REVIEW

Estrogen and progesterone receptors in breast cancer

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ABSTRACT  Breast cancer is the most common cancer in women worldwide. The majority of breast cancers show overexpression of estrogen receptors (ERs) and progesterone receptors (PRs). The development of drugs to target these hormone receptors, such as tamoxifen, has brought about significant improvement in survival for women with hormone receptor-positive breast cancers. Since information about ER and PR is vital for patient management, quality assurance is important to ensure accurate testing. In recent guidelines, the recommended definition of ER and PR positivity is 1% or more of cells that stain positive. Semiquantitative assessment of ER and PR is important for prognosis and, hence, management. Even with the development of genomic tests, hormone receptor status remains the most significant predictive and prognostic biomarker.

Breast cancer is the most common cancer in women worldwide and one of the leading causes of cancer-related deaths in women [1]. For the majority of women with breast cancer, the tumors when tested will show biological expression of receptors for estrogen and progesterone, hormones that are known to promote growth and proliferation of the tumor cells [2]. In the past 50 years, drugs have been developed to modulate the binding of estrogen to its receptor and bring about significant improvement in survival for the vast majority of patients with estrogen receptor-positive breast cancers [3, 4]. This article reviews the historical background to the discovery and relevance of hormone receptors in breast cancer, the development of standardized hormone receptor assays and the clinical relevance of testing for hormone receptor status in an era of molecular medicine.

It was known in the late 19th Century that the removal of the ovaries of women with breast cancer led to improved survival in many of the patients. However, the mechanism behind this improvement remained obscure, and Beatson originally thought it due to the interruption of nerve connections between the ovaries and the breast [5]. The discovery of receptors for estrogen and progesterone in breast tissue in the 1960s provided the evidence for a classical ligand-receptor pathway in which breast epithelial cells respond to the hormonal influences of estrogen and progesterone [6].

Molecular biology of the estrogen & progesterone receptor

The molecular mechanisms by which estrogen binds to its receptor are now well established. Estradiol diffuses across the breast epithelial membrane and binds to its receptor in the nucleus. This brings about a conformational change and estradiol bound to its receptor dimerizes with other receptors resulting in activation of estrogen-responsive genes. There are two different forms of the estrogen receptor (ER), α and β, coded for by two different genes, ESR1 and ESR2, respectively. The ER-α form is of clinical relevance, whilst the clinical significance of ER-β remains obscure. Consequently,
for the remainder of this review, the abbreviation ER refers to the α isoform. Progesterone binds in a similar fashion to estrogen to nuclear receptors. Like the ER, it is expressed in two different isoforms, PRA and PRB. However, unlike the ER these isoforms are produced by the same PR gene, the only difference being that PRA is a truncated form of PRB [7]. Assays for progesterone receptor (PR) currently used in the clinical setting bind to both PRA and PRB, or PRB.

The role of the ER & PR in breast cancer
Younger patients are more likely to be ER-negative (ER) compared with older patients. The Surveillance, Epidemiology and End Results (SEER) cancer registries in the USA showed that the ER-positive (ER+) age-specific breast cancer rates increased with age, but at a slower pace after ages 50–54 years, while the ER+ age-specific breast cancer rates did not increase after ages 50–54 years [8]. There is also a wide geographical variation in the proportion of ER+ breast cancers, being higher in the developed western countries and lower in the developing countries. In Chinese women in Hong Kong, ER+ cancers were seen in 53 and 61.6% of pre- and post-menopausal women with breast cancer, respectively, while PR+ breast cancers were found in 51.5 and 46.2% of pre- and post-menopausal women, respectively. These values are lower than those seen in USA, where the SEER cancer registries reported an overall ER+ rate of 77% and PR+ rate of 66% [9].

Even in the same country, the ER+ rate can vary between different ethnic groups, as seen in USA where it has been shown that black Americans are more likely to be ER+ compared with American Caucasians [10]. In a multiethnic Asian country, Malays were more likely to be ER+ compared with the Chinese and Indians [11].

Breast cancer is a heterogeneous disease and hormone receptor status can separate breast cancer into distinct subgroups, ER+PR−, ER−PR+, ER−PR− and ER+PR+. Using data from the SEER database, the ER and PR status of 155,175 women of at least 30 years old with a diagnosis of breast cancer between 1990 and 2001 were examined and it was found that 63.5% were ER+PR−, 12.8% were ER−PR+, 3.1% were ER−PR− and 20.6% were ER−PR+. The proportion of ER+PR+ and ER−PR+ increase with increasing age while the proportion of ER−PR− and ER+PR− breast cancer decrease with increasing age [9]. Risk factors for each subtype also differ, being significant for age, menopausal status, BMI after menopause, parity and past use of postmenopausal hormone-replacement therapy (HRT), as seen in a cohort study on 66,145 women participating in the Nurse Health Study from 1980 through to 2000, where 2096 incident cases of breast cancer were identified. Of these cases, 1281 (61.1%) were ER+PR−, 318 (15.2%) were ER−PR+, 80 were ER−PR− (3.8%) and 417 (19.9%) were ER−PR+. There were significant differences among the four subtypes with respect to risk factors. The incidence of ER+PR+ breast cancer increases in both the pre- and post-menopausal years by 11 and 4.6% per year, respectively; for ER−PR− breast cancers, the incidence increase is only 5% per year for premenopausal women and 1.3% per year in the postmenopausal years. Parity is inversely associated with ER+PR+ breast cancer but not with ER−PR− tumors. Age at first childbirth of less than 35 years increased the risk of ER−PR− breast cancer but not ER+PR+ breast cancer. Current use of postmenopausal HRT was associated with an increase in ER−PR− tumors but not of ER+PR+ tumors. However, past users of postmenopausal HRT increased the risk of ER+PR− rather than ER+PR+ breast cancer [12]. The risk factors associated with ER+PR+ breast cancer are similar to those for ER−PR− disease, whilst the risk factors for ER−PR+ breast cancer are similar to those for ER+PR− disease. A higher BMI after menopause was associated with ER+PR+ tumors and not ER−PR− tumors. In ER+ tumors, this association with BMI was seen only in PR− and not with PR+ breast cancer [12].

A high density of breast tissue as determined by mammography is a strong risk factor for breast cancer. A nested case–control study comparing the mammographic breast density of 667 controls with 607 breast cancer cases found that the mean percentage breast density on pre-diagnostic mammograms was significantly greater for ER+PR− breast tumors and not ER−PR− tumors. However, past use of postmenopausal HRT significantly increased the risk of ER+PR− breast cancer (37.3%) but not for ER−PR− breast cancer (28.9%) compared with controls (29.4%) after adjusting for age [13]. Since one of the determinants of mammographic density is exposure to estrogens [14], ER−PR− breast cancers are more likely to occur in a more ‘estrogenic’ environment.

It has been shown that the proportion of women with ER− breast cancer appears to have increased over time [11,15–16]. The SEER data have shown an increase of the proportion of ER− cancers from 75.4 to 77.5% in the 6-year period from 1992 to 1998 [18]. A study in Asia also demonstrated a 2% increase in the proportion of ER− cancers for every 5-year cohort, from 54.5%
in 1994–1998, to 56.4% in 1999–2003 and 58.4% in 2004–2008 [11]. While the incidence of ER+ breast cancers remains fairly constant, the increasing incidence of breast cancer is mainly due to the increase in incidence of ER+ breast cancers, hence giving rise to the higher proportion of ER+ breast cancers seen over time. Hormonal factors are believed to be the cause of this trend, as there are many chemicals in the environment that possess estrogen-mimicking properties, such as the organochlorine pesticides and polychlorinated biphenyls, which can enter the human breast and that have estrogenic activity [17]. There are differences in ER+ breast cancers between urban and rural areas, as seen in the Gharbiah population-based cancer registry in Egypt from 2001–2006, where it was shown that the urban ER+ incidence rate was two-times higher than the rural incidence rate [18]. With the incidence of breast cancer increasing at a higher rate in the developing countries, it is possible that the proportion of ER+ breast cancers will be similar throughout the world in the future.

Tumor size, grade and lymph node status are the most important prognostic factors for long-term survival from breast cancer [19]. The SEER database showed that women who had tumors that were ER+PR+ had significantly better survival than those who were ER+PR− and this effect was seen within each stage in both younger and older age groups. The improved survival was independent of disease stage, tumor grade, tumor histology or ethnicity [20].

The poorer prognosis seen in ER+PR− patients could be because of associated adverse prognostic factors. In the SEER database, it was seen that those diagnosed with ER+PR− cancers were more likely to be younger and Afro–American, have larger tumors, more advanced disease stage and higher tumor grade, and to present with axillary lymph node metastases [9]. In a study on a multiethnic Asian population of Malays, Chinese and Indians, ER+ cancers in a univariate analysis was associated with grade 3 cancers, later stages, Malay ethnicity and younger age; however, in a multivariate analysis, only high-grade and Malay ethnicity remained significantly associated with ER+ breast cancer [11].

The proportion of PR+ breast cancers is lower than ER+ breast cancers, and in the SEER breast cancer registries, 20% of ER+ breast cancers are PR− [9]. In ER− patients, where the PR is absent, overall survival, breast cancer-specific survival and disease-free survival are significantly poorer than for patients with tumors positive for both receptors. PR expression is a powerful, independent prognostic factor in ER+ lymph node-negative patients receiving endocrine therapy [22].

The gene expression of PR is dependent on estrogen and consequently PR expression has been considered to indicate an intact estrogen–ER response pathway. This raises the question as to whether ER+PR− breast cancers are a biological entity or a technical artefact, resulting from suboptimal fixation of tissue samples or assays of low sensitivity. Nadji et al. reviewed 5993 cases of invasive breast carcinomas for ER and PR by immunohistochemistry and did not find any cases of ER−PR+ tumors and concluded that the ER−PR+ entity is likely to be a technical artefact [23]. However, Rhodes and Jasani reviewed 4053 cases and found that the ER+PR− subtype constituted 3.2% of the cases, and was twice as likely to be seen in patients in the <51 years old compared with the >50-year age group, and concluded that the ER+PR− breast cancer is a distinct biological phenotype [24]. De Maeyer et al. reviewed 32 cases of breast carcinoma deemed to be ER+PR− and found that in 12 cases, when staining was repeated, five were considered false positive for PR and seven were false negative for ER, while the other 20 cases were actually ER+PR+ when a lower threshold for a positive result was used. They concluded that the reason for the low or negative staining of ER in PR+ cases was because of less sensitive immunohistochemistry techniques, especially in younger patients, higher tumor grades and HER2+ cases, which are known to be associated with lower levels of ER expression when assessed by quantitative analysis of ER using reverse transcription (RT)-PCR [25]. However, others have found immunohistochemistry a more sensitive method than RT-PCR in the assessment of estrogen receptors [26]. Consequently, a satisfactory explanation as to the occurrence of the ER+PR− phenotype remains obscure.

**The role of the PR in breast cancer**
The role of the PR in breast cancer remains controversial. While the rate of ER+ breast cancer increases with age, no such pattern is seen with PR, and the PR+ rate remains constant in all age groups [21]. The proportion of PR+ breast cancers is lower than ER+ breast cancers, and in the SEER breast cancer registries, 20% of ER+ breast cancers are PR− [9]. In ER− patients, where the PR is absent, overall survival, breast cancer-specific survival and disease-free survival are significantly poorer than for patients with tumors positive for both receptors. PR expression is a powerful, independent prognostic factor in ER+, lymph node-negative patients receiving endocrine therapy [22].

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**Testing for ER & PR in the clinical laboratory**
The original assays designed to measure hormone receptor levels in breast cancer tissues involved the use of radio labelled ligand-binding
assays (LBAs). This required the use of optimally frozen tissue from the tumor, which was then homogenized and mixed with known quantities of radiolabeled estradiol. Using dextran-coated charcoal, the receptor-bound radiolabeled estradiol was separated from the unbound ligand, and the amount of bound ligand estimated by the use of Scatchard analysis [27]. The advantage of this form of analysis was that it gave a quantitative estimate as to the amount of receptors present in the tumor. However, it had numerous disadvantages including the requirement of relatively large amounts of optimally frozen tissues different than that used to make the original diagnosis and the hazards of using radiolabeled ligands, and it is technically demanding. In addition, as the LBA required the use of homogenized tissue that could comprise not only invasive tumor, but also in situ tumor and normal glands, the assay was prone to false-positive results. Similarly, heterogeneity of ER expression in the homogenized tissue used for testing could give false-negative results [28]. The advent of receptor-specific antibodies for use in ELISA-based methods was considered to be an improvement and allowed for quantitative analysis without the use of radiolabeled ligand. However, it otherwise suffered from many of the same limitations as the LBA [29].

The ideal assay was considered one in which the invasive tumor component on which the diagnosis had been made could be also assessed for its expression of the ER and PR. An immunohistochemical assay was the obvious approach. However, until the early 1990s, the commercial antibodies to ER available for use in an immunohistochemical assay on formalin-fixed and paraffin-processed tissues produced results of a relatively poor quality [30,31]. It was not until the advent of heat-induced epitope retrieval by Shi et al. [32] that antibodies to ER became available for use in an immunohistochemical assay on formalin-fixed tissue sections [33–35]. Subsequently, numerous studies provided technical and clinical validation of this immunohistochemical approach for the assessment of ER and PR in clinical samples, with results showing good correlation with the longer-standing LBA assays [34,36–37]. Moreover, clinical studies demonstrated results using immunohistochemistry-predicted response to hormonal therapy more accurately than the older LBA [38–41]. Consequently, by the turn of the new millennium the vast majority of clinical laboratories were using immunohistochemistry as the ‘gold standard’ by which to test patients’ samples for ER and PR [42].

With LBA studies showing that patients with higher levels of receptor in their tumors responded better to hormonal therapy than those with only small amounts of ER [6,43–44], the practice of providing clinicians with an estimate on the amount of receptor present also continues with the immunohistochemical assay. However, a main disadvantage of the immunohistochemical approach is that it does not readily allow for quantitation. Image analysis systems to assess the staining intensity and proportion of the immunohistochemically stained invasive tumor are extremely expensive and not widely used. Instead, a ‘semi-quantitative’ approach is widely adopted in which the intensity of staining and proportion of invasive tumor cells staining is assessed microscopically by the pathologist [38,45–46]. With this approach it is important to define the cut-point above which the tumor is considered receptor-positive, and the patient likely to benefit with hormonal therapy, and below which other therapies should be considered. Current guidelines recommend that this cut-point be as low as 1% of the invasive tumor staining positively for the hormone receptors, with less than 1% considered negative [46]. This is based on the clinically validated studies of Harvey et al. [38], who were able to show that patients with even these low amounts of receptor in their tumor were included in the group of patients responding to hormonal therapy. Similarly, quantitation of the immunohistochemical results for ER and PR appears to add prognostic value, and is a more precise predictor of breast cancer-specific mortality risk than a simple determination of ER positivity [47].

The almost universal use of immunohistochemistry in the diagnostic laboratory as an aid to diagnosis, and the vast range of commercial antibodies and reagents available, has led to issues in standardization. This has been of particular concern with predictive assays, such as those for HER2, ER and PR, which require some degree of quantitative assessment. Considerable variation in the sensitivity of the ER and PR assays, with the potential for false-negative results, instigated the development of stringent quality assurance (QA) programs to monitor the results in clinical labs and help prevent against such occurrences [2,42,48]. Failure to instigate such QA measures has inevitably led to
reporting of false-negative results, and patients being denied hormonal therapy based on erroneous test results [43,44,48]. With the intention of averting such catastrophes in the future, internationally recognized groups, such as American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP), have produced evidence-based guidelines recommending the QA measures to adopt in the clinical testing of ER and PR [46]. Most laboratory accreditation programs expect laboratories to adopt these QA measures, or provide evidence that practice deviating from these recommendations does not adversely affect the quality and accuracy of the test results for predictive markers such as ER and PR.

The role of ER & PR in treatment decisions

While ER is essential in the algorithm for treatment decision-making, the role of the PR is less well-defined. Indeed, there have been calls to stop routine testing for PR on the basis that it makes little difference to the treatment, since ER+ patients will be eligible for hormonal therapy regardless of PR status, and the ER-PR+ entity is very rare and may be an artefact [49].

For women with ER+ breast cancer, 5 years of adjuvant tamoxifen, a selective estrogen receptor modulator, reduces the annual breast cancer death rate by 31%, regardless of use of chemotherapy or of age [50]. There has also been clinical evidence that ER+PR− breast cancer responds to tamoxifen better than ER-PR+ breast cancers [51,52], with a suggestion that lack of PR expression in ER+ tumors may be a surrogate marker of aberrant growth factor signaling pathways that could contribute to tamoxifen resistance, and complete estrogen withdrawal by aromatase inhibitors in postmenopausal women may be best for patients with these tumors [51]. However, the assessment of ER and PR did not identify patients with relative benefit from an aromatase inhibitor (anastrazole) over tamoxifen in the ATAC trial, and low ER or PR or high HER2 expression was associated with a high risk of recurrence with either anastrozole or tamoxifen [53].

Molecular mechanisms responsible for acquired endocrine resistance have been proposed, such as loss of ER expression, deregulation of various components of the ER pathway and alterations in cell cycle signaling [54].

Another important aspect of the role of ER and PR in treatment decision is when relapse occurs. It has been shown that there is instability in hormone receptors throughout tumor progression. One in three patients will experience alteration in ER and PR status, hence it is important to biopsy the metastatic site to obtain hormone receptor status before treatment [55]. The four breast cancer subtypes, Luminal A, Luminal B, HER2-overexpressing and triple-negative breast cancer depend on knowledge of ER, PR and HER2 expression (Table 1). The St Gallen consensus in 2011 [56] did not make use of ER or PR to differentiate between Luminal A or B – both these subtypes are defined as ER+ and/or PR+ – and suggested the use of Ki67 to differentiate between the two subtypes, a high Ki67 (defined as 14% and above) being HER2-Luminal B. However, the St Gallen consensus in 2013 [57] used PR to differentiate between these two subtypes, Luminal A being ER+ and PR+, while the HER2 Luminal B subtype is ER+ but PR− or ‘low’, the definition of ‘low’ PR being <20% of cells staining positive [58].

For clinical trials of adjuvant hormone therapy, ER and PR positivity based on immunohistochemical staining was defined by 10% immunoreactive invasive cells or more [59]. It would appear that adopting the recent ASCO/CAP guidelines recommending greater than or equal to 1% positively staining cells as hormone receptor-positive will lead to a higher proportion of patients being eligible for hormone therapy. The group of patients with “weak positive” tumors with 1–10% positive staining cells comprised approximately 5% of the breast cancers in the cohort investigated by Harvey et al. [58]. However, in a recent study the majority of breast cancers with this level of ER expression by immunohistochemistry were found to be basal-like following expression analysis [58]. This evidence needs to be carefully considered when predicting the probable response to hormonal therapy for this group of patients, or indeed their exclusion from clinical trials for triple-negative breast cancer [60].

Conclusion

The discovery of the hormone receptors ER and PR in the 1960s and the subsequent development of tamoxifen has made a significant impact on the survival of women with hormone receptor-positive breast cancer. Even with the development of other prognostic markers, such as HER2 and Ki67, and the use of expensive genomic tests such as OncotypeDx® (Genomic Health, CA,
USA) and MammaPrint (Agenda, Amsterdam, The Netherlands), hormone receptors play an important role, especially in low resource settings where such tests are unaffordable and Herceptin® (Genentech, CA, USA) for HER2-overexpressed breast cancer is not widely available. There is no doubt that hormone receptors are significant as a predictive as well as a prognostic factor. The ASCO and CAP guidelines have now defined a cut-off of 1% for positivity. However, it is important that a standardized quantitative assessment of the ER and PR is undertaken, in order to better define prognosis and management of women with hormone receptor-positive breast cancer.

**Future perspective**

With many centers adopting the 2010 ASCO/CAP guidelines on a cut-off point of 1% to define ER or PR positivity, it is probable that the rate of ER+ and/or PR+ tumors will increase, hence increasing the number of women who are eligible for hormone therapy. However, quantifying the degree of positivity is important, because a woman who has a tumor with 1% of cells stained positive for ER certainly cannot be treated in the same way as a woman whose tumor is 90% receptor-positive, although both will be classified as ER+ and evidence suggests that many of these tumors may well be basallike. One of the indications for chemotherapy is ER/PR negativity, and the patients with tumors with only 1–9% of invasive cells staining positively that were previously reported as ER would have received chemotherapy. The ASCO/CAP guidelines for ER and PR testing recommends three essential elements in the report: the percentage of tumor cells staining positively; the intensity of the staining; and an interpretation of the result. Two optional elements are: A) a cautionary statement added to an ER+ and PR+ interpretation when the histopathology is almost always associated with ER+ and PR+ results such as tubular, lobular and mucinous subtypes; and B) using the percentage and intensity provided, the pathologist may also provide a composite score such as the H score, the Allred Score or the Quick Score [46].

Following the diagnosis of breast cancer, the determination of hormone receptors, and, in particular, ER remains the most important test to determine therapy and management for the majority of patients. Hormone receptors were the earliest markers used for decision-making on the need for adjuvant therapy, and tamoxifen was the first ‘targeted’ therapy available for breast cancer. Tamoxifen, along with improved surgical interventions, is a therapy that has been credited for the improvement in survival in breast cancer seen over the years [61]. The discovery of the HER2 proto-oncogene led to the development of trastuzumab (Herceptin), another successful targeted therapy for breast cancer. Ki-67, a proliferative marker, has also now been added as one of the markers used in the St Gallen recommendations [57].

Genomic tests such as the OncotypeDx and MammaPrint have been developed to assist in decision-making on adjuvant therapy in early node-negative ER+ breast cancer. The ER and PR are important components of OncotypeDx and MammaPrint, which utilizes quantitative RT-PCR and has been shown to have good correlation with immunohistochemistry H scores. There is also good linear correlation between immunohistochemistry H-scores and quantitative RT-PCR expression values for ER and PR [26]. However, ER and PR immunohistochemistry in combination with HER2 and Ki67, as in the recently advocated ER, PR, Ki-67 and HER2 immunohistochemical score (IHC4), was compared with OncotypeDX and it was found that these four markers provided similar prognostic information to the OncotypeDX at a much lower cost [62].

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**Table 1. Breast cancer subtypes, definition and therapy (St Gallens Consensus 2013).**

<table>
<thead>
<tr>
<th>Breast cancer subtype</th>
<th>Definition</th>
<th>Type of therapy</th>
</tr>
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<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and PR- HER2 Ki-67 ‘low’ (defined as &lt;14%)</td>
<td>Endocrine therapy</td>
</tr>
<tr>
<td>Luminal B</td>
<td>Luminal B (HER2+) ER+ HER2 and at least one of: Ki-67 ‘high’ PR ‘negative or low’ (low defined as &lt;20%); Luminal B-like (HER2-); ER+ HER2 overexpressed or amplified; any Ki-67 any PR</td>
<td>Endocrine therapy ± cytotoxics</td>
</tr>
<tr>
<td>Luminal B-like (HER2-)</td>
<td>ER+ HER2 overexpressed or amplified; any Ki-67 any PR</td>
<td>Endocrine therapy + cytotoxics + anti HER2 therapy</td>
</tr>
<tr>
<td>HER2 overexpressing</td>
<td>HER2 overexpressed or amplified; ER and PR absent</td>
<td>Cytotoxics + anti-HER2 therapy</td>
</tr>
<tr>
<td>Triple negative</td>
<td>ER+ and PR+, HER2</td>
<td>Cytotoxics</td>
</tr>
</tbody>
</table>

ER: Estrogen receptor; PR: Progesterone receptor.

Data taken from [57].
EXECUTIVE SUMMARY

Background
• Breast cancer incidence rates are increasing world-wide and the increase in incidence appears to be in estrogen receptor (ER) breast cancer.

The role of ER & progesterone receptor in breast cancer
• Breast cancer is a heterogenous disease, and information on ER and progesterone receptor (PR) has led to the recognition of four expression patterns: ER+, PR+, ER-PR+ and ER-PR-, with differing risk factors and different outcomes, although there is controversy over whether the ER PR- subtype is a biological entity or a technical artefact.

Testing for ER & PR in the clinical laboratory
• Quality assurance is essential to ensure accurate determination of ER and PR, and international bodies such as the American Society of Clinical Oncology and College of American Pathologists provide guidance on the pre-analytical, analytical and post-analytical steps in the assessment of ER and PR status.
• The recommended definition of ER and PR positivity is 1% or more of cells that stain positive by immunohistochemistry. However, the ER and PR status of breast cancer is more than just a positive or negative result, and standardized semiquantitative assessment, such as the Allred Score and H score, is important for prognosis and hence management.

The role of ER & PR in treatment decision
• Even with the addition of other prognostic factors such as HER2, Ki67 and the use of genomic tests (i.e., OncotypeDx® [Genomic Health, CA, USA] and MammaPrint [Agendia, Amsterdam, The Netherlands]), ER and PR remain the most significant predictive and prognostic marker.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest
8 Chu KC, Anderson WF. Rates for breast cancer characteristics by estrogen and progesterone receptor status in the major racial/ethnic groups. Breast Cancer Res. Treat. 74, 199–211 (2002).
• The proportion of ER- breast cancers increase over time. Ethnicity and grade are independent factors for ER status.

Women with estrogen receptor (ER)+ progesterone receptor (PR)- breast cancer have a better survival than women with ER-PR+, ER-PR- and ER-PR+ breast cancer and this is independent of various demographic and clinical tumor characteristics.

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No writing assistance was utilized in the production of this manuscript.
The risk factor (i.e., age, menopausal status, BMI after menopause, the one-time adverse effect of first pregnancy and past use of postmenopausal hormones) differs for the different subtypes of breast cancer, ER+PR+, ER-PR+, ER-PR- and ER PR.  


44. Dowsett M, Houghton J, Iden C et al. Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor...


- Participation in quality assurance programmes is an effective means for identifying and ameliorating variables that influence the reliability of immunohistochemical assays for predictive markers, thereby assisting in technical validation and standardization.


- Up to 20% of current immunohistochemistry determinations of ER and PR testing worldwide may be inaccurate. These guidelines provide recommendations on accurate and reproducible assay performance. It is recommended that ER and PR assays be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of expected reactivity of internal (normal epithelial elements) and external controls.


- Quantitative immunohistochemical measures of ER and PR offers a more precise predictor for breast cancer-specific mortality risk than a simple determination of ER positivity.


- ER and PR status is important for differentiating the four molecular subtypes of breast cancer (i.e., Luminal A, Luminal B, HER2-overexpressing and triple-negative breast cancer). The quantitative assessment of PR can differentiate Luminal A from Luminal B with levels of >20% being Luminal B instead of Luminal A. These classifications are important for management guidelines.


- The ER, PR, Ki-67 and HER2 immunohistochemical score (IHC4), which is calculated using ER and PR percentage of positively stained cells, HER2, and Ki-67 is equivalent to the genomic tests in stratifying risk of relapse.