Chapter 10

The Cancer Spectrum Related to Hereditary and Familial Breast and Ovarian Cancers

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Hereditary Breast Cancer

Multiple factors are associated with an increased risk of developing breast cancer, including age, family history, exposure to reproductive hormones, dietary factors, benign breast diseases, and environmental factors. Recently, increasing interest has been devoted to the interaction between environmental and genetic factors. Family history has been recognized as an important risk factor for developing breast cancer. Individuals with a first-degree family member affected with breast cancer have a relative risk of 2.1 (95% CI = 2.0–2.2). Moreover, risk varies with the age at which the affected relative was diagnosed, the number of affected and unaffected family members and, finally, the closeness of the relationship [1].

In the mid-1990s, developments in the molecular genetics of cancer led to the identification of predisposing hereditary breast and/or ovarian cancer genes. Studies of linkage analysis showed that there is an autosomal dominant predisposition to breast cancer and led to the identification of several highly penetrant genes; these included BRCA1 and BRCA2, which cause inherited cancer in many breast-cancer-prone families.

Overall, 5–10% of primary breast cancers are inherited and 15–20% are familial [1, 2]. Hereditary and familial forms are identified by the individual and the family history. In familial forms, members of some families are prone to developing breast cancer in the absence of identifiable carcinogenic exposure. Affected individuals in these families may represent clustering of sporadic occurrences, multifactorial inheritance, the presence of low-penetrance genes, or common habits and similar life style. Close relatives are at moderately increased risk of developing that type of malignancy. However, the average age of onset is usual similar to that observed in the general population.

The family features that suggest a hereditary predisposition to breast cancer include: (a) multiple cases of breast and ovarian cancer in different generations of a family, suggesting an autosomal dominant transmission (vertical transmission) according to the Lynch criteria; (b) an early age of onset; (c) multiple primary cancers in the same individual (i.e., bilateral breast cancer or breast and
ovarian cancer); (d) male breast cancer. The presence of both breast and ovarian cancer in a family increases the likelihood of a cancer-predisposing mutation.

About 84% of hereditary breast cancers derive from BRCA1 and BRCA2 mutations that are characteristic of the hereditary breast/ovarian cancer (HBOC) syndrome, in which there is an autosomal dominant pattern of transmission, incomplete penetrance, and variable expressivity [2]. To date, for each of the BRCA genes approximately 3,400 sequence variants have been identified. Some specific mutations have been observed in defined ethnic groups, suggesting a founder effect. The most common in the United States are the three mutations commonly found in the BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) genes in Ashkenazi Jews. Founder mutations in other populations, including those from Iceland, Poland, and in Dutch kindreds also have been identified. Founder mutations have been described as well in geographically restricted areas of Italy [3–5].

Other known susceptibility genes, such as ATM, PTEN, p53, and STK11, are involved in hereditary breast cancer syndromes with a well-defined cancer spectrum. Unknown low-penetrance genes also seem to be involved in other, less frequent hereditary breast cancers [2]. Mutations in each of these genes produce different clinical phenotypes of specific cancers and, in some instance, other non-malignant abnormalities associated with different hereditary syndromes known to involve the breast as a tumor site within the cancer spectrum. These syndromes include Li-Fraumeni syndrome, Cowden’s syndrome, ataxia-telangiectasia, and Peutz-Jeghers syndrome [6, 7].

**BRCA1- and BRCA2-Associated Breast and Ovarian Cancers**

Recently, Chen and Parmigiani reported a meta-analysis of BRCA1 and BRCA2 penetrance. The mean cumulative risk at age 70 years was 57% (95% CI, 47–66%) for breast cancer and 40% (95% CI, 35–46%) for ovarian cancer in BRCA1 mutation carriers. In carriers of BRCA2 mutations, the mean cumulative risk at age 70 years was 49% (95% CI, 40–57%) for breast cancer and 18% (95% CI, 13–23%) for ovarian cancer [8].

Mutations in BRCA1 and BRCA2 particularly increase the risk of early-onset breast carcinoma. Whereas a woman’s likelihood of developing breast cancer before age 50 is normally only 2%, the risk is 33–50% for a woman with a mutation in one of the two genes. In women with breast cancer, mutations in BRCA1 have been associated with a 64% cumulative risk of contralateral breast cancer by age 70.

The variation in cancer risk among the studies involving families assessed for breast cancer clustering suggests allelic heterogeneity. Moreover, the variation in risk within families and over time suggests a role for genetic and epigenetic modifying factors. Nongenetic factors, such as menstrual and reproductive histories, contraceptive and hormone use, exercise and body weight, and environmental and occupational exposure, might explain some portion of the variation