Familial ovarian malignancy

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Familial ovarian cancer is a subset of ovarian cancer where there appears to be a definable genetic link in families. It accounts for less than 5% of cases of ovarian cancer seen at present. The main genes responsible, BRCA1 and BRCA2, are discussed. Screening and the prophylactic measures for women identified having a genetic trait are discussed.

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Ovarian cancer is diagnosed in 5400 women each year in England and Wales and approximately 70% will die from their disease. This cancer is the fourth commonest cause of female cancer death after cancer of the breast, lung and large bowel. Ovarian cancer is predominantly a disease of postmenopausal women with 95% of cases occurring after the age of 45 years. The lifetime risk of ovarian cancer to the age 70 years is 1%. Familial ovarian cancer is a subset of ovarian cancer where there appears to be a definable genetic link in families. It accounts for less than 5% of cases of ovarian cancer seen at present.

Genetic information, which includes information from family history and DNA-based testing, provides a means to identify people who have an increased risk of cancer. Identifying a person with an increased risk of cancer has significant advantages and disadvantages. The intrinsic benefits may include a more informed choice about many life decisions. The benefits of genetic information, and the improvement in quality of life as a result of knowledge about genetic susceptibility, may be accompanied by potential personal and social risks as well, e.g. reduced self-worth, guilt, family disruption, stigmatization, and loss of health, disability or life insurance.

Genetic information may sometimes provide a direct health benefit by demonstrating the lack of an inherited cancer susceptibility. Studies of family history of ovarian cancer suggest a possible association with breast cancer risk. A first-degree relative with ovarian cancer confers little or no risk for breast cancer. The presence of both breast and ovarian cancer in a family increases the likelihood that a cancer-predisposing mutation is present.

TABLE 1.
Genetic disorders associated with ovarian tumours

Carcinoma	BRCA1 mutation carriers
	BRCA2 mutation carriers
	Li–Fraumeni syndrome
	Hereditary non-polyposis colon cancer
Non-epithelial tumours	Puetz-Jeghers syndrome (sex cord and granulosa cell tumours)
	Gorlin's syndrome (ovarian fibroma)
	Ollier's syndrome (granulosa cell tumours)
	Mafucci's syndrome (granulosa cell tumours)
	Gonadal dysgenesis (gonadoblastoma)

AUTOSOMAL DOMINANT INHERITANCE OF BREAST AND OVARIAN CANCER PREDISPOSITION

The syndromes most associated thus far with an autosomal dominant inheritance are increased susceptibility to breast and ovarian cancer resulting from BRCA1 or BRCA2 mutations and Li–Fraumeni syndrome resulting from p53 mutations. Mutations in each of these genes produce different clinical phenotypes of characteristic malignancies and, in some instances, associated non-malignant abnormalities (*Table 1*). Ovarian cancer has also been associated with hereditary non-polyposis colon cancer (HNPCC). Statistical models have been developed to estimate a person's chance of having a BRCA1 or BRCA2 mutation based on personal and family history characteristics.

The family characteristics that suggest an autosomal dominant inheritance of a cancer predisposition gene include the following:

Vertical transmission of cancer predisposition
Vertical transmission refers to the presence of a genetic predisposition in sequential generations; to have the cancer predisposition gene, a person must inherit it from a parent

Males and females can inherit a cancer predisposition gene
However, a male who inherits a cancer predisposition gene and shows no evidence of it can still pass the predisposition on to his offspring

Inheritance risk of 50%
When a parent carries an autosomal dominant genetic predisposition, each child has a 50% chance of inheriting the predisposition

Other clinical characteristics
Cancers in people with an autosomal dominant predisposition gene typically occur at an earlier age than in sporadic cases (defined as cases not associated with genetic risk) and are more often multifocal or bilateral. Most known mutations that increase breast cancer risk also appear to increase risk for ovarian cancer and may increase risk of other cancers as well.

Primary cancers in a single individual
These could be multiple primary cancers of the same type (bilateral breast cancer) or primary cancer of different types, breast and ovarian cancer in the same individual.

Epidemiological studies have clearly established the role of family history as an important risk factor for ovarian cancer (Sutcliffe et al, 2000).

BRCA1/BRCA2

In 1990, a susceptibility gene for breast cancer called BRCA1 was mapped by genetic linkage to the long arm of chromosome 17, in the interval 17q12–21, and evidence for the coincident transmission of both breast and ovarian cancer susceptibility in linked families was observed (Hall et al, 1990). The BRCA1 gene was subsequently identified by positional cloning and has been found to contain 24 exons which encode a protein of 1863 amino acids. BRCA1 appears to be responsible for up to 90% of families with both breast cancer (four or more cases diagnosed in patients under the age of 60 years) and ovarian cancer (Easton et al, 1993).

A second breast cancer susceptibility gene, BRCA2, was localized to the long arm of chromosome 13 through linkage studies of 15 families with multiple cases of breast cancer that were not linked to BRCA1. Mutations in BRCA2 are also associated with ovarian cancer, prostate cancer, male breast cancer and pancreatic cancer (Gayther et al, 1997; Wooster et al, 1994). BRCA2 is also a large gene with 27 exons that encodes a protein of 3418 amino acids. Although not homologous genes, both BRCA1 and BRCA2 have an unusually large exon 11 and translational start sites in exon 2. Like BRCA1, BRCA2 is a tumour suppressor gene with loss of the unmutated allele found in tumour specimens.

BRCA1 AND BRCA2 FUNCTION

Women carrying germline mutations in BRCA1 or BRCA2 have a high lifetime risk for developing breast and or ovarian cancer. Both proteins are normally located in the nucleus and contain phosphorylated residues (Bertwistle et al, 1997; Chen et al, 1996). BRCA1 contains only two recognizable protein motifs, a RING finger domain near the N-terminus and a BRCT domain at the C-terminus. RING fingers are cysteine-rich sequences that coordinate the binding of two zinc ions and may facilitate both protein–protein and protein–DNA interactions. Both BRCA1 and BRCA2 are expressed in most tissues and cell types analysed, demonstrating that it is not tissue specific expression that leads to the phenotype of breast and ovarian cancer. A variety of evidence points to BRCA1 and BRCA2 being directly involved in the DNA repair process, suggesting that both hereditary susceptibility genes, e.g. p53, are involved in the complex pathways which maintain genomic integrity (Zhang et al, 1998).

Mutations in BRCA1 and BRCA2
Over 600 mutations and sequence variations in BRCA1 have already been described. While a small number of these mutations have been found repeatedly in unrelated families, the vast majority have not been reported in more than a few families. An estimated 30% of all BRCA1 mutations, including large genomic deletions and mutations that interfere with expression or stability of the BRCA1 transcript, are undetected by current technologies.

Prevalence and founder effects in BRCA1/BRCA2
Approximately 1 in 800 individuals in the general population may carry a pathogenic mutation in BRCA1. A family history of ovarian cancer in a first degree relative was also associated with an increased prevalence of BRCA1

mutations (25%, 95% confidence interval (CI) 3.2–65.1%). BRCA1 mutations were found 40% (95% CI 1.7–80.0%) of families with both breast and ovarian cancer (Couch and Hartmann, 1998).

In some cases the same mutation has been found in multiple unrelated families. This observation is consistent with the 'founder effect.' This occurs when a contemporary population can be traced back to a small isolated group of founders. Notably, a specific BRCA1 mutation (185delAG) and a BRCA2 mutation (6174delT) have been reported to be common in Ashkenazi Jews (those tracing their roots to Central and Eastern Europe). Carrier frequencies for these mutation have been determined in the general Jewish population, 1.1% for the BRCA1 185delAG mutation and 1.5% for the BRCA2 6174delT mutation.

Altogether, the frequency of these two mutations is approximately 1 in 50 among Ashkenazi Jews, and accounts for up to 90% of families with multiple cases of both breast and ovarian cancer in this group. Additional founder mutations have been described in the Netherlands (BRCA1 2804delAA and several large deletion mutations) and Iceland (BRCA2, 995del5).

The presence of these founder mutations has practical implications for genetic testing. Many laboratories offer directed testing specifically for 'ethnic specific' alleles. This greatly simplifies the technical aspects of the test but is not without pitfalls. Some Ashkenazi Jewish cancer families also carry mutations other than 185delAG and 6174delT.

Penetrance of mutations in BRCA1/BRCA2

The percentage of individuals carrying a given mutation that will manifest the disease is referred to as penetrance. Estimates of penetrance for BRCA1 and BRCA2 mutations range from 16% to 60% for ovarian cancer and 36% to 85% for breast cancer.

Ovarian cancer risk in carriers of these founder mutations is estimated to be 16% (95% CI 6–28%). These values are lower than risk estimates based on family studies alone. Men carrying BRCA1 and BRCA2 mutations are at a modestly increased risk of prostate cancer. Neither male nor female carriers are at an increased risk of colonic cancer.

Pathology and prognosis in BRCA1/BRCA2

Large studies with appropriate control populations will be required to determine if a survival advantage truly exists in BRCA1-related ovarian cancers. Although small series reported to date suggest that survival in BRCA1 carriers is better than in matched sporadic controls (Aida et al, 1998; Rubin et al, 1996), survival at present is a conflicting issue (Johannsson et al, 1998).

SCREENING IN FAMILIAL OVARIAN CANCER

In the general population, clinical examination of the ovaries has neither the specificity nor sensitivity to reliably identify early ovarian cancer. No data exist regarding the benefit of clinical examination of the ovaries (bimanual pelvic examination) in women at inherited risk of ovarian cancer.

Limited data are available on the potential benefit of screening with serum CA125 and or ultrasound in women at inherited risk for ovarian cancer. No data are available to address the effectiveness of ovarian cancer screening in preventing deaths from ovarian cancer.

In 1994, the National Institutes of Health (NIH) consensus statement on ovarian cancer recommended against routine screening of the general population for ovarian cancer with serum CA 125 or ultrasound (NIH Consensus Development Panel on Ovarian Cancer, 1995). The NIH consensus statement did, however, recommend that women at inherited risk for ovarian cancer undergo annual or semiannual screening for ovarian cancer with transvaginal ultrasound and serum CA 125. The Cancer Genetics Studies Consortium task force recommended that this screening start at 25 to 35 years of age. A phase II trial evaluating annual transvaginal ultrasound and serial CA 125 levels in 3000 high-risk women registered in the familial ovarian cancer screening (UKCCCR) study is currently underway.

ORAL CONTRACEPTIVES IN FAMILIAL OVARIAN CANCER

Oral contraceptives have a limited impact on the risk of ovarian cancer among women with a BRCA1 high-risk mutation or women at inherited risk of ovarian cancer. Women who took oral contraceptives for more than 6 years had a 60% reduction in risk. This reduction was similar for BRCA1 and BRCA2 high-risk mutation carriers.

PROPHYLACTIC OOPHORECTOMY IN FAMILIAL OVARIAN CANCER

Several case series of women at inherited risk for ovarian cancer suggest that prophylactic oophorectomy may decrease the risk of ovarian cancer (Struewing et al, 1995). However, the

peritoneum appears to remain at risk for the development of a Mullerian-type adenocarcinoma even after oophorectomy (Piver et al, 1993).

The NIH consensus statement on ovarian cancer recommended that women at inherited risk of ovarian cancer undergo prophylactic oophorectomy after completion of childbearing or at age 35 years. The Cancer Genetic Studies Consortium concluded that:

> **'there was insufficient evidence to recommend for or against prophylactic oophorectomy as a measure for reducing ovarian cancer risk.'**

In our practice, women from high-risk families are entered into the UKCCCR screening study. Information is given to them with respect to prophylactic oophorectomy. We perform a bilateral salpingo-oophorectomy using the laparoscopic approach if possible. In a consecutive series of 28 patients, there has only been one case where the procedure could not be completed laparoscopically. One patient was admitted 1 week after surgery with suspected small bowel obstruction which settled with conservative management.

All women are warned before the laparoscopic surgery that there is a small (undefined) chance of finding an unsuspected carcinoma. In the event of this finding confirmed by histology, the definitive cancer surgery is offered within 1 week. We do not routinely remove the uterus except in women with a history of HNPCC and those women who have gynaecological problems requiring hysterectomy in its own right.

CONCLUSION

Familial ovarian cancer accounts for a small proportion of women with ovarian cancer. However, with the identification of specific genes related to this condition women can be offered screening and prophylactic surgery before developing a cancer. Management of these women at a regional cancer genetics clinic allows correct identification of at-risk families. These patients are assured the best information relating to their condition with both expertise and the psychological and emotional support necessary. HM

Conflict of interest: none.

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KEY POINTS

- The lifetime risk of sporadic ovarian cancer to the age of 70 years is 1%.
- Familial ovarian cancer is a subset of ovarian cancer where there appears to be a definable genetic link in families that accounts for less than 5% of cases of ovarian cancer seen at present.
- The genetic syndromes most associated with an autosomal dominant inheritance of ovarian cancer are the result of BRCA1 or BRCA2 mutations and Li–Fraumeni syndrome the result of p53 mutations. Ovarian cancer has also been associated with hereditary non-polyposis colon cancer.
- BRCA1 and BRCA2 are directly involved in the DNA repair process and act as tumour suppressor genes.
- Approximately 1 in 800 individuals in the general population may carry a pathogenic mutation in BRCA1.
- The familial ovarian cancer screening study (UKCCCR) is currently underway screening 3000 high-risk women using ultrasound and CA-125.
- Prophylactic bilateral salpingo-oophorectomy may reduce the risk of ovarian cancer, although there is still a background risk of primary peritoneal cancer even after surgery.