A Review on the epigenetics of breast cancer and personalized medicine and a Review on the prevention and treatment of breast cancer metastasis were selected for the October 2013 AJP CME Program in Pathogenesis. The authors of the referenced articles and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.


Upon completion of this month’s journal-based CME activity, you will be able to:
- Discuss heritable and sporadic breast cancer.
- Describe the epigenetic mechanisms involved in breast cancer development.
- Understand the role of BRCA1 in heritable and sporadic breast cancer.
- Describe tumor metastasis.
- Discuss HER2-overexpressing breast cancers.
- Describe estrogen receptor positive (ER+) breast cancers and their metastatic potential.
- Understand the therapeutic options for breast cancer patients with bone metastasis.

1. Breast cancer is the most common cancer among women and ranks among the top five leading causes of cancer-related deaths, according to the World Health Organization. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1052-1063.]

   a. Inherited and acquired mutations in genetic material contribute to the development of breast cancer.
   b. Family history is the strongest risk factor for developing breast cancer.
   c. Inherited germline mutations in the BRCA1, BRCA2, and TP53 genes are high-risk factors for breast cancer development.
   d. Functional studies have identified BRCA1 and BRCA2 as proto-oncogenes that act in a manner similar to RAS and MYC.

2. In the development of cancer, epigenetic mechanisms are important in terms of both silencing of tumor suppressor genes and activation of oncogenes. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1052-1063.]

   a. Both silencing and activation occur through changes in chromatin configuration by which the accessibility of transcription factors is affected, with consequences for gene expression.
   b. In breast cancer, some tumor suppressor genes undergo CpG island promoter methylation, but in normal cells the promoter region is unmethylated.
   c. Recent data have demonstrated that H3K27Me3 is associated with increased mutation density in various types of cancers.
   d. The functional roles of genes inactivated by epigenetic mechanisms in breast cancer and other types of cancers are diverse and reflect various cancer hallmarks.
3. Breast cancer genomes usually contain thousands of genetic changes, of which only a small subset might actually drive development of the disease. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1052-1063.]

   a. In some cases, only a few mutations are found, reflecting the slow accumulation of acquired mutations over the lifetime of the individual.
   b. Some cases exhibit a large number of mutations, suggesting that DNA repair capacity has been affected coupled with induction of genetic instability.
   c. Genetic instability occurs in breast cancers arising in BRCA1 and BRCA2 mutation carriers, in whom the loss of the second wild-type allele is generally thought to be an important event leading to breast cancer development.
   d. Inactivation by CpG island promoter hypermethylation or other types of repressive epigenetic modifications in TP53 are commonly reported in breast cancer and other cancer types.

4. It is now well established that CpG island hypermethylation of the BRCA1 gene promoter region occurs in approximately 10% to 15% of all sporadic breast cancers. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1052-1063.]

   a. Sporadic breast cancers with acquired BRCA1 methylation have extensive DNA copy number changes suggestive of instability, similar to those observed in breast cancers arising in BRCA1 mutation carriers.
   b. BRCA1 dysfunctional breast cancers express estrogen and progesterone receptors and basal-like markers, such as CK18.
   c. Primary breast cancer cells with BRCA1 gene defects, caused by either inherited mutations or acquired promoter methylation, tend to be phenotypically poorly differentiated.
   d. Loss of BRCA1 gene products preferentially leads to the transformation of luminal progenitor cells with phenotypic similarities to the basal-like phenotype.

5. Metastasis is the migration of tumor cells from the primary tumor, followed by intravasation, survival, extravasation of the circulatory system, and progressive colonization of a distant site. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1084-1095.]

   a. Sixteen percent of breast cancer patients have stage IV disease at initial diagnosis.
   b. Hallmarks of metastasis include heterogeneity between primary tumors and metastases, redundancy of mechanistic pathways, variable dormancy, and contributions of cancer-initiating cells.
   c. Despite important progress in adjuvant and neoadjuvant therapies, metastatic disease often develops in breast cancer patients and remains the leading cause of their deaths.
   d. The complexity, heterogeneity, and genomic instability of metastatic breast cancer cells make their evaluation and therapy a challenging process.

6. The tyrosine kinase receptor proto-oncogene c-ErbB-2 (HER2) is overexpressed or amplified in approximately 25% of breast cancers and is a significant prognostic marker of shorter relapse-free and overall survival. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1084-1095.]

   a. HER2 is a transmembrane tyrosine kinase receptor and a member of the EGFR family, which also includes HER1 (EGFR), HER3, and HER4.
   b. HER2+ breast cancer patients derive significant benefit from HER2-targeted therapy, such as the humanized monoclonal antibody trastuzumab combined with chemotherapy in the adjuvant and metastatic settings.
   c. Approximately 30% of HER2-overexpressing breast cancers do not respond to trastuzumab.
   d. Two of the main downstream pathways activated by HER2 are the MAPK and PI3K–AKT pathways promoting cell survival, cell proliferation, and migration.

7. At diagnosis, 75% of breast tumors are estrogen receptor positive (ER+) and can potentially respond to tamoxifen, aromatase inhibitors, or other hormonal therapies. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1084-1095.]

   a. ER+ tumors tend to metastasize to the liver, and often metastasize early.
   b. ER can form multiprotein complexes with membrane-related factors, such as Src, G-proteins, RTK, and PELP1.
   c. Estrogen effects are mediated by two specific nuclear receptors, estrogen receptor α (ER-α) and estrogen receptor β (ER-β).
   d. Estrogen affects the cytokine milieu in the cancer microenvironment.
8. Breast cancer patients with bone metastases have distinct therapeutic options, including bisphosphonates and (more recently) denosumab, typically in combination with endocrine or HER2-directed therapies. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1084-1095.]

a. Bone metastases are triggered by changes in the bone microenvironment including hypoxia, acidic pH, and increased levels of extracellular calcium and growth factors.
b. The osteolytic vicious cycle is characterized as bone lysis with concurrent infiltration of metastatic tumor cells.
c. TGF-β and parathyroid hormone-related protein (PTHrP) both play an important role in osteolysis.
d. PTHrP, produced by luminal cells, activates osteoblasts but not osteoclasts.