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Review Article

ASSOCIATION OF FAMILIAL PROSTATE CANCER WITH BREAST CANCER SUSCEPTIBILITY GENE MUTATIONS

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ABSTRACT

Genetic alterations are one of the important known risk factors of prostate cancer. The family predisposition of breast and ovarian cancers may cause the severe progression of familial prostate cancer in some men. The association of germline mutations in *BRCA1* and *BRCA2* genes can cause breast cancer in almost 35% of women and 9% of men. Carriers of these pathogenic variants have a higher risk of causing prostate cancer. This study focused on the analysis of mutations causing prostate cancer around the world, associated with breast cancer susceptibility genes.

Keywords: Prostate cancer, Mutations, *BRCA1* and *BRCA2*.

1. INTRODUCTION

Prostate cancer is the 2nd most recurrently diagnosed cancer in men, and also the 5th leading cause of death worldwide [1]. In Prostate cancer, symptoms are not observed in the early onset of the disease. Incidence rates differ worldwide with the usage of different diagnostic tests. Prostate cancer frequency and death rates are strongly associated with age with the higher incidence being found in men over the age of 65 [1]. The early-stage prostate cancers are mostly latent and only 25% of cancers are known to be life-threatening [2]. Prostate-specific antigens (PSA), a glycoprotein expressed in prostate cancer, based on elevated plasmatic level of PSA shows the occurrence of prostate cancer. In some conditions, men show elevated PSA levels without cancer. So, tissue biopsy has made the standard diagnostic test to confirm the presence of malignancy [3]. To grade the prognosis of prostate cancer, Gleason score is used, which gives the potential rate of recurrence and mortality [4]. Prostate cancer can be treated in its early stages, so there will be no further development of metastases in patients. Once cancer reaches the metastatic stage, the survival chances are very less with aggressive cancer [5].

2. RISK FACTORS

The major possible risk factors for prostate cancer are firstly mentioned as age, lifestyle, food, ethnicity and molecular changes (genetic alterations), have shown the massive connections with the hereditary cancer progressions [6]. Prostate cancer is heterogeneous disease with multiphase development process [7]. African-American men develop aggressive kind of prostate cancer and the incidence rate is also higher when compared with the white men. Diet plays optimistic risk associated with prostate cancer, consuming higher amount of red meat, saturated animal fat and lower consumption of fruits and veggies, vitamins, minerals and coffee [8].

Using GLOBOCAN 2020 estimation, we have collected the incidence and mortality rates of the prostate cancer population across the world. The following pie charts show the number of new cases registered (Fig. 1), and the number of deaths recorded (Fig. 2) in 2020 due to prostate cancer irrespective of men of all ages. The numbers are given according to the continents. Total 14,14,259 new cases are recorded, where 4,73,344 (33.5%) which is highest among all the continents. Figure 2, shows that 3,75,304 prostate cancer deaths have been recorded in 2020, in which 1,20,593 (32.1%) are from Asia being highest in all continents [9].

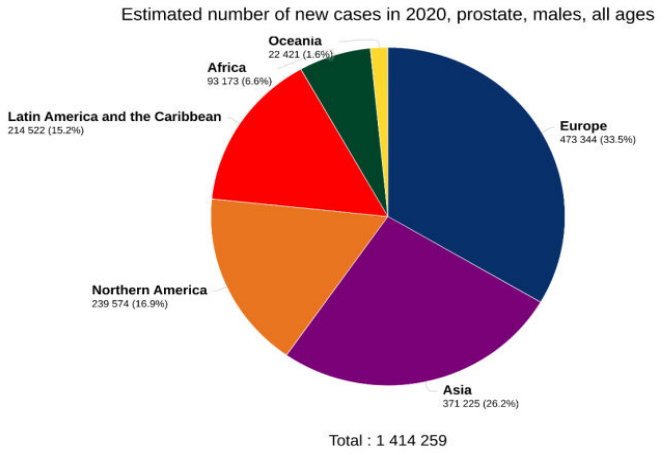

Fig. 1: The number of new Prostate cancer cases recorded in 2020, with respect to the seven continents

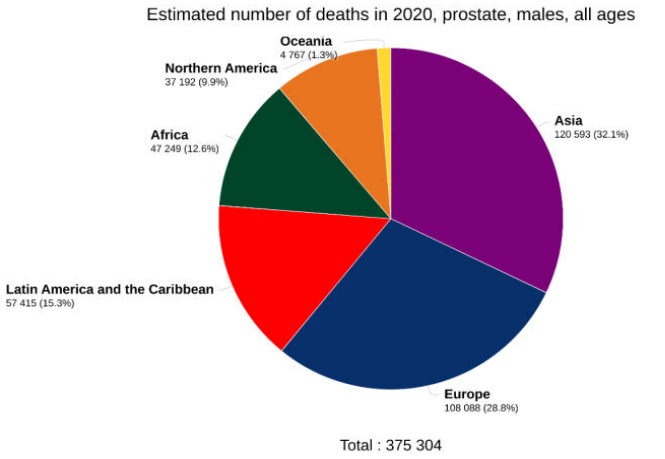

Fig. 2: The number of deaths recorded due to Prostate cancer in 2020, with respect to the seven continents

3. RELATIONSHIP BETWEEN BREAST, OVARIAN AND PROSTATE CANCER

Many studies have been observed the genetic epidemiology of familial association between the breast, ovarian and prostate cancer. Gene alteration in BRCA (breast cancer susceptibility gene) is responsible for familial clustering of these cancers. Around the world, breast cancer is known to be the leading most common carcinomas causing women. Nearly thirty lakhs breast cancer cases have been diagnosed in 2018 and over six lakhs deaths were recorded worldwide. Ovarian cancer being less common shows higher rate of mortality. Around three lakhs cases were diagnosed in the same year and almost two lakhs deaths recorded [10]. Prostate cancer is counted in the list of heritable cancers, showing higher chances of risks with familial breast cancer and familial prostate cancer. Studies have shown the risk for men with a history of breast or prostate cancer in his family has higher rate of getting aggressive prostate cancer [11]. BRCA1 and BRCA2 are the known confer genes till date which risks about 8.6 folds in men less than 65 year [12]. Familial cancer aggression is more affected in people of younger age, with the more than 3 affected generations. In first degree relatives risk is twice as compared with the normal cases [13].

Being tumor suppressor genes BRCA1 and BRCA2 both the gene follows autosomal dominant inheritance pattern [14, 15]. Both the genes encodes for large protein factors which helps in many cellular pathways. BRCA1 plays a key role in cellular functions like control system, processing, DNA damage and repair, chromatin remodeling and transcriptional regulation [16]. BRCA2 mainly participate in regulating the activity of RAD15, also manages DNA recombination and repairing process [17]. Loss of function in these genes can structurally and functionally alter the stability at genomic and chromosomal level [18]. Table 1 shows, about 50-65% of BRCA1 mutations can cause breast cancer and ovarian in females and 1.2% leads to male breast cancer. Also 1-3% can risk pancreas cancer, and 9% can risk for prostate cancer. Similarly, 40-55% BRCA2 mutations can leads to breast cancer, and up to 9% can cause male breast cancer. 2-7% mutations can leads to pancreas cancer, 15-25% mutations risks for ovarian cancer and 15% of mutations leads to prostate cancer.

Table 1: Association of the genes *BRCA1* and *BRCA2* in different hereditary cancers

Cancer site	*BRCA1*	*BRCA2*
Breast	50-65%	40-55%
Pancreas	1-3%	2-7%
Ovarian	40-65%	15-25%
Prostate	9%	15%

(Source: Petrucelli et al., 2016)

The pedigree chart (Fig. 3) shows the germline mutation in BRCA2 gene running in this family causing breast cancer in 50 year old woman, then the hereditary gene flows causing breast cancer in male of age 72 (offspring) in first generation. In second generation one of the offspring showed the germline mutation of BRCA2 and diagnosed with positive prostate cancer and also bilateral breast cancer at the age of 56 and 62 years respectively [19].

Most of the studies have shown the association of BRCA2 mutation for prostate cancer risk is stronger compared with the BRCA1 mutation. In case control study conducted by Ilir Agalliu *et al.* in 2009, included total 979 prostate cancer and 1251 control cases of Jewish men. The results were observed with three fold increased risk for BRCA2 mutations with the higher Gleason score and also the first degree family interactions can leads to stronger relationships. In case of BRCA1 mutation there was a poor link but the deletions were associated with the elevated Gleason score risking the tumor [20]. Lauren Brady *et al.* conducted a study in 2022, where they found the germline mutation in some group of genes penetrate the aggressive form of prostate cancer. The study included total 148 mutations where 32 were pathogenic. In that they identified two mutations with BRCA1 and three with BRCA2 genes and also each one mutations in BAP1 and BRRIP1 which are BRCA1 associated proteins [21].

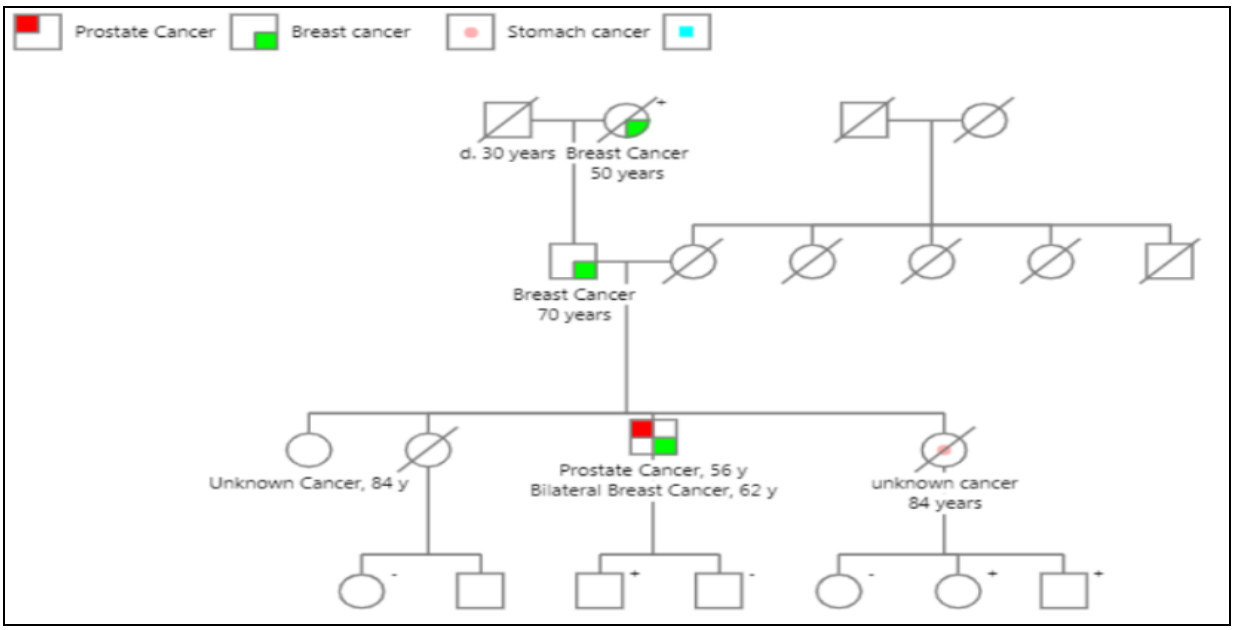

Fig. 3: Pedigree of germline mutation in BRCA2 flowing through this family causes hereditary breast and prostate cancer (*source: Freitas et al., 2018*)

We have done the population study on Prostate cancer BRCA1 and BRCA2 mutationfrom past 10 years and selected around 14 studies which conducted the mutational analysis of the candidate genes. Firstly Elena Castro et.al.in the year 2013 studied the outcome of 2019 prostate cancer patients association with the status of BRCA1/2 genes and also the survival rates of the patients having the positive gene mutation. He used Kaplan-Meier method to analyze the results and confirms the mutation results in more aggressiveness of the disease and have poor rate of survival chances from metastasis [22, 23]. In 2015, Qing Zhu *et al.* conducted a study on autoimmune response of BRCA1/2 in cancer and in total 107 tested patients of prostate cancer they found around 35 positive responses for the genes in which two patients shows combine gene mutations [24]. In the year 2017, Matti Annala *et al.* explained the outcome of heterozygocity tumor loss DNA repair deficient germline prostate cancer. He sequenced around 22 repair genes in 319 patients where he found 16 BRCA2 and one BRCA1 germaline mutation [25, 26]. In recurrence or developmental PCa germline mutations are very common among DNA repair genes. In 2018 Pedro Isaacsson Velho *et al.* worked on the association of these gene mutations in patients by germline testing. Around 150 samples were tested in which 43% have shown the germline mutation among which BRCA2 was found highest showing 14% result and similarly 9% of BRCA1 mutations were observed [27]. In the year 2019, Piper Nicolosi *et al.* studied on prostate cancer, its prevalence for germline variants. In testing of 3459, 38 were positive for BRCA1 mutation and 75 were positive for BRCA2 germline mutation [28]. In the same year, two studies were conducted by

Yukhihide M. *et al.* and Yishuo Wu *et al.* who worked on prostate cancer patients where the studies showed higher mutational rate in BRCA2 gene than BRCA1 gene. The studies included 7636 patients (in which 83 were showing BRCA2 mutation and 14 were showing BRCA1 mutations) and 1694 patients in which (20 responded positively for BRCA2 and 3 for BRCA1) respectively [29, 30]. In the year 2020, N. Segal *et al.* conducted a study where total 188 BRCA mutation (108 BRCA1, 80 BRCA2) carriers were screened for Prostate cancer. In 108 patients, 23 were positive for BRCA1 and in 80 patients 22 were positive for BRCA2 [31, 32]. So overall results shows that BRCA mutations are strongly affecting the patients who are diagnosing with prostate cancer.

Table 2: Summary of the population study of Prostate cancer BRCA1 and BRCA2 mutation from the past 10 years, selected from 14 studies which conducted the mutational analysis of the candidate genes

				BRCA1				*BRCA2*		
STUDY	YEAR	RACE	SAMPLES	MUTATION DETECTED	RR 95% CI VALUE	P-VALUE	SAMPLES	MUTATION DETECTED	RR 95% CI VALUE	P VALUE
Elena Castro et.al.	2013	UK	Cases: 2019 Control: 1940	18		0.021	Cases: 2019 Control: 1940	61		0.001
Elizabeth K. Bancroft et.al.	2014	UK	case: 376		2.35 (1.43-3.88)		case: 447		4.45 (2.99-6.61)	
Qing Zhu et.al.	2015	China	Cases: 107	30	3.9 (1.4–8.5)	< 0.001	Cases: 107	5	18.6 (13.2 - 25.3)	< 0.05
C.C. Pritchard et.al.	2016	US and UK	Cases: 692	6	3.9 (1.4–8.5)	0.005	Cases: 692	37	18.6 (13.2–25.3)	<0.001
MattiAnnala et.al.	2017	USA	Cases: 319	1			Cases: 319	16		
P. I. Velho et.al.	2017	Maryland	Cases: 150	2			Cases: 150	9		
Piper Nicolosi et.al.	2019	African Americans	Cases: 3459	38			Cases: 3436	75		
YukihideMomozawa et.al	2019	Japanease population	Cases: 7636	14	2.27 (0.9 - 5.71)	0.06	Cases: 7636	83	5.65 (3.55 - 9.32)	<.001
YishuoWua et.al.	2019	Chainease population	Cases: 1694	3	2.80 (0.15–165.43)	0.57	Cases: 1694	20	12.88 (3.07–114.95)	8.99E-06
Burcu F. Darst et.al.	2020	European-anscesty	Cases: 2770 Control: 2775	15	2.11 (0.37 -12.21)	0.8	Cases: 2770 Control: 2775	59	2.88 (1.22 - 6.83)	0.02
D. Wokolorczyk et.al.	2020	European population	Cases: 390 Control: 308	2	0.5-34.3	0.2	Cases: 390 Control: 308	4	0.4-134	0.1
Tommy Nyberg et.al.	2020	European population	case:791 control: 531	18 10			case: 731 control: 428	24 7		
N. Segal et.al.	2020	Isrel	Cases: 108	23		0.43	Cases: 80	22		0.43
Alyssa L. Smith et.al.	2022	French Canadian Jewish	Cases:150 Cases:236	0 1	0 (0 - 3.4) 3.3 (0 - 18.1)		Cases:150 Cases:236	6 2	4.0 (1.7 - 8.6) 6.7 (0.8 - 22.4)	

4. CONCLUSION

In conclusion, the review shows that there is a significant relationship associated with the BRCA2 mutations which not only be the major risk for developing hereditary and sporadic prostate cancer, it also helps to know the prognosis of the disease. BRCA1 mutation did not show a significant relation but it affects the patients and screening can help to identify and treat them, which decreases the aggressiveness of the disease. In future, sequencing and screening of these mutations can be the major biomarkers which helps in early detection of prostate cancer also helps in targeted therapies which directly act on particular cell and effective on metabolic level.

Conflict of interest

None declared

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