

Breast Cancer Recurrence

Background Information

Despite an overall improvement in breast cancer mortality, the unfortunate fact remains that many breast cancer patients will still experience a recurrence of their disease.

Types and treatment of breast cancer recurrence

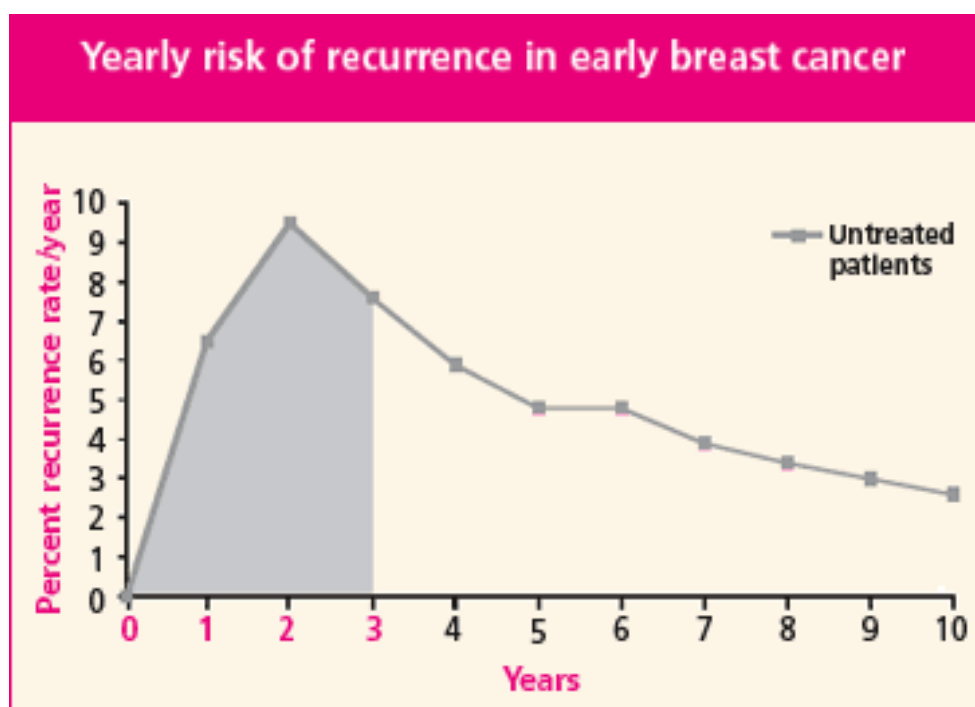
Recurrence describes the return of breast cancer after primary treatment.¹ There are three types of recurrent breast cancer:¹

- **Local recurrence** occurs when cancerous cells reappear at the original tumour site over time. Local breast cancer recurrence is not considered to be a spread of the cancer but rather due to failure of the initial treatment. Even after mastectomy, portions of breast skin and fat remain, making local recurrence possible, albeit uncommon. Rather, it is women treated with breast-conserving therapy and radiation who are at slightly higher risk of this type of recurrence. Treatment of locally recurring breast cancer depends on the initial therapy undertaken at the time of first diagnosis. If breast conserving surgery was originally performed, recurrent breast cancer will usually be treated with mastectomy.
- **Regional recurrence** is more serious than local recurrence because it usually indicates that the cancer has spread past the breast and underarm (auxiliary) lymph nodes. Regional recurrences of breast cancer can occur in the chest muscles, in the internal mammary lymph nodes under the breastbone and between the ribs, in the nodes above the collarbone and in the nodes surrounding the neck. The latter two sites of regional recurrence tend to suggest more aggressive cancers. Overall, regional recurrence is very common, occurring in approximately 2% - 5% of all breast cancer cases. Treatment can be complex however, including surgery to remove the cancerous node, radiotherapy, chemotherapy and adjuvant endocrine therapy depending on the previous treatment used.
- **Distant recurrence**, also known as **metastasis** is the most serious type of recurrence and is associated with significantly lower survival. Having left the confines of the breast tissue, the cancer usually spreads first to the axillary lymph nodes. In 65-75%^{2,3,4,5} of distant recurrences the breast cancer then spreads from the lymph nodes to the bone. More rarely, the breast cancer may metastasise to other sites including the lungs, liver, brain or other organs. Surgery is rarely an option for metastatic breast cancer because the cancer is not usually confined to one specific site on a given organ. Instead, treatment approaches include chemotherapy, radiation therapy or endocrine therapy.

A new cancer may occasionally occur years after the initial tumour, in a different area of the breast and with different pathology. Second cancers such as these are treated as new cancers, independent of the first cancer, and are not considered to constitute a recurrence.¹

When and how often does breast cancer recur?

Without additional therapy, 60% of women remain free from breast cancer five years after surgery.⁶ Breast cancer is most likely to recur within the first two years if no further treatment is given.⁷ The Early Breast Cancer Trialists Collaboration Group conducted a meta analysis of 55 clinical trials on breast cancer recurrence involving 37,000 patients. These results clearly show the clustering of recurrence risk in the first few years following initial diagnosis of early breast cancer for those patients not receiving adjuvant endocrine therapy.⁸



The cumulative incidence of recurrence and breast cancer-related deaths also continued to increase throughout the first 10 years after diagnosis, with a substantial portion of recurrences occurring beyond five years after diagnosis.⁸ The recurrence rate among patients who did not receive adjuvant hormonal therapy was nearly 50% in node-positive patients and 32.4% in node-negative patients in the 10 years post-

Unlike other forms of cancer, breast cancer is not considered to be cured if it does not recur within the first 5 years.⁷ Breast cancer can recur as many as 10 or 20 years after the initial diagnosis, however the risk of recurrence does decline over time.⁷

Risk factors for recurrence

The risk of breast cancer recurring depends on the individual characteristics of the patient and the tumour. Nevertheless, a number of common factors have been identified which can help to predict the risk of breast cancer recurrence. These prognostic indicators include:

- *Lymph node involvement* – whether the tumour has spread to the lymph nodes at the time of diagnosis (node positive) and, importantly, the number of lymph nodes in which the cancer has been found.⁹ Node-negative status at diagnosis has been commonly associated with favourable patient outcomes.⁹
- *Tumour size*⁹
- *Histological grade* – this is a calculation of how abnormal the cancer cells look when examined under a microscope and how fast they are growing.⁹ There are three features which determine a cancer's grade:⁹
 - The rate of cell division
 - The percentage of cancer composed of tubular structures (tubular structures are less aggressive than ductile carcinoma)
 - The change in cell size and uniformity

If a tumour is determined as Grade 3, for example, then there is a higher risk of recurrence than with a Grade 1 tumour.⁹

- *HER2/neu status* – this gene encodes a growth-promoting protein which helps control how cells divide and repair themselves.⁹ Positive or negative HER2/neu status is important in the control of abnormal or defective cells that could become cancerous and may carry implications for treatment.¹⁰ Immunotherapy with trastuzumab (Herceptin[®]) alone or with chemotherapy may be recommended for women whose breast cancer cells display a high level of HER2/neu protein. Herceptin is usually reserved for when hormonal treatment or chemotherapy are no longer proving effective.¹¹
- *Vessel vascular invasion* – the presence of cancer cells in the vessels within the cancer itself.⁹

- *Hormone receptor status* – reflects whether the cancer is oestrogen receptor positive (ER+), progesterone receptor positive (PgR+) or neither.⁹
- *Proliferation index* - prognostic factor in breast cancer. The Ki-67 protein is expressed in all phases of the cell cycle except G0 and serves as a marker for proliferation. Studies that have evaluated proliferation index by Ki-67 IHC in breast cancer have shown a significant correlation between high proliferation rates and shorter disease free and overall survival.^{12,13,14,15} The Ki-67 proliferation index is assessed by point counting 500 to 1000 cells, and is reported as percent positive cells.

Categorising 'low' risk

A group of experts in the field of breast cancer (the St Gallen International Consensus Panel) have adjudged that in order to qualify as 'low risk' for recurrence, patients with ER/PgR-positive breast cancer must meet all of the following criteria:

- Cancer has not spread to the lymph nodes
- Tumour is < 2 cm in greatest dimension
- The nuclei of cancer cells are small with little increase or variation in size compared with normal breast tissue cells, regular outlines and uniformity of nuclear chromatin
- No cancer cells have invaded the blood or vessels
- Cancer does not use the Her2/neu pathway to grow

Even for small tumours in the lowest risk category, the 10-year risk of breast cancer recurrence may be as high as 12% in the absence of adjuvant therapy.¹⁶

St Gallen definition of risk categories for patients with node-negative breast cancer¹⁷

Low risk	Node negative AND all of the following features: Pathologic tumour size ≤ 2 cm, AND Grade 1, AND Absence of peritumoural vascular invasion, AND HER2/neu gene neither over-expressed nor amplified, AND Age ≥ 35 years
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Intermediate risk	Node negative AND at least one of the following features: Pathologic tumour size >2cm, OR Grade 2-3, OR Presence of peritumoural vascular invasion, OR HER2/neu gene over-expressed or amplified, OR Age <35 years
	Node positive (1-3 nodes involved) AND HER2/neu gene neither over-expressed nor amplified
High risk	Node positive (1-3 nodes involved) AND HER2/neu gene over-expressed or amplified Node positive (4 or more involved nodes)

Reducing recurrence risk

Many studies have highlighted that adjuvant endocrine therapy is now an essential tool in the fight against breast cancer as it decreases the risk of recurrence by at least one third¹⁸ and can substantially improve long term survival.¹⁹ Adjuvant endocrine therapy largely consists of anti-oestrogens (*tamoxifen*) and aromatase inhibitors (*letrozole, anastrozole and exemestane*). However, the superiority of aromatase inhibitors over anti-oestrogens in reducing the risk of breast cancer recurrence in the post-surgery setting is now well established. In addition, chemotherapy treatment given post-surgery has been shown to significantly reduce the risk of recurrence.⁶

– Ends –

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