

# The risk of breast cancer due to *PALB2* gene mutations

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## Abstract

Mutations in the *PALB2* gene are a predisposing factor to the development of breast cancer. *PALB2* gene mutations have been detected in most breast cancer populations, but due to the rarity of their occurrence and the lack of information about their penetrance, they present a challenge when providing genetic counseling for families that have a history of breast cancer. The occurrence rate of *PALB2* mutations ranges from 0.1% to 1.5% depending on the population. Despite the rarity of this mutation, information on the status of *PALB2* mutations in carriers of this gene, as well as for members of their families who may be carriers, is of the utmost importance for clinical reasons, because these mutations are a high risk factor for breast cancer. There is a defined incidence of *PALB2* mutations in patients with breast cancer and negative *BRCA1/BRCA2*. People with a high risk of breast cancer and negative *BRCA1/BRCA2* should be tested for *PALB2* mutations.

**Key words:** *PALB2*, breast cancer, gene mutation

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*PALB2* is a protein that forms a complex with protein *BRCA2*. It functions as an assistant to the *BRCA1* and *BRCA2* proteins in repairing DNA damage, which is part of the body's defense against the development of cancer.<sup>1,2</sup> The *PALB2* protein supports the stabilization of the *BRCA2* protein and specifies its location in a cell's nucleus after DNA damage.<sup>1,3</sup> *BRCA1* regulates *BRCA2* and *PALB2* transfer to the damaged DNA. Cells with diminished *PALB2* protein have disruptions in the *BRCA1/BRCA2*-dependent DNA repair path.<sup>4</sup>

Mutations in the *PALB2* gene are a predisposing factor to the development of breast cancer. It has been suggested that *PALB2* mutations, being a high risk factor for breast cancer, are heterozygous germline mutations.<sup>5–7</sup> *PALB2* gene mutations have been detected in multiple breast cancer populations; however, due to the rarity of their occurrence and the lack of information about their penetrance, they present a challenge when providing genetic counseling for families that have a history of breast cancer.<sup>8</sup> Zhang et al. conducted a meta-analysis with the aim of determining the dependencies between the most common mutations of the *PALB2* gene and the risk of breast cancer and concluded that mutations in the *PALB2* gene are associated with an increased risk of breast cancer.<sup>2</sup>

## The risk of breast cancer among different populations of women with *PALB2* mutations

The risk of developing breast cancer in women with *PALB2* mutation has been studied by researchers around the world. Dansonka-Mieszkowska et al. conducted research among Polish women.<sup>3</sup> Their study shows that *PALB2* mutations lead to breast cancer in approximately 0.6% of all cases, and they state that the results of other studies are on the same level.<sup>7,9–12</sup> Dansonka-Mieszkowska et al. also discovered a novel deletion in the *PALB2* gene.<sup>3</sup>

*PALB2* mutations are mainly related to familial breast cancer.<sup>3,7,11,12</sup> Haanpää et al. note that over the past few years, it has become clear that women with a heterozygous germline mutation in the *PALB2* gene are exposed to an increased risk of breast cancer.<sup>5</sup> According to those authors, among Finnish women the percentage of cases of breast cancer with the occurrence of a *PALB2* mutation is 1%. Bogdanov et al. conducted a study on the occurrence of *PALB2* mutations in a population of Russian and German women, and reported that a mutation was detected in 4 out of 203 patients, which is 2%.<sup>13</sup> Those authors concluded that *PALB2* gene mutations contribute a small percentage to the development of bilateral breast cancer in Russia and Germany. The fact that 2 out of 4 mutations identified in the study were recurrences justifies special screening of cancer patients in Eastern and Central Europe.

The studies mentioned above do not specify the extent of the risk of breast cancer due to a mutation of the *PALB2* gene, which remained unclear until 2014. In 2011, Casadei et al. published a study in which they estimated the risk of breast cancer in carriers of *PALB2* mutations; they reported that the risk is 2 to 3 times higher for women 55 years of age and 3 to 4 times higher for women 85 years of age.<sup>14</sup> In 2013, Nikkila et al. estimated that the risk of developing breast cancer is 6 times greater in cases of *PALB2* heterozygosity.<sup>15</sup> In 2014 Antoniou et al. succeeded in determining the specific risk of breast cancer in individuals with a mutation of the *PALB2* gene.<sup>16</sup> They tested 362 women from 154 families and found that compared to the general population, the risk of breast cancer in people up to 40 years of age with *PALB2* mutation is 8 to 9 times higher; in individuals between 40 and 60 years of age the risk is 6 to 8 times higher; while in people over the age of 60 the risk is 5 times higher. In addition, the authors estimated that the absolute risk of breast cancer in women up to 70 years of age with *PALB2* mutations ranges from 33% for women without family histories of breast cancer to 58% for women with family histories. It is interesting that the risk of breast cancer is higher in women under the age of 40 years and declines in subsequent age groups.

Interestingly, *PALB2* mutations have not been observed in the population of Iceland<sup>17</sup>, but they have been detected in most of the populations studied to date. The incidence is low, ranging on average between 1–4%. In some populations, recurrent *PALB2* mutations have been identified; the risk of their occurrence is comparable to the risk of *BRCA* mutation occurrence.<sup>18</sup>

## Comparing *PALB2* mutation occurrence in women with familial breast cancer and in sporadic cases

As Smith wrote, "Mutations in the *PALB2* gene are responsible for a small but significant percentage of cancer risks in [familial breast cancer]".<sup>19</sup> Tischkowitz et al. conducted a study to determine the risk of breast cancer in women whose relatives had *PALB2* mutations and in those whose family members did not carry this mutation; the results indicated that the risk was higher in the women in the first group.<sup>20</sup> In the study by Haanpää et al. mentioned earlier, 3.6% of 56 patients at high risk for breast cancer had *PALB2* mutations.<sup>5</sup> Those authors believe that mutations are more common in women with familial breast cancer. Based on this, they assert that *PALB2* gene mutation testing should be incorporated into routine practice in Finland; they also suggest that *PALB2* gene mutations are common enough that routine testing would be valuable worldwide. Janatova et al. found 16 cases of *PALB2*

mutation in a total of 409 women from the Czech Republic, and a high incidence (5.5%) occurred in women with a family history of breast cancer.<sup>21</sup> Hartley et al. conducted a study that confirmed that while *PALB2* mutations are rare, an increase in the number of cases of breast cancer in a family increases the likelihood of *PALB2* mutations as well.<sup>8</sup> Women with 3 or more cases of breast cancer in the family have a 2.6% likelihood of having a *PALB2* mutation. Extensive research was carried out by Southley et al. on Australian women, both with and without breast cancer.<sup>22</sup> They selected women in whose families *PALB2* mutations occurred as well as those without *PALB2* mutations. The objective of the study was to assess the occurrence rate and penetrance of these mutations in Australian women. No *PALB2* mutations were found in the healthy women. Eight women (1%) from the group with breast cancer or *PALB2* mutations in the family also had *PALB2* mutations; among women with breast cancer and no family history of *PALB2* mutations, *PALB2* mutations occurred in 5 (0.4%) cases. The authors concluded that *PALB2* protein tests are justified when women are carriers of the *BRCA1* and *BRCA2* genes. In the case of women and family members who are carriers of the *PALB2* gene it is sufficient to provide reasonable prevention, screening and clinical management. Heikkinen et al. conducted a study in southern Finland in which they found *PALB2* mutations in 19 out of 947 women (2%) with familial breast cancers and in 8 out of 1274 (0.6%) women with sporadic breast cancers.<sup>23</sup> The authors also noted that carrying a *PALB2* mutation is connected with a shorter lifespan, especially in patients with familial breast cancer. However, Fernandes et al. conducted a study showing that 69 out of 1479 patients (4.7%) were carriers of *PALB2* mutations; 1.05% of the patients with familial breast cancer had *PALB2* mutations, whereas among the low-risk patients the percentage amounted to 0.38%.<sup>24</sup>

## ***PALB2* mutations with negative *BRCA1* and *BRCA2***

Many researchers have taken an interest in the question of *PALB2* mutations without *BRCA1* and *BRCA2* mutations and the possibilities of introducing tests for *PALB2* into routine practice. Blanco et al. investigated the incidence of mutations in *PALB2* patients with breast cancer and negative *BRCA1/BRCA2*, both with and without a history of pancreatic cancer in the family.<sup>25</sup> Those authors found that the frequency of *PALB2* mutations in their study group was 1.5%. According to them, previous studies indicated that the frequency of *PALB2* mutations in breast cancer families ranges from 0%<sup>26,27</sup>, through 2.1%<sup>28</sup> up to 4.8%<sup>29</sup> Haanpää et al. stated that people with high risk of breast cancer and negative *BRCA1/BRCA2* should be tested for *PALB2* mutations.<sup>5</sup> According to them, these mutations are common enough

that a single test for people with a high risk of cancer and negative *BRCA1/BRCA2* should be implemented around the world. Hartley et al. have the same opinion, considering *PALB2* mutations a “small but significant” number of all mutations in women in breast cancer families with negative *BRCA1/BRCA2*.<sup>8</sup> Janatova et al. also pointed out that *PALB2* gene mutation analysis is recommended for patients with hereditary breast cancer when *BRCA1* and *BRCA2* are negative, because of high frequency of *PALB2* mutations occurring in those patients.<sup>21</sup>

## **Another study**

Teo et al. compared cancer morphology with and without *PALB2* mutations, evaluating 28 cases of women with breast cancer with *PALB2* mutations and 828 cases without *PALB2* mutations, among which 58 women with breast cancer had *BRCA1* and *BRCA2* mutations.<sup>6</sup> Based on the results, the authors concluded that cancers with *PALB2* mutations demonstrate sclerosis and that this distinguishes them from other groups of cancers.

## **Summary**

*PALB2* mutations are rare; their occurrence rate ranges from 0.1% to 1.5% depending on the population.<sup>3,6,7,9,10,13,15,21</sup> Despite the rarity of these mutations, information on the status of *PALB2* mutations in carriers of this gene, as well as for the members of their families that may be carriers, is of the utmost importance for clinical reasons, because these mutations are a high risk factor for breast cancer. Identifying carriers of *PALB2* mutations means appropriate tests can be conducted and appropriate treatment can be selected. Among those therapies are some that allow repair dysfunctions of homologous DNA to be pinpointed.<sup>30</sup> Because of the risk of breast cancer recurrence in patients with *PALB2* mutations<sup>20</sup>, awareness of the presence of these mutations can lead to earlier detection of cancer and reduce the required treatment. The introduction of integrated *PALB2* testing to clinical practice is still a work in progress, and identifying carriers of *PALB2* mutations can help to facilitate this process.<sup>6</sup> Determination of *PALB2* status is also important because of cases of negative *BRCA1* and *BRCA2* in women with diagnosed breast cancer.

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