Screening for breast and ovarian cancer: the relevance of family history

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The recent identification of two breast and ovarian cancer susceptibility genes - BRCA1 and BRCA2 - has received a lot of publicity. Public and professional expectations of the availability and utility of genetic testing have been raised and the importance of a family history of breast cancer overemphasised. In this chapter, we examine the significance of a family history of breast or ovarian cancer in determining individual risk. A strategy for management is proposed, based on stratifying women with such a history into three different categories of risk for breast cancer: high, moderate and low. Some of the more controversial aspects of screening for breast and ovarian cancer are reviewed, including the issue of management of women who are at increased risk of these cancers by virtue of a family history, genetic predisposition, or both. There is a need for further research to clarify the most appropriate management of those at moderate risk of developing these cancers. A management strategy for women at high risk is proposed. We believe that adoption of this strategy will strengthen consistent information giving from primary to tertiary care.

The recent identification of the breast and ovarian cancer susceptibility genes BRCA1 and BRCA2 has fostered an unrealistic expectation that genetic tests will become readily available, together with an assumption that identifying women who carry a mutation in one of these genes will be of benefit to them. The importance of a family history of breast and ovarian cancer has been overemphasised, with many women seeking medical attention because they perceive themselves to be at substantial risk of inherited breast cancer. It is possible to identify women at increased risk of breast or ovarian cancer through a positive family history, as well as women who are at very high risk because they carry an alteration in one of the known breast cancer susceptibility genes. However, the most appropriate way of managing that risk is less clear.

In this paper, familial breast and ovarian cancer risks are reviewed, together with the evidence for the effectiveness of different strategies to manage that risk. We propose a strategy, based on existing evidence, for
Table 1 Relative risk (95% CI) of breast cancer by age of subject and age of affected relative

<table>
<thead>
<tr>
<th>Age of affected relative</th>
<th>&lt; 50 years</th>
<th>≥ 50 years</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>3.3 (2.8, 3.9)</td>
<td>1.8 (1.6, 2.0)</td>
<td>2.3 (2.2, 2.5)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>1.8 (1.5, 2.2)</td>
<td>1.7 (1.5, 2.0)</td>
<td>1.8 (1.6, 2.0)</td>
</tr>
<tr>
<td>All ages</td>
<td>2.4 (2.2, 2.7)</td>
<td>1.9 (1.8, 2.0)</td>
<td>2.1 (2.0, 2.2)</td>
</tr>
</tbody>
</table>

Any first degree relative

<table>
<thead>
<tr>
<th>Mother</th>
<th>&lt; 50 years</th>
<th>≥ 50 years</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>2.5 (1.6, 3.8)</td>
<td>1.7 (1.1, 2.6)</td>
<td>2.0 (1.7, 2.4)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>1.6 (1.1, 2.3)</td>
<td>1.7 (1.2, 2.4)</td>
<td>1.7 (1.5, 2.0)</td>
</tr>
<tr>
<td>All ages</td>
<td>2.2 (1.9, 2.6)</td>
<td>1.8 (1.6, 2.1)</td>
<td>2.0 (1.8, 2.1)</td>
</tr>
</tbody>
</table>

Sister

| < 50 years | 3.3 (2.1, 4.5) | 1.8 (1.2, 2.4) | 2.7 (2.4, 3.2) |
| ≥ 50 years | 3.0 (1.4, 4.6) | 1.9 (1.1, 2.7) | 2.0 (1.7, 2.4) |
| All ages | 3.0 (2.5, 3.5) | 2.0 (1.8, 2.3) | 2.3 (2.1, 2.4) |

Any second degree relative

| All ages | 1.7 (1.4, 2.0) | 1.6 (1.3, 2.0) | 1.5 (1.4, 1.6) |

managing women at increased risk of breast and ovarian cancer because of family history.

Breast cancer

Incidence and mortality

Breast cancer is the commonest cancer in women in westernised countries, and is responsible for 20% of all female cancers. In the UK, around 1 in 12 women will develop breast cancer at some time in their life. In the UK in 1991, there were 34,500 women newly diagnosed with the disease and around 14,000 deaths. Breast cancer is rare in women in their teens or early twenties, but the incidence rises with age, so that most cases occur in postmenopausal women (80%). About 15% of women with breast cancer have a family history of the disease and 5% of all cases may be caused by cancer predisposition genes. The prevalence of cancer predisposition genes is higher in young women diagnosed with breast cancer. For example a mutation in BRCA1 will be found in about 10% of women with breast cancer diagnosed before the age of 40 years.
**Familial breast cancer**

In this paper, we consider two main types of breast cancer: **genetic breast cancer**, which occurs in women with an alteration in a breast cancer susceptibility gene which has been inherited through the germline (this is synonymous with **inherited** breast cancer); and **sporadic** breast cancer, which occurs in women with no such predisposition. **Familial** breast cancer occurs in women who have a relative with breast cancer, and includes either sporadic or genetic breast cancer. This is because familial clustering of breast cancer may occur by chance, or as a consequence of increased genetic susceptibility, or shared environmental or lifestyle risk factors.

All women with a family history of breast cancer are at increased risk of breast cancer themselves. However, the extent of that risk will vary according to the nature of the family history, specifically which relative was affected, their age at diagnosis, the number of relatives affected, as well as the age of the woman concerned. The relative risks associated with different family histories have been summarised in a recent systematic review and meta-analysis (Table 1)\(^1\). However, the risk categories described in most studies are simple, being usually based on single factors. The risks associated with more complex histories are difficult to establish. For example, it is difficult to estimate with any precision the risk of breast cancer in a 40 year old woman with three sisters, whose mother and oldest sister developed breast cancer at the age of 65 and 51 years, respectively.

**Genetic breast cancer**

Epidemiological studies suggest that much of the familial clustering of breast cancer is due to the inheritance of dominant predisposing genes. The risks of breast cancer associated with these genes vary. Some, such as the BRCA genes, are associated with an absolute life-time risk of breast cancer of 70% or more, while others, such as some alleles of HRAS1, are associated with a life-time risk of 15%. Three major breast cancer susceptibility genes have now been identified: BRCA1, BRCA2 and p53. BRCA1 and BRCA2 are between them responsible for the majority (84%) of families with 4 or more members affected with either breast cancer before 60 years of age or ovarian cancer\(^2\). Germline mutations in p53 are rare and account for a tiny proportion of breast cancer cases (< 1%)\(^3\). The proportion of smaller families, that is those with only two or three affected members, which are due to BRCA1 or BRCA2 mutations is still unclear, but may be considerably lower. Population frequencies of the known breast cancer susceptibility genes are given in Table 2.
Table 2 Population frequencies of known breast cancer susceptibility genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Population carrier frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>0.006%</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>0.006%</td>
</tr>
<tr>
<td>HRAS1 rare allele</td>
<td>6%</td>
</tr>
<tr>
<td>AT mutation</td>
<td>1%</td>
</tr>
</tbody>
</table>

Breast and ovarian cancer risks

The risk of breast cancer in women with mutations in BRCA1 has been estimated indirectly from data collected on linkage families, as well as directly for women carrying one of the three Ashkenazim founder mutations (Table 3). The risk of breast cancer conferred by BRCA2 seems to be similar, but the risk of ovarian cancer is much lower. Estimates of risk using linkage families are likely to be too high, while so-called direct estimates from a highly select population with 3 common founder mutations may be too low. It is, therefore, likely that the true risk lies somewhere between these two estimates.

Table 3 Breast and ovarian cancer risks associated with mutations in BRCA1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Cumulative breast cancer risk % (95% CI)</th>
<th>Cumulative ovarian cancer risk % (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>51 (25-67)</td>
<td>23 (5-38)</td>
<td>Ford et al</td>
</tr>
<tr>
<td>70</td>
<td>85 (51-95)</td>
<td>63 (25-82)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>33 (23-44)</td>
<td>7 (2-14)</td>
<td>Streuwing et al</td>
</tr>
<tr>
<td>70</td>
<td>56 (40-73)</td>
<td>16 (6-28)</td>
<td></td>
</tr>
</tbody>
</table>

Mutations in more common genes, such as HRAS1, have been shown to confer a moderately increased risk of breast cancer. The so called ‘rare’ alleles of HRAS1, which are associated with an increased risk of breast cancer, are present in about 6% of the population. Because they are so common in comparison to BRCA1, the attributable risk is estimated at 9%, over twice as much as for BRCA1. Other candidate ‘low risk’ breast cancer genes for which there is already some evidence include the ataxia-telangiectasia gene and the vitamin D receptor gene.

Breast cancer screening

There are several potential methods for primary prevention, i.e. reducing the likelihood of developing breast cancer, including chemoprevention, prophylactic mastectomy and lifestyle modification, but discussion of...
these options is outside the scope of this article. Possible methods for early
detection (secondary prevention) include breast self-examination, clinical
breast examination and regular mammography.

Good evidence for the effectiveness of breast self-examination is lacking.
The results of observational studies have been conflicting\(^6\)-\(^{10}\), and
preliminary results from a randomised controlled trial failed to show
benefit\(^11\). Approximately 10% of breast cancers may be detected by
clinical examination alone. Expert panels have suggested that clinical
examination provides a useful adjunct to mammography in women at
very high risk of breast cancer\(^12\).

The mainstay of early detection of breast cancer is regular screening of
the breasts by mammography. Before considering the merits of
mammography in those at high risk, the arguments for and against
mammographic screening in women of average (or population) risk need
to be rehearsed and interpreted with respect to women at increased risk.
We will, therefore, review the contentious issues around screening in
general, before discussing the role of mammography in those at high risk.

The UK National Breast Screening Programme offers three yearly
mammography to women between the ages of 50 and 64 years. Women
over the age of 64 years can continue screening if they specifically
request it. The effectiveness of mammography for women aged 50–69
years of general population risk has been confirmed by several
randomised controlled trials. Meta-analyses of these trials have shown
that mammography will produce a relative reduction in breast cancer
mortality of around 30% in these women\(^13\). The absolute reduction in
risk is, however, small and it has been argued that the high financial
costs of a screening programme outweigh the marginal clinical
benefit\(^14,15\). The effectiveness of mammographic screening in younger
women is controversial. A US National Cancer Institute workshop
concluded that there was no proof of benefit for women under the age of
50 years\(^16\), though evidence of benefit in women aged 40–49 years is
mounting\(^17\) and some groups, including the American Cancer Society,
recommend screening for women aged 40–49 years. Even if the relative
risk reduction were the same as in older women, the absolute benefit
would be considerably reduced because breast cancer is less common in
this age group.

The potential harm caused by mammographic screening includes the
false reassurance of women with a false negative mammogram, the
adverse effects of unnecessary investigation of false positives and a
potential increased cancer risk associated with early and repeated
radiation exposure\(^18\). In true positives, there is the possibility of adverse
effects arising from methods used to confirm a presumptive positive
screening result. In small lesions detected by mammography, diagnosis is
usually confirmed by fine needle aspiration or core biopsy, and this may
result in the seeding of cancer cells along biopsy needle tracks\textsuperscript{19,20}. Thus, a tumour which may otherwise have remained localised could be inadvertently spread. Factors such as these have been suggested to explain the reduced mortality benefit seen in the most recent screening trials\textsuperscript{21}.

Perhaps the most serious concern is the generation of false positive results. About 5\% of women screened will have a mammographic abnormality, of whom only 10–20\% will subsequently be found to have cancer\textsuperscript{22}. A positive or suspicious mammogram inevitably leads to further studies or interventions including fine needle biopsy or open biopsy, all of which have an associated morbidity. In addition, until given the ‘all clear’, the fear and anxiety that go hand in hand with a possible diagnosis of cancer may be considerable in women with a false positive screening test.

The issues discussed above relate to women of general population risk, but the benefit:harm ratio may be quite different in women at increased risk because of family history. Various authors have argued that because women with a family history are at greater risk it is likely that the absolute benefit will be greater\textsuperscript{12,14,23,24}. This is likely to be true if the performance of the screening test is the same in high risk and average risk women. There is, in addition, the possibility of greater harm from mammography in some groups. For example, some genetic alterations may increase susceptibility to ionising radiation, though many experts believe the benefit of early detection will outweigh the risk\textsuperscript{12}. It has also been assumed that because the prevalence of cancer will be higher in a high risk group, the problem of false positives will be lessened, but no research data are available to confirm this. The biology of familial breast cancer is likely to differ from that of non-familial disease and subtle changes in little understood areas such as the screening–treatment interface could substantially alter the benefit:harm ratio.

In the absence of randomised controlled trial data, it is difficult to make firm recommendations on the value of mammography in women under the age of 50 years with a family history of breast cancer. There is an urgent need to institute a study to evaluate accurately the efficacy and cost-effectiveness of mammographic screening in this group of women.

\textbf{Proposed management}

Given the lack of evidence for benefit of mammography in women at increased risk of breast cancer, we do not believe it is appropriate to offer all women who have a family history of breast cancer mammographic screening outside that currently offered through the National Breast Screening Programme. We propose that women with such a history be classified into one of three groups according to the
Table 4  Criteria for breast cancer risk stratification

**High risk group**
1. Breast/breast ovarian families with 4 or more relatives on the same side of the family affected at any age.
2. Breast cancer (only) families with three affected relatives average age of diagnosis < 40 years.
3. Breast/ovarian cancer families with three affected relatives, average age at diagnosis of breast cancer < 60 years.
4. Families with one member with both breast and ovarian cancer.

**Moderate risk group**
1. One first degree female relative with breast cancer diagnosed under 40 years or 1 first degree male relative with breast cancer diagnosed at any age, or one first degree paternal female relative with breast cancer diagnosed under 60 years, or
2. Two first or second degree relatives with breast cancer diagnosed under 60 years on the same side of the family, or
3. Three first or second degree relatives with breast cancer at any age on the same side of the family, or
4. A first degree relative with bilateral breast cancer diagnosed under 60 years.

**Low risk group**
1. Women with a family history of breast cancer not fulfilling the criteria for the other two groups.

The magnitude of their risk and managed accordingly. The criteria used to stratify women into the three risk groups are given in Table 4. Broadly similar schemes are in use by many centres throughout the UK, the EC and Australia.

**High risk group.** Women in the high risk group are from families with a 20% or greater chance of breast cancer that is caused by a mutation in BRCA1. The probability that any individual in the family has a mutation will depend on her relationship to affected family members. The management of women in this group is best carried out under expert guidance and we recommend referral to a specialist cancer genetics clinic. Expert management would include a discussion of the advantages and disadvantages of instituting mutation searching, the advantages and disadvantages of direct genetic testing in unaffected individuals, and an examination of the available screening and treatment options. Most tertiary centres offer similar advice. There are no UK studies comparing different management strategies in terms of outcome.

**Moderate risk group.** Women in this category are at substantially increased risk of developing breast cancer below the age of 50 – at least 3 times the population risk – because of a positive family history, but are less likely to be carrying a mutation in one of the known breast cancer susceptibility genes. Given the lack of evidence of benefit for screening
for women in this group, no intervention should be offered outside the context of a research study. There has been much discussion about the most appropriate study design: a randomised controlled trial of screening versus no screening in women at high risk would be ideal, but this solution has been considered unworkable because most patients, having been accurately informed of their increased risk, will not accept a no-screen option and, therefore, it would not be possible to assemble a large enough control group to make any conclusions reached significant. A proposal to carry out a national observational study with complete mammographic, surgical and pathological data collection is currently under discussion. A suggested management that could be evaluated by such a study is given in Table 5.

Because precise estimation of risk for minor degrees of family history is difficult, any categorisation according to family history will be crude. Thus, some women falling outside the moderate risk criteria (i.e. they fall into the low risk group) will still have a risk of breast cancer three times greater than that of the general population. However, making great efforts to estimate risk precisely is inappropriate because the most appropriate intervention (if any) for this group of women is not yet clear.

Low risk group. Women in this category are at increased risk of breast cancer because of a positive family history which falls outside the criteria for the moderate risk group. Their relative risk is less than 3 times that for the general population. We do not believe that there is sufficient evidence to warrant mammography before the age of 50 years, but women in this group should be encouraged to enter the National Breast Screening Programme when appropriate.

Table 5 Proposed management of women at moderate risk of breast cancer

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>No mammography</td>
</tr>
<tr>
<td>30–34</td>
<td>Youngest affected first degree relative diagnosed age 40+ years</td>
</tr>
<tr>
<td></td>
<td>No mammography</td>
</tr>
<tr>
<td>30–34</td>
<td>Youngest affected first degree relative diagnosed age ≤ 39 years</td>
</tr>
<tr>
<td></td>
<td>Annual mammography from 5 years before the age of diagnosis of the youngest affected relative</td>
</tr>
<tr>
<td>35–49</td>
<td>Annual mammography</td>
</tr>
<tr>
<td>50 and over</td>
<td>Mammography every 18 months</td>
</tr>
</tbody>
</table>
Ovarian cancer

Ovarian cancer is the most common of the gynaecological malignancies, but is relatively rare compared to breast cancer. There are around 4,500 new cases per year in England and Wales. For the general population, the lifetime probability of developing ovarian cancer is 1 in 70 and the lifetime risk of death from ovarian cancer is approximately 1 in 120. Clinical staging of ovarian cancer is by the International Federation of Obstetrics and Gynaecology classification, which sub-divides ovarian cancer into four major groups according to the extent of tumour spread at presentation. The four stages are: Stage I, growth limited to one or both ovaries; Stage II, growth limited to one or both ovaries with pelvic extension; Stage III, growth involving one or both ovaries with intraperitoneal metastases outside the pelvis; and Stage IV, growth involving one or both ovaries with distant metastases.

Familial ovarian cancer

For the majority of women with a single affected first degree relative with ovarian cancer their risk of developing ovarian cancer is small. Their lifetime risk of developing ovarian cancer up to the age of 70 years is approximately 4%, equivalent to a relative risk of 3.1 (95% CI = 2.6–3.7). However, for women with more than one relative with ovarian cancer, the relative risk is 11.7 (95% CI = 5.3–25.9), which is equivalent to a lifetime risk of 14%. This lifetime risk will be higher if the two cases are first degree relatives of the proband. Certain other women may also be at a higher risk of ovarian cancer, such as those with a first degree relative with ovarian cancer and a breast cancer which has occurred under the age of 50 years, or two relatives with breast cancer diagnosed before 60 years on the same side of the family and who are first degree relatives, i.e. breast/ovarian cancer families. Women from some hereditary non-polyposis colorectal cancer (HNPCC) families, where a first degree relative has ovarian cancer, may also have a higher risk compared to women with only a single affected first degree relative with ovarian cancer.

Genetic ovarian cancer

Approximately 5–10% of ovarian cancers are inherited and three distinct hereditary patterns have been identified: ovarian cancer alone; ovarian and breast cancer; and ovarian and colon cancer in HNPCC
families. In most families affected with the breast and ovarian cancer syndrome or site-specific ovarian cancer, genetic linkage has been found to the BRCA1 locus on chromosome 17q21. The lifetime risk for developing ovarian cancer in patients harbouring germ-line mutations in BRCA1 is significantly increased over the general population and confers an ovarian cancer risk of up to 63% by age 70 years (Table 3).

Ovarian cancer screening

As for breast cancer, methods of primary prevention, such as prophylactic oophorectomy, are available, but discussion of these is outside the scope of this article.

Currently available screening strategies for ovarian cancer consist of transvaginal ultrasound and measurement of serum levels of CA125, a protein secreted by many ovarian cancers. The efficacy of these in reducing mortality has not been demonstrated in randomised trials and there are several characteristics of ovarian cancer which suggest that the benefit of screening may be limited. Although ovarian cancer demonstrates a variety of different stages at presentation similar to other carcinomas, the natural history of the condition is not well understood. It is not clear how ovarian cancers progress from early stage disease to advanced disease over a period of time. While this may be true in the majority of cases, there is evidence to suggest that many ovarian cancers may present de novo as advanced disease.

For a screening programme to be successful, not only is it necessary to detect disease at an early stage, but, more importantly, early treatment should be more effective than treatment of advanced disease whilst taking into account lead time bias. There is some doubt whether this is true for ovarian cancer. There have been documented cases of primary peritoneal cancer developing following prophylactic oophorectomy. Similarly, a subset of early stage tumours appear to undergo a rapid downhill course despite adequate treatment. At the other end of the spectrum, women with apparently advanced disease at initial presentation, achieve optimal clearance of tumour at surgery and are cured of their cancer. This would suggest that there are differences in the biology of the cancer, that affect prognosis regardless of stage at presentation.

Ultrasound. While ultrasound is effective at picking up ovarian abnormalities, it is poor at distinguishing benign from malignant pathology. In an early observational study of transabdominal ultrasound, 326 of 5,479 (5.9%) screened women subsequently
underwent laparotomy. Ovarian cancer was found in 9, but only 5 of these were primary cancers of the ovary. Some improvement in specificity can be obtained by using transvaginal sonography (TVS), colour Doppler flow imaging and a morphologic index. A screening trial of TVS yielded persistently abnormal scans in 1.4% of asymptomatic, postmenopausal women. Of these lesions, 90% were found to be benign at follow-up surgery. Both these studies were carried out in women of average risk, and it has been suggested that the false positive rate would be reduced if women at high risk were screened. However, in a study of both transabdominal and transvaginal sonography in self-referred women with a first- or second-degree relative with ovarian cancer, abnormalities requiring surgical exploration were found in 3.8% of screened women, of whom only 10% found to have ovarian cancer (5 of 6 had stage I disease). Five additional cases of cancer not detected by screening (3 ovarian and 2 peritoneal) were reported 2–44 months after the last ultrasound.

CA125. CA125 is a protein secreted by many ovarian cancers. Rising levels in women with previously undetectable or normal levels following treatment for ovarian cancer are a good indicator of recurrent disease, often preceding clinical evidence of recurrence by a period of 6 months. Unfortunately CA125 is not specific for ovarian cancer and levels are raised in many physiological and benign conditions such as pregnancy, menstruation, endometriosis and pelvic inflammatory disease. Perhaps more importantly, however, is the fact that, although 90% of women with ovarian cancer (stage 2 or greater) have elevated levels of CA125, only 50% of women with stage 1 disease have levels above the normal range.

The sensitivity of CA125 for the detection of ovarian cancer has been determined in two case-control studies using serum banks. For CA125 levels of ≥ 35 U/ml, sensitivity was estimated to be 20–57% for cases occurring within the first 3 years of follow-up, with a specificity of 95%. In a prospective cohort study of 9,320 postmenopausal women, 49 cancers were identified. One and five years following screening, a serum CA125 concentration of at least 30 U/ml was associated with a relative risk (95% CI) of cancer of 35.9 (18.3, 70.4) and of 14.3 (8.5, 24.4), respectively. At a CA125 concentration of 100 U/ml, the relative risks were 204.8 (79.0, 530.7) and 74.5 (31.1, 178.3), respectively. Women with CA125 levels below 30 U/ml had risks of 0.13 (0.03, 0.58) and 0.54 (0.32, 0.91), respectively.

In a screening programme using CA125 and based on 22,000 postmenopausal women, those with elevated CA125 levels (reference value of 30 U/ml) were examined subsequently with transabdominal ultrasound. Eleven of 19 cases of ovarian cancer occurring in this cohort...
were detected, an estimated sensitivity of 58% at the two year follow-up and a specificity of 99.9%\textsuperscript{39}. Three of the 11 cancers detected through screening were stage I. Another study of postmenopausal women using both CA125 and ultrasound obtained a specificity of 97.6% for CA125 levels of 35 U/ml\textsuperscript{40}.

As previously discussed, screening women at higher risk because of family history may yield greater absolute benefit. In one study of 386 women with a first-degree relative or multiple second degree relatives with ovarian cancer using ultrasound and CA125, 15 women underwent exploratory laparotomies, 10 as a result of abnormal ultrasound findings alone, 3 as a result of abnormal CA125 levels and ultrasound findings, and 2 women because of rising CA125 levels. No cancer was identified in any of these women, one of whom sustained unrecognised small bowel damage requiring further surgery\textsuperscript{40}.

**Proposed management**

The population incidence in the UK of ovarian cancer for women over the age of 45 years is 40/100,000 women/year. To screen this population and ensure a minimum of 1 diagnosis of ovarian cancer for every 10 laparotomies performed on the basis of a positive screen, the required specificity of the screening test is 99.6%. The only way of achieving this is by the sequential combination of CA125 with ultrasonography. To maintain the same positive predictive value in women who have a 4–5-fold increased risk, \textit{i.e.} women with an affected first degree relative, the required specificity is 98%. For women with a BRCA1 mutation who have a lifetime risk of approximately 45% the specificity required is 93%.

Given the lack of evidence on the efficacy of screening the general population for early ovarian cancer – either with regular ultrasound, regular tumour marker measurement or a combination of the two – and the uncertainty surrounding possible biological differences between genetic and sporadic ovarian cancer, the most attractive scientific solution would be the institution of a randomised trial of screening versus no-screening in the high risk population. As with breast cancer, a randomised controlled trial has been considered unfeasible because most patients, having been informed of their increased risk, will not accept a no-screen option.

The second most attractive option is a single arm screening study aiming to collect all the data necessary to make as accurate an analysis as possible of screening performance in this high risk group, and then compare screening performance in this group with performance including projected mortality reduction in the ongoing randomised
Table 6  Eligibility criteria for the UKCCCR National Familial Ovarian Cancer Screening Study

An eligible woman must be over 25 years of age and a first degree relative of an affected member of an ‘at risk’ family. At risk families are defined by the following criteria:

1. Two or more first degree relatives with ovarian cancer.
2. One first degree relative with ovarian cancer and one first degree relative with breast cancer diagnosed under 50 years of age.
3. One first degree relative with ovarian cancer and two first or second degree relatives with breast cancer diagnosed under 60 years of age.
4. An affected individual with one of the known ovarian cancer predisposing genes.
5. Three first degree relatives with colorectal cancer with at least one diagnosed before the age of 50 years and at least one first degree relative with ovarian cancer.

*A first degree female relative is mother, sister or daughter.
*b A second degree female relative is grandmother, grand-daughter, aunt or niece.

population studies. Such a study is the UKCCCR National Familial Ovarian Cancer Screening Study. The eligibility criteria for this study, given in Table 6, define a cohort of women at increased risk of ovarian cancer. The proposed management of this cohort is annual ultrasound and CA125 measurement. In this collaborative study, collection and analysis of family history data will be performed in the CRC Human Cancer Genetics Research Group in Cambridge, and collection and analysis of the screening data will be performed in the Ovarian Cancer Screening Unit in St Bartholomew’s Hospital, London. The clinical care of the patient remains with the local clinician, although the study team are happy to advise with interpretation of abnormal findings. Further details of this study may be obtained from the corresponding author.

Key points for clinical practice

- Any woman with a relative with breast cancer has an increased risk of developing breast cancer. The magnitude of that increased risk depends on the number of relatives with breast or ovarian cancer, the type of relatives affected, the ages at which cancer is diagnosed and the age of the ‘at risk’ individual.
- Two high penetrance breast/ovarian cancer genes have been identified and genetic testing is available in some genetic centres for a small number of families.
- The recent high profile genetic advances in breast and ovarian
cancer have raised unrealistic public and professional expectations of genetic testing.

- The efficacy of mammographic screening of women at average risk between 50 and 69 years has been proven in several randomised studies, but the effectiveness of mammographic screening in women below 50 years of age remains controversial.
- Women at moderate risk of breast cancer should only be offered annual mammography from the age of 35 years within the context of an evaluable research study.
- Women at significant risk of ovarian cancer should be offered annual ultrasound and CA125 measurement within the UKCCCR National Familial Ovarian Cancer Screening Study.
- Women with a family history of breast or ovarian cancer which falls outside the proposed criteria should receive an understandable accurate and supportive explanation, and not be offered regular or one-off investigation.
- Adoption of the proposed management strategy strengthens consistent information given from primary to secondary to tertiary care.

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References

Screening for familial breast and ovarian cancer

12 Burke W, Daly M, Garber J et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. JAMA 1997; 277: 997-1003
14 Wright CJ, Barber Mueller C. Screening mammography and public health policy: the need for perspective. Lancet 1995; 346: 29-32
17 Feig SA. Increased benefit from shorter screening mammography intervals for women ages 40-49 years. Cancer 1997; 80: 2033-9
19 Harter LP, Curtis JS, Ponto G, Craig PH. Malignant seeding of the needle track during stereotaxic core needle breast biopsy. Radiology 1992; 185: 713-4
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