PALB2 and the Risks for Cancer: Implications for Clinical Care

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Mutations in the *PALB2* gene are responsible for a small but significant percentage of cancer risks in familial breast and pancreatic cancer families. *PALB2* mutations may be associated with an increase in other cancer risks as well. This article will provide an overview of the *PALB2* gene, cancer risks associated with carrying a *PALB2* mutation, and implications for patient care.

PALB2, which is officially termed the partner and localizer of *BRCA2*, is located on chromosome 16p12.2 and is part of a family of genes classified as *FANC*, or Fanconi anemia complementation groups (National Library of Medicine, 2007). *PALB2* interacts with the *BRCA2* gene and is involved in homologous recombination and DNA repair (National Cancer Institute, 2014). It assists the *BRCA2* protein with maintaining cell stability by facilitating repair and regulation of the cell cycle (Zhang, Wang, Kang, Li, & Geng, 2013). *PALB2* also interacts with other genes such as *BRCA1* (Antoniou et al., 2014), *RAD51C*, the translesion polymerase pol η, and *MRG15*, all of which promote DNA repair and tumor suppression, and with *KEAP1*, which regulates the response to oxidative stress (Park, Zhang, & Andreassen, 2014). *PALB2* is categorized as a moderate-penetrance gene, as opposed to a high-penetrance gene, such as the *BRCA1* and *BRCA2* genes (see Figure 1). Moderate-penetrance genetic mutations are more common in the general population than high-penetrance genetic mutations, and they confer a less severe phenotype, therefore contributing to a moderately elevated relative risk of cancer (National Cancer Institute, 2014). *PALB2* testing is included in many next generation sequencing hereditary cancer panels. *PALB2* may also be called *FANCN* or Fanconi anemia complementation group N (National Library of Medicine, 2007).

PALB2 and Breast Cancer

PALB2 mutations are associated with an increased risk of breast cancer. The prevalence of *PALB*2 mutations in patients with familial breast cancer varies by population but is thought to be 0.6%–3.9% (Antoniou et al., 2014). In a study involving 923 individuals, all of whom had been ascertained from familial breast cancer families, the prevalence was 1.1% (Rahman et al., 2007). In another similarly sized study, the prevalence was 3.4% (Casadei et al., 2011). As with other inherited genetic mutations, specific *PALB2* founder mutations are associated with certain populations. In Finland, the *PALB2* c.1592delT mutation has been identified in 1% of women with breast cancer unselected for family history of the disease; in Canada, the *PALB2* c.2323C>T has been identified in 0.5% of French Canadian women with early onset breast cancer, also unselected for family history (Antoniou et al., 2014). A *PALB2* founder allele does not appear to be present among those of Ashkenazi Jewish ancestry (Casadei et al., 2011). Overall, *PALB2* mutations have been observed in families from many countries and in those from a variety of ethnic backgrounds.

PALB2 is a breast cancer susceptibility gene. A *PALB2* mutation confers an approximately two- to fourfold increase in female breast cancer risk (Casadei et al., 2011; Hoffstatter et al., 2011; Rahman et al., 2007) and varies based on age and family history of breast cancer. In younger individuals and in familial breast cancer families, the risk is higher. A study by Antoniou et al. (2014) found that the risk of breast cancer in female *PALB2* mutation carriers, when compared to the general population, is five times higher in women older than 60 years and eight to nine times higher in women younger than 40 years. The study also determined that the cumulative breast cancer risk for female *PALB2* mutation carriers is 14% by age 50 and 35% by age 70. For those without a family history of breast cancer, the absolute breast cancer risk to age 70 in carriers is 33%. That risk increases to 58% for those with two or more first-degree relatives who had been diagnosed with breast cancer by age 50 (Antoniou et al., 2014).

Male breast cancer is also associated with *PALB2* mutations. In a study of 115 male breast cancer cases, *PALB2* mutations accounted for 1%–2% of the breast cancers in that population (Ding, Steele, Kuan, Greilac, & Neuhausen, 2011). The relative risk of male breast cancer in carriers is estimated to be at least fourfold (Casadei et al., 2011) but may be much higher; a study by Antoniou et al. (2014) found the relative risk to be 8.3.

PALB2 and Pancreatic Cancer

PALB2 mutations are associated with an increased risk of pancreatic cancer. Such mutations have been identified in 3%–4% of familial pancreatic cancer families with an estimated overall prevalence of 3.1% (Hofstatter et al., 2011). As with familial breast cancer families, *PALB2* mutations appear to be more prevalent in those with a family history of pancreatic cancer as compared to those without a family history of pancreatic cancer.

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PALB2 is a pancreatic cancer susceptibility gene and is thought to be the most common hereditary pancreatic cancer gene, aside from *BRCA2* (Jones et al., 2009). The exact risk of pancreatic cancer that is associated with carrying a *PALB2* mutation has not been clearly established. However, a study by Casadei et al. (2011) documented a sixfold increase in pancreatic cancer in families of breast cancer probands with *PALB2* mutations. In all cases, *BRCA1* and *BRCA2* mutations had previously been ruled out. Although breast cancer and pancreatic cancer are often observed together in families, *PALB2* mutations have been identified in familial pancreatic cancer families testing negative for *BRCA1* and *BRCA2* mutations in which breast cancer has not been observed (Jones et al., 2009).

PALB2 and Other Cancers and Conditions

Although primarily responsible for an increased risk of breast cancer and pancreatic cancer, *PALB2* mutations may be responsible for an increased risk of other cancers as well. Some suggestion exists that *PALB2* may be associated with ovarian cancer because *PALB2* mutations have been identified in *BRCA1* and *BRCA2* mutation-negative families with histories of breast cancer and ovarian cancer. Casadei et al. (2011) found that ovarian cancer was more common in family members of *PALB2* mutation carriers as compared to families of non-*PALB2* mutation carriers. However, the difference was not significant. A study by Antoniou et al. (2014) determined that the relative risk of ovarian cancer in *PALB2* mutation carriers is 2.31%, but concluded that the increase was nonsignificant and required further investigation. *PALB2* has also been considered as a possible melanoma susceptibility gene because of the interaction between *PALB2* and *BRCA2*, as well as the increased risk of melanoma in *BRCA2* mutation carriers. However, a study by Aoude et al. (2014) did not find a causative relationship between *PALB2* mutations and melanoma.

Biallelic mutations, or mutations that occur in both copies of the gene, in *PALB2* can cause Fanconi anemia and are associated with early childhood cancers. *PALB2* was first characterized clinically in Fanconi anemia (Casadei et al., 2011). Fanconi anemia type N occurs when a person inherits two mutated copies of the *PALB2* gene. This all but eliminates *PALB2* activity in the cell and, therefore, increases the person's risk of developing several childhood cancers, including Wilms' tumor and medulloblastoma. Fanconi anemia is also associated with bone marrow suppression and the subsequent anemia that ensues (National Library of Medicine, 2007).

Implications for Patient Care

Clinical testing is available through a variety of genetic laboratories and may be considered in familial breast and pancreatic cancer families in which *BRCA1* and *BRCA2* or other high-penetrance genetic mutations have been ruled out. However, widely accepted guideline support for *PALB2* testing and for the management of *PALB2* mutation carriers is lacking. Management strategies, such as increased surveillance, that are applied to other conditions that similarly increase breast cancer and pancreatic cancer risk can be used.

In 2007, the American Cancer Society developed recommendations for increased breast cancer surveillance for women deemed at high risk for developing the disease, including those with a greater than 20%–25% lifetime breast cancer risk (Saslow et al., 2007). Increased breast cancer surveillance recommendations include annual mammography, annual breast magnetic resonance imaging (MRI), clinical breast examinations every 6–12 months, and breast self-awareness (National Comprehensive Cancer Network, 2014).

In 2010, the International Cancer of the Pancreas Screening Consortium developed and published consensus-driven recommendations for the management of patients at increased risk for familial pancreatic cancer. In the document, several risk factors were outlined, including a significant family history of the disease and a variety of specific genetic mutations. Carriers of *PALB2* mutations with one or more affected first-degree relatives with pancreatic cancer were recommended for screening. Pancreatic cancer screening should include endoscopic ultrasound (EUS), as well as MRI or magnetic resonance cholangiopancreatography, although the age at which to begin and the screening frequency were not clarified (Canto et al., 2013). Evidence shows that pancreatic cancer screening may be useful in the identification of early pancreatic lesions. Verna et al. (2010) reported that EUS and MRI detected early neoplastic pancreatic lesions in 12% of individuals with family histories of pancreatic cancer involved in the study.

Low- to Moderate-Penetrance Genes

- *CHEK2*
- *PALB2*
- *ATM*
- *BRIP1*
- *RAD50*
- *RAD51C*
- *RAD51D*
- *NBN*
- *BARD1*
- *NF1*
- *BMPR1A*
- *MRE11A*
- *SMAD4*
- *XRCC2*
- *ABRAXAS*

High-Penetrance Genes

- *BRCA1*
- *BRCA2*
- *PTEN*
- *TP53*
- *STK11*
- *CDH1*
- *MLH1*
- *MSH2*
- *MSH6*
- *EPCAM*
- *PMS2*
- *APC*
- *p16/CDKN2A*
- *PRSS1*

Figure 1. Selected List of Genes Associated With Breast Cancer and/or Pancreatic Cancer

Note. Based on information from Ambry Genetics Corp., 2014; Apostolou & Fostira, 2013; Canto et al., 2013; GeneDx, 2014; Myriad Genetics, 2014; National Cancer Institute, 2014.

Conclusion

PALB2 is a moderate-penetrance breast and pancreatic cancer susceptibility gene that confers a small but significant risk for the development of cancer in families. A tremendous amount of research still needs to be accomplished to further clarify the prevalence and the cancer risks associated with *PALB2* mutation carriers. As studies continue and more knowledge is attained, evidence-based guidelines for screening and management likely will be developed. In the interim, familial breast cancer and pancreatic cancer families must be evaluated thoroughly. Testing for moderately penetrant genetic mutations, such as *PALB2*, should also be considered in an effort to cultivate individualized management plans and provide information and answers to families at risk. *PALB2* testing may also prove important in the future as targeted therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors, are being developed; in these therapies, the homologous recombination

repair pathway is an essential component of drug development and predicted treatment response.

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Key words: breast cancer; pancreatic cancer; genetics; inherited cancer risk

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