

REVIEW ARTICLE

Risk assessment and management of high risk familial breast cancer

D G R Evans, F Laloo

J Med Genet 2002;**39**:865–871

The demand for genetic services by women with a family history of breast cancer has increased exponentially over the last few years. It is important that risks to women are accurately assessed and that processes are in place for appropriate counselling and management. The classification of risk into average, moderate, and high, depending upon the assessed lifetime risk of breast cancer, allows for the management of moderate risk women within cancer units and high risk women within the regional genetic centres. Management of high risk women includes discussion of options including screening, chemoprevention, and preventive surgery. The majority of these options are still unproven in the long term and continuing research is needed for their evaluation. Mutation screening and predictive testing are now a reality for a minority of families, allowing for a more informed basis for decisions regarding management options.

Moderate risk women should be offered annual mammography between 35 and 50 years within the cancer units.

RISK FACTORS (table 1)

Family history

The presence of a significant family history is the most important risk factor for the development of breast cancer. About 4–5% of breast cancer is thought to result from inheritance of a dominant cancer predisposing gene.^{4,5} While hereditary factors may play a part in a proportion of the rest, these are harder to evaluate. Except in very rare cases such as Cowden syndrome,⁶ there are no phenotypic clues that help to identify those who carry pathogenic mutations. Evaluation of the pedigree is therefore necessary to assess the likelihood that the predisposing gene is present within a family. Inheritance of a germline mutation or the deletion of a predisposing gene results in early onset, and frequently contralateral, breast cancer. Certain gene mutations also confer an increased susceptibility to other malignancies, such as ovary and sarcomas.^{7,8} Multiple primary cancers in one person, or related early onset cancers in a pedigree, are highly suggestive of a predisposing gene. To illustrate the importance of age, it is thought that over 25% of breast cancer under 30 years is the result of a mutation in a dominant gene, compared to less than 1% of the disease over 70 years.³ The important features in a family history are therefore:

- Age at onset.
- Bilateral disease.
- Multiple cases in the family (particularly on one side).
- Other related early onset tumours.
- Number of unaffected subjects (large families are more informative).

BACKGROUND

Breast cancer is the most common form of cancer affecting women. One in 10–12 women will develop the disease in their lifetime in the UK. Every year 39 000 women develop the disease in England and Wales and as a result 13 000 will die (Cancer Research Campaign Statistics).

Women at risk of breast cancer may be classified into average (population) risk, moderate risk (two to three times the population risk), and high risk (greater than three times the population risk). This paper will concentrate on risk assessment and management of the last group, those women at high risk of developing breast cancer.

There is some evidence that women with inherited breast cancer have a worse prognosis than a control population.¹ This is on the background of an already poor record of survival within the UK as compared to the rest of Europe and the USA. It is important, therefore, that a high risk population of women is identified and optimal management, either by screening or prevention, is offered.

Various systems are in place to ensure that appropriate referrals are seen within the regional genetics centre.² Within the north west region of England, nurse led clinics are being established within cancer units to triage high risk women and refer them into the regional genetics centre.³

See end of article for authors' affiliations

Correspondence to:
Professor D G R Evans,
University Department of
Medical Genetics and
Regional Genetic Service,
St Mary's Hospital,
Hathersage Road,
Manchester, M13 0JH, UK;
garth.evans@cmmc.nhs.uk

Table 1 Factors associated with an increased risk of breast cancer

Family history

Early menarche (<12 years)
Late first pregnancy (after 28 years)
Current use of the OCP and for 10 years after
Nulliparity
Late menopause
Prolonged use of HRT (particularly combined therapy)
Significant weight gain in adult life
Proliferative breast disease on biopsy (not benign disease such as a fibroadenoma)

Hormonal and reproductive risk factors

The incidence of breast cancer within the general population is increasing, and this may in part be related to the increasing use of exogenous hormones. Hormonal and reproductive factors have long been recognised to be important in the development of breast cancer.

It has been shown that prolonged exposure to endogenous oestrogens is an adverse risk factor for breast cancer.⁹ Breast cancer is, therefore, very uncommon in Turner syndrome, as these women rarely ovulate. Early menarche, as it prolongs exposure to oestrogens, increases the risk of breast cancer¹⁰ as does late menopause.¹¹

Exogenous oestrogens, either the combined oral contraceptive (COC) or hormone replacement therapy (HRT), also confer increased risks of breast cancer. The oestrogen element of the COC, although suppressing ovulation, will still stimulate the breast cells, although the extent of this increased risk is still controversial. A meta-analysis suggested that both during current use of the COC and 10 years post use there may be a 24% increase in risk of breast cancer.¹²

HRT is a further area of controversy. Long term treatment (>10 years) after the menopause is associated with a significant increase in risk. However, shorter treatments may still be associated with risk to those with a family history.¹³ In a large meta-analysis the risk appeared to increase cumulatively by 1-2% per year, but disappear within five years of cessation.¹² It is becoming clear that the risk from combined oestrogen/progesterone HRT is greater than for oestrogen only.^{14 15}

The age at first pregnancy influences the relative risk of breast cancer as pregnancy transforms breast parenchymal cells into a more stable state, resulting in less proliferation in the second half of the menstrual cycle. As a result, early first pregnancy offers some protection, while women having their first child over the age of 30 have double the risk of women delivering their first child under the age of 20 years.¹⁶

It is important to emphasise that these hormonal factors will in most cases alter risks only marginally, and even at the extremes only by a factor of two.¹⁷ Many women who have most of the unfavourable factors will not develop breast cancer and some, particularly if they have a germline mutation, will develop the disease despite favourable reproductive and hormonal factors. Hormonal factors may indeed have different effects on different genetic backgrounds. It has been suggested that in *BRCA2* mutation carriers, for example, an early pregnancy does not confer protection against breast cancer.¹⁸

RISK ESTIMATION

There are few families where it is possible to be sure of dominant inheritance. However, the breast cancer linkage consortium data (BCLC) suggest that in families with four or more cases of early onset or bilateral breast cancer, the risk of an unaffected woman inheriting a mutation in a predisposing gene is close to 50%. Epidemiological studies have shown that approximately 80% of mutation carriers in known predisposing genes (*BRCA1* and *BRCA2*) develop breast cancer in their lifetime. Therefore, unless there is significant family history on both sides of the family, the maximum risk counselled to an unaffected woman is 40-45% (including population risk). Breast cancer genes may be paternally inherited and a dominant history on the paternal side of the family would give at least a 20% additional lifetime risk to his daughters (probability of a mutation of 25% multiplied by 80% risk of developing breast cancer).

In the absence of a dominant family history, risk estimation is based on large epidemiological studies. These show a 1.5-3 fold increased risk with a family history of a single affected relative.^{4 5} The risk then increases with the increasing number of affected relatives. These risks also increase with the decreasing age at diagnosis of the affected relatives, so that an

unaffected woman with a first degree relative diagnosed with breast cancer at 35 years has a higher lifetime risk than a woman with a first degree relative diagnosed at 45 years. In the UK, risk estimation is based mainly in the Claus data set.⁵ However, in the USA the Gail model of risk estimation is widely used. This model is based on data from the Breast Cancer Detection and Demonstration Project (BCDDP) and combines factors including family history, breast biopsy data, and hormonal factors.^{19 20} Refinement of the model resulted in the production of graphs for the estimation of a person's risk of breast cancer.²⁰ One of the limitations of the Gail model may be the variation in the effect of hormonal factors on differing genetic backgrounds.

As well as these data sets allowing the estimation of risks, specific computer programs are available, including Cyrillic™ for the estimation of risk and BRCAPRO for the estimation of the likelihood of a *BRCA1/2* mutation. These programs take into consideration varying permutations of age of onset of diagnosis, number of affected and unaffected women, and hormonal factors, and as a consequence different programs will result in different risk estimations.²¹ Geneticists should be able to assess risk from a pedigree without the use of a computer program in order to ensure that results from the program are within the correct "ball park".

It is important to differentiate between lifetime and age specific risks. For example, some studies quote a nine-fold or greater risk associated with bilateral disease in a mother or proliferative breast disease in a first degree relative.^{22 23} If one then uses these risks and multiplies them on a lifetime incidence of 1 in 10, the estimated risk of developing a malignancy then becomes very high. As the population risks include both high and low risk subjects, it is not possible simply to multiply with the relative risks from these studies. For example, the relative risk of breast cancer in a woman with atypical ductal hyperplasia is halved if she remains disease free for 10 years.²⁴ Therefore the increase in risk is time specific and not cumulative.

Perhaps the best way to assess risk is to consider the strongest risk factor, which in our view is family history. If first line risk is assessed on this basis then minor adjustments can be made for other factors. It is arguable whether these hormonal and reproductive factors will have a noticeable effect on an 80% penetrant gene, other than to accelerate or delay the onset of breast cancer. Although studies do suggest an increase in risk in family history cases associated with these factors, this may simply represent an earlier expression of the gene. Generally, therefore, risk estimates are between 40% (50% probability of inheriting an 80% penetrant gene mutation) and 8-10% (population risk of breast cancer), although lower risks are occasionally given. Higher risks are only applicable when a woman at 40% genetic risk is shown to have a germline mutation, to have inherited a high risk allele, or to have proliferative breast disease.²⁵

The modification of such a person's risk is only likely with the demonstration or exclusion of a known family mutation.

When considering a woman with a family history of breast cancer, it is also important to be aware of any family history of ovarian cancer. Families with strong histories of both breast and ovarian cancer are likely to have mutations in *BRCA1* or *BRCA2*. A risk figure for ovarian cancer can then be calculated based on the probability of either a *BRCA1/2* mutation (see later).

COMMUNICATION OF RISK

Within the genetic counselling process, risk is an important and difficult concept to impart. A woman's perception of risk may vary depending on her own life experiences.²⁶ The way in which risks are expressed may also impinge upon comprehension, with some patients preferring risks communicated as gambling odds.²⁷ Often the patient's agenda may be to

ascertain whether or not they are eligible for a screening programme, and the actual risk figure becomes irrelevant.

Some women find the concept of lifetime risk and remaining risk useful, especially if they are approaching the age of 50. For example, an unaffected woman from a young onset breast cancer family may have a lifetime risk of breast cancer of 40%. However, if she is 60 years old, her probability of being a mutation carrier is only 25% (>60% mutation carriers would have developed the disease by this age) and therefore her remaining risk of developing breast cancer related to an inherited gene mutation is 20%. This is in addition to her population risk. This reflects the gradual equalisation of risk to population after 60 years in those with a strong family history. It is important to try to express the stage at which risk is present (in old age in the general population) and how much risk remains. Some women may prefer to know their risk per year. In a dominant family this may approximate to 1% per year from the late twenties for someone at 50% risk of inheriting the gene.

As with other genetic conditions, the communication of risk should be appropriate to the levels of comprehension of the patient.

MANAGEMENT OF HIGH RISK WOMEN

Early detection

Breast self-examination (BSE) has been advocated to increase breast awareness within the population. Early studies^{28,29} suggested that BSE was useful in the early detection of breast cancer, although later studies have suggested that it unduly raises anxiety without a definite benefit with regard to survival.³⁰ Currently, we discuss BSE as an adjuvant to a mammographic screening programme, with open access to the family history clinic in the event of an abnormality being detected.

Clinical breast examination has been shown to be useful in the detection of breast cancer. Indeed, a recent study in women aged 50-59 years³¹ showed that clinical examination was as sensitive as mammograms alone. The detection rate of malignancies increased with the use of both mammograms and clinical breast examination.

Ultrasound scanning of the breast is usually used as an adjunct to the diagnosis of a palpable lump or further delineation of a mammographic abnormality. A recent consensus³² has suggested that, in the general population, ultrasound screening has a high false positive rate and therefore should not be used. However, there is still debate about the use of ultrasound to screen within a subgroup of women at increased risk.³³ In practice, ultrasound may be used for screening in very young women (less than 30 years) with a very early onset family history.

Mammographic screening has been shown to be useful in the early detection of breast cancer and confers a survival advantage.³⁴ However, mammography is problematical in young women as the young breast is denser than a postmenopausal breast, resulting in greater difficulties with interpretation. Although the first evidence for a significant survival advantage is now emerging for the general population under 50 years,^{35,36} the frequency of disease is probably too low to justify population screening on economic grounds. The group of women at high risk owing to their family history is, however, a subgroup of the population in whom screening is probably advantageous. Our own work has shown that impalpable small lesions are detected in the 35-49 year age high risk group and that similar detection rates to the NHS Breast Screening Programme are thus attainable.³⁷ European recommendations³⁸⁻⁴⁰ suggest that mammograms should be offered on an annual basis to moderate and high risk women from the age of 35 years. These recommendations are based on empirical data.

This advantage may, however, be confined to those women at moderate risk of breast cancer. Recent data⁴¹ have suggested that the benefit to carriers of mutations in *BRCA1/2* may not be as great owing to the aggressive nature of tumours within this group.

Because of the (low) level of radiation associated with mammography, and a small theoretical risk of inducing a malignancy,⁴² there is concern regarding regular mammography of *TP53* and *ATM* mutation carriers.⁴³ As *BRCA2* has also been implicated in DNA repair, there may also be some risk to mutation carriers.

Magnetic resonance imaging (MRI) does not involve radiation and may be more sensitive than mammography, especially of the dense breast.⁴⁴ MRI has also been shown to have high sensitivity in the detection of early breast cancer. The high cost and scarcity of MRI scanners prevents the use of MRI except for the very high risk groups; a trial offering mammography to *BRCA1/2* and *TP53* mutation carriers only is currently continuing⁴⁵ within the UK and Australia. Recent data from the USA comparing the use of MRI, mammography, ultrasound, and clinical breast examination suggests that both the sensitivity and specificity of MRI is greater than that of mammography in *BRCA1/2* mutation carriers.⁴⁶

Ovarian screening

Owing to the increased risk of ovarian cancer with *BRCA1* and *BRCA2* mutations, families with either a proven mutation or with a family history of breast and ovarian cancer (or multiple ovarian cancer cases only) should be offered ovarian screening. Within the UK a randomised trial is currently under way to assess the efficacy of transvaginal ultrasound and CA125 measurement as a screening tool. An additional observational trial has been established for women at high risk of ovarian cancer from the age of 35 years (UKFOCSS trial).

PREVENTION OF BREAST CANCER

Hormonal manipulation

It has been suggested that manipulation of hormonal/reproductive factors may reduce the risks of breast cancer. These include:

- Plan family early.
- Avoid COC and HRT.
- Good diet.

Many women at their first attendance at a family history clinic will already have started a family and may have already used oral contraception, so that alteration of these factors becomes impossible. However, discussions regarding contraception and HRT are useful in certain cases. It has been suggested that the use of the COC will reduce the risk of ovarian cancer in *BRCA1* mutation carriers by up to 60%.⁴⁷ However, this may also decrease the age of onset of breast cancer (unpublished data). Careful discussions in order to ensure that the patients are aware of all the pros and cons of hormonal treatment and/or manipulation are needed.

Chemoprevention

The use of hormonal manipulation via the use of medication has been suggested as a preventive measure in breast cancer. It has long been recognised that removing the effect of oestrogen on the breast is a useful adjunct to treatment of breast cancer, and has therefore been postulated as a preventative measure. The identification of a group of women at high risk provides the possibility of obtaining sufficient events (development of breast cancer) in order to assess chemopreventive agents. A number of large collaborative trials are currently continuing.

Tamoxifen has been shown to reduce the risk of contralateral breast cancer in women with a previous breast primary⁴⁸ and a large American study has shown a reduction

in risk of breast cancer in asymptomatic women (at increased lifetime risk) by 40-50%.⁴⁹ It is well tolerated, although hot flushes and other menopausal symptoms are common and there are increased risks of thromboembolic events and endometrial cancer.⁴⁹ Tamoxifen also has a beneficial effect on bone density. However, two smaller studies did not show reduction in breast cancer risk.⁵⁰⁻⁵¹ The most recent results from IBIS (International Breast Intervention Study)⁵² have shown a 33% risk reduction with the use of Tamoxifen (68 breast cancers *v* 101). There remains, however, concern over the increased risk of endometrial malignancy and thromboembolic events associated with the use of Tamoxifen. Therefore, while Tamoxifen is currently licensed and recommended for prevention within the USA, its use as a preventive agent is still being assessed in the UK.

A new high risk trial, RAZOR, is being piloted in the UK and Australia involving suppressing the ovaries with Zoladex (GnRH agonist) and protecting the bones (and breasts) with Raloxifene. Variations of this are being undertaken in the USA and mainland Europe. Other studies under way include the administration of retinoids in Italy and the trials comparing Tamoxifen with Raloxifene in America. Recruitment to these trials of high risk women within the UK has been disappointing and this may be because of a reluctance to be randomised to placebo.⁵³

Preventive surgery

Prophylactic mastectomy is now an option for women at high risk of breast cancer. The group to whom this surgery is mentioned varies with each centre,⁵⁴ but is now accepted as an option for *BRCA1/2* and *TP53* mutation carriers. If removal of breast tissue is incomplete, such as with sparing of the nipple, then a residual risk of breast cancer remains.⁵⁵ None of the different surgical procedures will completely remove all breast tissue, and therefore there will always be a (small) residual risk of breast malignancy. It is also important to emphasise that aesthetically this is not a cosmetic procedure. Both of these issues need to be discussed with individual women before surgery.

Evidence from a study of nearly 1000 women at the Mayo Clinic in the USA suggests that breast cancer risk is substantially reduced (by 90%) even with subcutaneous mastectomy.⁵⁶ This is now being confirmed in *BRCA1* and *BRCA2* mutation carriers.⁵⁷

There have been few long term studies of either the physical or psychological sequelae of prophylactic surgery. Some women may be psychologically unprepared for the outcome as cosmesis may not be as a woman expects. The general anaesthetic and surgical risks also need to be taken into account. However, a recent study⁵⁸ has shown significant benefit to women who choose the option compared to those who do not in terms of anxiety and cancer related worry. It is nonetheless important that a comprehensive protocol for preparing

women is in place, including a psychological assessment.⁵⁹ Increasingly, women at high risk in the UK are opting for preventative mastectomy. This is likely to increase further when genetic testing is more widely available and women at 80-90% lifetime risk of breast cancer are identified. Two recent reports from our own Group and The Netherlands show an uptake of around 50% in unaffected mutation carriers.⁵³⁻⁶⁰ Indeed, high risk women are more likely to choose prophylactic surgery than prevention trials.⁵³

Prophylactic oophorectomy (including removal of the fallopian tubes) has been used in women with *BRCA1/2* mutations in order to reduce the risk of ovarian cancer. As with mastectomies, the removal of every ovarian epithelial cell cannot be guaranteed, and therefore there is a residual risk of ovarian malignancy. Tobacman *et al*⁶¹ reported primary peritoneal cancer in 3/28 women undergoing prophylactic oophorectomy. Struwing *et al*⁶² more recently showed that oophorectomy reduced the risk of ovarian or primary peritoneal cancer by approximately half in a small study. A more recent large multicentre study⁶³ showed that this risk reduction in *BRCA1/2* mutation carriers may be as high as 90-95%. It has also been shown that in women with a *BRCA1/2* mutation, prophylactic oophorectomy decreases the risk of breast cancer⁶⁴ and that this risk reduction is unaffected by the subsequent use of HRT. Prophylactic oophorectomy in high risk women may then decrease the risk of both breast and ovarian cancer.

Long term studies are needed to assess the impact of both early detection and preventative treatment on the mortality of women with a high risk of breast cancer.

THE BREAST CANCER GENES

Evidence from the BCLC suggests that familial breast cancer is heterogeneous and that there are a number of different genes involved in predisposition to this disease.⁶⁵ While a number of different genes have been cloned, work is continuing to localise and clone the remaining genes. The current known genetic conditions and locations of genes is shown in table 2.

BRCA1 and *BRCA2*

BRCA1 on the long arm of chromosome 17⁶⁶ and *BRCA2* on the long arm of chromosome 13⁶⁷ were cloned over five years ago. They are thought to account for over 80% of highly penetrant inherited breast cancer with a combined population frequency of approximately 0.2%.⁶⁸ The majority of families with breast and ovarian cancers are the result of mutations in *BRCA1*, with up to 20% resulting from mutations in *BRCA2*.⁶⁹

Mutations in both genes confer an increased lifetime risk of breast cancer of 85% with a lifetime risk of ovarian cancer of 60% with *BRCA1* and 10-20% with *BRCA2*.⁶⁸⁻⁷⁰ It is probable that the majority of so-called site specific ovarian cancer families are the result of mutations in *BRCA1*. Supportive evidence for this comes from the long term follow up of apparently site

Table 2 Hereditary conditions predisposing to breast cancer

Disease	Other tumour susceptibility	Inheritance	%		Location
			BC	HPBC	
Familial breast <i>BRCA1</i>	Ovary, prostate	AD	1.7	50	17q21
Familial breast <i>BRCA2</i>	Ovary, prostate, male breast cancer	AD	1.2	35	13q12
Li-Fraumeni <i>TP53</i>	Sarcoma, brain, adrenocortical	AD	0.1	1	17p13.1
Ataxia-telangiectasia <i>ATM</i>	Homozygotes (leukaemias)	AR	0	0	11q22.3
	Heterozygotes (gastric)		2	4-8	
Cowden <i>PTEN</i>	Skin, thyroid, bowel	AD	<1	<1	10q23.3
Reifenstein	?	XLR	<1	0	Xq11
<i>Hras</i> variant		AD	78	0	11p15.5
hCHK2	Breast	AD	4	0	22q12.1

AD, Autosomal dominant; AR, autosomal recessive; XLR, X linked recessive; HPBC, highly penetrant hereditary breast cancer (eg >3 affected relatives).

specific families and new cancers in families from the UKCCCR familial ovarian cancer study.⁷¹

Early evidence from the International Linkage Consortium suggests that although *BRCA1* and *BRCA2* account for the great majority of families with four or more affected cases under 60 years with breast/ovarian cancer, they account for far less of the predicted hereditary component of smaller families.⁶⁵ For instance, a family with two affected sisters under 50 years would have a >50% chance of being the result of a predisposing gene, yet *BRCA1/2* mutations only account for about 15% of these families.

A number of different studies have assessed the penetrance of *BRCA1* and *BRCA2* mutations. These appear to vary with ascertainment; for example, population studies⁷²⁻⁷³ show a lower penetrance than those estimated by the Breast Cancer Linkage Consortium.⁶⁸⁻⁷⁴ It has been suggested⁷⁵ that a number of low penetrant breast cancer genes may affect the penetrance of *BRCA1* and *BRCA2* resulting in the variable estimates published. However, communicated risks should be appropriate to the pattern of malignancies within the family being counselled.

TP53

Germline mutations of the *TP53* gene on the short arm of chromosome 17 are known to account for over 70% of cases of the Li-Fraumeni syndrome.⁷⁶ Early onset breast cancers are common within this syndrome, with the majority of women being diagnosed under the age of 40 years.⁷⁷ However, the overall contribution of germline *TP53* mutations to familial breast cancer is probably relatively small.

ATM

Heterozygous carriers of the ataxia-telangiectasia (*ATM*) gene are known to be at a five-fold risk of breast cancer.⁷⁸ While the initial carrier frequency of this gene was thought to be high, this was based on five complementation groupings. It has since been shown that a single gene on 11q causes the disease.⁷⁹ Although initial studies did not indicate that *ATM* appeared to be a major gene in breast cancer predisposition, there is now emerging evidence that mutations can be associated with high risk in families.⁸⁰

PTEN

PTEN (10q) mutations have been found in Cowden syndrome.⁸¹ While this condition is known to be associated with an increased risk of breast cancer,⁸² mutations within this gene do not appear to account for high risk families. However, two cases of male breast cancer have been described in association with Cowden syndrome.⁸³

PREDICTIVE GENETIC TESTING

A predictive test determines whether an unaffected person carries a familial mutation. Many women attend a genetic clinic for the purpose of having a "genetic test" to determine whether they are at increased risk of developing breast cancer and in the majority of cases this test is unavailable and inappropriate. Women in the general population without a family history would have a less than 0.1% chance of carrying a mutation in *BRCA1*. Therefore a negative screen would not reduce their risks of breast cancer even if the mutation screen were 100% sensitive. Those with a first degree relative with breast cancer diagnosed at 40 years of age, having a 1 in 6 lifetime risk, would not receive any real reduction in their probability of developing the disease and therefore management would not be altered. Even women with a strong family history of breast and ovarian cancer and a 90% sensitivity for mutation testing would not have sufficient risk reduction to cease screening or preventative measures (D F Easton, personal communication).

Predictive testing should therefore only be offered when a pathogenic mutation has been identified within a family. This will allow complete reassurance to those who have not inherited the family mutation and allow informed risk estimates of breast and ovarian cancer to those with the mutation.

The only potential exception to this is within a population with strong "founder" mutations, such as the Ashkenazi population. Within this population, three mutations in *BRCA1/2* occur with a frequency of about 2.5%⁸⁴⁻⁸⁶ and may account for over 90% of the highly penetrant families. Smaller aggregates of malignancy may also be the result of these founder mutations⁸⁷ with the result that mutation screening in unaffected subjects without a known family mutation becomes a useful option.

UPTAKE OF GENETIC TESTING

Evidence suggests that about 60% of eligible women undertake a genetic test for breast cancer predisposition.⁸⁸⁻⁹⁰ Various theoretical surveys of women who may only be at fairly small risk of carrying a *BRCA1/2* mutation would also suggest a high uptake.⁹¹ However, when the poor predictive value of testing unaffected relatives is explained to subjects, the uptake may well be very much lower. The actual uptake in tested families is still much lower than predicted from previous surveys and needs to be extended to families who have not been contaminated by being involved in large scale research. This is now possible with the large number of families in which mutations have been found (approximately 600 in the UK). Little is also known about the outcome of testing. Early results from psychosocial studies suggest that subjects are benefited from a low risk result and may not be adversely affected by a high risk result. From a health economic viewpoint, it is essential to know what options women will undertake. If >50% of women opt for preventive surgery, provisions may need to be made for this. However, the greatest "economic" benefit may arise from a preventive strategy that means that many fewer women have to undergo chemotherapy for metastatic disease.

CONCLUSIONS

There have been huge advances in our knowledge of hereditary breast cancer over the last 10-12 years. While it is now possible to offer definitive testing in a few high risk families, much is still to be learnt about the remaining genes that confer low to moderate increases in risk. In the meantime, further evidence has to be gathered as to the efficacy of screening and preventive options. Guidelines for the appropriate management have recently been published for the UK³⁸ and similar approaches are being used in other parts of Europe and North America. Long term planning within the NHS in terms of manpower and resources is needed to counsel optimally and manage women at high risk of developing breast cancer.

Authors' affiliations

D G R Evans, F Lalloo, University Department of Medical Genetics and Regional Genetics Service, St Mary's Hospital, Manchester M13 0JH, UK

REFERENCES

- 1 Foulkes W, Wong N, Brunet JS, Begin LR, Zhang JC, Martinez JJ, Rozen F, Tonin PN, Narod SA, Karp SE, Pollak MN. Germ-line *BRCA1* mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. *Clin Cancer Res* 1997;3:2465-9.
- 2 Wonderling D, Hopwood P, Cull A, Douglas F, Watson M, Burn J, McPherson K. A descriptive study of UK cancer genetics services: an emerging clinical response to the new genetics. *Br J Cancer* 2001;85:166-70.
- 3 McAllister M, O'Malley K, Hopwood P, Kerr B, Howell A, Evans DGR. Management of women with a family history of breast cancer in the North West Region of England: training for implementing a vision of the future. *J Med Genet* 2002;39:531-5.

- 4 **Newman B**, Austin M, Lee M, King MC. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high risk families. *Proc Natl Acad Sci USA* 1988;**85**:3044-8.
- 5 **Claus EB**, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer; implications for risk prediction. *Cancer* 1994;**73**:643-51.
- 6 **Nelen MR**, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MMM, Easton DF, Eeles RA, Hodgson S, Mulvihill JJ, Murday V, Tucker MA, Mariman ECM, Starink TM, Ponder BAJ, Ropers HH, Kremer H, Longy M, Eng C. Localisation of the gene for Cowden disease to chromosome 10q22-23. *Nat Genet* 1996;**13**:114-16.
- 7 **Malkin D**, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, Friend SH. Germline p53 mutations in a familial syndrome of breast cancer, sarcomas and other neoplasms. *Science* 1990;**250**:1233-8.
- 8 **Easton DF**, Ford D, Bishop DT. Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1-mutation carriers. *Am J Hum Genet* 1995;**56**:265-71.
- 9 **Colditz GA**. Relationship between estrogen levels, use of hormone replacement therapy and breast cancer. *J Natl Cancer Inst* 1998;**90**:814-23.
- 10 **Kamper JB**, Whittemore AS, Paffenberger RSJ. Combined effect of childbearing, menstrual events and body size on age-specific breast cancer risk. *Am J Epidemiol* 1988;**128**:962-79.
- 11 **Trichopoulos D**, MacMahon B, Cole P. The menopause and breast cancer risk. *J Natl Cancer Inst* 1972;**48**:605-13.
- 12 **Collaborative Group on Hormonal Factors in Breast Cancer**. 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* 1996;**347**:1713-27.
- 13 **Steinberg KK**, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders D, Berkman RL. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA* 1985;**265**:1985-90.
- 14 **Ross RK**, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;**92**:328-32.
- 15 **Schairer C**, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;**283**:485-91.
- 16 **MacMahon B**, Cole P, Brown J. Etiology of breast cancer: a review. *J Natl Cancer Inst* 1973;**50**:21-42.
- 17 **Evans DGR**, Fentiman IS, McPherson K, Asbury D, Ponder BAJ, Howell A. Familial breast cancer. *BMJ* 1994;**308**:183-7.
- 18 **Jernstrom H**, Lerman C, Ghadirian P, Lynch HT, Weber B, Garber J, Daly M, Olopade OI, Foulkes WD, Warner E, Brunet JS, Narod SA. Pregnancy and risk of early breast cancer in carriers of BRCA1 and BRCA2. *Lancet* 1999;**354**:1846-50.
- 19 **Gail MH**, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualised probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;**81**:1879-86.
- 20 **Benichou J**, Gail MH, Mulvihill JJ. Graphs to estimate an individualized risk of breast cancer. *J Clin Oncol* 1996;**14**:103-10.
- 21 **Berg J**, Holloway S, Ferguson R, Porteous M. Genetic risk assessment for breast cancer - a comparison of different methods. *J Med Genet* 2000;**37**(suppl 1):S19.
- 22 **Chaudary MA**, Millis RR, Bulbrook RD, Hayward JL. Family history and bilateral primary breast cancer. *Breast Cancer Res Treat* 1985;**5**:201-5.
- 23 **Skolnick MH**, Cannon-Albright L, Goldgar DE, Ward JH, Marshall CJ, Schumann B, Hogle H, McWhorter WP, Wright EC, Tran TD, Bishop DT, Kushner JP, Eyre HJ. Inheritance of proliferative breast disease in breast cancer kindreds. *Science* 1990;**250**:1715-20.
- 24 **Dupont WD**, Page DL. Relative risk of breast cancer varies with time since diagnosis of atypical hyperplasia. *Hum Pathol* 1989;**20**:723-5.
- 25 **Dupont WD**, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;**312**:146-51.
- 26 **Shapiro DE**, Boggs SR, Melamed BG, Graham-Pole J. The effect of varied physician affect on recall, anxiety, and perceptions in women at risk for breast cancer: an analogue study. *Health Psychol* 1992;**11**:61-6.
- 27 **Evans DGR**, Blair V, Greenhalgh R, Hopwood P, Howell A. The impact of genetic counselling on risk perception in women with a family history of breast cancer. *Br J Cancer* 1994;**70**:934-8.
- 28 **Foster RS**, Constanza MC. Breast self examination practices and breast cancer survival. *Cancer* 1984;**53**:999-1005.
- 29 **Feldman J**, Carter A, Nicasri A, Hosat ST. Breast self examination: relationship to stage of breast cancer at diagnosis. *Cancer* 1981;**47**:2740-5.
- 30 **Baxter N**. Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer? *Can Med Assoc J* 2001;**164**:1837-46.
- 31 **Miller AB**, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *J Natl Cancer Inst* 2000;**92**:1490-9.
- 32 **The W**, Wilson AR. The role of ultrasound in breast cancer screening. A consensus statement by the European Group for Breast Cancer Screening. *Eur J Cancer* 1998;**34**:449-50.
- 33 **O'Driscoll D**, Warren R, Mackay J, Britton P, Day NE. Screening with breast ultrasound in a population at moderate risk due to family history. *J Med Screen* 2001;**8**:106-9.
- 34 **Tabár L**, Fagerberg G, Gad A, Badlertop L, Holmberg LH, Grontoft O, Ljunquist U, Lundstrom B, Manson JC, Eklund G, Day NE. Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985;**i**:829-32.
- 35 **Tabár L**, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, Smith RA. Efficacy of breast cancer screening by age. *Cancer* 1995;**75**:2507-17.
- 36 **Swedish Cancer Society and the Swedish National Board of Health and Welfare**. Breast-cancer screening with mammography in women aged 40-49 years. *Int J Cancer* 1996;**68**:693-9.
- 37 **Lalloo F**, Boggis CRM, Evans DGR, Shenton A, Threlfall AG, Howell A. Screening by mammography, women with a family history of breast cancer. *Eur J Cancer* 1998;**34**:937-40.
- 38 **Eccles DM**, Evans DG, Mackay J. Guidelines for a genetic risk based approach to advising women with a family history of breast cancer. UK Cancer Family Study Group (UKCFSG). *J Med Genet* 2000;**37**:203-9.
- 39 **Eisinger F**, Alby N, Bremond A, Dauplat J, Espie M, Janiaud P, Kuttann F, Lebrun JP, Lefranc JP, Pierret J, Sobol H, Stoppa-Lyonnet D, Thouvenin D, Tristant H, Feingold J. Recommendations for medical management of hereditary breast and ovarian cancer: the French National Ad Hoc Committee. *Ann Oncol* 1998;**9**:939-50.
- 40 **Moller P**, Evans G, Haites N, Vasen H, Reis MM, Anderson E, Apold J, Hodgson S, Eccles D, Olsson H, Stoppa-Lyonnet D, Chang-Claude J, Morrison PJ, Bevilacqua G, Heimdal K, Maehle L, Lalloo F, Gregory H, Preece P, Borg A, Nevin NC, Caligo M, Steel CM. Guidelines for follow-up of women at high risk for inherited breast cancer: consensus statement from the Biomed 2 Demonstration Programme on Inherited Breast Cancer. *Dis Markers* 1999;**15**:207-11.
- 41 **Brekelmans CT**, Seynaeve C, Bartels CC, Tilanus-Linthorst MM, Meijers-Heijboer EJ, Crepin CM, van Geel AA, Menke M, Verhoog LC, Van Den OA, Obdeijn IM, Klijn JG. Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *J Clin Oncol* 2001;**19**:924-30.
- 42 **Law J**. Cancers detected and induced in mammographic screening: new screening schedules and younger women with family history. *Br J Radiol* 1997;**70**:62-9.
- 43 **Varley JM**, McGown G, Thorncroft M, James LA, Margison GP, Foster G, Evans DGR, Harris M, Kelsey AM, Birch JM. Are there low-penetrance TP53 alleles? Evidence from childhood adrenocortical tumors. *Am J Hum Genet* 1999;**65**:995-1006.
- 44 **Drew PJ**, Monson JRT. Magnetic resonance mammography. *Br J Surg* 1996;**83**:1316-18.
- 45 **Brown J**, Buckley D, Coulthard A, Dixon AK, Dixon JM, Easton DF, Eeles RA, Evans DG, Gilbert FG, Graves M, Hayes C, Jenkins JP, Jones AP, Keevil SF, Leach MO, Liney GP, Moss SM, Padhani AR, Parker GJ, Pointon LJ, Ponder BA, Redpath TW, Sloane JP, Turnbull LW, Walker LG, Warren RM. Magnetic resonance imaging screening in women at genetic risk of breast cancer: imaging and analysis protocol for the UK multicentre study. UK MRI Breast Screening Study Advisory Group. *Magn Reson Imaging* 2000;**18**:765-76.
- 46 **Warner E**, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, Goel V, Ramsay E, Chart PL, Cole DE, Taylor GA, Cutrara M, Samuels TH, Murphy JP, Murphy JM, Narod SA. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol* 2001;**19**:3524-31.
- 47 **Narod SA**, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, Brunet JS, Ponder BA. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 1998;**339**:424-8.
- 48 **Powles TJ**, Tillyer CR, Jones AL, Ashley SE, Treleaven J, Davey JB, McKinna A. Prevention of breast cancer with tamoxifen - an update on the Royal Marsden Hospital Pilot Programme. *Eur J Cancer* 1990;**26**:680-4.
- 49 **Fisher B**, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;**90**:1371-88.
- 50 **Veronesi U**, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, Boyle P, on behalf of the Italian Tamoxifen Prevention Study. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial amongst hysterectomised women. *Lancet* 1998;**352**:93-7.
- 51 **Powles T**, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J, Davey J. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998;**352**:98-101.
- 52 **IBIS working party and principal investigators**. First results from the IBIS Breast Cancer Prevention Trial. *Lancet* (in press).
- 53 **Evans D**, Lalloo F, Shenton A, Boggis C, Howell A. Uptake of screening and prevention in women at very high risk of breast cancer. *Lancet* 2001;**358**:889-90.
- 54 **Evans DGR**, Anderson E, Lalloo F, Vasen H, Beckmann M, Eccles D, Hodgson S, Moller P, Chang-Claude J, Morrison P, Stoppa-Lyonnet D, Steel M, Haites N. Utilisation of prophylactic mastectomy in 10 European centres. *Dis Markers* 1999;**15**:148-51.
- 55 **Goodnight JE**, Quagliana JM, Morton DL. Failure of subcutaneous mastectomy to prevent the development of breast cancer. *J Surg Oncol* 1984;**26**:198-201.
- 56 **Hartmann LC**, Schiadh DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, Petty PM, Sellers TA, Johnson JL, McDonnell SK, Frost MH, Jenkins RB. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999;**340**:77-84.

- 57 **Meijers-Heijboer H**, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, Bartels CC, Verhoog LC, van den Ouweland AM, Niermeijer MF, Brekelmans CT, Klijn JG. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;**345**:159-64.
- 58 **Hopwood P**, Lee A, Shenton A, Baildam A, Brain A, Lalloo F, Evans G, Howell A. Clinical follow-up after bilateral risk reducing ('prophylactic') mastectomy: mental health and body image outcomes. *Psychooncology* 2000;**9**:462-72.
- 59 **Lalloo F**, Hopwood P, Baildam A, Brain A, Howell A, Evans DGR. Preventative mastectomy in women with an increased lifetime risk of breast cancer. *Eur J Surg Oncol* 2000;**26**:711-13.
- 60 **Meijers-Heijboer EJ**, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, Dukel L, Devilee P, van den Ouweland AM, van Geel AN, Klijn JG. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet* 2000;**355**:2015-20.
- 61 **Tobacman JK**, Tucker MA, Kase R, Greene MH, Costa J, Fraumeni JF. Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian cancer-prone families. *Lancet* 1982;ii:795-7.
- 62 **Struewing JP**, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA. Prophylactic oophorectomy in inherited breast/ovarian cancer families. *J Natl Cancer Inst Monogr* 1995;**17**:33-5.
- 63 **Rebbek T**, Lynch HT, Neuhausen S, Narod S, van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade O, Weber BL. Prophylactic oophorectomy in carriers of BRCA1 and BRCA2 mutations. *N Engl J Med* 2002;**346**:1616-22.
- 64 **Rebbek TR**, Levin AM, Eisen A, Snyder C, Watson P, Cannon-Albright L, Isaacs C, Olopade O, Garber JE, Godwin AK, Daly MB, Narod SA, Neuhausen SL, Lynch HT, Weber BL. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst* 1999;**91**:1475-9.
- 65 **Narod SA**, Ford D, Devilee P, Barkardottir RB, Lynch HT, Smith SA, Ponder BAJ, Weber BL, Garber JE, Birch JM, Cornelis RS, Kelsell DP, Spurr NK, Smyth E, Haites N, Sobol H, Bignon YJ, Chang-Claude J, Hamann U, Lindblom A, Borg A, Piver MS, Gallion HH, Struewing JP, Whittemore A, Tonin P, Goldgar DE, Easton DF, Breast Cancer Linkage Consortium. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. *Am J Hum Genet* 1995;**56**:254-64.
- 66 **Miki Y**, Swensen J, Shattuck-Eidens D, Futreal A, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barrett C, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH. A strong candidate for the breast and ovarian cancer susceptibility gene, BRCA1. *Science* 1994;**266**:66-71.
- 67 **Wooster R**, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, Fields P, Marshall G, Narod S, Lenoir GM, Lynch H, Feunteun J, Devilee P, Cornelisse C, Menko FH, Daly PA, Ormiston W, McManus R, Pye C, Lewis CM, Cannon-Albright LA, Peto J, Ponder BAJ, Skolnick MH, Easton DF, Goldgar DE, Stratton MR. Identification of the breast cancer gene BRCA2. *Nature* 1995;**378**:789-91.
- 68 **Ford D**, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbek TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M, and the Breast Cancer Linkage Consortium. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet* 1998;**62**:676-89.
- 69 **Gayther SA**, Mangion J, Russell P, Seal S, Barfoot S, Ponder BAJ, Stratton MR, Easton D. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. *Nat Genet* 1997;**15**:103-5.
- 70 **Ford D**, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994;**343**:692-5.
- 71 **Sutcliffe S**, Pharoah PDP, Easton DF, Ponder BAJ, UKCCCR Familial Ovarian Cancer Study Group. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. *Int J Cancer* 2000;**87**:110-17.
- 72 **Struewing JP**, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman M, Brody L, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;**336**:1401-8.
- 73 **Hopper JL**, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, Easton DF, Venter DJ. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:741-7.
- 74 **Thompson D**, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. *Am J Hum Genet* 2001;**68**:410-19.
- 75 **Antoniou AC**, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, Easton DF. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* 2002;**86**:76-83.
- 76 **Varley JM**, Evans DGR, Birch JM. Li-Fraumeni syndrome - a molecular and clinical review. *Br J Cancer* 1997;**76**:1-14.
- 77 **Sidransky D**, Tokino T, Helzlsouer K, Zehnbauser B, Rausch G, Shelton B, Prestigiacomo L, Vogelstein B, Davidson N. Inherited p53 gene mutations in breast cancer. *Cancer Res* 1992;**52**:2984-6.
- 78 **Swift ML**, Reitnauer PJ, Marrell D, Chase CL. Breast and other cancers in families with ataxia telangiectasia. *N Engl J Med* 1987;**316**:1289-94.
- 79 **Savitsky K**, Bar-shira A, Gilad S, Rotman G, Ziu Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995;**268**:1749-53.
- 80 **Chenevix-Trench G**, Spurdle AB, Gatei M, Kelly H, Marsh A, Chen X, Donn K, Cummings M, Nyholt D, Jenkins MA, Scott C, Pupo GM, Dork T, Bendix R, Kirk J, Tucker K, McCredie MR, Hopper JL, Sambrook J, Mann GJ, Khanna KK. Dominant negative ATM mutations in breast cancer families. *J Natl Cancer Inst* 2002;**94**:205-15.
- 81 **Liaw D**, Marsh DJ, Li J, Dahia PLM, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacock M, Eng C, Parsons R. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997;**16**:64-7.
- 82 **Eng C**. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000;**37**:828-30.
- 83 **Fackenthal JD**, Marsh DJ, Richardson AL, Cummings SA, Eng C, Robinson BG, Olopade OI. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. *J Med Genet* 2001;**38**:159-64.
- 84 **Struewing JP**, Abeliovich D, Peretz T, Avishai N, Kaback MM, Collins FS, Brody LC. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat Genet* 1995;**11**:198-200.
- 85 **Oddoux C**, Struewing JP, Clayton CM, Neuhausen S, Brody LC, Kaback M, Haas B, Norton L, Borgen P, Jhanwar S, Goldgar D, Ostrer H, Offit K. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish Individuals is approximately 1%. *Nat Genet* 1996;**14**:188-90.
- 86 **Roa BB**, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996;**14**:185-7.
- 87 **Lalloo F**, Cochrane S, Bulman B, Varley J, Elles R, Howell A, Evans DGR. An evaluation of common breast cancer gene mutations in a population of Ashkenazi Jews. *J Med Genet* 1998;**35**:10-12.
- 88 **Watson M**, Murday V, Lloyd S, Ponder B, Averill D, Eeles R. Genetic testing in breast/ovarian cancer (BRCA1) families. *Lancet* 1995;**346**:583.
- 89 **Lerman C**, Narod S, Schulman K, Hughes C, Gomez-Camirero A, Bonney G, Gold K, Trock B, Main D, Lynch J, Fulmore C, Snyder C, Lemon SJ, Conway T, Tonin P, Lenoir G, Lynch H. BRCA1 testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes. *JAMA* 1996;**275**:1885-92.
- 90 **Lerman C**, Daly M, Masney A, Balshem A. Attitudes about genetic testing for breast-ovarian cancer susceptibility. *J Clin Oncol* 1994;**12**:843-50.
- 91 **Chaliki H**, Loader S, Levenkron JC, Logan-Young W, Hall WJ, Rowley PT. Women's receptivity to testing for a genetic susceptibility to breast cancer. *Am J Public Health* 1995;**85**:1133-5.