

The Role of Immune Therapy in Breast Cancer

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Abstract: The immune system involves collection of cells that protect the body from microbes and bacteria and hence tries to protect the body from diseases. Innate immunity and adaptive immunity are the two divisions in which the defense of the body against microbes works. Cancer immunotherapy refers to a biological therapy that tries to suppress or stimulate the immune system of an individual with the help of substances such that the body becomes capable of fighting cancer, and other infections or diseases. This literature reviewed aimed to review many aspects regarding immune therapy regarding breast cancer.

Key words: Immune system, breast cancer, Immunity

I. Introduction

Cancer immunotherapy refers to a biological therapy that tries to suppress or stimulate the immune system of an individual with the help of substances such that the body becomes capable of fighting cancer, and other infections or diseases. There are certain immunotherapies available that can target particular cells in the body, and hence these are particularly essential for cancer patients. Targeted therapy is the newest development in cancer treatment.¹ When breast cancer is considered, there are several types of breast cancers that can affect women, with some forms being rare, and also some where two or three forms of cancers occur within the same form.²

Breast Cancer (C50): 2011

Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK

		England	Wales	Scotland	Northern Ireland	UK
Male	Cases	303	11	30	5	349
	Crude Rate	1.2	0.7	1.2	0.6	1.1
	AS Rate	0.9	0.5	0.9	0.5	0.9
	AS Rate - 95% LCL	0.8	0.2	0.6	0.1	0.8
	AS Rate - 95% UCL	1	0.9	1.2	0.9	1
Female	Cases	41,523	2,569	4,578	1,266	49,936
	Crude Rate	153.9	164.8	169.1	136.9	155.3
	AS Rate	124.8	123.3	130.2	118.4	125.1
	AS Rate - 95% LCL	123.6	118.5	126.4	111.8	124
	AS Rate - 95% UCL	126	128	133.9	124.9	126.2

figure 1: Statistics of incidences of breast cancer.³

The different forms of breast cancers include: Ductal carcinoma in situ, Lobular carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma which are more common. The less common types include inflammatory breast cancer, triple negative breast cancer, paget disease of the nipple, phyllodes tumor, and angiosarcoma.²

The above figure reflects on the statistics of cases of breast cancer in the UK, as recorded for the year 2011. It can be observed that the number of cases is significant and hence immunotherapy seems to be highly essential, particularly for women are the most affected ones. Although the concept of immunotherapy has developed as a revolution over the recent times; however its roots can be found dated back to 1778 when the first vaccine was administered against smallpox by Edward Jenner who was an English physician.⁴

II. Breast Cancer and Immuno system:

The immune system involves collection of cells that protect the body from microbes and bacteria and hence tries to protect the body from diseases. Innate immunity and adaptive immunity are the two divisions in which the defense of the body against microbes works.⁵

Innate and Adaptive Immune Systems:

The innate immune system is such where cells and proteins are ready to fight the microbes always and hence protect the body at the site where the infection takes place. The major constituents of this system include

physical epithelial barriers, phagocytic leucocytes, dendritic cells, natural killer cell which is a special type of lymphocyte, and circulating plasma proteins.⁵

The adaptive system is different from the innate immune system in the sense that it is initiated to overcome or avoid the innate immune defense systems. The constituents that make up the system normally remain silent. However, when the system is initiated, the constituents activate, proliferate, and create the effective mechanisms that can fight effectively against the microbes thereby eliminating or neutralizing the microbes. Adaptive immune responses are of two types – humoral immunity produces B lymphocytes mediated by antibodies and cell mediated immunity, which is recognized by T lymphocytes.⁵

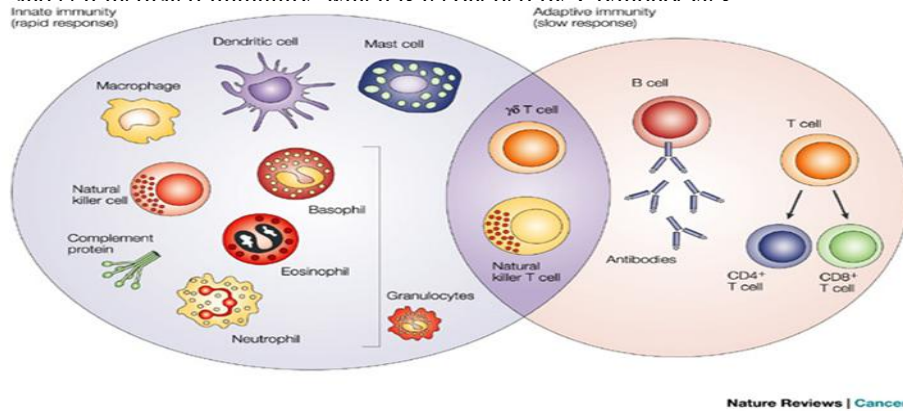


Figure 1: Innate and Adaptive Immune Systems.⁶

Correlation between breast cancer and immune system:

Studies have found that both the innate and the adaptive immune systems of the body have the capability to prevent deterioration in women who are affected by breast cancer. Studies have obtained that CD47 has a significant role to play in the intercellular signaling. Recurrence in breast cancer could be predicted by the expression of CD47 and SIRPA in bone marrow, which has been found to be correlated. SIRPA represents a protein that regulates signals and its correlation with CD47 is believed to be responsible for the progression of breast cancer.⁷

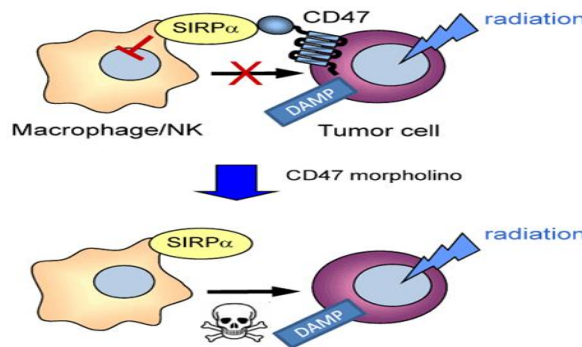


Figure 2: Radiosensitization of tumors by CD 47 Blockade.⁸

The cells of breast cancer initiate like normal cells of the body but the difference is that their growth does not remain under control, and hence the formation of cancer occurs. The immune system is associated with breast cancer in the sense that it has the capability to prevent the abnormal growth of the cancer cells in the breasts. In many cases even when the cancer cells are growing, their growth seem to be normal like the normal cells of the body. In such cases, the abnormal cells become capable of escaping the immune system of the body and hence multiply without the immune system even learning about it.⁹

Thus it is understood that the incidence of the cancer is much more when the immune system of the body fails to identify the initiation and growth of the abnormal cells. T cell is a special type of immune cell that is highly responsible and associated with response of the immune system against cancer cells.¹⁰

III. Immunotherapy (treatment):

A. Types of Treatment Available for Breast Cancer Patients

There are different types of treatment that are available for patients affected with breast cancer. While some of the available treatments are standards, others are being clinically tested for use. The six standard treatments for breast cancer include: surgery, sentinel lymph node biopsy post which surgery takes place,

radiation therapy, chemotherapy, hormone therapy, and targeted therapy. With the help of surgery, the cancer is completely removed from the breasts.¹¹

The sentinel lymph node biopsy involves removal of the sentinel lymph node when the surgery is conducted thereby inhibiting the lymphatic drainage from the tumor. The other therapies mentioned make use of either the radiation such as x-rays (radiation therapy), or drugs (chemotherapy), or removal of hormones causing cancer (hormone therapy). Targeted therapy directly targets the affected cells and treats them to remove the cancer. A new clinical trial being tested is the use of high dose chemotherapy with stem cell transplant for cancer treatment.¹²

Immune checkpoint inhibitor:

T-cell exhaustion arises from continual contact to antigens resulting in upregulation of inhibitory receptors. These inhibitory receptors have been observed to be acting as immune checkpoints for breast cancer patients. They act by allowing monoclonal antibodies to rescue the antitumor T cells which would otherwise become exhausted. As a result, clinical responses have been found to be achieved in cancer patients. Ipilimumab was the first immune checkpoint inhibitor that was tested clinically which has also been approved by the US Food and Drug Administration in 2011.¹³

The suppressive function of the T regulatory cells can be inhibited by an increase of the ratio of CD8+ T cells to Foxp3+ T regulatory cells, enabled through Anti-CTLA-4 mAb therapy that can enhance the antitumor function of the CD8 + T cells. A subpopulation of tumor-infiltrating CD4+ T cells has been found to be expanded by CTLA-4 blockade. This enables expression of high levels of inducible T-cell costimulator (ICOS). These cells are known to play significant role in providing therapeutic activity for breast cancer patients. Another inhibitory co-receptor is PD-1 which can be expressed on T cells that are activated and exhausted.¹³

From trials conducted by Hoos and its report, it could be obtained that once the immunotherapeutic agent is used for cancer treatment, the immune system gets activated. Thus before the clinical end points are reached, the measurement of immune response acts as a biomarker for assessment. Reliable and reproducible assays are required for effective measurement of the biomarker. The enzyme-linked immunosorbent spot (ELISPOT), intracellular cytokine staining (ICS) and human leukocyte antigen (HLA)-peptide multimerstaining assays are the most common for T-cell immune response assessments. Immune related response criteria are used for accommodation of the different patterns of response which are connected with immunotherapy.¹⁴

Therapeutic Vaccines:

With the help of cancer vaccines, it is possible to stimulate the immune systems of the patients such that the tumor cells can be recognized and killed by the vaccines. There is a tumor associated antigen in the vaccines that extracts an immune response when introduced in the body of the cancer patient. There are different systems through which vaccines can be administered into the body of the patients, such as the whole-cell vaccines, viral vector vaccines, and dendritic cell vaccines. Sipuleucel-T which is a dendritic cell vaccine is the most effective of all these systems that has been approved by the U.S. Food and Drug Administration.¹⁵

However for the purpose of treatment of breast cancer, there is another type of vaccine which is the peptide vaccine. The formation of peptide vaccines happens by seizing small amino acid sequence from the antigen associated with the tumor. HER2 oncoprotein is the tumor related antigen which is used in most of the cases of breast cancer that promotes growth of the tumor. After the peptide is obtained from the antigen, it is combined with an immunoadjuvant which in turn results in stimulation of an immune response.¹⁵

Gene directed enzyme prodrug therapy (GDEPT) enables the cytotoxic suicide gene to be delivered encoding a prodrug activating enzyme. These genes have their particular use in cancer therapy. Several antitumor effects of the genes such as HSV-TK, CD, and cytochrome P450 have been obtained in clinical trials as a result of which further clinical trials are being processed on these genes.¹⁶

Adoptive T-cell Transfer:

The adoptive T-cell therapy involves transfusion of lymphocytes has the ability to enhance the antitumor ability of the immune system of the body, enhance the efficacy of the vaccines, and restrict graft-versus-host disease. In this therapy, the T-cells are isolated from specimens of fresh patient biopsy and tumor specific T-cells outside of the patient are progressively selected using high levels of IL 2 and different cell cultures.¹⁷

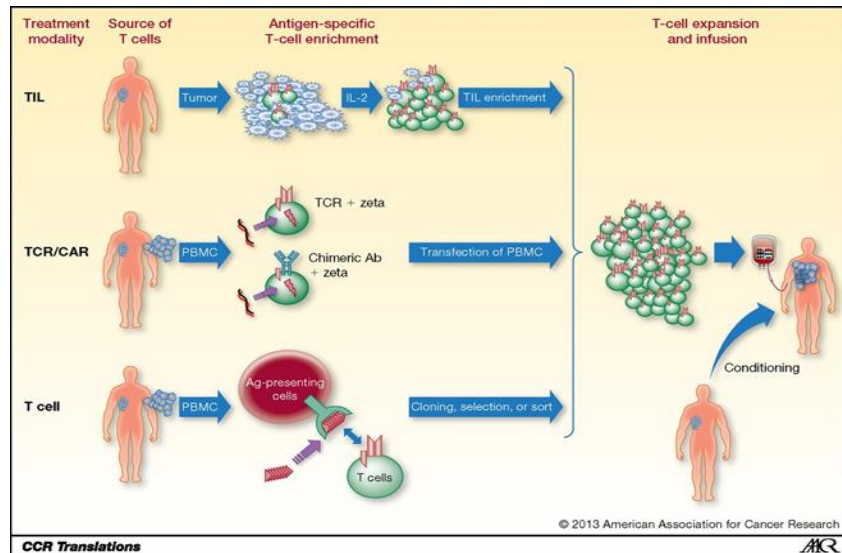


Figure 3: Adoptive T cell transfer.¹⁸

As Carvalho et al (2014) explained in their research that CD4+ T-cells are triggered in reaction to factors that are soluble and has been classified into categories, Th1 and Th2. Tumoricidal activities are triggered after the cytokines generated from Th1 and Th2 coordinate with the operations of the cytotoxic CD8+ T-cells. The T-cells which are regulatory have immunosuppressive properties maintaining immune tolerance. Such activities are capable of putting restrictions on response of the T cells against the self antigens allowing prevention of inflammatory and autoimmune diseases.¹⁹

B. Current Breast Cancer Therapy

Breast cancer research and treatment measures are being studied across different medical centers across the world. New laboratory and imaging tests are being continuously performed to determine the causes and treatments of breast cancer, trying to deliver more advanced measures of prevention and treatment of the disease. Some of the current measures of treatment that are dependent upon include the surgery, new drugs, targeted therapies, bisphosphonates, denosumab, and vitamin d. Bisphosphonates are new drugs that are capable of strengthening and decreasing the risks of bones being fractured that have been destabilized by metastatic breast cancer.²⁰

The standard treatments of breast cancer are those that are accepted as appropriate by experts and hence are widely used for treatment of breast cancer in patients across the globe. The options for treatment of breast cancer largely depend on the stage of the cancer in the patient. The size of the tumor against the size of the breast determines the type of treatment that might be required. Also, such treatments depend on the general health of the patient, their age, their stage of menopause (in women), family history for the disease, and other risk factors.²¹

Stage 0 of breast cancer in most cases necessitate and can be cured through breast-conserving surgery which is followed by radiation therapy. In case of stages 1, 2, 3a and 3c of the disease, there are combinations of treatments that can be used on the patients. In some cases surgery is conducted followed by radiation therapy while in some other cases mastectomy is conducted on the patients, where in both these cases lymph nodes under the arms of the women are generally removed. Whether radiation therapy is used after mastectomy or not, depends on the particular cases of breast cancer patients.²¹

In some cases of stages 3b and 3c, operations can also not be performed on the patients. Thus in these cases, chemotherapy is most popularly used which in some cases might be followed by other treatments, such as targeted therapies as well. In stage 4 case of breast cancer, generally treatments such as chemotherapy, radiation therapy, hormone therapy and targeted therapies are used. These are either used individually or in combination depending on the particular case of the patient.²¹

The case of metastatic breast cancer is such that the cancer spreads to other organs other than the breasts. Thus other organs such as liver, lung, and brain get affected by the cancer that started from the breasts. This cancer has no treatment. This means that metastatic cancer cannot be completely cured through any of the standard treatment measures that are available. However, the treatment measures can be applied on the patient that can lengthen the life of the patient, by delaying the progression of the growth of the cancer cells. The patient can hence be relieved to a great extent from the symptoms of breast cancer, thereby improving upon the quality of life of the patient.²²

The Role of Immunotherapy in Breast Cancer:

The role of the immune system in breast cancer is complex and offers many promising avenues for the detection, prognostication and treatment of breast cancer. These roles are summarised in Figure 1.

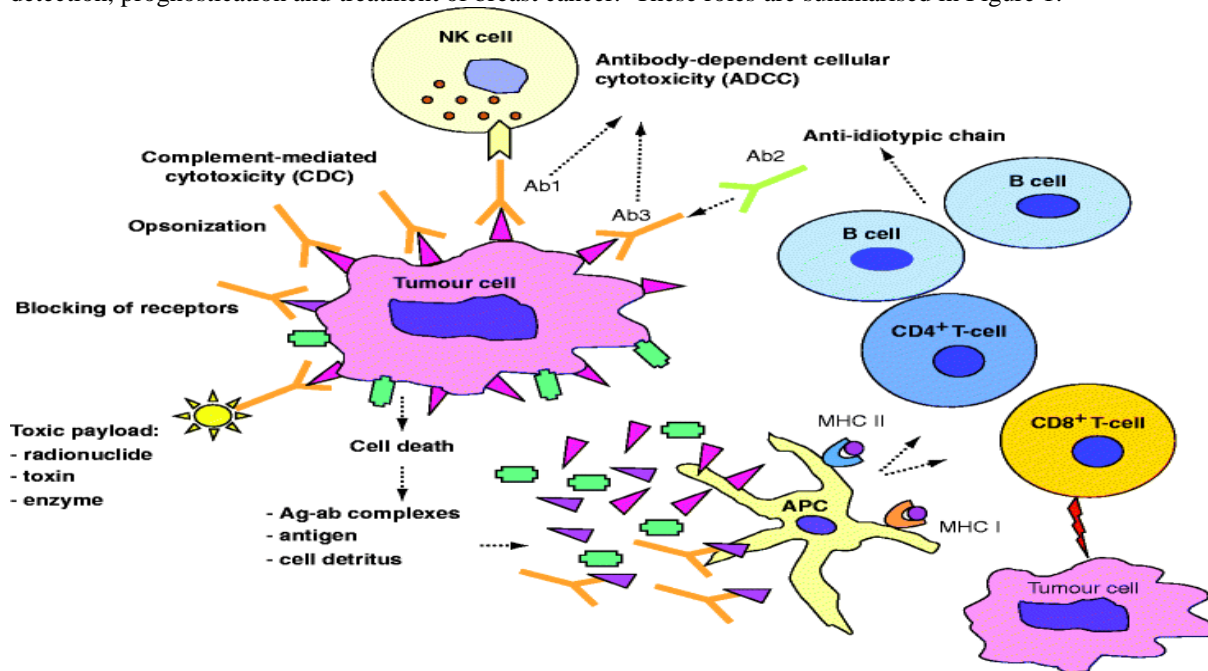


Figure 1: roles of the immune system in breast cancer.²³

One of the earliest immunotherapies brought into clinical use is trastuzumab, a recombinant monoclonal antibody that targets the HER2 gene. This gene is amplified in 25-30% of patients and increases the aggressiveness of tumours.²⁴ More recent research has shown that trastuzumab also induces antibody-dependant cell-mediated cytotoxicity, enhancing tumour infiltration by macrophages, natural killer and T- and B-lymphocytes.²⁵ However, trastuzumab has high cardiac toxicity; and in recent years, a significant proportion of tumours have begun to show resistance. Several new monoclonal antibody drugs are being developed which target HER2, including pertuzumab, trastuzumab-DM1 and tanespimycin.²⁶ However, more recent research has shown that the role of such drugs may be more complex than originally thought, as will be discussed below. Tumours can be infiltrated by circulating lymphocytes; specifically ‘helper’ CD4 T-cells and cytolytic ‘killer’ CD8 cells. T-lymphocytes also attack migrating tumour cells, as shown in Figure 1.²⁷ Specific immunity mediated by such cells has long been suspected of playing a significant anti-cancer role; with regional lymph nodes providing a barrier against tumour expansion. This provides a very promising avenue of research in the development of new treatments.²⁸

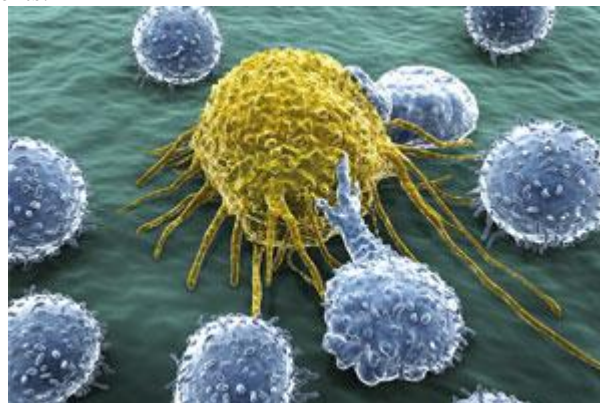


Figure 1: T-lymphocytes attacking a migrating tumour cell.²⁷

Sotirou and co-workers have hypothesised that increased lymphocyte infiltration of tumours would improve prognosis in some types of breast cancer. Their research has shown that this is indeed the case, with relapse risk being reduced by up to 17% and death risk by up to 27%.²⁹ Post-chemotherapy lymphocyte infiltration may also be associated with better outcomes in patients who do not achieve complete pathologic response to first-line chemotherapy.²⁵

Tumour infiltration by CD8+ cytotoxic T-cells has been associated with better patient survival in basal-like breast cancers; however, no significant effect was observed in non-basal, triple-negative breast cancers or in other intrinsic molecular subtypes. This is thought to be due to a CD8+ cell-mediated type 1 immune response which enhances the accumulation and anti-tumour activity of both CD4+ and CD8+ cells.³⁰

CD4+ and T-regulator (T-reg) cells have been investigated as specific markers for prognosis. Increased numbers of circulating T-reg cells may contribute to increased metastatic potential in HER2/neu-positive cells; increased numbers of T-reg cells have also been found to be present in patients with invasive ductal carcinomas as opposed to invasive lobular cancers. T-reg cells are currently being investigated as potential markers for breast cancer prognosis.³¹

In cases where the tumour is extensively infiltrated, it has been shown that a CD4+ subset known as Tfh (T-follicular helper) cells are located in tertiary lymphoid structures (TLS) near to the tumour. Since Tfh cells are specific to the tumour-associated TLS, these have been used to devise a scoring system, known as the immunological grade, to measure the extent of lymphocyte infiltration. This is being investigated for its effectiveness at evaluating potential anti-tumour responses and making treatment decisions following biopsy or surgery.³²

T-cells have also been implicated in distant metastatic relapse, with loss of immune balance in cross-talk between T-cells and tumour cells in the bone marrow being suggested as a possible reason.³³

The ratio of neutrophils to lymphocytes (NLR) has been known for a number of years to be a strong predictor of mortality in a wide range of cancers; specifically colorectal, pancreatic, hepatocellular, gastric and lung cancers. An investigation using a cohort of 316 unselected breast cancer patients showed that patients with NLR >3.3 had higher mortality rates than those with NLR < 1.8, meaning that NLR has potential as a simple prognostic test for breast cancer patients.³⁴

The identification of tumour-specific antigens allows the development of new monoclonal antibodies as potential therapeutic drugs. One such example is chondroitin sulphate proteoglycan 4 (CSPG4); in a study of 44 primary tumour lesions, this protein was found to be present in 32; it was also found in the pleural effusions of 12 metastatic breast cancer patients. A CSPG-4-specific monoclonal antibody was found to significantly inhibit growth, migration, and adhesion of tumour cells *in vitro*.³⁵

The tumour antigen NY-ESO-1 (ESO) has been identified as a potentially important target for immunotherapy in breast cancer patients. It is thought that lymph-node invasion by tumour cells triggers an antibody response to ESO; with patients who had a spontaneous antibody (ESO Ab+ patients) having significantly higher amounts of lymph-node infiltration; this means that in addition to being a potential therapeutic target, ESO also has possibilities as a predictive and prognostic marker.³⁶

The role of the immune system in breast cancer raises the possibility of developing an effective vaccine. A dendritic cell vaccine has been developed for estrogen receptor (ER)/ progesterin receptor (PR) double-negative breast cancer; this was generated from CD14+ precursors and has been shown to enhance Th1 cytokine secretion and an increase in natural killer, CD8+ and IFN- γ + cells; however, it also decreased the amount of CD3+ T cells and CD3+ HLA-DR+ T cells in the peripheral blood. The vaccine significantly increased 3-year progression-free survival rates from 31% to 76.9%.³⁷

E75 is a vaccine that has been developed for node positive and high-risk, node negative breast cancers in which tumours express HER2. In a clinical trial, the vaccine showed a strong trend towards preventing recurrence of this type of breast cancer over a 5-year follow-up period. In order to further evaluate the effectiveness of E75, a randomized, double-blind, placebo-controlled, multi-centre phase III registration trial has now been initiated.³⁸

MDTH/AEG-1 is a gene that is over-expressed in 40% of breast cancer patients; it is associated with increased chemo-resistance and lung metastasis, leading to poor outcomes. A MDTH/AEG-1 based DNA vaccine, delivered by attenuated *Salmonella typhimurium*, was shown to initiate a strong CD8+ cytotoxic-T-cell mediated immune response, increasing chemo-sensitivity to doxorubicin as well as inhibiting lung metastasis. The vaccine prolonged the life of tumour-bearing mice, without significant side-effects.³⁹

IV. Conclusion:

It could be obtained from the above study that breast cancer has severe implications on health of women in particular and hence researchers are continuously trying and researching out new methods of treatment through clinical trials. Thus while there are standard methods of treatment for breast cancer, there are clinical trials as well being tried and tested. The immune system of the body could be obtained to have significant correlation with breast cancer. Different treatments of the cancer could also be studied through the research where the treatments for different stages of the cancer could also be obtained. Also, it could be obtained that when the case becomes metastatic then the cancer spreads from breasts to other organs in the body and becomes non curable.

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