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Talking Genes in Breast and Pancreatic Malignancies

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ABSTRACT

Introduction: Both breast and pancreatic cancers have high mortality rates. Breast cancer is the second leading cause of cancer death in females, while pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer death. Almost 4-16 % of individuals with pancreatic cancer have a family history of the disease. Intra-ductal papillary mucinous neoplasms (IPMNs) are cystic lesions that received more attention lately due to their associations with PDAC and other solid organ tumors, such as breast cancer. Aim: The purpose of this article is to discuss the association of the familiar pancreatic cancer (FPC), sporadic pancreatic cancer, and IPMNs with the breast cancer. Results: Mutations in *BRCA2, BRCA1, p16 and PALB2 play a major role in* the genetic etiologies of familial pancreatic cancer. In familial and sporadic pancreatic cancers, mutations in *BRCA2* are associated with a high incidence of PDAC, while mutations in *BRCA1have shown inconsistent results.* Data is insufficient to prove an association between IPMNs and breast cancer. Conclusion: The familial clustering of PDAC is not well understood. Further studies are required for greater comprehension of the genetic basis of PDAC and the association between IPMNs and breast cancer.

Key Words: Breast cancer, pancreatic ductal adenocarcinoma (PDAC), IPMNs, BRCA1, BRCA2

1. INTRODUCTION

Both breast and pancreatic cancers have high mortality rates. Breast cancer is the second leading cause of cancer death in females,(1) while PDAC is the fourth most common cause of cancer death.(2)Although the majority of PDAC cases are nonhereditary, approximately 10-15 % of PDAC are attributable to genetic causes. (3, 4)The hereditary risk for PDAC presents in two categories. The first one includes inherited cancer syndromes that associate with PDAC, such as: Peutz Jeghers syndrome, hereditary nonpolyposis colorectal cancer, hereditary pancreatitis, familial atypical multiple mole melanoma, and hereditary breast /ovarian cancer. The second category is the FPC which is characterized as at least two first degree relatives with PDAC who do not fulfill the criteria of any other inherited cancer syndrome. Although the genetic foundation of the familial aggregation of PDAC remains ambiguous, some remarkable pancreatic cancer genes were identified, such as: *BRCA1, BRCA2 and PALB2,* (5, 6) which suggests a genetic correlation with breast cancer. Furthermore, pancreatic cystic neoplasms such as intra-ductal papillary mucinous neoplasms (IPMNs) might be associated with breast cancer as well. (7-9)

2. BRCA2

BRCA2 is a tumor suppressor gene located on chromosome 13q whose protein functions in DNA restoration. Mutations in *BRCA 2* gene are inherited in an autosomal dominant pattern with incomplete penetrance .(10) Although they are uncommon in the general population, they are more prevalent in some racial groups, such as Ashkenazi Jews. The carriers of these mutations may exhibit two distinct cancer phenotypes.(11, 12) The first one exemplifies BRCA2 mutation carriers who have a high prevalence of breast and ovarian malignancies, and might be furthermore distinguished based on the incidence of PDAC. The other one represents BRCA2 mutation carriers who have pancreatic cancer and without history of FPC or breast cancer.

3. BRCA2 AND FPC

BRCA2 mutations are the most common inherited propensity to PDAC. Some studies attempted to investigate the incidence of PDAC

in BRAC2 mutation carriers, others aimed to examine the prevalence of BRCA2 mutations in families with FPC. A large study of 173 breast-ovarian cancer families with BRCA2 mutations from Europe and North America , carriers had 3.5 fold increased incidence of PDAC (95% CI 1.9–6.6) compared to non-carriers.(13) In a retrospective study conducted by Couch et al,(14) *BRCA2* mutations accounted for 6% of families meeting the criteria of FPC (⩾ 2 first-degree relatives were affected with PDAC). In contrast to these results, Lal *et al*(15) couldn't identify any *BRCA2* mutations in four PDAC individuals classified as high-risk for FPC or in twelve individuals classified as intermediate risk for FPC. The reason for this contradiction could be due to small sample size in the high-risk population and less strict classification criteria in the intermediate risk population.

Murphy et al (16) investigated the role of the *BRCA2* mutations in FPC relatives. BRCA2 mutations were found in 5 of 29 patients (17.2%). Similarly, Hahn et al (17) identified BRCA2 mutations in 12-19% of European families of non-Jewish descent in which at least two first-degree relatives had history of PDAC.

Unlike other hereditary cancers, the onset of hereditary PDAC is late and similar to that seen in sporadic PDAC, which could be related to the fact that the inactivation of *BRCA2* in the pancreatic duct lesions is a late event.(18)

4. BRCA2 AND SPORADIC PANCREATIC CANCER

The majority of the BRCA2 mutations that are associated with sporadic pancreatic cancers were reported in Ashkenazi Jewish; the most common one is BRCA2 6174delT which was replicated in multiple studies. In a study conducted by Ozcelik et al, the incidence of germline BRCA2 6174delT mutation in Ashkenazi Jewish with PDAC was higher than its incidence in general Ashkenazi population (10 % vs 1.36 % , respectively).(19) A decade later, Ferrone et al(20) identified *BRCA2* 6174delT mutation in 4.1 % of Ashkenazi Jewish individuals who underwent surgical resection for PDAC. Other less common BRCA2 germline mutations such as 6174delT and 6158insT were identified in 9.8 % of individuals with PDAC.(11)(Table1)

5. BRCA1 AND FPC

Similar to *BRCA2, BRCA1*is a tumor suppressor gene whose protein product functions in DNA repair.(21)However, the risk of PDAC in *BRCA1* mutation carriers is not well proved because the results of the *BRCA*1 mutation studies have been less consistent. The Breast Cancer Linkage Consortium examined 11 847 patients from 699 families segregating a *BRCA1* mutation across thirty centers in Europe and North America, and found 2-fold increase risk of PDAC.(22) Brose and colleagues studied 381 females with BRCA1 mutations in 147 families at University of Pennsylvania and University of Michigan and reported 3-fold higher risk of PDAC in *BRCA1* mutation carriers compared with the general population.(23)

Other researchers were unable to prove a connection between *BRCA1* mutations and PDAC. Axilbund et al analyzed BRCA1 mutation in 66 patients with FDC and none of them were found to have deleterious BRCA1 gene mutation.(24)

Study	Population/ Number N	BRCA1 Mutations	BRCA2 Mutations	% n=Number
Goggings et al ,1996 (11)	Sporadic N=245	–	6174delT 6158insT	9.8% n=4
Ozcelik at al,1997(19)	Ashkenazi Jews N=41	–	6174delT	10% n=4
Murphy et al, 2002 (16)	Familial N=29 families (6 Ashkenazi Jewish descent)	–	6174delT	17% n=5
Hanhn el al, 2003(17)	Familial n=26 families, 64 patients	–	4075delGT 6672insT 6819delT GR2034C G3078E 10323del-Cins11	19% n=5/26
Ferrone et al,2009 (20)	Jewish patients N=145 patients	185delAG 5382insC	6174delT	5.5% n=2 BRCA1,6 BRCA2

Table 1. Comparison Between Studies Evaluating BRCA1 and BRCA2 Mutations in Patients with Familial and Sporadic PDAC

6. PALB2

PALB2 is a breast cancer susceptibility gene; its protein is essential for BRCA2 anchorage to nuclear structures.(25) Its association with BRCA2 made it a susceptibility gene to other *BRCA2*-related cancers such as PDAC. It is reported to be the second most common mutated gene for hereditary PDAC,(6) (New York, N.Y. however the absolute and relative risk for the evolution of PDAC in individuals with PALB2 mutation is unclear.(26)Jones and colleagues studied the PALB2 mutation in 96 FPC patients, and three truncating PALB2 mutations were identified (3.1%).(27)A European study also detected three truncating PALB2 mutations on FPC families, mostly in individuals with concomitant breast cancer.(26)

7. INTRA-DUCTAL PAPILLARY MUCINOUS NEOPLASM AND BREAST CANCER

Intra-ductal papillary mucinous neoplasm (IPMNs) is an intra-ductal tumor described as excessive mucin production, dilation of pancreatic ducts and potential malignancy. (28) They were initially discovered by Ohashi et al in 1982. (29)Multiple studies attempted to determine the association between IPMNs and extra-pancreatic malignancies (EPMs) have showed mixed results. Lucas et al reported that 28.6 % of Ashkenazi Jewish individuals who underwent IPMNs resection had *BRCA1* or *BRCA2* mutations.(8) In a retrospective study conducted in Israel to evaluate the association between IPMNs and EPMs , 4% of all tested individuals (6.7% of the tested Ashkenazi Jewish) carried the BRCA2 mutations.(7) A national population based study, using data from the Surveillance Epidemiology and End Results (SEER), studied the incidence of primary extra pancreatic cancer in patients with invasive IPMNs and sporadic PDAC. Interestingly, breast cancer was the second most common site (19.9%) after the digestive system (24.9 %).(9)In the same study, most of the breast cancer cases were diagnosed

Study	Study Design	Ethnicity	IPMN patients(n)	Control group patients(n)	Breast cancer percentage in IPMN patients	**Most common EPNs sites**
Riall et al, 2007 (9)	National population-based observational cohort	Western	992	18655 PDAC	19.9%	-colorectal -Breast -Prostate
Baumgaertner et al, 2008 (27)	Case-Control	Western	178	356 GP	29 %	-Breast -Prostate -Colorectal
Reid-Lombardo et al, 2010 (28)	Retrospective	Western	471	471 PDAC 1413 RC	5 %	-Skin -Breast -Prostate
Lubezky et al, 2012 (7)	Retrospective	Eastern	82	150/PDAC	19%	Colorectal -Prostate -Breast
Larghi et al, 2013 (34)	Multicenter Cohot study	Western	390	-	15.5 %	-Breast -Colorectal -Renal
Marchegiani et al ,2015 (29)	Mutli-center observational study	Western	1340	-	5.9%	(in females) - Breast -Colorectal -GYN
Panic et al ,2018 (35)	Single center study	Western	198	-	6.8%	-Colorectal -Breast -Renal

GP: General population , RC : Referral Control

Table 2. Comparison Between Studies Evaluating Breast Cancer Incidence in Patients with Intra-ductal Papillary Mucinous Neoplasms

before the diagnosis of IPMN or PDAC.(9) One limitation of the study is that SEER database did not include individuals with noninvasive forms of IPMN or patients who were treated non-operatively.

In a case control study evaluated the prevalence of EPMs in 178 European patients with resected IPMNs, the most frequent localization of EPMs was shown to be breast (30%). The prevalence of breast cancers was twice as high as that of the control population.(30) In a retrospective cohort study conducted to study the frequency of EPMs in patients with IPMN compared with those with PDAC and a general referral population , breast cancer was found in 5 % of individuals with IPMN (20 of 471).(31)

In a multicenter observational study performed in Europe to investigate the occurrence of EPMs, breast cancer was reported to be the most common EPMs in female in.(32) The standardized incidence ration (SIR) was 1.76 (95 % CI 0.81–3.35.) which is not significantly greater than general population.(32) (Table.2)

Screening and Genetic testing

Since *BRCA1* and *BRCA2* might be associated with PDAC, deliberation as to whether all *BRCA1/2* mutation carriers need to be screened for PDAC should be considered. Some studies revealed that PDAC screening in high risk patients successfully detected PDAC at early stage.(33)The current consensus recommend *BRCA2* mutation carriers who are at least 50 year old and have first degree relative with PDAC or two non -first degree relatives with PDAC to be screened for PDAC.(34, 35) Screening for *BRCA1/2* mutations should be considered in Ashkenazi Jewish patients who have a personal or family history of PDAC regardless of the family history of breast and ovarian cancer.(36)

Up till now, the data is unsupportive of screening patients with IPMNs for breast cancer as breast cancer likely occurs before or concurrently with the IPMNs and no high incidence of breast cancer during follow up was reported. (37)More importantly, the median age of the breast cancer diagnosis falls within the screening recommendations for breast cancer.

8. CONCLUSION

Most of the genetic basis for familial clustering of pancreatic cancer remains unknown. Mutations in *BRCA1, BRCA2* and *PALB2* genes explain only a small part of it.(24) Large sample studies are required to provide a better understanding of the role of these genes in pancreatic cancer susceptibility.

To date, no studies prove that IPMN patients are at risk of developing breast cancer(37) and the data is in insufficient to provide guidelines for surveillance for secondary malignancies in patients with IPMNs. Future prospective studies about the association between IPMNs and breast cancer are warranted.

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