

Association between breast cancer and gallbladder cancer: Evidence from two independent biliary tract cancer cohorts

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ABSTRACT

Introduction: Currently, no conclusive evidence exists regarding the association between biliary tract cancer (BTC) and other primary malignancies. Our study aims to explore a potential correlation between BTC and breast cancer. To test the hypothesis of a differential association between breast cancer and gallbladder cancer (GC) compared with other BTC subtypes (non-GC), both a training and a validation cohort were analyzed.

Methods: Data from 1,687 patients with BTC were collected and analyzed, of whom 12.1% ($n = 204$) were included in the training cohort and 87.9% ($n = 1,483$) in the validation cohort.

Results: In the training cohort, 7.3% of the overall population ($n = 15/204$) had also history of breast cancer: 9 out of 35 patients with GC (25.7%) and 6 out of 169 with non-GC (3.5%) (OR 9.40, 95% confidence interval (CI) 3.09–28.62, $p < 0.01$). In the validation cohort, 2.9% of the overall population ($n = 43/1,483$) had also history of breast cancer: 13 out of 252 patients with GC (5.1%) and 30 out of 1,231

with non-GC (2.4%) (OR 2.18, 95% CI 1.12–4.24, $p = 0.02$). Combining the training and validation cohorts, the diagnosis of breast cancer preceded BTC in 54 out of 58 of the patients with both the tumors (93.1%).

Conclusions: Our study demonstrates a higher prevalence of prior breast cancer in patients with GC compared with patients with other BTC subtypes across both training and validation cohorts. Future studies starting with breast cancer populations and investigating their subsequent risk of BTC, particularly GC, are warranted.

INTRODUCTION

Biliary tract cancer (BTC) is a highly aggressive and heterogeneous group of neoplasms originating from the biliary tree. It represents the second most common primary hepatic malignancy, following hepatocellular carcinoma. Although rare, its incidence has been rising in Western countries over the past two decades, now accounting for up to 2% of all gastrointestinal cancers, and it carries a poor prognosis, with a 5-year overall survival of only 20% [1, 2].

In recent years, increasing attention has been given to the classification of BTC according to the site of origin: intrahepatic cholangiocarcinoma (iCCA), gallbladder carcinoma (GC), and extrahepatic cholangiocarcinoma (eCCA), the latter further divided into perihilar and distal subtypes [3]. These anatomical distinctions are associated with marked epidemiological, clinical, histological, and molecular differences. Globally, the incidence of BTC ranges from 0.3 to 6 cases per 100,000 inhabitants per year, with significant geographic variability [4]. In over 60% of cases, the diagnosis is established when curative surgery is no longer achievable, making systemic therapy the initial treatment option [5]. This consists of a combination of chemotherapy with cisplatin and gemcitabine together with immunotherapy, either the programmed cell death ligand 1 (PD-L1) inhibitor durvalumab or the PD-1 inhibitor pembrolizumab. These regimens currently represent the standard of care for BTC in the first-line setting, as supported by the results of the phase III TOPAZ-1 and KEYNOTE-966 trials [6–14] and by the data deriving from recent real-world studies [15–18]. More recently, the molecular profiling of these neoplasms has enabled the investigation and approval of targeted agents, thereby broadening the therapeutic landscape in the second-line setting for patients harboring specific genetic alterations [19–29].

Beyond epidemiology, each subtype is characterized by a specific genomic landscape. The introduction of next-generation sequencing (NGS) has enabled the identification of potentially targetable mutations, which show distinct distributions across histological subtypes. More than half of iCCA cases harbor actionable genetic alterations, most frequently involving IDH1/2, FGFR2, BRAF, BRCA1/2, HER2, ALK, RET, and NTRK. In contrast, eCCA more often presents mutations in KRAS, TP53, ARID1A, and SMAD4, which are typically non-actionable [30–31]. GC displays a different molecular profile, with alterations in more than 5% of cases in ATM,

HER2, and PIK3CA, as reported by a systematic review by Kuipers et al. analyzing 62 studies. In addition, they confirmed TP53 as the most frequently detected mutation (weighted average 57%), followed by SHH (20%), ELF3 (19%), ARID1A (14%), and SMAD4 (13%). Frequent gene amplifications included CCNE1, CDK4, HER2, FRS2, KRAS, MDM2, and MYC, while CDKN2A and CDKN2B emerged as the most common deletions [32].

Over the years, several studies have also explored the potential role of germline mutations in BTC. Maynard et al. investigated 131 patients, reporting germline alterations most frequently in iCCA (63.4%), followed by GC (16.8%), eCCA (16%), and unclassified cases (3.8%). Among high-penetrance cancer susceptibility genes, BRCA1 and BRCA2 were the most prevalent, accounting for 5.3% of the entire BTC cohort, followed by PALB2, BAP1, and PMS2 [33]. BRCA1/2 were originally identified as major drivers of inherited breast cancer susceptibility, as consistently demonstrated across multiple studies [34].

Currently, no conclusive evidence exists regarding the association between BTC and other primary malignancies. Building on prior clinical observations, the present study aims to explore a potential correlation between BTC and breast cancer. Specifically, our analysis will compare patients with GC versus non-GC subtypes in relation to the history of breast cancer, given the established role of some germline and somatic mutations, such as HER2 alterations, in both breast and gallbladder carcinogenesis. To validate this hypothesis, we employed both a training and a validation cohort.

RESULTS

Two subgroups according to BTC site were defined in both the training and validation cohorts: GC and non-GC.

In the training cohort ($n = 204$), 17.1% ($n = 35$) had a diagnosis of GC, whilst 82.8% ($n = 169$) were classified as non-GC; 7.3% of the entire population ($n = 15$) had history of breast cancer: 9 out of 35 patients (25.7%) with GC and 6 out of 169 (3.5%) with non-GC (OR 9.40, 95% CI 3.09–28.62, $p < 0.01$). Characteristics of patients with previous history of breast cancer were reported in Supplementary Table 1.

In the validation cohort ($n = 1483$), 17.0% ($n = 252$) had a diagnosis of GC, while 83.0% ($n = 1231$) were classified as non-GC. Previous history of breast cancer was identified in 2.9% of the entire population ($n = 43$):

Table 1: Summary of the results in the training and validation cohorts

Cohort	Total <i>n.</i>	GC, <i>n.</i> (%)	Non-GC, <i>n.</i> (%)	Breast cancer, total, <i>n.</i> (%)	Breast cancer in GC, <i>n.</i> (%)	Breast cancer in Non-GC, <i>n.</i> (%)	OR (95% CI)	<i>p</i> -value	Median interval (years, 95% CI)
Training	204	35 (17.1%)	169 (82.8%)	15 (7.3%)	9 (25.7%)	6 (3.5%)	9.40 (3.09–28.62)	<0.01	7.3 (4.9–9.7)
Validation	1483	252 (17.0%)	1231 (83.0%)	43 (2.9%)	13 (5.1%)	24 (2.4%)	2.18 (1.12–4.24)	<0.02	7.1 (4.8–9.3)
Pooled	1687	287 (17.0%)	1400 (83.0%)	58 (3.4%)	22 (7.7%)	30 (2.1%)	–	–	GC: 6.9 (4.1–9.8) Non-GC: 7.2 (4.9–9.5)

Abbreviations: CI: confidence interval; GC: gallbladder cancer; *n*: number; OR: odds ratio.

Table 2: Genomic alterations in patients with gallbladder cancer

TP53	CDKN2A	APC	CCNE1
CDK4	CDKN2B	KRAS	SETD2
DNMT3A	RNF43	EPHB4	PRKCI
MLL2	SMARCA4	CCND1	CDK6
ARID1A	ALK	FGFR2	CSF3R
BAP1	FANCL	FGF23	MYCL1
PBRM1	STK11	KDM5A	INPP4B
PTCH1	MAP3K13	KDM6A	MEN1
TGFBR2	SMAD4	FGF10	MSH6
FGF4	ERBB2	BRCA2	NOTCH2
MDM2	STAG2	EED	CTNNB1
IDH1	JAK2	KEAP1	FANCG
MTAP	FBXW7	TERC	RB1
FGF3	CDH1	FGF6	MET
ERRFI1	TERT	ERBB3	FGF19
MUTYH	RBM10	TSC2	CCND2
LYN	MRE11A	NF1	NRAS

13 out of 252 patients (5.1%) with GC and 30 out of 1231 (2.4%) with non-GC (OR 2.18, 95% CI 1.12–4.24, *p* = 0.02). Characteristics of patients with previous history of breast cancer were reported in Supplementary Table 1.

Combining the training and validation cohorts, the diagnosis of breast cancer preceded BTC in 54 out of 58 of the patients with both the tumors (93.1%). The median interval between the diagnosis of the first and the second cancer was 7.3 years (95% CI 4.9–9.7) in the training cohort and 7.1 years (95% CI 4.8–9.3) in the validation one. The median interval between the two tumor diagnoses was 6.9 years (95% CI 4.1–9.8) in GC subgroup and 7.2 years (95% CI 4.9–9.5) in non-GC subgroup. A summary of these results was reported in Table 1.

Histological subtypes and molecular characteristics

In the validation cohort it was possible to retrieve details on breast cancer histology in a subgroup of 27

patients. The majority was either luminal A or B according to the breast carcinoma molecular subclassification: indeed, 88.9% (*n* = 8/9) with GC had positive hormonal receptors profile; for the non-GC subgroup, 83.3% (*n* = 15/18) were either luminal A or B. Only 1 patient in the non-GC subgroup showed HER2 3+ expression.

Of the 172 patients whose tumors received a Comprehensive Genome Profiling with Foundation One CdX in the training cohort, the 28 with GC were further investigated. In this subgroup, those having positive and negative breast cancer history were 7 and 21, respectively. 68 total mutations available were retrieved from the genetic analysis of the 28 selected patients (Table 2).

Within the validation cohort, a total of 34 tumors were sequenced with Foundation One CdX, 24 of which with the diagnosis of GC. In this subgroup, those who have positive and negative breast cancer history were 3 and 21, respectively.

Thereafter, we analyzed the subgroup of patients with GC having received a Comprehensive Genome Profiling with Foundation One CdX of the training and validation cohorts combined, obtaining 10 patients having both breast and GC diagnosis, and 42 patients with GC without history of breast cancer. Then, only those alterations retrieved in at least 10% of the patients of this subgroup have been considered for further statistical analyses. So, the gene mutations selected were 11: TP53, ARID1A, MDM2, CDKN2A, CDKN2B, MTAP, STK11, HER2, KRAS, SMAD4, and APC (Figure 1).

According to Fisher exact calculation, HER2 (20.0% vs. 9.7%, $p = 0.58$), MDM2 (40.0% vs. 12.2%, $p = 0.06$), CDKN2A (50.0% vs. 29.3%, $p = 0.27$), MTAP (20.0% vs. 12.2% $p = 0.61$), ARID1A (30.0% vs. 19.5%, $p = 0.67$), CDKN2B (30.0% vs. 21.9%, $p = 0.68$) mutations were more frequent in those with positive breast cancer history, although no statistically significant difference was observed. STK11 mutations were present only in patients with negative breast cancer history (19.5% vs. 0.0%, $p = 0.33$). No major differences in mutations were observed for the following genes: TP53 (60.0% vs. 56.1% in positive and negative history, respectively, $p = 1.00$), SMAD4 (10.0% vs. 9.7%, $p = 1.00$), KRAS (10.0% vs. 14.6% $p = 1.00$), APC (10.0% vs. 9.7%, $p = 1.00$) (Figure 1).

DISCUSSION

The present work reports on one of the first analyses exploring the association between breast cancer and BTC. The history of breast cancer was more frequently observed in GC patients compared with non-GC patients,

both in the training cohort (25.7% vs. 3.5%) and in the validation cohort (5.1% vs. 2.4%). In most cases, breast carcinoma was diagnosed before BTC, regardless of anatomical subtype, with an average interval of seven years between the two diagnoses. This pattern may largely reflect epidemiological differences between the two malignancies, as breast cancer is considerably more common in the general population and typically develops at a younger age, whereas BTC are relatively rare and tend to present later in life. From a clinical perspective, this temporal pattern may also suggest that breast cancer represents the first manifestation of an underlying biological susceptibility that could later predispose a subset of patients to the development of biliary tract malignancies, although this hypothesis requires further investigation.

In our population, breast carcinomas associated with BTC were predominantly hormone receptor-positive, classified as either luminal A or luminal B. These features were consistently observed in both GC and non-GC subgroups, with the only exception being a single case of HER2 3+ breast cancer identified in the non-GC subgroup. The predominance of luminal subtypes in our cohort is noteworthy, as these tumors are typically characterized by a strong dependence on hormonal signaling pathways, raising the possibility that endocrine-related mechanisms may contribute, at least in part, to the observed association between breast cancer and GC.

The potential link between BTC tumorigenesis and hormone receptor expression has been only marginally investigated, with conflicting evidence to date. Sex hormones are known to influence gallbladder physiology, with delayed bile emptying documented

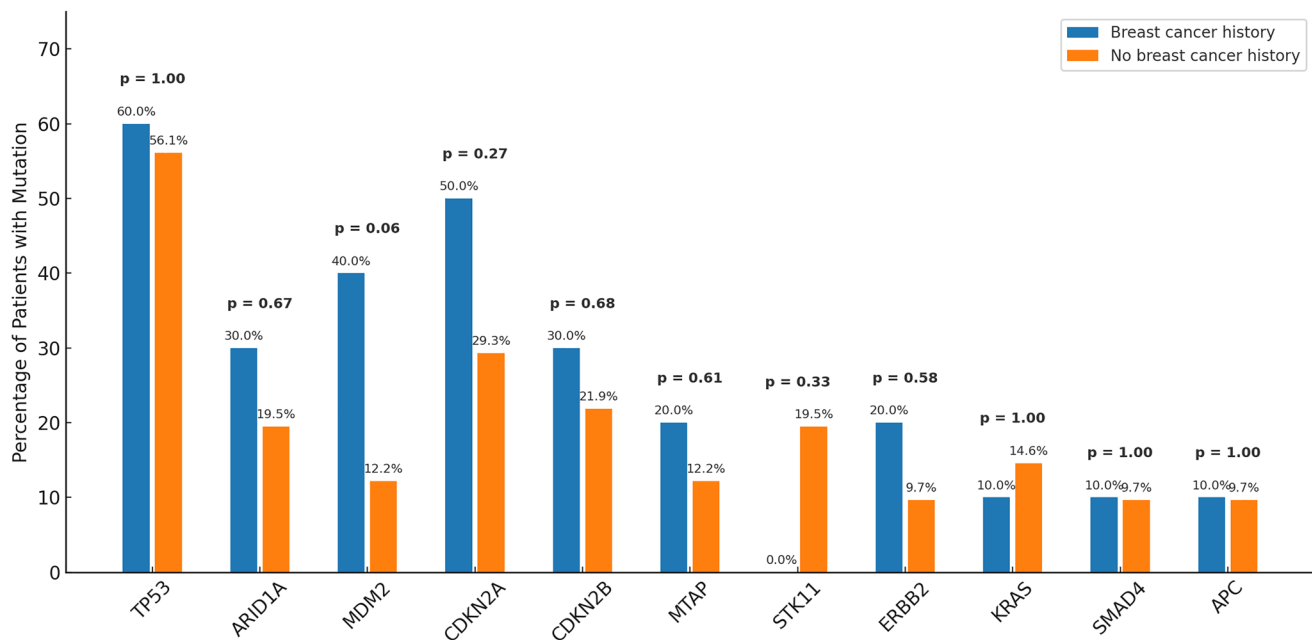


Figure 1: Genomic alterations in patients with gallbladder cancer.

during pregnancy and the luteal phase of the menstrual cycle [35]. Expression of estrogen receptor (ER) and progesterone receptor (PR) has been described in both benign and malignant gallbladder lesions, potentially contributing to the metaplasia–dysplasia sequence in chronically inflamed mucosa of female patients [36–37]. Estrogen-related receptor alpha has been shown to promote GC proliferation and invasion through the induction of epithelial–mesenchymal transition and has been proposed as a potential biomarker and therapeutic target [38]. However, robust supporting evidence about this potential link has not yet emerged in the literature [35–38]. Taken together, these observations suggest that hormonal signaling may represent a biologically plausible but still insufficiently explored mechanism linking breast and gallbladder carcinogenesis. In our view, this area deserves renewed attention, particularly in the context of hormone receptor–positive malignancies.

Genetic predisposition is another emerging field of interest. However, only anecdotal reports and single-institution series have specifically addressed the germline background of GC. Several germline alterations, including BRCA1/2, BAP1, and STK11, have been associated with cancer predisposition syndromes involving multiple organs [39–40]. In the BTC setting, data remain scarce, and no definitive evidence exists regarding germline predisposition according to anatomical subtype. Recently, Wardell et al. identified deleterious BRCA1/2 germline mutations in 6 of 146 (4.1%) Japanese patients with BTC, while other studies have reported associations between germline defects in DNA mismatch repair genes or POLD1/POLE and an increased risk of BTC [41–42]. Nonetheless, further studies are required to clarify the contribution of germline mutations in GC. Considering the well-established role of germline alterations in breast cancer susceptibility, it is tempting to speculate that shared inherited mechanisms may contribute to the co-occurrence of these malignancies in a subset of patients. Future studies incorporating systematic germline testing may help clarify whether a common predisposition underlies this association.

In our analysis, somatic genomic differences were noted between patients with GC with and without a history of breast cancer, although without any statistically significant difference. STK11 mutations were exclusively found in patients with GC without breast cancer history, whereas alterations in ARID1A, MDM2, CDKN2A, CDKN2B, HER2, and MTAP were more common among those with diagnosis of breast cancer. The enrichment of HER2 alterations in this group was not unexpected, given its established role in both breast and gallbladder carcinogenesis [43–44]. Although these findings should be interpreted cautiously given the limited sample size, they may provide preliminary signals suggesting partially overlapping molecular pathways between the two tumor types.

The increased frequency of MDM2 mutations in GC patients with breast cancer history (40.0% vs. 12.2%, $p = 0.06$) warrants attention. MDM2, an E3 ubiquitin-protein ligase, is a well-known inhibitor of TP53 [45]. In breast cancer, its expression has been linked to ER-alpha signaling, with evidence supporting a role in ER-alpha ubiquitination and degradation. Notably, MDM2 mutations are more commonly associated with luminal A and B breast cancers [46–50]. These observations may explain the higher prevalence of MDM2 mutations in patients with GC with a history of breast cancer, although confirmation in larger cohorts is required. If confirmed, these findings could suggest that alterations in the TP53–MDM2 regulatory axis might represent a shared biological vulnerability across these malignancies.

We also observed a high frequency of ARID1A mutations in patients with GC and diagnosis of breast cancer (30.0%). ARID1A encodes a key stabilizer of the BRG1/BRM-associated factor (BAF) complex, a regulator of chromatin remodeling and transcription [51]. ARID1A loss has been implicated in the pathogenesis of several hormone-dependent malignancies, including breast, ovarian, and endometrial cancers. In ER-positive breast cancer, ARID1A normally binds within ER-associated enhancers, and its loss facilitates tumor progression [52]. Recent studies on ER-positive breast cancer suggest that ARID1A loss affects cellular plasticity, influencing luminal lineage-defining transcription factors such as ER, FOXA1, and GATA3 [53]. These mechanisms may also contribute to our findings, though larger-scale studies are needed to validate this hypothesis. From a broader perspective, these observations reinforce the concept that epigenetic dysregulation may represent an additional link between hormone-dependent tumors and certain BTC subtypes.

Our study has several limitations. First, its retrospective design may have introduced inaccuracies in medical history reporting, particularly for breast cancer diagnoses occurring many years prior to BTC. Predisposition to develop breast cancer in patients affected by BTC might be underestimated, as the unfavorable prognosis of the latter one limits patient observation along time. Clearly, this limitation might have impacted the proportion of patients with prior history compared to those with subsequent history of breast cancer observed in our population. In addition, the retrospective nature of our datasets may have influenced the different reported percentages of patients with GC and breast cancer in the training and validation cohorts, highlighting the need for further studies to ensure greater robustness of our findings. Second, we lacked comprehensive biological data for all breast cancer cases, and molecular information such as Ki-67, HER2 status, and ER/PR expression was unavailable for part of the validation cohort. Third, NGS profiling was not uniformly performed across BTC

samples, limiting the generalizability of our genomic findings. Finally, no germline testing was available in our series. The role of germline testing in BTC remains debated and is not yet implemented in routine practice in Italy or Spain. Despite these limitations, our study provides an initial signal that may stimulate further research in this underexplored area.

In conclusion, our study demonstrates a higher prevalence of prior breast cancer in patients with GC compared with patients with other BTC subtypes across both training and validation cohorts. Future studies starting from breast cancer populations and investigating their subsequent risk of BTC, particularly GC, are warranted. From a clinical standpoint, a better understanding of this association could have relevant implications for risk stratification and long-term follow-up strategies in selected patient populations. Should these findings be confirmed, dedicated surveillance strategies for GC in patients with a history of breast cancer may be justified.

MATERIALS AND METHODS

The study population included patients with diagnosis of BTC (any stage), including iCCA, eCCA and GC. Data were retrospectively collected from 3 sites in 2 countries (Italy and Spain).

The training cohort enrolled 204 patients with diagnosis of BTC between 2021 and 2023 at San Raffaele Institution, Milan, Italy. For the validation cohort, other two Academic Centers were involved: Vall d'Hebron Institute of Oncology (VHIO) in Spain and Veneto Institute of Oncology (IOV) in Italy. Data from a total of 1483 patients diagnosed with BTC were collected between 2015 and 2023.

In patients where tissue samples were available, Comprehensive Genome Profiling of the primary tumors was performed using FOUNDATION Cdx technology.

Statistical analysis

Categorical variables, including sex, primary tumor site, and history of breast cancer, were summarized as absolute numbers of cases and corresponding percentages, to provide a clear description of the distribution within the study population. Continuous variables were instead reported as medians along with their 95% confidence intervals (CIs), thereby ensuring a more accurate representation of central tendency and variability compared with simple means.

To assess the association between the presence or absence of a prior diagnosis of breast cancer and the occurrence of BTC, we retrospectively calculated Odds Ratios (ORs) with the respective 95% CIs. This approach allowed us to quantify the magnitude of the relationship between the two independent groups, namely patients with or without a history of breast cancer, and to determine

whether the observed differences were of potential clinical significance.

Comparisons of categorical patient and tumor characteristics between these groups were conducted using Fisher's exact test, which is particularly suitable when dealing with small sample sizes or sparse distributions. This statistical test provided a robust evaluation of whether the distribution of key variables, such as sex, anatomical site, or other clinical features, differed significantly across groups.

All statistical analyses, including descriptive statistics, calculation of Odds Ratios, and Fisher's exact tests, were performed using MedCalc Statistical Software (MedCalc Software Ltd, Ostend, Belgium).

AUTHOR CONTRIBUTIONS

Conception and design: Andrea Casadei-Gardini, Mara Persano, Margherita Rimini. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: Andrea Casadei-Gardini, Mara Persano, Margherita Rimini. Writing, review, and/or revision of the manuscript: Andrea Casadei-Gardini, Mara Persano, Margherita Rimini. Final approval of manuscript: All authors.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

Andrea Casadei Gardini reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, and Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, and Servier; travel expenses from AstraZeneca; research grants (to the institution) from AstraZeneca, and Eisai.

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Mara Persano, Margherita Rimini, Antonio De Rosa, Daniel López-Valbuena, Mario Domenico Rizzato, Florian Castet, Caterina Soldà, Gloria Castillo, Teresa Macarulla, Silvia Camera, Francesco Vitiello, Federico Rossari, Federica Pedica, Francesca Ratti, Francesco De Cobelli, and Paolo Giorgio Arcidiacono declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

ETHICAL STATEMENT

The ethics committee of each involved center approved this trial, in agreement with the provisions of the Good Clinical Practice guidelines, the Declaration of Helsinki, the local laws, and the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 regarding the protection of natural persons and the processing of personal data.

CONSENT

All patients provided written informed consent before enrollment in the study.

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Association between breast cancer and gallbladder cancer: Evidence from two independent biliary tract cancer cohorts

SUPPLEMENTARY MATERIALS

Supplementary Table 1: Baseline characteristics of patients with history of breast cancer

Characteristics	Training cohort	Validation cohort	<i>p</i> -value
Gender			
Male	0 (0.0%)	1 (2.3%)	1.00
Female	15 (100.0%)	42 (97.7%)	
Age at breast cancer diagnosis			
<70 yrs	13 (86.7%)	31 (72.1%)	0.32
≥70 yrs	2 (13.3%)	12 (27.9%)	
Age at BTC diagnosis			
<70 yrs	4 (26.7%)	21 (48.8%)	0.22
≥70 yrs	11 (73.3%)	22 (51.2%)	
Primary site			
Non-GC	6 (40.0%)	30 (69.8%)	0.06
GC	9 (60.0%)	13 (30.2%)	
Surgery for BTC			
Yes	12 (80.0%)	24 (55.8%)	0.12
No	3 (20.0%)	19 (44.2%)	
NGS for BTC			
Yes	4 (93.3%)	22 (51.2%)	<0.01
No	11 (6.7%)	21 (48.8%)	
Type of NGS			
Foundation One CdX	13 (86.7%)	13 (26.5%)	0.05
Others	1 (6.7%)	9 (20.9%)	

Abbreviations: BTC: biliary tract cancer; GC: gallbladder cancer; NGS: next-generation sequencing; yrs: years.