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Guidelines for the management of women at increased familial risk of breast cancer

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Abstract

The Guidelines were prepared by an international expert panel on behalf of the Association of Breast Surgery. The majority of women who have a relative with breast cancer are not themselves at significantly increased risk. The Guidelines propose a management strategy, including genetic assessment, chemo-prevention, risk reducing surgery and radiological screening, based on risk assessment of the individual. The Guidelines are based on evidence where available, or on consensus statements from surgeons, radiologists, geneticists and clinical psychologists.

Keywords: Guidelines; Breast cancer; BASO; Risk; Recommendations

1. Introduction

The aim of these guidelines is to provide a potential management strategy for women at familial risk of breast cancer. A summary of the available evidence is presented and the guidelines are based on evidence where available or on consensus statements from breast surgeons, radiologists, geneticists and clinical psychologists.

These Guidelines were developed by an expert panel on behalf of the Association of Breast Surgery with wide input from all the professional groups involved. Although they are based on the United Kingdom (UK) model of healthcare, the overall recommendations are applicable to all women at familial risk of breast cancer.

Although women in the UK have a general awareness of the issues concerning breast cancer there is a poor understanding of their own individual risks [1]. The purpose of a Family History Clinic in the Breast Unit is to:

- provide access to accurate information for women, their families and their general practitioners (G.P.'s)
- assess an individual woman's risk and to communicate it in a manner that is appropriate
- provide further counselling if required
- provide radiological screening according to the Unit's protocols and encourage participation in clinical trials
- provide information on chemo-prevention and to encourage participation in clinical trials
- to refer high-risk women to a clinical geneticist according to agreed regional protocols
- to ensure access to risk-reducing surgery where this is considered appropriate

There is no mandatory requirement for a Breast Unit to have a Family History Clinic but the Unit should have clear guidelines on the management of women at familial risk and these should be disseminated to G.P.'s. The clinic may be run by Breast Care Nurse Specialists who have received appropriate training. Women who are under follow-up and who develop symptoms should

[1] See Appendix for Panel members.

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have a means of rapid access to the Unit's symptomatic clinic.

Recommendation

- All Breast Units should have a protocol for the management of women at familial risk

Level of Evidence IV Grade D

2. Familial risk

2.1. Risk estimation

An average woman in the UK has an approximately 11%, or 1 in 9, life-time risk of developing breast cancer. However there is substantial evidence that women both underestimate and overestimate their risk and also have a poor understanding of the average age of the disease [1]. Breast cancer is uncommon in younger women and, in the absence of a family history, a woman entering her 30s has a 1 in 250 chance of developing breast cancer during the subsequent decade, rising to 1 in 75 at age 40 years for the following decade.

The aim of risk assessment is to define an individual's risk into three broad categories of standard- (risk not significantly above the normal population), moderate- or high-risk upon which her subsequent management will depend (Table 1).

Only 5–10% of breast cancers are due to high-risk susceptibility genes, but a higher proportion than this have a family history and estimating the risk in this group can be complex. The Gail model is frequently used for risk estimation and is a well validated model but, although it includes epidemiological factors, it does not adequately weight familial risk factors [2]. It is not therefore an appropriate model for the Family History clinic. The tables published by Claus are also well validated and, in a simple pedigree, give a good estimate of risk [3]. The tables do not take account of unaffected relatives and in a large family will therefore overestimate the risk in these circumstances. Neither do they include paternal relatives or cases of ovarian cancer, both of which may increase risk [4,5].

Table 1
Risk groups

Risk group	% of Population	Lifetime risk	Relative lifetime risk
Standard	97%	<1:6	RR <2
Moderate	2%	1:4 to 1:6	RR 2–3
High	<1%	>1:4	RR >3

RR, relative risk.

Risk may also be assessed by use of a computer program such as the Cyrillic program based on Claus or the Tyrer–Cuzick program, although these have not yet been fully validated [6]. The BRCA Pro model was designed to determine probability of a *BRCA1/2* mutation and should not be used for breast cancer risk estimation.

It is therefore recommended that at the present time risk is best assessed by referral to Table 2, which is based upon the published guidelines of the UK Cancer Family Study Group in consultation with the Strang Cancer Prevention Center, New York [7].

2.2. Communicating risk

Women attending a risk assessment have a poor understanding of the population risk of breast cancer or of their personal risk: as many are likely to overestimate as underestimate both risks [1]. Genetic risk counselling significantly improves risk accuracy in approximately 50% of women but others continue to over- or underestimate [8,10]. No single method of risk presentation is currently superior and it is recommended that risk is presented in more than one way (e.g. Odd's ratio lifetime risk, annual risk per 1000 women, risk at a certain age or for a specific time period). Risk counselling does not have a negative impact on psychological well-being, even in under-estimators, but cancer worry is significantly greater in women who overestimate their personal risk [9,11–13]. No significant associations have been found between risk perception and family history or a range of demographic and psychological variables [9,11,14]. The Trial of Genetic Assessment in Breast Cancer (TRACE) study, a prospective study examining the psychological and resource implications of family history clinics concluded that the psychological outcome following a surgical consultation was similar to that with a geneticist but that increased time spent with a woman was not reflected in decreased anxiety levels [15,16].

Recommendation

- Women at potentially increased familial risk of breast cancer should be defined according to standard, moderate or high-risk group

Level of Evidence III Grade C

3. Breast cancer genetics

3.1. Introduction

Only approximately 5–10% of breast cancer cases are due to high-risk breast cancer predisposition genes, and just under a half of these are due to mutations (alterations

Table 2
Potential management strategy for women at increased familial risk

Family history	Lifetime risk	Risk group	Early mammography[a]	Refer to genetics clinic
Breast cancer				
1 relative <40 years of age	1 in 6	Moderate	Yes	No except[b]
2 relatives <50 and >40 years of age	1 in 4–5	Moderate/high	Yes	Yes
2 relatives <60 and >50 years of age	1 in 5–6	Moderate	Yes	No[b]
3 relatives <60 years of age	1 in 4	Moderate	Yes	No except[b] and[c]
1 relative with bilateral breast cancer	1 in 3–6	Moderate (unless average age <40 years)	Yes	No except[b] or average age <50 years
2 relatives <40 years of age	1 in 3–4	High	Yes	Yes
3 relatives <50 years of age	1 in 3	High	Yes	Yes
4 relatives any age	Just under 1 in 2 to 1 in 3	High	Yes	Yes
Breast/Ovarian cancer				
1 Ovarian cancer any age + 1 breast <50 years of age	1 in 3–6	Moderate/high	Yes[d] (+ ovarian screening)	Yes
>1 Ovarian cancer ± breast cancer any age	1 in 3	High	Yes[d] (+ ovarian screening)	Yes
Childhood cancer				
Childhood tumour <20 years plus two other cancers <60 years of age	Variable—seek advice	Seek advice	Seek advice (a small proportion will be Li-Fraumeni syndrome)	Yes

The ages in the Table are based on average age at diagnosis and the lifetime risks are derived from the Cyrillic computer version (Cyrillic 3) of the Claus model which gives lower risk than the Claus tables.

[a] Annual mammography from age 40 to age 50 years of age (and then National Health Service Breast Screening Programme (NHSBSP)).

[b] Ethnic origin may make mutation searching and mutation probability higher (e.g. in the Ashkenazim who have approximately a 20% chance of a *BRCA1/2* mutation of one of three specific types versus <10% of other Caucasian groups in the United Kingdom (UK).

[c] Some centres are collecting these families for research for further more moderate risk breast cancer genes.

[d] Screening for ovarian cancer is not of proven benefit at present and should only be undertaken within a clinical trial.

in the genetic code) of the breast cancer genes, *BRCA1* and *BRCA2*. A minority of cases are due to very rare genetic syndromes or rare high-risk genes (e.g. ataxia telangiectasia, Li-Fraumeni syndrome- mainly due to the gene *TP53*; Cowden's syndrome—mainly due to the *PTEN* gene). Although the first draft of the Human Genome Project was published in February 2001, the function of many of the expressed genes is unknown. There is a high expectation of what genetics can currently deliver and although data are starting to accrue on the effectiveness of prevention methods in breast cancer predisposition gene carriers, many are still experimental and further data are needed before certain measures can be actively promoted.

3.2. Referral to genetics clinic

The Family History Clinic should provide an opportunity to explain the appropriateness of genetic testing. The Harper report suggests that screening is managed in Cancer Units and that genetic testing is conducted in Cancer Genetics Clinics attached to the Cancer Centre. There are no current guidelines on the suggested care pathway for a proven breast cancer predisposition gene carrier. The concept of a 'Carrier Clinic', modelled along the lines of a multidisciplinary oncology clinic or with dual trained oncology/genetics staff, is a model in some countries and a few centres in the UK.

Table 2 represents a potential management strategy for those women who present with concern about their family history (based upon Eccles and colleagues and in consultation with the Strang Cancer Prevention Center, New York, United States of America (USA)) [7].

Ovarian cancer is a marker of higher genetic risk and so brings most women into the high-risk category and will result in recommendations for genetic referral. The genetics consultation should involve confirmation of the diagnosis of ovarian cancer as this verification will result in a revision of the diagnosis in approximately 17% of cases.

3.3. Genetic testing

It is recommended that all genetic testing occurs within a Cancer Genetics Clinic after genetic counselling. In general, the criteria for testing in the UK is that there should be at least a 20% probability of the presence of a mutation. This is more stringent than the current American Society of Clinical Oncologists (ASCO) guidelines on genetic testing that suggest a >10% probability of a breast cancer gene being present. Candidates for genetic testing are:

BRCA testing

- Single case of breast cancer at <40 years of age if Ashkenazi
- Two breast cancer cases <40 or three <50 years of age
- Four cases of breast cancer at <60 years of age
- >4 cases of breast cancer any age
- Ovarian and breast cancer in a family (breast cancer <50 years of age if only one ovarian and one breast cancer case)
- Early onset female breast cancer at <60 years of age and male breast cancer at any age

TP53 testing

- Li-Fraumeni syndrome (sarcoma at <45 years of age with a first-degree relative with cancer at <45 years of age and another close relative with cancer at <45 years of age)

PTEN testing

- Clinical features of Cowden's syndrome (tricholemmomas of the skin, hamartomas on the edge of the tongue, multiple and very early onset fibroadenomas, which can be associated with gynaecological abnormalities and colonic hamartomatous polyps)

ATM testing

- Clinical features of ataxia telangiectasia in the family

In general, testing needs a living affected family member from whom to take a blood sample to identify the specific mutation that may be present in the family (the DIAGNOSTIC genetic test). If positive, this means that if a test in an unaffected relative (the PREDICTIVE genetic test) is negative, this is a true negative. Exceptions, where an unaffected individual is offered genetic testing without prior diagnostic testing in the family, include:

- When the affected relatives are all deceased, are uncontactable or refuse to give a blood sample for diagnostic testing. The unaffected testee should receive genetic counselling that a negative test in this situation cannot exclude the presence of a breast cancer predisposition gene. This is because in the absence of a mutation being identified on diagnostic genetic testing, there is uncertainty as to whether the genetic test is testing the relevant breast cancer gene as further genes are as yet undiscovered. Mostly this situation is considered if the individual states that they wish to have prophylactic surgery if they test positive.
- A risk-reduction can be offered to individuals who test negative in families with no prior diagnostic test if the family is from certain racial groups with a high probability of some specific mutations. An example is the Ashkenazim.

Recommendation

- Women at high-risk of familial breast cancer should be referred to a genetics clinic according to an agreed protocol

Level of Evidence IV Grade D

4. Breast cancer prevention

4.1. Diet and lifestyle

Most significant risk factors associated with breast cancer such as gender, age, early menarche and parity cannot be changed. There is no convincing evidence to suggest that modifying diet or lifestyle will have an impact on risk, but women at increased risk of breast cancer could be advised to reduce dietary fat, avoid obesity, reduce alcohol consumption and take regular exercise [17].

4.2. Chemo-prevention

Four large prospective, randomised studies have addressed the issue of breast cancer prevention with tamoxifen. The largest study, National Surgical Adjuvant Breast Project (NSABP)-P1, recruited over 13 000 women with a minimum estimated risk of breast cancer of >1.66% per annum (p.a.) and randomised them to Tamoxifen 20 mg daily for 5 years versus placebo [18]. The overall reduction in the incidence of invasive cancer was 49% ($P<0.0001$) and for non-invasive cancer 50% ($P<0.002$). This reduction was independent of age and relative risk, but was seen only for ER-positive tumours. There was no significant reduction for ER-negative tumours. Tamoxifen was associated with a relative risk of 2.53 of developing endometrial cancer, although all tumours were stage 1 and not associated with any deaths. The rates of stroke, deep vein thrombosis (DVT), and pulmonary embolism were elevated in women on tamoxifen and this risk was greater in women over 50 years of age. There was no evidence of an effect on ischaemic heart disease, but hip fractures were reduced. A detailed analysis of the complex risks and benefits of tamoxifen has been undertaken by Gail

and this suggests that young women with no uterus and a high-risk of breast cancer have the greatest benefit [19].

A study from the Royal Marsden Hospital randomised 2471 women, all of whom had at least one first-degree relative with breast cancer under the age of 50 years or with bilateral cancer to tamoxifen or placebo [20]. This study has not demonstrated a significant reduction in breast cancer incidence despite having sufficient statistical power to do so. It is assumed that one potential reason for this is the relatively large number of women who are likely to be *BRCA1*, *BRCA2* or other gene mutation carriers in comparison to the NSABP-P1 study. Women with *BRCA1* mutations are more likely to have ER-negative tumours and potentially receive less benefit from Tamoxifen.

The third published study from Italy randomised 5408 women of relatively low-risk of breast cancer. All women had had a hysterectomy, and most an oophorectomy, Compliance in this study was low, as was the statistical power. To date, no significant chemo-preventive effect of tamoxifen has been demonstrated [21].

The International Breast Cancer Prevention study (IBIS I) is a double-blind placebo-controlled randomised trial of tamoxifen, 20 mg/day for 5 years, in approximately 7000 women from the UK, Europe, Australia and New Zealand who were aged 35–70 years [22]. The frequency of breast cancer was reduced by a third among women given tamoxifen (69 breast cancers in 3578 women in the tamoxifen group and 101 breast cancers in 3566 in the placebo group). The incidence of endometrial cancer was doubled in the tamoxifen group (11 instances compared with 5 in the control group), but this increase was not statistically significant, and all cases were localised (stage 1) and curable by hysterectomy.

However, tamoxifen use was associated with a more than doubling in the risk of thrombo-embolic complications, especially after surgery or long periods of immobilisation. The investigators comment that the increased risk of blood-clotting complications could also contribute to the higher death rate from all causes in women given tamoxifen.

The value of tamoxifen use in *BRCA1* and *BRCA2* mutation carriers is not established and nor is the optimum duration of benefit.

An overview of the main outcomes of all the current published studies confirms a 38% overall reduction in breast cancer incidence with tamoxifen, but recommends that its use is restricted to women at high-risk of breast cancer and low-risk of potential side-effects [23].

In conclusion, although tamoxifen when used as adjuvant therapy for breast cancer can clearly reduce the risk of recurrence and death, there is, at present, no clear overall risk to benefit ratio for its use in chemo-prevention. Further long-term follow-up to study breast-cancer incidence and mortality, other causes of death, and side-effects in the current trials remains essential.

Raloxifene is a selective oestrogen receptor modulator (SERM) that was initially used in a prospective placebo controlled trial in women with osteoporosis. This study, the multiple outcomes of raloxifene (MORE) study, demonstrated a potential chemo-preventive action which is now being further investigated in the Tamoxifen and Raloxifene (STAR) trial [24].

An early report from the ATAC study in which the aromatase inhibitor anastrazole was used in an adjuvant setting for post-menopausal women with early breast cancer suggests that aromatase inhibitors may also have a significant chemo-preventive effect [25]. Patients in the anastrazole-alone arm of this study had a reduction in contra-lateral cancers of 58% compared with those on Tamoxifen alone.

Further studies in the UK are anticipated using other agents including aromatase inhibitors.

Recommendation

- Women who are eligible should be offered the opportunity to participate in prospective chemo-prevention studies

Level of evidence 1a Grade A

4.3. Risk-reducing mastectomy

The role of bilateral risk-reducing mastectomy or "prophylactic mastectomy" has been controversial for several reasons including the psychosocial significance of the breast in western cultures, the wide acceptance of breast conservation in surgery for early breast cancer and the previous lack of data on its efficacy.

Surgery was used in some centres for many years with the aim of preventing breast cancer with little published data on its efficacy. The procedure was often performed for indications which are no longer thought to put individual women at increased risk. Pennisi reported that after subcutaneous mastectomy only 1% of women subsequently developed breast cancer, but some of the criteria used to select the high-risk group would now be questioned [26,27].

The term bilateral risk-reducing mastectomy (BRMx) is deemed preferable to "prophylactic mastectomy". There are no randomised controlled trials published to endorse its use, but two studies have found that risk-reducing mastectomy reduces the risk of breast cancer by 90% in high-risk and *BRCA1/2* mutation carriers [28–30].

In Hartmann's study, 639 women were divided into "medium-risk" and "high-risk" groups on the basis of family history. The reduction in expected breast cancer

incidence was 90% and there was a dramatic difference in the numbers of cancers occurring in treated women compared with their sisters who had not undergone BRMx [28]. Subsequently, 12 gene mutation carriers were identified from within the 110 highest-risk women, but not one developed breast cancer after a median follow-up of over 16 years [30].

The Dutch study reported on 139 women with *BRCA1* or *BRCA2* mutations, of whom 76 underwent BRMx and 63 were followed by surveillance, which included: self-examination, 6 monthly professional examination, annual mammography and, from 1995, magnetic resonance imaging (MRI). Eight cancers were detected in the surveillance group, consistent with statistical estimates, but none was observed in the 76 who had undergone surgery [29].

Both studies have methodological limitations, but they suggest that bilateral risk-reducing mastectomy is a most effective strategy in high-risk women.

The aims of BRMx are to:

- reduce the incidence of breast cancer in high-risk women, e.g. *BRCA1* or *BRCA2* mutation carriers
- reduce mortality from breast cancer in high-risk women.
- relieve anxiety
- balance the reduction in risk against cosmetic outcome, with subsequent quality of life issues.

The surgical procedure should aim to remove substantially all of the 'at risk' breast tissue, but there should be a balance between reduction of cancer risk and cosmetic outcome. Cases of carcinoma developing in residual breast tissue are documented for both subcutaneous and total mastectomy [31–33].

Most women undergoing BRMx will request breast reconstruction. They should be offered the choice of whether or not to preserve the nipple, but they should be informed that approximately 10% of breast cancers arise deep to the nipple areola complex although, conversely, over 90% do not [34]. The possibility of ischaemic nipple loss must be discussed.

4.4. Patient selection

Women should be offered BRMx only on the basis of a strict selection and management plan, such as the Manchester Protocol [35]. Family history and 'high-risk' status must be confirmed by the involvement of a Clinical Geneticist. Surgery should not be offered to women whose calculated risk is less than 1 in 4. Individual women should be informed, not only of the rationale of surgery, but also other risk-reducing options including screening and chemo-prevention trials. It is likely that a minority of the women to whom it is offered will undergo BRMx.

A psychological assessment is essential to ensure that an appropriate decision is made. Personal attitudes to breast cancer and risk perceptions must be explored and realistic expectations of surgery and reconstruction emphasised. Profound relief of anxiety has been found following surgery, but support with psychosocial issues is important [35].

The availability of genetic testing may influence patient choice. Referral to a specialist breast surgeon or plastic and reconstructive surgeon working within the breast unit protocol may follow. The techniques, limitations, complications and uncertainties of surgery should all be discussed both from the perspective of cancer risk reduction and also for reconstructive breast surgery. A specialist breast care nurse must be involved. It is recommended that a minimum of two surgical consultations separated by two months should take place before surgery is undertaken.

4.5. Surgical technique

Breast reconstruction will involve several operations, especially if the nipple areola complex is resected and is subsequently reconstructed.

The BRMx procedure should aim to remove virtually all the 'at risk' breast tissue. An appropriate incision should be planned to suit each individual patient taking into account the principle of access to the areas at highest risk, the upper outer quadrant and axillary tail, and aesthetic outcome. Breast reconstruction should be by submuscular tissue expander/permanent implant placement, or by bilateral myocutaneous tissue flap transfer. Choice of incision will also depend upon the ptosis and size of the breasts. Examples of incisions that fulfil these criteria include circum-areolar, Wise pattern and curved transverse incisions.

BRMx should be undertaken only by specialist surgeons within a specialist unit with full multidisciplinary experience and support. The surgery can be technically demanding with consequent risk of complications and cosmetic/aesthetic results need to be optimised. The decision to proceed with surgery must be unhurried, with ample time for reflection and consultations.

Consultations for risk-reducing mastectomy should include:

- a clinical geneticist, psychiatrist (or clinical psychologist) and specialist surgeon working within an agreed unit protocol
- objective confirmation of family history (at least two confirmed cases wherever possible)
- risk calculation/genetic test feasibility
- discussion of screening, chemo-prevention and surgery
- description of operation choices
- limitations and residual risk

- reconstruction choices
- the options for the nipple areola complex
- morbidity, scarring and recovery
- specialist breast nurse discussions
- psychological assessment
- realistic expectation of results

Risk-reducing mastectomy should not usually proceed if:-

- risk has not been verified
- fictitious family history or Munchausen's syndrome
- BRMx is not the woman's own choice
- imminent result of genetic testing
- current psychiatric disorder including clinical depression, cancer phobia or body dysmorphic syndrome
- co-morbidity outweighs clinical benefit
- unrealistic expectations

After completion of BRMx and reconstruction, patients should be seen annually and data on outcomes collected prospectively and subjected to regular clinical audit.

Recommendations

- Risk-reducing mastectomy may significantly reduce, but not eliminate, the risk of subsequent breast cancer and should be offered to women where appropriate

Level of Evidence II b Grade B

- Units undertaking risk-reducing mastectomy should have agreed protocols

Level of Evidence IV Grade D

4.6. Prophylactic oophorectomy to reduce the breast cancer risk

The ability to test for mutations in *BRCA1* and *BRCA2* genes can identify individuals at risk from families with inherited cancer syndromes, particularly breast/ovary cancers. Bilateral prophylactic oophorectomy can significantly lower ovarian cancer risk in women who carry *BRCA1* mutations [37–39]. Oophorectomy lowers the risk of breast cancer, even in women who have previously used hormone replacement therapy (HRT). The risk-reduction is limited to women who undergo oophorectomy whilst still pre-menopausal. The magnitude of risk-reduction approaches 50% in common with that associated with Tamoxifen use in breast cancer prevention trials. Ongoing chemo-prevention trials reconfirm the preventative effect of hormonal intervention and whilst chemo-prevention studies are still underway, prophylactic oophorectomy should not routinely be recommended solely to reduce the breast cancer risk.

Recommendation

- Prophylactic oophorectomy should not be routinely recommended solely for reduction in breast cancer risk

Level of Evidence II b Grade B

- Prophylactic oophorectomy should be discussed as an option to reduce ovarian cancer risk in *BRCA 1* and *BRCA 2* carriers

Level of Evidence II a Grade B

4.7. Psychosocial issues

A small, but increasing, proportion of women at high-risk consider the option of risk-reducing surgery. Psychosocial and sexual outcomes are as yet uncertain, but research designed to assess short- and medium-term effects will shortly be available. The provision of psychological assessment and counselling has been recommended prior to breast surgery, as well as detailed genetic assessment and discussion with the surgical team. Partners should be encouraged to participate in this pre-op preparation. Experience to date suggests that most women undergoing BRMx have marked relief from cancer worry, but those who have surgical complications may need additional psychological support [36]. In the hands of specialist breast and/or reconstructive surgeons, cosmetic results can achieve a high standard resulting in minimal body image concerns [40]. The potential for psychosexual problems following oophorectomy should not be underestimated: these may be related to age and menopausal status, but advice about the use of HRT is unclear. Precise information on uptake and outcomes is awaited [41].

5. Radiological screening

5.1. Breast imaging

There are no published randomised controlled trials examining the effectiveness of mammographic screening in women under 50 years of age with a family history of breast cancer, but a prospective evaluation of mammographic surveillance services in this group, funded by

the National Health Service Research and Development (NHS R&D) Health Technology Assessment Programme, is about to commence. However, the published studies do suggest that mammographic screening a high-risk group of women under 50 years of age may detect cancer at a rate equivalent to that seen in women at normal risk and 10 years older [42–49]. It is recognised that the sensitivity of mammography in younger women is significantly reduced and there are concerns regarding radiation exposure in a group of women who may have an increased sensitivity to radiation. Addition of ultrasound to mammography may increase sensitivity in younger women [50]. Only one published study has prospectively compared ultrasound, mammography and magnetic resonance imaging (MRI) [51]. In this study of 196 high-risk women, MRI was superior to ultrasound or mammography. Other initial studies also support MRI as having a greater sensitivity to mammography in high-risk women [52,53].

5.2. Mammographic screening of patients at increased risk of breast cancer

The following recommendations are extracted from the 'Guidance on Screening and Symptomatic Imaging' by the Royal College of Radiologists [54].

Only a small proportion of breast cancer is hereditary and linked to highly penetrant dominant genes [55]. Evidence that mammographic screening offers any benefit to women with a significant family history of breast cancer is still limited because of the small size of most studies compared with the large randomised control trials [42,44,45,47,48,51,54,56]. The results, in terms of number and stage of cancer detected, in women deemed at high-risk because of their family history screened between 40 and 50 years of age are comparable to population screening of women over 50 years of age. Breast MR has shown potential as a sensitive screening test, but is extremely expensive. A trial is underway in the UK evaluating the use of MR as a screening test in high-risk women [57]. The recommendations are therefore based on the currently suggested 'best practice':

- Any mammographic screening of women in this risk group should be planned, follow agreed Unit protocols and be subject to prospective data collection.
- Women who participate should only do so with fully informed consent, to include information about possible benefits and possible risks (rates of false-positive and false-negative results and their implication for false reassurance and interventions for what may prove to be benign disease; the potential radiation risks associated with frequent mammography carried out from a young age).
- Risk assessment and counselling are fundamental prerequisites to mammographic screening in these circumstances; up to one-half of those referred for family history screening are not at significantly increased risk of developing breast cancer.
- It is recommended that family history screening should be carried out under the direct supervision of a clinician who has a special interest in family history breast cancer screening.
- Mammography may be part of routine family history screening and should be performed following protocols agreed between the clinicians in charge of the family history service and the specialist radiologist. These protocols should clearly define eligibility criteria and the methods and frequency of screening examinations and a formal mechanism for ensuring that any abnormalities detected are assessed further without delay by a specialist multidisciplinary breast team.
- Family history risk decreases with age and, for most women with significant family history who are aged 50 years or more, the screening as provided by the National Health Service Breast Screening (NHSBSP) is likely to be sufficient.
- The use of mammography in screening 'at-risk' women under 35 years of age should not be routine.
- The radiologist(s) should ensure that mammography performed as part of family history screening is of optimal quality and that unnecessary exposure to radiation is avoided. The optimum frequency for performing mammography as part of screening women at increased risk of breast cancer is uncertain and depends on age. It is suggested that screening mammography should be more frequent in younger women [58]. It is recommended that screening mammography should be performed every 1–2 years. More frequent mammography is not recommended.

Recommendations

- Mammographic screening of women at familial risk is of unproven benefit and should only be undertaken according to strict unit protocols or, preferably, within a clinical trial

Level of Evidence III Grade C

6. Breast clinical and self-examination

It is difficult to assess the efficacy of clinical breast examination in women at increased risk of breast cancer.

Although several screening studies have included clinical examination, no subgroup analysis of 'at risk' women was performed and nor are there any randomised studies comparing clinical examination with other screening modalities. A retrospective study of high-risk women from the Royal Marsden Hospital demonstrated that 14 of 31 cancers (45%) would have been missed if mammography alone had been undertaken without clinical examination [49].

Breast self-examination is often advocated, but its effectiveness is unproven and only one randomised study has been undertaken in women 'at risk' [59].

For details of the chairman and panel members who put together these guidelines, please see Appendix A. Current clinical trials and principle recommendation and grades of evidence are summarised in Appendix B.

Appendix A

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Appendix B

Current Clinical Trials

Mammography

Evaluation of Mammographic Surveillance services in women under 50 years of age with a Family History of Breast Cancer (FH01)

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Chemo-prevention

International Breast Cancer Intervention Study II (IBIS II)

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MRI versus chemo-prevention versus risk-reducing surgery

The RAZOR study [60]

Recommendations and level of evidence

Management of women at familial risk according to risk group

The management of women at familial risk should be determined by their risk group as defined previously (Table 1).

Standard-risk

- Should ideally be managed in primary care
- May require reassurance from Family History Clinic
- Are unlikely to benefit significantly from either early screening or chemo-preventative intervention

Moderate-risk

- Consider referral by their GP to a Family History Clinic
- Consider offering mammographic screening according to Unit protocols, and preferably within a clinical trial
- Should be recommended to consider chemo-prevention where appropriate and given information on clinical trials

High-risk

- Should be offered referral by their GP to a Family History Clinic and/or Geneticist
- Should be offered mammographic screening according to Unit protocols and preferably within a clinical trial
- Should be recommended to consider chemo-prevention where appropriate and given information on clinical trials
- Should be referred by the Family History Clinic to a Geneticist according to agreed protocols
- Receive appropriate advice and access to risk-reducing surgery

Principal recommendations and grade of evidence

The definitions of the types of evidence are based on the US Agency for Health Care Policy and Research. The Grading of Recommendations is from Eccles M and colleagues [61]

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
Iia	Evidence obtained from at least one well-designed controlled study without randomisation.
Iib	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grade	Recommendation
A	Directly based on category I evidence
B	Directly based on category II evidence, or extrapolated recommendation from category I evidence
C	Directly based on category III evidence, or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence, or extrapolated recommendation from category I, II, or III evidence

Summary of Recommendations

Recommendation

- All Breast Units should have a protocol for the management of women at familial risk

Level of Evidence IV Grade D

Recommendation

- Women at potentially increased familial risk of breast cancer should be defined according to standard-, moderate- or high-risk groups

Level of Evidence III Grade C

Recommendation

- Women who are eligible should be offered the opportunity to participate in prospective chemo-prevention studies

Level of Evidence I a Grade A

Recommendation

- Women at high-risk of familial breast cancer should be referred to a genetics clinic according to an agreed protocol

Level of Evidence IV Grade D

Recommendations

- Risk-reducing mastectomy may significantly reduce, but not eliminate, the risk of subsequent breast cancer and should be offered to women where appropriate

Level of Evidence II b Grade B

- Units undertaking risk-reducing mastectomy should have agreed protocols

Level of Evidence IV Grade D

Recommendation

- Prophylactic oophorectomy should not be routinely recommended solely to reduce breast cancer risk

Level of Evidence II b Grade B

- Prophylactic oophorectomy should be discussed as an option to reduce ovarian cancer risk in *BRCA 1* and *BRCA 2* carriers

Level of Evidence II a Grade B

Recommendations

- Mammographic screening of women at familial risk is of unproven benefit and should only be undertaken according to strict unit protocols or, preferably, within a clinical trial

Level of Evidence III Grade C

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