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 *PALB2* 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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