

Some Genetic Aspects of Breast Cancer

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Introduction

Of the 1.5 million women who will be diagnosed with cancer of the breast this year, up to 15% according to some studies, will be hereditary (genetic) in origin.(1)

It is probably true to say that no other diagnosis strikes as much fear and anxiety in women as that of being told that they are suspected of having developed breast cancer. A woman equates her breasts with her femininity, sexuality, and psyche and their immediate vision of such a prospect is one of an early and painful death, following massive surgical disfigurement, with loss of self esteem through what they believe is their loss of womanhood. Added to this lies the extreme fear of abandoning their families, children and loved ones, and since hereditary cancer occurs in younger women, often under the age of forty, its effects are that much more intense and devastating.

Undoubtedly these factors cause women to avoid screening procedures and delay seeking medical advice until it is often too late, and often with catastrophic consequences.

Epidemiology

Cancer of the breast has increased considerably in the past two decades affecting as many as 1: 8 women and has become a major health hazard throughout the world, whilst at the same time mortality figures show an annual increase of 2%. (2)

Breast cancer is the commonest cancer in Europe and North America affecting a vast number of women. There are however global variations which show that women in the Far East, China and especially Japan are five times less likely to develop breast cancer. This confirms the hypothesis that there exists a local protective environmental factor which unfortunately is lost when Japanese women migrate, especially to the USA. (3)

At the other extreme lie populations such as the Ashkenazi Jews, Icelanders, as well as other populations and ethnic groups in whom breast cancer appears to be at least three times more common. In the USA, white women are known to be far more susceptible than Latinos and African Americans, although mortality in these groups is much higher than in white women, suggesting that socio-economic and cultural factors are responsible. (4)

Risk Factors

1. The risk factors implicated in the etiology of breast cancer are known to be *multifactorial*, including both genetic and environmental factors, but there are many others that have been implicated at one time or another.
2. *The existence of non-genetic* risk factors is indicated by the large variations in incidence in different countries and different groups and can be age related, involving late menopause, early menarche, nulliparity, late age at pregnancy, lactation, excessive placental weight, smoking, excessive alcohol consumption and many others.
3. *Hormones* such as estrogens and progestogens are well known and widely reported as being responsible in the genesis of breast cancer and are regarded

as *tumor promoters* for their role in causing gene mutations which lead to tumor formation.

4. In addition *genetic substances at the cellular level* such as Oncogenes and tumor Suppressor genes (eg HER-2) are amplified regulatory cellular genes associated with cellular cycle and division. Disruption in their function causes mutations which affect the dividing cell, promoting tumor formation. Their existence is associated with poor prognosis (5)
5. *Genetic predisposition*, especially in women with a family history who are known to be more susceptible in developing early, bilateral breast cancer as well as ovarian and other cancers. (Table, Summary risk factors)

Diagnostic procedures

The importance of a meticulous medical history and thorough breast examination can not be overstressed.

1.) *Mammography* is mandatory and reliable radiological assessment of the findings of paramount importance. Absence of reliability can have catastrophic consequences. This sad fact was recently highlighted in reports from the UK (January 2006) and at other times in the past, where retrospective examination of mammograms showed that up to 2500 women in the Manchester area, who were given the *all clear* had in fact had cancer at the time. Many had already developed advanced, untreatable disease and some had died. (6)

2.) In addition to expert radiological translation, *expert pathological examination* of biopsies can not be overstressed, for exactly the same reasons as above.

3.) *Genetic testing* must be carried out on all women with a known or suspected history of breast cancer in the family, and where there is bilateral disease.

4.) In women belonging to ethnic groups known to be susceptible to breast cancer such as the Ashkenazi's.

5.) Where there is co-existence or suspicion of ovarian cancer.

6.) In women developing cancer at an early age.

Genetics of breast Cancer

Genetic research in the past twenty years has made it possible to pry into man's very genetic fabric and detect what is affecting him at present, determine what his ancestors perished from in the past and foretell with great certainty what his offspring and their offspring will be plagued from in the future. (7)

Genetic disease is not to be underestimated. In a world wide context, genetic disease of which breast cancer is one, is known to be responsible for up to 30% of all pediatric hospital admissions.

It is responsible for 15% of all diagnoses for mental retardation, and 3% of all live births have a genetic or chromosomal dysfunction.

More than 4000 genetic disorders have been identified and over 100 are of chromosomal origin. (8)

Studies in hereditary breast cancer show that 8-15% of all those women affected are due to heredity.

In some ethnic groups such as the Ashkenazi Jewish women as many as 35% of all cases have been identified to be of genetic origin.

Furthermore specific genes are known to be responsible for the development of breast cancer, and after much research in the past fifteen years, these genes have been identified as BRCA1,(identified in 1991, cloned in 1994, situated on the long arm of chromosome 17)

BRCA2, (identified 1994, cloned 1998, and is located on the short arm of chromosome 13)

p53, with others that have so far not been classified.

These genes have also been found to predispose to ovarian cancer as well as other primary cancers.

It has also been shown that tumor formation is due to two major regulatory classes of genes.

- *Oncogenes are mutated photogenes* whose normal function is to regulate cell cycle and division
- *Tumor suppressor genes are cell cycle regulators* and function as terminators of cell division, leading to the apoptosis of mutated cells.

Disturbed function in these genes leads to abnormal cell division control and termination leading to tumor formation (9)

BRCA1 and BRCA2 normally function as tumor suppressors and repair enzymes. They are associated with ovarian cancer, BRCA1 more than BRCA2. and predispose to the development of bilateral disease, at an earlier age.

Both these genes are also associated with male breast cancer, prostate, colon and pancreatic cancer. (10)

Since their recognition more than 500 mutations are attributed to BRCA1 and BRCA2. The repeated appearance of a given mutation within a highly inbred population such as the Ashkenazi's, points to a *Founder mutation* which has been passed on for many hundreds of years.

It has been estimated that the 185delAG mutation in BRCA1 has been occurring in the Ashkenazi's for 46 generations (1150 years) and the 617delT mutation in BRCA2 has been occurring for 29 generations or 725 years.

These *founder mutations* have also been identified in other countries and populations in Russia, Sweden, Holland, Norway, Scotland, Belgium, French Canada, probably because of the Jewish migrations at times of persecution during the past centuries.

Iceland which has a highly inbred population has a *Founder* mutation in BRCA2 which differs from that found in the Ashkenazi's. (11)

Of all the inherited breast cancer cases 84% are associated with BRCA1 and BRCA2 mutations. The remainder 16% are associated with other genes broadly described as BRCA3 and are incriminated for causing cancers in more than one organ system.

The recently identified p53 gene, is associated with early onset bilateral breast cancer, soft tissue sarcomas, and leukemias as seen in the Li- Fraumeni syndrome.

P53, is a tumor suppressor gene involved in DNA damage repair which when mutated can give rise to the development of different cancers.

A number of other genetic conditions are known to confer an increased risk to also developing breast cancer as for example some forms of colon cancer

Hereditary breast cancer is known to be a risk factor for the development of other primary cancers even in women who had survived ten years or more.

In recent world wide multi center, retrospective studies, data were collected from cancer registries from Europe, Canada, Australia and Singapore. 527,527 cases who were

treated between 1943 up to 2000 were analyzed to determine the risk of developing other primary cancers. This risk was calculated to be in excess of 25% for each year. Of the total, 133,000 of the women were followed up for more than 10 years. Analysis showed that an excess risk exists beyond 10 years, even among women who had been symptom free for the decade following diagnosis. The findings of the analysis showed a more than double risk for developing soft tissue sarcoma
Increased the risk for thyroid cancer by 60%. Non-melanoma skin cancer by 58%
Leukemia and Endothelial cancers by 52%. Ovarian cancer by 52%
Stomach cancer by 48%. Melanoma by 29%
Kidney cancer by 27%. Lung cancer by 24%
Colorectal cancer by 22% (12)

Discussion

Breast cancer has become a major health hazard in all societies all round the world. Its incidence is increasing by 2% each year whilst mortality follows the same pattern with over 400,000 deaths per year, at present levels. Hereditary cancer is associated with specific markers, BRCA1, BRCA2, p53 whilst others are now under investigation. There is a multitude of risk factors. Apart from heredity, there are a great many environmental factors that are implicated. It is known that some populations ie the Ashkenazi's, Icelanders, there exist Founder genes conferring higher susceptibility whilst at the other extreme, local protective factors reduce (Japan, Far East) cancer by as much as five times. Long term survival in hereditary cancer cases is unfortunately no guarantee that other primary cancers in other organ systems will not develop. On the contrary there seems to be an excess risk even in women who had been symptom free for more than ten years.

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