Screening women at moderate risk of breast cancer

Breast cancer risk is grouped into high risk, moderate risk and woman at or near population risk. Who are moderate-risk women? How is their risk assessed? What is the evidence and best practice for screening moderate-risk women?

Breast cancer is the commonest cancer in Britain with 44 659 new cases per year (2004) (Cancer Research UK, 2007) with a one in nine lifetime risk. It can be hereditary, familial or sporadic. Hereditary cancers are caused by a direct germline mutation of the tumour suppressor genes breast cancer 1 and 2 early onset (BRCA1 and BRCA2), which are highly penetrant and autosomally dominant. Other relevant genes include p53 (associated with Li–Fraumeni syndrome), the ATM gene (associated with ataxia telangectasia), STK11 associated with Peutz–Jeghers syndrome, PTEN, CKH2 and more. Mutations in these genes are rare, accounting for 5–10% of breast cancers (Cipollini et al, 2004). Familial breast cancers do not have these highly penetrant genes but up to 20% of all breast cancers show a significant family history indicating background genetic factors, as yet poorly understood. These may be low-risk susceptibly genes with polygenic interactions. Having a first-degree relative with a history of breast cancer is one of the strongest risk factors for breast cancer, after age. Relative risk is 1.5–2.4 times higher than for those without a family history (Pharoah et al, 1997) (*Tables 1* and *2*).

Table 1. Women's risk of breast cancer by age

Age (years)	Risk of developing breast cancer
25	1 in 15 000
30	1 in 1900
40	1 in 200
50	1 in 50
60	1 in 23
70	1 in 15
80	1 in 11
85+	1 in 10
Over lifetime	1 in 9

From Cancer Research UK (2007)

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This article will review the women who are at moderate risk of developing breast cancer, the evidence for screening these women, how screening is currently offered for moderate-risk women, whether screening is harmful to this group of women, and any lifestyle recommendations.

Women at moderate risk of developing breast cancer

In 2004 the National Institute for Clinical Excellence (NICE) in the UK issued guidelines for assessing the risk of breast cancer. Three categories of risk were developed: moderate risk (often called increased risk), high risk, and at, or near to, population risk. A woman with a family history that fits the guidelines below (*Tables 3* and *4*) is said to be at moderate risk of developing breast cancer. Such women should be referred to secondary or tertiary care for appropriate screening. Overall this group has a one in six lifetime risk. A family history of malignancies of breast and ovary is taken into account since both are associated with some BRCA 1 and 2 germline mutations.

Clinicians who counsel women need a rapid method to estimate risk for individuals. The Breast Cancer Detection Demonstration Project (BCDDP) model (sometimes called the Gail model) and Claus model are the most widely used risk assessment tools (Claus et al, 1994) (*Table 5*).

Table 2. Family history and the risk of breast cancer

Relative status	Relative risk	95% confidence intervals
Any relative	1.9	1.7–2.0
First-degree relative	2.1	2.0–2.2
Mother	2.0	1.8–2.1
Sister	2.3	2.1–2.4
Daughter	1.8	1.6–2.0
Mother and sister	3.6	2.5–5.0
Second-degree relative	1.5	1.4–1.6

From Pharaoh et al (1997)

Evidence for screening women at moderate risk

Film-screen mammography has been the method of screening breast cancer for over 20 years with the UK National Breast Screening programme inviting women from 50–70 years for two-view mammography. But most hereditary and many familial breast cancers occur in premenopausal women; the value of population screening mammography is significantly lower below the age of 50 years because of increased breast density (Warner et al, 2001). What is known about screening mammography in younger women who are at moderate risk of developing breast cancer?

There have been a number of randomized prospective trials designed to evaluate the efficacy of mammography screening and impact on mortality reduction. Other evidence comes from cohort studies and service screening.

Evidence from population studies

The Canadian National Breast Screening Study (CNBSS–1) in 1980 was the first trial specifically designed to assess women between 40 and 49 years of age. After 7 years there was excess mortality in the screened group, which did not reach significance. After a median follow up of 13 years, the relative risk of breast cancer deaths in the screened group did, however, fall (Miller et al, 2002). This study has been criticized on the grounds of technical factors, contamination of control groups and randomization, but has led the way for many more robust studies looking at screening of moderate-risk women.

Tabar et al (2003) compared deaths from breast cancer diagnosed in the 20 years before screening was introduced (1958–77) with those from breast cancer diagnosed in the 20 years after the introduction of screening (1978–97), in 210 000 women aged 20–69 years, allowance being made in the statistical analysis for all potential confounding factors. In the 40–49-year age group, deaths from breast cancer fell significantly in those who were screened.

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) age trial looked at the effectiveness of mammographic screening starting at the age of 40 years, compared with starting at the age of 50 years, in reducing mortality from breast cancer. Findings of 160 921 women at follow up 10.7 years later showed decreased breast cancer mortality in the intervention group, but the absolute risk reduction of 4% did not reach statistical significance (Moss et al, 2006). Recruitment has now finished; follow-up screening data will be published at the end of the surveillance period in 2010.

The above trials provide mounting evidence of mortality benefit in screening women aged 40–49 years. Overall mammographic screening in women below the age of 50 years reduces breast cancer mortality by approximately 16–18% but takes 12–14 years to emerge. Where the incidence of cancer is higher, as in high-risk women, this screening effect is likely to be greater. This is in comparison with a 25% mortality reduction in women over 50 years with benefit emerging after 7–9 years.

Evidence from women with a family history of breast cancer

Kerlikowske et al (2000) studied women with and without a first-degree relative with breast cancer. Cancer detection was 1.3–2.0-fold higher among women with a family history than in women of a similar age without such a history. The positive predictive value of mammography was higher in women with a family history than in those without.

Table 3. Moderate risk managed within secondary care

One relative	One first degree relative with breast cancer diagnosed <40 years
Two relatives	Two first or second degree relatives with breast cancer diagnosed at an average age of <50 years
	One first degree relative and one second degree relative with breast cancer diagnosed at an average age >50 years but <60 years
Three relatives	One first degree relative and two first or second degree relatives with breast cancer diagnosed at an average age > 60 years

All relatives must be blood relatives on the same side of the family

Table 4. Moderate risk managed within tertiary care (clinical genetics)

One relative	One bilateral breast cancer confirmed separate primary cancers, average age of diagnosis <50 years
	One individual with both breast and ovarian cancer, where the ovarian cancer is diagnosed at any age and breast cancer diagnosed <50 years
Two relatives	One bilateral breast cancer and one first or second degree relatives breast cancer, average age of diagnosis of all cancers <60 years
	Male breast cancer at any age plus one first or second degree relatives with breast cancer <50 years
	One ovarian cancer at any age plus one first or second degree relatives breast cancer <50 years
Three relatives	Male breast cancer at any age plus two first or second degree relatives with breast cancer <60 years
	One ovarian cancer at any age plus two first or second degree relatives breast cancer <60 years

All relatives must be blood relatives on the same side of the family

Table 5. Ten-year and lifetime risk of breast cancer

	10-year risk at 40–49 years	Lifetime risk
At or near population risk	<3%	<17%
Moderate or raised risk	3–8%	>17%–<30%
High risk (BRCA genes)	>8%	>30% (50–85%)

A woman's age should be assumed to be 40 for a woman in her forties. A 10-year risk should be then calculated for the age range 40–49 years. (National Institute for Clinical Excellence, 2006)

The Moderna trial (Cortesi et al, 2006) studied breast cancer screening in women with different family histories and stratified them into four risk groups. The incidence of breast cancer in the BRCA high and intermediate groups was higher than expected compared to the age-matched control group and was statistically significant.

Gui et al (2006) screened 1132 women at moderate and high risk of breast cancer, using annual clinical examination and mammography from the age of 35 years. The moderate and high-risk groups had breast cancers diagnosed at an earlier age (mean 54 and 51 years respectively) compared to the standard risk group (mean 63 years).

Maurice et al (2006) compared diagnosed breast cancer patients with a family history having 12–18-monthly mammographic screening, with patients of the same age range, no family history and no exposure to screening. Survival was significantly better in the family history group for breast cancer death and for disease-free survival. They concluded that screening younger women with a family history of breast cancer leads to survival benefit.

Further evidence will emerge as the Family History Screening Study (FH01) Management Committee, Steering Committee and Collaborators (2006) finish recruiting 6600 women aged 40–44 years at recruitment, with a significant family history of breast cancer. They will be offered annual mammography and followed up for 5 years. The principal comparison group will be the control group of the UK Breast Screening Age Trial. Published results will be expected in 2011. In the future the FH01 will look at screening women aged 30–40 years (FH02) as there is no current evidence to confirm a benefit in screening in these young women.

How is screening currently offered for moderate-risk women?

UK NICE guidelines (2006) recommend 'all women 40–49 years satisfying referral criteria to secondary or specialist care (at raised/moderate risk or greater) should be offered annual mammographic surveillance.' Magnetic resonance imaging (MRI) is only offered in the high-risk group and those with known genetic mutations. The role of MRI in high-risk women will not be discussed in this review.

Is screening harmful in women at moderate risk?

There are three main disadvantages to consider in screening moderate-risk women: radiation dose, lead time, and false positives and false negatives.

Radiation dose

Mammography uses low kV radiation which itself can induce breast cancer. The radiation effect is cumulative and it is assumed that the risk as a result of radiation induction occurs at a uniform rate after a 10-year latent period following exposure. These points must be considered when screening younger women who will ultimately have more years of mammographic radiation exposure and therefore increased potential of induced breast cancer. A breast screening programme in these women must be justified by demonstrating benefits which exceed the associated risks, in particular the risk of inducing future breast cancers.

There is evidence in the literature estimating the number of induced cancers expected following regular mammograms. Law et al (2007) conclude there is little, if any, risk of detriment exceeding benefit down to the age of 40 years. Annual two-view screening should not be considered below the age of 35 years for women with no family history. For those with a family history, mammography should only be considered if the family member was diagnosed below the age of 40 years. Berrington de Gonzalez and Reeves (2005) concluded that for a 20% reduction in mortality there was a net decrease in mortality from screening from 40 years. Screening below this age was potentially detrimental. The denser breast tissue of younger women requires a higher radiation dose, with decreased cancer sensitivity because there is masking. Mammographic density has also been shown to be a powerful predictor of breast cancer risk (McCormack and dos Santos Silva, 2006). Women who have a breast density of 75% or greater have an almost five-fold increased risk of breast cancer.

There is increasing concern that mammography may cause excess harm in certain population groups. Some genetic alterations may increase susceptibility to ionizing radiation. For example, 1.4% of the general population who are heterozygous for the ataxia telangectasia gene have an excess risk of cancer, particularly breast cancer in women. Both homozygotes and heterozygotes of ataxia telangectasia are unusually sensitive to ionizing radiation and may have a six-fold increased risk of developing breast cancer following exposure (Swift et al, 1991).

A glimmer of hope comes in the form of digital *vs* film mammography. Pisano et al (2005), in a prospective multicentre study, showed the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women. Most radiology departments are changing to digital mammograms to reflect this.

Lead time

If breast cancer is detected by screening but there is not a reduction in breast cancer mortality then the patient is given a notice of impending death with no tangible gain. This 'lead time' is usually 2–4 years of needless anxiety.

False positives and false negatives

There is psychological harm from false reassurance in women with false negative mammograms and psychological harm and effects of unnecessary investigations of false positives (Brett et al, 2005). About 5% of women

screened will have a mammographic abnormality, but of these only 10–20% will have cancer. Therefore further investigations may lead to more radiation, aspirations and biopsies which all have an associated morbidity.

Lifestyle recommendations for women at moderate risk

Evidence from literature shows a number of factors associated with the increased risk of breast cancer.

Hormonal environment

Much of this is associated with the hormonal environment of a woman's breast tissue and protection is afforded by late menarche, early first pregnancy (under 28 years) and early menopause. The number of pregnancies and breast feeding may have a small protective effect. Overall pregnancy transforms breast parenchyma into a more stable state and progesterone in pregnancy is protective as it may induce terminal differentiation in pluripotential stem cells.

Oral contraceptive pill and hormone replacement therapy

Both the oral contraceptive pill and hormone replacement therapy are associated with an increased risk of breast cancer. The oral contraceptive pill is associated with a 20% increased risk that persists for 10 years after cessation of use. The risks associated with hormone replacement therapy are greater for oestrogen-progestogen therapy than for oestrogen-only, differ by histological type of breast cancer, and are substantially attenuated with increasing body mass index (Reeves et al, 2006).

Diet, alcohol and obesity

Much thought is now being turned to modifiable risk factors in our environment. Michels et al (2007) reviewed all the prospective observational studies trying to link diet and breast cancer but concluded that, to date, there is no association that is consistent, strong, and statistically significant, with the exception of alcohol intake, being overweight, and weight gain. Other articles report stronger links with certain dietary components but overall their associations are less clear.

Diet

An increased risk of breast cancer with red meat and dairy product consumption has been reported in a number of studies. It is postulated this may be caused by elevated oestrogen and progesterone levels from intensive farming methods, which may have an effect on hormone-related cancers such as breast cancer (Ganmaa and Sato, 2005). Vitamin D is thought to act as a cancer chemopreventive agent. Many studies are linking low vitamin D levels with an increased risk of breast cancer in both pre- and postmenopausal women. The apparent protection in premenopausal women may be more pronounced for more aggressive breast tumours (Lin et al, 2007).

Alcohol

Alcohol consumption is consistently linked to increased breast cancer risk with the relative risk of breast cancer increased for each extra unit of alcohol consumed (Hamajima et al, 2002). This needs to be put into context of the J-shaped curve associated with alcohol and mortality risk where overall mortality is lowest from cardiovascular risk with moderate consumption of 3–15 units/week (White et al, 2002).

Obesity

Weight gain of more than 10 kg during adult life increases the risk of postmenopausal breast cancer (relative risk=1.2–2.3) (Sonnenschein et al, 1999). This is supported by the most recent evidence from Michels et al (2007).

Physical activity

The benefits of exercise have been proven with many conditions, but attempts to relate exercise to breast cancer risk have been conflicting. Some trials have shown lower rates of breast cancer in more active postmenopausal women, but others have not. Lifelong physical activity from adolescence has been suggested to reduce risk in latter life but this subject needs further investigation (Chan et al, 2007).

Conclusions

With such a high incidence of breast cancer, many women have a family member diagnosed with breast cancer. The media attention given to cancer genetics and breast cancer families renders patients anxious with raised medical expectations. Careful consideration of a patient's personal risk through family history, age and hormonal factors can be used to categorize risk and give an individual risk assessment to reassure or to plan future screening. The cost effectiveness and radiation risks of screening younger women are not truly known but the momentum for screening more women for breast cancer cannot be halted. BJHM

Conflict of interest: none.

KEY POINTS

- Breast cancer can be hereditary, familial or sporadic, high risk, moderate risk or population risk.
- The population risk is one in nine, moderate risk is one in six, and high risk is one in three or greater of breast cancer.
- Age and family history are the strongest risk factors for breast cancer.
- There is mortality benefit to screening women from 40 years with or without a family history but not below that age unless in the high risk group.
- Radiation dose vigilance is important in younger women and certain genetic predispositions because of the potential induction of breast cancer from radiation.
- A number of lifestyle factors show links to increased risk of breast cancer.

Berrington de Gonzalez A, Reeves G (2005) Mammographic screening before age 50 years in the UK. Comparison of the radiation risks with the mortality benefits. *Br J Cancer* **93:** 590–6

Brett J, Bankhead C, Henderson B, Watson E, Austoker J (2005) The psychological impact of mammographic screening. A systematic review. *Psychooncology* **14:** 917–38

Cancer Research UK (2007) UK Breast Cancer incidence statistics. (info.cancerresearchuk.org/cancerstats/types/breast/incidence/ accessed 11 October 2007)

Chan MF, Dowsett M, Folkerd E et al (2007) Usual physical activity and endogenous sex hormones in postmenopausal women: the European prospective investigation into cancer-norfolk population study. *Cancer Epidemiol Biomarkers Prev* **16:** 900–5

Cipollini G, Tommasi S, Paradiso A et al (2004) Genetic alterations in hereditary breast cancer. *Ann Oncol* **15**: i7–i13

Claus EB, Risch N, Thompson WD (1994) Autosomal dominant inheritance of early onset breast cancer. *Cancer* **73:** 643–51

Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* **347:** 1713–27

Cortesi L, Turchetti D, Marchi I (2006) Breast cancer screening in women at increased risk according to different family histories: an update of the Modena Study Group experience. *BMC Cancer* **6:** 210

FH01 Management Committee, Steering Committee and Collaborators (2006) The challenge of evaluating annual mammography screening for young women with a family history of breast cancer. *J Med Screen* **13:** 177–82

Ganmaa D, Sato A (2005) The possible role of female sex hormones in milk from pregnant cows in the development of breast, ovarian and corpus uteri cancers. *Med Hypotheses* **65:** 1028–37

Gui GP, Kadayaprath G, Darhouse N et al (2006) Clinical outcome and service implications of screening women at increased breast cancer risk from a family history. *Eur J Surg Oncol* **32:** 719–24

Hamajima N, Hirose K, Tajima K et al (2002) Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* **18**: 1234–45

Kerlikowske K, Carney PA, Geller B (2000) Performance of screening mammography among women with and without a first degree relative with breast cancer. *Ann Intern Med* **133:** 855–63

Law J, Faulkner K, Young KC (2007) Risk factors for induction of breast cancer by X-rays and their implications for breast screening. *Br J Radiol* **80:** 261–6

Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM (2007) Intakes of calcium and vitamin D and breast cancer risk in women. *Arch Intern Med* **167:** 1050–9

Maurice A, Evans DG, Shenton A, Ashcroft L, Baildam A, Barr L (2006) Screening younger women with a family history of breast cancer–does early detection improve outcome? *Eur J Cancer* **42:** 1385–90

McCormack VA, dos Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* **15:** 1159–69

Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB (2007) Diet and breast cancer: a review of the prospective observational studies. *Cancer* **15:** 2712–49

Miller AB, To T, Baines CJ, Wall C (2002) The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* **137:** 305–12

Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L (2006) Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* **368:** 2053–60

National Institute for Clinical Excellence (2004) *Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care.* Clinical Guidance 14. National Institute for Clinical Excellence, London

National Institute for Clinical Excellence (2006) *Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care.* Clinical guideline 41. National Institute for Clinical Excellence, London

Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA (1997) Family history and the risk of breast cancer: a systematic review and mete-analysis. *Int J Cancer* **71:** 800–9

Pisano ED, Gatsonis C, Hendrick E et al (2005) Diagnostic performance of digital versus film mammography for breast cancer screening. *N Engl J Med* **353:** 1773–83

Reeves GK, Beral V, Green J, Gathani T, Bull D (2006) Million Women Study Collaborators. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* **7:** 910–18

Sonnenschein E, Toniolo P, Terry MB et al (1999) Body fat distribution and obesity in pre- and postmenopausal breast cancer. *Int J Epidemiol* **28:** 1026–31

Swift M, Morrell D, Massey RB, Chase CL (1991) Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Engl J Med* **325:** 1831–6

Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW (2003) Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet* **361:** 1405–10

Warner E, Plewes DB, Shumak RS et al (2001) Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol* **19:** 3524–31

White IR, Altmann DR, Nanchahal K (2002) Alcohol consumption and mortality: modelling risks for men and women at different ages. *BMJ* **325:** 191