Review Article

The Role of BRCA2 Mutation Status as Diagnostic, Predictive, and Prognosis Biomarker for Pancreatic Cancer

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Pancreatic cancer is one of the deadliest cancers worldwide, and life expectancy after diagnosis is often short. Most pancreatic tumours appear sporadically and have been highly related to habits such as cigarette smoking, high alcohol intake, high carbohydrate, and sugar consumption. Other observational studies have suggested the association between pancreatic cancer and exposure to arsenic, lead, or cadmium. Aside from these factors, chronic pancreatitis and diabetes have also come to be considered as risk factors for these kinds of tumours. Studies have found that 10% of pancreatic cancer cases arise from an inherited syndrome related to some genetic alterations. One of these alterations includes mutation in *BRCA2* gene. *BRCA2* mutations impair DNA damage response and homologous recombination by direct regulation of RAD51. In light of these findings that link genetic factors to tumour development, DNA damage agents have been proposed as target therapies for pancreatic cancer patients carrying *BRCA2* mutations. Some of these drugs include platinum-based agents and PARP inhibitors. However, the acquired resistance to PARP inhibitors has created a need for new chemotherapeutic strategies to target *BRCA2*. The present systematic review collects and analyses the role of *BRCA2* alterations to be used in early diagnosis of an inherited syndrome associated with familiar cancer and as a prognostic and predictive biomarker for the management of pancreatic cancer patients.

1. Introduction

In 1994, *BRCA2* (breast cancer gene 2) was located in chromosome 13ql2-13 by the group led by Wooster et al. [1]. Transmission of this gene follows an autosomal dominant pattern with incomplete penetrance [2]. Soon thereafter, *BRCA2* was reported as a tumour suppressor gene based on evidence of loss of heterozygosity in 7 out of 8 familial breast cancers [3]. Subsequently, *BRCA2* was associated with high-risk breast and ovarian cancer with a large component of heritability [4–7], although the risk for ovarian cancer due to *BRCA2* is much lower than the risk associated with *BRCA1* [8].

Only one year after this gene was discovered, the association between *BRCA2* and pancreatic cancer was assessed by Schutte et al. [9]. It was found that pancreatic cancer appeared in some individuals with a history of familial breast cancer associated with *BRCA2* alterations [10]; thus, it was estimated that 10% of cases of pancreatic cancer have an underlying inherited component [11, 12].

Worldwide pancreatic cancer incidence has increased from 185,000 in the 1980s [13] to 227,000 cases per year in 2014 [14]. In 2007, the highest incidence of pancreatic cancer was in the Baltic countries and central and eastern Europe. In northern European countries and the UK, this cancer has risen over most recent years and is rising in countries of southern, central, and eastern Europe [15]. It is hypothesised that this increase could be associated with increased consumption of high-sugar or carbohydrate-rich foods [16] or simply reflects the ageing of the population in recent decades.

Nowadays, the primary acquired risk factors for pancreatic cancer are cigarette smoking (HR = 1.74), high alcohol consumption (HR = 1.1–1.5), obesity (body mass index > 30; HR = 1.2–1.5), and some infectious diseases that include *Helicobacter pylori (HR = 1.5), Hepatitis B virus,* or *Human Immunodeficiency virus* [17–19]. Interestingly, other studies suggested that heavy consumption of cooking and table salt appeared to be significantly associated with pancreatic cancer
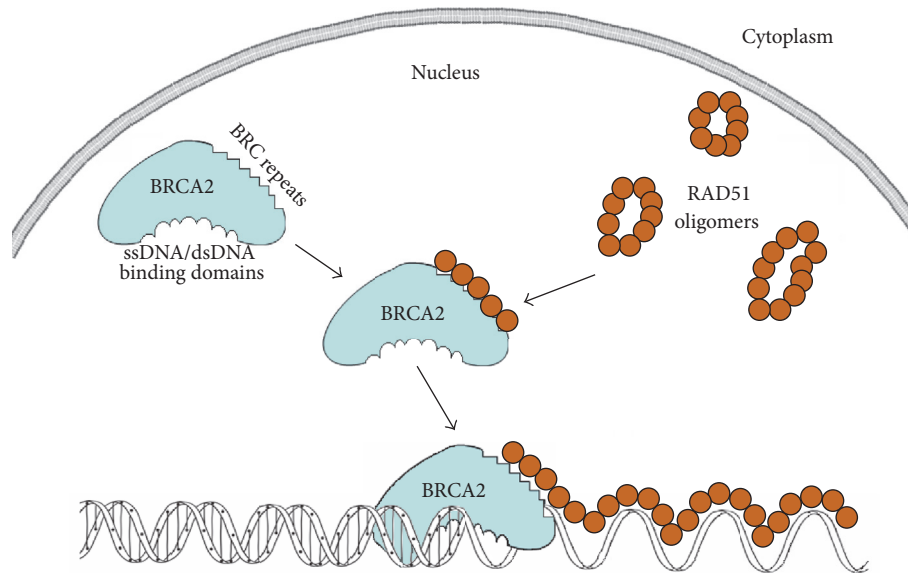
FIGURE 1: DNA damage response model performed by BRCA2 and RAD51. Dephosphorylation of BRCA2 at Ser3291 enables RAD51 binding to BRCA2 in BRC repeats and the subsequent binding to double-strand DNA. RAD51 oligomers bind to single-strand DNA at the site of damage that enables its repairs.

($P = 0.009$ and $P = 0.0001$, resp.), and a similar correlation was found with smoked food ($P < 0.01$) [20].

Interestingly, observational studies link pancreatic cancer incidence to cadmium, arsenic, and lead exposure [21]. The countries with the highest levels of arsenic (more than 10 μg/L, values recommended by the World Health Organization [22]) are those with highest incidence of pancreatic cancer. These countries include Baltic countries (especially Finland) and central and eastern European countries such as Austria, Czech Republic, Slovakia, and Hungary [23].

Pancreatic cancer has long been related to family history of pancreatic cancer (HR = 2.20, 95%; CI = 1.16–4.19) and melanoma (HR = 1.74, 95%; CI = 1.03–2.95), upon breast, ovarian, lung, gastrointestinal, or prostate cancer [24]. In addition, diabetes has also been associated with pancreatic cancer (HR = 1.4–2.2) [25].

Surgical resection is currently the best option so far to improve survival [26]. Mean life expectancy for pancreatic cancer is 1.4 years reaching 3.5 years for surgically resected patients versus 0.8 years for nonoperated patients ($P < 0.001$) [27]. However, cancers of the pancreas are usually asymptomatic, and the disease only becomes apparent after the tumour invades surrounding tissues or metastasises to distant organs [28]. As a result, there is a pressing need to find new approaches and strategies; of these, targeted therapies hold particular promise, and BRCA2 is one such therapy that has great potential. BRCA2 regulates sister chromatid cohesion and/or alignment [29] and plays a key role in response to DNA damage by direct regulation of RAD51 recombination (Figure 1).

2. BRCA2 in DNA Damage Response

The first attempt to associate BRCA2 with DNA damage response was as a cofactor associated with human RAD51-dependent DNA repair of double-strand breaks through 8 evolutionarily conserved BRC motifs encoded in exon 11 of BRCA2 (Figure 1) [30]. The milestone of DNA strand exchange is RAD51 protein which is closely related to other tumour suppressor genes such as TP53, ATM, BRCA1, BLM, and FANCD2. Preclinical studies showed that BRCA2 disruptions sensitize mice embryos to ionising radiation [30], which was previously observed in RAD51 knockout mice embryos [31]. Furthermore, mice carrying truncations on BRCA2 loci were one-third smaller than their wild-type littermates and had improper tissue differentiation, sterility, and a shorter overall survival [32, 33].

On the other hand, BRCA2 is essential for repair of double-strand breaks by homologous recombination [34]. BRCA2 alterations led to elevated P53 and P21 expression, spontaneous accumulation of chromosomal abnormalities, and aberrant chromatid exchanges, which suggests its role in pancreatic tumorigenesis (Figure 2). The aforementioned properties make BRCA2 a crucial factor to maintain cell homeostasis.

3. BRCA2 as a Prognostic Biomarker of Pancreatic Cancer

BRCA2 inactivation is due mainly to genomic mutations. The most common mutations of BRCA2 found in pancreatic cancer patients are 6174delT frameshift mutation, 6158insT mutation, splice site mutation 16-2A > G, and the splice site mutation 15-1G > A [35, 36]. Another variant located in the $3'$-untranslated region is significantly associated with lower expression of brca2 RNA and, consequently, with sporadic pancreatic cancer (HR = 1.3; $P < 0.0001$) [37]. BRCA2 inactivation has been reported to be a late event in sporadic pancreatic tumorigenesis [38] preceded by KRAS mutation
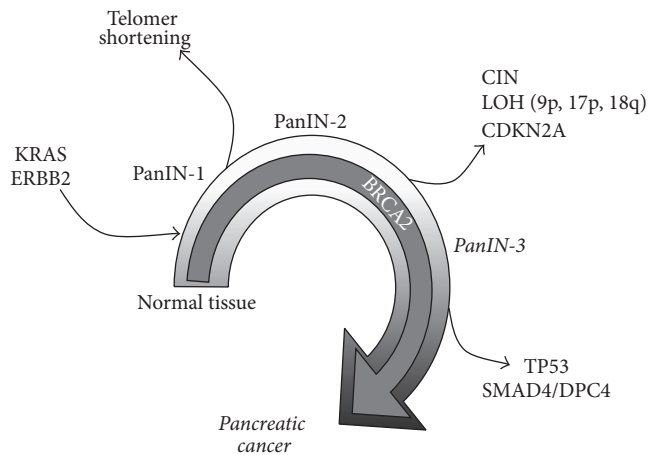
FIGURE 2: Transformation model of familiar pancreatic adenocarcinoma. Ingoing arrows concern oncogenic effectors that are acquired in the cancer progression. Outgoing arrows highlight tumour suppressor factors that become inactivated in pancreatic cancer. PanIN: pancreatic intraepithelial neoplasia; CIN: chromosome instability; LOH: loss of heterozygosity.

(G12D) or loss of *TP53* [39, 40]. Overall, *BRCA2* could be used to determine patient prognosis.

Ashkenazi Jews have been one of the most closely studied ethnic groups concerning the significance of *BRCA2* mutations and family involved pancreatic cancer. Struewing et al. found that >90% of Ashkenazi patients that carried *BRCA2* mutations detected in blood sample showed an association with increased risk of pancreatic cancer [41]. The 6174delT mutation of *BRCA2* was determined to be present in 1% (CI = 0.6–1.5) of 1.255 Jewish individuals [42]. Another study performed with 26 European families reported that 19% (CI = 7% to 39%) of the families with first-degree relatives with pancreatic cancer had either a mutation or a splice variant of *BRCA2* [43]. Murphy et al. reported 17% of *BRCA2* mutations in 31 samples from pancreatic cancer patients with at least two first-degree relatives affected by pancreatic cancer [35]. One study found 6% (10 of 180 families) with *BRCA2* mutation and moderate or high-risk pancreatic cancer predisposition and 6% (8 of 146) of families that presented two or more first-degree relatives affected with pancreatic cancer [44].

This kind of studies performed with high-risk pancreatic cancer families provides a true enlightenment of *BRCA2*-associated pancreatic cancer; however, *BRCA2* has not been directly related to patient outcome.

Pancreatic cancers with a high familial component are associated with mutations not only in *BRCA2* but also in *ATM, CDKN2, PALB2, PRSS1, STK11,* or mismatch repair (MMR) family genes [45]. MMR genes allow continuous point mutations in repeats regions of DNA known as microsatellites that become unstable. Alterations in microsatellites are found in oncogenes associated with initiation and progression of cancer [46]. Several MMR genes are involved in the acquisition of aggressive phenotype of cancer [47]. For example, alterations on EXO1, MLH1, MSH2, MSH3, MSH6, PMS2, PMS2L3, RECQL, TP73, and TREX1 were statistically significantly associated with overall

survival of pancreatic cancer patients [48]. Nevertheless, the predisposition to pancreatic cancer by MMR family genes is due mainly to mutations in *MLH1* and *MSH2* and it is estimated to be <5% [49].

4. *BRCA2* as Predictive Biomarker in Pancreatic Cancer

BRCA2 mutations impair DNA repair; thus, they are considered biomarkers of genomic instability and DNA damage repair deficiency. Therefore, *BRCA2* mutations could be used as predictive biomarkers of response to some DNA damage agents. Some of these compounds include platinum-based agents and PARP inhibitors. They are considered targeted therapies indicated for BRCA2-positive tumours according to some good results achieved in clinical trials [50]. Platinum-based drugs are, despite their toxicity, one of the gold-standard chemotherapies administered to pancreatic cancer patients. Cisplatin, carboplatin, and oxaliplatin are some of the mostly used in clinical practice and allow cross-linking and forming DNA adducts which trigger apoptosis cascade [51].

Oliver et al. presented a cohort of pancreatic cancer patients; of them, those with family history of breast, ovarian, or pancreatic cancers showed significantly increased survival after platinum-based chemotherapy compared to other patients without family history (22.9 versus 6.3 months, $P < 0.01$) [52]. A case report of a 60-year-old pancreatic adenocarcinoma patient carrying the *BRCA2* mutation, 1153insertionT, presented recurrence after gemcitabine treatment but showed a complete response after cisplatin and gemcitabine as second-line therapy [53]. Subsequently, another study with pancreatic cancer patients with positive *BRCA1/2* mutations showed improved outcome after treatment with platinum-based chemotherapy. Here, patients with locally advanced disease were pathologically downstaged and those with metastatic disease had significant increase in their progression-free survival [54]. Golan et al. reported that stage III/IV patients treated with platinum-based chemotherapy carrying *BRCA1/2* mutations had improved overall survival *compared to* those patients treated with other drugs (22 versus 9 months, resp.; $P = 0.039$) [55]. One study reported that 5 out of 8 patients with pancreatic ductal adenocarcinomas that were treated with platinum-based chemotherapy presented *BRCA2* mutation. Of these 5 patients, 2 had complete radiological response and 2 had partial responses to platinum treatment [56]. All the above-mentioned studies suggest that *BRCA2* mutations predict not only platinum response but also better outcome and longer survival for pancreatic cancer patients with advanced disease.

Poly(ADP-ribose) polymerase inhibitors (PARPi) prevent the repair of double-strand DNA breaks, homologous recombination, and replication repair performed by the PARP family of proteins [57]. A preclinical study with CAPAN-1 cell line has suggested that 6174delT mutation of *BRCA2* is highly sensitive to PARPi [58]. However, another study also performed with pancreatic cancer cell lines reported how a PARPi increases sensitivity to chemoradiotherapy independently of *BRCA2* mutation status [59].

TABLE 1: Clinical trials for *BRCA2* mutated pancreatic cancer patients.

Clinical trial	Phase	Study type	Drugs	Sponsor	Inclusion criteria
NCT02309632	Screening	Nonrandomized	Screening of high-risk individuals	University of Arkansas	Peutz-Jegher's Syndrome BRCA1 mutation carrier BRCA2 mutation carrier Ataxia-telangiectasia Familial atypical malignant melanoma syndrome Colorectal neoplasms, hereditary nonpolyposis Hereditary pancreatitis
NCT02000089	Prospective observational	Cohort	Human synthetic secretin	Johns Hopkins University	Pancreas cancer Peutz-Jeghers Syndrome Gene mutation Germline mutation carrier Lynch Syndrome
NCT02775461	Prospective observational	Cohort	—	Icahn School of Medicine at Mount Sinai	Pancreas cancer Pancreatitis Chronic pancreatitis Pancreatic cyst Family history of pancreas cancer Genetic mutations
NCT01585805	Phase II	Randomized	Gemcitabine, cisplatin with or without veliparib or veliparib alone	National Cancer Institute	BRCA1 mutation carrier BRCA2 mutation carrier Metastatic pancreatic adenocarcinoma Pancreatic adenocarcinoma Recurrent pancreatic carcinoma Stage III pancreatic cancer Stage IV pancreatic cancer
NCT01102569	Prospective observational	Cohort	—	Columbia University	BRCA1 mutation carrier BRCA2 mutation carrier
NCT00438906	Prospective observational	Cohort	Human synthetic secretin	Johns Hopkins University	Pancreatic neoplasm Peutz-Jeghers Syndrome
NCT01233505	Phase I	Interventional	Veliparib, oxaliplatin, capecitabine	National Cancer Institute	Advanced solid tumors BRCA1 mutation carrier BRCA2 mutation carrier
NCT02703545	Prospective observational	Cohort	—	Johns Hopkins University	Peutz-Jeghers Syndrome Familial pancreas cancer BRCA1 mutation carrier BRCA2 mutation carrier Hereditary pancreatitis
NCT00714701	Prospective observational	Cohort	—	Sidney Kimmel Comprehensive Cancer Center	Early pancreatic neoplasia Familial pancreatic neoplasia
NCT00892736	Phase I	Interventional	Veliparib	National Cancer Institute	Advanced solid tumors BRCA1 mutation carrier BRCA2 mutation carrier Estrogen receptor negative HER2/Neu negative

TABLE 1: Continued.

Clinical trial	Phase	Study type	Drugs	Sponsor	Inclusion criteria
NCT01339650	Phase I	Interventional	ABT-767	AbbVie	Advanced solid tumors BRCA1 mutation carrier BRCA2 mutation carrier
NCT01078662	Phase II	Interventional	Olaparib	AstraZeneca	Advanced solid tumors BRCA1 mutation carrier BRCA2 mutation carrier

A different drug popularly used in pancreatic cancer treatment is gemcitabine and is able to induce DNA damage response and PARP degradation [60]. Gemcitabine in combination with PARPi showed promising antitumor activity compared to PBS, gemcitabine, or PARPi alone, in in vivo models of pancreatic cancer [61].

In clinical studies, *BRCA2*-positive status has been associated with better response to PARPi alone or in combination with other drugs. In one study, 3 out of 4 patients with a known *BRCA1* or *BRCA2* mutation showed partial response after receiving PARPi alone or in combination with platinum-based chemotherapy [62]. In a phase I/II trial of PARPi in combination with 5FU and oxaliplatin that included 2 patients with *BRCA2* mutation, one showed a partial response and the other achieved complete response [63]. Another phase IB trial of PARPi in combination with gemcitabine and platinum-based chemotherapy reported that *BRCA*-mutated patients achieved partial response in 56% and stable disease in 44% of cases. However, 62% of *BRCA* wild-type patients remained with stable disease and 25% with progression [64].

To date, personalised therapies in pancreatic cancer could improve patient survival if assisted by breakthrough techniques used in molecular diagnosis. Deep sequencing currently offers a high-throughput method of dissecting the underlying mechanisms of tumorigenicity, leading to new strategies for personalised medicine. However, pancreatic cancer genotype is highly heterogeneous, and this heterogeneity involves its therapeutic ineffectiveness [65]. The IMPaCT clinical trial was set out to improve patient survival using deep sequencing to guide treatment decisions. In the study, patients carrying BRCA2 mutations were eligible to receive targeted treatment based on 5FU and mitomycin versus gemcitabine alone [66]. Nevertheless, no consistent conclusions arose from this trial due to the low number of patients recruited with *BRCA2* mutations [67].

Nevertheless, patients could present acquired resistance to platinum-based chemotherapy by accumulation of secondary genomic alterations, such as *BCR-ABL* point mutations, in which case the *BRCA2* mutation effect is bypassed [68]. Table 1 summarises ongoing or recently completed clinical trials recruiting *BRCA2* mutated pancreatic cancer patients.

5. Conclusions

Pancreatic cancer is one of the most deadly cancers worldwide, and despite new methods of early diagnosis, surgery, and drug discovery, tumour cells tend to scatter and metastasise to vital organs, thereby reducing survival significantly. It is also highly resistant to treatments and responds poorly to chemoradiotherapy; indeed, chemoradiotherapy is used in most of cases as a palliative therapy. Therefore, patients are encouraged to participate in clinical trials regardless of disease stage.

Some studies attribute the increasing incidence of sporadic pancreatic cancer to the ageing of the population. However, several studies have reported different factors associated with this neoplasm. Obesity, cigarette smoking, high alcohol intake, and chronic pancreatitis are the most relevant factors [69].

On the other hand, it is estimated that 10% of pancreatic cancer cases are due to an inherited syndrome [11, 12] caused by mutations in the *BRCA1* or *BRCA2* genes [10]. Most of the clinical studies that relate pancreatic cancer to *BRCA2* mutations have been performed on Ashkenazim. Although this fact limits the findings' applicability to other populations, there is nonetheless great potential in the study of the heritability of *BRCA2* mutation and pancreatic cancer incidence [41, 42].

Several preclinical and clinical studies have suggested the potential use of *BRCA2* mutations as biomarkers for DNA damage agents' response like platinum-based chemotherapy and PARPi. Clinical trials have evaluated *BRCA2* as a predictive biomarker for use in platinum-based therapies but they were mainly retrospective and with a scarce cohort of patients. Thus, further multicenter prospective studies using larger cohorts are required to investigate multitarget therapies and their potential to minimize resistance to therapy.

Competing Interests

The authors declare no conflict of interests.

Acknowledgments

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