DOI:10.31557/APJCB.2023.8.1.69

REVIEW

Prostate Cancer: Germline Mutations in *BRCA1* and *BRCA2*

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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 lethal 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*

Asian Pac J Cancer Biol, **8 (1)**, 69-73

Submission Date: 10/21/2022 Acceptance Date: 01/17/2023

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].

Risk factors

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

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 (Figure 1), and the number of deaths recorded (Figure 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%) are from Europe, followed by 3,71,225 (26.2%) are from Asia, 2,39,574 (16.9%) from North America, 2,14,522 (15.2%) are from Latin America and the Caribbean, 93,173 (6.6%) are from Africa, and lastly 22,421 (1.6%) are from Oceania (Figure 1) [8]. 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, 1,08,088 (28.8%) are from Europe, 57,415 (15.3%) are from Latin

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Table 1. Association of the Genes *BRCA1* and *BRCA2* in Different Hereditary Cancers [13]

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

America and the Caribbean, followed by 47,249 (12.6%) from Africa, 37,192 (9.9%) are from North America, and lastly 4,767 (1.3%) are from Oceania [8].

Relationship between Breast, Ovarian and Prostate Cancer

Many studies have observed the genetic epidemiology of familial association between Breast, Ovarian and Prostate cancer. Gene alteration in BRCA (breast cancer susceptibility gene) is responsible for the familial clustering of these cancers. Around the world, Breast cancer is known to be the leading most common carcinoma causing women. Nearly thirty lakhs breast cancer cases have been diagnosed in 2018 and over six lakhs deaths were recorded worldwide. Ovarian cancer is less common and shows a higher rate of mortality. Around three lakhs cases were diagnosed in the same year and almost two lakhs deaths were recorded [9]. 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 their family has a higher rate of getting aggressive prostate cancer [10]. *BRCA1* and *BRCA2* are the known confer genes to date that risk about 8.6 folds in men less than 65 years [11]. Familial cancer aggression is more affected in people of younger age, with more than 3 affected generations. In first-degree relatives, the risk is twice as compared with the normal cases [12].

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

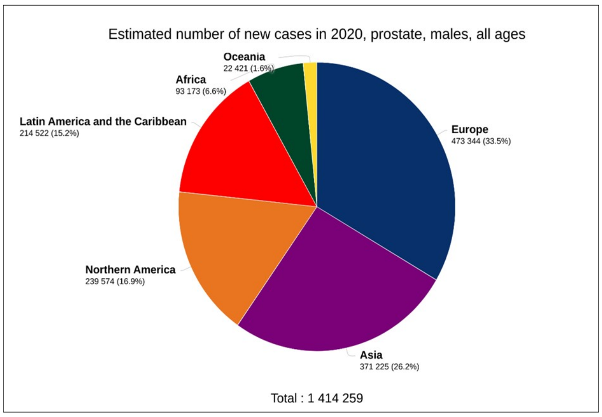

Figure 1. The Number of New Prostate Cancer Cases Recorded in 2020, with Respect to the Seven Continents.

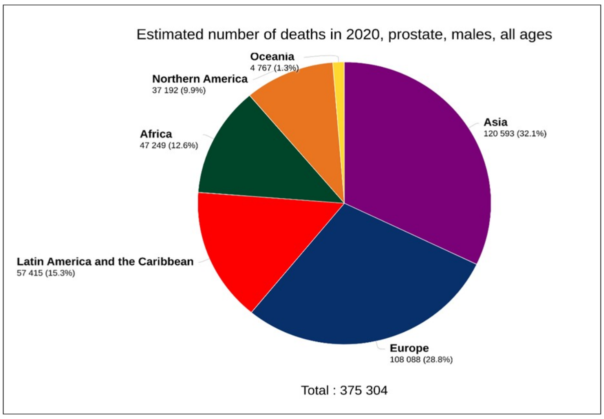

Figure 2. The Number of Deaths Recorded due to Prostate Cancer in 2020, with Respect to the Seven Continents.

The pedigree chart (Figure 3) shows the germline mutation in the *BRCA2* gene running in this family causing breast cancer in 50-year-old women, then the hereditary gene flows causing breast cancer in males of age 72 (offspring) in the first generation. In the second generation, one of the offspring showed the germline mutation of *BRCA2* and was diagnosed with positive prostate cancer and also bilateral breast cancer at the age of 56 and 62 years respectively [18].

Most of the studies have shown the association of *BRCA2* mutation for prostate cancer risk is stronger compared with the *BRCA1* mutation. In a case-control study conducted by Ilir Agalliu et. al. In 2009, including a total of 979 prostate cancer and 1251 control cases of Jewish men. The results were observed with a three-fold increased risk for *BRCA2* mutations with the higher Gleason score and also the first-degree family interactions can lead to stronger relationships. In the case of the *BRCA1* mutation, there was a poor link but the deletions were associated with the elevated Gleason score risking the tumour [19]. Lauren Brady et.al. Conducted a study in 2022, where they found that germline mutation in some groups of genes penetrates the aggressive form of prostate cancer. The study included a total of 148 mutations where 32 were pathogenic. In that, they identified two mutations with *BRCA1* and three with *BRCA2* genes. And also, each mutation in BAP1 and BRRIP1 which are *BRCA1*-associated proteins [17].

We have reviewed the population study on Prostate cancer *BRCA1* and *BRCA2* mutation from the past 10

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. [20]	2013	UK	Cases: 2019 Control: 1940	18		0.021	Cases: 2019 Control: 1940	61		0.001
Elizabeth K. Bancroft et.al [21]	2014	UK	case: 376		2.35 (1.43-3.88)		case: 447		4.45 (2.99-6.61)	
Qing Zhu et.al. [22]	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. [23]	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
Matti Annala et.al. [24]	2017	USA	Cases: 319	1			Cases: 319	16		
P. I. Velho et.al. [25]	2017	Maryland	Cases: 150	2			Cases: 150	9		
Piper Nicolosi et.al. [26]	2019	African Americans	Cases: 3459	38			Cases: 3436	75		
Yukihide Momozawa et.al [31]	2019	Japanease population	Cases: 7636	14	2.27 (0.9 - 5.71)	0.06	Cases: 7636	83	5.65 (3.55 - 9.32)	<.001
Yishuo Wua et.al. [27]	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. [32]	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. Wokołorczyk et.al. [33]	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. [34]	2020	European population	Case:791 Control: 531	8 10			Case: 731 Control: 428	247		
N. Segal et.al. [29]	2020	Isrel	Cases: 108	23		0.43	Cases: 80	22		0.43
Alyssa L. Smith et.al. [30]	2022	French Canadian Jewish	Cases:150 Cases:236	0 1	0 (0 - 3.4) 3.3 (0 - 18.1)		Cases:150 Cases:236	62	4.0 (1.7 - 8.6) 6.7 (0.8 - 22.4)	

years and selected around 14 studies which conducted the mutational analysis of the candidate genes (Table 2). Firstly, Elena Castro et. al. in the year 2013 studied the outcome of 2019 prostate cancer patient's association with the status of *BRCA1/2* genes and also the survival rates of the patients having the positive gene mutation. He used the Kaplan-Meier method to analyze the results and confirms the mutation results in more aggressiveness of the disease and have a poor rate of survival chances from metastasis [20,21]. In 2015 Qing Zhu et. al. conducted a study on the autoimmune response of *BRCA1/2* in cancer and in a total of 107 tested patients of prostate cancer he found around 35 positive responses for the genes in which two patients show combine gene mutations [22]. In the year 2017 Matti Annala et. al. explained the outcome of heterozygosity tumour loss DNA repair deficient germline prostate cancer. He sequenced around 22 repair genes in 319 patients where he found 16 *BRCA2* and one *BRCA1* germline mutation [23, 24]. 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 this gene mutation in patients by germline testing. Around 150 samples were tested of which 43% have shown the germline mutation among which *BRCA2* was found highest showing 14% results and similarly 9% of *BRCA1* mutations were observed [25]. In the year 2019 Piper Nicolosi et. al. studied prostate cancer its prevalence for germline variants. In testing of 3459, 38 were positive for the *BRCA1* mutation and 75 were positive for the *BRCA2* germline mutation [26]. 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 rates in the *BRCA2* gene than the *BRCA1* gene. The studies included 7636 patients (of which 83 were showing *BRCA2* mutation and

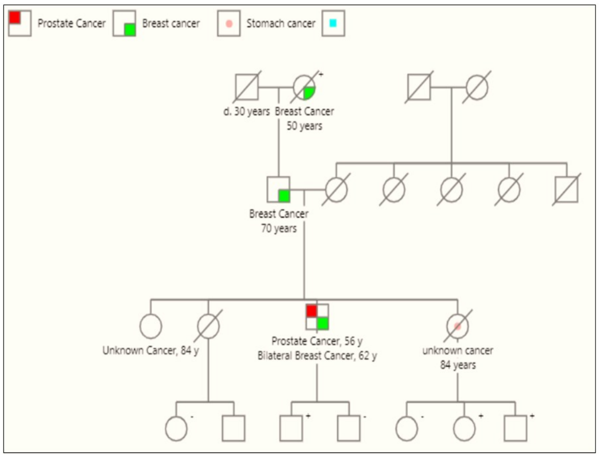

Figure 3. Pedigree of germline mutation in *BRCA2* flowing through this family causes hereditary breast and prostate cancer [18].

14 were showing *BRCA1* mutations) and 1694 patients in which (20 responded positively for *BRCA2* and 3 for *BRCA1*) respectively [27,28]. In the year 2020 N. Segal et. al. conducted a study where a total of 188 BRCA mutation (108 *BRCA1*, 80 *BRCA2*) carriers are screened for Prostate cancer. In 108 patients 23 were positive for *BRCA1* and in 80 patients 22 were positive for *BRCA2* [29,30]. So overall results show that BRCA mutations are strongly affecting patients who are diagnosed with prostate cancer.

In conclusion, the study 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 relationship 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 help in the early detection of Prostate cancer and also helps in targeted therapies which directly act on particular cell and are effective on the metabolic level.

Acknowledgments

Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute .
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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