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A guideline for the management of women at substantially increased risk of breast cancer development

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Summary

The aim of this guideline is to provide a potential management strategy of women at high risk for breast cancer development. A summary of the available evidence is presented, including genetic risk assessment, chemoprevention, risk-reducing surgery and radiological screening, based on risk assessment of the individual. Recent progress in the diagnostic methods and therapeutic options for breast cancer does not prevent the death of at least one third of these patients from their disease. The focus on breast cancer prevention, especially for the group of women that is designated as high-risk, may reduce mortality. The determination of the group of women who are more likely to develop breast cancer will allow a targeted specific counselling and the application of preventative measures. All Cancer Centres and Units should develop an integrated network of breast cancer care using common clinical guidelines, management protocols and strategies of care (Recommendation grade D). All Breast Units should have a protocol for the management of women at high risk (Recommendation grade D).

Key words: breast cancer, familial risk, guidelines, prevention, recommendations, women at high risk

1. Aim of the guideline and evidence-based recommendations

This guideline is not intended to be prescriptive since it is not possible to take into account every local circumstance. The main aim is to assist cancer centers, cancer units and primary care centers, as well as cancer practitioners to produce their own guidelines for the management of patients with increased risk of breast cancer development.

In any case the configuration of evidence-based guidelines with reliability grading in recommendations is absolutely needed. This is necessary not only for the validity of the guideline but also for the potentiality in judgment and readjustment of recommendations according to the new data that arise in continuing medical practice. Although there is a solid body of knowledge for the proper general management of breast cancer, in the case of management of women at substantially increased risk of breast cancer development the evidence is rather inadequate and ambiguous.

The definitions of the types of evidence and the

Appendix 1. Level type of evidence and recommendation grading

Level	*Statements of evidence*
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
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	*Grades of recommendation*
A	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (Evidence levels Ia, Ib)
B	Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (Evidence levels IIa, IIb) or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (Evidence level IV) or extrapolated recommendation from category I, II, or III evidence

grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research [1,2] and are set out in Appendix 1.

2. Breast cancer epidemiology and general statistics

Even in the current era of cancer prevention and early detection, breast cancer holds several grievous records as it is the most common form of malignant disease among women in the best part of the developed world, the most common cause of death from cancer (although exceeded by lung cancer in some countries), and the most common cause of death from any cause below the age of 50. The incidence of breast cancer varies widely between countries (it is less common in Asia and countries of the developing world) and is about 5 times higher in North America than in Japan. In general, the average lifetime risk of developing breast cancer in Western countries is approximately 1:8 to 1:12 women [3-7]. Consequently, more than 1,000,000 new cases of breast cancer are diagnosed annually worldwide.

3. Conventional breast cancer risk factors

Breast cancer is a multifactorial disease. Several endogenous and exogenous factors may be involved in breast cancer incidence and morbidity. Although the breast cancer risk estimation requires assessing a number of risk factors, age, personal and family history should be considered by far the most influential factors in breast cancer development.

3.1 Age: Age is most important in breast cancer development. The risk increases with increasing age. Breast cancer is uncommon in women below 30 years of age and shows a sharp increase of incidence, over 10-fold, until the age of 50. In women aged 80-85 years the risk is 15 times higher than that in women aged 30-35 [8,9].

3.2 Personal history: It is estimated that about 20% of women in the US will undergo a breast biopsy for benign breast disorder by the age of 50. There is agreement that non-proliferative lesions carry no increased risk of developing invasive cancer. In contrast, epithelial proliferative changes do result in an increased risk, particularly if these changes are associated with atypia [10,11]. Atypical hyperplasia, whether lobular or ductal, is associated with a 4-5-fold increase in breast cancer risk; women having atypical hyperplasia and a first-degree relative with breast cancer have an 11-fold increase in risk over those without proliferative atypical changes [11]. Proliferative lesions without atypia (moderate or florid hyperplasia, papilloma with fibrovascular core) are associated with a modest (1.5-2-fold) increase in risk [10-12].

History of premalignant lesions, such as LCIS and DCIS (LCIS: lobular carcinoma *in situ*, DCIS: ductal carcinoma *in situ*), is associated with an increased risk of subsequent invasive cancer [13-15]. Current data suggest that LCIS is a risk factor rather than the anatomic precursor of invasive carcinoma and for this reason mastectomies performed for LCIS should be considered prophylactic rather than therapeutic. The relative risk of developing invasive breast cancer in patients with LCIS ranges from 6.9 to 12 [13-15]. On the other hand, DCIS is more likely to be a "precursor" of the disease and constitutes a higher risk of invasive disease for the same but not for the opposite breast [16]. The treatment of DCIS is now less controversial and there is general agreement that lumpectomy with

breast irradiation is effective in most patients with non-multicentric DCIS [16,17].

Prior history of breast cancer constitutes an increased risk for cancer development in the contralateral breast. The risk has been estimated to be about 1% per year of survival, with a cumulative lifetime risk increasing to 5 times over the general population risk [18-20). Other factors that increase the risk of developing contralateral breast cancer include hereditary [21,22] and familial [23,24] breast cancer, radiation exposure at a young age [25], LCIS [26], lobular invasive carcinoma, and proliferative changes in the remaining breast, especially when associated with atypia, and multicentric cancer [27]. Young age at primary breast cancer diagnosis may be associated with an increased susceptibility for bilateral breast cancer, rather because of the increased probability of living long enough to develop a metachronous breast cancer or it may be indicative of an underlying predisposition to malignant transformation and this may explain the development of a metachronous contralateral breast cancer [28].

3.3 Family history: Family history is probably the most well recognized risk factor for breast cancer. A family history of breast cancer in a first-degree relative (i.e. mother, sisters, and daughters) has an additive effect on the risk of breast cancer development. In general, fewer than 5% of women in whom biopsy shows no proliferative changes are likely to have breast cancer in the subsequent 25 years; nevertheless, nearly 40% of women with atypical hyperplasia and a family history of breast cancer will eventually get the disease [8,29]. The risk for first-degree relatives is higher if breast cancer has been diagnosed at an early age and it is even higher when the patient has bilateral breast cancer diagnosed at an early age [30]. However, the cancer cases may have accumulated randomly, if the family is very large and the cancer cases have been diagnosed at older ages.

Women in Western countries have an average lifetime risk of approximately 8-11% for developing breast cancer. Familial breast cancer (referring to one or more first-or second-degree relatives) is a different entity from hereditary breast cancer [31]. The cumulative risk of women with a family history for developing breast cancer rarely exceeds 30% [32]. Hereditary breast cancer is defined as a subset of familial breast cancer in which the incidence of the disease is related to autosomal dominant, highly penetrant mutated genes predisposing to cancer, such as the hereditary breast-ovarian cancer syndrome. It is estimated that approximately 5-10% of breast cancers are due to a specific inherited mutation that generates an extremely high risk of breast cancer development [33].

3.4 Menarche and menopause: The duration of active menstrual cycles of a woman is related to the risk for breast cancer development. An early menarche and late menopause increase subsequent risk of breast cancer. Women with menarche at the age of 11-14 years have a 10-30% greater risk for developing breast cancer later in life in comparison with women who have the menarche at the age of 16. Women having the menopause when more than 55 years have a 50% higher risk, while women having the menopause at the age of 45 or younger have a 30% lower risk for breast cancer development [34,35].

3.5 Reproductive factors: Nulliparous women have a higher risk than parous. A first pregnancy after the age of 35 years and nulliparity are associated with nearly double breast cancer risk. A larger number of children and the prolonged breast-feeding also reduce the risk of breast cancer [36,37].

3.6 Anthropometric variables: Body weight and height influence the risk of breast cancer. Greater birth weight and obesity after the menopause, as well as greater height have been found to be associated with an increase in risk of breast cancer [38].

3.7 Dietary variables: The available evidence suggests that increased nutritional intake of energy, of dietary fat, of meat and alcohol may all increase the risk for breast cancer development, and that increased dietary intake of fibre, fruits and vegetables, antioxidant vitamins, and phytoestrogens may all reduce this risk [39].

3.8 Physical activity: Physical activity and body exercise are associated with leanness, later onset of menarche, greater frequency of amenorrhea, all these factors being associated with a reduced risk of breast cancer [40].

3.9 Sex hormones: There are few data showing that higher levels of endogenous sex hormone levels are unequivocally related to greater breast cancer risk. There is also convincing evidence that prolactin levels are relevant to breast cancer risk. However, the results of case-control and cohort studies of endogenous sex hormones in relation to breast cancer risk remain inconsistent [41].

Hormone replacement therapy (HRT) increases the risk of breast cancer in current and recent users. The relative risk increases by about 2% for every year of use. The magnitude of the HRT effect on breast cancer risk is similar to that of a delayed menopause. No increased risk exists in women who stopped using HRT more than 5 years [42].

The relationship of oral contraceptives to breast cancer risk has been analyzed by the Collaborative Group on Hormonal Factors in Breast Cancer. Based on worldwide epidemiological evidence, a small in-

crease of breast cancer relative risks (RR) was found in women taking oral contraceptives (current users or for those who had stopped 1-4 years previously), while a relative risk increase of low significance or no excess risk was found after stopping the contraceptive use for 5-9 or more than 10 years, respectively [43].

3.10 Radiation: The effects of ionizing radiation on breast parenchyma are dose-dependent. Although low doses of radiation exposure (e.g. from usual diagnostic radiography) are not associated with an increased risk for breast cancer development, higher doses induce carcinogenic effects on breast parenchyma [44]. Moderate exposures, such as those associated with chest radiographs after pneumothorax treatment of tuberculosis [45], are associated with a significant elevation in breast cancer risk. High-dose radiation exposure, such as during the course of mantle radiation therapy for Hodgkin's disease, are associated with a significantly increased risk for breast cancer [46]. Age at the time of radiation exposure is another significant factor that should be considered, especially in some subgroups of high-risk women (i.e. ataxia-telangiectasia mutation carriers) [47].

3.11 Miscellaneous: The mammographic pattern of breast parenchyma may indicate a possible risk factor for breast cancer development. The relative risks associated with mammographic findings are low or modest. Women with mammographically dense or glandular parenchyma are considered to be at higher risk for breast cancer development than women with fatty or atrophic breasts [48,49].

4. Breast cancer genetics

Only 5-10% of breast cancer cases are due to high-risk susceptibility genes, but a higher proportion have a family history and estimating the risk in this group can be complex. Among the cases of inherited breast cancer (5-10%), less than half are due to mutations (alterations in the genetic code) of the breast cancer genes BRCA1 and BRCA2. The cause of a minority of these cases is due to very rare genetic syndromes or rare high-risk genes (e.g. ataxia-telangiectasia; Li-Fraumeni syndrome- mainly due to the TP53 gene; Cowden's syndrome-mainly due to the PTEN gene). Despite the obvious importance of mutations in BRCA1 and BRCA2 in the etiology of breast cancer, these mutations are present in only a small proportion of subjects with breast cancer and a relatively small proportion of those with a family history of the disease [50]. 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 are high expectations of what genetics can currently deliver and although data on the effectiveness of prevention methods in breast cancer predisposition gene carriers are starting to accrue, many are still experimental and further data are needed before certain measures can be actively promoted [51].

5. Assessment of breast cancer risk

5.1 Common models for risk estimation: During the last two decades several models have been developed to assist in more precise risk estimation. These methods enable the quantitative estimation of the individual woman's risk for breast cancer development, by combining multiple risk factors into a comprehensible risk expression. It is expected that quantitative risk estimation will reduce the variation in management recommendations among physicians. However, all of these models are defective and have some limiting factors [52-54].

The aim of risk assessment is to define an individual's risk into 3 broad categories of standard (risk not significantly above the normal population), moderate or high risk, which will be intended to the designation of management strategies (Table 1) [51]. A common approach to estimate breast cancer risk is the Gail model [52]. By a detailed case-control analysis, the determined risk variables in the Gail model are: (a) the number of first-degree relatives with breast cancer, (b) the age at first live birth, (c) the age at menarche, (d) the number of breast biopsies, and (e) the history of atypical hyperplasia. The RR for each of these 5 factors is multiplied to provide a composite risk. This statistical model is a useful tool to estimate a woman's individualized absolute risk of developing breast cancer and is a well-validated model [55-57]. The method has been used in clinical counseling of concerned women and has served to identify women eligible for chemoprevention trials [58]. However, although it includes epidemiological factors, it does not adequately weighs familial risk factors and women with a genetic predisposition and has not been validated in

Table 1. Risk groups and the respective lifetime and relative lifetime risks

Risk group	*Population (%)*	*Lifetime risk*	*Relative lifetime risk*
Standard	97	< 1:6	< 2
Moderate	2	1:4 - 1:6	2 - 3
High	< 1	> 1:4	>3

breast cancer risk of younger women [56,57,59,60]. In women who carry genes predisposing to the development of breast cancer the Gail model underestimates the absolute risk [61].

The Claus model [54] is intended to estimate risks over a series of 10-year intervals by age for women with first-degree relatives (mothers, sisters, daughters) or second-degree relatives (grandmothers or aunts, maternal or paternal) with breast cancer. The calculations are based solely on genetic relationships. The Claus model, although not perfect, comes closer to reflecting genetic risk. It should be noted that when results of genetic testing are available for a family member with a known genetic predisposition, the model no longer applies to that individual and risk figures should be taken from the gene- or mutation-specific estimates only. The Claus Tables do not take into account 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 [57,62].

5.2 Genetic risk: As mentioned above, the Claus Tables are appropriate to assess risk of familial breast cancer. According to the American Society of Clinical Oncology, factors indicating a high probability that a woman is at risk for genetically transmitted breast cancer include: (a) a family with >2 breast cancer cases and one or more cases of ovarian cancer diagnosed at any age; (b) a family with >3 breast cancer cases diagnosed before 50 years of age; and (c) sister pairs with two of the following cancers diagnosed before the age of 50 years: 2 breast cancers, 2 ovarian cancers, or a breast and ovarian cancer [63]. The Scottish Intercollegiate Guidelines Network (SIGN) in collaboration with the Scottish Cancer Therapy Network developed a national clinical guideline for breast cancer where women at substantially increased risk of breast cancer are classified in two categories: (a) women who have 3 (or more) times the population risk of developing breast cancer, and (b) women at very high risk in whom direct gene testing might be appropriate (Table 2) [64].

Table 3 presents the potential management strategy for women at increased familial risk, based on the published guidelines of the UK Cancer Family Study Group in consultation with the Strang Cancer Prevention Center, New York [65].

Table 2. Familial breast cancer: Criteria for identifying women at substantially increased risk

The following categories identify women who have 3 (or more) times the population risk of developing breast cancer:
A woman who has: • One first-degree relative with bilateral breast cancer or breast and ovarian cancer; *or* • One first-degree relative with breast cancer diagnosed under the age of 40 years or one first-degree male relative with breast cancer diagnosed at any age; *or* • Two first- or second-degree relatives with breast cancer diagnosed under the age of 60 years or ovarian cancer at any age on the same side of the family; *or* • Three first- or second-degree relatives with breast or ovarian cancer on the same side of the family
Criteria for identifying women at very high risk in whom direct gene testing might be appropriate:
• Families with four or more relatives affected with either breast or ovarian cancer in three generations and one alive affected individual

In this context a first-degree female relative is mother, sister or daughter. A second-degree female relative is grandmother, granddaughter, aunt or niece

6. Management and prevention strategies

6.1 Breast cancer counselling: Women attending a program for 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 [66]. Genetic risk counselling significantly improves risk validation accuracy in approximately 50% of women but the remaining continue to over- or underestimate them [67,68]. No single method of risk presentation is currently superior and it is recommended to analyze risk in more than one way. 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. The psychological consequences of belonging to the ''high-risk'' group should also be taken into consideration, since a woman's recognition of her increased breast cancer risk may have significant adverse reactions (anxiety, guilt, depression, and reduced self-esteem). The guilt felt by specific mutation carriers who pass the disease genes to their children is enormous. These adverse psychological sequelae have significant practical implication, since it is has been shown that women in such settings have difficulty adhering to routine, intense surveillance recommendations. Nevertheless, no significant associations have been found between risk perception and family history, or a range of demographic and psychological variables, and a number of empirical studies have investigated some of these psychosocial issues with reassuring results [69-73].

Accurate risk estimation is needed to provide rational management recommendations. During breast

Table 3. Potential management strategies for women at increased familial risk. The ages are based on average age at diagnosis and the lifetime risks are derived from the computer version (Cyrillic 3) of the Claus model, which gives lower risk than the Claus tables

Family history	*Lifetime risk*	*Risk group*	*Early mammography*[1]	*Refer to genetics clinic*
Breast cancer				
1 relative < 40 years	1:6	Moderate	Yes	No, except[2]
2 relatives > 40 and < 50 years	1:4-5	Moderate/high	Yes	Yes
2 relatives > 50 and < 60 years	1:5-6	Moderate	Yes	No[2]
3 relatives < 60 years of age	1:4	Moderate	Yes	No, except[2] and[3]
1 relative with bilateral breast cancer	1:3-6	Moderate (unless average age<40 years)	Yes	No, except[2] or average age <50 years
2 relatives < 40 years	1 in 3-4	High	Yes	Yes
3 relatives < 50 years	1 in 3	High	Yes	Yes
4 relatives any age	<1:2 to 1:3	High	Yes	Yes
Breast/Ovarian cancer				
1 ovarian cancer any age+ 1 breast cancer < 50 years	1 in 3-6	Moderate/high	Yes[4] (+ovarian screening)	Yes
>1 ovarian cancer ± breast cancer any age	1 in 3	High	Yes[4] (+ovarian screening)	Yes
Childhood cancer				
Childhood tumor < 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

[1]Annual mammography from 40 to 50 years of age; [2]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; [3]Some centres are collecting these families for research for further more moderate risk breast cancer genes; [4]Screening for ovarian cancer is not of proven benefit at present and should only be undertaken within a clinical trial

cancer risk counselling the physician should discuss with the woman the prognosis of breast cancer, the risks and benefits of alternative means of prevention and early diagnosis, in a supportive but nondirective way, present the facts and withhold personal opinions or preferences. The process of counselling is often a long procedure during which all the appropriate family and personal history is carefully collected with verification of crucial facts with medical records [61,73].

Although women have a general awareness of the issues concerning breast cancer, there is a poor understanding of their own individual risks. The purpose of a Counselling Clinic in Breast Units is to: (a) provide access to accurate information for women, their families and their general practitioners (G.Ps); (b) assess an individual woman's risk; (c) provide further counselling if required; (d) provide radiological screening according to the Unit's protocols and encourage participation in clinical trials; (e) provide information on chemoprevention and encourage participation in clinical trials; (f) refer high-risk women to a clinical geneticist according to agreed regional protocols; (g) ensure access to risk-reducing surgery where this is considered appropriate. The Breast Unit should have clear guidelines on the management of women at familial risk and these should be disseminated to G.Ps. 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 have rapid access to the Unit's symptomatic clinic.

Since the G.P. and primary health care team provide ongoing care for patients in the community, their role in the care of patients with breast cancer is central to providing good overall care. Better uptake of breast screening may be achieved by primary care professionals encouraging attendance. Their role is triple: (a) to promote the early detection of breast cancer; (b) to ensure the appropriate referral of women with breast symptoms; (c) to provide and coordinate the care of women with breast cancer and, as appropriate, their families. A list of conditions that require referral to hospital for assessment is provided in Appendix 2. Some women with breast symptoms can at least initially be managed by their G.P. Such conditions are also listed in Appendix 2 [74-76].

6.2 Breast self- and clinical examination: Monthly self-examination is recommended to begin in early adult life (by the age of 20 years) in order to establish a regular habit and allow familiarity with the normal characteristics of breast tissue. Annual or twice yearly clinical examination is recommended, beginning at the age of 25-35 years [77]. Although in previous studies it has been shown that breast self-examination and clinical examination failed to reduce

Appendix 2. Conditions that require referral to a breast specialist or can be initially managed in general practice

Conditions that require referral to a breast specialist include:

Lump
- any new discrete lump
- new lump in pre-existing nodularity
- asymmetrical nodularity that persists at re-examination after menstruation
- abscess or breast inflammation which does not settle after one course of antibiotics
- cyst persistently refilling or recurrent cyst (if the patient has recurrent multiple cysts and the G.P. has the necessary skills, then aspiration is acceptable)

Pain
- if associated with a lump
- intractable pain that interferes with a patient's lifestyle or sleep and which has failed to respond to reassurance, simple measures such as wearing a well supporting bra, and common drugs
- unilateral persistent pain in post menopausal women

Nipple discharge
- all women aged 50 and over
- women under 50 with:
  bloodstained discharge; or
  bilateral discharge sufficient to stain clothes; or
  persistent single duct discharge

Nipple retraction or distortion, nipple eczema

Change in skin contour

Conditions that can be initially managed in general practice:

- Young women (<35 years) with tender, lumpy breasts and older women with symmetrical nodularity, provided they have no localized abnormality
- Women with minor and moderate degrees of breast pain without a discrete palpable lesion
- Women aged under 50 who have nipple discharge that is from more than one duct or is intermittent and is neither bloodstained nor troublesome

the mortality rate from breast cancer [78,79], it is possible that the limited sensitivity of mammography in younger women (due to the more fibrous breast parenchyma at this age group) makes breast self-examination and clinical examination of greater value for the high-risk woman than for women of average risk [77]. A retrospective study of high-risk women from the Royal Marsden Hospital demonstrated that 45% (14 of 31) of breast cancers would have been missed if mammography alone had been undertaken without clinical examination [80]. 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, neither subgroup analysis of "at risk" women was carried out, nor randomized studies comparing clinical examination with other screening modalities were performed. Breast self-examination is often advocated, but its effectiveness is unproven and only one randomized study has been undertaken in women "at risk" [81].

6.3 Genetic testing: The psychological impact of genetic counseling and of the options that arise from genetic counselling should be monitored very closely [82]. It is recommended that all genetic testing should occur within a Cancer Genetics Clinic after genetic counselling. The criteria for testing in the UK require that there should be >20% probability of the presence of a mutation. However, the American Society of Clinical Oncology (ASCO) guidelines on genetic testing suggest a >10% probability of a breast cancer mutated gene being present. Candidates for mutations of BRCA1/2 genetic testing are: (1) single case of breast cancer at < 40 years of age if Ashkenazi; (2) 2 breast cancer cases at < 40 years or 3 < 50 years of age; (3) 4 cases of breast cancer at < 60 years of age; (4) >4 cases of breast cancer at any age; (5) ovarian and breast cancer in a family (breast cancer at < 50 years of age if only one ovarian and one breast cancer case); and (6) early onset female breast cancer at <60 years of age and male breast cancer at any age. Candidates for mutations of TP53 gene testing are: 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). Candidates for PTEN testing are subjects with 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). Candidates for ATM testing are individuals with clinical features of ataxia-telangiectasia in the family.

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, and a test in an unaffected relative (the predictive genetic test) is negative, this means a true-negative result. Exceptions, when an unaffected individual is offered for genetic testing without prior diagnostic testing in the family, include the case that the affected relatives are all deceased, or are uncontactable, or refuse to give a blood sample for diagnostic testing. The unaffected testee should be told that a negative test in this situation cannot exclude the presence of a breast cancer predisposition gene. This is because there is uncertainty as to whether the genetic test is testing the relevant breast cancer gene, as further genes are as yet undiscovered. This situation is considered if the individual states that wishes to have prophylactic surgery performed if the test is positive.

A risk-reduction can be offered to individuals with negative test (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.

6.4 Breast imaging

6.4.1 Mammography: There are no published randomized controlled trials examining the effectiveness of mammographic screening in women less than 50 years of age with a family history of breast cancer. In general, in women at high risk, annual mammography is suggested, beginning at the age 25-35 years [47,77,83]. Within this interval, the age at which regular screening is initiated should be determined by the risk parameters of the individual being tested. Nevertheless, the limitations of mammography in the screening of young women are well known. It is usually stated that the false-negative rate for mammography is about 10%; however, this percentage is derived from studies in women over the age of 50 [84]. For younger women, the false-negative rate is much higher (up to 38%) [85,86]. Similarly, false-positive results in mammography are more common in younger women [87]. However, the published studies do suggest that mammographic screening in high-risk groups of women less than 50 years of age may detect cancer at a rate equivalent to that seen in women at normal risk and 10 years older [80,88-91]. As it is recognized that the sensitivity of mammography in younger women is significantly reduced, there are concerns regarding radiation exposure in a group of women who may have an increased sensitivity to radiation. The potentially increased risk of breast cancer from repeated radiation exposure (when mammography starts at an early age) should also be taken into consideration. Interestingly, this risk may be even higher in patients with an inherited cancer predisposition, e.g. as carriers of the ataxia-telangiectasia gene and the p53 gene, which are known to have increased radiosensitivity [47,83].

It is noted that only a small proportion of breast cancer is hereditary and linked to highly penetrant dominant genes [92]. Evidence that mammographic screening offers some benefit to women with a significant family history of breast cancer is still limited because of the small size of most relevant studies [88,90,91,93-95]. The following recommendations are based on the currently suggested "best practice" and are in accordance with the 'Guidance on Screening and Symptomatic Imaging' by the Royal College of Radiologists [96]: (i) any mammographic screening of women in this risk group should be planned, should follow agreed Unit protocols and be subject to prospective data collection; (ii) 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); (iii) 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; (iv) it is recommended that family history screening should be carried out under the direct supervision of a clinician who has a special interest in breast cancer family history screening; (v) 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; (vi) family history risk decreases with age and, for most women with significant family history aged 50 years or more, the screening as provided by the National Health Service Breast Screening (NHSBSP) is likely to be sufficient; (vii) the use of mammography in screening women "at-risk" under 35 years of age should not be routine; (viii) 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 screening mammography in 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 [97]. It is recommended that screening mammography should be performed every 1-2 years. More frequent mammography is not recommended.

6.4.2 Breast ultrasonography: Annual breast ultrasonography has been proposed as an alternative for the screening at an early age in high-risk women, because of the concerns on the safety of screening mammography in this group of women [98]. However, the role of ultrasonography as a screening tool remains undefined. Addition of ultrasound to mammography may increase sensitivity in younger women [99].

6.4.3 Breast magnetic resonance imaging (MRI): Breast MRI has shown potential as a sensitive screening test, but it is extremely expensive. A trial is underway in the UK evaluating the use of MRI as screening test in high-risk women [100]. Only one published

study has prospectively compared ultrasound, mammography and MRI [101]. In this study of 196 high-risk women, MRI was superior to ultrasound or mammography. Other initial studies also support that MRI has a greater sensitivity than mammography in high-risk women [102,103]. Breast MRI may reduce any theoretical risk for increasing breast cancer risk from multiple radiation doses associated with frequent mammographic evaluation at an early age and can be helpful in the evaluation of the high-risk young woman with dense breast parenchyma, in which the limitations of mammography are well known. Consequently, breast MRI seems to be very helpful for the screening of mutation carriers [98,104].

6.5 Surgical prophylaxis

6.5.1 Bilateral risk-reducing mastectomy (BRM): The role of BRM or "prophylactic mastectomy" has been controversial for several reasons including the psychosocial significance of the breast in western cultures and the wide acceptance of breast conservation in surgery for early breast cancer. BRM was used in some centres for many years with the aim of preventing breast cancer with little published data on its efficacy. This controversy over prophylactic mastectomy is reflected in a recent consensus statement: "No recommendation is made for or against prophylactic mastectomy; this is an option, but evidence of benefit is lacking and case reports have documented the occurrence of cancer following prophylactic surgery" [77]. Two different procedures have been proposed for the surgical prevention of breast cancer: total mastectomy (usually with breast reconstruction) and subcutaneous mastectomy [105]. Total mastectomy removes the mammary gland mass with the nipple/ areola complex and a variable amount (ellipse) of overlying skin to allow excision of the underlying breast parenchyma. Subcutaneous mastectomy removes as much as possible of the breast tissue, but the overlying skin and the nipple/areola complex are preserved [106]. For preventing devascularization, breast tissue must be left behind under the nipple and the areola. This results in more breast parenchyma left behind after prophylactic surgery. Advocates of subcutaneous mastectomy argue that the cosmetic results achieved by this procedure are superior to total mastectomy. The surgical procedure should aim at removing substantially all of the 'at risk' breast tissue, but there should be a balance between reduction of cancer risk and cosmetic outcome.

However, since the aim of prophylactic mastectomy is to remove as much of the breast parenchyma as possible, the procedure of choice is total mastectomy [47,105]. Because of the difficulty in achieving total extirpation of the breast tissue prophylactic mastectomy reduces the prophylactic effect of surgery [47,105,107]. Breast carcinoma can develop in the remaining breast parenchyma and cases of carcinoma developing in residual breast tissue are documented for both subcutaneous and total mastectomy [108-112]. It was 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 [112,113]. However, many studies showed that prophylactic mastectomy significantly reduces, but does not totally eliminate the risk of subsequent breast cancer in carefully selected patients [114-116]. It was demonstrated that the risk-reducing mastectomy reduces the risk of breast cancer by 90% in high-risk and BRCA1/2 mutation carriers [112,116-118].

It is suggested that BRM is a most effective strategy in high-risk women. The aims of BRM are to: (i) reduce the incidence of breast cancer in high-risk women, as in BRCA1 or BRCA2 mutation carriers; (ii) reduce mortality from breast cancer in high-risk women; (iii) relieve anxiety; (iv) balance the reduction in risk against cosmetic outcome, with subsequent quality of life issues. Most of the women that undergo BRM 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 [119]. Prophylactic mastectomy is associated with certain morbidity and significant psycho-emotional consequences [120,121].

Women should be offered BRM only on the basis of a strict selection and management plan [122]. 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 1:4. Individual women should be informed not only of the rationale of surgery, but also about other prevention options such as screening and chemoprevention trials. It is likely that a minority of the women to whom it is offered will undergo BRM. A psychological assessment is essential to ensure that an appropriate decision is made. The availability of genetic testing may influence patient choice. BRM should be undertaken only by specialist surgeons within a specialist unit with full multidisciplinary experience and support. 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.

Consultations for BRM should include: (i) a clinical geneticist, psychiatrist (or clinical psychologist) and specialist surgeon working within an agreed unit protocol; (ii) objective confirmation of family history

(at least 2 confirmed cases wherever possible); (iii) risk calculation/genetic test feasibility; (iv) discussion of screening, chemoprevention and surgery; (v) description of operation options; (vi) limitations and residual risk; (vii) reconstruction options; (viii) the options for the nipple-areola complex; (ix) morbidity, scarring and recovery; (x) specialist breast nurse discussions; (xi) psychological assessment; (xii) realistic expectation of results. Risk-reducing mastectomy should not usually proceed if: (i) risk has not been verified; (ii) fictitious family history or Munchausen's syndrome; (iii) BRM is not the woman's own choice; (iv) impeding result of genetic testing; (v) current psychiatric disorder including clinical depression or phobias or body dysmorphic syndrome; (vi) co-morbidity outweighs clinical benefit; (vii) unrealistic expectations. After completion of BRM and reconstruction, patients should be seen annually and data on outcomes be collected prospectively and subjected to regular clinical audit.

6.5.2 Risk-reducing prophylactic oophorectomy: The screening for mutations in BRCA1 and BRCA2 genes can identify individuals at risk from families with inherited breast/ovary cancer syndromes. Bilateral prophylactic oophorectomy can significantly lower ovarian cancer risk in women who carry BRCA1 mutations [123-125]. Oophorectomy lowers the risk of breast cancer, even in women who have previously used HRT. Nevertheless, the risk reduction is limited to pre menopausal women who undergo oophorectomy. The magnitude of risk reduction approaches 50% and it is similar with that associated with tamoxifen use in breast cancer prevention trials. Prophylactic oophorectomy should not routinely be recommended solely to reduce the breast cancer risk.

6.6 Chemoprevention: There is a potential primary prevention of breast cancer in women at high risk with the use of medications, such as tamoxifen and raloxifene. The largest study of breast cancer prevention with tamoxifen, the National Surgical Adjuvant Breast Project (NSABP)-P1, recruited 13,388 women with a minimum estimated risk of breast cancer of >1.66% per annum (p.a.) and randomized them to tamoxifen 20 mg daily for 5 years *versus* placebo, and found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up of 55 months [126]. The women that were enrolled into the trial were considered as high-risk because they were >60 years of age, or were between 35 and 59 years of age with a 5-year predicted risk for breast cancer of at least 1.66% (using the Gail model), or they had lobular carcinoma *in situ*. The decreased risk occurred in all age groups, and was 44% in women 49 years of age or younger, 51% in those between 50 and 59 years, and 55% in those 60 years or older. In women with a history of either LCIS or atypical hyperplasia, the risk of invasive cancer was reduced by 56% and 86%, respectively. Particularly important was the finding that the drug reduced the occurrence of ER-positive tumors by 69%, whereas there was no such reduction in the occurrence of ER-negative tumors. Tamoxifen administration resulted in a reduction in hip, radius, and spine fractures (19% reduction). An increased rate of endometrial cancer, predominantly in women 50 years of age or older, was observed in the tamoxifen group. No liver cancers or increase in colon, rectal, ovarian, or other tumors occurred in the tamoxifen group. Higher rates of stroke, pulmonary embolism, and deep-vein thrombosis were observed more frequently in the 50-year or older women who received tamoxifen. Development of cataract was marginally increased. The incidence of hot flashes and vaginal discharge was increased in the tamoxifen group.

On the other hand, two European trials showed that tamoxifen prophylaxis did not reduce the incidence of breast cancer significantly. A study from the Royal Marsden Hospital [127] randomized 2,471 women who had at least one first degree relative with breast cancer under the age of 50 years or with bilateral cancer to tamoxifen or placebo groups. This study failed to demonstrate a significant reduction in breast cancer incidence despite having sufficient statistical power to do so. It was assumed that one potential reason for this was the relatively large number of women who were 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 tumors and potentially receive less benefit from tamoxifen. The Italian Tamoxifen Prevention study [128] randomized 5,408 women of relatively low risk of breast cancer who had undergone prior hysterectomy for non-cancerous reasons (thus having no risk of endometrial cancer), with or without ovariectomy; these women were randomized to receive placebo or tamoxifen 20mg per day for 5 years. As in the English trial, 14% of women were on HRT. The study was terminated early due to a high drop out rate. Compliance in this study was low, as was the statistical power. In an update of the Italian Tamoxifen Trial, tamoxifen still did not significantly protect against breast cancer [129].

The conflicting results of these studies can be explained by the dissimilarity in design, number of participants, population, the allowance of the use of HRT, few breast cancer events, and greater rates of non-compliance in the two European studies. However, many questions remain unanswered, such as what is and how long lasts the protective effect of tamoxifen, which is the role of tamoxifen in women on HRT and

in those with specific breast cancer genotypes (i.e., BRCA1/BRCA2 mutation carriers).

The International Breast Cancer Prevention study (IBIS I) is a double-blind placebo-controlled randomized trial of tamoxifen 20 mg/day for 5 years, in 7,152 healthy women, aged 35-70 years, at increased risk of breast cancer [130]. The first results indicate that prophylactic tamoxifen reduced the risk of breast cancer by about a third (32%). The incidence of endometrial cancer was doubled in the tamoxifen group, but this increase was not statistically significant. 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, but the combined evidence indicates that mortality from non-breast-cancer causes is not increased by tamoxifen.

However, the overall risk to benefit ratio for the use of tamoxifen in prevention is still unclear and the group of healthy high-risk women for whom the benefits of tamoxifen clearly outweigh any risks need to be identified. 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 [131].

Raloxifene is a selective estrogen receptor modulator (SERM) that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting. Among postmenopausal women with osteoporosis it was found that the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with raloxifene [132]. Raloxifene did not increase the risk of endometrial cancer. The STAR (Study of Tamoxifen and Raloxifene) trial is an ongoing study aiming to compare the effects of tamoxifen and raloxifene regarding the prevention of breast cancer in high-risk postmenopausal women [133].

Recently, there has been intense interest on the possible role of aromatase inhibitors in the prevention of breast cancer development. An early report from the ATAC study in which the aromatase inhibitor anastrazole was used in an adjuvant setting for postmenopausal women with early breast cancer suggests that aromatase inhibitors may also have a significant chemopreventive effect [134]. Patients in the anastrazole-alone arm of this study had a reduction in contralateral breast cancer of 58% compared with those on tamoxifen alone.

6.7 Diet and lifestyle: Most significant risk factors associated with breast cancer such as gender, age, early menarche and parity cannot be changed. Although diet and lifestyle factors may have an impact on breast cancer risk, there is no convincing evidence to suggest that modifying diet or lifestyle will result in reduced risk. However, even if dietary or lifestyle modifications alone are not likely to be a sufficient method for breast cancer prevention, women at increased risk of breast cancer could be advised to reduce dietary fat, avoid obesity, reduce alcohol consumption and take regular exercise [135,136].

Currently, no data exist to compare the prophylactic options in breast cancer prevention. Thus, many questions remain unanswered concerning the optimal management of the high-risk woman. Nevertheless, patient counselling has a central role in the decision-making process and should be based on a multidisciplinary approach. Finally, the woman will make the final decision based on the amount of risk she is willing to accept.

A number of useful recommendations for the management of women at high risk for developing breast cancer and the respective grades of evidence were selected by the authors and are presented in Appendix 3. A general guideline on the management of women at familial risk as it is determined by their risk group is presented in Table 4.

Table 4. Management of women at familial risk according to risk group

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 chemopreventive intervention

Moderate risk
- Consider referral by their G.P. to a Family History Clinic
- Consider offering mammographic screening according to Unit protocols and preferably within a clinical trial
- Should be recommended to consider chemoprevention where appropriate, and be given information on clinical trials

High risk
- Should be offered referral by their G.P. 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 chemoprevention where appropriate, and be 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

Appendix 3. A list of useful recommendations for the management of women at high risk for developing breast cancer and the respective grades of evidence

No.	*Recommendation*	*Grade*
1	Centres and units should develop an integrated network of cancer care using common clinical guidelines, management protocols and strategies of care	**D**
2	All Breast Units should have a protocol for the management of women at familial risk	**D**
3	All staff should be encouraged to develop communication skills by attending appropriate courses	**A**
4	All members of the primary care team should be aware of the concerns women have about breast screening, and should encourage attendance	**D**
5	Women should be encouraged to become aware of the feel and shape of their breasts, so that they are familiar with what is normal for them	**D**
6	Women should be encouraged to report any change from normal to their G.P.	**D**
7	Clear lines of communication should be maintained between the primary care team and staff in the Breast Unit	**D**
8	The G.P. should be made aware of the information given to the patient and relatives	**D**
9	Patients attending for diagnostic purposes should be seen on at least one occasion by a trained breast specialist	**D**
10	Patients with breast cancer should be managed by a multidisciplinary team within a designated Breast Unit	**B**
11	Women at potentially increased familial risk of breast cancer should be defined according to standard, moderate or high risk group	**C**
12	All screening and treatment of individuals at high risk should be part of a clinically audited programme	**D**
13	Women at high risk of familial breast cancer should be referred to a genetics clinic according to an agreed protocol	**D**
14	Breast screening services should meet the standards set by National Breast Screening Programmes	**D**
15	A baseline mammogram prior to commencement of HRT is not recommended	**D**
16	Mammography should not be performed as the only or first diagnostic test for symptomatic disease	**D**
17	Women with LCIS or severe atypical hyperplasia should have annual or biennial mammography	**D**
18	Frequency of screening procedures in women at high risk of breast cancer: <40 years: biennial mammography and annual clinical examination 40-50 years: annual mammography and clinical examination 50+ years: depending on the risk	**D**
19	Women who are eligible should be offered the opportunity to participate in prospective chemoprevention studies	**A**
20	Risk-reducing mastectomy may significantly reduce, but not eliminate, the risk of subsequent breast cancer and should be offered to women where appropriate	**B**
21	Units undertaking risk-reducing mastectomy should have agreed protocols	**D**
22	Prophylactic oophorectomy should not be routinely recommended solely for reduction in breast cancer risk	**B**
23	Prophylactic oophorectomy should be discussed as an option to reduce ovarian cancer risk in BRCA1 and BRCA2 carriers	**B**
24	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	**C**
25	All professionals involved in the management of patients with breast cancer should have a high index of suspicion regarding the presence of psychological and psychiatric problems	**B**
26	Patients with significant psychological problems should be assessed by a liaison psychiatrist or clinical psychologist	**A**
27	Patients should be given appropriate information over a period of time, since what they may wish or need to know may vary over time	**B**
28	Women should have the opportunity to discuss treatment options	**B**
29	Women should be involved in decision-making to the extent they wish	**B**
30	If appropriately trained personnel are available, women should be offered relaxation-based interventions	**A**
31	If clinically appropriate, women should be offered breast conservation provided they wish to be involved in decision-making	**A**
32	Women with clinically significant anxiety or depression should be referred for specialist help from a clinical psychologist or psychiatrist	**A**
33	All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse for information and support at every stage of diagnosis and treatment	**D**
34	All those involved in the management of patients with breast cancer should be alert to psychosocial difficulties in other family members, including partners and children	**B**
35	Family and friends of women with a potential or known diagnosis of breast cancer should have access to a breast care nurse, if the patient feels that this is appropriate	**C**
36	Nurses undertaking a counselling role should have a counselling qualification, or be supported to do so	**B**
37	Breast care nurses should have appropriate education and experience	**D**

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