Role of Moderate Risk Susceptibility Genes in Development of Breast Cancer

Kouser Abbas \(^a\), Amtul Sami \(^b\), Ufaque batool \(^a\) and Ubedullah Shaikh \(^c\)\(^*\)

\(^a\) Department of Physiology, Basic Medical and Science Institute, Jinnah Postgraduate Medical Center, Karachi, Pakistan.

\(^b\) Department of Microbiology and Molecular Biotechnology, Women University Swabi Khyber Pakhtunkhwa (KPK), Pakistan.

\(^c\) Department of Sindh Government Health, Services Hospital, Karachi Sindh, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i15B35696

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/83447

Received 12 December 2021
Accepted 20 February 2022
Published 24 February 2022

ABSTRACT

Breast cancer is the most common cause of mortality in females globally and affects the lives of millions of women. It is a leading cause of mortality worldwide, but the dynamics have been changed because of advanced screening and treatment protocols [1]. In the United States, breast cancer has been ranked second most common cause of cancer-related death in women, with the most common being lung cancer [2]. To improve cancer screening, a personalized approach has been discussed, but its implication over large populations can be difficult and require expertise. Early detection leads to a good prognosis whereas the late diagnosis of breast cancer is a challenge for both patient and doctor [3]. Breast cancer became the most prevalently diagnosed cancer worldwide as of 2021 accounting for 12% of new annual cases worldwide, according to the World Health Organization. In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. Multigene panel testing has identified various genes predisposed to...
breast cancer development. These genes have different penetrance abilities. BRCA1 and BRCA2 genes are the best known high penetrance gene of hereditary breast cancer. Their discovery has revolutionized the effect in cancer assessment. Tumors from BRCA1 and BRCA2 show distinctive clinicopathological characteristics as compared with other genes causing tumors. Beyond BRCA1 and BRCA2, advances in molecular technique have led to the identification of other genes associated with breast cancer. Some other the high penetrance genes are TP53, PTEN, STK11, and CDH1. Besides high penetrance gene, moderate to low penetrance genes are also recognized as a cancer predisposing genes: PALB, BRIP1, ATM, CHEK2, BARD1, NBN, NF1, RAD51C, RAD51D. Along with risk of breast cancer development these genes also predispose to other malignancies, as well as some genetic disorders.

Keywords: Breast cancer; ovarian cancer; BERCA1; BERCA2; tumor.

1. INTRODUCTION

Breast cancer is the most common cause of mortality in females globally and affects the lives of millions of women. It is the leading cause of mortality worldwide, but the dynamics have been changed because of advanced screening and treatment protocols [1]. In the United States breast cancer has been ranked second most common cause of cancer related death in women, with the most common being lung cancer [2]. To improve cancer screening a personalized approach has been discussed, but its implication over large populations can be difficult and requires expertise. Early detection leads to a good prognosis, whereas late diagnosis of breast cancer is a challenge for both patient and doctor [3]. The incidence of breast cancer and mortality rate is highest in women after menopause and is also affected by racial disparities [4]. Breast cancer became the most prevalently diagnosed cancer worldwide as of 2021 accounting for 12% of new annual cases worldwide, according to the World Health Organization. In the U.S every 1 in 8 women develops invasive breast cancer in her lifetime [5]. In 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world’s most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer [6]. Breast cancer is more prevalent in Black women than in white women under 45. Black women are more at risk of dying from breast cancer. The risk is lower in Asian, Hispanic, and Native American women. Ashkenazi women have a higher rate of BRCA mutation therefore higher risk of breast cancer [5]. It is a leading cause of cancer-related death in women globally. Worldwide, it is accounted for 684,996 deaths [95% UI, 675,493-694,633] at an age-adjusted rate of 13.6/100,000. Although prevalence rates were highest in developed regions, the countries in Asia, Africa shared 63% of total deaths in 2020 [7]. Countries with low to medium income are expected to have an increased incidence of breast cancer because of lifestyle westernization (e.g., delayed pregnancies, reduced breastfeeding, low age at menarche, reduced physical activity, and poor diet), early cancer detection and registration [8].

| Table 1. Modifiable And Non-Modifiable Risk Factors |
|-----------------------------------------------------|
| **Non-Modifiable Factors** | **Modifiable Factors** |
| Female sex | Hormone replacement therapy |
| Older age | Diethylstilbestrol |
| Family history (of breast or ovarian cancer) | Physical activity |
| Genetic mutations | Overweight obesity |
| Race/ethnicity | Alcohol intake |
| Pregnancy and breastfeeding | Smoking |
| Menstrual period and menopause | Insufficient vitamin supplementation |
| Density of breast tissue | Excessive exposure to artificial light |
| Previous history of breast cancer | Intake of processed food |
| Non-cancerous breast diseases | Exposure to chemicals |
Several procedures have been implemented to reduce the incidence and mortality rate of breast cancer including general preventive measures and screening programs for early detection of cancer and treatment and for this Breast Health Global Initiative (BHGI) is making proper guidelines and approaches [9].

According to World Health Organization, Breast cancer occurs from the cell lining (epithelium) of the ducts (85%) or lobules (15%) in the glandular tissue of the breast. When it is confined within the lobules or ducts it is in-situ and when spread beyond it is metastasis [6]. Many risk factors have been recognized including both modifiable and non-modifiable risk factors. Table.1 [4].

World Health Organization has classified at least 18 different histological types of breast cancer [10]. Invasive Breast cancer is categorized into two main groups Invasive breast cancer of no special type previously known as Invasive ductal carcinoma accounting for 40-80% [11]. About 25% of invasive breast cancer shows distinguish growth pattern and cytological appearance hence known as specific subtypes [e.g., invasive lobular carcinoma, tubular, mucinous A, mucinous B, neuroendocrine] [12]. Molecular classification is independent of histological subtypes, based on mRNA gene expression four molecular subtypes have been identified [Luminal, HER-2 enriched, Basal-like, and Normal breast-like] [13]. Luminal is further divided into luminal A and Luminal B, both A and B subtype and HER-2 enriched come under the category of non-basal invasive breast cancer. Basal-like breast cancer (TNBC) is previously also called triple-negative due to the absence of estrogen receptor (ER−), progesterone receptor (PR−), and human growth factor neu receptor (HER2) responsible for about 10% of all breast cancer [14].

2. GENETIC RISK FACTORS FOR DEVELOPMENT OF BREAST CANCER

There are various factors increasing the development of breast cancer and having protective effects on breast cancer. Factors decreasing the chances of breast cancer include pregnancy at an early age, high parity, breast feeding, healthy diet, daily physical activity.and use of chemo preventive agents. Genetic polymorphisms account for sensitivity of environmental carcinogens and their impact on cancer genes. Single nucleotide polymorphisms with double strand DNA breaks and caspase 8 gene are found to be associated with breast cancer risk [15]. Positive family history for breast cancer is the most important risk factor and almost 20% cancer patients have affected first degree relatives. In females with family history, the cancer usually occurs bilaterally and in early age with autosomal inheritance [16].

3. GENES RELATED TO BREAST CANCER

3.1 BRCA 1

The discovery of the BRCA1 gene was a significant development in explicating the genetic etiology of breast cancer. The inactivating mutation of BERCA protein raises the risk of the development of breast, ovarian, and other cancer. It is high penetrance autosomal dominant gene for breast cancer. Germine mutation of BRCA1 and BRCA2 accounts for 25% risk of familial breast cancer [17,18,19], and therefore 5-10% overall risk for all breast cancer [20]. BRCA1 is located on chromosome17 long arm [21]. Main functions of BRCA1 include cellular regulation, DNA damage control, cell cycle control, transcription process control, and ubiquitination [21]. These functions contribute to its tumor suppressive abilities. BRCA1 mutation accounts for 40-45% of hereditary breast cancer. In about 80% of families with increase incidence of breast and ovarian cancer BRCA1 mutation is mainly responsible. However BRCA1 expression is increasingly reduced in sporadic cancer [22]. Estrogen receptor marker is usually absent in 90% of patients having BRCA1 mutation [23]. BRCA1 mutation carriers are also deficient in expressing PR cells and reduced number of HER2 expressing cells [24]. BRCA1 related tumors are similar in genotype, phenotype, and clinical expression to sporadic basal-like tumors (Triple Negative Breast Cnacer [TNBC] [24]. Basal-like tumors have defective BRCA1 pathways. Over 60% of promoter genes underwent methylation resulting in downregulation of BRCA1 [25].

3.2 BRCA 2

Tumor suppressor BRCA2 gene (MIM600185) is a high penetrance autosomal dominant gene. An approximated cumulative risk of breast cancer is 27-84% for BRCA2 carriers at 70 years of age and corresponding ovarian cancer risks are 11-30% [26]. Many detrimental mutations are small deletion or insertion during transcription that results in truncated protein translation. The
frequency of these mutations differs in different populations particularly in founder populations [16]. BRCA2 is located on chromosome 13 and encoded a larger protein than BRCA1. Its tumor suppressing roles are instrumental in repair of double stranded DNA break, genomic instability regulation, cell cycle regulation, cell growth, apoptosis, and chromosomal remodeling [27]. BRCA2 is an estrogen positive variant with similar expression of PR cells but lower frequency of HER2 cells [24]. The estimated prevalence of BRCA1/2 in general populations are 1:400 to 1:500 of people [28], BRCA2-related tumor is less distinctive than BRCA1-related tumor with higher grading, high mitotic index, and less distinctive tubule formation [16]. Bi-allelic form of germline mutation of BRCA2 has an association with subgroup of fanconi anemia that raises the susceptibility of childhood tumor [29]. The therapeutic applications of BRCA1/2 include assessment of cancer risk, prognosis, and therapeutic intervention required [30].

3.3 CHEK2

Cell cycle checkpoint kinase 2 gene (CHEK2 or CHK2) has been identified as an intermediate penetrance breast cancer risk gene because of its involvement in DNA repair mechanism and replication regulation [31,32]. The product of this gene works as serine/threonine protein kinase that phosphorylates BRCA1, p53, and Cdc25 family proteins [33]. Three germline mutation has been identified in different studies: 1100delC, R145W, I157T and distinguishingly recognized to be associated with breast cancer [34,35]. The 1100delC mutation is the most extensively studied and it results from deletion of single cytosine at 1100 position on gene that causes lack of kinase function of protein [36]. The other common variant I157T have substitution mutation of isoleusine to threonine and missence mutation in R145W producing truncating protein product that lost its ability to bind with BRCA1, p53, and Cdc25 family [33]. Prevalence of CHEK2 mutation especially 1100delC mutation is varied in different populations. The prevalence is in Finland (6.8%) followed by Netherland (4.9%), in U.K and Germany it is 1.2% and 0.8% respectively [37].

3.4 P53

Tumor protein 53 (TP53) is a tumor suppressor gene responsible for decoding p53 phosphoprotein [38]. It is on chromosome 17p13.1. it plays a crucial role in regulation of genes, apoptosis, DNA repair, and cell cycle arrest [39]. Basal-like tumors have high risk of somatic mutation in TP53 [40] although TNBC is not associated with increased risk of TP53. In a cohort of 2,134 BRCA1/BRCA2 negative women with familial breast cancer the mutation rate of TP53 was 0.52% and carriers were HER2 positive [41]. Li-Fraumeni Syndrome (LFS) is associated with TP53 mutation and lifetime risk of breast cancer in LFS is 25-79% [42].

3.5 PTEN

Phosphatase and tensin homolog (PTEN) are another most frequently mutated human gene after PT53. It is involved in the regulating of phosphoinositol-3-kinase and AKT signaling pathways [43]. Germline mutation in PTEN is also found in Cowden Syndrome which has life time risk of breast cancer of about 50% [44]. According to NCCN guidelines, screening of women with PTEN mutation should start at 25 years of age with breast examination, yearly mammography, breast MRI screening with contrast at 30-35 years of age [45]. Most PTEN associated tumors is luminal in nature than TNBC [46].

3.6 PALB2

PALB2 is a localizer and stabilizer of BRCA2 gene it binds with BRCA2 protein and regulates its nuclear structures such as chromatin, nuclear matrix and also recombinational repair and checkpoints functions promoter. Its gene is located on chromosome 16p12.2 [47]. It is now ranked as a high risk breast cancer gene accounting for odd ratio (OR) of 7.46 [48]. It shows aggressive disease progression. Finland reported over 50% women with PALB2 mutation presented with TNBC [49]. PALB2 gene is also associated with Fanconi anemia in its biallelic form. However monoallelic form of PALB2 gene accounts higher risk of breast cancer for both sexes [50], estimated of about 53% for female and 1% for male by the age of 80 [51]. The risk of ovarian cancer [52] and pancreatic cancer [53] has also low increased in PALB2 gene mutation accounting for 5% and 2-3% respectively [51].

3.7 STK11

Serine/threonine protein kinase 11 (previously LKB1) is a high penetrant gene for breast cancer [54]. It is present on chromosome 19p13.3 and encodes serine and threonine and its main functions are regulation of energy metabolism.
and cell polarity [55]. Peutz-jehgers syndrome was found to be caused by germline mutation in STK11 gene [56]. It is an autosomal dominant disorder with features of melanocytic macules of the lips, buccal mucosa and digits, multiple gastrointestinal hamartomatous polyps, and increased risk of various cancers. Patients with STK11 carriers having lifetime risk of breast cancer is 32-54% and other gynaecological tumors (cervical, ovarian, uterine) is 13% by the age of 60 [57]. According to NCCN guidelines, the screening starts at the age of 25 and it includes clinical examination of breast 6 monthly, yearly mammography, and breast MRI [58].

3.8 CDH1

The Cadherin 1 (CDH1) gene encodes an adhesion molecules and has main function is to maintain cell morphology [44] through it prevents invasiveness and metastatization [59] and also acting as tumor suppressor [60]. Hereditary diffuse gastric cancer syndrome (HDGC) is associated with germline mutation in CDH1 [61]. It is an autosomal dominant disorder characterized by diffuse-type gastric cancer (DGC) and lobular type breast cancer (LBC). The women having cumulative risk of lobular breast cancer with germline mutation of CDH1 accounting of 39-52% by 80 years of age [62]. It is unlikely that CDH1 germline mutation has an association with TNBC because most of the CDH1 mutated lobular breast cancer are ER positive. Accordingly, germline mutation of CDH1 in women with TNBC was very rare of about 0.0-0.3% [46].

3.9 ATM

The ataxia telangiectasia mutated (ATM) gene is present on chromosome 11q22.3 and encodes phosphatidylinositol-3-kinase protein. It is also acts as a tumor suppressor gene and and involve in repair of DNA damage by phosphorylation process and cell cycle control [63]. Ataxia telangiectasia is associated with biallelic form of ATM germline mutated gene. It is an autosomal recessive disorder containing features are cerebellar ataxia, telangiectases, immune defect, and various predisposition to malignancy [64]. On the other hand monoallelic form of ATM mutated gene is associated with cumulative risk of breast cancer accounts for 17-52% during lifetime [65]. According to NCCN guidelines, screening should start at the age of 40 in women with an ATM mutated gene, it includes annual mammography with consideration of tomosynthesis, breast MRI with contrast [45]. Studies have observed that ATM mutated tumors are enriched with ER positive tumors [41]. The risks have been increased to five folds in patients with non TNBC tumors for ATM mutation in comparison to TNBC tumors [46].

3.10 RAD51

The RAD51 gene encodes a protein that is responsible for the repair of double stranded DNA break. In mammals, seven RAD51 paralog has been recognized: RAD51, RAD51B, RAD51D, XRCC2, XRCC3, and DMC1 [66]. Biallelic form of RAD51, RAD51C, and XRCC2 are associated with Fanconi anemia [67]. On contrary, monoallelic form of RAD51 and its paralog has malignant predisposition, specifically RAD51B, RAD51C, and RAD51D has ovarian cancer risk and RAD51D, RAD51B, and XCCR2 has breast cancer risk [68,69]. Greater than three fol increased risk has been associated with RAD51D mutation. Mutation rate ranges from 0.20 to 0.95% in patients with TNBC in compared to non-TNBC, in them rates are lower (0.5%) [46]. According to NCCN guidelines, screening should start at the age of 45-50 or earlier based on family history [45].

4. CONCLUSION

Breast cancer comes under the category of top 10 most common and most deathly tumor for women and genetic predisposition plays a crucial role among risk factors for cancer development. Discovery of BRCA1 and BRCA2 has been done decades ago as a high pentrance predisposing gene for breast cancer. Accurate estimation of cancer risk assessment, as well as surveillance protocols for early detection and prevention are available [70,71]. New NCCN guideline stated that genetic testing can be done in a patient diagnose with TNBC at ≥60 years with or without significant family history of breast cancer [72]. Screening programe that has been set, should be prioritized because it has a critical importance in decreasing the mortality rate of breast cancer. The importance to identify genetic etiology extends beyond risk assessment as it is also helpful in management strategy and therapy selection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics 2018. CA Cancer J Clin. 2018;68(1):7–30.

3. Narod SA. Personalised medicine and population health: Breast and ovarian cancer. Hum Genet. 2018;137(10):769–778.

4. Yedjou CG, Tchounwou PB, Payton M, Miele L, Fonseca DD, Lowe Let al. Assessing the racial and ethnic disparities in breast cancer mortality in the United States. Int J Environ Res Publ Health. 2017;14:486-90.

5. U.S Breast Cancer Statistics. Available:https://www.breastcancer.org/symptoms/understand_bc/statistics

6. Breast Cancer WHO. Available:https://www.who.int/news-room/fact-sheets/detail/breast-cancer

7. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Obser-Vatory: Cancer Today. International Agency for Research on Cancer; Lyon, France: 2020. [(accessed on 9 July 2021)] Available:https://gco.iarc.fr/today

8. Porter P. Westernizing Women’s Risks? Breast Cancer in Lower-Income Countries. N. Engl. J. Med. 2008;358:213–216.

9. Duggan C, Dvaladze A, Rositch AF, Ginsburg O, Yip C, Horton S, et al. The Breast Health Global Initiative 2018 Global Summit on Improving Breast Healthcare Through Resource-Stratified Phased Implementation: Methods and overview. Cancer. 2020;126:2339–2352.

10. Tavassoli FA. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. World Health Organization Classification of Tumours; Lyon, France; 2003.

11. Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, et al. Refinement of breast cancer classification by molecular characterization of histological special types. J. Pathol. 2008;216:141–150.

12. Erber R, Hartmann A. Histology of Luminal Breast Cancer. Breast Care. 2020;15:327–336.

13. Perou C, Srlie T, Eisen M, Van De Rijn M, Jeffrey S, Rees CA, et al. Molecular portraits of human breast tumours. Nat. Cell Biol. 2000;406:747–752.

14. Anderson WF, Rosenber PS, Prat A, Perou CM, Sherman ME. How many etiological subtypes of breast cancer: Two, three, four, or more? J. Natl. Cancer Inst. 2014;106-10.

15. Zhang B, Beeghly-Fadiel A, Long J, Zheng W. Genetic variants associated with breastcancer risk: Comprehensive research synopsis, meta-analysis, and epidemiological evidence. Lancet Oncol. 2011;12:477–488.

16. Mavaddat N, Antoniou AC, Easton DF, García-Closas M. Genetic susceptibility to breast cancer. Mol Oncol. 2010;4:174–191.

17. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. 2000;83(10):1301–8.

18. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. Nat Genet. 2008;40(1):17–22.

19. Melchor L, Benitez J. The complex genetic landscape of familial breast cancer. Hum Genet. 2013;132(8):845–63.

20. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer. 1996;77(11):2318–24.

21. Wong MW, Nordfors C, Mossman D, Pecenpetelovska G, Avery-Kiejdza KA, Talseth-Palmer B, et al. BRIP1, PALB2, and RAD51C mutation analysis reveals their relative importance as genetic susceptibility factors for breast cancer. Breast Cancer Research and Treatment. 2011;127:859–9.

22. Rosen EM, Fan S, Pestell RG, Goldberg JD. BRCA1 gene in breast cancer. J Cell Physiol. 2003;196(1):19-41.

23. Lakhani, SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, McGuffog L, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2,
and p53 in patients with mutations in BRCA1 and BRCA2. J. Clin. Oncol. 2002;20:2310–2318.

24. Yehiely F, Moyano JV, Evans JR, Nielsen TO, Cryns VL. Deconstructing the molecular portrait of basal-like breast cancer. Trends Mol. Med. 2006;12:537–544.

25. Weigelt, B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: How special are they?. Molecular oncology. 2010;4(3):192–208.

26. Jara L, Morales S, de Mayo T. Mutations in BRCA1, BRCA2 and other breast and ovarian cancer susceptibility genes in Central and South American populations. Biol Res. 2017;50:35-9.

27. Hawsawi YM, Al-Numair NS, Sobahy TM, Al-Ajmi AM, Al-Harbi RM, Baghdadi MA, Oyouni AA, Alamer OM. The role of BRCA1/2 in hereditary and familial breast and ovarian cancers. Mol Genet Genomic Med. 2019;7(9):e879.

28. Comen E, Davids M, Kirchhoff T, Hudis C, Offit K, Robson M. Relative contributions of BRCA1 and BRCA2 mutations to "triple-negative" breast cancer in Ashkenazi Women. Breast Cancer Research and Treatment. 2011;129:185–190.

29. Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, De Die-Smulders C, et al. Biallelic inactivation of BRCA2 in Fanconi anemia. Science. 2002;297:606–9.

30. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434:913–7.

31. Kriege M, Hollestelle A, Jager A, et al. Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients:impact of adjuvant chemotherapy. Br J Cancer. 2014;111:1004–13.

32. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al. Low-penetration susceptibility to breast cancer due to CHEK2 * 1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet. 2002;31:55–9.

33. Domagala P, Wokolorczyk D, Cybulski C, et al. Different CHEK2 germline mutations are associated with distinct immunophenotypic molecular subtypes of breast cancer. Breast Cancer Res Treat. 2012;132:937-45.

34. Desrichard A, Bidet Y, Uhrhammer N, Bignon YJ. CHEK2 contribution to hereditary breast cancer in non-BRCA families. Breast Cancer Res. 2011;13:R119.

35. Elamrani A, Moumad K, Attaleb M, et al. Absence of CHEK2 1100delC, R145W and I157T mutations in breast cancer in a Moroccan population. Breast Cancer Res Treat. 2014;2:6–9.

36. Chen W, Yurong S, Liansheng N. Breast cancer low-penetration allele 1100delC in the CHEK2 gene: not present in the Chinese familial. Adv Therapy. 2008;25:496–501.

37. Haytural H, Yalcinkaya N, Akan G, Arikan S, Ozkok E, Cakmakoglu B, et al. Identification of a novel BRCA2 and CHEK2 A-C-G-C haplotype in Turkish patients affected with breast cancer. Asian Pac J Cancer Prev. 2013;14(5):3229-35.

38. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144(5):646–674.

39. Harris CC. Structure and function of the p53 tumor suppressor gene: Clues for rational cancer therapeutic strategies. J. Natl. Cancer Inst. 1996;88:1442–5.

40. Dumay A, Feugeas J, Wittmer E, et al. Distinct tumor protein p53 mutants in breast cancer subgroups. Int J Cancer. 2013;132(5):1227–1231.

41. Slavin TP, Maxwell KN, Lilyquist J. The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk. Npj Breast Cancer. 2017;3(1):22-9.

42. Masciarei S, Dillon DA, Rath M, Robson M, Weitzel JN, Balmana J, et al. Breast cancer phenotype in women with TP53 germline mutations: A Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133(5):1125–1130.

43. Yin Y, Shen WH. PTEN: A new guardian of the genome. Oncogene. 2008;27(41):5443–5453.

44. Vargas AC, Reis-Filho JS, Lakhani SR. Phenotype-genotype correlation in familial breast cancer. Journal of Mammary Gland Biology and Neoplasia. 2011;16(1):27–40.

45. National Comprehensive Cancer Network (NCCN) Guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. [accessed on 7 February 2020];2020 Version 1. Available:https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

46. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer phenotype in women with TP53 germline mutations: A Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133(5):1125–1130.
cancer tested with a 25-gene panel of hereditary cancer genes. Cancer. 2017;123(10):1721–1730.

47. Xia B, Sheng Q, Nakanishi K. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Molecular Cell. 2006;22(6):719–729.

48. Couch FJ, Shimelis H, Hu C. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncology. 2017;3(9):1190–1196.

49. Heikkinen T, Karkkainen H, Aaltonen K. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clinical Cancer Research. 2009;15(9):3214–3222.

50. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N. Engl. J. Med. 2014;371:497–506.

51. Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, et al. Cancer Risks Associated with Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J. Clin. Oncol; 2019. DOI: 10.1200/JCO.19.01907

52. Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J. Natl. Cancer Inst. 2015;107:1.

53. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009;324:217.

54. Rousset-Jablonski C, Gompel A. Screening for familial cancer risk: Focus on breast cancer. Maturitas. 2017;105:69–77.

55. Xu X, Jin D, Durgan J, Hall A. LKB1 controls human bronchial epithelial morphogenesis through p114RhoGEF-dependent RhoA activation. Mol. Cell. Biol. 2013;33:2671–2682.

56. McGarrity TJ, Amos CI, Baker MJ, Peutz-Jeghers Syndrome. In: Adam M.P., Ardinger HH, Pagon RA, editors. GeneReviews. University of Washington; Seattle, WA, USA; 2001. [(accessed on 7 February 2020)]. [Updated 2016] Available:https://www.ncbi.nlm.nih.gov/books/NBK1266

57. Syngal S, Brand RE, Church JM, Giadiello FM, Hampel HL, Burt RW. American College of Gastroenterology ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am. J. Gastroenterol. 2015;110:223–262.

58. National Comprehensive Cancer Network (NCCN) Guidelines: Genetic/Familial High-Risk Assessment: Colorectal. [Updated on 7 February 2020].

59. Key to abbreviations. Available:https://www.nccn.org/professionals/physician_gls/pdf/gastro.pdf

60. Thompson D, Duedal S, Kirner J, McGuffog L, Last J, Reiman A, et al. Hereditary diffuse gastric cancer: Updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J. Med. Genet. 2015;52:361–374.

61. Zaki-Dizaji M, Akrami SM, Abolhassani H, Rezaei N, Aghamohammadi A. Ataxia telangiectasia syndrome: Moonlighting ATM. Expert Rev. Clin. Immunol. 2017;13:1155–1172.

62. Kaurah P, Huntsman DG. Hereditary Diffuse Gastric Cancer. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews. University of Washington; Seattle, WA, USA; 2002.

63. Van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: Updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J. Med. Genet. 2015;52:361–374.

64. Gatti R, Ataxia-Telangiectasia PS. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews. University of Washington; Seattle, WA, USA; 1999. [(accessed on 7 February 2020)]. [Updated 2016]

65. Available:https://www.ncbi.nlm.nih.gov/books/NBK26468

66. Thompson D, Duedal S, Kirner J, McGuffog L, Last J, Reiman A, et al. Cancer risks and mortality in heterozygous ATM mutation carriers. J. Natl. Cancer Inst. 2005;97:813–822.

67. Kawabata M, Kawabata T, Nishibori M. Role of reca/RAD51 family proteins in mammals. Acta Med. Okayama. 2005;59:1–9.

68. Mehta PA, Tolar J. Fanconi Anemia. Peutz-Jeghers Syndrome. In: Adam MP, Ardinger HH, Pagon RA, editors.
GeneReviews. University of Washington; Seattle, WA, USA; 2002. [accessed on 7 February 2020]. [Updated 2018] Available:https://www.ncbi.nlm.nih.gov/books/NBK1401

68. Song H, Dicks E, Ramus SJ, Tyrer JP, Intermaggio MP, Hayward J. et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J. Clin. Oncol. 2015;33:2901–2907.

69. Golmard L, Castéra L, Krieger S, Moncoutier V, Abidallah K, Tenreiro H, et al. Contribution of germline deleterious variants in the RAD51 paralogs to breast and ovarian cancers. Eur. J. Hum. Genet. 2017;25:1345–1353.

70. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N. Engl. J. Med. 2015;372:2243–2257.

71. Nielsen FC, van Overeem Hansen T, Srensen C.S. Hereditary breast and ovarian cancer: New genes in confined pathways. Nat. Rev. Cancer. 2016;16:599–612.

72. National Comprehensive Cancer Network. GenEtic/Familial High-Risk Assessment: Breast and Ovarian Cancer; 2019.

© 2022 Abbas et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/83447