

## Carcinogenesis and Effect of BRCA-1 and BRCA-2 Mutation on Breast Cancer Development

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**Abstract:** Cancer is the most important factor of death after cardiovascular diseases in human populations. So, the reserachers consider cancer as a factor of 13% of deaths that occur in the world. However, breast cancer is the most common type of cancer in women. Statistics show that the number of patients referred to America's Breast Cancer Clinic increased from 3745 in 2003 to 6671 in 2009 and cases of breast cancer diagnosed each year increase from 110 to 529. due to the growing statistics, understanding the maina factor of breast cancer (heredity) is very important which is considered less than other factors directly involved in development of breast cancer. The aim of this paper is to examine the effect of this factor on other factors contributed to breast cancer development.

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### Introduction

Cancer is a major health concern in the United States of America and all over the world. The disorder can occur at any age, but its prevalence increases with age. in 1997, cancer was the mortality factor of about 2/7 millions persons which was 13% of all deaths in that year. It is predicted that this amount increase in the upcoming years because of changes to life styles and higher life expectancy in the world. (1)

Now, breast cancer is one of the most prevalent types of cancer in women. The researchers estimate that one out of every eight American women is suffered from cancer in her lifetime. The American Cancer Society states that approximately 232,340 cases of invasive breast cancer will be diagnosed in American women by the end of 201. of these, about 64,640 cases is carcinoma in Situ. Also, about 39,620 women will die because of cancer. (2). The studies show that the prevalence rate of cancer increased in women since 2000 but it decreased 7% in 2002 to 2003. the researchers treated non-hormone therapy after menopausal ages as probable cause of reduction. Because the performed studies in these years showed that hormone therapy after the menopausal age can be associated to high risk of developing breast cancer and heart diseases. (3).

Breast cancer is the second leading cause of death in women, so that one out of every 36 women dies because of this disease. (about 3%). Fortunately, mortality rate of breast cancer decreased since 1989 and it is considered that reduction rate is due to early diagnosis of disease by screening (Genetic examination) and pathogenesis in young women. (4). Scientists believe that genetic factors have effective role in increasing the risk of breast and ovarian

cancer. So, the genetic researchers account heredity and mutation as the main factor of 5% to 10% of cancers development. (5, 6). The aim of this study is to review the effect of inheritance on other risk factors of breast cancer.

### Discussion

#### Carcinogenesis and Effective Factors on This Process

Carcinogenesis is the process in which normal cells are transformed to cancer cells. Therefore, some factors are involved in this kind of processes such as:

- Initiating agents or carcinogen: initiating agent is a chemical, biological or physical agent that is able to make permanent and irreversible changes directly in molecular structure of genetic component of cell which causes cells susceptible to become cancer cells in prolonged or continuous exposure to promoting agents. The initiating agent can
  - divide completely DNA chain in one or more locations
  - remove the chain constituents of DNA (such as carbohydrates and bases)
  - cause errors to restore DNA

Initiating agent may influences on initial point of contact and aggregation, metabolism or secretion point of carcinogens. Factors such as environment viruses, genetic factors and life style can be initiating agent of carcinogenesis.

Promoting agent accelerate transformation of normal cell to cancer cell by changing the genetic information of cell. Hormones, herbal products and drugs are examples of promoting agents. These agents do not react directly with genetic materials of cell and they can not cause mutation in DNA of cell. Although, the promoting agents accelerate the neo-

plastic changes with cooperation of initiating agents, but they can not cause cancer by itself. It is worth noting that the effects of promoting agents are temporary and reversible.

- **Complete Carcinogen:** complete carcinogen is an agent which has initiating and promoting properties together and it can cause cancer by itself. Capability of an agent as the complete carcinogen depends on dose. Radiation is an example of dose-dependent complete carcinogen.

- **Reversal Agent:** this agent can inhibit the effects of promoting agents by stimulating the cellular metabolic pathways that lead to destruction of carcinogens or change of initiating power of chemical carcinogens. Some drugs, enzymes and vitamins are examples of this type of agent.

- **Oncogenes:** oncogen is a gene that has evolved to control tissue growth and restoration. Oncogen is a genetic code that sends signals in on and off mode. These signals are exchanged by cells to control reproduction. Oncogen include proto oncogenes (part of DNA that regulate normal reproduction and repair of cell) and Anti oncogen, (part of DNA that stop the cell division). Oncogenes are target of carcinogen and they can make mutation. Also, they put proto oncogenes directly in on-mode and hinder sending of off-signal by oncogenes.

- **Promotion:** the microscopic structure of tumor cells is changed during reproduction which called promotion. These changes convert the weak malignant or pre-neoplasm tumor to a fast-growing invasive tumor. Tumor promotion may be observed as a change in growth rate, invasive power, and number of metastases, morphological properties and response to treatment. Promotion results from emergence of a type of cell that can grow or implement metabolism faster than other tumor cells. Thus, this cell becomes predominant cell. Cytotoxic drugs accelerate tumor development aided by mutation that may accelerate emergence of some type of tumors which are more malignant.

- **Heterogeneity:** the concept of heterogeneity is closely related to development or progression. This concept refers to differences between single cells within a tumor. As said, the cancer cells have more random mutations because of genetic instability. These mutations make colonies that their acquired genetic differences may cause heterogeneity in tumor. Cells within a tumor can create metastases in surrounding tissues depending on their invasive power.

- **Transformation:** transformation is a multi-stages process in which cells become progressively indistinguishable after exposure to the initiating agent. Probably, this transformation results from the genetic changes of cells which disrupt proliferation

control of cell. Many researchers believe that approximately 80% of known cancers in human are result of exposure to environment carcinogens. (7)

#### **Important Carcinogens**

It is evident that carcinogens have special role in formation of carcinogenesis process, so it is necessary to state briefly various types of carcinogens:

- **Hormonal Carcinogens:** hormonal changes are result of excessive production of hormones in the body or excessive consumption of hormones. The four major types of cancer (prostate, ovarian, breast and endometrial) is developed in sensitive tissues to hormones (target tissues). Although the target tissues need hormones to grow and function normally, but little evidences suggest that hormones have direct carcinogenic effect. However, hormones do not react with nucleic acids, but sensitizing of cell against the carcinogen agent and modifying the tumor growth lead to promotion of carcinogenic process.

- **Chemical Carcinogens:** chemical carcinogens are compounds or elements that cause a change in DNA such as alkylating and acetylating agents, heterocyclic polycyclic aromatic hydrocarbons, pesticides and fungi.

- **Viral Carcinogens:** These types of carcinogens choose particular tissues and make them infectious. It is believed that the immune system sufficiency determine the person's sensitivity to viral carcinogens.

- **Radiation-induced Carcinogens:** radiation can damage cell that influences on oncogenes or anti-oncogenes and cause cancer risk.

- **Immune System Weakness Induced Carcinogens:** the immune system of body can control proliferation of cancer cells in normal conditions, because the cancer cells often have antigens which are different from the body's antigens. So the immune system treats them as alien agents and destroys them. However, if the immune system is suppressed due to factors such as malnutrition, chronic diseases and aging, the person will get cancer.

- **Heredity and Carcinogen:** hereditary cancer syndrome occurs following the mutation in initiating cells. This mutation passes to next generations, but remember that a trait which is genetically transferred to future generations is only susceptibility to cancer not real cancer. (8)

#### **Breast Cancer (Non-Invasive and Invasive Carcinoma):**

Breast cancer is uncontrolled growth of breast tissue that is divided to 2 categories: non-invasive and invasive carcinoma. Non-invasive breast carcinoma is mainly diagnosed during the screening mammography. Currently, about 20%-25% of diagnosed breast cancers are carcinoma in situ. This

disease is characterized by proliferating of malignant cells within the ducts and lobules with no invasion into surrounding tissue. Thus, carcinoma in situ is the type of non-invasive breast cancer (breast cancer in zero stage). There are 2 types of non-invasive carcinomas: lobular carcinoma (LCIS) which originates from milk glands and ductal carcinoma (DCIS) which originates from milk ducts. Breast ductal carcinoma is the most prevalent type of breast cancer. But LCIS is an incidental finding that is detected in pathological evaluation of breast biopsy. (9).

Invasive breast carcinoma is classified to infiltrative carcinoma of breast lobules and infiltrative carcinoma of breast ducts. Infiltrative carcinoma of breast ducts is the most common type of breast cancer' histology that accounts for 75% of breast cancer cases. But infiltrative carcinoma of breast lobules is rare and includes 5%-10% of all breast cancer cases. Today, researchers believe that whatever is the type of cancer, genetic and heredity can play major role to cancer development. There is growing evidences suggesting that breast cancer is correlated with genetic changes. Furthermore, studies show that the most known cancer risk is that one of the first-degree relatives of patient have had suffered from hereditary cancer which is transferred as dominant autosomal. The first report on density of breast cancer in some families dated back to Roman medical books in 1000 A.D. studies of 1930 showed that the relative risk of breast cancer in individuals who have had cancerous patient among their first-degree relatives is 2-3 times more than others. (10).

Now, the obtained information emphasize on change or mutation of normal genes and effect of progestins which accelerate or slow the breast cancer growth. The researchers identified 2 types of mutations as contributing factor of breast cancer:

1- BRCA-1 Mutation which is associated to breast and ovarian cancer. 2 -BRCA-2 which is risk factor of breast cancer but less involved in ovarian cancer development.

Therefore, it is obvious that inheriting the mutated BRCA gene increases the risk of cancer.

### **Correlation Analysis of Risk Factors of Breast Cancer and Genetic Factor**

#### **Age and BRCA-1 and BRCA-2 Mutations**

Age is one of the contributing factors of cancer. Researchers believe that most breast cancer cases in women occurred after the age of 50 but for the women whom heredity is a risk factor, breast or ovarian cancer is seen at younger ages. (12)

#### **Menarche and Menopause Ages and BRCA-1 and BRCA-2 Mutation**

Generally, early menarche (before age 12) or late menopause (after age 50) is other factors that

increase the risk of breast cancer. It is believed that the women who give birth to their first child after age 30 are twice more susceptible to breast cancer than the women whom their first birth is before age 20. There is little evidences about the effect of BRCA-1 and BRCA-2 mutations on development of breast cancer so that the researchers state that there is no correlation between menarche or menopause age and estrogen or +ER dependent cancers. It should be noted that only one-third of breast cancers are estrogen or +ER dependent cancer and the tumor growth depends on estrogen supply in these types of cancers. (11, 13, 14, 15)

#### **Use of Oral Contraceptives and BRCA-1 and BRCA-2 Mutation**

Long-term oral contraceptives usage is another factor that increases the risk of breast cancer especially in people who have mutated BRCA. But on the other hand, some researchers believe that hormonal drugs usage is a way to prevent ovarian cancer in BRCA-1 and BRCA-2 mutation cases. (16).

#### **Hormone Therapy (HRT) and BRCA-1 and BRCA-2 Mutation**

Evidences show that there is direct relationship between HRT and breast cancer development in people whom cancer is a hereditary disease in their families. So long-term HRT increase the risk of breast cancer in these patients. But short-term HRT do not make difference between those who have family history of this disease and others. Hence, researchers suggest that short-term HRT for menopausal symptom relief do not increase the risk of breast cancer even in people who have family history of this disease. (17, 18, 19)

#### **Radiation and BRCA-1 and BRCA-2 Mutation**

As said before, being exposed to radiation is one of the important factors of carcinogenesis. Traced left by bombing of Hiroshima and Nagasaki is the evidence for this claim. Today, scientists suggest that the BRCA-1 and BRCA-2 mutation increase substantially the risk of breast cancer. Even the risk of breast cancer increases depended to radiation dose in imaging and therapeutic procedures in people who have mutated BRCA-1 and BRCA-2, so the extensive studies in Europe showed that exposure to such radiation before age 20 increase the risk of breast cancer. (20)

#### **Alcohol Consumption and BRCA-1 and BRCA-2 Mutation**

Alcohol consumption is another risk factor of breast cancer so that it can increase the risk of breast cancer up to 10%. (21, 22). Several studies showed that alcohol has no effect on breast cancer development in people with mutated BRCA-1, BRCA-2 compared with others. (23, 24)

### **Obesity, Physical Activity and BRCA-1 and BRCA-2 Mutation**

Obesity is another factor which increases the risk of breast cancer especially after menopause ages. There is no study about the effect of obesity on risk of breast cancer in people who have family history of this disease, but the result of one study showed that physical activity can reduce the risk of breast cancer in people with mutated BRCA-1, BRCA-2. (25, 26)

### **Benign diseases Development and BRCA-1 and BRCA-2 Mutation**

Development of benign diseases of breast is another risk factor of breast cancer but the level of risk depends on other risk factors such as menarche age, first pregnancy age and family history of breast cancer. Therefore, heredity has role in this risk factor. On the other hand, the people whom their breast tissue density has been diagnosed in mammography survey are exposed to more risk of breast cancer than other if they have family history of this disease. (27)

### **Other Factors and BRCA-1 and BRCA-2 Mutation**

At last, other risk factors that have minor role in breast cancer than other important factors (such as smoking) can increase the risk of breast cancer in people with family history of this disease. For example, extensive studies have shown that N-acetyl transferase is a risk factor of breast cancer in smoker women that increase significantly the risk of breast cancer in people with mutated BRCA-1, BRCA-2. (28)

### **Discussion**

The main factor of cancer can be considered as combination of important factors such as lifestyle, environmental factors, hormonal factors and other unknown factors. But genetic is another important factor in development of cancer. Although, this factor can not cause cancer lonely but it increase the effect of other carcinogens. For instance, mutation of BRCA-1 and BRCA-2 along with other risk factors increases the breast cancer or respective cancers risk such as ovarian cancer so that breast cancer is developed earlier in these persons rather than other people who have had some exposure to other carcinogenic factors. So it seems that understanding the effect of heredity on other risk factors of breast cancer will help to protect people and prevention against the disease.

### **Conclusion**

The measures taken to mitigate the carcinogenic factors in people who are genetically at risk of breast cancer can decrease the disease risk and its mortality. As abovementioned, the mutated genes or heredity is a hidden factor of breast cancer

development but this factor cannot cause cancer by itself. This factor can increase the risk of breast cancer and reduce the age of cancer development in some cases along with other carcinogenic factors. Thus, identifying people who have mutated genes and keeping them away from various carcinogenic factors can reduce the incidence of disease or increase the survival rate of these patients.

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