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Review Article

The Breast Cancer Genes

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Abstract

Breast cancer, almost exclusively a disease of the women, accounts for 10% of 10 million new cancer cases each year and causes 370,000 deaths annually although the incidence in Asia is low. Risk factors for breast cancers belong to different domains. Those associated with the highest relative risk belong to the genetic domain. The only group of women with mutated breast cancer genes had an average lifetime risk of developing breast cancer was calculated to be 65.3%. Genetic counseling and genetic study might help surgeons as well as the patients to better estimate the risk of developing breast cancer disease.

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The cellular changes that characterize cancer are initiated by various degrees of interaction between host factors and exogenous agents. Although, host factors other than genes play a role in the development of the disease, some of these are increasingly being recognized as also being under genetic influence. Cancer occurs because of mutations in the genes responsible for cell multiplication and repair. This does not mean that the disease is heritable. It seems to be clear that these changes require a particular interaction with the environmental factors for induction. Genetics may therefore eventually play an important role in control of cancer. It helps in identifications of individuals at risk for a specific cancer leading to preventive or screening strategies for an individual or his or her family members.

Breast cancer, almost exclusively a disease of the women, accounts for 10% of 10 million new cancer cases each year and causes 370,000 deaths annually although the incidence in Asia is low.[1] Risk factors for breast cancers belong to different domains. Those associated with the highest relative risk belong to the genetic domain. The only group of women with mutated breast cancer genes had an average lifetime risk of developing breast cancer was calculated to be 65.3%.[2] Genetic counseling and genetic study might help surgeons as well as the patients to better estimate the risk of developing breast cancer disease.

The discovery of breast cancer genes BRCA1 and BRCA2 has led to an explosive development in cancer screening for women at risk. We often appreciate that someone has the breast cancer gene. In fact, everyone has these genes as part of the normal genetic makeup. Patients who are at risk for breast cancer carry mutations of these genes. The molecular diagnostic assays screen for these mutations.

Although several hundred mutations have been found, these are not all of the mutations so it is possible that a patient may have a mutation of the gene, which is not detected by routine screening. There is also an interesting association between

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some mutations and some ethnic groups. There is one mutation that is present in 20-30% of breast cancers in Ashkenazi Jews.

The following table highlights some of the salient features of these two genes.[3]

Characteristic	BRCA1	BRCA2
Chromosome	17q21	13q12
Gene	100kb	70kg
Protein	1863 amino acids	3418 amino acids
Function	Tumor suppressor Interacts with nuclear protein. Possible role in DNA repair	Tumor suppressor Interacts with nuclear protein. Possible role in DNA repair
Mutations	>500 identified	>200 identified
Risk of breast CA	>70% by age 80 yrs	>60% by age 70 yrs
Age at onset	40-50 yrs	50 yrs and older
Risk of other tumors	30-60% of ovarian Cancer by 70 yrs Prostate and colon cancer	Male breast cancer, ovary, bladder, prostate, pancreas
Mutations in non familial breast cancer	<5%	<5%
Epidemiology	Specific mutations more common in some ethnic groups	Specific mutations more common in some ethnic groups
Pathology of breast CA	Higher incidence of medullary CA (13%) and higher-grade tumors. DCIS less frequent	Variable types, may depend on specific mutation

Over 2 percent of Ashkenazi Jews carry mutations in BRCA1 or BRCA2 that confer increased risks of breast, ovarian, and prostate cancer. The risks of breast cancer may be overestimated, but they fall well below previous estimates based on subjects from high-risk families.[4]

Almost half (48%) of women in southern Sweden with early-onset breast cancer have some family history of breast or ovarian cancer, and 9.0% of early-onset breast cancer cases are associated with a germ line mutation in BRCA1 or BRCA2. Mutation carriers were more prevalent among young women, women with at least one first- or second-degree relative with breast or ovarian cancer, and women with bilateral breast cancer.[5]

Mutations in the BRCA1 and BRCA2 genes make approximately equal contributions to early-onset breast cancer in Britain and account for a small proportion of the familial risk of breast cancer.[6]

Mutations in the genes BRCA1 and BRCA2 are rare in the population and account for a small fraction of all breast cancer in the UK. They account for less than one fifth of the familial risk of breast cancer. Eligibility criteria for BRCA1 and BRCA2 mutation testing based on family history and age of onset will identify only a small proportion of mutation carriers.[7]

Cancers in carriers of BRCA1 and BRCA2 mutations were, on average, of a higher overall grade than in controls. However, when the three grade indices were considered independently, breast cancers in BRCA1-mutation carriers showed more pleomorphism, a higher mitotic count, and less tubule formation than controls, whereas cancers in BRCA2-mutation carriers showed less tubule formation, but no difference in pleomorphism or mitotic count.

The histology of breast cancers in predisposed women differs from that in sporadic cases, and there are differences between breast cancers in carriers of BRCA1 and BRCA2 mutations. The findings suggest that breast cancer due to BRCA1, has a different natural history to BRCA2 or apparently sporadic disease, which may have implications.[8]

A mutation in the BRCA1 gene may confer substantial risk for breast and/or ovarian cancer. However, knowledge regarding all possible mutations and the relationship between risk factors and mutations is incomplete.

These data suggest that the presence of multiple primary cancer of any kind may predict for an increased likelihood of finding a BRCA1 or BRCA2 mutation and supports previous studies

suggesting that BRCA1 and BRCA2 mutations may be associated with an increased susceptibility to cancers other than breast and ovarian cancer.[9]

Risks of ovarian, breast, and stomach cancers and leukaemias/lymphomas were increased nine-, five-, six- and threefold, respectively, among first-degree relatives of cases carrying BRCA1 mutations, compared with relatives of non-carriers, and risk of colorectal cancer was increased threefold for relatives of cases carrying BRCA2 mutations. For carriers of BRCA1 mutations, the estimated penetrance by age 80 years was 36% for ovarian cancer and 68% for breast cancer.

For cancers of all sites combined, the estimated penetrance of BRCA2 mutations was greater for males than for females, 53% versus 38%. Past studies may have underestimated the contribution of BRCA2 to ovarian cancer, because mutations in this gene cause predominantly late-onset cancer, and previous work has focused more on early-onset disease. If confirmed in future studies, the trend in breast-cancer penetrance, according to mutation location along the BRCA1 coding sequence, may have significant impact on treatment decisions for carriers of BRCA1-mutations. As well, BRCA2 mutations may prove to be a greater cause of cancer in male carriers than previously has been thought.[10]

Recent studies suggest that BRCA1 modulates proliferation, chemosensitivity, repair of DNA strand breaks, apoptosis induction, and expression of certain key cellular regulatory proteins (including BRCA2 and p300) in human prostate cancer cells. These activities are consistent with a putative prostate tumor suppressor function of BRCA1.[11]

Significantly breast cancers with BRCA1 mutations and breast cancers with BRCA2 mutations express different groups of genes. Some studies suggested that a heritable mutation influences the gene-expression profile of the cancer.[12]

Using logistic regression analysis, we provide a method for evaluating the probability of a woman's carrying a deleterious BRCA1 mutation for a wide range of cases, which can be an important tool for clinicians as they incorporate genetic susceptibility testing into their medical practice.[13]

The lifetime risk of breast cancer appears similar to the risk in BRCA1 carriers, but there was some suggestion of a lower risk in BRCA2 carriers <50 years of age.[14] However carriers of BRCA1 and BRCA2 mutations appeared to have neither better nor worse survival prognosis.[15]

Because mutations in BRCA1 and BRCA2 in women with breast cancer are associated with an increased risk of ovarian cancer, analysis of these genes should be considered for women diagnosed with breast cancer who have a high probability of carrying a mutation.[16]

In BRCA1 and BRCA2 mutation carriers, MRI is more sensitive for detecting breast cancers than mammography, ultrasound, or CBE alone. Whether surveillance regimens that include MRI will reduce mortality from breast cancer in high-risk women requires further investigation.[17]

Tamoxifen reduced breast cancer incidence among healthy BRCA2 carriers by 62%, similar to the reduction in incidence of ER-positive breast cancer among all women in the Breast Cancer Prevention Trial. In contrast, tamoxifen use beginning at age 35 years or older did not reduce breast cancer incidence among healthy women with inherited BRCA1 mutations. Whether tamoxifen use at a younger age would reduce breast cancer incidence among healthy women with BRCA1 mutations remains unknown.[18]

As prophylactic surgeries are becoming more common secondary to advances in molecular diagnostics, pathologists need to be aware that surgical specimens from these patients may require more rigorous examination to uncover early neoplastic changes.[19]

In women with a BRCA1 or BRCA2 mutation, prophylactic bilateral total mastectomy reduces the incidence of breast cancer at three years of follow-up.[20]

With the advent of different modalities of treatment for breast cancer, we are moving towards more conservative surgery than radical and traumatic one during the last three decades. So it will be more rational to wait for more information on breast cancer genes before deciding for prophylactic bilateral mastectomy in patients with BRCA1 and BRCA2 genetic mutation.

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