

## Overall Survival and Clinical Characteristics of BRCA-Associated Cholangiocarcinoma: A Multicenter Retrospective Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Cholangiocarcinoma • BRCA-associated • Germline • somatic • PARPi

### ABSTRACT

**Background.** Biliary tract malignancies, in particular cholangiocarcinomas (CCA), are rare tumors that carry a poor prognosis. *BRCA2* mutation carriers have an increased risk of developing CCA with a reported relative risk of ~5 according to the Breast Cancer Linkage Consortium. In addition to this risk, there are potential therapeutic implications in those harboring somatic and/or germline (GL) *BRCA* mutations. Therefore, it is important to define the clinical characteristics of GL/somatic *BRCA1/2* variants in CCA patients.

**Materials and Methods.** We performed a multicenter retrospective analysis of CCA patients diagnosed between January 2000 and December 2013 with GL or somatic variants in *BRCA1/2* genes detected by GL mutations testing and/or by tumor next generation sequencing. Cases were identified from clinical databases at participating institutions. Data including demographics, clinical history, surgical procedures, and systemic chemotherapy or radiation were extracted from patients' records.

**Results.** Overall, 18 cases were identified: 5 carriers of GL *BRCA1/2* mutations (4 *BRCA2*; 1 *BRCA1*) and 13 harboring

somatic variations (7 *BRCA1*; 6 *BRCA2*). Mean age at diagnosis was 60, SD ± 10 years (range 36–75 years), with male and female prevalence rates of 61.2% and 38.8%, respectively. Stage at diagnosis was I (*n* = 4), II (*n* = 3), III (*n* = 3), and IV (*n* = 8). Six patients had extrahepatic CCA and the rest intrahepatic CCA. Thirteen patients received platinum-based therapy and four were treated with poly ADP ribose polymerase inhibitors, of whom one experienced sustained disease response with a progression-free survival of 42.6 months. Median overall survival from diagnosis for patients with stage I/II in this study was 40.3 months (95% confidence interval [CI], 6.73–108.15) and with stages III/IV was 25 months (95% CI, 15.23–40.57).

**Conclusion.** BRCA-associated CCA is uncommon. This multicenter retrospective study provides a thorough clinical analysis of a BRCA-associated CCA cohort, which can serve as a benchmark for future development and design of expanded analyses and clinical trials. *The Oncologist* 2017;22:804–810

**Implications for Practice:** BRCA-associated CCA is uncommon but a very important subtype of hepatic malignancies, due to its rising prevalence. Better clinical characterization of this subtype might allow application of targeted therapy for CCA patients with germline or somatic mutations in *BRCA1/2* genes, especially due to previously reported success of such therapies in other BRCA-associated malignancies. Thus this study, first of its kind, provides a basis for future multi-centered analyses in larger cohorts, as well as clinical trials. Additionally, this study emphasizes the importance of both germline and somatic genotyping for all CCA patients.

### INTRODUCTION

Cholangiocarcinomas (CCA) are adenocarcinomas that arise from the malignant transformation of bile duct epithelium anywhere along the biliary tree from small bile ducts and bile ductules (intrahepatic CCA [ICC]) to large bile ducts at the hilum of the liver or outside the liver (extrahepatic CCA [ECC]) [1].

Although CCA is a relatively uncommon tumor, with incidence rates ranging from 0.8 to 2 per 100,000 in the Western world [2, 3], it is the second most common primary hepatic malignancy after hepatocellular carcinoma and accounts for 3% of malignant tumors of the gastrointestinal system and 15% of

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primary hepatic malignancies [4–6]. Most patients are diagnosed with inoperable disease, and median survival is ~6 months for ICC patients and less than a year for ECC [1]. Even when deemed operable, only 20%–40% patients who undergo surgery achieve clear (R0) margins [7, 8]. This translates to a dismal prognosis, with 5-year overall survival (OS) rates of less than 5% [9]. Moreover, CCA's rates are increasing globally in recent years with no effective targeted molecular therapies currently approved [10–12].

Recent discoveries of somatic genomic alterations have led to exploration of new potential therapeutic targets [13]. In particular, a comprehensive analysis published by Nakamura et al. reported a high rate (93/239—38.9%) of potentially targetable somatic genetic alterations in analyzed CCA cases [14]. The potential targets included kinases (*FGFR1*, *FGFR2*, *FGFR3*, *PIK3CA*, *ALK*, *EGFR*, *ERBB2*, *BRAF*, and *AKT3*), oncogenes (*IDH1*, *IDH2*, *CCND1*, *CCND3*, and *MDM2*), and, notably, tumor-suppressor genes *BRCA1* and *BRCA2*.

In another study, 75 CCA cases were genotyped for targetable somatic mutations, revealing that 16% and 40% of detected alterations in ICC and ECC cases, respectively, were affecting genes associated with DNA repair pathways, including *MSH6*, *BAP1*, *ATM*, *MLH1*, *MSH2*, and *BRCA1* and *BRCA2* [15].

The contribution of germline (GL) mutations in *BRCA1/2* genes to the development of bile duct malignancies has previously been reported. Data from the early 2000s by the Breast Cancer Linkage Consortium (BCLC) reported that the relative risk (RR) of developing gall bladder or bile duct cancer among *BRCA2* carriers is 4.97 (95% confidence interval [CI] 1.50–16.52), whereas other established RR factors for CCA development such as infection with liver parasites, hepatitis C virus, and hepatitis B virus are 4.8, 1.8, and 2.6, respectively [16, 17].

*BRCA1* and *BRCA2* proteins are involved in the DNA damage response mediated via homologous recombination (HR) [18, 19]. *BRCA1/2*-mutated cells are HR deficient and hence accumulate DNA double-strand breaks, resulting in genomic instability and increased predisposition to malignant transformation [20], rendering *BRCA1/2* mutation carriers with a distinct clinical phenotype of increased sensitivity to DNA damaging therapies [21–23]. Additionally, somatic biallelic inactivation of the *BRCA1* or *BRCA2* genes confers sensitivity to poly ADP ribose polymerase (PARP) inhibition [24].

It is unknown if and to what extent the clinical course and therapeutic response of *BRCA*-associated CCA are distinct from non-*BRCA* carriers. To gain insight, this multicenter retrospective study on *BRCA*-associated cases was initiated and is reported herein.

## MATERIALS AND METHODS

### Study Population

A multicenter retrospective analysis was performed. Patients with GL or somatic *BRCA1/2*-associated CCA diagnosed between January 2000 and December 2013 were identified from clinical databases at five participating institutions: Sheba Medical Center, MD Anderson Cancer Center, Mount Sinai Hospital Toronto, The Ohio State University Medical Center, and University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.

**Table 1.** Study population demographic and clinical characteristics

Characteristics	n (%)
Age at diagnosis	
Mean ± SD (years)	60 ± 10
Range	36–75
Gender	
Male	11 (61.2)
Female	7 (38.8)
Type of tumor	
ICC	12 (67.7)
ECC	6 (33.3)
AJCC clinical stage	
I/II	7 (39)
III/IV	11 (61)
Smoking history	
Smokers	8 (44.4)
Nonsmokers	10 (55.6)
Personal history of malignancy	
Any malignancy	4 (22.2)
BRCA-associated malignancy <sup>a</sup>	3 (16.66)
Family history of malignancy	
Any malignancy	14 (77.7)
First-degree relative	12 (85.71)
BRCA-associated malignancy	5 (27.7)
Familial BRCA-associated <sup>b</sup>	2 (11.1)
Treatments	
Platinum-based only	13 (72.2)
PARPi only	4 (22.2)
Both	3 (16.66)

<sup>a</sup>BRCA-associated malignancies include breast, ovarian, prostate, and pancreatic cancer.

<sup>b</sup>Patients with ≥2 first-degree relatives with BRCA-associated malignancies.

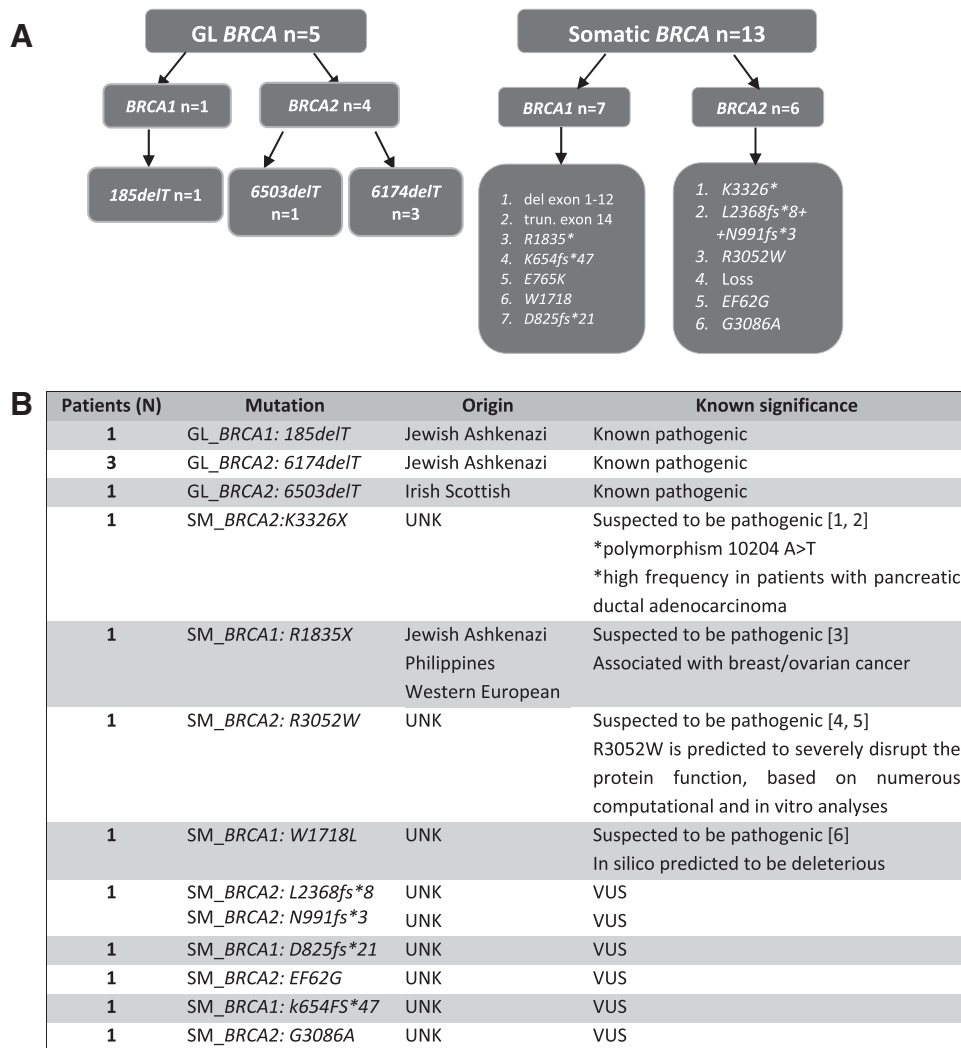
Abbreviations: AJCC, American Joint Committee on Cancer; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; PARPi, poly ADP ribose polymerase inhibitor.

### Data Collection

Data on participants' demographics, clinical history, personal and family history of cancer, past surgical procedures specifically pertaining to CCA, systemic chemotherapy, and response to treatment were extracted from patients' records or from existing institutional review board (IRB)-approved institutional databases. Clinical stage was classified according to the seventh edition of the American Joint Committee on Cancer staging criteria [25]. The IRB of each participating institute approved this study and/or the collection of data within an institutional database for future nonhuman subject research.

### DNA Analysis

At Sheba Medical Center, GL *BRCA1/2* mutational status analysis was performed at the Oncogenetics Unit, and each patient was genotyped for at least 3 to a maximum of 14 predominant *BRCA1* and *BRCA2* mutations using previously described assays [26, 27].



**Figure 1.** Distribution of all analyzed mutations according to their origin and type (A) and characterization of all analyzed mutation based on known pathogenicity and origin (B).

Abbreviations: GL, germline; UNK, unknown; VUS, variants of unknown significance.

Somatic mutational analysis from extracted cancerous tissue was performed commercially using next-generation sequencing technique according to each institution's laboratory practice. Samples collected at Mount Sinai Hospital were analyzed in a clinical Advanced Molecular Diagnostics lab [28]; samples collected at MD Anderson, The Ohio State University Medical Center, and University of California, San Francisco Medical Center were analyzed at Foundation Medicine [29].

### Statistical Analysis

OS was defined as the time from the date of diagnosis to the date of death from any cause using GraphPad Prism software. If a patient is not known to have died, the OS was censored until the date of last follow-up. Progression-free survival (PFS) was censored as well and defined as the time elapsed until recurrence or appearance of a new metastatic lesion.

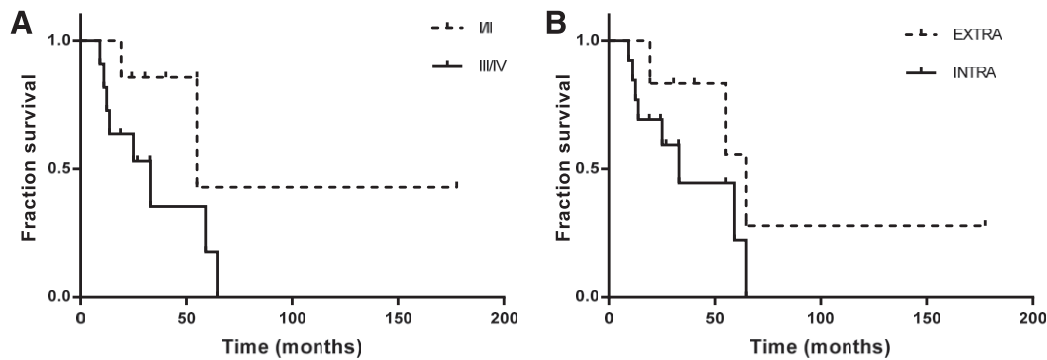
## RESULTS

### Demographic Features and Clinical Characteristics

Overall, we identified 18 cases of CCA harboring either GL ( $n = 5$ ) or somatic ( $n = 13$ ) BRCA1/2 variations. Mean age at the time of diagnosis was 60 (SD  $\pm 10$ ), range 36–75 years; 61.2% were males and the majority (15/18) were white, of whom four were of Jewish Ashkenazi origin. Distribution of stage at diagnosis was as follows: stage I ( $n = 4$ ), stage II ( $n = 3$ ), stage III ( $n = 3$ ), and stage IV ( $n = 8$ ). Six patients had ECC and twelve patients had ICC (Table 1).

### Family and Personal History of Malignancies

Four patients were diagnosed with cancer prior to their current CCA diagnosis, and three of them had BRCA-associated tumors: two breast and one pancreatic cancer. Most cases (14/18–77.8%) had a first- (85.71%) or second- (14.3%) degree relative diagnosed with cancer, and in 5/14 cases, BRCA-associated malignancies (breast, ovarian, prostate, and pancreatic) were noted in these affected family members (Table 1).



**Figure 2.** Overall survival of study population. **(A):** Patients diagnosed with cholangiocarcinoma (CCA) at stages I/II versus III/IV. **(B):** Extra versus Intra hepatic CCA.

**Table 2.** PFS and OS of patients receiving PARPi

Pt ID	OS (months)	PFS (months)	Ongoing PARPi (Y/N)	Previously treated with platinum (Y/N)
SHB-3	64.76	42.6	N	Y
SHB-1	33.04	3.68	N	N
SHB-2	11.01	2.04	N	Y
UCSF-1	32.77	4.66	Y	Y

Abbreviations: OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PFS, progression-free survival; Pt ID, patient identification.

## Characterization of Identified Mutations

### GL Mutations in *BRCA1/2*

All identified GL mutations are known pathogenic mutations and are predominant in either the Jewish Ashkenazi or Irish Scottish ancestry (Fig. 1A) [23, 24, 30].

### Somatic Variations in *BRCA1/2*

Thirteen additional mutations were somatically identified; these included previously reported and known deleterious mutations, variants with suspected pathogenicity, and variants of unknown significance (VUS). All identified somatic variations are summarized in Figure 1A and 1B.

### OS and PFS of Analyzed Patients

Median OS for patients with stage I/II was 40.27 months (95% CI, 6.73–108.15) and with stages III/IV was 25 months (95% CI, 15.23–40.57, Fig. 2A). Median OS in ICC and ECC was 24.67 (95% CI, 16.42–37.15) and 47.65 (95%CI, 3.96–125.21) months, respectively (Fig. 2B).

### Treatment with Platinum/PARP Inhibitors

Overall, 13 patients received platinum-based treatment, and four patients received PARP inhibitor (PARPi) therapy. All these latter cases were diagnosed with advanced stage disease. Treatment with PARPi resulted in a favorable response, with one patient's OS censored at 64.76 months and a PFS of 42.6 months. Data are summarized in Table 2.

### Known and/or Predicted Deleterious Mutations in *BRCA1/2* Versus Unknown Variants

Of the 18 mutations detected, nine were previously reported either with a known founder effect or predicted/suspected to be pathogenic. An additional six were unknown variants with nonverified knowledge of pathogenic potential. Patients bearing

either known pathogenic mutations or unknown variants and treated with either platinum-based therapy or PARPi demonstrated more favorable OS, ranging from 11.01 to 64.78 months for all patients censored (Table 3).

## DISCUSSION

In the presented retrospective study, we report 18 cases of *BRCA*-associated CCA from five participating institutions. All patients evaluated harbored either GL or somatic variations in *BRCA1/2* genes.

The founder mutations of Ashkenazi Jewish origin, such as 185delAG in the *BRCA1* gene and 6174delT in the *BRCA2* gene, were identified in the GL of four of the enrolled patients. An additional founder mutation, 6503delTT in *BRCA2*, the frequency of which is enriched in Central and Northern European populations, was identified in the GL DNA of one patient.

We also identified a variety of somatic variants derived from tumor tissue of participating patients, some of which were previously described as pathogenic or suspected to be pathogenic and also VUS. The potentially pathogenic variants identified here include a known *BRCA2* polymorphism variant K3326X (10204 A > T substitution), which occurs with a higher frequency in individuals with familial pancreatic adenocarcinoma [31]. The K3326X variant was also demonstrated to be associated with the risk of developing breast and ovarian cancers independent of other pathogenic variants in *BRCA2* [32]. The reported substitution leads to the appearance of a premature stop codon, resulting in the loss of the final 93 amino acids in the *BRCA2* protein. Importantly, the C-terminus of *BRCA2* is thought to be functional [33]. Another variant identified in *BRCA1*-R1835X and associated with breast/ovarian cancer in populations of Ashkenazi, Philippines, and Western European origin [34] eliminates the last 29 amino acid residues of *BRCA1*,

**Table 3.** OS in patients treated with platinum compounds and/or PARPi

Patient ID	BRCA mutation	Stage	Treatment	Time on treatment (months)	OS (months)	Status AWD/DOD <sup>a</sup>
Pathogenic variants						
MSH-1	BRCA2 GL_6174delT	I	Surgery		177.66	AWD
			ADJ: Gemcitabine + radiation	1		
			First-line: Radiation	0.5		
MSH-2	BRCA2 GL_6503delT	I	Surgery		40.27	AWD
			ADJ Gemcitabine	3		
			First-line: Gemcitabine + <b>Cisplatin</b>	33		
SHB-1	BRCA1 GL_185delAG	III	Surgery		33.04	DOD
			+ ADJ Gemcitabine	5		
			<b>First-line: PARPi</b>	3		
SHB-2	BRCA2 GL_6174delT	IV	First-line: <b>Oxaliplatin</b> + Gemcitabine	4	11.01	DOD
			<b>Second-line: PARPi</b>	2		
SHB-3	BRCA2 GL_6174delT	IV	Surgery		64.76	DOD
			First-line: Gemcitabine	1		
			Second-line: <b>Cisplatin</b> + 5FU	5		
			<b>Third-line: PARPi</b>	36		
Suspected pathogenic variants						
MDA-1	BRCA2 SM_K3326*	III	First-line: <b>Carboplatin</b> + Etoposide	3	12.36	DOD
			Second-line: Abraxane	NA		
MDA-6	BRCA2 SM_R3052W	IVB	First-line: Gemcitabine + <b>Cisplatin</b> + RFAx2	NA	59.18	DOD
			Second-line: <b>FOLFOX</b>	2		
MDA-7	BRCA1 SM_R1835*	IVA	First-line: Gemcitabine + <b>Cisplatin</b>	6	25.02	DOD
			Second-line: Gemcitabine + Capecitabine	2		
			Third-line: FOLFIRI + Traceva	3		
UCSF-5	BRCA1 SM_W1718	I	Surgery		55	AWD
Variants of unknown significance						
MDA-2	BRCA2 SM_L2368FS*8 BRCA2 SM_N991FS*3	IVB	First-line: Capecitabine + Gemcitabine	1	26.89	AWD
MDA-5	BRCA1 SM_D825FS*21	II	Surgery		19.23	DOD
			ADJ Gemcitabine + <b>Cispaltin</b>	5		
			First-line: Gemcitabine + <b>Cisplatin</b>	NA		
UCSF-1	BRCA2 SM_EF62G	III	Surgery		32.77	AWD
			ADJ: Gemcitabine + <b>Cisplatin</b>	5		
			<b>First-line: PARPi</b>	4.6		
UCSF-2	BRCA1 SM_K654FS*47	I	Surgery		24.33	AWD
			First-line: Gemcitabine + <b>Cisplatin</b>	1.6		
UCSF-3	BRCA2 SM_G3086A	IV	First-line: Gemcitabine + <b>Cisplatin</b>	7.3	13.67	DOD
UCSF-4	BRCA1 SM_E765K	IV	First-line: Gemcitabine + <b>Cisplatin</b>	16.6	18.9	AWD
Structural variants (DNA deletions/truncations)						
MDA-3	BRCA1 del exon 1-12	II	Surgery		30.54	AWD
			ADJ Capecitabine + Radiation	1		
			First-line: Gemcitabine + <b>Cisplatin</b>	28 (ongoing)		
MDA-4	BRCA1 trunc exon14	IVA	Gemcitabine	NA	9.2	DOD
MDA-8	BRCA2 loss	II	Surgery		55.03	DOD
			First-line: Gemcitabine + <b>Cisplatin</b>	9		
			Second-line: FOLFIRI	11		

<sup>a</sup>Censor date September 2015. Treatment with platinum agents and/or PARPi are indicated in bold.

Abbreviations: 5-FU, 5-Fluorouracil; ADJ, adjuvant treatment; AWD, alive with disease; DOD, deceased of disease; FOLFIRI, FOLinic acid + Fluorouracil + IRLinotecan combination; FOLFOX, FOLinic acid + Fluorouracil + Oxaliplatin combination; NA, not available; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; RFA, radiofrequency ablation.

which might lead to impaired interactions with various BRCA1 binding proteins [35].

Several cases of substitutions of R3052 in *BRCA2* to glutamine (R3052Q) or tryptophan (R3052W) have been reported. The R3052W variant specifically has been identified in multiple breast cancer families by Myriad Genetic Laboratories [36]. Farugia et al. describe a large family with seven cases of breast cancer, all harboring the R3052W mutation [37]. Arginine 3052 is located in the interface between oligonucleotide/oligosaccharide-binding folds and makes hydrogen bonds with neighboring amino acid residues, thus linking them together [38]. Hence, substitution at this position might have a deleterious effect given that the newly created amino acid has different chemical characteristics. Indeed, the *BRCA2* R3052W variant's pathogenic potential was demonstrated in various designated in vitro assays. For instance, mouse embryonic stem (ES) cell functional analysis of both the R3052Q and R3052W variants demonstrated that ES cells expressing the R3052W variant didn't survive, whereas R3052Q expression had no effect. Additionally, R3052W variant's influence of HR repair was analyzed using an in vitro green fluorescent protein-dependent homology-directed repair reporter assay, in which R3052W displayed reduced homologous recombination-dependent (HRD) activity compared with wild-type *BRCA2*, which supports the notion of its deleterious effect in DNA repair activity [37].

VUS identified in this study need further verification and analysis to confirm their pathogenic potential or lack thereof. Additionally, whether patients and their families should be screened for VUS in the GL is controversial.

In this multicenter retrospective cohort, the median age of diagnosis, stage, and gender prevalence were similar to the Surveillance, Epidemiology, and End Results program (SEER) [39]. For CCA patients harboring pathogenic variations in *BRCA1/2* genes who were treated with platinum-based and/or PARPi therapy, survival outcomes appear longer than SEER historical controls. Superior response to treatment with platinum-based agents and/or PARPi was demonstrated in patients with breast, ovarian, and pancreatic cancer harboring mutations in *BRCA1/2* genes in clinical trials and retrospective analyses [40]. A number of PARPi agents are being pursued and hold promise for personalized treatment for patients with GL or somatic *BRCA* mutations. Therefore, genetic testing for known founder mutations is currently recommended for high-risk populations [41–44]. Subsequently, family members of patients with identified GL mutations are offered to undergo genetic screening.

The results of this study support the rationale for somatic and/or GL *BRCA* genotyping in all patients diagnosed with CCA, the latter initially in populations in which founder mutations occur, such as Jewish Ashkenazi and Irish Scottish, and/or when family history or other clinical features indicate *BRCA* testing.

The limitations of this study, including the small sample size, its retrospective nature, the combination of somatic and GL variants, and the nondifferentiation between clearly pathogenic and VUS, make any conclusions tentative at best. Most importantly, we do not have sufficient information on non-*BRCA*-associated CCA cases identified in each participating institution with which we can compare our findings.

Our findings in this *BRCA* carriers CCA cohort are further reinforced by recently reported genomic similarity between CCA tumors and tumors of pancreatic, diffuse glioma, and small

cell (SC) lung origins, which demonstrates that tumor genotype can impact treatment response and must be incorporated along with anatomic site of origin into treatment decisions [45]. CCA and pancreatic tumors bearing variants in the same DNA repair pathway may share molecular burden with each other, and thus approaching *BRCA*-associated CCA similarly to *BRCA*-associated pancreatic ductal adenocarcinoma may be beneficial to a population of selected patients.

The data presented here are plausible to suggest conducting a prospective multicenter basket trial for *BRCA*-associated CCA, with either GL or somatic identified variations, and applying PARPi as a potential study arm, allowing for a more profound analysis of larger patients' cohorts [46]. The clinical relevance of somatic *BRCA* mutations can thus be analyzed in the setting of a prospective clinical trial. A similar approach was previously demonstrated in the Biomarker-Integrated Approaches of Targeted Therapy for lung cancer elimination trial for personalizing therapy for lung cancer, which represents the first completed, prospective, biomarker-based study in which non-small cell lung cancer patients were adaptively randomized to different therapeutic options based on relevant molecular biomarkers analyzed in fresh core needle biopsy specimens [47].

## CONCLUSION

The data presented herein provide the first clinical characterization of a multicenter cohort of CCA patients with GL or somatic *BRCA* variants. With the rising prevalence of CCA and the success of targeted therapy in other *BRCA*-associated tumors, this study provides a framework for future multicenter cohort analyses in *BRCA*-associated CCA and supports the development of a genotype-directed clinical trial in this important population. Additionally, this study demonstrates a rationale for both GL/tumor genotyping for CCA patients and genetic screening for individuals with a known family history of *BRCA*-associated malignancies, especially those with known genetic predispositions and ethnic backgrounds.

## AUTHOR CONTRIBUTIONS

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**Provision of study material or patients:** Talia Golan, Robin K. Kelley, Andrea G. Bocobo, Ayelet Borgida, Rachna T. Shroff, Spring Holter, Steven Gallinger, Daniel H. Ahn, Dan Aderka, Jain Apurva, Tanois Bekaii-Saab, Milind Javle

**Collection and/or assembly of data:** Talia Golan, Maria Raitses-Gurevich, Robin K. Kelley, Andrea G. Bocobo, Ayelet Borgida, Rachna T. Shroff, Spring Holter, Steven Gallinger, Daniel H. Ahn, Dan Aderka, Jain Apurva, Tanois Bekaii-Saab, Milind Javle

**Data analysis and interpretation:** Talia Golan, Maria Raitses-Gurevich, Milind Javle

**Manuscript writing:** Talia Golan, Maria Raitses-Gurevich, Eitan Friedman, Milind Javle

**Final approval of manuscript:** Talia Golan, Maria Raitses-Gurevich, Robin K. Kelley, Andrea G. Bocobo, Ayelet Borgida, Rachna T. Shroff, Spring Holter, Steven Gallinger, Daniel H. Ahn, Dan Aderka, Jain Apurva, Tanois Bekaii-Saab, Eitan Friedman, Milind Javle

## DISCLOSURES

**Robin K. Kelley:** Agios, Arqule (C/A), Agios, Eli Lilly and Co., Merck, Novartis, (RF); **Rachna T. Shroff:** Amgen, Codiak Biosciences, Celgene (C/A), Agios, Celgene, Eli Lilly (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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