Breast Cancer Risk Associated With *CHEK2* Mutations

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG

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

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will be estimated for a carrier of a *CHEK2* mutation if the patient's family history is strong. Limited data suggest that *CHEK2* mutations may be protective against lung cancer (Narod, 2010).

Implications for Nurses

Identification of individuals and families at risk for hereditary breast cancer includes a comprehensive family history of three generations that documents age at onset for a diagnosis of all cancers. Key indicators of hereditary risk include early age of onset of breast cancer, multiple affected generations, multiple family members affected with breast cancer, an excess of bilateral breast cancer, and a diagnosis of male breast cancer. Such families, where hereditary risk is suspected, should be referred to credentialed genetics professionals for further evaluation. Such professionals include master's-prepared genetics counselors and advance practice nurses with an advance practice nurse in genetics (APNG) credential (Mahon, 2013b).

Oncology nurses should anticipate that, following genetic risk assessment and counseling, many of these families will undergo genetic testing. The norm is now to order NGS panel testing, which includes high-penetrance, high-risk genes such as the *BRCA1* and *BRCA2*, as well as moderate-risk, moderate-penetrance genes such as *CHEK2*. Such testing will continue to identify more and more families affected with deleterious mutations in the *CHEK2* gene. Once a mutation is detected in a family, single-site testing can identify other family members who potentially have increased risk for developing breast cancer.

Mutations in *CHEK2* are associated with moderate penetrance and risk of developing breast cancer. The risk of developing breast cancer is variable and probably less than 50% in most families (Narod, 2010). With this level of risk, increased surveillance with more frequent professional examinations (ideally by a breast surgeon), as well as earlier mammography and breast magnetic resonance imaging, are appropriate surveillance recommendations (Cybulski et al., 2011). In general, prevention strategies, such as prophylactic mastectomies, cannot be recommended with current data (Apostolou & Fostira, 2013; Hollestelle, Wasielewski, Martens, & Schutte, 2010). Offering prophylactic surgery to women is very controversial when they have less than a 50% lifetime risk of developing breast cancer for which reasonable screening is associated with early detection when treatment is most likely to be effective (Cybulski et al., 2011).

Women without cancer could be considered to be candidates for tamoxifen, although no randomized trials have been conducted to assess the effectiveness of tamoxifen in *CHEK2* carriers. The age at which to begin prophylaxis is not clear and consideration should be given to the woman's family history because it may be associated with early onset breast cancer. This recommendation is based on the observation that about 70% of *CHEK2* cancers are estrogen and progesterone positive (Narod, 2010; Tung & Silver, 2011).

At present, it is difficult to predict the clinical course of *CHEK2*-related breast cancer or provide the patient with information about the prognosis and natural history of such a cancer. Some anecdotal evidence shows that a breast cancer associated with a *CHEK2* mutation may have a poorer prognosis and be associated with decreased survival (Narod, 2010). For those individuals diagnosed with breast cancer, an estimated risk of about 1% per year exists for a second primary breast cancer (Narod, 2010). No clinical trials have been conducted to determine if breast cancers associated with *CHEK2* mutations have a better response to specific chemotherapy agents. For this reason, women with breast cancer are treated with conventional chemotherapy protocols based on the histologic and pathologic characteristics of the tumor. Because *CHEK2* carriers with breast cancer have an increased risk of a second primary breast cancer, it is reasonable to consider tamoxifen for prevention following their definitive treatment for breast cancer (Cybulski et al., 2011).

Deleterious *CHEK2* mutations have also been associated with an increased risk of developing prostate cancer (Narod, 2010). If a man has a *CHEK2* mutation and a first-degree relative with prostate cancer, prostate screening should be considered based on the age of onset in the family and should include both digital rectal examination and prostate specific antigen testing.

The full range of cancers associated with *CHEK2* mutations has not yet been fully identified, but evidence shows that *CHEK2* increases the risk for thyroid and kidney cancers (Narod, 2010). Providers should be aware of these possible increased risks, but no formal recommendations for screening have been made.

Conclusion

Genetic counseling for *CHEK2* is very challenging and associated with uncertainty for the patient because the risk of cancer depends not only on whether or not the individual has the mutation, but also on the patient's family history of breast cancer. Families need support as they try to understand these findings. Early identification of individuals at increased risk of breast cancer because of *CHEK2* mutations may lead to enhanced screening and prevention strategies and potentially improved overall survival for this group of patients. Genetic counseling for most of these moderate-risk, moderate-penetrance new genes can be complicated. Further evaluation and genetic analysis in large series of patients will determine actual cancer risks and optimal management strategies. Patients with known mutations should be instructed to check with their healthcare provider and genetics professional on a regular basis to determine if there are changes in the recommendations for surveillance or prevention.

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, is a professor in the Department of Internal Medicine and the School of Nursing at Saint Louis University in Missouri. No financial relationships to disclose. Mahon can be reached at mahonsm@slu.edu, with copy to editor at ONFEditor@ons.org.

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