CANCER BIOLOGY & THERAPY
2019, VOL. 20, NO. 7, 949–955
https://doi.org/10.1080/15384047.2019.1595274

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BEDSIDE-TO-BENCH REPORT

Pancreatic acinar cell carcinoma is associated with *BRCA2* germline mutations: a case report and literature review

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ABSTRACT

Acinar cell carcinoma (ACC) is a rare pancreatic neoplasm with dismal prognosis. Insights into the molecular basis of ACC can pave the way for the application of more effective, personalized therapies and detection of patients with hereditary predisposition.

Molecular analysis revealed a germline *BRCA2* (and *CHEK2*) mutation in a patient with a rare pancreatic ACC with extensive intraductal growth. Somatic loss of the wild-type *BRCA2* allele in the tumor indicated the causal relationship of ACC with the germline defect. A thorough literature review identified another nine ACCs associated with germline *BRCA2* mutation and two ACCs associated with germline *BRCA1* mutation, resulting in a prevalence of *BRCA1/2* germline mutations in almost 7% of ACCs. Moreover, somatic *BRCA1/2* alterations are reported in 16% of sporadic ACCs. Overall, about one fifth (22%) of all pancreatic ACCs exhibit BRCA1/2 deficiency.

This study underscores the important role of *BRCA1/2* mutations in pancreatic ACC. All ACC patients should undergo genetic testing for *BRCA1/2* mutations to identify carriers of pathogenic variants. This will allow to select patients that can benefit from targeted therapies directed against *BRCA1/2*-deficient tumors and is also crucial as a referral to genetic screening for the relatives of affected individuals carrying germline *BRCA1/2* alterations.

Abbreviations: ACC: acinar cell carcinoma; HBOC: Hereditary Breast and Ovarian Cancer; LOH: loss of heterozygosity; PARP: poly (ADP-ribose) polymerase; PDAC: pancreatic ductal adenocarcinoma; PP: pancreatic panniculitis; SD: standard deviation; WES: whole-exome sequencing.

ARTICLE HISTORY
Received 12 October 2018
Accepted 26 December 2018

KEYWORDS
Acinar cell carcinoma of the pancreas; germline mutation; somatic mutation; *BRCA1*; *BRCA2*

Introduction

Acinar cell carcinoma (ACC) is a rare pancreatic malignancy with poor prognosis accounting for <2% of all pancreatic tumors in adults and for about 15% in pediatric cases.[1–3] At time of diagnosis, 50–60% of patients have distant metastasis and an advanced stage of disease leading to low survival rate and overall dismal prognosis.[1,4] Nonetheless, 5-year survival of ACC patients is 45% which is higher compared to only 7% in conventional pancreatic ductal adenocarcinoma (PDAC).[1] About 15% of ACC patients present with pancreatic panniculitis (PP), characterized by subcutaneous fat necrosis.[1,4]

The genomic landscape of ACC is distinct from other pancreatic tumors.[3,5–8] Typical genetic alterations observed in PDAC are normally not detected in ACC or occur rarely, i.e., mutations in *KRAS* (~2% ACCs vs. >90% PDACs), *TP53* (9–23% vs. 75%), *CDKN2A* (14% vs. 90%), *SMAD4* (14–19% vs. 55%).[6,9] Rare mutations in *BRAF, GNAS* and *JAK1* and fusions in *BRAF* and *RAF* (detected in 23% of ACCs) indicate that a minority of ACCs can evolve due to driver events in oncogenes.[6,9] Recent sequencing studies revealed that ACCs carry on average about 65 non-synonymous somatic mutations per tumor. Importantly, ACC appears to have few recurrent gene mutations since there were no genes mutated in more than 30% of ACC.[6] Twenty to 25% of ACCs harbor abnormalities in Wnt/β-catenin pathway, including mutations in *APC* and *CTNNB1* genes.[8] The lack of highly recurrent mutations suggests that other genetic mechanisms drive tumor progression in ACC.[3] Indeed, extensive chromosomal instability appears to be a defining feature of ACC distinguishing it from other pancreatic malignancies, potentially contributing to disease severity, progression and chemotherapy resistance.[2,3,6,7,10] Amongst others loss of heterozygosity (LOH) of chromosomes 11p (~50% of ACCs), 17p (*TP53* locus; 39%), and 18q (*SMAD4* locus; 57%) is frequently detected.[6–8] Importantly, despite the genetic heterogeneity, approximately 44% of ACCs harbor potentially targetable genetic abnormalities in DNA repair by homologous recombination (*BRCA1/2, PALB2, BRIP1, BAP1*, and *ATM*), JAK-STAT signaling cascade (*JAK1*), MAPK pathway (*BRAF*), and cell cycle control (*CDKN2A, ID3*, and *APC*).[3,6,9]

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Although the association of *BRCA1/2* mutations with familial and sporadic PDAC is established,[11] there is only limited data on the role of *BRCA1/2* genes in ACC.[2,7] Since *BRCA1/2* mutations are targets for therapy with platinum-based chemotherapeutics and poly (ADP-ribose) polymerase (PARP) inhibitors,[12] it is important to determine the role of BRCA1/2 deficiency in the pathogenesis of pancreatic ACC. In addition, recognition of ACC as a phenotypic expression of a germline *BRCA1/2* mutations is crucial for screening of patients and their families.

Here we describe a rare case of an ACC in a patient with a germline *BRCA2* mutation, provide molecular evidence for a causal link between *BRCA2* germline mutation and ACC, and review the literature on the role of germline and somatic *BRCA1/2* mutations in ACC.

Case report

A 52-year-old man carrying a germline *BRCA2* mutation presented with steatorrhea, abdominal pain and weight loss. His mother died at age 41 from breast cancer, and his sister was diagnosed with high grade serous ovarian adenocarcinoma. Abdominal CT scan revealed a tumor in the body and tail of the pancreas, suggestive of adenocarcinoma arising from the main-duct intraductal papillary mucinous neoplasm (IPMN). Endoscopic ultrasound with fine-needle aspiration cytology was performed and showed cytology consistent with ACC (Figure 1(a,b)). The patient underwent total pancreatectomy and histological examination confirmed an ACC with extensive intraductal spread (Figure 1(c,d)).[13] One out of 11 lymph nodes showed metastasis. All surgical margins were free of tumor.

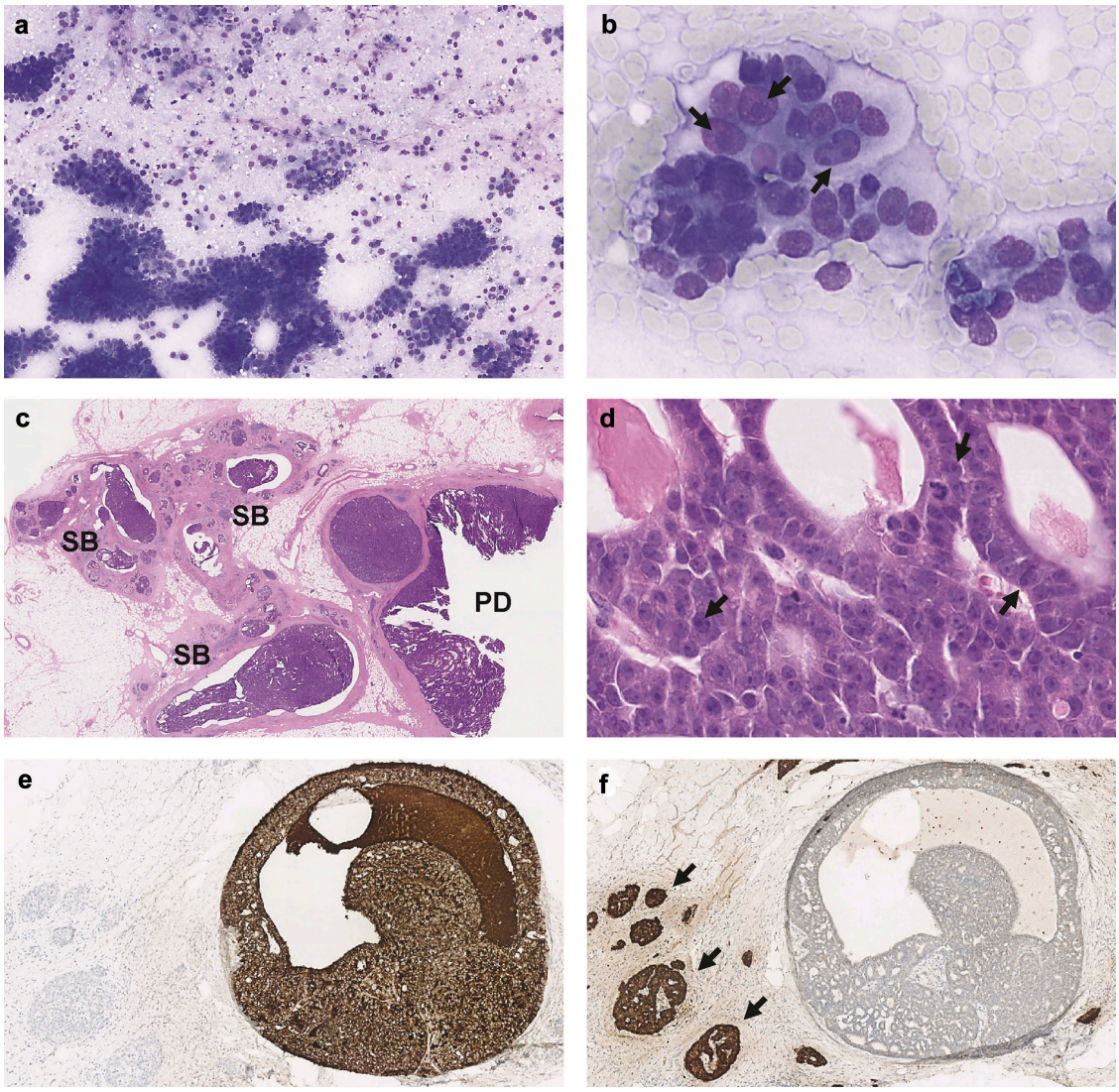

Figure 1. Fine needle aspiration cytology showed a highly cellular specimen consisting of a monotonous population of single cells and clusters of cells with a moderate amount of basophilic cytoplasm (a). The nuclei are round to oval with moderate anisonucleosis and a single prominent nucleolus (arrows) (b). Histologically the tumor showed extensive intraductal growth in the main pancreatic duct (PD) and side branches (SB) (c). The tumor was composed of uniform cells with granular cytoplasm and nucleoli with a single prominent nucleolus (arrows), forming small lumina (d). Immunohistochemically, the tumor cells were strongly positive for BCL10 (e) and negative for Chromogranin A (f). Note the opposite staining patterns in the adjacent islets of Langerhans (arrows). PD, pancreatic duct; SB, side branch of pancreatic duct.

Since the histopathological examination did not show adenocarcinoma, no adjuvant chemotherapy with gemcitabine was indicated. The patient recovered well, but six months postoperatively, multiple metastases appeared involving the lung, liver, peritoneum, and skin. Chemotherapy with oxaliplatin, 85 mg/m^2 of body-surface area; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 given as a 46 hours continuous infusion, every 2 weeks (FOLFIRINOX) was initiated.[14] The first evaluation CT scan showed partial response of liver metastases. Dose adjustments were made due to hematological toxicity. However, after more than one year of treatment (24 cycles), the neuropathy was too invalidating to perform his work and FOLFIRINOX was stopped. Unfortunately, the patient died three months later because of disease progression.

Materials and methods

Immunohistochemistry

Immunohistochemistry was performed using standard conditions in the Benchmark Ultra autostainer (Ventana Medical Systems, Inc. A Member of the Roche Group, Tucson, AZ, USA) with the following antibodies: Alpha-1-antitrypsin (1:20000; clone zmaat3, Zymed), β-catenin (1:40; clone 14, Cellmarque), BCL10 (1:400; clone 331.3, Santa Cruz), Chromogranin A (1:6400; clone LK2H10, Thermo Fisher Scientific), Cytokeratin 7 (1:6400; clone OV-TL 12/30, Biogenex), Cytokeratin 19 (1:100; clone B170, Novocastra), Cytokeratin 20 (1:200; clone Ks20.8, Dako), SMAD4 (1:800; clone EP6184, Abcam), MLH1 (1:20; clone G168-15, Pharmingen), MSH2 (1:50; clone G219-1129, Cellmarque), MSH6 (1:200; clone EPR3945, Abcam), PMS2 (1:25; clone EPR3947, Cellmarque), p53 (1:6000; clone DO-7, Dako), and Synaptophysin (1:100; clone 27G12, Novocastra).

DNA isolation

Genomic DNA was isolated from paraffin-embedded tissue. After deparaffinization, DNA was isolated using the Puregene DNA Isolation kit (Gentra Systems, Minneapolis, MN, USA). DNA concentrations were measured using the PicoGreen Double-Stranded DNA Quantitation kit (Molecular Probes, Leiden, The Netherlands).

DNA sequencing

Next-generation sequencing was performed using the Ion AmpliSeq Cancer Hotspot Panel v2, which includes 50 cancer-related genes and which was supplemented with five additional genes (Table 1), and the Oncomine BRCA Panel which includes the entire coding region of *BRCA1* and *BRCA2* (Thermo Fisher Scientific). Library preparation and sequencing using the Ion PGM System were performed as described previously.[15]

Multiplex ligation-dependent probe amplification (MLPA)

MLPA was performed to confirm LOH of *BRCA2* using BRCA2/CHEK2 P045 probemix (MRC Holland, Amsterdam, The Netherlands) according to manufacturer's instructions.

Table 1. List of 50 target genes of the Ion AmpliSeq Cancer Hotspot Panel v2 supplemented with five additional genes.

ABL1	*CSF1R*	*GNA11*	*KRAS*	*PTEN*
AKT1	*CTNNB1*	*GNAS*	***MDM2***	*PTPN11*
ALK	*EGFR*	*GNAQ*	*MET*	*RB1*
APC	*ERBB2*	*HNF1A*	*MLH1*	*RET*
ARAF	*ERBB4*	*HRAS*	*MPL*	*SMAD4*
ATM	*EZH2*	*IDH1*	***MYD88***	*SMARCB1*
BRAF	*FBXW7*	*JAK2*	*NOTCH1*	*SMO*
CALR	*FGFR1*	*JAK3*	*NPM1*	*SRC*
CDH1	*FGFR2*	*IDH2*	*NRAS*	*STK11*
CDKN2A	*FGFR3*	*KDR*	*PDGFRA*	*TP53*
CRAF	*FLT3*	*KIT*	*PIK3CA*	*VHL*

In bold are indicated five additional genes that were added to the 50 target genes of the Ion AmpliSeq Cancer Hotspot Panel v2.

Results were normalized on all control probes present in the kit and normal samples without copy number alterations. Deletions and duplications were defined as ratios of <0.55 and >1.45, respectively. The assay was performed in duplicate.

Results

Histopathology and immunohistochemistry

Histopathological examination of the tumor confirmed the diagnosis of pancreatic ACC. The tumor demonstrated strong positivity for pancreatic acinar cell marker BCL10 (Figure 1(e)). Cytokeratins 19 and 7 stained positive and Cytokeratin 20 was negative. Partial expression was observed for Alpha-1-antitrypsin. Chromogranin A (Figure 1(f)) and Synaptophysin were negative. Expression of p53 was wild-type, and β-catenin showed only membranous localization. No loss of SMAD4 or any of the mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) was detected.

Molecular analysis

No mutations were found using the Cancer Hotspot Panel (Table 1). BRCA sequencing revealed an inactivating *BRCA2* mutation (NM_000059.3: c.7974C>G or p.Tyr2658*, VAF 80% indicating the loss of the wild-type allele), which is considered pathogenic by ClinVar.[16] Sequence analysis of DNA isolated from a blood sample at clinical genetics showed that this is a germline mutation. MLPA analysis revealed loss of one *BRCA2* allele in the tumor tissue, further confirming biallelic inactivation of BRCA2. In addition, somatic LOH of *BRCA1* was detected by BRCA sequencing and a germline *CHEK2* mutation (c.1100delC or p.Thr367Metfs) was identified by MLPA.

Literature review of pancreatic ACCs associated with germline *BRCA1/2* mutations

Literature review of ACC in patients with a germline *BRCA2* mutation identified nine additional cases (Table 2).[7,17–21] The mean age at diagnosis was 62 years (SD: 8.7; range: 50–78), which is similar to sporadic cases.[4] Including the current patient, seven males (67%) and three females (33%) were identified, resulting in male-to-female ratio of 2.3:1, corresponding to the male predominance in sporadic ACC.[1,2] All specified *BRCA2* mutations were truncating.[7,17,21] Noteworthy, in all six cases

Table 2. Germline *BRCA1/2* mutations in pancreatic ACCs.

Reference, first author	Year	Sex	Age at diagnosis (y)	Gene	CDS Mutation	LOH	Protein	Personal history (y)	Family history (y)
Current case	2018	M	52	*BRCA2*	c.7974C>G	Yes	p.Y2658*	No	Mother: breast cancer (died at 41); sister: serous ovarian adenocarcinoma
Li[21]	2018	M	59	*BRCA2*	NS	NS	p.I332fs	Hepatitis A for 10 years	Father: died from lung cancer; mother and brother: hepatic carcinoma
Lowery[24]	2018	NS	NS	*BRCA1*	NS	NS	NS	NS	NS
Naeyaert[19a]	2016	M	59	*BRCA2*	NS	NS	NS	T2DM, hypercholesterolemia	*BRCA2*-mutation related breast cancer
Ploquin[18]	2015	M	50	*BRCA2*	NS	NS	NS	Localized prostatic adenocarcinoma (61)	Mother (60), sister (34): breast cancer; brother: bladder cancer. Patient's cousin and two sons are carriers of *BRCA2* mutation
Furukawa[7]	2015	F	78	*BRCA2*	c.7115C>G	Yes	p.S2372*	NS	NS
		M	59	*BRCA2*	c.4021del	Yes	p.S1341fs	NS	NS
Lowery[22,23]	2011	M	NS	*BRCA1*	NS	NS	NS	Acromegaly, colonic adenocarcinoma, papillary renal cell carcinoma	Multiple first- and second-degree relatives with early-onset breast cancer
Gandhi[20a, b]	2010	F	63	*BRCA2*	NS	NS	NS	Ovarian cancer	NS
Skouldis[17]	2010	M	70	*BRCA2*	c.771_775del[c]	Yes	p.Asn257fs	NS	NS
		F	59	*BRCA2*	c.771_775del[c]	Yes	p.Asn257fs	Lobular breast cancer (58)	NS
		M	71	*BRCA2*	c.771_775del[c]	Yes	p.Asn257fs	NS	NS

Y, year; LOH, loss of heterozygosity; M, male; F, female; NS, not stated; T2DM, type 2 diabetes mellitus.
[a]Patient presented with PP as an initial manifestation of pancreatic ACC.
[b]Likely pancreatic ACC and likely *germline BRCA2* mutation.
[c]Formerly known as 999del5.

with known zygosity, loss of the wild-type *BRCA2* allele was detected.[7,17] Three out of 10 patients had a previous personal history of another *BRCA2*-associated malignancy, including breast, ovarian and prostate cancers.[17,18,20] In addition, three patients, including the current, had a family history of *BRCA2*-associated malignancies and/or family member(s) harboring germline *BRCA2* mutations.[18,19] Two patients presented with PP as the initial manifestation of ACC.[19,20] In addition, literature search identified two ACC patients with *BRCA1* germline mutation.[22–24] Among 46 ACCs tested by germline sequencing (Furukawa et al.[7] (n = 7), Jakel et al.[3] (n = 22), Lowery et al.[24] (n = 17)), one patient (2.2%) with *BRCA1*[24] and two patients (4.3%) with *BRCA2*[7] mutations were detected.

Literature review of somatic *BRCA1/2* mutations in pancreatic ACC

Review of literature detected 12 ACCs with somatic *BRCA2* mutations and four – with somatic *BRCA1* mutations (Table 3).[6,7,9,25,26] Of note, all four ACCs with somatic *BRCA1* mutations were identified in a single study based on comprehensive genomic profiling of tumor series consisting of 44 ACCs,[9] whereas 11 out of 12 ACCs containing somatic *BRCA2* mutations were detected in genome sequencing studies[6,7,9] and one additional ACC was described in a case study and patient-derived animal model.[25,26]

Among ACCs (n = 94) tested for the presence of somatic *BRCA1/2* alterations with genome sequencing approaches (Chmielecki et al.[9] (n = 44), Jiao et al.[6] (n = 21), Furukawa et al.[7] (n = 7), Jakel et al.[3] (n = 22)),[3,6,7,9] overall 15/94 ACCs (16%) harbored a somatic mutation in either *BRCA1* or *BRCA2*. Specifically, 11/94 ACCs (11.7%) contained in total of 12 somatic *BRCA2* mutations, and 4/94 ACCs (4.3%) exhibited one somatic *BRCA1* mutation each. The majority of *BRCA2* mutations were frameshifts introducing a premature stop codon.[7,9] Two somatic *BRCA2* variants were missense mutations leading to the change of corresponding amino acid.[6,9] In silico analysis indicated that these are likely benign variants that should be considered as passenger mutations.

Discussion

Important lessons can be learned from tumors occurring in hereditary settings.[27] We describe a novel case of a patient with a germline *BRCA2* mutation and pancreatic ACC, and review the literature on the prevalence of germline and somatic *BRCA1/2* alterations in ACC. Increasing evidence suggests that at least a subgroup of ACCs develops on basis of germline and somatic *BRCA1/2* mutations, however their role in the onset of pancreatic ACC is not yet well recognized. Despite the rarity of ACC, hampering large studies, it is crucial to establish the link between ACC and *BRCA1/2* mutations in view of the importance to recognize potentially hereditary tumors and identify patients that may benefit from targeted therapies.

Including the current case, a total of 10 ACC patients with germline *BRCA2* mutations have now been reported (Table 2).[7,17–21] Loss of the wild-type *BRCA2* allele, observed in

Table 3. Somatic *BRCA1/2* mutations in pancreatic ACCs.

Reference, first author	Year	Type of ACC	Sex	Age at diagnosis (y)	Gene	CDS Mutation	Protein	Mutation reference
Furukawa[7]	2015	Pure ACC	M	67	*BRCA2*	c.8297delC[a]	p.T2766fs	COSM4972287
Chmielecki[9]	2014	Pure ACC	NS	NS	*BRCA1*	NS	p.E1250fs	COSM4603639
		Pure ACC	NS	NS	*BRCA1*	NS	p.E23fs	COSM1666624
		Mixed ACC/NE	NS	NS	*BRCA1*	NS	splice	NS
		Mixed ACC/DA	NS	NS	*BRCA1*	NS	p.W1508*	COSM4603640
		Pure ACC	NS	NS	*BRCA2*	NS	p.R3128*	COSM4603643
		Pure ACC	NS	NS	*BRCA2*	NS	p.N1706fs	COSM4603646
		Pure ACC	NS	NS	*BRCA2*	NS	p.S1951fs	COSM4603648
		Pure ACC	NS	NS	*BRCA2*	NS	p.W563fs	COSM4603651
		Unknown ACC[b]	NS	NS	*BRCA2*	NS	p.S1982fs	COSM166356
			NS	NS	*BRCA2*	NS	p.Q1987fs	COSM4603645
		Mixed ACC/NE, Unknown ACC[c]	NS	NS	*BRCA2*	NS	p.R645fs	COSM4603647
		Mixed ACC/NE	NS	NS	*BRCA2*	NS	p.N433fs	COSM4603649
		Unknown ACC[c]	NS	NS	*BRCA2*	NS	p.L659fs	COSM4603650
		Mixed ACC/DA/NE	NS	NS	*BRCA2*	c.4535G>A	p.R1512H[d]	COSM4603642
Jiao[6]	2014	Pure ACC	M	66	*BRCA2*	c.1437C>G	p.D479E[d]	COSM1734236
Hall,[26] Armstrong[25e]	2016, 2011	Pure ACC	M	61	*BRCA2*	c.1755_1759del[a]	p.Lys585fs	NS

ACC, acinar cell carcinoma; Y, year; M, male; F, female; NS, not stated; NE, neuroendocrine; DA, ductal.
[a]Loss of heterozygosity.
[b]Unknown ACC stands for ACC with incomplete histological analysis.
[c]Same unknown ACC.
[d]Likely benign variants.
[e]Hall et al. (2016) developed a xenograft murine model derived from the liver metastasis of the patient with ACC described in paper by Armstrong et al. (2011), therefore, data was collected from these two reports.

all cases with known zygosity,[7,17] supports the causal relation between *BRCA2* germline mutation and the onset of ACC. Moreover, literature review showed that somatic *BRCA2* alterations occur in about 12% of ACCs.[6,7,9] Involvement of *BRCA1* in the onset of ACC remains elusive, although there are indications of this association. So far, only two patients with pancreatic ACC were reported to carry a germline *BRCA1* mutation.[22–24] Somatic *BRCA1* alterations were observed in 4.3% of ACCs.[3,6,7,9] However, even more pancreatic ACCs may lack functional BRCA1/2. An immunohistochemical analysis showed loss of BRCA2 expression in 5 out of 11 ACCs (45%)[7] and a recent whole-exome sequencing (WES) study showed a mutational signature associated with BRCA1/2 deficiency in 10 out of 22 ACCs (45%) despite the absence of *BRCA1/2* mutations.[3] Methylation of the *BRCA1* promoter was observed in 67% of ACCs in comparison to 28% of PDACs and 50% of islet carcinomas,[28] potentially indicating that silencing of *BRCA1* is a discriminative characteristic of ACC contributing to its pathogenesis. Importantly, sequencing studies revealed that about 7% of ACCs exhibited germline and up to 16% – somatic mutations in either *BRCA1* or *BRCA2* genes. Based on abovementioned mechanisms, up to 22% of pancreatic ACCs might exhibit BRCA1/2 deficiency (Table 4). In addition, loss of one *BRCA2* allele due to monosomy of chromosome 13 was reported in two ACCs,[29] and *BRCA2* amplification – in one ACC.[30] Further research is needed to define whether these alterations drive the pathogenesis of pancreatic ACC or occur mainly as passengers due to extensive chromosomal instability observed in this tumor type.

Of note, the actual prevalence of both germline and somatic *BRCA1/2* mutations in pancreatic ACC can be under- or overestimated mainly due to the rarity of this tumor type, lack of large-scale genomic analyses and possible underrepresentation in literature. Patients with ACC and germline *BRCA1/2* alterations were often described in case reports[7,17–20,22,23] hindering the possibility to estimate real portion of ACCs emerged due to *BRCA1/2* germline mutations. The heterogeneity observed between sequencing studies is also remarkable: only one out of four studies detected somatic *BRCA1* mutations, and one WES study did not identify any *BRCA1/2* mutation in 22 ACCs.[3]

Importantly, all cases of pancreatic ACC in patients with germline[7,17] and somatic[7,26] *BRCA2* mutations with known zygosity demonstrated loss of the wild-type allele indicating a driver role in the tumorigenesis of pancreatic ACC. Moreover, among seven pancreatic cancer cases in the Icelandic Cancer Registry harboring germline Icelandic founder *BRCA2*^{999del5} mutation, LOH was observed in all three ACCs (included in this review), but only in one out of four PDACs.[17] In the *Kras*^{G12D}-driven murine model of pancreatic cancer harboring a heterozygous pathogenic germline *Brca2* mutation, acinar tumors developed in 5 out of 28 mice (~18%) solely in the cohort with biallelic *Brca2* inactivation. Authors hypothesized that LOH of *BRCA2* plays a defining role in the triggering of pancreatic carcinogenesis towards acinar lineage,[17] however, further research is needed to elucidate the exact role of zygosity status and loss of wild-type *BRCA2* allele in the pathogenesis of ACC.

BRCA1 and *2* encode proteins that are crucial for DNA repair by homologous recombination.[31] Due to their pivotal role in maintenance of genome integrity, *BRCA1/2*-deficient tumors are particularly sensitive to therapies introducing cross-linking and DNA damage, namely platinum-based chemotherapies and PARP inhibitors.[32] Furukawa et al. reported complete remission in a patient with ACC and liver metastasis and somatic *BRCA2* mutation after treatment with cisplatinum.[7] Similarly, Ploquin et al. described a prolonged 14-year relapse-free survival of a male *BRCA2* germline mutation carrier with ACC and multiple liver and spleen metastases.[18] This patient was treated with the GEMOX regimen and demonstrated highest response rate to oxaliplatin chemotherapy.[18] A xenograft murine model PA-018, derived from the ACC patient with somatic biallelic *BRCA2* mutation,[25] demonstrated the most pronounced and continuous response to oxaliplatin.[26] Several studies further reported

increased sensitivity to platinum chemotherapeutics in other *BRCA1/2*-deficient cancers,[12,33,34] further emphasizing the relevance of platinum-based therapies in patients with *BRCA1/2*-related ACC. In our case, this advantageous effect was observed as well.

PARP inhibitors exploit the phenomenon of "synthetic lethality" when defects in certain genes are tolerated by cells if occur separately, but are lethal in case of co-occurrence.[35] Clinical utility of PARP inhibitors is based on the "two-hit" paradigm for tumor suppressor genes, enabling them to selectively target *BRCA1/2*-deficient cells while having no effect on *BRCA1/2* wild-type or heterozygous cells.[17] Tumors of *BRCA1/2* germline mutation carriers in approximately 80% of cases experience inactivation of wild-type allele by LOH.[31] Moreover, a recent study by Lowery et al. detected LOH of *BRCA1* (60%) and *BRCA2* (60%) in germline *BRCA* mutation carriers with exocrine pancreatic malignancies.[24] Since LOH of *BRCA2* gene was observed in all reported cases of ACC with known zygosity, these tumors are expected to be sensitive to PARP inhibitors. Notably, in a recent case report, Li et al. described a first case of a patient with unresectable advanced pancreatic ACC and a germline *BRCA2* mutation that demonstrated a partial response to the treatment with an oral PARP inhibitor olaparib.[21]

Overall, up to 22% of pancreatic ACCs exhibit various BRCA1/2 alterations (Table 4). This warrants genetic screening for the presence of *BRCA1/2* deficiency in all patients diagnosed with pancreatic ACC. Notably, genetic testing of *BRCA1/2* genes is widely utilized for patients with breast and ovarian cancers, whereas the prevalence of these mutations in unselected cohort of patients is reported to be only 3% and 10%, respectively.[36] Germline mutations in *BRCA1/2* predispose to a range of cancers associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome.[37] Given that pancreatic ACC can be a phenotypical expression of germline *BRCA1/2* mutations, screening of affected individuals for their carrier status will provide important insights on hereditary predisposition to HBOC also for their unaffected relatives, which can undergo genetic screening to identify their status and potentially benefit from preventive measures.

Table 4. BRCA1/2 alterations observed in pancreatic ACC tumor series.

	in studied ACC tumor series			
Molecular alteration	Frequency	Percentage	Reference	Year
Germline *BRCA1/2* mutations	3/46[a]	7%	Lowery[24]	2018
			Jäkel[3]	2017
			Furukawa[7]	2015
Somatic *BRCA1/2* mutations	15/94[b]	16%	Jäkel[3]	2017
			Furukawa[7]	2015
			Chmielecki[9]	2014
			Jiao[6]	2014
IHC loss of BRCA2 expression	5/11	45%	Furukawa[7]	2015
Methylation of *BRCA1* promoter	8/12	67%	Guo[28]	2014
Mutational signature associated with BRCA1/2 deficiency	10/22	45%	Jäkel[3]	2017
Overall	**41/185**	**22%**		

ACC, acinar cell carcinoma; IHC, immunohistochemistry.
[a]Two ACCs with *BRCA2* and one with *BRCA1* germline mutation.
[b]11 ACCs with *BRCA2* and 4 with *BRCA1* somatic mutations.

To conclude, occurrence of ACCs in carriers of *BRCA2* germline mutations strongly suggests that at least a part of ACCs arise due to germline *BRCA2* mutations. In addition, somatic *BRCA1/2* alterations and mutational signature associated with *BRCA1/2* deficiency are found in a significant subset of sporadic ACCs. ACC patients should be screened for the presence of *BRCA1/2* deficiency, in order to apply personalized therapy and to identify patients with hereditary pancreatic cancer. Overall, this will promote early detection and may improve survival of ACC patients.

Authors contributions

VK – drafting of the manuscript, acquisition of data, analysis and interpretation of data; NHM – acquisition of data, critical revision of the manuscript for important intellectual content; FHMM – acquisition of data, analysis and interpretation of data; MJLL – critical revision of the manuscript for important intellectual content; GJAO – critical revision of the manuscript for important intellectual content; IDN – critical revision of the manuscript for important intellectual content; WWJL – acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content; LAAB – study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

Disclosure of interest

The authors report no conflict of interest.

Funding

This work was supported by the Dutch Cancer Society under Grant KWF 2016 10289.

Ethical approval

This article was written with an approval of the patient.

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