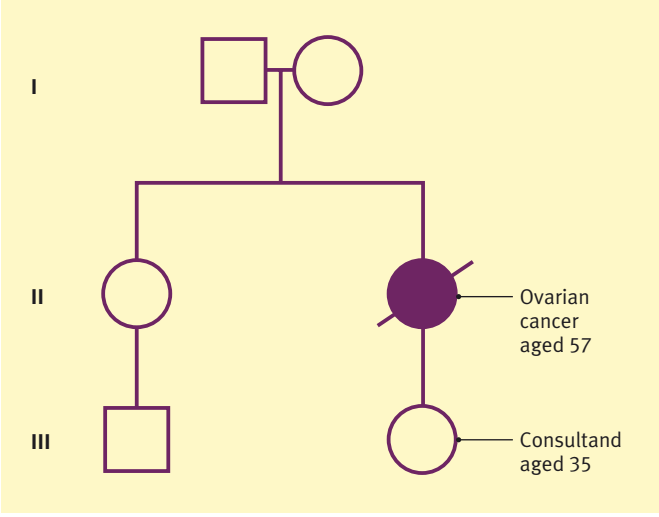

Figure 1 Scenario 1: a single case of ovarian cancer.

Scenario 2: ovarian cancer in association with a family history of breast cancer

A 40-year-old woman presents with a family history of breast and ovarian cancer. A detailed pedigree shows that her sister was diagnosed with breast cancer at 35 years, her mother was diagnosed with ovarian cancer at 45 years, her maternal grandmother died from breast cancer at 55 years, her maternal aunt was diagnosed with breast cancer at 49 years and a cousin, the daughter of her maternal uncle, was diagnosed with breast cancer at 39 years (Figure 2). She is concerned about her risk of developing these cancers.

This is a very significant family history of breast and ovarian cancer and there is a high probability that there is an underlying genetic cause. Families at high risk of developing ovarian cancer are those that fulfil any of the following criteria:

- The family contains two or more individuals with ovarian cancer at any ages who are first-degree relatives of each other.
- The family contains one individual with ovarian cancer at any age and one individual with breast cancer diagnosed before the age of 50, who are first-degree relatives of each other.
- The family contains one individual with ovarian cancer at any age and two individuals with breast cancer diagnosed under 60 years of age, who are first-degree relatives of each other.
- The family contains three individuals with cancer, two of whom have colorectal cancer with at least one case diagnosed before 50 years of age and one case of ovarian cancer connected by first degree relationships.
- The family contains an affected individual with a pathogenic mutation in one of the known ovarian cancer predisposition genes.

Evidence of paternal transmission is also acceptable or a male intervening relative between two affected women on the same side of the family.

There are problems associated with using pedigree information to assess risk. Many families nowadays are not large enough to reach the above criteria, and families with a preponderance of males may also not reach the criteria, despite carrying a mutation in an ovarian cancer susceptibility gene. Despite these caveats, it still remains the most useful tool for assessing risk.

Two genes have been identified that predispose to both breast and ovarian cancer – *BRCA1* and *BRCA2*. These genes show autosomal dominant inheritance with high penetrance and can be inherited from either the mother or father.

BRCA1

BRCA1 is located on the long arm of chromosome 17 and encodes a protein of 1863 amino acids, which appears to be involved in transcription-coupled repair of DNA damage, is a tumour suppressor gene and may interact with many other proteins, including other tumour suppressors and proteins that regulate cell division. Mutations in *BRCA1*:

- Account for the majority (about 75%) of families with inherited ovarian cancer.
- Are carried by about 0.11% of women in the general population.
- Have a higher carrier frequency in certain populations, notably the Ashkenazi Jewish population where about 1 in 100 women are carriers, accounting for the high incidence of ovarian cancer in this population.

Studies looking at families with four or more relatives with breast/ovarian cancer with *BRCA1* mutations indicate that the cumulative risk for ovarian cancer is 29% by age 50 and 44% by age 70. The risk for breast cancer is higher in these families, with 51% developing breast cancer by age 50 and 85% by age 70. There appears to be a genotype/phenotype correlation with mutations in *BRCA1*, with the highest ovarian cancer risk being associated with mutations in the 5' third of the gene.

BRCA2

BRCA2 is located on the long arm of chromosome 13 and encodes a protein of 3418 amino acids, which appears to be involved directly in the repair of damaged DNA, is a tumour suppressor gene and may interact with many other proteins, including other

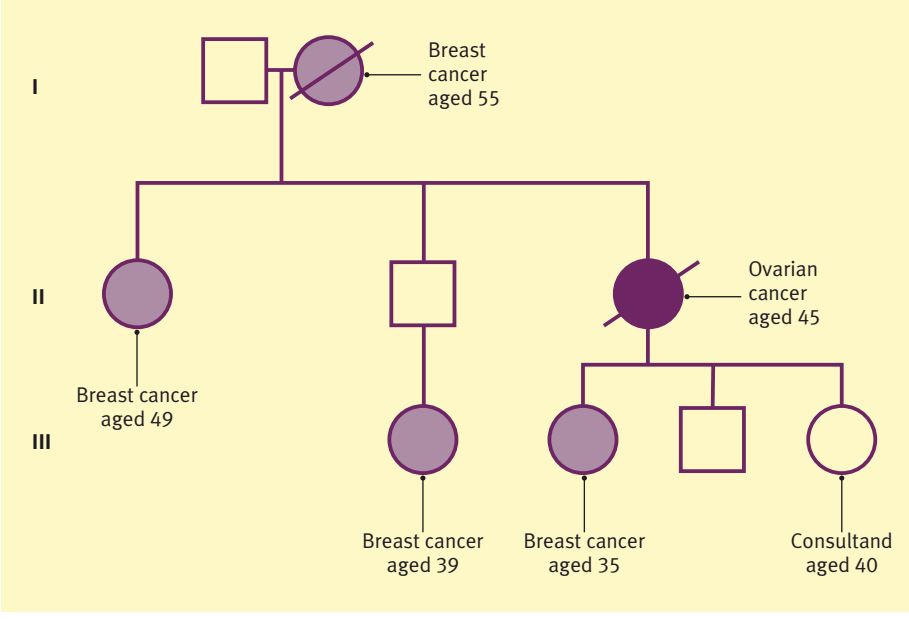

Figure 2 Scenario 2: ovarian cancer in association with a family history of breast cancer.