

Analysis of Role of Protein in Different Stages of Cancer Using Weighted Multi Expert Neural Networks System

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Abstract - Cancer occurs as a result of mutations, or abnormal changes, in the genes responsible for regulating the growth of cells and keeping them healthy. The cells in our bodies replace themselves through an orderly process of cell growth: healthy new cells take over as old ones die out. Cell, in due course of time, gains the ability to keep dividing without control or order, producing more cells just like it and forming a tumor. The breast has developed from cells in the breast due to a malignant tumor. In this paper an attempt is made to find out the role of protein in reaching the different stages of breast cancer on the basis of experts opinion using the weighted multi expert neural networks system

Key Words: Neural Networks, BRCA1 and BRCA2, P53, RB1, PTEN, c-MYC, ErbB2, CDH1, CCND1, Different stages of cancer, Protein

I. INTRODUCTION TO WEIGHTED MULTI EXPERT NEURAL NETWORK

In this section we just recall the notion of neural network called the Weighted Multi Expert Neural Network (Wt.M.E.N.N) constructed using the fuzzy neural networks. This Wt.M.E.N.N., guarantees equal representation of opinion of each expert; hence this method has an advantage over the Fuzzy Neural Networks. Neural Network learning can be either supervised one or an unsupervised one. In a supervised learning algorithm, learning is guided by specifying, for each training input pattern the class to which the pattern is supposed to belong. In an unsupervised one, the network forms its own classification of patterns. The classification is based on commonalties in certain features of input pattern. Since the data is an unsupervised one we make use of Wt.M.E.N.N. In any supervised learning, a training set of correct input-output pairs is given so as to minimize the error, but in an unsupervised one the output is purely based on the input data. We just recall the definition of Neural Network

Definition 1.1

A neural network is a computational structure that is inspired by observed process in natural network of biological neurons in the brain. It consists of simple computational units, called

neurons that are highly interconnected. Each interconnection has a strength that is expressed by a number referred as weight.

Definition 1.2

The bias defines the value of the weighted sum of inputs around which the output of neuron is most sensitive to changes in the sum. Now we proceed on to define the notion of Weighted Multi Expert Neural Network. In Neural Network bias plays an important role. So we take the bias as an input with value -1 and its corresponding weight is the sum of the average of the other input weights. In general, using this newly constructed Weighted Multi Expert Neural Network (Wt. M.E.N.N.), we can extend to 'n' number of experts. Then, the output of the neuron is defined by

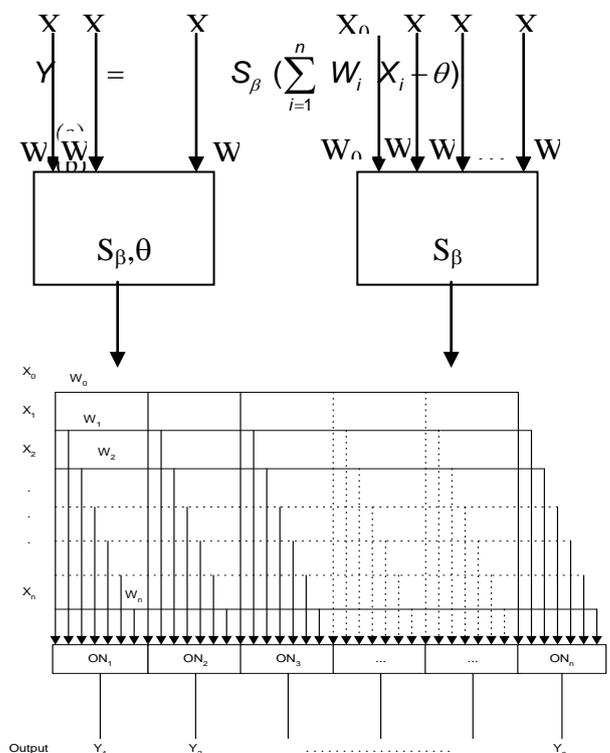


Fig. 1.1 Two equivalent representation of a neuron activated by a sigmoid function S_{β} with bias θ .

The class of sigmoid function S_{β} , defined by the formula.

$$S_{\beta}(a) = (1 + \exp \{-\beta a\})^{-1}$$

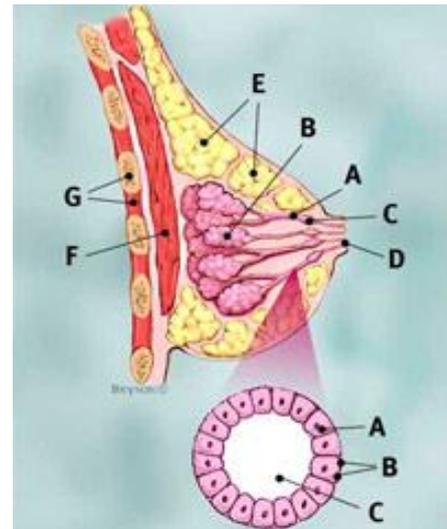
$$Y = S_{\beta} \left(\sum_{i=1}^n W_i X_i - \theta \right)$$

where β is a positive constant (Steepness parameter), θ is called the bias of the neuron, since θ the bias is considered as an input, $x_0 = -1$ and the associated weight $w_0 = \theta$.

Then the output now is given by Breast cancer is an uncontrolled growth of breast cells. To better understand breast cancer, it helps to understand how any cancer can develop. Cancer occurs as a result of mutations, or abnormal changes, in the genes responsible for regulating the growth of cells and keeping them healthy. The genes are in each cell's nucleus, which acts as the "control room" of each cell. Normally, the cells in our bodies replace themselves through an orderly process of cell growth: healthy new cells take over as old ones die out. But over time, mutations can "turn on" certain genes and "turn off" others in a cell. That changed cell gains the ability to keep dividing without control or order, producing more cells just like it and forming a tumor.

A tumor can be benign (not dangerous to health) or malignant (has the potential to be dangerous). Benign tumors are not considered cancerous: their cells are close to normal in appearance, they grow slowly, and they do not invade nearby tissues or spread to other parts of the body. Malignant tumors are cancerous. Left unchecked, malignant cells eventually can spread beyond the original tumor to other parts of the body. The term "breast cancer" refers to a malignant tumor that has developed from cells in the breast. Usually breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can begin in the stromal tissues, which include the fatty and fibrous connective tissues of the breast.

Over time, cancer cells can invade nearby healthy breast tissue and make their way into the underarm lymph nodes, small organs that filter out foreign substances in the body. If cancer cells get into the lymph nodes, they then have a pathway into other parts of the body. The breast cancer's stage refers to how far the cancer cells have spread beyond the original tumor. Breast cancer is always caused by a genetic abnormality (a "mistake" in the genetic material). However, only 5-10% of cancers are due to an abnormality inherited from your mother or father. About 90% of breast cancers are due to genetic abnormalities that happen as a result of the aging process and the "wear and tear" of life in general.



Breast Anatomy

$$Y = S_{\beta} \left(\sum_{i=0}^n W_i X_i \right),$$

where W_i is the weights given by the experts and $S_{\beta}(a) = (1 + \exp \{-\beta a\})^{-1}$. The multi expert neural network system with opinion's weights.

II. DESCRIPTION AND JUSTIFICATION

There are steps every person can take to help the body stay as healthy as possible and lower risk of breast cancer or a breast cancer recurrence (such as maintaining a healthy weight, not smoking, limiting alcohol, and exercising regularly). Learn what you can do to manage breast cancer risk factors. Always remember, breast cancer is never anyone's fault. Feeling guilty, or telling yourself that breast cancer happened because of something you or anyone else did, is not productive.

For more information about staging, please visit the Breast cancer, a dreaded disease, has got deadlier for the modern woman who is becoming vulnerable to the illness. Experts project breast cancer to strike approximately 2.5 lakh women in India by 2015. "Breast cancer has overtaken cervical cancer to become the leading cause of cancer-related mortality among women living in metropolitan cities," says the Indian Council of Medical Research which places incidence of the disease at 30 to 33 per 1,00,000 women in urban India.

Smart government-sponsored advertising that spreads awareness about self screening as well as timely checkups, which include mammographies and diet control, prove good safety mechanisms for early detection crucial to curb the spread of the curable disease, advice doctors.

"We have seen a considerable change in the level of awareness among women in semi urban and urban areas. Initially they were shy but when we told them about the gravity of the

disease and the ease with which they can do a self exam, we found women losing their reticence,” says Isha Bhandari, ROKO Cancer, a voluntary organisation that runs mobile cancer units across India.

The number of breast cancer cases in India is about 100,000 women each year and there will be approximately 2,50,000 new cases of breast cancer in India by 2015, says ICMR. The Roko cancer mobile units — air-conditioned buses — ply in remote areas providing pre-cancer screening facilities, play relevant audio visuals and carry educational kits to be distributed in various camps. “We started the campaign almost four years ago and aim to make mammography tests a routine for every woman in this country. We are also working for a polio like campaign to reach the masses,” says Ms. Bhandari. Cancer rates could further increase by 50 per cent to 15 million new cases in the year 2020, according to the World Cancer Report, the most comprehensive global examination of the disease to date.

The report also reveals the developing world is expected to account for more than half of all cancer cases in the world by 2020. The WHO is also warning that Asia’s annual death toll from cancer, currently at about 4 million, could reach 6.4 million by 2030 if current trends continue. Said to be a western disease, the incidence of new cases in Asia is rising by around 60 per cent in some parts. “The rise is particularly affecting younger women between 30 and 40 years. Unlike in the West where typically women after 50 years get early stage disease, breast cancer in Asian women occurs at a younger age and is usually presented and diagnosed at a later stage,” Dr. Col. C. S. Pant, Vice Chairperson for the Forum for Breast Cancer Protection. The forum, supported by Hard Rock Cafe, is organising a women’s car rally from Delhi to Agra, to raise funds and generate awareness about breast cancer prevention and its early detection. Though there is no known cause for the illness, a cure is possible if detected early. “I have been in this field for over 25 years and have found that breast cancer creates psychological havoc for a young woman usually in her 40s and with one or two children,” says Dr. Pant.

“The fault, to a certain extent, lies with the doctors too who do not encourage screening. Every woman after 40 should go for a mammogram test,” Ms. Bhandari.

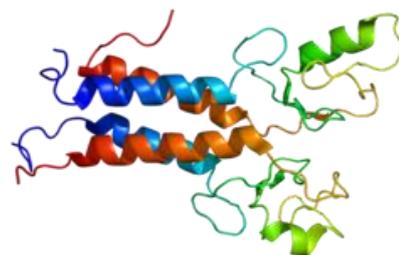
III. ADAPTATION OF THE WT.M.E.N.N. TO THE PROBLEM

Here we described the problem together with the assumed notations and construct the neural network based on the experts opinion on a few factors like.

X₁ -BRCA1 and BRCA2

Stages of Breast Cancer

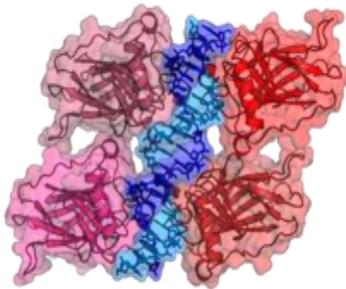
Stage	Definition
Stage 0	Cancer cells remain inside the breast duct, without invasion into normal adjacent breast tissue.
Stage IA	The tumor measures up to 2 cm AND the cancer has not spread outside the breast; no lymph nodes are involved
Stage IB	There is no tumor in the breast; instead, small groups of cancer cells - larger than 0.2 millimeter but not larger than 2 millimeters - are found in the lymph nodes OR there is a tumor in the breast that is no larger than 2 centimeters, and there are small groups of cancer cells - larger than 0.2 millimeter but not larger than 2 millimeters - in the lymph nodes.
Stage IIA	No tumor can be found in the breast, but cancer cells are found in the axillary lymph nodes (the lymph nodes under the arm) OR the tumor measures 2 centimeters or smaller and has spread to the axillary lymph nodes OR the tumor is larger than 2 but no larger than 5 centimeters and has not spread to the axillary lymph nodes.
Stage IIB	The tumor is larger than 2 but no larger than 5 centimeters and has spread to the axillary lymph nodes OR the tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes.
Stage IIIA	No tumor is found in the breast. Cancer is found in axillary lymph nodes that are sticking together or to other structures, or cancer may be found in lymph nodes near the breastbone OR the tumor is any size. Cancer has spread to the axillary lymph nodes, which are sticking together or to other structures, or cancer may be found in lymph nodes near the breastbone.
Stage IIIB	The tumor may be any size and has spread to the chest wall and/or skin of the breast AND may have spread to axillary lymph nodes that are clumped together or sticking to other structures, or cancer may have spread to lymph nodes near the breastbone. Inflammatory breast cancer is considered at least stage IIIB.
Stage IIIC	There may either be no sign of cancer in the breast or a tumor may be any size and may have spread to the chest wall and/or the skin of the breast AND the cancer has spread to lymph nodes either above or below the collarbone AND the cancer may have spread to axillary lymph nodes or to lymph nodes near the breastbone.
Stage IV	The cancer has spread — or metastasized — to other parts of the body.



BRCA1 is also known as the caretaker gene. Responsible for repairing the DNA .Produces a protein called the breast cancer type 1 susceptibility protein which takes care of the repair of

DNA .Major site of occurrence is breast tissues. Actively involved in DNA repair and destroying cell of DNA that cannot be repaired in tissues of breast. The repair of BRCA1 will have a detrimental effect on its regular process. Combines with other genes of tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC).Plays important role in transcription, DNA repair of double-stranded breaks ubiquitination.Variations of this genes can lead to increased breast cancer .Women with an abnormal BRCA1 or BRCA2 gene have up to a 80% risk of developing breast cancer by age 90.

X₂- P53



Also known as protein 53 or tumor protein 53.Regulates cell cycle and functions as tumor suppressor thus preventing cancer .Also referred as guardian of genome as it prevents genome mutation. It initiates apoptosis when it finds the DNA unreparable..Mutations that deactivate p53 in cancer usually occur in the Dna binding domain. Mutation destroy the process of DNA binding to the target sequence .Thus prevents the transcriptional activation of genes.

X₃-RB1

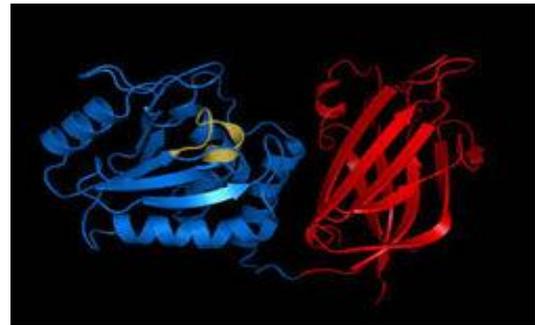


Responsible for making a protein called pRB responsible for tumor suppressor. It is referred as retinoblastoma protein. Specific to prevent cell growth by stopping the cell cycle. Essential for chromatin remodeling enzyme such as methylases acetylases.

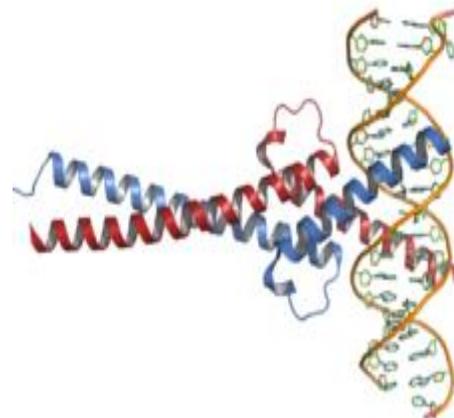
Suppress tumor by action of its phosphatase protein .This protein responsible for prevent rapid division of cells. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase.It negatively regulates intracellular levels

ofphosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating Akt/PKB signaling pathway.It is found in all tissues of the body. Mutation will lead to inhibiting the enzyme activity thus increases cell proliferation and decreases cell death. It is generally mutated at large numbers at a very high frequency

X₄-PTEN

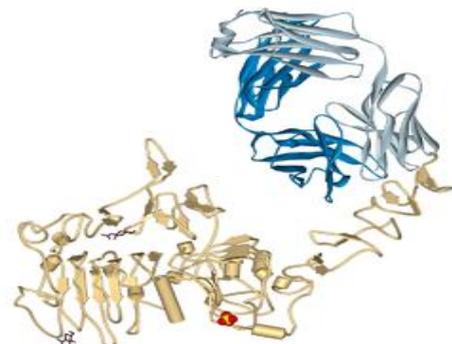


X₅-c-MYC



It is a regulator gene that codes for transcriptional factors. It is believed to be associated with the anti-cancer drug therapy. Inactivation of SUMO-activating enzyme in the presence of Myc hyperactivation results in cell death in cancer cells. Hence inhibitors of SUMOylation may be a possible treatment for cancer

X₆-ErbB2



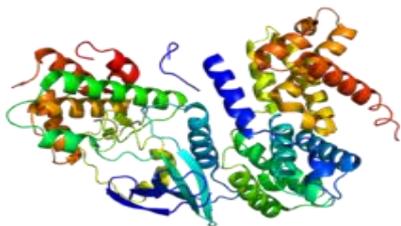
Also known as Neu, HER2 (human epidermal growth factor receptor 2.Amplification or over expression of this gene plays a

important role in development of breast cancer. Recent research shows that it is an important biomarker and a target for cancer treatment. Causes approximately 30 % of breast cancer in woman. It usually occurs with GRB7 which is a proto-oncogene .
 X_7 -CDH1



Cadherin-1 also known as CAM 120/80. It is a protein that in humans is encoded by the CDH1 gene. Loss of function is thought to contribute to cancer. Activated by increasing proliferation, invasion, and/or metastasis. E-cadherin downregulation decreases the strength of cellular adhesion within a tissue, resulting in an increase in cellular motility. This in turn may allow cancer cells to cross the basement membrane and invade surrounding tissues. High percentage in invasive ductal carcinoma. Fairly less percentage in lobular carcinoma.

X_8 -CCND1



This gene transcribes the protein G1/S-specific cyclin-D1. Cyclins function as regulators of CDKs (cyclin dependent kinase). This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb. Over expression of this gene, alters cell cycle progression. Each input X_0, X_1, \dots, X_5 are associated with real numbers called the weights, namely W_0, W_1, \dots, W_5 whose value lie in the interval [0,1]. We have obtained 7 experts opinion, the corresponding weightage are given by the following table:

	W_0	W_1	W_2	W_3	W_4	W_5	W_6	W_7
Expert 1	0.68	0.52	0.62	0.8	0.62	0.78	0.58	0.79
Expert 2	0.78	0.85	0.85	0.76	0.58	0.98	0.65	0.71
Expert 3	0.78	0.43	0.68	0.79	0.46	0.75	0.71	0.62
Expert 4	0.71	0.86	0.43	0.86	0.6	0.98	0.81	0.76
Expert 5	0.51	0.68	0.7	0.89	0.61	0.81	0.65	0.93
Expert 6	0.82	0.78	0.58	0.9	0.43	0.78	0.71	0.69

The average of the weightage are given by the experts namely E_1, E_2, \dots, E_7

E_1	E_2	E_3	E_4	E_5	E_6
0.67375	0.77	0.69875	0.75125	0.7225	0.755

By taking the input as the average of the weightage given by the experts and the value of bias is kept as in the case of neural network to be -1 .

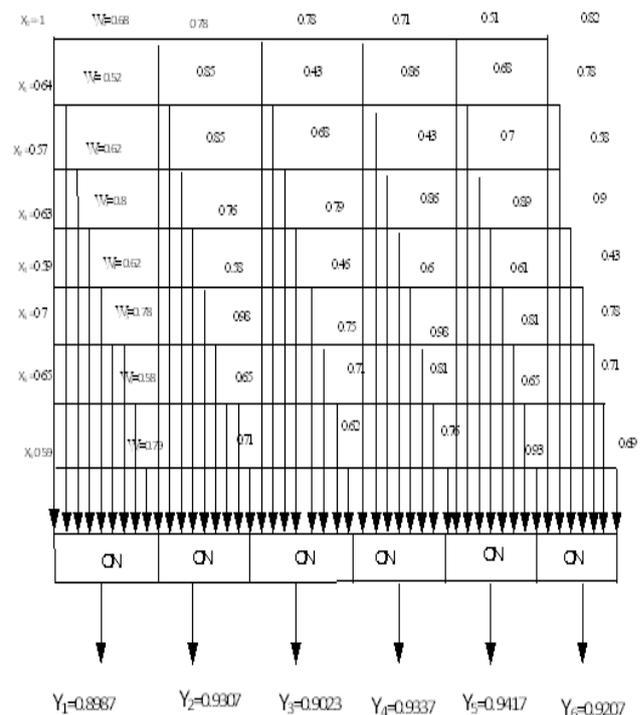
X_0	X_1	X_2	X_3	X_4	X_5	X_6	X_7
-1	0.64	0.57	0.63	0.59	0.7	0.65	0.59

In general, using this newly constructed Weighted Multi Expert Neural Network (Wt.M.E.N.N.), we can extend to 7 number of experts say E_1, E_2, \dots, E_7 and their corresponding output is given by,

$$Y_i = S_\beta \left(\sum_{i=0}^7 W_i X_i \right), \text{ where } W_i \text{ is the weights given by the experts and } S_\beta(a) = (1 + \exp \{-\beta a\})^{-1}.$$

We now model this by the weighted multi expert neural network (Wt.M.E.N.N) and in our opinion this Wt.M.E.N.N, takes the weight of every expert equally even before the data is processed for result.

The multi expert neural network system of experts opinion with weightages of the seven experts



From the output, we see that the overall opinion of the experts regarding the female infanticide happen to be > 0.5 . Thus to make a fuzzy analysis we using the same experts define the fuzzy set μ

taking the opinion of the experts, E_1, \dots, E_7 as the universal set E .

M.E.N.N

	Average Weight	Wt. M.E.N.N.	Fuzzy set value $\mu[E]$	Difference between Wt. M.E.N.N. and $\mu[E]$
Expert 1	0.67375	0.8987	0.9	0.0013
Expert 2	0.77	0.9307	0.95	0.0193
Expert 3	0.69875	0.9023	0.95	0.0477
Expert 4	0.75125	0.9337	0.95	0.0163
Expert 5	0.7225	0.9417	0.95	0.0083
Expert 6	0.755	0.9207	0.95	0.0293

The membership function μ given by the experts :

$$\mu : E \rightarrow [0, 1] \text{ where } E = \{E_1, \dots, E_7\}$$

$$\mu(E) = \begin{cases} 0 & E_i < 0.80 \\ 0.85 & 0.80 \leq E_i < 0.85 \\ 0.9 & 0.85 \leq E_i < 0.90 \\ 0.95 & 0.9 \leq E_i < 0.95 \\ 1.00 & 0.95 \leq E_i < 1.0 \end{cases}$$

where $i = 0, 1, 2, \dots, 7$

Now using the fuzzy membership grade given by the same experts and the output got from the Wt.M.E.N.N., we draw it comparison table of fuzzy set value and it output from Wt.

IV. CONCLUSION

The TNM classification for staging breast cancer is based on the size of the cancer where it originally started in the body and the locations to which it has travelled. These cancer characteristics are described as the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, neck, and inside the chest, and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis. The main stages are: Stage 0 which is in situ disease or Paget's disease of the nipple. Stage 0 is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

Stages 1–3 are within the breast or regional lymph nodes.

Stage 4 is a metastatic cancer. Metastatic breast cancer has a less favorable prognosis.

Stage I

These cancers are still relatively small and either have not spread to the lymph nodes (N0) or have a tiny area of cancer spread in the sentinel lymph node (N1mi).

Local therapy: Stage I cancers can be treated with either BCS (lumpectomy, partial mastectomy) or mastectomy. The lymph nodes will also need to be evaluated, with a sentinel lymph node biopsy or an axillary lymph node dissection. Breast reconstruction can be done either at the same time as surgery or later.

Radiation therapy is usually given after BCS. Women may consider BCS *without* radiation therapy if they are at least 70 years old and ALL of the following are true:

- The tumor was 2 cm or less across and it has been completely removed.
- The tumor contains hormone receptors and hormone therapy is given.
- None of the lymph nodes removed contained cancer.

Some women who do not meet these criteria may be tempted to avoid radiation, but studies have shown that not getting radiation increases the chances of the cancer coming back.

Stage II

These cancers are larger and/or have spread to a few nearby lymph nodes.

Local therapy: Surgery and radiation therapy options for stage II tumors are similar to those for stage I tumors, except that for stage II, radiation therapy to the chest wall may be considered even after mastectomy if the tumor is large (more than 5 cm across) or cancer cells are found in several lymph nodes.

A woman's chance for survival from breast cancer does not seem to be affected by whether she gets chemo before or after her breast surgery.

Stage III

For a cancer to be stage III, the tumor must be large (greater than 5 cm or about 2 inches across) or growing into nearby tissues (the skin over the breast or the muscle underneath), or the cancer has spread to many nearby lymph nodes. Local treatment for some stage III breast cancers is largely the same as that for stage II breast cancers. Tumors that are small enough (and have not grown into nearby tissues) may be removed by BCS (such as lumpectomy) which is followed by radiation therapy. Otherwise, the treatment is mastectomy (with or without breast reconstruction). Sentinel lymph node biopsy may be an option for some patients, but most require an axillary lymph node dissection. Surgery is usually followed by adjuvant systemic chemotherapy, and/or hormone therapy, and/or trastuzumab. Radiation after mastectomy is often recommended.

Chemotherapy: Chemo is usually recommended for all women with an invasive breast cancer whose tumor is hormone

receptor-negative, and for women with hormone receptor-positive tumors who might additionally benefit from having chemo along with their hormone therapy, based on the stage and characteristics of their tumor.

Stage IV

Stage IV cancers have spread beyond the breast and lymph nodes to other parts of the body. Breast cancer most commonly spreads to the bones, liver, and lung. As the cancer progresses, it may spread to the brain, but it can affect any organ, even the eye.

Although surgery and/or radiation may be useful in some situations (see below), systemic therapy is the main treatment. Depending on many factors, this may consist of hormone therapy, chemotherapy, targeted therapies, or some combination of these treatments. Treatment can shrink tumors, improve symptoms, and help patients live longer, but it isn't able to cure these cancers (make the cancer go away and stay away).

Radiation therapy and/or surgery may also be used in certain situations, such as:

- When the breast tumor is causing an open wound in the breast (or chest)
- To treat a small number of metastases in a certain area
- To prevent bone fractures
- When an area of cancer spread is pressing on the spinal cord
- To treat a blockage in the liver
- To provide relief of pain or other symptoms
- When the cancer has spread to the brain

If your doctor recommends such local treatments, it is important that you understand their goal—whether it is to try to cure the cancer or to prevent or treat symptoms.. Genes code proteins suppress by the mutations Mutations of proteins, By our study we could see that X_1 -BRCA1 and BRCA2 and X_8 -CCND1

- ❖ Lose the target function
 - ❖ Works against the immune system itself
 - ❖ Remains switched off, inactive, neutral with out any function
- BCCA2 and BRCA2 will inherited by generator. The cancer starts from stage 1 itself but remains, dormant, only when the symptoms are exaggerated; the person becomes aware of his situation .

The factors relating to cancer are germline mutation, over expression, under expression and mutation. These factors effects on the genes cause cancer. Over expression, under expression mutation occurs due to amplification or slowdown of gene

process. However the greater incidence for cancer causing is GERMLINE MUTATION by hereditary.

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