Pathological and epidemiological factors associated with advanced stage at diagnosis of breast cancer

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Background: Breast cancer is a highly heterogeneous disease, but the stage at presentation significantly influences outcome. It is important to dissect the pathobiological and epidemiological factors that influence the stage at presentation in order to develop effective strategies to improve clinical outcome.

Sources of data: PubMed references relating to breast cancer subtypes, molecular classification of breast cancer, genetic susceptibility, young women and breast cancer.

Areas of agreement: HER-2 positive, basal-like tumours and inflammatory breast cancers (IBC) more frequently present as late stage disease. Socioeconomic, cultural and ethnic background also influence stage at presentation.

Areas of controversy: The biology of IBC is poorly understood. Relative contribution of social and genetic factors in certain ethnic groups.

Growing points: Molecular determinants of breast cancer behaviour. Genetic and biological factors influencing disease phenotype in different ethnic groups.

Areas timely for developing research: Biology of basal-like tumours and IBC. Role of predisposition of genetic variants in determining breast cancer phenotypes. Biological differences in breast cancer from different ethnic groups.

Keywords: molecular subtypes/basal-like/SNP/MicroRNA/microenvironment/socioeconomic deprivation/ethnicity

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Pathological factors associated with advanced stage breast cancer

Breast cancer is a highly heterogeneous disease with some cases being associated with slow growth and excellent prognosis whilst other tumours exhibit a highly aggressive clinical course. In the current routine clinical practice, breast cancer is classified on the basis of morphological characteristics, with tumours being allocated into types, including infiltrating ductal carcinoma of no special type, and a large number of ‘special types’ including, amongst others, infiltrating lobular carcinoma, tubular, mucinous, medullary and adenoid cystic carcinoma. Breast cancers are then further categorized according to their histological grade, which is based on the degree of cellular differentiation, nuclear pleomorphism and mitotic count. There is a clear relationship between the basic pathological features of a tumour and its clinical behaviour. Thus, certain types of tumours are typically associated with smaller size and earlier stage at presentation, such as tubular carcinomas, compared with other types such as infiltrating ductal carcinoma. Furthermore, tumours of high histological grade are more likely to be large at presentation and to be associated with local or distant metastasis, compared with low histological grade tumours. Whilst histopathological factors provide important prognostic information, it is becoming clear that the fundamental biological characteristics of a tumour more accurately determine the clinical course and behaviour of a given tumour.

Molecular subtypes influence disease behaviour

Conventional morphological features to some extent reflect the underlying biological characteristics; however, recent advances in molecular technologies applied to breast cancers have further refined the ability to categorize tumours according to their underlying biology. A seminal work by Perou et al. used mRNA isolated from tumour samples applied to cDNA microarray chips to identify an ‘intrinsic gene set’ that categorized breast cancers into subgroups based on their gene expression profile. Using unsupervised hierarchical cluster analysis, where tumour samples are clustered together according to similarity in their gene expression profile, they identified five major tumour groups. These included oestrogen receptor (ER) positive subgroups termed Luminal A and Luminal B, and three predominantly ER-negative subgroups: one characterized by the over-expression of Her2 and related genes, termed the Her2 subtype, the second characterized by the high-level expression of genes normally associated with myoepithelial or...
basal cells, termed basal-like tumours and a third group exhibiting a varied gene expression profile termed normal-like (Table 1). These subgroups have been shown to be of clinical significance, with both Her2 and basal-like categories exhibiting significantly poorer outcome than the luminal and normal-like groups. Whilst both subtypes confer a worse prognosis in a stage-independent manner, both are also associated with more advanced stage at presentation. It is not yet clear why these tumour subtypes exhibit more aggressive behaviour, and this is an area of considerable research, however, it has been suggested that both Her2 and basal-like tumours contain a greater percentage of stem cell-like cells, as demonstrated by ALDH positivity and CD44+/CD24− phenotype, and this may contribute to their clinical behaviour.

Inflammatory breast cancer (IBC) is a clinically and biologically distinct entity, characterized by the presence of tumour emboli in dermal lymphatic channels and presenting with generalized breast tenderness. IBC frequently presents at an advanced stage, with the majority of patients having axillary lymph node involvement at diagnosis and up to 35% presenting with distant metastases. This may in part relate to the association with Her2, since up to 50% of IBC over-express Her2, compared with ~20% in non-IBC breast cancers. However, IBC show other distinct biological characteristics that could influence their behaviour. They are highly angiogenic and angioinvasive, exhibiting high levels of expression of pro-angiogenic factors that may contribute to early metastatic spread. Whole genome expression profiling has aimed both to identify a gene signature that can discriminate IBC from non-IBC and that might help elucidate the biological mechanisms underlying its aggressive behaviour. It was shown that IBC strongly over-express genes associated with the basal-like phenotype, vascular-associated genes and immune-related genes. A number of the genes up-regulated in IBC are known to be involved in cell migration and invasion, such as integrin β4 and VASP, whilst other genes play a role in angiogenesis, including ARNT which encodes the β subunit of hypoxia-inducible factor 1 (HIF1). IBC were also shown to have high level expression of proliferation-associated genes. A number of genes involved in the negative regulation of angiogenesis and invasion were found to be down-regulated in IBC, and interestingly several of the down-regulated genes were located at 5q11-14, a site frequently exhibiting loss of heterozygosity in basal-like tumours. These results suggest that the late-stage presentation and poor prognosis of IBC is linked to its biological characteristics, and this may provide the key to identifying new targeted therapies for this aggressive disease.

There is growing understanding of another family of regulatory molecules that may influence breast cancer behaviour: the microRNAs
Table 1 Features of different molecular subtypes of breast cancer.

<table>
<thead>
<tr>
<th></th>
<th>Normal like</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Her-2</th>
<th>Basal like</th>
<th>Claudin low</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>6</td>
<td>29</td>
<td>21</td>
<td>17</td>
<td>16</td>
<td>11</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>ER+ (%)</td>
<td>79</td>
<td>96</td>
<td>96</td>
<td>41</td>
<td>10</td>
<td>22</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>PR+ (%)</td>
<td>42</td>
<td>72</td>
<td>47</td>
<td>28</td>
<td>10</td>
<td>23</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>HER2+ (%)</td>
<td>46</td>
<td>10</td>
<td>20</td>
<td>69</td>
<td>11</td>
<td>14%</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>Triple negative (%)</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>18</td>
<td>77</td>
<td>66</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>44</td>
<td>23</td>
<td>50</td>
<td>68</td>
<td>89</td>
<td>59</td>
<td>Prat et al. 61</td>
</tr>
<tr>
<td>Morphology</td>
<td>IDC, ILC, tubular, mucinous, neuroendocrine</td>
<td>IDC, pleomorphic lobular</td>
<td>IDC</td>
<td>IDC, metaplastic, medullary</td>
<td>IDC, metaplastic, medullary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferation (%)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Moderate-high</td>
<td>High</td>
<td>high</td>
<td>Prat et al. 61; Cheang et al. 63; Masuda 62</td>
</tr>
<tr>
<td>Germline mutation pCR (%)</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>39</td>
<td>73</td>
<td>39</td>
<td>Prat et al. 61; Chang et al. 63; Prat et al. 61</td>
</tr>
<tr>
<td>PS3 mutation (%)</td>
<td>66</td>
<td>16</td>
<td>71</td>
<td>86</td>
<td>75</td>
<td>n/a</td>
<td>Joshi et al. 65</td>
</tr>
<tr>
<td>NF-κβ TFBS (%)</td>
<td>65</td>
<td>61</td>
<td>53</td>
<td>100</td>
<td>78</td>
<td>n/a</td>
<td>Joshi et al. 65</td>
</tr>
</tbody>
</table>

NF-κβ TFBS, nuclear factor kappa beta transcription factor-binding sites; pCR, pathological complete response.
(miRNAs). MiRNAs are small (20–24 nucleotides) non-coding RNA gene products that regulate genes at the post-transcriptional levels, affecting stability or translational efficiency of the target RNA. Depending on the target gene, miRNAs can act either as oncogenes by inhibiting the expression of a tumour suppressor, or as tumour suppressors, by inhibiting the expression of an oncogene. Indeed, one miRNA is able to down-regulate hundreds of target genes and therefore altered expression of a single miRNA could be a very efficient means of controlling tumour behaviour. Several studies have identified up-regulation of the miRNA hsa-MiR-21 (miR-21) in breast cancer, and found this to be significantly associated with advanced stage at presentation, with 79.7% of stage III cases showing high level miR-21 compared with 47% of stages I and II. Furthermore, the elevated levels of miR-21 are correlated with overall poor survival from breast cancer. Target genes of miR-21 include RAB6A, a member of the RAS oncogene family; TGFβ-induced protein; TGFβ receptor II; Bcl2 and the apoptosis-related gene programmed cell death 4 (PCD4). MiR-21 has also been shown to regulate PTEN, an established tumour-suppressor gene that is frequently down-regulated in breast cancer, so this may be one of the mechanisms by which miR-21 exerts its oncogenic effect. A direct effect of miR-21 in control of tumour progression has been demonstrated in model systems, where knock-down of miR-21 in MCF-7 breast cancer cells resulted in enhanced apoptosis and reduced cell proliferation, and in MDA MB 231 cells, MiR-21 knock-down resulted in reduced invasion and reduced lung metastases, mediated, at least in part, through up-regulation of PCD4 and maspin. These studies demonstrate how the underlying biological characteristics of a tumour influence behaviour and could determine stage at presentation.

Microenvironmental determinants of disease behaviour

A number of chemokines have been implicated in playing a role in breast cancer progression, in particular CCL2 and CCL5. CCL2 (also known as monocyte chemotactic protein-1) and CCL5 (also known as regulated on activation normal T cell expressed and secreted) are up-regulated in many breast cancers, either by the tumour cells themselves or by host microenvironment populations including macrophages and fibroblasts, and as their names imply, they stimulate the migration of monocytes and T cells into the tumour site. Elevated levels of both CCL2 and CCL5 proteins in tumours, and in some studies, elevated serum levels of these chemokines, have been strongly associated with advanced stage of disease in breast cancer. It is now well
established that high levels of tumour-associated macrophages (TAMs) correlate with poor prognosis in breast cancer, and it has been suggested that the relationship between high levels of these chemokines and poor prognosis is mediated by the recruitment of TAMs into the tumour microenvironment which then release a wide range of tumour-promoting factors including cytokines, growth factors and matrix-degrading proteins.\textsuperscript{16–18} Furthermore, CCL2 in particular has been shown to exhibit potent angiogenic activity, both via the recruitment of TAM as well as by acting directly on endothelial cells.\textsuperscript{19} Animal models also suggest that the induction of these chemokines at sites of metastatic spread contributes to the development of the microenvironmental niche favouring metastatic growth.\textsuperscript{20,21} The breast cancer cell line MDA MB 231 leads to induction of CCL2 in osteoblasts which stimulates osteoclast activation and degradation of the bony matrix.\textsuperscript{20,21} A recent study has shown that CCL2 promotes breast cancer metastasis to both lung and bone through interaction with its receptor CCR2 on organ-specific stromal cells.\textsuperscript{22} Targeting CCL2 with function-blocking neutralizing antibodies significantly reduced lung and bone metastasis, further supporting a role for this chemokine in the metastatic process.\textsuperscript{22}

Thus, it is clear that in addition to the fundamental biological characteristics of the tumour cells, the nature of interactions with the host microenvironment also can have a profound impact on tumour progression and tumour stage. The possibility that genetic factors may determine the relative significance of these interactions in different individuals and so influence the rate of disease progression is discussed further below.

Genetic modifiers of breast cancer behaviour

Breast cancer susceptibility genes

Whilst there is a familial component in many breast cancers, dominant gene mutations account for only a small proportion of breast cancers. Of these, mutations in BRCA1 and BRCA2 are the commonest. It has become clear over recent years that breast cancers associated with BRCA1 mutations, in particular, have a characteristic phenotype, frequently exhibiting features of the basal-like subgroup.\textsuperscript{23} As already discussed, the basal-like tumours are recognized as being an aggressive tumour subtype, frequently presenting at an advanced tumour stage, and this may underlie the aggressive nature and advanced stage at presentation of many of the breast cancers arising in BRCA1-mutation carriers. Another rare, but aggressive, tumour subtype is breast cancer
arising in Li-Fraumeni syndrome, characterized by germline TP53 mutations. Typically such tumours arise in very young women, and a recent study suggests that germline TP53 mutation promotes oncogenic development along a very specific pathway, such that the resultant breast cancers are frequently ER and PR positive, but also exhibit Her2 amplification. This phenotype, may underlie the characteristic aggressive behaviour and late presentation seen in such patients.

Single nucleotide polymorphisms

Whilst key genetic mutations in oncogenes and tumour suppressor genes are thought to drive tumour development, there is growing understanding of how more subtle genetic variation may influence both breast cancer risk and the heterogeneous nature of the disease. Single nucleotide polymorphisms (SNPs) are variations in DNA sequence and though many appear to be functionally silent some do influence the level of gene expression or protein function.

In breast cancer, the most significant association between the disease and specific SNPs was reported in 2009, when five SNPs were shown to significantly enhance an individual’s risk of developing breast cancer. There has been much less focus on how SNPs may influence the behaviour of breast cancer in an individual, though sequence variations in several relevant gene families, including chemokines, matrix-degrading enzymes and growth factors, have been reported. It is suggested that these gene variations may explain the heterogenous behaviour of breast cancer, accounting for differences in behaviour between individuals. The association of over-expression of CCL2 with advanced stage of breast cancer has been discussed. Genetic variations commonly occur in the regulatory regions of chemokine genes and can influence their transcriptional activity. Consistent with this, SNPs have been described in the promoter region of CCL2, and whilst no difference in allele frequency has been observed between breast cancer patients and control populations, there is a strong correlation between the $-2518$ A/G SNP, which leads to elevated transcriptional activity, in patients with metastasis compared with those without.

Another important gene family showing common, functionally relevant, genetic variations is the matrix metalloproteinase family (MMP). MMP activity has been implicated in multiple stages of tumour invasion and spread, and SNPs in the promoter regions of several of the MMP lead to enhanced transcriptional activity and elevated protease levels. In breast cancer, high-expressing SNPs in MMP-1 and MMP-9 have been shown to correlate with advanced tumour stage. Although primarily tumour promoting, some MMP, such as MMP-8, are
emerging as tumour suppressors, where an increased expression of MMP-8 in breast cancer cells has been shown to inhibit the tumour metastatic behaviour.29 This hitherto unrecognized functional diversity in the MMP family may explain the lack of success of broad spectrum MMP inhibitors in early clinical trials. It recently has been shown that SNPs in the MMP-8 gene, which reduce MMP-8 expression levels, are associated with increased breast cancer metastasis in breast cancer patients.30

These clinical studies strongly suggest that intrinsic host factors can influence how a breast cancer may behave but do not directly address either the relative impact of such genetic variations or the potential mechanisms involved. Studies using animal models have contributed significantly to elucidating these factors. A functionally relevant SNP in the fibroblast growth factor receptor (FGFR) 4 has been described in which there is a nucleotide change in codon 388 converting glycine to arginine in the transmembrane region of the receptor and this is thought to alter receptor regulation and stability leading to enhanced activity.31 The FGFR4 Arg388 SNP has been associated with advanced stage breast cancer in some31 but not other32 clinical studies. The functional consequences of this variation, and the potential reason for these conflicting reports has been elegantly demonstrated in two mouse models of breast cancer.33 This group generated an FGFR4Arg388 knock-in mouse and crossed this with two mouse mammary cancer models: WAP-TGFα and MMTV-PyMT models. They showed that FGFR4Arg388 promotes the progression of breast cancer in the WAP-TGFα model but not the MMTV-PyMT model, and went on to demonstrate that the tumour-promoting effects of this variant allele was dependent on the tumour oncogenic background, promoting

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>HER-2 and basal-like associated with poorer prognosis</th>
</tr>
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<tbody>
<tr>
<td>IBC</td>
<td>Frequent LN involvement</td>
</tr>
<tr>
<td></td>
<td>Higher expression of pro-angiogenic factors contributing to metastatic potential</td>
</tr>
<tr>
<td></td>
<td>Over-expression of genes associated with basal-like phenotype, cell migration and invasion and angiogenesis</td>
</tr>
<tr>
<td>High expression</td>
<td>Down-regulation of genes involved in stimulation of angiogenesis and invasion</td>
</tr>
<tr>
<td>of MiRNA</td>
<td>Up-regulation of hsa-MiRNA</td>
</tr>
<tr>
<td>CCL 2 expression</td>
<td>High expression associated with advanced stage and potent angiogenic activity</td>
</tr>
<tr>
<td>Germline genetic</td>
<td>Favours metastatic growth at potential sites following induction of this chemokine and others like CCL 5 and TAM</td>
</tr>
<tr>
<td>mutations</td>
<td>BRCA1 mutation exhibits features similar to basal-like phenotype</td>
</tr>
<tr>
<td>SNP</td>
<td>High-expressing SNPs in MMP-1 and MMP-9 correlate with advanced stage</td>
</tr>
<tr>
<td></td>
<td>SNPs in the MMP-8 gene that reduce MMP-8 expression are associated with increase in metastases</td>
</tr>
</tbody>
</table>

Table 2 Pathological and biological factors contributing to late stage presentation.
migration only in EGFR over-expressing tumour cells.\textsuperscript{33} This emphasizes the complex interplay between tumour biological characteristics and host genetic background, but also convincingly demonstrates the important contribution of such genetic variation to the heterogeneity of disease behaviour. The key pathological and biological factors influencing stage at presentation are summarized in Table 2.

Epidemiological factors

Age and reproductive factors

Young age at the time of diagnosis of breast cancer has repeatedly been reported as an adverse risk factor and the majority of studies suggest that young women with breast cancer have poorer survival.\textsuperscript{34,35} Younger women present with more advanced stage disease, having larger tumours than older women and more frequently present as lymph node positive.\textsuperscript{35} Whilst this may in part be attributed to delayed presentation or increased mammographic density impacting on diagnosis, there is also convincing evidence that young women have more biologically aggressive tumours. Some studies have suggested that prognosis is progressively worse with decreasing age; however, a more recent analysis suggests the major threshold in differing prognosis is 45 years, with no significant difference in survival in women aged <30, 30–34 and 35–39 years.\textsuperscript{34} Clearly, those tumours arising as a result of germline genetic abnormalities, including BRCA1/2 and TP53 mutation, will be clustered to this younger age group, and, as already discussed, these tumours are associated with a more aggressive phenotype. However, this constitutes a minority of cases, even in young patients, but there still appear to be biological differences in the non-inherited young breast cancer cases. Some,\textsuperscript{34} but not all\textsuperscript{35} studies report a higher incidence of ER-negative tumours in young patients. A recent genome-wide analysis of breast cancers arising in women <45 years compared with those arising in a group >61 years identified a set of 367 genes that differed significantly between the two groups. Genes unique to the breast cancers in younger women included those involved in immune function, hypoxia, the BRCA1 pathway, apoptosis and many oncogenic signalling pathways, including AKT, PTEN and MAP kinase. The tumours in young women were also more likely to be Her2 positive and over-express EGFR.\textsuperscript{34} These findings have important implications regarding therapeutic options in younger women, since they imply that distinct genetic aberrations occur in these aggressive tumours and many provide novel therapeutic targets.
Another factor that may contribute to the more advanced stage at diagnosis and poorer prognosis in young women with breast cancer relates to reproductive factors. It is generally accepted that full-term pregnancy confers a protective effect from breast cancer, suggested to be a result of the process of breast tissue differentiation that results following pregnancy. However, a transient increase in risk of breast cancer in the years immediately following childbirth has been reported and during this period, some studies have shown women to have a significantly poorer prognosis and present with more advanced stage disease. Other studies indicate pregnancy-associated breast cancer (PABC) not to be an adverse prognostic factor for survival when corrected for age and stage at diagnosis. Thus, whereas PABC is more likely to be steroid receptor negative and higher grade; features associated with poorer prognosis, PABC itself may not be an adverse prognostic factor. It is hypothesized that the poorer prognosis of breast cancer associated with recent pregnancy may relate to exposure to endogenous steroid hormones, which are likely to promote tumour growth and have been implicated in inducing tumour initiation; however, breast cancers arising within 2 years of a pregnancy are much more likely to be ER negative. This seems counter-intuitive, though the relationship with hormonal exposure may be explained by the finding that ER-negative breast cancers are more likely to be prolactin-receptor positive. Prolactin has been shown to be involved in both the initiation and promotion of breast cancer, thus, the elevated levels of prolactin during pregnancy may be implicated in the development and rapid progression of breast cancers observed in this group. The poorer prognosis in women with a recent pregnancy may be confounded by young age of the patient, since young age itself confers reduced survival, as discussed above. However, in one study, even amongst older age groups (in this case of 35 years or older) the highest proportion of advanced stage disease was found amongst those women diagnosed within 2–6 years of their pregnancy. Furthermore, in the younger age group, advanced stage disease was more frequent amongst those with a recent pregnancy compared with age-matched nulliparous women, suggesting an additive effect on young age alone. Other compounding factors include delayed diagnosis in pregnant or recently pregnant women as a result of imaging difficulties in this situation, but it is thought that this cannot fully account for the high proportion of late stage disease as long as 2–6 years following pregnancy.
Socioeconomic factors

Breast cancer incidence is higher in more affluent countries and in women of higher socioeconomic status but breast cancer mortality is higher in women of lower socioeconomic status and from less affluent countries. The impact of socioeconomic deprivation (SED) on prognosis in breast cancer remains perhaps one of the most controversial and complex areas in understanding disease behaviour. There are many reasons why SED may contribute to poorer outcome: access to and receipt of adequate health care and treatment; co-morbidity; tumour biology and stage at presentation. Several large population-based studies have found that patients living in more deprived areas were significantly more likely to have stage III or IV breast cancer at the time of diagnosis, though other studies do not support this. The possible reasons cited for differences in stage at presentation include later presentation and lower rates of uptake of mammographic screening, though another large study stated that the exclusion of cases that were screen detected, in both affluent and deprived women, had no impact on the discrepancy between these two patient groups. It remains the case that women from deprived areas present with later stage disease and do worse. Biological factors alone cannot account for the differences in mortality, and the real reasons for the discrepancy remain unclear, but surely need to be addressed. The key epidemiological factors influencing stage at presentation are summarized in Table 3.

Breast screening programmes

One argument to explain the differences seen in socioeconomic status and stage at presentation of breast cancer would be differences in uptake of breast screening programmes. It is generally accepted that the effect of regular mammographic breast screening in a population causes a significant breast cancer mortality reduction and the probability of presenting with late stage breast cancer is higher in women

Table 3 Epidemiological factors influencing late stage in presentation.

<table>
<thead>
<tr>
<th>Age and reproductive factors</th>
<th>Higher frequency of LN-positive disease in young women</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2 and TP53 mutations in young patients</td>
<td></td>
</tr>
<tr>
<td>Higher incidence of HER-2 positive disease and over-expression of EGFR</td>
<td></td>
</tr>
<tr>
<td>Imaging restriction for pregnant and young patients</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status (SES)</td>
<td>Low SES have poorer uptake of NHS BSP</td>
</tr>
<tr>
<td>Higher mortality associated with low SES</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Poorer uptake of NHS BSP</td>
</tr>
<tr>
<td></td>
<td>Higher incidence of basal-like phenotype</td>
</tr>
<tr>
<td></td>
<td>Higher mortality in age-matched patients with smaller tumours</td>
</tr>
</tbody>
</table>
who do not attend for breast screening. It has been shown that women of lower socioeconomic status are significantly less likely to attend breast screening programmes and this is also true of ethnic minority groups, as will be discussed later in this review. Clearly, in countries where there are marked differences in access to health care and to screening programmes, there is likely to be an influence on stage at presentation in breast cancer and other tumours.

Ethnicity-related differences in breast cancer

One important factor influencing stage at presentation is ethnicity. There appear to be marked variations in the clinical pattern and, indeed, the biology of breast cancer between women of different ethnic groups. Published data are lacking in some groups but there are numerous studies comparing, in particular, African-American and white American women.

The incidence of breast cancer in African-American women is lower than that of white American women whilst age-adjusted mortality figures for breast cancer are higher. Black American and African women have been shown to present with a more advanced stage of disease and at a younger age. In contrast, however, a study from our group has shown that whilst British Black women presented significantly younger than white British women, there is no difference in stage at presentation between the two groups. In this study the two groups were socioeconomically matched and had access to the same levels of health care without confounding factors such as health insurance, which have been noted in African-American studies. Interestingly, our study showed no difference in the overall survival between British Black and British White patients, except in those women with small tumours (≤2 cm) where Black British women were more than twice as likely to die of their disease. Thus, there appear to be biological differences in the disease occurring in Black British and African-American women. Gene expression profiling has demonstrated a higher frequency of the basal-like subgroup in young African American women. This phenotype is known to confer a poorer prognosis and is also over-represented in BRCA1-mutated breast cancer, though there is no suggestion that deleterious BRCA1 mutations are more common in black women.

The differences highlighted between the Black British and African-American populations may be attributable to underlying genetic differences, but also may reflect the differences between the two healthcare systems. African-American and other non-white women are less likely to utilize breast screening programmes than their white
counterparts\(^5^8\) and there have been significant efforts to remedy this problem in the USA. Interestingly, this large study also showed that Asian and Native American women had significantly lower rates of advanced stage tumours even after accounting for previous mammographic screening, whilst African-American women were most likely to present with late stage disease,\(^5^8\) although socioeconomic status was not adjusted for. Several studies have looked at ethnic differences in breast cancer and the effects of screening mammography intervention\(^4^7,^5^6,^5^9\) and it appears that even among women with similar screening histories African American still present with more advanced tumours than their white counterparts, so increasing mammographic screening uptake may not be the whole answer.

Attitudes and beliefs towards breast cancer and health can vary significantly between ethnic groups. Religious and cultural beliefs in the African-American community may make it much less likely that a woman will seek medical attention promptly with new breast signs or symptoms, attend invites to breast screening programmes and even accept stand treatment protocols,\(^9,^6^0\) all of which are likely to contribute to the stage of presentation and outcome figures that are observed when compared with their white counterparts. Improved health education programmes and breast cancer focus groups within specific ‘at-risk’ communities may help encourage earlier presentation and subsequently improve outcome. Whether the biological differences in breast cancers arising in these different populations will still result in late stage at presentation and subsequent poor outcome even when/if these social and healthcare factors are adjusted for remains to be seen.

**Summary**

Breast cancer is a highly heterogeneous disease, but one factor that significantly influences outcome is stage at presentation. Presentation with advanced stage breast cancer may be a result of various pathobiological and epidemiological factors.

It is evident that certain biological subtypes of breast cancer are more likely to present at an advanced stage offering poorer prognosis for patients. Various factors have been indentified that contribute to more aggressive disease within these sub-types such as high expression of angiogenic factors and up-regulation of genes involved in cell migration and invasion in IBC, whilst breast cancers arising in patients with germline BRCA1 mutations frequently exhibit a basal-like phenotype and hence an aggressive clinical course. Despite these observations the biological mechanism underlying these more aggressive subgroups of breast cancers are poorly understood.
In addition to the biological features of disease it is important to appreciate that cultural differences within ethnic minority groups, differences in socioeconomic status within and between communities and reproductive patterns dependant on personal preference or cultural influence have an impact on late stage of presentation. These differences are apparent in the poor uptake of breast screening seen in patients of lower socioeconomic status and ethnic minority groups, which likely is a significant contributing factor to late stage at presentation. While cultural factors influence the patterns of presentation of different ethnic groups, there is also growing evidence that there are underlying biological differences that influence disease phenotype in different ethnic groups, and may further contribute to stage at presentation.

Limitations in the effectiveness of imaging in younger patients, with difficulties in interpretation due to factors such as high mammographic density or the complexity of hormonal influence on breast tissue during pregnancy, can delay diagnosis resulting in late presentation in this age group.

Understanding and addressing these disparate factors that influence stage of disease at presentation is key to efforts to develop effective diagnostic and therapeutic strategies for improved clinical outcome.

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Factors associated with advanced stage breast cancer


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