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Risk factors, genetic mutations and prevention of breast cancer

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Abstract

Breast cancer is the second leading cause of cancer deaths among women. The breast is generally common site of noncutaneous cancer among women. Numerous genetic and clinical factors are involved in increasing the risk of developing breast cancer among women. This review focused on pathogenesis, related genes, risk factors and preventive methods that implement on the breast cancer over past years strategies in present use to stop breast cancer, as well as prospective approach that could be used in future. A set of somatic alterations as well as mutations and also gene amplifications are involved in etiology of various forms of breast cancer. Diagnosis of breast cancer at the Initial stages is one of the most excellent approaches to prevent this disease. Presently, people have supplementary drug option for the chemoprevention of breast cancer, while prevention using biological methods has been in recent times developed to recover quality of life of patients suffering from breast cancer. In addition, prevention clinical trials are starting to estimate multi agent cancer prevention approach with the expectation of improved effectiveness over single agents.

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Introduction

Breast cancer is the most common cancers in women accounting about 570,000 deaths in 2015. More than 1.5 million women are diagnosed by means of breast cancer each year all over the world (Siegel RL *et al.*, 2017). In America, it is expected that 40% of every one new cancer cases along with women are reported with breast cancer in 2017. Breast cancer is a metastatic cancer and be able to generally transfer to remote organs such as the liver, lung and brain that are primarily accounts for its incurability. In the early hours, diagnosis of breast cancer can go ahead to a excellent prognosis and high rate of survival. Mammography is extensively used for showing approach in detecting of breast cancer and helpful to decrease rate of mortality successfully. Screening methods such as Magnetic Resonance Imaging that is more sensitive than mammography and have as well been apply and intentional during last decade. There are several risk factors such as sex, aging, estrogen, family history, gene mutations and unhealthy lifestyle which can enlarge the likelihood of increasing breast cancer. The majority of breast cancer happen in women and number of cases is 100 times advanced in women as compared in men (Siegel RL *et al.*, 2017).

Age is the prominent risk factor for the onset of breast cancer however life styles and diet play important roles in breast cancer. Deregulation and mutations of common breast cancer genes including *HER2, PIKC3A, BRCA1* and *BRCA2* and some other genes play important roles in breast cancer (Davis *et al.*, 2014). High-risk risk such as *BRCA2* explain approximately 20% of the inherited susceptibility, intermediate-risk genes in DNA-repair genes increase this proportion by ~5% (Hamdi *et al.*, 2016). Natural therapies have been developed in recent years and helpful to for breast cancer. This review focused on current studies of the pathogenesis, genes involved and their role in breast cancer, risk factors such, level of estrogen, life style, reproductive factors and biological prevention of breast cancer in more advanced way than the past years.

Risk Factors Involved

Various factors linked to breast cancer such as age, level of estrogen, life style and reproductive factors that is needed to more understanding in relation to breast cancer. In addition to these factors numerous genetic factors linked to breast cancer.

Age

Age is one of the mainly important risk factors of breast cancer since the occurrence of breast cancer is extremely associated to the growing age. In 2016, about 99.3% and 71.2% of every breast cancer connected deaths in America were report in women above the age of 40 and 60, correspondingly (Siegel *et al.*, 2017).

Level of Estrogen

Both type of estrogens mainly endogenous and exogenous estrogens linked with the possibility risk of breast cancer. The endogenous estrogen is typically produced by ovary in premenopausal of women and ovariectomy can decrease the possibility of breast cancer. The most important source of exogenous estrogen are the oral contraceptives and hormone replacement therapy. The oral contraceptives generally use since 1960s and the formulations have been upgrade to lessen side-effects. On the other hand, the OR is higher than 1.5 for African and American women and Iranian populations (Bethea *et al.*, 2015).

Life Style

Modern lifestyles such as extreme use of alcohol consumption and as well as much nutritional fat intake can add to the risk of breast cancer. Alcohol use can raise the level of estrogen related hormones in blood and stimulate the estrogen receptor pathways. A Meta analysis based on 53 epidemiological studies shows that an intake of 35-44 grams of alcohol per day can raise the risk of breast cancer by 32%, with a 7.1% enlarge in the RR for each extra 10 grams of alcohol per day (Majima *et al.*, 2002).

Reproductive factors

Reproductive factors included early menarche, delayed menopause, delayed age at first pregnancy and small parity raise the breast cancer risk. Every 1 year interruption in menopause raises the risk of breast cancer by 3%. Every 1 year stoppage in menarche or every extra birth decrease the danger of breast cancer by 5% or 10%, respectively (Dall *et al.*, 2017).

Genes involved in breast Cancer

5 -10 % of every one breast cancer events outcome due to germ line mutations in recognized receptiveness genes of breast cancer. In accordance with magnitude of their effect in breast cancer and mutation recurrence, these genes are divided into three types "high-penetrance," "moderate-penetrance," and "low-penetrance" genes (Hirshfield *et al.*, 2010). 10 to 15% of heritable breast cancer owing to germ line mutations in various forms of breast cancer genes such as BRCA1 and also BRCA2 (Jiao *et al.*, 2017). A mutation in other high risk genes STK11, PTEN, CDH1 and TP53 lead to growth of breast cancer. NF1 is a high penetrate gene that cause neuroectodermal disease due to autosomal dominant inheritance and it a broad changeability in expression of gene (Khalil *et al.*, 2015).

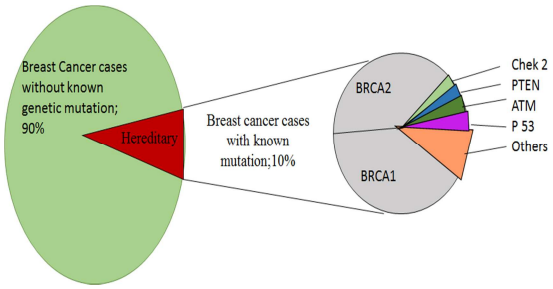

Fig.1. Percentage of hereditary and non-hereditary breast cancer.

BRCA1 and BRCA2

BRCA1 and *BRCA2* genes are important because they response in DNA damage and they play functional role in homologous recombination. Premature truncations of *BRCA1* and *BRCA2* proteins caused by nonsense or frame-shift mutations proved to be predominant genomic aberrations underlying susceptibility. The significance of uncertain genes were observed in quarter of patients, however the recurrence of these predominantly missense mutations in variants of unknown significance but however dropped to somewhere in the range of 2 and 5 % as extensive databases of hereditary variations and "high-hazard" kindreds were made. The risk of breast cancer could be increased greatly if an individual inherits deleterious mutations in either *BRCA1* or *BRCA2* genes. *BRCA1/2* mutations are inherited in an autosomal dominant manner even though the second allele is normal. Totally, about 20-25% of hereditary breast cancers and 5-10% of all breast cancers are caused by *BRCA1/2* mutations (Paluch *et al* 2016).

BRCA1 and BRCA2 mutation in women

In women by age 70 years, germ line mutations in *BRCA1* and *BRCA2* gene possess a high chance of developing breast cancer. Starting examinations in view of various case families, detailed a female breast cancer chance at age 70 years in *BRCA1* and *BRCA2* mutation carriers of 85% and 84% respectively (Ford *et al.*, 1998).

BRCA1 and BRCA2 mutation in men

In male the most common mutations are *BRCA2* as compared to *BRCA1*. 60 to 76% of breast cancer in male are due to germ line mutations in *BRCA2* in high risk breast cancer families, whereas frequency of mutation in BRCA1 ranges from 10 to 16 % (Ford *et al.*, 1998).

TP53

p53 play an important role in regulating different cellular activities that directly suppress the tumor formation like DNA repairing and cell-cycle control but there are sufficient evidences that p53 also regulates some other activities as well such as mitochondrial respiration and glycolysis.

CHEK2

CHEK2 1100delC was the first breast cancer risk allele that was determined. Identification of the *CHEK2* 1100delC mutation as a breast cancer-associated allele induced mutational screening of the whole *CHEK2* gene sequence. However, at present, only a small number of rare mutations and missense variants have been declared in breast cancer cases (Bogdanova *et al.*, 2005).

ATM

ATM was primary investigate as a breast cancer tendency gene by study population that report an enlarged breast cancer peril in relations of patients through ataxia telangiectasia, is a recessive syndrome caused by *ATM* gene mutation. Presently there is no clear idea about the role of *ATM* in men predisposed to breast cancer (Rizzolo *et al.*, 2011).

PTEN

Gene PTEN behaves as tumor suppressor gene in germline. It is well known that p53 have an important role in controlling various cellular function that are directly linked with tumor destruction, such as DNA repairing and cell-cycle control but there are enough evidence that p53 also controls many other activities like mitochondrial respiration and glycolysis (Matoba *et al.*, 2006).

Prevention

For treatment of breast cancer advances have been taken into action in clinical trials. The current preventive measures include screening, chemoprevention and biological prevention.

Screening

90% cancer deaths results from tumor metastasis. Early detection is the breast cancer impediment. Mammography is successful screening technique to make use of low energy X-rays to attain high-resolution images of breast. The whole testing procedure just last for 20 minutes and it not need any contrast enhancing chemical agent .On the other hand death rate among women not dccraesed among age group 30-40 years old. MRI is an additional extensively used screening means for breast cancer. It is further sensitive than mammography in high risk women, particularly to detect the persistent ductal carcinoma (Valastyn *et al.,* 2011).

Chemoprevention

The traditional meaning of chemotherapy through Sporn is the employ of pharmacologic or natural agents with the intention of slow down the growth of invasive breast cancer moreover by overcrowding the DNA harm that start carcinogenesis and also by impressive or reversing the development of premalignant cells such damage has by now occur. Estrogen receptor is main target for chemotherapy since more than 70% of breast cancers are ER positive breast cancers. Estrogen receptor modulators and the aromatase inhibitors are two most important classes of antiestrogen drugs. Tamoxifen (TAM) that has been use to care for breast cancer for more than 30 years (Bezovic *et al.*, 2012).

Biological prevention

In biological prevention, primarily famous as monoclonal antibodies for the breast cancer, to be developed to get better the value of life in breast cancer patients. One of the main targets of these monoclonal antibodies is HER2. Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody that is the first HER2 targeted drug to be accepted by the FDA. It can directly act together with C terminal portion of domain IV in the extracellular fraction of HER2 (Cho *et al.*, 2013).

Conclusion

Breast cancer receptiveness genes in *BRCA1* and *BRCA2* has altered the managing of breast cancer patients with family history of breast cancer. Numerous models has been designed and are presently use to review the pre test chance to identify *BRCA1/2* germ line mutations in persons at risk for inherited breast and also ovarian cancer. More analysis of BRCA1, BRCA2, and genes relted to breast cancer will permit the clarification of pathogenesis of this disease. Great steps have been taken in to action to determine the disease etiology but needed advance investigation. These studies will helpful in determination and also to assess the significance of new genes concerned in breast cancer etiology so with the intention of scientists be able to define improved therapies and cancer prevention. By using modern sequencing technology, individual genome sequencing might be a prevailing technique to estimate the risk of breast cancer. Improved medicines with fewer side effects and favorable risk advantage ratio require to be developed in future. Improved medicines through less side effects and a positive benefit ratio require to be developed in the future.

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