Breast Cancer Risk Associated With *CHEK2* Mutations

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Most efforts to identify individuals who have a hereditary predisposition for developing breast cancer had focused on the *BRCA1* and *BRCA2* genes. Less common susceptibility genes also are associated with increased risk for developing breast cancer, but until recently have often gone undetected. With the advent of next generation sequencing (NGS), many families with suspected hereditary risk are undergoing testing for multiple genes associated with increased cancer risk (Mahon, 2013a). One gene that is commonly included on NGS hereditary breast cancer panels is *CHEK2*. Increasingly, oncology nurses will encounter patients and families affected with mutations on this gene and need to understand the implications it has for screening and treatment.

Biology of the *CHEK2* Gene

The official name of *CHEK2* is checkpoint kinase 2 (Shannon & Chittenden, 2012). The cytogenetic location of *CHEK2* is 22q12.1, which means it is located on the long (q) arm of chromosome 22 at position 12.1 from base pair 28,687,742 to base pair 28,741,833. *CHEK2* was first linked to breast cancer susceptibility in 2002, and commercial testing is now readily available (Narod, 2010). This gene is passed from generation to generation through autosomal dominant transmission.

The *CHEK2* gene provides instructions for making a protein called checkpoint kinase 2, which interacts directly with *BRCA1*. That protein acts as a tumor suppressor and regulates cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. The *CHEK2* protein can be activated when either DNA becomes damaged or when breakage of the DNA strands occurs during replication processes when chromosomes exchange genetic material. DNA damage occurs for multiple reasons, including exposure to toxic chemicals, radiation, or ultraviolet light. The *CHEK2* gene is activated by the *ATM* gene, in response to double stranded breaks (Gage, Wattendorf, & Henry, 2012). *CHEK2* is in the middle of a pathway that functions to detect and then determine the cellular response to DNA damage (Tung & Silver, 2011). *CHEK2* interacts with several other proteins, including the *TP53* gene. Together, the *CHEK2*, *TP53*, and other proteins in the pathway halt cell division and determine whether a cell will repair the damage or undergo apoptosis. Ultimately, this process prevents cells with mutated DNA from dividing and forming tumors.

Cancer Risks Associated With *CHEK2*

Inherited mutations in the *CHEK2* gene have been identified in some cases of breast cancer, particularly in European populations. The most commonly seen *CHEK2* mutation is associated with the deletion of a single nucleotide at position 1100, known as 1100delC. This is considered a founder mutation and is most commonly found in Caucasian individuals of Northern and Eastern European origin, including descendants of Europeans, such as French Canadians, Jews, and Brazilians (Apostolou & Fostira, 2013; Bodmer & Tomlinson, 2010; Narod, 2010). The 1100delC mutation is known to lead to the production of an abnormally short, nonfunctional version of the *CHEK2* protein. Without this protein, cells are unable to regulate cell division properly. The *CHEK2* variant 1100delC is estimated to account for about 5% of cases of non-*BRCA* breast cancer in German populations (Márquez-Rodas, Solís, Cobo, & Martín, 2012). Three other founder variants of *CHEK2*, IVS2_1G_A, del5395, and I157T, are associated with increased breast cancer risk and also have been associated with breast cancer in Eastern European populations. Two of these (IVS2_1G_A and del5395) are protein-truncating mutations, and one (I157T) is a missense variant (Cybulski et al., 2011).

Penetrance of the various *CHEK2* mutations is variable and usually incomplete (Maxwell & Nathanson, 2013). Mutations in *CHEK2* are considered of medium penetrance and occur with medium frequency for genetic mutations associated with hereditary breast cancer (Gage et al., 2012). *CHEK2* mutations are associated with almost a 3-fold increase (25%) in the risk of breast cancer in women and a 10-fold increase in the risk of breast cancer in men (Narod, 2010). The risk is higher when more family members are affected with breast cancer.

For carriers of a mutation in *CHEK2*, the risk of breast cancer for females with a positive family history of breast cancer is greater than that for a carrier of the same mutation who has no family history of breast cancer (Narod, 2010). Women who are homozygous for this mutation have a significantly higher six-fold risk of developing breast cancer (Lalloo & Evans, 2012). This finding has led to the reasoning that *CHEK2* is a modifier of other (possibly unidentified) susceptibility genes for breast cancer. For this reason, during genetic counseling, a relatively higher risk of breast cancer

ONF, 41(6), 692–694.
doi: 10.1188/14.ONF.692-694