Updates in the Evaluation and Management of Breast Cancer

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) list risk factors and protective factors associated with breast cancer, (2) recognize the prognostic and therapeutic significance of tumor estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression for breast cancer, (3) describe the current trends in the locoregional and systemic management of operable early-stage breast cancer, and (4) recall the current goals and standard of care management of metastatic breast cancer.

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Abstract

Breast cancer is the most commonly diagnosed cancer worldwide. More than 200,000 new cases of invasive breast cancer are diagnosed annually in the United States; approximately 40,000 patients die of the disease. The etiology of most breast cancer cases is unknown, although multiple factors predisposing to the disease have been identified. Apart from increasing age and female sex, these other factors account for only a minority of breast cancer diagnoses. This article provides an overview of the management of noninvasive and invasive breast cancer, which is often complex and varies according to patient factors, disease stage, and breast cancer subtype. Although much progress has been made, continued research endeavors are ongoing; enrollment of eligible patients in prospective clinical trials is an essential way to improve patient outcomes.

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Breast cancer is the most frequently diagnosed cancer and is a common cause of cancer-related death in women, accounting for 25% of cancer cases and 15% of cancer-related deaths worldwide.[1] As breast cancer is a heterogeneous disease, it

is challenging to diagnose and treat.[2] Global incidence patterns are influenced by risk factors and the availability of mammography.[1] The highest breast cancer incidence rates are in North America, Australia, New Zealand, and Northern and Western Europe. Mortality rates are influenced by the occurrence of the disease and the availability of screening programs and appropriate treatment. Despite lower breast cancer incidence, breast cancer mortality rates are higher in many low-income countries, for example, in sub−Saharan Africa, because of later stage at diagnosis, suboptimal access to treatment, more aggressive biological subtypes, and younger age at diagnosis.[3,4]

Factors associated with an increased risk of breast cancer include older age, female sex, positive family history, deleterious gene sequence variations (*BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, and others; for expansion of gene symbols, use search tool at www.genenames.org),[5] increased mammographic breast density, reproductive factors (eg, nulliparity, early age at menarche, late age at menopause, and late age at first full-term pregnancy), a sedentary lifestyle, alcohol consumption, excess body weight (postmenopausal women), menopausal hormone therapy (combined estrogen- and progesterone-based treatments), and prior medical radiation therapy to the thorax, especially during childhood.[6-8] Prospective studies have also found an association between smoking and breast cancer.[9] Conversely, physical activity and breastfeeding are associated with a reduction in breast cancer risk.[10,11]

Breast cancer can be classified by molecular and histopathological features. The most common histologic subtype comprising 80% to 85% of all invasive breast cancers is infiltrating ductal carcinoma. Infiltrating lobular carcinoma accounts for approximately 10% to 15% of cases, whereas other rarer histologic subtypes account for 1% or less.[12] Approximately 75% of patients with breast cancer have hormone receptor (HR)−positive disease, that is, estrogen receptor (ER) and/or progesterone receptor (PR) expression of 1% or more.[2] Endocrine therapy targeting ER is a fundamental component of treatment in both adjuvant and metastatic settings for these patients. Furthermore, 15% to 20% of breast cancers are human epidermal growth factor receptor 2 (HER2)−positive as determined by HER2 protein overexpression measured by immunohistochemistry or gene amplification measured by fluorescence in situ hybridization.[13] Human epidermal growth factor receptor 2 is 1 of 4 transmembrane human epidermal growth factor receptors belonging to the ErbB family involved in signal transduction pathways that mediate cell growth and differentiation. Tumors with overexpression/amplification of HER2 were associated with poor outcomes before the advent of the HER2-directed monoclonal antibody trastuzumab. Trastuzumab, typically administered in conjunction with chemotherapy, has dramatically improved disease-free survival (DFS) and overall survival (OS) clinical outcomes.[14,15] Finally, triple negative breast cancer (TNBC) describes tumors that do not express ER and PR and do not overexpress HER2. Triple negative breast cancer is heterogeneous in that it can be classified by several molecular subtypes with variable prognoses.[16] The eighth edition of the American Joint Committee on Cancer breast cancer staging manual was clinically implemented in 2018. Notably, traditional tumor/node/metastasis anatomic staging was preserved; however, staging further incorporates prognostic biomarkers including tumor grade, ER, PR, HER2, and Oncotype DX Breast Recurrence Score. Breast cancer staging has now become quite complex with more than 150 combinations of anatomic and prognostic staging groups. The full citation can be referenced for complete staging information.[17]

Landmark studies have classified breast cancer into at least 4 distinct intrinsic subtypes by molecular phenotype,[18,19] for example, luminal A, luminal B, HER2-enriched, and basal-like. Luminal A and B breast carcinomas are positive for ER and/or PR expression. The luminal B subtype is distinguished by less prominent HR expression, higher rates of proliferation, and/or HER2/neu gene amplification.[20] Tumors with the HER2-enriched phenotype are negative for ER and PR expression and positive for HER2 gene amplification. Most breast carcinomas belong to one of these groups, and therapies targeting these receptors