CARCINOMA IN SITU AND PATIENTS AT HIGH RISK OF BREAST CANCER

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Carcinoma in situ

Ductal carcinoma in situ: (left) comedo type carcinoma with extensive necrosis adjacent to viable malignant cells enclosed by basement membrane; (above) with central visible microcalcification.

Lobular carcinoma in situ.

Classification of ductal carcinoma in situ

Histology	Cytology	Necrosis	Calcification
Comedo	High grade	Extensive	Branched
Intermediate	Intermediate	Limited	Limited
Non-comedo*	Low grade	Absent	Microfoci, inconsistent

*Cribriform, solid, or micropapillary.

Two main types of non-invasive (in situ) cancer can be recognised from the histological pattern of disease and cell type. Ductal carcinoma in situ is the most common form of non-invasive carcinoma (making up 3-4% of symptomatic and 17% of screen detected cancers) and is characterised by ducts and ductules expanded by large irregular cells with large irregular nuclei. In contrast, lobular carcinoma in situ is rare (0.5% of symptomatic and 1% of screen detected cancers) and presents as an expansion of the whole lobule by smaller regular cells with regular, round or oval nuclei.

There has been a lack of agreement among pathologists about whether small lesions should be considered as hyperplasia or in situ carcinoma. In general, lesions that involve only a few membrane bound spaces and that measure less than 2-3 mm in their greatest diameter should be regarded as hyperplastic lesions (with or without atypia) and not in situ carcinoma. There is better agreement about larger lesions.

Ductal carcinoma in situ

Different classifications of ductal carcinoma in situ have been described, and these correlate to some degree with mammographic patterns of microcalcification.

Presentation—Patients with symptomatic ductal carcinoma in situ present with a breast mass, nipple discharge, or Paget's disease. Screen detected carcinoma is most commonly associated with microcalcification, which may be localised or widespread and is characteristically branching and of variable size and density.

Mammograms showing microcalcification characteristic of ductal carcinoma in situ: localised (left) and widespread (right).

Rate of development of non-invasive and invasive carcinoma after treatment of ductal carcinoma in situ by wide excision alone or wide excision and radiotherapy. (All sizes and types of lesions of ductal carcinoma in situ were included in this study.)

Recommended treatment for ductal carcinoma in situ*

Localised carcinoma (<4 cm)†

- Wide local excision
Ensure that mammographic lesion has been completely excised with clear histological margins
Re-excite if margins are involved
Consider mastectomy if carcinoma >4 cm in size or if micropapillary
- Consider postoperative radiotherapy if comedo type carcinoma
- Consider tamoxifen, 20 mg a day

Widespread carcinoma (≥4 cm)†

- Mastectomy (with or without breast reconstruction)
- Consider tamoxifen

*Outside trials of experimental treatments.

†Extent of carcinoma can be estimated in 80% of patients by measuring extent of malignant microcalcification on mammograms.

Areas of investigation currently being studied in clinical trials

- Natural course of screen detected ductal carcinoma in situ treated by wide excision
- Role of tamoxifen in reducing recurrence after complete excision of localised ductal carcinoma in situ
- Role of radiotherapy in reducing recurrence after complete excision of localised ductal carcinoma in situ

Features of ductal and lobular carcinoma in situ

	Ductal carcinoma	Lobular carcinoma
Average age	late 50s	late 40s
Menopausal status	70% postmenopausal	70% premenopausal
Clinical signs	Breast mass, Paget's disease, nipple discharge	None
Mammographic signs	Microcalcification	None
Risk of subsequent carcinoma	30-50% at 10-18 years	25-30% at 15-20 years
Site of subsequent carcinoma:		
Same breast	99%	50-60%
Other breast	1%	40-50%

Natural course—Several studies have assessed the risk of subsequent invasive carcinoma in patients in whom ductal carcinoma in situ was missed by the pathologist or the diagnosis was made but mastectomy was not performed. About one third of these patients developed invasive breast cancer in the same breast during follow up of 10-18 years.

Treatment—Symptomatic ductal carcinoma in situ involves much larger areas of the breast than carcinoma in situ detected by screening and has traditionally been treated by mastectomy. Such treatment is associated with excellent long term outcome (98% survival at five years). With the advent of breast screening and the use of conservative surgery for invasive carcinoma, limited surgery has been increasingly used for localised carcinoma in situ. Wide excision alone seems to produce satisfactory local control in non-comedo ductal carcinoma in situ (up to 5% recurrence at eight years) but not in comedo carcinoma (30-50% recurrence at eight years). Preliminary data (with follow up of less than four years) from an American study indicate that radiotherapy may reduce the rate of recurrence after excision of a localised area of ductal carcinoma in situ, but it is not clear whether the benefits of radiotherapy relate to all types of ductal carcinoma in situ or whether radiotherapy has any long term adverse effects. Tamoxifen might be expected to reduce the rate of recurrence and the rate of contralateral disease and so may be worthwhile. Mastectomy is still appropriate treatment for widespread carcinoma in situ; micropapillary ductal carcinoma in situ has a particular tendency to be widespread. Axillary surgery is not indicated in localised ductal carcinoma in situ; but axillary nodal metastases are seen in up to 5% of more widespread disease because of unsuspected microinvasion. Clinical trials are now under way to determine optimum treatment for screen detected ductal carcinoma in situ.

Lobular carcinoma in situ

Lobular carcinoma in situ is better defined than ductal carcinoma. Some doctors still use the term lobular neoplasia, which refers to both atypical lobular hyperplasia and lobular carcinoma in situ, largely because of the histological homogeneity of these two conditions. As these lesions have a different natural course, they should be classified separately.

Presentation is often an incidental finding during a breast biopsy and there are no characteristic clinical or mammographic features.

Natural course—About 15-20% of women with a diagnosis of lobular carcinoma in situ will develop breast cancer in the same breast, and a further 10-15% will develop an invasive carcinoma in the contralateral breast.

Treatment—There are three possible approaches: observation, with yearly bilateral mammography; entering the patient into a trial of treatments to prevent breast cancer; or bilateral mastectomy. Bilateral mastectomy should be confined to women who experience severe anxiety that significantly reduces their quality of life. The standard treatment is observation.

Patients at high risk of breast cancer

Relative risk of invasive breast cancer associated with benign diseases

No increased risk

Mild hyperplasia
Duct ectasia
Apocrine metaplasia
Simple fibroadenomas
Microcysts
Periductal mastitis
Adenosis

Slightly increased risk (1.5-2 times)

Palpable cysts (cystic disease)
Moderate and florid hyperplasia
Papilloma
Complex fibroadenomas
Sclerosing adenosis

Moderately increased risk (4-5 times)

Atypical hyperplasia

A variety of risk factors have been identified for breast cancer. Factors that are associated with a slightly elevated risk (<2 times) are not clinically relevant and require no specific action. This includes most of the aspects of lifestyle that are risk factors (age at first pregnancy, history of breast feeding, and diet). The only factors associated with significantly increased risks of subsequent breast cancer are certain types of previous benign breast disease and family history.

Previous breast disease

Women with palpable breast cysts, particularly those who develop multiple cysts, and women with certain histological features on biopsy (complex fibroadenomas, duct papillomas, sclerosing adenosis, and moderate or florid usual type hyperplasia) are at some increased risk of breast cancer. However, only women with atypical hyperplasia are at a significantly increased risk. There is an interaction between atypical hyperplasia and family history: women with both atypical hyperplasia and a first degree relative (mother, daughter, or sister) with breast cancer have an absolute risk of 20-30% of developing breast cancer within the next 15-20 years.

Family history

Between 2% and 10% of patients with breast cancer have a genetic abnormality that predisposes them to develop the disease. The presence of a predisposing breast cancer mutation can be suspected from the following:

- Several cases (strictly speaking, a high proportion) of breast cancer in a single family
- Early onset of breast cancer in affected relatives; not all genetically determined breast cancers present in young women, but the earlier the onset the greater the risk that it is genetic
- The presence of multiple epithelial cancers in family members, including bilateral breast cancer or ovarian, colon, and prostate cancer; the combination of breast and ovarian cancers is particularly common in families with a "cancer gene"

Risk of subsequent development of invasive carcinoma in patients with no epithelial proliferation, proliferative disease without atypia (moderate or florid hyperplasia), atypical hyperplasia, or atypical hyperplasia and a family history of cancer.

Creating a family pedigree—For people who present with a family history of cancer it is necessary to create a family pedigree to confirm that a predisposing mutation is probably present—genetic susceptibility is transmitted as an autosomal dominant trait with limited penetrance—and to estimate the probability that any member of the family has the mutation. The second task is becoming easier as "breast cancer genes" are identified. At present, however, risk is calculated mainly by statistical methods. Word of mouth histories are often inaccurate or incomplete. To assess risk it is necessary to extend and verify details of family histories by examining hospital records; pathology reports; data from cancer registers; and public records of births, marriages, and deaths. Distinctive patterns may then be recognised to allow identification of families carrying a mutation in a particular breast cancer gene such as BRCA1, BRCA2, or p53. In such a family any woman who has not yet developed breast cancer has a less than 50% of chance of carrying the gene, and the risk of having inherited the gene and developing breast cancer decreases as the woman's age increases. For example, if all affected family members developed breast cancer by the age of 45 a female relative aged 55 is unlikely to have inherited the relevant mutation, and her risk of getting breast cancer is little greater than that of the general population.

Edinburgh pedigree 2000 typed for 42D6 and MFD188, markers for polymorphism in chromosome 17. All subjects who developed breast or ovarian cancer had the 2/12 pattern of inheritance for the two markers.

Risk of developing breast cancer associated with risk factors

Factors present	Approximate risk
Atypical hyperplasia (specifically defined)	10-15% in next 15-20 years
Atypical hyperplasia and family history of breast cancer*	20-30% in next 15-20 years
Carrier of mutant BRCA1 gene	80-85% during lifetime

*Disease in first degree relative (mother, sister, or daughter).

Currently, regular breast screening is limited to women aged 50 or over.

Patient who underwent bilateral subcutaneous mastectomies and immediate breast reconstruction because she was considered to be at very high risk of developing breast cancer.

Genetic linkage analysis can be performed if tissue or blood are available from a substantial number of affected members of a family. Such an analysis looks at the inheritance of markers that flank a particular gene, such as the BRCA1 gene on the long arm of chromosome 17. Family members at risk can then be tested for these markers, and marker patterns can be used to assess whether a person is likely to be carrying the affected gene. Genetic linkage is of value principally for women from families carrying a BRCA1 gene mutation. Although this locus is probably involved in only 2% of all breast cancers, it may account for up to 40% of all familial breast cancers. Figures for BRCA2 may be similar. Now that the BRCA1 gene has been cloned, when the precise mutation can be characterised in one affected member of a family, peripheral blood analysis of relatives at risk will identify other carriers of the mutation. Carriers of a mutated breast cancer gene have an 80-85% chance of developing the disease. Genetic analysis is likely to become feasible for BRCA2 and other breast cancer genes in the next few years.

Management of women at high risk

Women at high risk of breast cancer may also be at risk of other cancers, and a coordinated approach to their management is required. Studies have shown that about a third of women with a family history of breast cancer underestimate their own risk by more than half, while a quarter exaggerate their risks by more than this. Many centres now have clinics for women who have a family history of or who are at high risk of breast cancer; these clinics provide the genetic counselling and psychological support that these women need.

There are three possible interventions that might reduce mortality in women at risk:

- Instituting regular screening
- Preventing development of breast cancer
- Performing bilateral subcutaneous mastectomies

Regular screening—As yet there is no evidence that regular screening of high risk groups of women aged under 50 reduces mortality, and no randomised studies are presently under way to determine whether screening such women is of value. Current recommendations are that women with a strong family history of breast cancer should be screened by mammography, with screening starting at an age five to 10 years younger than that of the youngest relative to have developed the disease. Ultrasonography is being assessed as a screening tool in younger women, but there is as yet no evidence that it is of value. Nuclear magnetic resonance imaging with computer analysis is also being investigated as a technique that can be repeated regularly to screen high risk women.

Prevention of breast cancer—Studies are under way to assess the value of tamoxifen and retinoids in women at high risk of breast cancer, but the results from these studies will not be available for 10-20 years. Hormonal manipulation by oophorectomy combined with tamoxifen or low dose oestrogen replacement would be expected to reduce the risk of breast cancer while at the same time removing a common site of cancer development (the ovaries) in families in which ovarian cancer and breast cancer are clearly linked. Recent reports indicate that postmenopausal women taking tamoxifen as adjuvant treatment for breast cancer have an increased risk of developing endometrial cancer and cancer at other sites. Tamoxifen should be used as a preventative treatment only in clinical trials, and patients in such trials should be informed of both the potential risks and benefits.

Bilateral subcutaneous mastectomy performed at five years younger than the youngest family relative to have developed breast cancer might be considered appropriate for women from families that carry the BRCA1 or BRCA2 gene mutations proved by DNA analysis. These operations should be performed by experienced surgeons to ensure that all breast tissue is removed and so that immediate breast reconstruction can be performed.

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