Breast cancer awareness in the genomic landscape

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18 Oct 2022

Researchers at the University of Pretoria (UP) are making today matter by battling aggressive breast cancer through identifying genes that make African women more susceptible to certain forms of breast cancer. However, this is no easy task as very little genomic information is known about African populations. This is just one of UP's research projects that aim to ensure that there is a clear benefit for society, and that in the future many more lives could be saved from the scourge of cancer.

October is Breast Cancer Awareness Month in South Africa. It highlights an important drive by public healthcare organisations and the private sector to increase breast cancer awareness.

Breast cancer is the most prevalent cancer in women globally. According to the World Health Organization approximately 2.5 million women are diagnosed with breast cancer annually with a mortality rate of almost 700 000 women.

In South Africa it is estimated that approximately 1 in 27 women will develop breast cancer in their lifetime. Since the end of 2020, an estimated number of 7.8 million women have been living with breast cancer.

Cancer is caused by mutations in the genome. Many gene mutations may occur during a person's life and are therefore not inherited. The latter may be triggered by risk factors including acute or chronic stress, carcinogens, alcohol consumption, tobacco products, diet, lack of physical activity, environmental pollutants, ultraviolet radiation, reproductive and hormonal factors, occupational exposures, infection-attributable cancers, number of pregnancies and age.

Developing breast cancer can also be an inherited genetic risk. About 5% to 10% of breast cancer cases are thought to be hereditary. Specific genetic variants (mutations) that women inherit from their parents may affect their probability of developing breast cancer. Having a first or second degree relative with breast cancer may increase the risk of being diagnosed with breast cancer by two to three-fold.

Breast cancer susceptibility genes typically contain specific variants that decrease the ability of the woman's body to repair damaged DNA. There are two types of variants that play a role in breast cancer. The first type is referred to as a germ line variant that is inherited. When specific germ line variants occur the body is less likely to repair detrimental mutations that may cause cancer. The second type of variant is called a somatic variant and this takes place when DNA damage occurs during a woman's lifetime and is found in the DNA of cancerous cells.

Germ line variants may increase a woman's susceptibility to get breast cancer. While variants in several germ line breast cancer susceptibility genes play a role, the most-researched genes are involved in the repair of damaged DNA and include BRCA1 and BRCA2, followed by PALB2. Examples of other important genes are ATM and TP53.

Having inherited specific mutations in BRCA1 or BRCA2 may increase a women's risk of developing breast cancer up to 7 out of 10 times by the age of 80 years. PALB2 interacts with BRCA2 in DNA repair processes.

Literature has shown that women with mutations in PALB2 may experience a 35% likelihood to develop breast cancer by the age of 70 years. Other important genes are ATM and TP53. Detrimental variants in BRCA1 and BRCA2 are responsible for 90% of inherited breast cancer, however, many breast cancer patients have been shown not to have a BRCA1 or BRCA2 mutation.

They way breast cancer is diagnosed has developed significantly during the past years. It is attempted to target the treatment to the type of breast cancer that is identified in the patient. The classification is as follows:

Breast cancer is classified as Luminal A, Luminal B, HER2+, triple negative, Claudin-low and Normal-like. In terms of common markers, testing is done for the presence of the progesterone receptor (PR), estrogen receptor (ER) and for human epidermal growth factor receptor 2 (HER2) status. The presence of ER and PR implies that they can be treated with receptor-targeted treatment methods, where high HER2 levels typically indicate fast cancer growth, but may be targeted with drugs aimed at HER2.

Cancers without ER and PR and having low HER2 levels are termed triple-negative and are typically more challenging to treat and require chemotherapy.

The type of breast cancer as described above will assist in determining the path to follow in terms of ER, PR and HER2-targeted treatments and the need for precision targeted-therapy, surgery, chemotherapy, and radiation. Therefore, unlike many years ago, there is no blanket treatment for breast cancer, but it is individualized according to the type of cancer and the presence of specific gene variants.

An important factor is that the majority of studies to design breast cancer susceptibility tests have been conducted on European and Asian populations and breast cancer tests have been mainly designed from the latter data.

Only a small number of gene panel tests have been performed for African populations, with Nigerian patients and with patients from Uganda and Cameroon. Recent research conducted by Eygelaar, Janse van Rensburg and Joubert from the University of Pretoria in 2022 investigated 165 South African breast cancer patients from various ethnolinguistic groups and indicated 9% of women with a family history of breast cancer (higher than the other two studies mentioned above). The UP team identified pathogenic/likely pathogenic variants in 13 patients in 10 different genes including BRCA1, BRCA2, PALB2 and others.

Larger scale cancer susceptibility gene studies are crucial in South Africa and the rest of Africa and future research should include large whole exome (protein-coding part of the genome) or genome sequencing studies.

Recently human genome sequencing has become much more affordable and several studies are taking place in Africa and specifically South Africa. This will inform researchers about the frequency of not only breast-cancer susceptibility variants in Africans, but also about variants that influence a wealth of other inheritable conditions.

The complete strategy for the elimination of cancer requires a combination of awareness to address the burden of this disease, prevention strategies, contributing to early detection, promoting health and well-being education, together with the acceleration of science and discovery and progress in technology.

We do what we do every day, because we want to make a difference in someone's life. Our life's journey has been truly shaped by people suffering from cancer and by family, friends, colleagues, peers, our executive and students, as well as

indirectly by every individual who has crossed their paths.

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Side Bar

According to the American Cancer Society the most common symptom of breast cancer is a new lump or mass (although most breast lumps are *not* cancer). A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can also be soft, round, tender, or even painful.

- Swelling of all or part of a breast (even if no lump is felt)
- Skin dimpling (sometimes looking like an orange peel)
- Breast or nipple pain
- Nipple retraction (turning inward)
- Nipple or breast skin that is red, dry, flaking, or thickened
- Nipple discharge (other than breast milk)
- Swollen lymph nodes under the arm or near the collar bone

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