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# Pancreatic cancer; Pathogenic mutation of the BRCA1 gene

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**ABSTRACT**

Pancreatic cancer, although rare, ranks seventh in terms of cancer-related mortality, with a low five-year survival rate after diagnosis. Globally, it accounts for approximately 1.6-1.2% of cancer cases. In Mexico, it is also a significant cause of mortality, ranking sixth or seventh.

This type of cancer tends to occur more frequently in individuals over the age of 71, but there has been a marked increase in its incidence among younger patients. One of the most common risk factors is a family history of the disease, and a close relationship has often been noted between pancreatic cancer and newly diagnosed diabetes mellitus.

The primary objective of this study is to understand pancreatic cancer prevention in patients carrying the pathogenic mutation of the BRCA1 gene and explore innovative therapies. Both the BRCA1 and BRCA2 genes have been associated with various cancer types, such as breast, ovarian, and pancreatic cancer. In the case of the latter, it is believed that these genes may contribute to cancer by causing DNA damage.

The diagnosis of pancreatic cancer is based on imaging studies and biopsies. Furthermore, various treatment options are examined, including neoadjuvant therapies and potential therapeutic approaches.

**KEYWORDS:** Pancreatic cancer, BRCA 1, Pancreatic cancer treatment, Cancer diagnosis

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## INTRODUCTION

Pancreatic cancer is a neoplasm that presents complications such as weight loss, jaundice, and low bone density. These complications may arise due to energy loss to the tumor, treatment-related side effects, or direct pressure on the stomach, bile ducts, or intestines. Globally, it has an incidence rate of approximately 1.6-1.2%, and in Mexico, it ranks sixth in women and seventh in men in terms of mortality [1, 8].

The presentation typically occurs after the age of 71 in the United States of America; however, there has been an observed increase in younger patients. The incidence varies depending on the age of presentation, with 4.34% of cases being among those aged 25 to 29 years, 2.47% among those aged 30 to 34 years, and 0.77% among those aged 45 to 49 years. The rising pancreatic cancer incidence is directly related to the increasing prevalence of obesity since obesity and smoking contribute as risk factors in 5 to 10% of cases.[1,4]

Genetic alterations play a role in the development of pancreatic adenocarcinoma, with mutations in the BRCA1 gene being one of the most significant in this pathology. Additionally, these mutations have been associated with other tumors such as breast and ovarian cancer.[1]

The BRCA1 gene plays a regulatory role in the S and G2 phases of the cell cycle, where it oversees faithful homologous recombination. When a mutation occurs in this gene, or in BRCA2, it can lead to a break in the double helix of DNA [2]. The prevalence of this mutation has been reported to be in the range of 0.1% to 0.2% of the worldwide population, which confers a 3.5 to 6.5 times higher risk of developing pancreatic cancer [1].

Just as the guidelines of the North American Society for Gastrointestinal Endoscopy recommend in section 3b, patients with a pathogenic mutation in the BRCA1 gene should undergo imaging studies to diagnose pancreatic cancer in the earliest stage as possible [3].

Survival of more than five years has been demonstrated in patients who underwent mutagenic BRCA1 gene resection therapy, showing a dramatic improvement compared to other conventional therapies, which have demonstrated a lower survival rate. This opens up the possibility for further research into the demonstrated benefits [1, 7].

In conclusion, there is a need for the further investigation of innovative treatment of pancreatic cancer, which would contribute to the understanding of pancreatic

cancer prevention in patients with pathogenic BRCA1 mutations.

## DEFINITION

Pancreatic cancer is one of the rarest but, above all, one of the deadliest cancers worldwide, with a survival rate of less than 5 years after diagnosis [3].

It occurs when cells start to grow uncontrollably, mutating in their DNA and losing their proper function. It comprises several histologic types, with pancreatic adenocarcinoma being the most common type, accounting for about 90% of cases [3].

Pancreatic cancer risk factors include advanced age, family history, smoking, obesity, alcohol consumption, pancreatitis, and diabetes. Conversely, it has been observed that allergies and asthma serve as a protective factor level against pancreatic cancer. This is believed to be because people with immune systems that are constantly active can develop greater tumor immunity due to their levels of IgE [4].

There are certain genes that are considered high-risk factors associated with pancreatic cancer. BRCA1 and BRCA2 are tumor suppressor genes that function in response to DNA damage and are responsible for producing proteins to repair such damage. It is possible for these mutated genes to be inherited from parents carrying this variant, thereby increasing the likelihood of inheriting some form of cancer [1].

There are several types of cancers associated with mutations in the BRCA1 and BRCA2 genes, including breast, ovarian, and pancreatic cancer. BRCA1 and BRCA2 code for tumor suppressor proteins, analogously of 220 and 384 kDa, which play a significant role in the DNA damage response (DDR) pathway. These damages are characterized by single-strand breaks (SSB) and double-strand breaks (DSB), which activate the DDR pathway with the aim of repairing the damaged site, either by halting the cell cycle or leading the cells to undergo apoptosis if the damage is irreversible [2].

## EPIDEMIOLOGY

The prevalence is slightly higher in men than in women and slightly higher in African Americans than in Caucasians. It is most commonly diagnosed between the ages of 65 and 74, with an average age of 70 years. The most important genes in this type of cancer are BRCA1, BRCA2, and ATM [9, 6].

In Japan, numerous studies on cancer were conducted, including skin, larynx, bladder, rectal/urinary tract, stomach, liver, breast, uterine body, colon, rectum, thyroid, mouth/pharynx, ovary, lung, esophagus, gallbladder/biliary tract, and pancreas. Based on the results obtained, statistics were compiled, indicating that the survival rate for pancreatic cancer is the lowest among the various types of cancer studied. As mentioned earlier, a five-year survival rate for this cancer was found, with adenocarcinoma being the most common type, representing 90% of all diagnosed pancreatic cancers [6, 4].

Globally, pancreatic cancer is the twelfth most common cancer but ranks seventh in terms of cancer-related deaths [4].

The symptoms of pancreatic cancer generally begin to appear in the advanced stage of the disease and depend on the location of the tumor. More than two-thirds of cases arise in the head of the pancreas (in the duodenal curve). Symptoms that may be present when the tumor is in this location include weight loss (92%), jaundice (82%), abdominal pain (72%), anorexia (64%), pale stools (63%), and clay-colored stools (62%), which are caused by bile duct obstruction [9].

If the cancer occurs in the body or tail of the pancreas, patients may experience unexplained weight loss, vague abdominal or mid-back pain, nausea, anorexia, and early satiety [9].

Regarding physical examination, a detailed abdominal examination should be performed, looking for any pain, abdominal distension, or palpable masses. In the early stages, patients often remain asymptomatic, but those in advanced stages exhibit the previously mentioned symptoms. Recurrent and migratory venous thromboembolism, hepatomegaly, or ascites can also occur [9].

It is also important to mention that patients diagnosed with new-onset diabetes mellitus have been identified as a high-risk group. This is because there is a strong association between new-onset diabetes and pancreatic cancer, as nearly half of the patients diagnosed with this type of cancer already have a diabetes diagnosis at that time. Furthermore, 75% to 88% of these cases received their diabetes diagnosis in the 24 months preceding their pancreatic cancer diagnosis [9].

There is evidence suggesting that new-onset diabetes mellitus carries a 4 to 8 times higher risk of developing pancreatic cancer within the first 3 years of meeting the diagnostic criteria for diabetes. This risk increase is significant in these patients compared to those with common cancers. Furthermore, it is also suggested that new-onset diabetes develops as a secondary consequence of the tumor-secreted product and not as a result of the tumor infiltration effects [9].

A study by "Pannala et al" found that the incidence of diabetes in patients with pancreatic cancer is independent of the tumor location or stage [9].

Epidemiological studies have shown that diabetes is a risk factor for at least 3 years, with a relative risk between 1.5 and 2.0.[9]

Studies have found that diabetes may be related to pancreatic cancer in 47% of cases, while another study found that 68% of patients with pancreatic cancer also have diabetes. It is believed that hyperinsulinemia, along with elevated proinflammatory levels, may also contribute to this elevated risk [9].

Only a small portion of the pancreas is involved when diabetes develops in patients with pancreatic cancer, suggesting a pathophysiological mechanism that involves a simple loss of beta cells [9].

**DIAGNOSIS**

An early diagnosis is associated with a better prognosis. When the disease is detected in patients who do not present any symptoms, they have a better chance of survival and are more likely to undergo surgical intervention with the possibility of completely removing the cancer. However, pancreatic cancer is often diagnosed in advanced stages in the majority of patients [3].

The most commonly used tumor marker for diagnosis is CA 19-9. It is used to monitor therapeutic response, but its utility in diagnosing cancer in early stages is limited due to certain constraints, as it is considered to be not very sensitive and specific [5].

This test measures the CA 19-9 protein in the blood. When it is found in elevated levels, it can be a positive alarm sign for pancreatic cancer. However, it is not considered very sensitive and specific on its own, as it can also be a sign of other conditions such as gallstones, pancreatitis, colorectal cancer, or cirrhosis, among others. Therefore, it is necessary to accompany it with other studies to make an accurate diagnosis [5].

To diagnose pancreatic cancer, several steps are involved. First, the patient's family, medical, and non-medical history are reviewed. Then, a physical examination is conducted to look for signs of the disease. Blood samples are taken to check for the CA19-9 antigen, and tests are performed to diagnose and stage the tumor. Imaging techniques are used to detect the location of neoplasms at any stage, and in case surgical procedures are needed, they provide better precision for tumor delineation [5].

A computed tomography (CT) scan is often one of the most commonly used methods when pancreatic cancer is suspected. It helps determine if there is a tumor, its size, and whether it can be removed or if it affects other parts of the body [5].

The diagnosis is confirmed through a biopsy, where a sample of tissue is taken and analyzed, either with a fine or thick needle. Pathology examines whether there are cancerous cells present [5].

**TREATMENT**

The use of platinum-based agents in patients with gBRCA (BRCA gene) 1 and 2 with PDAC (pancreatic ductal adenocarcinoma) is based on their ability to induce cytotoxicity by forming DNA adducts, which create cross-links between DNA strands and interstrands. These complexes interfere with the regular replication and transcription of DNA, activating DNA damage response (DDR) pathways, base excision repair (BER) pathways, and homologous recombination (HR).

The effectiveness of this treatment in patients with germline homologous recombination deficiency (gHRD) has been tested in breast and ovarian cancers. Several studies have shown anti-tumor activity of platinum-based agents in patients with gBRCA 1-2 PDAC, with observed improvements in comparison to other patients [2].

The study suggests that this type of treatment may improve the median overall survival (mOS) in 22 patients with stage III-IV PDAC and gBRCA 1-2 compared to 21 patients with gBRCA1-2 treated without platinum-based regimens. Despite the limitations in the aforementioned studies, gBRCA 1-2 serves as a predictive marker for the response in patients with advanced-stage PDAC and inoperable PDAC patients [2].

In another phase III trial, the POLO trial, 247 metastatic gBRCA 1-2 patients receiving initial platinum-based treatments were studied. The result was a disease control rate (DCR) of 82% in patients after 16 weeks. In another phase II study, 50 patients with gBRCA 1-2/Gpalb2 (palb2 gene) and stage III-IV PDAC were treated with low doses of gemcitabine (600 mg) and cisplatin (25 mg) on days 3 and 10 every 21 days, with or without veliparib. In both of the aforementioned studies, it was concluded that the DCR in patients with PV (platinum-based regimens) is higher compared to the population not treated with gemcitabine plus nab-paclitaxel [2].

Preclinical data show that cisplatin and oxaliplatin, despite being structurally distinct from each other, are capable of forming the same types of adducts at the same DNA sites. Additionally, DNA adducts are recognized by cellular proteins such as mismatch recognition proteins and damage recognition proteins, which bind to cisplatin adducts with higher affinity than to oxaliplatin adducts. Therefore, this difference may result in different platinum activity [2].

Furthermore, oxaliplatin exhibits lower activity due to its cytotoxicity, which is mitigated by ribosome biogenesis stress induction, leading to an unfavorable scenario for synthetic lethality. Despite the aforementioned points, there have been no direct comparisons between these two drugs in gHRD patients, making it impossible to draw a definitive conclusion [2]

However, the recommended standard treatment for gBRCA 1-2 patients remains controversial. The previously mentioned POLO trial reported a response rate of approximately 50%, with more than 80% of patients being treated with regimens derived from FOLFIRINOX, compared to 65-67% of patients treated with cisplatin in another O'Reilly trial [2]

*Other chemotherapeutic agents.*

Alkylating agents like cyclophosphamide, which are used in breast and ovarian cancer, have shown potential for increasing efficacy in gBRCA1-2 patients in recent trials [2].

In a phase II trial called INFORM, comparing cisplatin with cyclophosphamide plus doxorubicin as neoadjuvant treatment in gBRCA1-2 breast cancer patients, the combination of single-agent cisplatin was found to be superior [2].

The preclinical data on alkylating agents like chlorambucil and temozolomide show an increase in antitumor activity in different tumor cell lines and xenografts with deficient BRCA1-2 presence. Chlorambucil was also studied in pancreatic cancer cell lines, BRCA2-deficient Capan 1, and BRCA2 wild-type MiaPaca 2, showing high viability activity in samples treated with cisplatin and PARP inhibitors (PARPi) [2].

Likewise, temozolomide showed a high in vitro antitumor effect in BRCA1-deficient glioblastoma cell lines with p53 expression. Improved activity was demonstrated in the combination of temozolomide with PARPi independent of BRCA1. Also, in patients with Ewing's sarcoma, further improvement was observed with the addition of irinotecan [2].

Topoisomerase I inhibitors derived from camptothecin induce antitumoral activity in breast cancer PDX with gBRCA/gBRCAness mutations, triggering SSD induced by topoisomerase I inhibition [2].

Furthermore, the combination of irinotecan and olaparib showed synergy in colon and gastric cancer cell lines with BRCA1-2 deficiency, as well as in patient-derived xenografts treated with cisplatin and PARPi [2].

Mitomycin C, being an antitumor antibiotic, has demonstrated irreversible damage through DSB (double-strand break) in monoallelic and biallelic xenografts of gastric and colon cancer with gBRCA2, thus promoting cellular apoptosis by activating p53. This antibiotic has shown a decrease in CA 125 serum biomarkers. [2]

Trabectedin, a semi-synthetic alkaloid that binds to the minor groove of DNA and forms DNA adducts, appears to exert significant activity in gHRD tumors. It's worth noting that although trabectedin is used as a salvage therapy in patients with PDAC, it has shown an early decrease in citrines and quinolines during treatment. Currently, there is only a limited amount of reports on cases that have used chemotherapy drugs other than platinum in gHRD patients. [2]

*Role of PARPi alone or in combination with chemotherapy in gBRCA1-2 PDAC treatment.*

As mentioned earlier, PARPi-2 plays an important role in HR (homologous recombination) repair and enzyme guidance in gBRCA1-2 tumors, which can induce an accumulation of unrepaired SSBs (single-strand breaks). Currently, there are at least 6 different PARPi in clinical development at various stages, with different functions for PARP trapping inhibition. The development of PARPi is significant because it is the standard of care in BRCA-related cancers. However, its role in PDAC disease and maintenance therapy, in combination with other therapies, has only recently been explored, and much remains unknown. [2]

PARPi as first-line treatment, while veliparib has lower trapping activity compared to other PARPi, it has been the most studied in advanced PDAC, even with discouraging results. Currently, talazoparib, a next-generation PARPi, is under investigation. It has preclinical data showing catalytic inhibition and a high PARP trapping potential, being 100 times greater than other PARPi. [2]

*Radiation therapy plays a role in cancer treatment.*

Ionizing radiation creates antitumor activity by producing oxygen-free radicals, which are harmful to DNA. Preclinical studies show that 1 Gy of radiation induces approximately 1000 SSB (single-strand breaks) and 35 DSB (double-strand breaks) in cellular DNA. However, the effectiveness of radiation therapy is also influenced by tissue-specific radiosensitivity. [2]

BRCA1-2 deficient cancer cells exhibit greater sensitivity to radiation therapy compared to wild-type cells. It has been shown that BRCA2-mutated cells are more responsive to radiation therapy than BRCA2-competent cells, even when PARPi is administered at very low doses. [2]

In other treatments such as immunotherapy, they have not shown good results in PDAC. This is because the excessive infiltration of immunosuppressive cells into the tumor environment is responsible for the cold immunity of PDAC. Although this treatment has a poor prognosis, the combination of PARPi and immunotherapies in patients with gBRCA1-2 has scientific foundations, which mention that the tumor mutation burden and inflammatory activity are related to DDR deficiency. [2]

*Tumor resistance.*

Tumor resistance occurs with platinum-based drugs like the previously mentioned PARPi, and it is more common in breast and ovarian cancers with gBRCA1-2 mutations. [2]

Acquired or secondary resistance occurs in 1/3 of patients with gBRCA1-2 PDAC and is attributed to prolonged exposure to platinum or PARPi, leading to selective pressure on resistant cell clones.

However, primary mutation is considered a fallacy because single nucleotide reversion mutations (SNVs) involve another nucleotide, with or without deletions. These types of mutations or alterations affect the repair process and can result in reversion mutations. Secondary mutations are not influenced by treatment, although there are exceptions that may be enriched in carriers of gBRCA2 treated with PARPi compared to those treated with platinum. The development of secondary mutations is induced by the repair mechanism carried out by gBRCA1-2 mutation during replicative stress. [2]

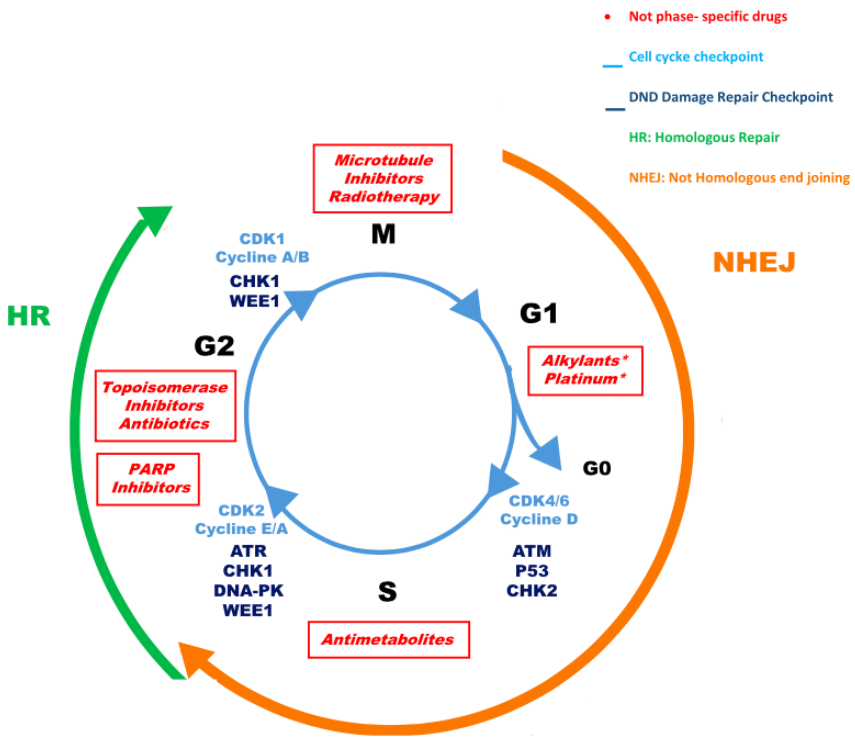


**Fig. 2.** Cell Cycle and DNA Repair Mechanisms. Not phase- specific drugs, Cell cycke checkpoint, DND Damage Repair Checkpoint, HR: Homologous Repair, NHEJ: Not Homologous end joining.

* Marina Macchini, Federico Centonze, Umberto Peretti, Giulia Orsi, Anna Maria Militello, Maria Maddalena Valente, Stefano Cascinu, Michele Reni, Treatment opportunities and future perspectives for pancreatic cancer patients with germline BRCA1-2 pathogenic variants, Cancer Treatment Reviews, Volume 100, 2021, 102262, ISSN 0305-7372.

## DISCUSSION

The aim of this research is to understand the role of the BRCA1 gene mutation in pancreatic cancer, as it is a relatively rare cancer in clinical practice but has a very high mortality rate. It is estimated that the survival rate for this condition is 5 years, with mortality rates in Mexico ranking sixth in women and seventh in men, typically occurring in individuals around 70 years of age. However, the age range for diagnosis is decreasing, with more and more young patients being diagnosed with pancreatic cancer.

As mentioned earlier, the research initially focused on the BRCA1 gene, but upon investigating various articles, it became clear that the BRCA2 gene also plays a role in the mentioned cancers. It was found that mutations in these two genes lead to the production of proteins that damage DNA, causing single-strand or double-strand breaks.

Throughout this research, it became evident that there are various treatment methods, some more effective than others. Platinum-based treatment is the one with the most evidence of its effectiveness in treating this type of cancer.

This study highlights the importance of understanding the role of mutations in the BRCA1 and BRCA2 genes in pancreatic cancer, as these mutations can significantly increase the risk of developing this disease. Additionally, pancreatic cancer is highly lethal and is usually diagnosed in advanced stages, making it crucial to research and develop effective treatments to improve survival rates.

It is mentioned that platinum-based treatments, such as cisplatin and oxaliplatin, have shown anti-tumor activity in patients with mutations in the BRCA1 and BRCA2 genes. However, it is also noted that there is still controversy over which of these treatments is more effective, and further research and clinical trials are needed to determine the most appropriate approach.

In addition to platinum-based treatments, other options are explored, such as PARP inhibitors and other chemotherapeutic agents, which may also have benefits for patients with BRCA mutations.

## CONCLUSIONS

In conclusion, pancreatic cancer is currently a risk not only for older adults but also increasingly affecting younger patients. Therefore, it is essential to continue searching for ways to achieve early and timely diagnosis, along with effective treatment. Currently, there is no highly effective treatment for pancreatic cancer, with platinum-based therapy being one of the approaches that come closest to improving patients' quality of life.

Regarding the relationship with BRCA1, it is more frequently associated with breast and ovarian cancer. This

article focused on understanding the connection between the occurrence of breast and ovarian cancer with pancreatic cancer.

Similarly, a close relationship was found with new-onset type 2 diabetes mellitus, which has been identified as a risk factor for developing pancreatic cancer. This connection is particularly relevant in the context of the obesity and type 2 diabetes mellitus pandemic. It opens the door to future research to investigate whether there is a correlation between young patients presenting this pathogenic mutation and the development of pancreatic cancer.

In summary, pancreatic cancer remains a challenging and deadly disease, emphasizing the need for ongoing research to improve early detection and treatment options. Additionally, understanding the genetic factors, such as BRCA mutations, that contribute to pancreatic cancer can aid in identifying individuals at higher risk and potentially developing targeted therapies in the future.

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