The Breast 28 (2016) 136–144

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Women at high risk of breast cancer: Molecular characteristics, clinical presentation and management

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ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form
4 May 2016
Accepted 13 May 2016
Available online 16 June 2016

Keywords:
Breast cancer
Hereditary breast cancer
Breast cancer risk

ABSTRACT

The presence of breast cancer in any first-degree female relative in general nearly doubles the risk for a proband and the risk gradually increases with the number of affected relatives. Current advances in molecular oncology and oncogenetics may enable the identification of high-risk individuals with breast-cancer predisposition. The best-known forms of hereditary breast cancer (HBC) are caused by mutations in the high-penetrance genes *BRCA1* and *BRCA2*. Other genes, including *PTEN, TP53, STK11/LKB1, CDH1, PALB2*, *CHEK2, ATM, MRE11, RAD50, NBS1, BRIP1, FANCA, FANCC, FANCM, RAD51, RAD51B, RAD51C, RAD51D,* and *XRCC2* have been described as high- or moderate-penetrance breast cancer-susceptibility genes. The majority of breast cancer-susceptibility genes code for tumor suppressor proteins that are involved in critical processes of DNA repair pathways. This is of particular importance for those women who, due to their increased risk of breast cancer, may be subjected to more frequent screening but due to their repair deficiency might be at the risk of developing radiation-induced malignancies. It has been proven that cancers arising from the most frequent *BRCA1* gene mutation carriers differ significantly from the sporadic disease of age-matched controls in their histopathological appearances and molecular characteristics. The increased depth of mutation detection brought by next-generation sequencing and a better understanding of the mechanisms through which these mutations cause the disease will bring novel insights in terms of oncological prevention, diagnostics, and therapeutic options for HBC patients.

Introduction

Cancer has emerged as the leading cause of morbidity and mortality in European populations [2]. The most common diagnose among women worldwide is breast cancer (excluding non-melanoma skin cancers), occurring with the highest incidence in developed countries including the EU, Australia, and the US. Overall, 464,000 women developed breast cancer and 131,000 women died of this diagnosis in Europe in 2012 [18]. It has been estimated that 10–12% of women will develop breast cancer over the course of their life. In contrast to incidence, which has been rising constantly during the last two decades in most countries, the mortality rate has remained stable (data from www.dep.iarc.fr; and seer.cancer.gov), indicating an improvement in breast cancer diagnostics and care.

Numerous genetic, lifestyle and environmental factors affect the risk of breast cancer development ([43]; Table 1). Among these, genetic factors are of particular importance. The presence of breast cancer in any first-degree female relative in general nearly doubles the risk for a proband and the risk gradually increases with the number of affected relatives [7]. Current advances in molecular oncology and oncogenetics enable the identification of high-risk individuals who may benefit from the knowledge about their breast cancer-predisposition in terms of oncological prevention, diagnostics, and therapeutic options.

Breast cancer development

The development of cancer is caused by a gradual and lifelong accumulation of acquired (somatic) mutations and epigenetic

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http://dx.doi.org/10.1016/j.breast.2016.05.006
0960-9776/

Table 1
Risk factors influencing breast cancer development.

Genetic risk factors

- Family history of breast cancer
  The pooled estimate of statistically significant relative risk (RR) associated with various family histories in the large meta-analysis was as follows: any relative, RR = 1.9; a first-degree relative, RR = 2.1; mother, RR = 2.0; sister, RR = 2.3; daughter, RR = 1.8; mother and sister, RR = 3.6; and a second-degree relative, RR = 1.5. Risks were higher in subjects aged under 50 and when the relative had been diagnosed before age 50 [57].
- Personal history of breast cancer
  Younger age at first breast cancer was associated with a significantly higher risk of contralateral breast cancer. The 25-year cumulative risk of contralateral breast cancer in patients (from *BRCA1/2*-negative families) diagnosed at age <40 was 28.4%, for patients diagnosed at age ≥50 it was 12.9% [62].
- Breast condition
  High breast tissue density on mammograms is a strong risk factor. Women with high-density mammograms face a risk up to six times that of women with low-density mammograms [52]. Benign breast diseases (benign proliferative breast disease, breast cysts, fibroadenoma, breast inflammatory diseases) also increase the risk.
- Menoactivity
  Age at menopause increases the risk by ~3% per year. Decreased risk is associated with late menarche (11 vs. 15 years, RR = 0.69) [8].
- Height
  Tall (170 cm) women aged 30–70 have a 12% higher cumulative breast cancer incidence than short (155 cm) women [8].

Lifestyle risk factors

- Dietary factors
  Alcohol consumption increases the risk of breast cancer up to age 70 by 7%. A woman with a weight-gain of ~27 kg (60 pounds) at age 18–50 had a 19% higher cumulative risk than a woman with a stable weight or an average weight gain of ~8.6 kg (19 pounds) [8].
- Physical activity
  Both pre-diagnosis and post-diagnosis, any physical activity was associated with reduced breast cancer-specific mortality (RR = 0.82) [82].
- Pregnancy
  Pregnancy at age <29 decreases the risk, pregnancy at age >35 increases the risk [8].
- Pharmacotherapy
  Antiestrogens – the use of antiestrogens (tamoxifen, raloxifen) reduces the risk. Due to side effects, their use should be restricted to high-risk women with a strong family history of cancer or mutations in breast cancer-susceptibility genes [52].
  HRT – the duration of postmenopausal use of hormone-replacement therapy increases the risk of breast cancer significantly, by 2.3% per year of use [8].
- Radiation exposure
  A case-control study of 105 women who developed breast cancer within a cohort of 3817 1-year young female survivors of Hodgkin disease treated by radiotherapy showed that breast cancer risk correlates with the obtained dose of radiation. A radiation dose of ≥4 Gy delivered to the breast was associated with a 3.2-fold increase in the risk. In patients who received a radiation dose of ≥40 Gy the risk increased 8.0-fold [73].

changes that, in the case of breast cancer, affect mammary tissue cells and their progenitors [58]. Recent genome-wide analyses of tumor samples have enabled a comprehensive identification of mutations, including those that direct the process of tumorigenesis and are referred to as driver mutations [71]. Multiple driver mutations that have been identified in breast cancer explain its molecular complexity and illustrate its clinical heterogeneity [70]. Driver mutations frequently affect genes that code for proteins maintaining physiological tissue homeostasis. Tumorigenesis is a specific disorder, characterized by progressive cell growth across the normal tissue architecture and body building plan. Therefore, the most characteristic molecular events wherein normal cells are transformed into cancer cells include an activation of the cell division cycle and evasion of apoptosis in cells with impaired maturation and abrogated senescence. The development of tumor-promoting mutations is accelerated in cells with defects in DNA repair pathways controlling genomic DNA integrity. It has been suggested that these pathways represent a critical anti-cancer barrier [4]. Interestingly, most breast cancer-susceptibility genes code for tumor suppressor proteins that are involved in processes of DNA repair and mainly in highly complex mechanisms of the DNA double-strand break (DDSB) repair (Fig. 1); however, the exact molecular mechanism through which hereditary alterations trigger the development of hereditary breast cancer remain to be elucidated.

Family history of breast cancer and breast cancer risk factors

The probability of breast cancer development is higher in high-risk individuals carrying causative germline (constitutive) mutations in the breast cancer-susceptibility genes [60] responsible for hereditary breast cancer (HBC). Patients with HBC form a small but important fraction of breast cancer patients. It has been estimated that heritable factors contribute to 27% of breast cancer cases [39], and the presence of breast cancer in at least one first-degree relative has been documented in 13% of cases [7]. Approximately 5–10% of breast cancer cases are HBC, developed in carriers of mutations in breast cancer-susceptibility genes. Several common signs may indicate the presence of a pathogenic mutation in breast cancer-susceptibility genes (Table 2). An increased overall cancer risk, an early onset of the disease, an increased probability of second primary tumors, and adverse disease outcomes multiply the overall burden of breast cancer in this population also because of the loss of productivity and increased medical expenses. Therefore, there is a considerable clinical need to address specific and tailored care for this high-risk population.

Use of biomarkers for definition of high-risk women. Breast cancer susceptibility genes

The main breast cancer-susceptibility genes (*BRCA1* and *BRCA2*) were discovered in the last decade of the 20th century [49,81]. Since this pioneering discovery, many other breast cancer-susceptibility genes have been characterized; however, none of the others shows a mutation frequency and clinical importance comparable to *BRCA1* and *BRCA2*.

All breast cancer-susceptibility genes have variable penetrance, which is determined by the proportion of carriers who develop breast cancer over the course of their lifetime. Breast cancer-susceptibility genes are usually divided into the categories of high-, moderate-, and low-penetrance genes, respectively, reflecting the relative risk of breast cancer development in mutation carriers. The best-known group is that of high-penetrance genes (*BRCA1*, *BRCA2*, *p53*, *PTEN*, *STK11*, *CDH1*) increasing breast cancer risk more than four-times. Pathogenic mutations in these genes are responsible for approximately 25% of all HBC cases. The carriers of