

*Ministry of Defence*

## **Synopsis of Causation**

### **Breast Cancer**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1. Breast cancer affects one in 9 women during their lifetime, with a total of 1,050,000 new cases in the world per annum. In the United Kingdom, there are approximately 41,000 new cases per annum and 1% of all cases of breast cancer arise in men.<sup>1</sup>
- 1.2. A breast cancer is defined as a malignant tumour that arises from the terminal duct lobular unit within the breast.
- 1.3. If the breast cancer cells remain confined by the basement membrane of the terminal duct lobular unit, then this is termed an “in situ” or “non-invasive” cancer. These “in situ” or “non-invasive” cancers are then further categorised according to their histological appearances as being “ductal carcinoma in situ” or “lobular carcinoma in situ” types.
- 1.4. If the breast cancer cells spread through and are no longer contained by the basement membrane, this is termed “invasive” breast carcinoma.
- 1.5. Invasive breast carcinomas can be categorised according to their histological appearances and features. The commonest types are invasive ductal carcinoma (approximately 85%) and invasive lobular carcinoma (approximately 15%).
- 1.6. Some invasive breast cancers are termed “cancers of special type” and include the following types of cancer – tubular, mucoïd, cribriform, papillary and medullary. The special types of cancer have a better prognosis than invasive carcinomas of no special type.
- 1.7. The cancers of no special type can be graded according to their histological appearance, taking into account their nuclear pleomorphism, degree of tubule formation and number of mitoses. Grade 1 tumours are the least aggressive with grade 2 being intermediate, and the most aggressive tumours are those categorised as grade 3. This grading correlates with overall survival.
- 1.8. The commonly used staging systems are the TNM and the UICC systems described as follows:
  - Tis - cancer in situ.
  - T1 - less than or equal to 2cm.
  - T2 - 2 to 5cm.
  - T3- greater than 5cm.
  - T4a - fixed to chest wall.
  - T4b - fixed to skin or skin involved.
  - T4c - both of the above.
  - T4d - inflammatory cancer.

N0 - no regional nodes.

Nx - cannot be assessed.

N1 - palpable axillary nodes.

N2 - fixed, involved axillary nodes.

N3 - ipsilateral internal thoracic node involvement.

Mx - cannot be assessed.

M0 - no evidence of metastases.

M1 - distant metastases.

1.9. The UICC stage and its relationship to the TNM system is as follows:

Stage I - T1, N0, M0.

Stage II - T1N1M0; T2N0-1M0.

Stage III - any T N2-3M0; T3 any N M0; T4 any N, M.

Stage IV - any T, any N, M1.

## 2. Clinical Features

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- 2.1. Breast cancer can present because of the presence of disease within the breast, as a consequence of lymph node disease, or with symptoms due to disseminated metastatic disease. In addition, breast cancer may be detected in asymptomatic individuals by the National Health Service Breast Screening Programme.
- 2.2. In the United Kingdom, the National Health Service Breast Screening Programme currently offers mammography to all women between the ages of 50 and 64 years, at 3 yearly intervals. This is by invitation to attend for screening and is delivered on a rotating basis via the general practitioner.<sup>2</sup> More recently, this is being extended to women aged between 65 and 70 years. Breast cancer may be detected in asymptomatic patients on the basis of a mammographic abnormality. However, in a small number of patients the detected mammographic abnormality may also be detected by a clinical examination.
- 2.3. A primary breast cancer within the breast may present as a palpable lump, or may manifest itself by causing an abnormality in the skin of the breast. This may be skin retraction, dimpling of the skin, inflammation of the skin or a *peau d'orange* appearance of the skin of the breast. The disease may also present as an abnormality in the nipple-areola complex. This may be either as a bloody discharge or the appearances of Paget's disease of the nipple, which has the appearance of eczema-like skin changes of the nipple and areola.
- 2.4. Breast cancer may present with axillary lymphadenopathy. The underlying disease may or may not be detectable clinically or by radiological imaging investigations of the breast.
- 2.5. In a small number of patients the initial presentation may be as a consequence of metastatic disease. The most common sites of metastases are the bones, liver and lungs. Patients with metastatic disease may present with bone pain, pathological fractures or spinal cord compression due to either bone or soft tissue disease compressing the spinal cord or cauda equina. Others may present with symptoms due to hepatic or pulmonary involvement or more rarely other organ systems.

## 3. Aetiology

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- 3.1. The aetiology of breast cancer remains undefined. However, the following are recognised to be risk factors.
- 3.2. **Age and Sex.** Age and sex are the most important risk factors as breast cancer incidence increases with age, with 80% of women being more than 50 years.<sup>3</sup> At the age of up to 30 the risk of an individual developing breast cancer is 1 in 1,900, but rises to 1 in 15 by the age of 70. The overall lifetime risk is 1 in 9. Approximately 1% of all cases of breast cancer occur in men.
- 3.3. **Genetic factors.**
  - 3.3.1. Genetic predisposition and family history are risk factors for breast cancer.
  - 3.3.2. There is a genetic predisposition to breast cancer in 5% to 10% of individuals. The magnitude of the risk depends on the number of relatives affected, the age of onset of the disease, their relationship and whether the breast cancer was bilateral.
  - 3.3.3. If one first-degree relative is affected (mother, sister or daughter) before the age of 50 years, then the risk for an individual is twice that of the general population.
  - 3.3.4. If two first-degree relatives are affected, the risk is 4 to 6 times that of the general population.
  - 3.3.5. Certain gene mutations have been identified in patients with breast cancer and are usually inherited as autosomal dominants with a variable degree of penetrance, for example, BRCA1 (2% of breast cancers), BRCA2 (associated with male breast cancers), and the p53 gene.<sup>4</sup>
- 3.4. **Previous breast disease.**
  - 3.4.1. **Benign breast diseases and the risk of breast cancer.**

Although most benign breast disorders do not increase the risk of breast cancer, there are certain benign conditions of the breast whose presence is associated with an increased risk of breast cancer.

Atypical ductal hyperplasia and atypical lobular hyperplasia increase the risk by fourfold to sixfold.<sup>5</sup>

Other benign conditions are relevant such as sclerosing adenosis (1.5x risk), solitary papilloma (1.5-2x risk), moderate or florid hyperplasia without atypia (1.5-2x risk). Also, the presence of ductal carcinoma in situ or lobular carcinoma in situ increases the risk of invasive breast cancer occurring by a factor of ten.<sup>6</sup>

- 3.5. **Previous breast cancer and risk of a second primary breast cancer.** If an individual has had a previous breast cancer, there is an increased risk of developing a contralateral breast cancer. This is most likely to occur in younger patients, and estimates of the risk of individuals developing a contralateral cancer vary from 1 in 20 to 1 in 5.<sup>7,8</sup>
- 3.6. **Chemical Factors.** Certain hormonal factors related to menarche, menopause, parity and breast-feeding may influence the risk of breast cancer:
- 3.6.1. Evidence has accumulated to indicate that exposure to oestrogens and progestagens is associated with an increased risk of developing breast cancer.
- 3.6.2. Women with early menarche have increased risk (threefold if menarche occurs before the age of 11 years).
- 3.6.3. Women with a later menopause are at increased risk (double the risk if menopause occurs after the age of 54 years).
- 3.6.4. In parous women who have not breast fed, the risk of breast cancer increases with the age at birth of their first child by 3% per annum.<sup>9</sup>
- 3.6.5. Subsequently, the birth of each additional child reduces the risk of breast cancer by 7%.<sup>9</sup>
- 3.6.6. Then, if an individual breast-feeds, there is a further reduction in breast cancer risk which correlates with the length of time that breast-feeding takes place. There is a further 4.3% reduction in breast cancer for each additional year of breast-feeding.<sup>9</sup>
- 3.7. **Oral contraceptive usage and breast cancer risk.**
- 3.7.1. A detailed analysis of the risk of oral contraception and breast cancer was provided by the Collaborative Group on Hormonal Factors in Breast Cancer who examined 53,297 women with breast cancer and 100,239 controls.<sup>10,11</sup> The key findings were:
- The relative risk of breast cancer was 1.24 for women currently using oral contraception compared with non-users
  - After stopping oral contraception, the risk decreases and has disappeared 10 years after discontinuation of oral contraception
  - However, cancers that did occur in women using the oral contraceptive were 12% less likely to have spread beyond the breast than in those arising in non-users of contraception
  - The relative risk is higher in those women aged less than 35 years
- 3.7.2. Another recent review has highlighted that breast cancer risk is increased in those taking more than 35µg/day of ethinyloestradiol, with an increased and cumulative dose of progestagens and with longer duration of oral contraceptive usage.<sup>12</sup>
- 3.8. **Hormone replacement therapy (HRT) and breast cancer risk.**

3.8.1. The use of HRT in postmenopausal women is associated with an increased risk of breast cancer. The Collaborative Group on Hormonal Factors in Breast Cancer analysed more than 52,000 women from 51 studies.<sup>13</sup> The key findings to emerge from this study were:

- In individuals using HRT (or within 1-4 years of stopping), the relative risk of developing breast cancer increased by 1.023 for every year of usage
- In those using HRT for longer than 5 years, the relative risk was 1.35
- This increased risk of breast cancer reduces after discontinuation of HRT and by 5 years it has largely disappeared
- This study did not find any difference as a result of differences in type of HRT preparation used, or in doses taken

3.8.2. More recently, the Million Women Study<sup>14</sup> has provided a more detailed insight into the relationship between HRT and breast cancer risk. More than 1,000,000 women who had 9,364 breast cancers were evaluated and the key findings are summarised below:

- Current users of HRT had a relative risk of 1.66 of developing breast cancer.
- Past users of HRT were not at an increased risk of breast cancer.
- For those taking oestrogen preparations, the risk was 1.3.
- For those taking combined oestrogen and progesterone combinations, the risk was 2.0.
- For those taking tibolone, the risk was 1.45.
- There was little variation in the results according to the type of preparation or doses used.

### 3.9. Alcohol consumption and breast cancer risk.

3.9.1. A recent analysis of the results of 53 epidemiological studies, involving more than 60,000 women with breast cancer, has examined the relationship of alcohol to breast cancer risk.<sup>15</sup> The main findings were:

- There is a linear increase in breast cancer risk with increasing alcohol consumption.
- The relative risk of breast cancer is 1.32 for women drinking between 35g and 44g of alcohol per day. The relative risk of breast cancer is 1.46 for women drinking 45 or more grams of alcohol per day.
- There was a 7.1% increase in the relative risk of breast cancer for

each additional 10g of alcohol consumed per day.

- Therefore, it has been estimated that 4% of all breast cancers are attributable to alcohol consumption.

### 3.10. Diet, obesity, exercise and breast cancer risk.

3.10.1. The role of specific dietary nutrients in the aetiology of breast cancer has not been fully clarified. However, the following generalisations have emerged regarding the roles of fat, anti-oxidants, vitamins and dietary fibre consumption.<sup>16-18</sup>

- Obesity increases the risk of breast cancer in postmenopausal women by approximately 30% for women with a Body Mass Index (BMI) of greater than 31kg/m<sup>2</sup>. A BMI of greater than 35 kg/m<sup>2</sup> is associated with a doubling of the risk of breast cancer
- Consumption of fruit and vegetables does not seem to be associated with the risk of breast cancer in the latest studies
- Dietary supplementation with anti-oxidant vitamins has not been shown to reduce the risk of breast cancer
- The role of dietary fat consumption in breast cancer risk is controversial but a pooled analysis did not demonstrate a relationship. However, there are methodological concerns regarding many of these studies and further clarification is required to understand this area fully
- Dietary fibre intake is not associated with breast cancer risk
- Avoiding weight gain during adult years can reduce breast cancer risk and regular exercise may reduce the risk of an individual developing breast cancer by up to 30%

3.11. **Exposure to pesticides and other environmental factors and breast cancer risk.** The possible role of a variety of environmental chemicals and electromagnetic radiation in breast carcinogenesis has been recently reviewed in detail.<sup>19,20</sup> The following has emerged:

- **Benzene and related compounds.** One study of premenopausal breast cancer has indicated that exposure to polycyclic aromatic hydrocarbons was associated with a relative risk of breast cancer of 1.64, but rising to 1.95 for those individuals exposed to high doses of benzene
- **Polychlorinated biphenol (PCB).** At least three studies have shown no effect of PCB on breast cancer risk, although one other small study of 15 patients with breast cancer who had lived near to an explosion which released dioxins did suggest that breast cancer risk was associated with dioxin-like PCB

- **Organochlorines.** In studies of exposure to organochlorines, increased levels of these substances have been found in breast cancer tissue when compared with tissue obtained from controls. However, when levels of organochlorines in the serum were measured, the results have been conflicting. One study demonstrated a correlation between breast cancer risk and elevated serum levels, while other studies have not found any such association
- **Organic solvents.** Epidemiological studies that have investigated the relationship between breast cancer and organic solvents (used in paint, glue, varnish and particularly the laundry and cleaning services) have suggested that there may be a weak association between exposure and risk. However, the limitations of these studies and possible confounding variables have limited the conclusions that can be drawn from them
- **Metals.** One study has indicated that exposure to metals was associated with a small increase in breast cancer risk (relative risk 1.05 to 1.16). The basis for this is unclear but many metals can have oestrogenic activity

### 3.12. **Cigarette smoking and the risk of breast cancer.**

3.12.1. The relationship between cigarette smoking and breast cancer is unclear at the present time. In 2001 a review of the literature indicated that in 6 out of 11 studies the risk of breast cancer was increased by 1.5x or greater. However the situation is complex because others have shown that the risk is greatest in passive smokers when compared to active smokers, is greatest in those who smoke for prolonged periods of time and smoke before a first full term pregnancy.<sup>19,21,22</sup> However, further studies are required to fully define and understand the risk of cigarette smoking.

### 3.13. **Disturbance of circadian rhythm and breast cancer risk.**

3.13.1. At least two studies have indicated that there may be a risk between disturbance of circadian rhythm and breast cancer risk, possibly due to the effects of melatonin on oestrogen release by the ovaries.<sup>23</sup>

3.13.2. Breast cancer risk was increased in individuals who did not sleep during the night, when melatonin levels would be expected to be at their highest level. Their relative risk of breast cancer was 1.14.<sup>23</sup>

3.13.3. Female nurses have an increased risk of breast cancer when taking part in rotating night shifts.<sup>24</sup> In women who had worked for 1-14 years, or 15-29 years, on rotating shifts, their relative risk of breast cancer was 1.08.

### 3.14. **Physical agents: Exposure to diagnostic irradiation and breast cancer risk.**

3.14.1. The use of diagnostic irradiation can increase the risk of breast cancer.

- 3.14.2. The use of diagnostic mammography is associated with an extremely small risk of breast cancer. It has been estimated that for every 2 million women who have had a mammogram, there will be one extra breast cancer occurring at 10 years.
  - 3.14.3. Multiple chest x-rays (mean dose of 79cGy) increase the relative risk of developing breast cancer to 1.29.<sup>25</sup>
  - 3.14.4. Recently, it was estimated that in individuals receiving diagnostic x-rays, this will cause 29 breast cancers per year in the UK in women less than 75 years of age.<sup>26</sup>
- 3.15. **Physical agents:** previous irradiation treatment for Hodgkin's disease and breast cancer risk.
- 3.15.1. Following mantle radiotherapy for the treatment of Hodgkin's disease, the risk of breast cancer is up to 75 times that of the general population.<sup>27</sup> There is a latency period of approximately 13.5 to 17 years and patients have a mean age of 41 years at diagnosis of breast cancer.<sup>28</sup> The breast cancers that occur in these patients are more likely to be in the medial side of the breast and up to 20% of patients have bilateral cancers.<sup>28</sup>
  - 3.15.2. The person's age at the time of irradiation is important as the greatest risk is in those treated before puberty. In particular, it has been estimated that patients treated when younger than 15 years of age have a 136 times increased risk of breast cancer. The risk diminishes with age and it appears that women older than 30 years of age when treated do not have an increased risk of breast cancer.<sup>29</sup> Furthermore, the risk increases linearly with increasing doses of irradiation.
  - 3.15.3. In these studies a typical dose of approximately 35 to 40Gy was used. The radiotherapy technique has now changed to a lower dose (for example, 30Gy) and "wide field" radiotherapy is not given now. This results in less volume of tissue being irradiated and there would be an anticipated reduction in the risk of breast cancer. However, the magnitude of this reduction in risk is not known at the present time.
- 3.16. **Exposure to an atomic bomb and breast cancer risk.**
- 3.16.1. Studies of individuals who have survived an atomic bomb explosion show an increased risk of breast cancer. The risk of breast cancer is determined by the dose of radiation to which the individual has been exposed<sup>30</sup> and the relationship is linear. There is no dose of radiation below which the risk ceases.<sup>31,32</sup> To quantify this, the excess relative risk of developing breast cancer is thought to be 1.56 per Sv of irradiation that is received by an individual.
  - 3.16.2. In addition, the age at which an individual receives this radiation exposure affects the risk of breast cancer developing and the risk is greater at younger ages of exposure. It has also been shown that this age-related effect is not apparent until 10 years after exposure to radiation. However, as the individuals then age following exposure, their risk of breast cancer decreases.<sup>30</sup>

- 3.17. **Exposure to nuclear weapons test programmes.** Evidence as to the risk of cancer arising from participation (21,357 people) in the 21 explosions in the UK nuclear weapons test programme is now available in the most recent of 3 analyses.<sup>33-35</sup> For all cancers considered together, there was no increased risk in those individuals who had participated in nuclear test programmes, when compared with a control population (relative risk was 1.01).<sup>33-35</sup> Furthermore, there was no statistical association between individual cancer types and radiation exposure.
- 3.18. **Exposure to radiation dose typically experienced by nuclear workers.** The risk of cancer arising in radiation workers has been reported in the “15 country study” involved 407,391 radiation industry workers.<sup>36</sup> Although breast cancer was not specifically reported on, the findings indicated that there was a “small excess risk of cancer (other than leukaemias) , even at low doses and dose rates typically experienced by nuclear workers”. The excess risk was 0.97 per Sv (95% CI 0.14-1.97).<sup>36</sup>
- 3.19. **Cosmic radiation and breast cancer risk.** The role of exposure to cosmic radiation experienced by flight crews, and its relationship to breast cancer, remains unclear. In a recent review of the published epidemiological studies, some studies had shown an increased incidence of breast cancer amongst female flight attendants.<sup>37,38</sup> However, the relationship is not fully defined because of other confounding factors in these studies which limit the conclusions that can be drawn, such as the effects of reproductive history, abnormalities of circadian rhythm, exposure to aviation fuel etc. Further studies are required to address this issue.<sup>39</sup>
- 3.20. **Exposure to solar radiation and breast cancer risk.** Two studies have shown a negative association with exposure to ultraviolet-B light and breast cancer risk.<sup>40,41</sup>
- 3.21. **Exposure to electric and magnetic fields.** Radiation is generated by electrical transmission cables and by any device which is powered by electricity. While it is recognised that such electromagnetic fields can affect melatonin production by the pituitary and thus provide a theoretical basis for this to be an aetiological agent in breast cancer, the evidence has been conflicting. A meta-analysis of 43 studies examining this relationship has been published.<sup>42</sup> Although the results were variable in individual studies, the overall relative risk of developing breast cancer with this exposure was 1.12 (95%CI 1.09-1.15). This is in keeping with the recent Norwegian study which also demonstrated a relative risk of 1.13 for women exposed at work, and with a higher risk (1.58) for those living near high-voltage power lines.<sup>43</sup>
- 3.22. **Specific issues in the aetiology of breast cancer arising in males.** The factors involved in the causation of breast cancer in males remain unclear. However, abnormalities in the testis (undescended, orchitis, orchidectomy), family history of breast cancer and previous exposure to irradiation for Hodgkin’s disease have been shown to increase the risk of developing breast cancer.<sup>44, 45</sup> Klinefelter’s syndrome is associated with a fifty fold increased risk of breast cancer<sup>46</sup> but gynaecomastia does not appear to increase breast cancer risk.

## 4. Prognosis

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- 4.1. In the absence of detectable metastatic disease, the prognosis of patients with breast cancer is determined by several factors. Three key factors are lymph node status, degree of tumour differentiation (as determined histologically) and size of the tumour.
- 4.2. These three factors can be combined together as the Nottingham Prognostic Index (NPI), which is widely used to allow an individual patient to be placed into one of 3 groups – a good prognosis, a moderate prognosis and a poor prognosis.<sup>47,48</sup>
- 4.3. The formula for the Nottingham Prognostic Index is as follows:  
$$\text{NPI} = 0.2 \times \text{tumour size (cm)} + \text{lymph node status} + \text{tumour grade (I-III)}$$

(Lymph node status: no involved nodes score 1, 1-3 involved nodes score 2, greater than 3 involved nodes score 3).
- 4.4. An NPI of less than or equal to 3.4 is associated with a good prognosis, 3.41 to 5.4 with a moderate prognosis and greater than 5.4 indicates a poor prognosis.
- 4.5. Patients in the good prognostic group have a 10 year survival of 85%, while patients with an NPI of equal to or less than 2.4 have a 10 year survival of 94%.
- 4.6. A variety of other prognostic factors has been described, including hormone receptor status, lymphovascular invasion, HER2 status, Ki67 expression, cyclin expression and the use of genomic analysis. However, at the present time, these add relatively little to the evaluation of a patient's prognosis as indicated by the NPI, except that those patients who are over-expressers of HER2 can have their prognosis altered by anti-HER2 therapy (see below).<sup>49,50</sup>
- 4.7. The prognosis of a patient can be modified significantly by the use of adjuvant systemic therapies and the following are summarised from the most recent Early Breast Cancer Trialist Collaborative Group report.<sup>51</sup>
- 4.8. **Adjuvant chemotherapy.**
  - 4.8.1. Patients who receive a 6 month course of an anthracycline-based polychemotherapy (FAC or FEC) have a reduction in their annual breast cancer death rate by 38% for patients younger than 50 years of age and by 20% for those aged between 50 and 69 years at the time of diagnosis.
  - 4.8.2. These results are dependant on an individual patient's oestrogen receptor status or other characteristics of the tumour.
- 4.9. **Adjuvant hormone therapy.**
  - 4.9.1. For patients with a positive oestrogen receptor status of their tumours, 5 years of tamoxifen therapy will reduce the annual risk of death by 1% and improve disease-free survival by 20%.

- 4.9.2. This reduction in death rate is independent of the patient's age, progesterone receptor status or whether they have also had adjuvant chemotherapy.
- 4.10. The median survival of patients with liver metastases is 12 months (longer in some series)<sup>52</sup> although, in those with only bone metastases, the median survival may be up to 24 to 36 months.
  - 4.10.1. Although there is no one standard care for patients with metastatic breast cancer, improvements in symptom control, with small improvements in survival, can be achieved with the use of chemotherapy, endocrine therapy, biological therapy (trastuzumab) or combinations of these.<sup>53</sup>

## 5. Summary

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- 5.1. Breast cancer occurs in 1 in 9 women, and 1% of all cases occur in men.
- 5.2. Different histological types of breast cancer can be identified.
- 5.3. Several factors which predispose to breast cancer have been identified and the risk of developing breast cancer can be quantified for some of these predisposing factors.
- 5.4. The prognosis for patients with breast cancer depends primarily on the histological type of tumour, the grade of tumour, the size of tumour and whether there has been tumour spread to the lymph nodes.
- 5.5. Three of these factors (tumour size, tumour grade and lymph node status) can be combined together in a formula to give a numerical value, which enables an individual patient's prognosis to be determined.
- 5.6. Although there are other prognostic indicators which have been identified at the present time, they do not add significantly to determining a patient's prognosis more than the key factors identified in 5.5.
- 5.7. The prognosis can be improved substantially in selected patients by the appropriate use of system adjuvant therapies, such as chemotherapy and hormone therapy.

## **6. Related Synopses**

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None

## 7. Glossary

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adjuvant	Therapy that is given immediately after radiation or surgery in order to destroy any cancer cells that may remain.
axillary lymphadenopathy	Lymph nodes enlarged in the axilla.
BMI	Body Mass Index.
brac1, brac2	Specific genes in which mutations occur, which then place an individual at an increased risk of developing breast cancer. Under normal circumstances these genes are involved in protection of the cell against DNA damage and in DNA repair.
carcinoma	Cancer that begins in the lining or covering of an organ.
contralateral	On or relating to the opposite side of the body.
disseminated	Spread (of a disease) throughout the body.
endocrine therapy	Hormone therapy. Manipulation of hormones in order to treat a disease or condition.
fac	5-fluorouacil, doxorubicin, cyclophosphamide.
fec	5-fluorouacil, epirubicin, cyclophosphamide.
hepatic	Relating to the liver.
histological	Of, or referring to, histology (the study of the structure of living tissue under a microscope.)

Hodgkin's disease	A cancer marked by progressive painless enlargement of lymph nodes throughout the body. A form of lymphoma.
hormone receptor status	Oestrogen and progesterone receptors detected usually by immunohistochemical examination of the primary breast tumour.
hyperplasia	The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue.
ipsilateral	Located on or affecting the same side of the body
lymph node stages	A= all nodal areas sampled are negative for tumour. B= only the lower axillary node of the internal mammary node are positive. C= the apical axillary node or both lymph node chains are positive for tumour.
malignant	Cancerous. Malignant tumours have the ability to invade adjacent tissues and spread throughout the body. As such, malignant tumours can become life threatening.
mantle radiotherapy	Radiotherapy to the mantle field - the area including the neck, chest and axillary lymph nodes.
menarche	The onset of menstrual periods.
metastatic	Relating to the spread of cancer from one part of the body to another.
NPI	Nottingham Prognostic Index.

Paget's disease	This is a rare form of breast cancer, located on the surface of the breast.
pulmonary	Relating to the lungs.
terminal duct lobular unit	Blindly ending structure in the breast.
TNM	Tumour, nodes and metastases.
trastuzumab	An antibody which binds to the human epidermal growth factor receptor 2, which is over-expressed in some breast cancers. Interfering with this growth pathway with this antibody can cause death of the tumour cell (apoptosis). It is used therapeutically in combination with chemotherapy and increases survival in patients with metastatic breast cancer.
tubular, mucoid, cribriform, papillary and medullary	Specific types of breast cancer which are distinguished by their histological features.
UICC	International Union Against Cancer.

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