Medical and Research Publications
International Open Access

Review Article **Journal of MAR Oncology (Volume 5 Issue 6)**

The Role of BRCA1 and BRCA2 Genes in Breast Cancer in the South of Khuzestan Province (Dezful) Iran

Anis Dorchin *[1], Dr. Mohammad Dorchin [2]

1. Bachelor of Genetics; Master of Biochemistry; Department of Biochemistry, Islamic Azad University, Central Tehran Branch, Tehran, Iran.

2. Oncology radiotherapy specialists; Oncology Department; Dezful University of Medical Sciences, Dezful, Iran.

Corresponding Author: Anis Dorchin, Bachelor of Genetics; Master of Biochemistry; Department of Biochemistry, Islamic Azad University, Central Tehran Branch, Tehran, Iran.

Received Date: May 09, 2023

Published Date: June 01, 2023

Abstract

Introduction: *For a long time, various theories were expressed about the genetic nature of breast cancer, and with the advancement of medical genetics, more attention was paid to these hypotheses, and now we know that BRCA1 and BRCA2 gene mutations in germ cells cause the risk of infection. They become breastand ovarian cancer. BRCA1 and BRCA2 genes are responsible for 20-25% of breast cancer cases, which is why we consider it hereditary. Most of the mutations in BRCA1 and BRCA2 genes cause premature loss of proteins. The present study was conducted with the aim of investigating the role of BRCA1/2 gene mutations in breast cancer in Khuzestan province with the center of Dezful city.*

Method: *In this review study, information related to the role of BRCA1/2 genes in breast cancer through patients referred to Raha Cancer Center, as well as collecting documented information from colleagues in the north of Khuzestan province, Iran, as well as searching Pub databases. Med,Medline, Science Iranian Database and related websites available in Iran were searched. The time period in the selection of articles was from 2015 to 2022 for 7 years. Among the collected information, several articles were cited. BRCA1 and BRCA2 genes and their importance in breast cancer became the focus of researchers' attention.*

Findings: *This review study shows the identification of gene mutations of BRCA1 and BRCA2 carriers in the south of Iran, especially Dezful city, and the necessity of screening for families with There is breast cancer and also the expansion of this study to investigate the mutations of these two genes in the clinical programs of the country is predicted.*

Conclusion: *In the south of Iran, like other studies in Iran and the world; BRCA1/2 genes have a great importance and influence in the occurrence and development of breast cancer and these genes can be consideredas molecular indicators in the early diagnosis of breast cancer.*

Key words: *Breast Cancer; Dezful city; cancer genetics; BRCA1 gene; BRCA2 gene*

Introduction

Breast cancer is one of the most common cancers it is women. The probability of getting this cancer during life it is 10% for women. This cancer in developing countries found about 10% of all cancers and 23% of cancers constitutes women **(**1**)**.

More than 15% of healthy women at least one person with breast cancer in relatives have first degree and experimental data show that the risk of breast cancer in these women is double **(**2**)**.This cancer is the second most deadly cancer among women is after lung cancer **(**3**)**.

Today, many efforts are made to increase the incidence rate mortality in breast cancer through methods reduce early detection. If detected in time, this cancer can be prevented by preventive methods prevents breast cancer to a large extent. Although proper screening can prevent the development of cancer stop, but usually in advanced types of cancer, treatment is consequential. In general, cancer is the result a combination of different factors including: hereditary mutations and it is an environmental factor, the main cause of cancer. The defect is in the genes and mostly isolated it occurs spontaneously in somatic cells **(**4**)**.

The highest prevalence of breast cancer in the countries western and developing countries in the 50-60 age group year, while the highest incidence of Breast cancer in Iran at the age of 40-50 y/o group.

Different methods for detecting hereditary mutations identified, analysis of mutations in the sequence BRCA1 and BRCA2 genes by chain reaction polymerase and direct sequencing were able to detect hundreds of mutations points, deletions and additions of nucleotides in this show genes.

Annealing-dependent probe amplification method multiple **(**MLPA = Multiplex Ligation-Probe Amplification dependent**)** and quantitative multiple potential method PCR of short fluorescent fragments **(**QMPSF= Quantitative Multiplex PCR of Short Fluorescent fragments**)** also were developed to identify gene rearrangements. Including other methods of identifying genetic mutations through methylation, it is possible from LOH **(**8-10**)**.

Recent advances in molecular genetics and agents breast cancer diagnosis, in better understanding of biology it helps to change and transform healthy tissue into cancerous tissue.

The present review study aims to introduce mutation- BRCA1/2 genes and its importance in the risk of contracting breast cancer was done.

Method

First, search in Pub Med databases, Scopus, Medline, Web of Science, Science Iranian Database and websites it was related to the topic under study. Words the main keys were identified, including: BRCA mutation, BRCA1, BRCA2, breast cancer and they were Iran. Also, the time frame in the selection of articles from the year was 2015 to 2022 for 7 years.

In the first stage, articles were selected from the studies of candidate genes, studies genome-Wide associations and Meta-Analysis were achieved these articles provide information about

BRCA1/2 mutations, their frequency and importance in breast cancer as suppressor genes they had identified a tumor.

After the title and abstract articles were reviewed, articles were screened they took that in terms of indicators such as geographical area, lifestyle and personality; They were close to the south of Iran, and in the next stages, it was valuable for us to study that in terms of the number of samples control group, suitable study design is specified they were. Finally, 32 articles as qualified articles which had a high degree of connection with the subject, selection and the review were based on them.

Findings:

BRCA genes

BRCA1 and BRCA2 as the most susceptible genes breast cancer is known and several they have a cellular function that includes a vital role in DNA repair is homologous **(**11**)**. Proteins BRCA1 and BRCA2 play a vital role in DNA repair there are two broken strands that this process by the process of homologous recombination is repaired **(**12**)**. Therefore, hereditary mutation in any of these genes along with lack of heterorigosity, cells to instability chromosome and greatly increase the probability to change and predisposes to the development of cancer **(**13**)**.

Carriers of BRCA1 and BRCA2 gene mutations, 10-20 times more likely to get breast cancer **(**14, 15**)** because of the ability to repair DNA damaged, they have through the double-stranded DNA repair process broken, BRCA1 and BRCA2 genes to they belong to the tumor suppressor gene family.

The performance of these genes in normal cells, providing stability and stability DNA and help prevent uncontrolled growth it is cellular **(**16**)**.

Published data of percentage BRCA1 and BRCA2 mutations to develop Breast cancer up to the age of

70 years old **(**except for women Ashkenazi or other ethnic groups with a high percentage of probability estimate - for breast cancer**)** in range 35-84% **(**17,18**)**.

Multiple cases of breast cancer, risk of cancer breast in relation to BRCA1 mutation 52% and BRCA2 is 32%. In families with Hx of ovarian cancer, risk of ovarian cancer in relation 84% BRCA1 mutations and 14% BRCA2 mutations **(**19**)**.

Evidence of a strong association between Fanconi anemia **(**FA**)** and the BRCA pathway **(**20**)**.

BRCA1 gene

BRCA1 gene **(**MIM≠113705**)** as the first the most influential gene causing breast cancer was identified in 1994 it was the risk of breast cancer and also the risk it increases the incidence of ovarian cancer **(**21**)**. This Gene on chromosome 11q21 it is located in genomic DNA and has 22 exons coding and 2 non-coding exons and a protein with it produces 1103 amino acids **(**21**)**.

The second finger Ring at the end of NH2 of BRCA1 protein identification **(**46-20 amino acids**)**. Exon 11 of this gene is intermediate domains with RAD51 **(**22**)**, RAD50 and it includes FANCA **(**24, 23**)**.

More than 500 different types of mutations have been identified in this gene which includes are single nucleotide substitutions **(**SNPs**)**, mutation in germ cells, deletion and insertion. Emergence of BRCA1 gene is under complex regulation. The transcription of this gene is under the control of two promoters

Produce β and α, which are two distinct transcripts **(**25**)**.

BRCA2 gene

BRCA2 gene as the second most influential gene locus chromosome 13q12 it is from genomic DNA.

This gene has 21 exons is that a protein encodes 3411 amino acids. More than 300 type of mutations in the BRCA2 gene it has been identified that most of these mutations are of the type the end codons are **(**26**)**. The second C-terminal it is a conserved region in BRCA2 protein and with ssDNA and DSS1 are bound for recombination homologue is required **(**27**)**.

Number of mutations in BRCA

BRCA1 and BRCA2 mutations are mostly mutations in germ line cells, somatic mutations and promoter methylation **(**28**)**.

Majority of coding regions and splice regions these genes are routinely screened for mutations have became. However, there were several groups of this Genomic deletions and rearrangements have been identified which are inside the genes that have been used by the method based on PCR have not been identified **(**29**)**.

Frequency of BRCA mutations

BIC reports show that the most common mutation- the identified BRCA1 genes include 185delAG **(**5.10%**)** 5382 insC 1.1% and a nonsense mutation is of the type of codon change **(**1.1% C61G**) (**30**)**.

BRCA1/BRCA2 ratio

In most of the reported studies, the frequency of mutations BRCA1 is more frequent than BRCA2 mutations on the contrary, in the study of Nelson, **(**31,32,14**)** Musk **(**2012**)** showed that the mutation in the gene BRCA2 is more than BRCA1 mutations**(** 33**)**.

Effectors mutations and transporter distribution

Although hundreds of rare damaging mutations of the BRCA1 gene are presented, but the prevalence and phenotype of in BRCA mutations **(**40**)**. Countries and races are different major differences in the frequency of specific mutations in populations there are different **(**41**)**. This means that **(**Within specific populations, some specific mutations they are common and specific to certain geographical areas are **(**effective mutations**)**. For example, in Iran 185delAG and 5382insC mutations in contrast they are extremely rare worldwide **(**42**)**.

However, in Ashkenazi Jewish population, three effective mutations 187delAG and 5382insC of BRCA1 and 6174delT of BRCA2 have been well identified and these are estimated to be 2% of the population **(**43, 44**)**. These three mutations include 98 to 99% of all mutations detected in this population **(**45**)**.

The risk of breast cancer with gene mutations BRCA for women

Probability of breast cancer in women who are carriers BRCA1 and BRCA2 gene mutations are is high .In the presence of a pathogenic BRCA1 mutation, cumulative risk of breast cancer is 60-85% and ovarian cancer risk is 40-60%. Carrier women BRCA2 mutation had 50-50% risk of breast cancer and 30% risk of ovarian cancer **(**55-56**)**.

The risk of breast cancer with gene mutations BRCA for Men

BRCA gene mutations are autosomal dominant **(**AD**)** inherit both male and female offspring of mutation genes they inherit the trait from their parents with equal chances.

Consequently, men may be carriers of the mutation.Breast cancer in men are a rare disease.

At families with high risk of cancer breast/ovary, BRCA1 gene mutations and BRCA2 is estimated to be with 16% and 76% of male breast cancer is related **(**19**)**.

Suffering from breast, pancreas, stomach and blood cancers in men who are BRCA mutation carriers, above the report has been the risk of prostate and pancreatic cancer Especially in BRCA2 mutation carrier men and age increases less than 05 years **(**51**)**.

Some gene studies related to BRCA1/2 in Iran

Nematzadeh et al. **(**2014**)** a search based on articles published until January 2014 did that In Medline Pub Med, Science Iranian Database, Google and websites were present and associated with BRCA1/2 gene mutations they were from Iranian families **(**71**)**.

Koshiar et al. **(**2013**)** effective gene mutations 185delAG and 5382insC of BRCA1 in 31 female patients with breast cancer and 21 healthy women at risk above and their results showed that both gene mutations are present in both groups of women **(**42**)**.

Hereditary breast cancer screening

Screening for breast cancer in BRCA1 carriers BRCA2 including annual review of resonance imaging it is magnetic **(**MRI**)**. The sensitivity of MRI shows Given that it is more than mammography.

MRI screening must be done annually from the age of 25 -65 year should be done. Mammography is a low-cost alternative. But in cohort studies of BRCA carriers, People who were only screened by mammography, Cancer rates have been shown to be unexpectedly higher. When the annual MRI done the accuracy of mammography-based diagnoses increases **(**77**)**.

Prevention of hereditary breast cancer

Prevention strategy in the short-term interval period which provides protection in the long term, ideal will be. Preventive strategies can be divided into two Division divided. A section is about people who Providing temporary protection and the other part is related to people which offers lifetime protection **(**78**)**. Breast conserving surgery, the treatment of choice for stages I and II breast cancer in the world. Mastectomy Prophylactic almost complete protection against cancer the breast provides that in this way a large part of breast tissue or all breast tissue is removed from the body **(**79**)**.

Discussion

Breast cancer is one of the most expensive because of its high prevalence diseases and social injuries and economic issues it is very important for our society. On the other hand as mothers, women are one of the pillars of the family in the society, and this disease affects people at the age of maximum personal and social activity. That if not diagnosed and treated on time, without exception, it will lead the affected person to death.

From since Iran is located in the middle part of Asia and Breast cancer is the fifth major cause among Iranian women death and as the first cancer among cancers the diagnosis is known, the importance of identifying affected people in the early stages is that in how to diagnose breast cancer in the early stages and how to do it proper treatment, the life expectancy of more than 10% of the higher sufferers will go early detection of breast cancer can reduce economic costs, and early detection of breast cancer is more likely there is treatment and increasing the life span of the affected person**(**85**)**. Also, in order to diagnose and predict people with breast cancer using genetic markers an important step can be taken. About a decade since the discovery of the BRCA1/2 genes goes on. BRCA1/2 genes are tumor suppressor genes and mutations of these genes can lead to familial breast cancer. Many studies have shown that BRCA1 genes and BRCA2 can be used as a reference to identify and screen cancer patients from healthy people even in the early stages. These genes are one of the first genes that cause breast cancer. High frequency

of gene mutations BRCA1 and BRCA2 show that when the gene product is defective, it causes it to lose its function and breast cancer appears.

In normal cells, BRCA1 and BRCA2 genes they help to prevent cancer and their role by making proteins that cells do protect them from growing uncontrollably. Now if there is a mutation in these genes, they cause breast cancer, and if a copy of these genes is inherited from the parents, the risk of breast cancer in a person is high. Many screening studies have shown that the rate of BRCA1 mutations is around 45% and this mutation rate in families with breast cancer ranges from 1 to 35% **(**86**)**. Cells lacking BRCA1 and BRCA2 are unable to repair DNA strands broken by the recombination process they are not homologous and therefore the repair process is carried out through error-prone paths such as the non-homologous junction terminal. These cells may undergo mutation During the DNA strand repair, they often suffer from rearrangements Cumulative chromosomal rearrangements during cell division become **(**11**)**. The studies conducted so far in Iran on BRCA Although it has been used to determine the range of BRCA mutations in Iranian patients with breast cancer It is helpful, but with limitations such as not providing appropriate prevention strategies, screening and counseling strategies based on mutation data. They have faced each other. Therefore, more studies should be done larger experimental groups to determine the extent BRCA mutation and determination of founder mutations in Iranian population, because the effect of many BRCA mutations on the protein is still unknown It is difficult to predict its consequences on breast and ovarian cancer.

Therefore, it is suggested that a large number People undergoing genetic testing for BRCA mutations be placed to the results of these people; Report mutations that have clinical significance and lead to providing solutions in risk assessment, counseling and care be preventive also in the discussion of reduction strategy Breast Cancer risk in women at high risk of breast and ovarian cancer, breast cancer specialists, genetic counselors, obstetrician-gynecologists, and primary care physicians play an important role. Assessment of risk factors Pathogenesis and family history acquisition, two An important step in assessing the risk of breast cancer They are ovaries. Although genetic testing can Diagnosed with high risk of breast and ovarian cancer.

However, genetic tests may be 100% not accurate if the result of a test is negative, a person still has a chance of getting breast cancer, and if the result of a test is positive, there is still a 15-20% chance. There is a possibility that a person will not get breast cancer. Also genetic testing is expensive and costs from

$400 to $3,000 vary depending on the type of test. However, more studies to clarify the nature BRCA1/2 and hereditary breast cancer are required.

Conclusion

BRCA1/2 genes have great importance and influence in the incidence and they have the development of breast cancer and these genes can be molecular indicators in early diagnosis breast cancer introduced widely from these genes in medical diagnosis laboratories as a diagnostic method in the early stages of breast cancer to prescribe the appropriate drugs used. So identification of gene mutations of BRCA1 carriers and BRCA2 in breast cancer clinical management programs in families with a family history of breast cancer it is important to privacy; and screening for mutations of these two genes are usually suggested in clinical programs to prevent the recurrence of primary cancer and to prevent breast and ovarian cancer in the second stage, which requires that there is more information about the prevalence of BRCA mutations and its impact on the general population and issues such as the effectiveness of screening that includes risk stratification Incidence, use of system support and patient acceptance It is education, it should be considered.

References

1. Coley HM. Mechanisms and strategies to overcome chemotherapy resistance in metastatic breast cancer. Cancer Treat Rev 2008; 34**(**4**)**:378-90.

2. Ripperger T, Gadzicki D, Meindi A, Schlegelberger B. Breast cancer susceptibility: current knowledge and implications for genetic counseling. Eur J Hum Genet 2009; 17**(**6**)**:722-31.

3. Falagas ME, Zarkadoulia EA, Ioannidou EN, Peppas G, Christodoulou C, Rafailidis PI. The effect of psychosocial factors on breast cancer outcome: a systematic review. Breast Cancer Res 2007; 9**(**4**)**:R44.

4. Tabor MP, Brakenhoff RH, Ruijter-Schippers HJ, Kummer JA, Leemans CR, Braakhuis BJ. Genetically altered fields as origin of locally recurrent head and neck cancer: a retrospective study. Clin Cancer Res 2004; 10**(**11**)**:3607-13.

5. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al. Breast cancer in Iran: an epidemiological review. Breast J 2007; 13**(**4**)**:383-91.

6. Lin Y, Kikuchi S, Tamakoshi K, Kondo T, Niwa Y, Yatsuya H, et al. Active smoking, passive smoking and breast cancer risk: findings from the Japan collaborative cohort study for evaluation of cancer Risk. J Epidemiol 2008; 18**(**2**)**:77-83.

7. Zabetian Hoseini M, Nassiri MR, Aslaminejad A, Ghafarzadegan K, Mouseghi A, Ghovvati S, et al. Measurment of human progesterone receptor A expression in normal and breast cancer tissue using real-time PCR technigue. Iran J Obstet Gynecol Infertil 2012;15**(**1**)**:51-9. **(**Persian**)**.

8. Rohlfs EM, Puget N, Graham ML, Weber BL, Garber JE, Skrzynia C, et al. An Alu-mediated 7.1 kb deletion of BRCA1 exons 8 and 9 in breast and ovarian cancer families that results in alternative splicing of exon 10. Genes Chromosomes Cancer 2000; 28**(**3**)**:300-7.

9. Casilli F, Di Rocco ZC, Gad S, Tournier I, Stoppa-Lyonnet D, Frebourg T, et al. Rapid detection of novel BRCA1 rearrangements in high-risk breast-ovarian cancer families using multiplex PCR of short fluorescent fragments. Hum Mutat 2002; 20**(**3**)**:218-26.

10. Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res 2002; 30**(**12**)**:e57.

11. Gudmundsdottir KA, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. Oncogene 2006; 25**(**43**)**:5864-74.

12. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002; 108**(**2**)**:171-82.

13. Scully R, Livingston DM. In search of the tumour-suppressor functions of BRCA1 and BRCA2. Nature 2000; 408**(**6811**)**:429-32.

14. Kurian AW. BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications. Curr Opin Obstet Gynecol 2010; 22**(**1**)**:72-8.

15. Antoniou A, Cunningham A, Peto J, Evans DG, Lalloo F, Narod SA, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008; 98**(**8**)**:1457-66.

16. Scully R, Ganesan S, Vlasakova K, Chen J, Socolovsky M, Livingston DM. Genetic analysis of BRCA1 function in a defined tumor cell line. Mol Cell 1999; 4**(**6**)**:1093-9.

17. Brose MS, Rebbeck TR, Calzone KA, Calzone KA, Stopfer JE, Nathanson KL, et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 2002; 94(18):1365-72.

18. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003; 72(5):1117-30.

19. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998; 62(3):676-89.

20. Kooshyar MM, Nassiri MR, Karimiani EG, Doosti M, Nasiri K, Rodbari Z. Chromosomal analysis and BRCA2*617delT/88delTG and BRIP1(c.2392C>T) mutations of Fanconi anemia in Iranian family, and its correlation to breast cancer susceptibility. J Chem Pharmaceut Res 2015; 7(10):147-53.

21. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266(5182):66-71.

22. Scully R, Anderson SF, Chao DM, Wei W, Ye L, Young RA, et al. BRCA1 is a component of the RNA polymerase II holoenzyme. Proc Natl Acad Sci U S A 1997; 94(11):5605-10.

23. Zhong Q, Chen CF, Li S, Chen Y, Wang CC, Xiao J, et al. Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. Science 1999; 285(5428):747-50.

24. Folias A, Matkovic M, Bruun D, Reid S, Hejna J, Grompe M, et al. BRCA1 interacts directly with the Fanconi anemia protein FANCA. Hum Mol Genet 2002; 11(21):2591-7.

25. Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990; 250(4988):1684-9.

26. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378(6559):789-92.

27. Yang H, Jeffrey PD, Miller J, Kinnucan E, Sun Y, Thoma NH, et al. BRCA2 function in DNA binding and recombination from a BRCA2-DSS1-ssDNA structure. Science 2002; 297(5588):1837-48.

28. Hogervorst FB, Nederlof PM, Gille JJ, McElgunn CJ, Grippeling M, Pruntel R, et al. Large genomic deletions and duplications in the BRCA1 gene identified by a novel quantitative method. Cancer Res 2003; 63**(**7**)**:1449-53.

29. Mazoyer S. Genomic rearrangements in the BRCA1 and BRCA2 genes. Hum Mutat 2005; 25**(**5**)**:415-22.

30. Wang F, Fang Q, Ge Z, Yu N, Xu S, Fan X. Common BRCA1 and BRCA2 mutations in breast cancer families: a meta- analysis from systematic review. Mol Biol Rep 2012; 39**(**3**)**:2109-18.

31. Hall MJ, Reid JE, Burbidge LA, Pruss D, Deffenbaugh AM, Frye C, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer 2009; 115**(**10**)**:2222-33.

32. Keshavarzi F, Javadi GR, Zeinali S. BRCA1 and BRCA2 germline mutations in 85 Iranian breast cancer patients. Fam Cancer 2012; 11**(**1**)**:57-67.

33. Nelson-Moseke AC, Jeter JM, Cui H, Roe DJ, Chambers SK, Laukaitis CM, et al. An unusual BRCA mutation distribution in a high risk cancer genetics clinic. Fam Cancer 2012; 11**(**1**)**:83-7.

34. Ramus SJ, Friedman LS, Gayther SA, Ponder BA, Bobrow L, van der Looji M, et al. A breast/ovarian cancer patient with germline mutations in both BRCA1 and BRCA2. Nat Genet 1997; 15**(**1**)**:14-5.

35. Lavie O, Narod S, Lejbkowicz F, Dishon S, Goldberg Y, Gemer O, et al. Double heterozygosity in the BRCA1 and BRCA2 genes in the Jewish population. Ann Oncol 2011; 22**(**4**)**:964-6.

36. Nomizu T, Matsuzaki M, Katagata N, Kobayashi Y, Sakuma T, Monma T, et al. A case of familial breast cancer with double heterozygosity for BRCA1 and BRCA2 genes. Breast Cancer 2012; 22**(**5**)**:557-61.

37. Easton DF, Ford D. Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers, Breast Cancer Link- age Consortium. Am J Hum Genet 1995; 56**(**1**)**:265-71.

38. Narod SA, Goldgar D, Cannon-Albright L, WeberB, Moslehi R, Ives E, et al. Risk modifiers in carriers of BRCA1 mutations. Int J Cancer 1995; 64**(**6**)**:394-8.

39. Heidemann S, Fischer C, Engel C, Fischer B, Harder L, Schlegelberger B, et al. Double heterozygosity for mutation in BRCA1 and BRCA2 in German breast cancer patients: implications on test strategies and clinical management. Breast Cancer Res Treat 2012; 134(3):1229-39.

40. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene 2004; 23(38):6445-70.

41. Ferla R, Calo V, Cascio S, Rinaldi G, Badalamenti G, Carreca I, et al. Founder mutations in BRCA1 and BRCA 2 genes. Ann Oncol 2007; 18(6):93-8.

42. Kooshyar MM, Nassiri M, Mahdavi M, Doosti M, Parizadeh A. Identification of germline BRCA1 mutations among breast cancer families in Iran, an experience from Northeastern Iran. Asian Pac J Cancer Prev 2013; 14(7):4339-45.

43. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet 1996; 14(2):185-7.

44. Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, et al. Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am J Hum Genet 1998; 63(1):45- 51.

45. Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 2002; 20(6):1480-90.

46. Thorlacius S, Olafsdottir G, Tryggvadottir L, Neuhausen S, Jonasson JG, Tavtigian SV, et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 1996; 13(1):117-9.

47. Einbeigi Z, Bergman A, Meis-Kindblom JM, Flodin A, Bjursell C, Martinsson T, et al. Occurrence of both breast and ovarian cancer in a woman is a mark er for the BRCA gene mutations: a population-based study from western Sweden. Fam Cancer 2007; 6(1):35-41.

48. Sogaard M, Kruger SK, Cox M, Wozniak E, Hogdall E, Hogdall C, et al. BRCA1 and BRCA2 mutation prevalence and clinical characteristics in an ovarian cancer case population from Denmark. Clin Cancer Res 2008; 14(12):3761-7.

49. Valarmathi M, Agarwal A, Deo SS, Shukla NK, Satya N. BRCA1 germline mutations in Indian familial breast cancer. Hum Mutat 2002; 21(1):98-9.

50. Pal T, Permuth-Wey J, Holtje T, Sutphen R. BRCA1 and BRCA2 mutations in a study of African American breast cancer patients. Cancer Epidemiol Biomarkers Prev 2004; 13(11):1794-9.

51. Liede A, Jack E, Hegele RA, Narod SA. A BRCA1 mutation in native North American families. Hum Mutat 2002; 19(4):460.

52. Clark SL, Rodriguez AM, Snyder RR, Hankins GD, Boehning D. Structure-function of the tumor suppressor BRCA1. Comput Struct Biotechnol J 2012; 1(1):e201204005.

53. Thompson D, Easton D, Breast Cancer Linkage Consortium. Variation in BRCA1 cancer risks by mutation position. Cancer Epidemiol Biomarkers Prev 2002; 11(4):329-36.

54. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin–cohort study in Ontario, Canada. J Natl Cancer Inst 2006; 98(23):1694-706.

55. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer 2012; 12(1):68-78.

56. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer 2008; 8:155.

57. Schwartz GF, Hughes KS, Lynch HT, Fabian CJ, Fentiman IS, Robson ME, et al. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April 2007. Cancer 2008; 113(10):2627-37.

58. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007; 25(11):1329-33.

59. Mohamad HB, Apffelstaedt JP. Counseling for male BRCA mutation carriers: a review. Breast 2008; 17(5):441-50.

60. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004; 22(4):735-42.

61. Satagopan JM, Boyd J, Kauff ND, Robson M, Scheuer L, Narod S, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2002; 8(12):3776-81.

62. 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(9):2310-8.

63. Vaziri SA, Krumroy LM, Elson P, Elson P, Budd GT, Darlington G, et al. Breast tumor immunophenotype of BRCA1- mutation carriers is influenced by age at diagnosis. Clin Cancer Res 2001; 7(7):1937-45.

64. Phillips KA. Immunophenotypic and pathologic differences between BRCA1 and BRCA2 hereditary breast cancers. J Clin Oncol 2000; 18(21 Suppl):107S-12.

65. Adem C, Reynolds C, Soderberg CL, Slezak JM, McDonnell SK, Sebo TJ, et al. Pathologic characteristics of breast parenchyma in patients with hereditary breast carcinoma, including BRCA1 and BRCA2 mutation carriers. Cancer 2003; 97(1):1-11.

66. van der Groep P, Bouter A, van der Zanden R, Siccama I, Menko FH, Gille JJ, et al. Distinction between hereditary and sporadic breast cancer on the basis of clinicopathological data. J Clin Pathol 2006; 59(6):611-7.

67. Foulkes WD, Brunet JS, Stefansson IM, Straume O, Chappuis PO, Begin LR, et al. The prognostic implication of the basal-like (cyclin Ehigh/p27low/p53+/glomeruloid-microvascular-proliferation+) phenotype of BRCA1-related breast cancer. Cancer Res 2004; 64(3):830-5.

68. Verhoog LC, Brekelmans CT, Seynaeve C, Dahmen G, van Geel AN, Bartels CC, et al. Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 1999; 17(11):3396-402.

69. Senst N, Llacuachaqui M, Lubinski J, Lynch H, Armel S, Neuhausen S, et al. Parental origin of mutation and the risk of breast cancer in a prospective study of women with a BRCA1 or BRCA2 mutation. Clin Genet 2012; 84(1):43-6.

70. Cortesi L, Turchetti D, Bertoni C, Bellei R, Mangone L, Vinceti M, et al. Comparison between genotype and phenotype identifies a high-risk population carrying BRCA1 mutations. Genes Chromosomes Cancer 2000; 27**(**2**)**:130-5.

71. Neamatzadeh H, Shiryazdi SM, Kalantar SM. BRCA1 and BRCA2 mutations in Iranian breast cancer patients: a systematic review. J Res Med Sci 2015; 20**(**3**)**:284-93.

72. Saleh-Gohari N, Mohammadi-Anaie M, Kalantari-Khandani B. BRCA1 gene mutations in breast cancer patients from Kerman Province, Iran. Iran J Cancer Prev 2012; 5**(**4**)**:210-5.

73. Yassaee VR, Zeinali S, Harirchi I, Jarvandi S, Mohagheghi MA, Hornby DP, et al. Novel mutations in the BRCA1 and BRCA2 genes in Iranian women with early-onset breast cancer. Breast Cancer Res 2002; 4**(**4**)**:R6.

74. Mehdipour P, Hosseini-Asl S, Savabi-E A, Habibi L, Alvandi E, Atri M. Low frequency of 185delAG founder mutation of BRCA1 gene in Iranian breast cancer patients. J Cancer Mol 2006; 2**(**3**)**:123-7.

75. Fattahi MJ, Mojtahedi Z, Karimaghaee N, Talei AR, Banani SJ, Ghaderi A. Analysis of BRCA1 and BRCA2 mutations in southern Iranian breast cancer patients. Arch Iran Med 2009; 12**(**6**)**:584-7.

76. Ghorbanpoor S, Bidmeshkipoor A, Mirmomeni MH, Khazaee S. Role of BRCA1 gene mutations in sporadic cases of breast cancer in Kermanshah. Sci J Kurdistan Univ Med Sci 2010; 14**(**4**)**:60-71. **(**Persian**)**.

77. Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. A prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol 2011; 29**(**13**)**:1664-9.

78. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast- cancer prevention in postmenopausal women. N Engl J Med 2011; 364**(**25**)**:2381-91.

79. Nooshinfar E, Bashash D, Khodakarami N, Mohamadi G, Taghavi A, Shahani M, et al. Melatonin and its importance in Breast cancer prevention and treatment **(**A purposed review article**)**. Iran J Obstet Gynecol Infertil 2014; 17**(**118**)**:10-21. **(**Persian**)**.

80. Akbari ME, Khayamzadeh M, Khoshnevis SJ, Nafisi N, Akbari A. Five and ten years survival in breast cancer patients mastectomies vs. breast conserving surgeries personal experience. Iran J Cancer Prev 2012; 1(2):53-6.

81. Gronwald J, Tung N, Foulkes WD, Offit K, Gershoni R, Daly M, et al. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 2006; 118(9):2281-4.

82. Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res 2009; 69(9):3850-5.

83. Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, et al. Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature 2010; 468(7320):98-102.

84. Khadivi R, Harrirchi I, Akbari ME. Ten year breast cancer screening and follow up in 52200 women in Shahre-Kord, Iran (1997-2006). Iran J Cancer Prev 2008; 1(2):73-7.

85. Sadjadi A, Sadjadi M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. Asian Pac J Cancer Prev 2005; 6(3):359-63.

86. Bougie O, Weberpals JI. Clinical considerations of BRCA1- and BRCA2-mutation carriers: a review. Int J Surg Oncol 2011; 2011:374012.

87. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer 2004; 4(9):665-76.

88. Xu B, Kim ST, Kastan MB. Involvement of Brca1 in S-phase and G(2)-phase checkpoints after ionizing irradiation. Mol Cell Biol 2001; 21(10):3445-50.