Fortnightly Review

Familial breast cancer

D G R Evans, I S Fentiman, K McPherson, D Asbury, B A J Ponder, A Howell

There is now unequivocal evidence that a small proportion of breast cancer cases, perhaps 4-5%, are due to highly penetrant dominant genes.^{1,4} The recent publicity surrounding breast cancer in general, the national screening programme,⁵ and trials of prevention have heightened awareness in families where the disease has already occurred. This has led to demands for advice about risks and what to do about them. Women wish to know not only their own risks but also the risks to their daughters. The needs of these women are being met by general practitioners, surgeons, oncologists, and an increasing number of specialist cancer family history clinics. Access to such clinics is now possible in most regions. In this article we consider how best to give advice and what to do with regard to prevention and screening for women at high risk of developing cancer. The new potential for precise genetic diagnosis in some families raises important additional psychological and ethical issues.

Advances in genetics

From studies of the pattern of distribution of breast and other cancers in families it has been known for some time that inheritance is usually dominantly transmitted.^{6,7} To find the defective gene or genes somewhere in the genome is a daunting task. Nevertheless, the past two years have seen the identification of mutations in one gene (p53) and the location of another (BRCA1) that are now known to predispose to breast cancer.

p53

Dr Steven Friend and colleagues in Boston guessed that the defect in a rare breast cancer family syndrome (the Li Fraumeni syndrome, in which breast cancer occurs at a young age associated with soft tissue sarcoma, osteosarcoma, adrenal tumours, gliomas, and other often childhood tumours^{8,9}) may be caused by a mutation in the p53 tumour suppressor gene on the short arm of chromosome 17 (17p).⁴ Studies by his and other groups have shown that germline mutations in the p53 gene can be found in about half of families with this syndrome. Inherited mutations in the p53 gene may account for only a small percentage of breast cancers, but when a specific mutation can be identified in a family specific predictive tests can give reassurance to an average of half of first degree relatives and three quarters of second degree relatives who can be shown not to have inherited the gene.

BRCA 1

In 1990 Marie-Claire King and colleagues discovered that a DNA marker located on 17q was co-inherited with breast cancer in several large families.³ From worldwide collaboration on linkage

Summary points

- Only about 5% of breast cancer is due to highly penetrant dominant genes
- Familial breast cancer is more likely with early age at presentation, several affected relatives, bilaterality, and a history of related cancers
- There may be more than five genes causing familial breast cancer; the most important of these (BRCA1) has been located on chromosome 17, and DNA tests are possible for a few suitable families
- DNA predictive tests raise several ethical issues, and adequate counselling must precede decisions whether to request testing
- Family history clinics offer counselling, screening, and a focus for research into better methods of detection and prevention of breast cancer

analysis it appears that this gene (BRCA1) is probably of greater importance to public health than p53. This gene is estimated to account for about 45% of families with several cases of breast cancer^{10,11} and up to 67% of such families where the age at onset of the cancers is less than 45. Almost all families with epithelial ovarian cancer in addition to several cases of breast cancer carry the BRCA1 gene.^{11,12}

More genes that predispose to breast cancer will undoubtedly be found. For example, epidemiological evidence suggests that heterozygous carriers of the ataxia telangiectasia gene (about 1% of the population) have a threefold to fivefold greater risk of breast cancer.¹³ Genes may predispose specifically to breast cancer or may predispose to breast cancer and cancer in other sites such as the colon and endometrium (table).¹⁴ For a small but increasing group of people a predictive diagnosis as to whether they carry a faulty gene will shortly be a reality.

Genetic testing

Currently, genetic tests to predict whether someone has inherited a gene predisposing to breast cancer are available only to families where it is possible to prove that a mutation in a particular gene is responsible for the familial clustering. This means that at present tests are confined to some large families with four or more cases of breast cancer or where there is ovarian cancer in addition to three or more cases of breast cancer (at least some of the cases of breast cancer must have occurred in women aged under 50). Testing also

Department of Medical Genetics, St Mary's Hospital, Manchester M13 0JH
D G R Evans, consultant in medical genetics

ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT
I S Fentiman, consultant surgeon

Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT
K McPherson, professor

Department of Radiology, Nightingale Breast Screening Unit, Withington Hospital, Manchester M20 8LR
D Asbury, consultant radiologist

CRC Human Cancer Genetics Research Group, Department of Pathology, University of Cambridge, Cambridge CB2 1QP
B A J Ponder, director

Department of Medical Oncology, Christie Hospital, Manchester M20 9BX
A Howell, senior lecturer in medical oncology

Correspondence to: Dr Evans.

BMJ 1994;308:183-7

Disease	Other tumour susceptibility	Inheritance	% Of familial breast cancer	Location
Familial breast cancer (BRCA1)	Ovary or prostate	Autosomal dominant	45	17q
Li Fraumeni	Sarcoma, leukaemia, brain, adrenal	Autosomal dominant	1-5	17p(p53)
Lynch type 2	Bowel (proximal), endometrium, ovary, pancreas, stomach	Autosomal dominant	75	2p, 18q, ?Others
Ataxia telangiectasia:				
Homozygous	Leukaemia and other sites	Autosomal recessive	?	11q, ?Others
Heterozygous	Other sites			
Cowden's	Skin and other sites	Autosomal dominant	< 1	?
Reifenstein's	?	?X linked recessive	< 1	X

depends on the availability of DNA from relatives in whom cancer has been detected, even if this is only from histological samples. An even smaller group of families with the Li Fraumeni syndrome in which at least one affected member has been shown to have a p53 mutation would also be suitable for predictive testing.

Psychological implications

A common reaction to the serious threat of breast cancer is denial, which has been shown to be harmful because of delays in seeking advice for breast lumps. Many women will not wish to know whether they are genetically predisposed to breast cancer, just as many pregnant women do not wish to know the sex of their fetus by prenatal ultrasonography. For those who seek advice and wish to undergo a predictive genetic test, it is most important that they understand all the implications. Objective evaluation may be particularly difficult for a woman who seeks advice shortly after learning that her sister or mother has breast cancer.

How to identify risk

FAMILIAL RISK FACTORS

Epidemiologists often express risk in terms of a person's increased risk compared with the general population. This, however, may be difficult to translate into the real risk for an individual. For example, a 30 year old woman whose mother and sister have had breast cancer has a 44-fold greater risk of breast cancer compared with the general population.² Clearly a relative risk of 44 cannot mean that a woman is at 44 times the general population lifetime risk of breast cancer, which is 1 in 12. The relative risk applies only to that particular age. For example, the risk of a woman developing breast cancer in her 30th year is 1 in 8000; 44 times this risk is 1 in 182. However, once this woman has reached 60 years and is still unaffected her relative risk will differ little from that of the general population.¹⁵ This is because if she had had any genetic tendency, it would probably have expressed itself by this age.

It is probably easier for women (and their doctors) to understand cumulative risks. A woman wants to know her risk of developing breast cancer in her lifetime or at least over a fixed period such as 10 years or until she is, for example, 60 years old. Cumulative risks can be estimated from epidemiological studies in which the incidence of breast cancer in women with one or more affected relatives is compared with the incidence in women without an affected relative. The most comprehensive data in this field are from the Cancer and Steroid Hormone Study Group in the United States.² Some downward adjustment of risks is needed, however, if these results are to be applied to the United Kingdom because the lifetime risk of breast cancer is 1 in 12 in the United Kingdom compared with 1 in 10 in the United States. Among women with one affected first degree relative, the risk of cancer increases with decreasing age at which the breast cancer was diagnosed in the affected relative (fig 1). For example, a

woman's cumulative risk at age 60 is 10% if her sister developed breast cancer between the ages of 30 and 39, but the risk is only 5% (close to the population figure) if the sister developed breast cancer aged 50-54. If two or more relatives were affected the risks are much higher. For example, a woman with two affected relatives, one of whom developed the disease aged under 50, has a 25% chance of developing the disease by the age of 65.

FIG 1—Cumulative incidence of breast cancer with age among women whose mother or sister had developed cancer at various ages. From Claus *et al*²

A woman's risk also changes substantially with her age. Thus, a woman aged 40 with two first degree relatives who had breast cancer might have a lifetime risk as high as 1 in 4, but at 70 years old her residual risk would differ little from that of the general population. This is because most breast cancers that are due to inherited predisposition occur before the age of 65 (fig 2). If a woman with a strong family history of breast cancer reaches the age of 65 unaffected she probably did not inherit the predisposition in the first place. Figure 3 illustrates the point. Individual 403 has a 50% chance of inheriting a gene with a lifetime penetrance of 80%. As she has not lived through any of her at risk period, her lifetime risk of breast cancer is 40%, with 70% of this risk occurring between the ages of 30 and 50. Individual 402, her cousin, also had a

FIG 2—Cumulative risk of developing breast cancer with age among women with genetic susceptibility to breast cancer and among general population. From Easton *et al*¹¹

lifetime risk of 40%, but her remaining risk is now only about 16%—because she is unaffected at the age of 51 her initial 50% chance of carrying the gene has reduced to 21%, giving a remaining risk of about 10%, to which must be added the risk to a member of the general population at that age (about 6.5%). Individual 403 still has a 25% chance of passing the gene on to her children, whereas individual 402 now has only a 10.5% chance of so doing. Family pedigrees are not usually as clear as this to allow genetic reasoning to be used. For less convincing pedigrees, empirical data from epidemiological studies are necessary.

FIG 3—Family tree showing cases of breast cancer associated with typical dominantly transmitted susceptibility to breast cancer

Endocrine risk factors

Risk of breast cancer in the general population is tripled if menarche occurs at the age of 10 rather than 15, if the age at first live birth is 35 rather than 20, or if menopause occurs at age 55 rather than 45.¹⁶ These hormonal risk factors, however, are not of much practical consequence since most women fall between the values cited and there is confounding between the different risk factors. Several studies have investigated whether unfavourable endocrine risk factors can interact with unfavourable familial risk factors. Some have shown significant synergy in risk with most hormonal factors,^{17,18} while others have found none.¹⁹ Studies have found no correlation with age at menarche¹⁸ or age at first birth.²⁰ Only one study examined families with clearly hereditary breast cancer, with inconclusive results.²⁰ In most studies if family history is defined at all it simply consists of a single affected first degree relative. The true interaction between family history and endocrine factors remains to be determined.

EXOGENOUS HORMONES

The effect of exogenous hormones on risks of familial breast cancer is controversial. In the general population, prolonged use of oral contraceptives before first pregnancy is thought to increase risk.²¹ Among

women with a family history of breast cancer, one study found no significant effect associated with early use of oral contraceptives²² while another showed that use of oral contraceptives was more prevalent in women with cancer.²³ There were no data about contraceptive use after first pregnancy in this group of women. Hormone replacement therapy appears to increase risk of breast cancer marginally in the general population.²⁴ Recent studies have shown that such treatment may also increase risk in those with a family history of breast cancer.²⁵⁻²⁸ A meta-analysis of five studies showed a significant doubling of risk among women who had ever used hormone replacement therapy.²⁹ This analysis, however, contained one large study which showed no effect,³⁰ while another showed that treatment had a protective effect among women who had undergone breast biopsies.³¹ Again there are problems with the definition of family history: it was specified only in the two negative studies, both of which contained as many patients as the other studies combined.

At present it is probably wise to advise sparing use of hormone replacement therapy if at all in this high risk group. There is, however, a case for use of hormone replacement therapy after oophorectomy, which is often performed on women with a combined risk for ovarian and breast cancer and often many years before the natural menopause. In such cases hysterectomy at the time of oophorectomy will allow hormone replacement therapy with low doses of oestrogen alone.

PROLIFERATIVE BREAST DISEASE

Most studies of women with a family history of breast cancer are not sufficiently powerful to detect possibly weak effects in familial subgroups. It is therefore not surprising that inconsistent results are obtained. There are, however, definitive results for the association between proliferative disease of the breast (epithelial hyperplasia and atypical ductal hyperplasia) and family history, thanks to the studies of Dupont and Page.³² They showed that in the 10 years after detection of atypical ductal hyperplasia by biopsy the risk of breast cancer was increased fivefold in women with no family history of breast cancer and 11-fold in women with a family history. After about 10 years the risk falls substantially.³³

If proliferative breast disease is a marker of inheritance of the faulty gene in breast cancer families its presence would have a major impact on risk. There is no evidence of this in Dupont and Page's studies, but in a study of fine needle aspiration cytology of breasts of women with a family history of breast cancer segregation analysis suggested that the proliferative disease was segregating with breast cancer.³⁴ If this result is confirmed aspiration cytology may have a useful role in determining risk.

RELATIVE VALUE OF RISK FACTORS

If a family history clearly indicates a strong inherited risk environmental and other risk factors will be of marginal importance. Exceptions to this are risk factors such as atypical ductal hyperplasia which may indicate that a woman carries the faulty gene. In future, however, intervention with drugs such as tamoxifen may significantly decrease risks. In women with a less convincing family history other risk factors are more important. In view of the importance of familial factors it is worthwhile storing DNA from blood or histological material from women with breast cancer of early onset or women with a suggestive family history.

Value of family history clinics

Referral to a family history clinic (see box for guidelines for referral) allows confirmation of a

woman's family history to obtain as precise a definition of risk as possible, discussion of the meaning of the risks, possible early detection of cancer by mammography and breast examination, and the opportunity for women to take part in prevention studies and other research programmes. Most women seem to welcome the opportunity to discuss their fears of breast cancer with experts and to be incorporated into an ongoing follow up programme if appropriate. Women who attend family history clinics realise that they are at increased risk, but their assessment of that risk varies widely. We asked women to estimate their risks by answering a questionnaire before discussion of their case with the clinician.³⁵ The women were asked what they thought their own risk of developing breast cancer was during their lifetime and what they thought the population lifetime risk was. Figure 4 shows how diverse the perception of risk was: 29% of the women underestimated their own risks by more than half, while 23% exaggerated their risk by more than this. The women who overestimated their risk presumably gained some reassurance from being told that their risks were lower than they thought, but many women were given higher risks than they had originally estimated. Although our impression is that this does not produce excessive anxiety, we are currently assessing anxiety in relation to ascribed risk.

It is standard practice for women at high risk of breast cancer to undergo annual breast examination in the clinic with mammography from the age of 35 or from five years before the earliest onset of cancer in their family. However, the effectiveness of mammography in the general population is marginal at ages below 50, the period at which women with a family history of breast cancer are at their greatest risk. No data are available on the effectiveness of mammography among high risk women, for whom the pick up rates should be much higher. National collaboration between risk clinics coordinated through the National Screening Programme is needed to assess the value of screening, but high risk women are unlikely to accept randomisation into non-screened groups. Annual mammography seems to be necessary: Swedish studies have shown that annual screening of women aged under 80 detects over 60% of breast cancers, but when screening is done once every two years 70% of women with breast cancer present between screens.³⁶ Annual screening is therefore being used in the British trial of screening for women aged under 50 (H Cuckle, personal communication).

Prevention trials

Both adjuvant treatment after surgery for early breast cancer and breast screening reduce mortality from the disease, but neither is likely to reduce mortality by more than 30%.³⁷ Identification of women at high risk therefore provides the possibility of sufficient events (development of breast cancer) to

FIG 4—Estimation of lifetime risk of breast cancer for general population and for self made by 308 women with family history of breast cancer (12 women did not give answer for general population and 18 did not give answer for self)

Guidelines for referral to a family history clinic for breast cancer

- Mother or sister developed breast cancer when aged <40
- Mother or sister developed breast cancer before age of 50, and another close relative on same side of family developed cancer of breast, ovary, colon, or endometrium or a sarcoma before age of 65
- Mother or sister developed breast cancer when aged 50-65, and one other close relative on same side of family developed cancer of the breast, ovary, endometrium, or colorectum or a sarcoma before age of 50
- Mother or sister developed double primary cancer (of the breast and any one of ovary, colon, or endometrium or a sarcoma); at least one of the tumours occurred before age of 50 and the breast cancer occurred before age 65
- Dominant history of breast cancer (four or more cases of breast or ovarian cancer, or both, on same side of family at any age)
- History of related malignancy in mother or father (cancer of colorectum, ovary, or endometrium or sarcoma before age of 50), and at least one of their first degree relatives developed breast cancer before age of 50
- Two or more cancers of related types (breast, ovary, colorectum, or endometrium or a sarcoma) in close relatives on father's side, but not necessarily including father, with one cancer diagnosed before age of 50

make prevention trials a worthwhile possibility. Three major groups of trials of prevention are currently in progress: reduction in fat intake in Canada; administration of retinoids in Italy; and administration of the antioestrogen tamoxifen in the United Kingdom, United States, Australasia, and mainland Europe. The third group of trials followed a pilot trial in London,³⁸ which has received recent governmental approval for extension to centres throughout the United Kingdom. Tamoxifen or placebo is administered daily to women aged 45-60 who are at risk (relative risk ≥ 2 ; commonest entry criteria is mother or sister who developed breast cancer when aged ≤ 50) and women aged 35-45 who are at higher risk.

Surgery

An energetic attempt to reduce the risk of breast cancer would include the option of prophylactic bilateral mastectomy. Until better and less mutilating procedures become available, this would take the form of bilateral total mastectomy with or without reconstruction. A single stage procedure requires 6-8 hours of anaesthesia, with its attendant risks. Many surgeons would advocate a two stage procedure with reconstruction carried out later, and some plastic surgeons think this gives a better cosmetic outcome. An easier option would be bilateral subcutaneous mastectomy with immediate subpectoral placement of a prosthesis. This should be resisted because subcutaneous mastectomy does not fully ablate the mammary epithelium. Women with ductal carcinoma in situ who have been treated by subcutaneous mastectomy have shown a rate of progression to invasive disease similar to that after biopsy alone,³⁹ although removal of over 90% of the breast epithelium at risk ought to reduce risk somewhat.

In future it may be possible to ablate the breast epithelium and yet avoid surgery. It is possible to selectively catheterise the mammary ducts to carry out ductograms in women with suspected intraduct papilloma or carcinoma.⁴⁰ With this approach it should

be possible to introduce sclerosing agents or possibly linked radionuclides to selectively destroy the ductal and lobular epithelium. This would leave the mammary stroma intact, thereby achieving the necessary field ablation without mutilation. Clearly the efficiency of such an approach must be evaluated.

Another problem is the best treatment for breast cancer in young women with a genetic predisposition to the disease. Even though the primary lesion may be small and apparently suitable for conservative treatment, the risk of bilateral or multicentric breast cancer (with the entire mammary epithelium at risk of malignant transformation) would suggest mastectomy as the better option. This may be strenuously resisted by some women,⁴¹ and the best choice of surgery remains to be determined.

Other research

Family history clinics provide an ideal focus, not only for investigation of large families to identify breast cancer genes, but for other approaches to identify women at risk more precisely. These approaches include assessing the value of fine needle aspiration for analysis and detection of early genetic events and evaluating possible phenotypic markers of risk such as changes in breast temperature, stromal influences, and breast secretions.

Legal considerations

There are cases of people who may be at risk of HIV infection being asked by insurance companies to undergo HIV testing, and similar problems may well be faced by women with a family history of breast cancer who seek life insurance. They may be asked to undergo testing against their own wishes in order to obtain insurance at standard rates. This development has to be resisted strenuously. Interested third parties should not be able to force women to undergo testing when the implications of the result are so complex.

Conclusions

Family history clinics provide a forum for giving a professional service to women at risk of developing breast cancer and an exceptional opportunity for conducting research, which will almost certainly lead to improved methods of detection and prevention. Cloning of the various familial breast cancer genes will allow specific mutation analysis in families and the identification of those who are truly at high risk. Expensive and scarce screening techniques that are likely to be far more accurate than conventional methods (for example magnetic resonance imaging with gadolinium enhancement) may be possible for the small group of women with over 80% risk of developing breast cancer. The tests will also allow reassurance of a larger group of women who have not inherited a faulty gene, and this should bring savings by avoiding unnecessary early screening. The accurate identification of women at high risk will raise difficult ethical questions regarding optimal treatment but will enable us to target preventive and therapeutic strategies more precisely than is currently the case.

1 Newman B, Austin MA, Lee M, King M. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families. *Proc Natl Acad Sci USA* 1988;85:3044-8.

2 Claus EB, Risch NJ, Thompson WD. Age at onset as an indicator of familial risk of breast cancer. *Am J Epidemiol* 1990;131:961-72.

3 Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al.

Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990;250:1684-9.

4 Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, et al. Germline p53 mutations in cancer families. *Science* 1990;250:1233-8.

5 *Breast cancer screening: Forrest report*. London: HMSO, 1988.

6 Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty four kindreds. *Cancer Res* 1988;48:5358-62.

7 Anderson DE. A genetic study of human breast cancer. *J Natl Cancer Inst* 1972;48:1029-34.

8 Shrivastava S, Zou Z, Pirolo K, Blattner W, Chang EH. Germline transmission of a mutated p53 gene in a cancer-prone family with Li Fraumeni syndrome. *Nature* 1990;348:747-9.

9 Santibanez-Koref MF, Birch JM, Hartley AL, Morris Jones PH, Craft AW, Eden T, et al. p53 germline mutations in Li Fraumeni syndrome. *Lancet* 1991;338:1490-1.

10 King MC. Breast cancer genes: how many, where and who are they? *Nature Genetics* 1992;2:89-90.

11 Easton DF, Bishop DT, Ford D, Crockford GP, the Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 1993;52:678-701.

12 Narod SA, Feunteun J, Lynch HT, Watson P, Conway T, Lynch J, et al. Familial breast-ovarian cancer locus on chromosome 17q12-q23. *Lancet* 1991;338:82-3.

13 Swift ML, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia telangiectasia. *N Engl J Med* 1987;316:1289-94.

14 Lynch HT, Lanspa SJ, Bonan BM, Smyth T, Watson P, Lynch JF. Hereditary non-polyposis colorectal cancer Lynch syndromes I and II. *Gastroenterol Clin North Am* 1988;174:679-715.

15 Roseman DL, Straus AK, Shorey W. A positive family history of breast cancer. *Arch Intern Med* 1990;150:191-4.

16 Lynch HT, Watson P, Lynch JF. Epidemiology and risk factors. *Clinical Obstet Gynecol* 1989;32:750-60.

17 Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schaiver C, et al. Projecting individualised probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879-86.

18 Anderson DE, Badzioch MD. Combined effect of family history and reproductive factors in breast cancer risk. *Cancer* 1989;63:349-53.

19 Parazzani F, La Vecchia C, Negri E, Francheschi S, Boccione L. Menstrual and reproductive factors and breast cancer in women with a family history of the disease. *Int J Cancer* 1992;51:677-81.

20 Lynch HT, Albano WA, Layton MA, Kimberling WJ, Lynch JF. Breast cancer, genetics, and age at first pregnancy. *J Med Genet* 1984;21:96-8.

21 Chilvers CED, Deacon JM. Oral contraceptives and breast cancer. *Br J Cancer* 1990;61:1-4.

22 Olsson H, Moller TR, Ranstam J. Early oral contraceptive use and premenopausal breast cancer—final report from a study in southern Sweden. *J Natl Cancer Inst* 1989;81:1000-4.

23 Black MM, Barclay THC, Polednak A, Kwon CS, Leis HP, Pilnik S. Family history, oral contraceptive usage and breast cancer. *Cancer* 1983;51:2147-51.

24 Whitcroft SIJ, Stevenson JC. Hormone replacement therapy: risks and benefits. *Clin Endocrinol* 1992;36:15-20.

25 Hoover R, Glass A, Finkle WD, Azevedo D, Milne K. Conjugated estrogens and breast cancer risk in women. *J Natl Cancer Inst* 1981;67:815-20.

26 Kaufman DW, Palmer JR, de Mouzon J, Rosenberg L, Stolley PD, Warshauer ME, et al. Estrogen replacement therapy and the risk of breast cancer: results from the case-control surveillance study. *Am J Epidemiol* 1991;134:1375-85.

27 La Vecchia C, Decarli A, Parazzini F, Gentile A, Liberati C, Franceschi S. Non-contraceptive estrogens and the risk of breast cancer in women. *Int J Cancer* 1986;38:853-8.

28 Nomura AMY, Kolonel LN, Hirohata T, Lee J. The association of replacement estrogens with breast cancer. *Int J Cancer* 1986;37:49-53.

29 Steinberg KK, Thacker SB, Smith S, Stroup DF, Zack MM, Flanders WD, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA* 1991;265:1985-90.

30 Brinton LA, Hoover R, Fraumeni JF. Menopausal oestrogens and breast cancer risk: an expanded case-control study. *Br J Cancer* 1986;54:825-32.

31 Dupont WD, Page DL, Rogers LW, Parl FF. Influence of exogenous estrogens, proliferative breast disease, and other variables on breast cancer risk. *Cancer* 1989;63:948-57.

32 Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;312:146-51.

33 Dupont WD, Page DL. Relative risk of breast cancer varies with time since diagnosis of atypical hyperplasia. *Hum Pathol* 1989;20:723-5.

34 Skolnick MH, Cannon-Albright LA, Goldgar DE, Ward JH, Marshall CJ, Schumann GB, et al. Inheritance of proliferative breast disease in breast cancer kindreds. *Science* 1990;250:1715-20.

35 Evans DGR, Burnell LD, Hopwood P, Howell A. Perception of risk in women with a family history of breast cancer. *Br J Cancer* 1993;67:612-4.

36 Tabar L, Faberberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer* 1987;56:547-51.

37 Roebuck EJ. Mammography and screening for breast cancer. *BMJ* 1986;292:223-6.

38 Powles TJ, Tillyer CR, Jones AL, Ashley SE, Treleavan J, Davey JB, et al. Prevention of breast cancer with tamoxifen—an update on the Royal Marsden Hospital pilot programme. *Eur J Cancer* 1990;26:680-4.

39 Price P, Sinnott HD, Gusterson B, Walsh G, A'Hern RP, McKinna JA. Duct carcinoma in situ: predictors of local recurrence and progression in patients treated by surgery alone. *Br J Cancer* 1990;61:869-72.

40 Sartorius OW, Smith HS, Morris P, Benedict D, Friesen L. Cytologic evaluation of breast fluid in the detection of breast disease. *J Natl Cancer Inst* 1977;59:1073-80.

41 Evans DGR, Donnai D, Ribeiro G, Warrell D. Ovarian cancer family and prophylactic choices. *J Med Genet* 1992;29:416-8.

(Accepted 12 October 1993)