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Breast Cancer: An Overview

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Breast cancer is not a new disease. The oldest known reference to it was recorded by the Egyptians. Hippocrates, the father of medicine, described some of its clinical symptoms. At the end of the first century A.D., Leonidas was operating on malignant breast lumps. Circa 130 A.D., Galen developed some clinical criteria for procedures involving the surgery of these tumors. Galen's ideas remained vital until the 16th century.

The early development of epidemiology concentrated on life style. This approach can be traced back at least to 1700, when Bernardino Ramazzini in Italy noticed an unusually high rate of breast cancer in nuns and speculated that it related to their celibacy and childlessness. An 1844 report in Verona followed up some observations containing comparisons of breast and uterine cancer rates from the city's death registry between the years 1760-1839. The analyses suggested that married women were more than twice as likely to die of uterine cancer than from breast cancer, while nuns were 9 times more likely to die of breast cancer than from uterine cancer. The relative risk of breast cancer for nuns was found to be 22 times higher[1].

The Middle Ages and the Renaissance provide an extensive literature relating to breast cancer, including conventional treatments as well as some which were quite bizzare (e.g witchcraft).

In the late 17th century the Frenchman Henri Francois leDran was the first to notice the tendency of breast (and other cancers) to metastasize. LeDran proposed that cancer was a local disease in early stages, but after spreading to the lymphatic nodes signaled a poorer prognosis.

In the late 19th century the first important information was provided that implicated the ovaries as inducers of tumors of the breast. In 1889, the German scientist Albert Schinzer proposed removing the ovaries in the case of breast cancer, in this way attempting to arrest further tumor development.

In Scotland in the early 20th century George Thomas Beatson widely published papers regarding the use of oophorectomy (removing the ovaries) in obtaining positive responses in a few breast cancer patients. The basis for his findings was the observation that removal of the ovaries in cows prolonged lactation. This suggested to him that interference with the ovarian function in patients with breast cancer might also have some favorable effect[1].

Saint Agatha is the patron saint of those who suffer breast disease. She was martyred having her breasts removed in Sicily in the 3rd century[2].

Recent years have seen remarkable progress of clinical research and experimental laboratory results in breast cancer treatment. Scientific investigation has concentrated its efforts to identify and understand the genetic alterations associated with the malignant changes in breast cancer[3].

Breast cancer is common, the leading cause of death in women between the ages of 35 and 54. In North America, breast cancer is the most prevalent cause of cancer deaths among women of all ages. A woman living to age 80 in North America has 1 chance in 9 of developing invasive breast cancer. The number of cases continues to soar[4].

American women are now twice as likely to develop breast cancer than they were a century ago and most of this increase in incidence has occurred over the past thirty years. Since 1973 the incidence of breast cancer among white women has increased by 34% and among black women by 47%[5]. In the US in 1996 alone, 186,000 women learned they had breast cancer and about 46,000 died from it. The log-log plot of incidence versus age shows a straight line increase with every year of life[6].

Breast cancer rates vary considerably among European countries. Highest incidences are found in western and northern European countries and lowest incidences in eastern and southern European countries[7].

Breast cancer incidence has increased steadily in the past three to four decades. Throughout the world this pattern has been observed, while the rate of occurrence varies widely among different countries. Oriental countries like China and Japan have the lowest rates. Because of the lack of uniform occurrence, it is believed that environmental-especially dietary-factors are a major determinant of risk[8].

Japanese, Chinese and other oriental women have a risk to develop breast cancer at a rate of only 20/100,000[9]. Oriental women have substantially lower concentrations of estrogens and progesterone and their

height and weight are markedly less than those in other ethnic groups. Height and weight are critical regulators of age of menarche and have substantial effects on plasma concentrations of estrogens. Large increases in the rate of breast cancer occur in populations migrating from nations with a low incidence to those with a high incidence of breast cancer, again indicating the existence of environmental factors[10].

In men breast cancer is about 1/150th as frequent as in women. It usually presents itself as a unilateral lump in the breast and is generally not diagnosed promptly. When male breast cancer is matched to female breast cancer by age and stage, its overall prognosis is identical. Approximately 90% of male breast cancers have estrogen receptors and approximately 60% of cases with metastatic disease respond to endocrine therapy[11].

The three dates in a woman's life that have a major impact on breast cancer incidence are:

- age of first menstruation (menarche)
- age at first full-term pregnancy
- age of menopause[12]

Women who experience menarche at age 16 have only 50 to 60% of the lifetime breast cancer risk of women who experience menarche at age 12. Similarly, menopause occurring 10 years before the median age (52 years), whether natural or surgically induced, reduces lifetime breast cancer risk by about 35%[13]. Women who have a first full-term pregnancy by age 18 have only 30 to 40% of the breast cancer risk faced by others. Thus, length of menstrual life-particularly the fraction occurring before the first full-term pregnancy-is a substantial component of the total risk of breast cancer[12].

The role of diet in breast cancer etiology is controversial. While there are associative links between total caloric intake and breast cancer risk, the strongest link is with high dietary fat intake[8]. However, within the range of dietary fat intake common in Western cultures, there is no convincing evidence that variations in dietary fat alter breast cancer risk[14].

There is a risk associated with even moderate alcohol intake; the mechanism is unknown. Recommendations favoring abstinence from alcohol must be weighed against social pressures and the possible cardioprotective effects of moderate alcohol intake[15].

Women without functioning ovaries who never receive estrogen replacement therapy do not develop breast cancer[16]. The potential role of exogenous hormones in breast cancer is of extraordinary importance because millions of American women regularly use oral contraceptives. The most credible analyses of oral contraceptive use suggest that these agents cause little, if any, increased risk of breast cancer. The data suggest that the use of oral contraceptives is highly protective against malignancy in general, but has little impact on breast cancer[17].

Far more controversial are the data surrounding Hormone Replacement Therapy (HRT). HRT with estrogens alone, usually in the form of equine conjugated estrogens, provides less than the physiologic equivalent of premenopausal estrogens but is associated with an increased risk of endometrial cancer, a reduction in the symptoms of estrogen deprivation and a reduction in deaths due to cardiovascular disease. Analyses suggest a small increase in breast cancer incidence associated with HRT, particularly with high dosage and a long duration of treatment. For the average woman, the negative effect on the breast is far outweighed by the positive effects on the bones and heart. Preliminary data suggest that there is a reduction in the risk of colon cancer as well[18].

The addition of progestin to HRT regimens drastically reduces the risk of endometrial cancer[19]. It is not clear whether the protective effects against cardiovascular and osteoporotic diseases are altered. However, progestins are copromoters of breast cancer in model systems and an increased risk of breast cancer is possible. Whether a history of previous biopsy findings of atypical hyperplasia or *in situ* carcinoma or a strong family history of breast cancer alter the risk-to-benefit ratios for HRT is unknown. It is likely that the average woman benefits from HRT[20,21]. HRT is undergoing paradigm shift. Recently doctors have increasingly begun to recognize harmful effects in treatments once thought to be beneficial to menopausal women. A new study done by Christopher Li adds more weight to the link between hormone use and breast cancer. The study found that two types of cancer which increased with hormones are lobular and lobular-ductal mixed. Both types of invasive cancer have increased 65% from 1987-99[22]. Ironically, JAMA published a goverment study purporting that combined estrogen-progestin treatment improves mental outlook and memory.

Hormone replacement therapy increases breast density. Dense tissue contains more glandular tissue and is a risk factor for breast cancer. The explanation might be that the excess of glandular tissue in the dense breast provides much more cells potentially able to transform into neoplastic cells. High density of breast can lead to impaired sensitivity of mammographic screaning[23].

Two studies of twins showed that the population variation in the percentage of densew tissue revealed during mammography has high heritability at any given age[24].

In addition to the other factors, radiation may be a risk factor in younger women. Women who have been exposed to radiation before age 30 have a substantially increased risk of breast cancer, whereas radiation exposure after age 30 appears to have minimal effect on the breast[25].

Two complementary approaches have been taken to elucidate at a molecular level the process of malignant progression of human breast cancer. One approach has focused on the genetics of somatic mutations frequently found in primary breast tumors[25]. The other approach has focused on the expression of specific gene products present in primary breast tumors or breast cancer cell lines[26].

The activation of expression of certain growth factors, growth factor receptors and nuclear proteins occurs as a direct consequence of gene amplification of cancer cells. These *loci* include the c-myc protooncogene on chromosome 8q24[27], an amplicon on chromosome 11q13 that contains the INT2 (FGF3), HST1 (FGF4)[28] PRAD1 and EMS1 genes[29] and the c-erb B2 protooncogene on chromosome 17q[30]. In addition, BEK (bacterial expressed kinase) and FLG (FMS like gene), two members of the FGF receptor (FGFR) gene family, are amplified in 11.5% and 12.7% of breast cancer, respectively[31].

By far the most frequent type of mutation found in primary breast cancers is Loss of Heterozygosity (LOH). This is a common feature of many kinds of malignancy and occurs as a consequence of either interstitial deletions, chromosome loss or aberrant mitotic recombinational events. It is thought that LOH reveals within the affected region of the genome the presence of a recessive mutation in the remaining allele of a tumor supressor gene or genes[32]. At present, 20 of the 41 chromosome arms in the human genome have been shown to be affected by LOH in primary breast tumors. However, only two of the putative genes for LOH have been identified, p53 on chromosome 17p12[33] and Rb on chromosome 13q14[34].

Tumor suppressor genes are believed to be involved in the normal suppression of cellular proliferation[32]. Studies have focused on defining the regions of each chromosome arm containing putative target tumor suppressor genes and will lead to the recognition of their function and, eventually, whether or not they are affected by LOH[35].

Familial breast cancer occurs in about 5% of patients. Analysis of families with a history of breast cancer demonstrates the existence of a breast cancer susceptibility gene on the long arm of human chromosome 17. This gene was named BRCA1. Mutations of the BRCA1 gene are responsible for 45% of families with a high incidence of breast cancer and at least 80% of families with an increased incidence of both breast and ovarian cancer[36].

The BRCA1 gene has been cloned and found to be a large gene that shows only limited homology to other known genes[37]. Near the amino terminus of the predicted protein is a RING-finger motif associated with DNA binding proteins and gene regulation. Virtually all inherited mutations cause the BRCA1 protein to be prematurely truncated, in keeping with its predicted role as a tumor suppressor gene[38].

DNA sequencing has been used to identify mutations within the BRCA1 gene. Mutations were identified in 16% of women with a family history of breast cancer. The rates were found to be higher among women from families with a history of both breast cancer and ovarian cancer[39]. There is some evidence to suggest that mutations at the 5' end of the gene carry a higher risk of ovarian cancer than those at the 3' end. BRCA1 is infrequently mutated in sporadic breast or ovarian cancer, although LOH in regions adjacent to BRCA1 is common, suggesting that other genes close to BRCA1 may be important in sporadic forms of both types of tumor[40].

Another breast cancer susceptibility gene, BRCA2, on chromosome 13q12-13 has been recently cloned and germline mutations in breast cancer families have been identified[41]. Mutations in BRCA2 appear to account for an additional 45% of familial breast cancer. BRCA2 is associated with a lower risk of ovarian cancer than BRCA1 and a higher risk of male breast cancer[11]. Somatic mutations of BRCA2 in sporadic breast and ovarian cancer are very rare. Between them, BRCA1 and BRCA2 may be responsible f or about 90% of hereditary breast cancers[40].

In patients with breast cancer, amplification of the HER-2/neu gene has proven to be a significant predictor of both overall survival and susceptibility to relapse. The human homologue of the rat neu gene, called c-erbB2 or HER-2, shows extensive homology to the epidermal growth factor receptor c-erbB1[42]. Amplification results in overexpression of gene product. The product of the c-erbB2 gene together with the products of related genes c-erbB3 and c-erbB4, were shown to act as receptors for the ligand heregulin. It is likely that heregulin-mediated activation of these receptors plays a role in breast cancer. Also, increased production of the normal protein products of amplified proto-oncogenes contributes to the development of the malignancy[43].

Defects in other genes, such as p53, the ataxia telangiectasia gene and other as yet unidentified breast cancer susceptibility genes are likely to explain the predisposition to breast cancer in other familial cases.

Alterations in at least five separate genes can result in an increased risk of developing breast cancer. As an example is the rare presentation of breast cancer called Li-Fraumeni Syndrome (LFS). This syndrome occurs when three first degree relatives develop cancer under the age of 45 and one of the three cancers is a sarcoma. In Li-Fraumeni Syndrome, the most frequent malignancy is breast cancer[44]. Affected members of LFS families frequently carry germline p53 mutations[45].

The most commonly mutated gene identified in human breast cancer is p53[46]. The role of this gene is to produce phosphoprotein p53 in the nucleus. Loss of heterozygosity or overexpression of mutated p53 protein occurs in about 30-55% of human breast cancers[47]. Mutations of p53 render the cell unable to die of apoptosis. Alterations of p53 showed a poor response to endocrine therapy. Both endocrine and many chemotherapeutic agents act by inducing apoptosis. Consequently, the turning off of p53 makes induction of apoptosis impossible, resulting in a poor response to chemotherapy[48].

In the Retinoblastoma (RB) gene, loss of heterozygosity occurs in about 25% of primary breast cancer patients and 10-20% of them show evidence of gene inactivation[49]. There is no data available on the relation between loss of heterozygosity of the RB gene and response to treatment[49].

The myc gene may spontaneously stimulate proliferation. C-myc, with amplification, is known to bind and inactivate the Rb-1 gene product and, in this way, to decrease tumor suppression[50].

Expression of nm23, a putative metastasis suppressor gene mapped to chromosome 17q21, has been detected in human breast cancers[51]. Already studies have demonstrated a significant association between reduced nm23 expression and aggressive cancer behavior[51].

Mutations in the ras gene, which frequently are found in other cancers, are not found in breast cancer, although increased levels of Ha-ras have been observed[76].

Growth factors, differentiation factors and hormones are important elements in the proper development and functioning of multicellular organisms. Polypeptides such as these work as intercellular messengers governing proliferation, differentiation and the process of metabolism. Growth factors have the ability to bind to factor-specific cell-surface receptors exhibiting protein tyrosine kinase activity[52].

Receptor Tyrosine Kinases (RTKs) all have similar molecular structure. All RTKs are dimers and contain a glycosylated extracellular ligand binding domain, a hydrophobic transmembrane region and a cytoplasmic domain containing a tyrosine kinase catalytic domain[52].

RTKs have been classified into nine subgroups based on sequence similarity and distinct structural characteristics. These include the EGF receptor family, the insulin receptor family, the PDGF/MCSF-1/Steel receptor family, the VEGF family, the hepatocyte growth factor family, the neurotrophin receptor family, the FGF receptor family, the Eph-like receptor tyrosine kinase family and the Axl-receptor tyrosine kinases[53].

RTKs are all activated in the same manner: ligand binding to the extracellular domain causes receptor dimerization and oligomerization. Oligomerization of receptors will increase the activity of tyrosine kinases, which will lead to enhancement of ligand binding affinity. Oligomerization leads to the autophosphorylation of the receptor as well as of the cellular substrates. Upon kinase activation, RTKs are able to turn on a number of different intercellular signaling pathways that will ultimately lead to cell proliferation, differentiation and metabolic activity.

The importance of RTK signaling in the determination of cellular activity and cell fate has implications for carcinogenesis. Within receptor tyrosine kinases a number of mutations can occur which can lead to altered signaling. RTKs can be constitutively activated through mutations in the binding domain that cause a conformational change leading to the constant oligomerization/activation of receptors. Deletions or mutations within the cytoplasmic domain will lead to increased receptor signaling through increased tyrosine kinase activity or enhanced substrate affinity. Nevertheless, most mutations resulting in a constitutively activated receptor tyrosine kinase are not directly transforming.

In cancer, involvement of RTKs has been linked to their autocrine activation and receptor overexpression. This combination results in unregulated receptor signaling, increased signaling of proliferation and the overcoming of apoptosis[52,53].

Epidermal Growth Factors (EGFs) as well as Transforming Growth Factor Alpha (TGFα), both of which can activate EGF receptors, are produced locally in normal and malignant tissues. Malignant tumors frequently contain higher numbers of EGFR than normal tissues, but there is no agreement on the prognostic value of EGFR[54]. Some studies suggest that expression of EGFR is associated with a lack of response to endocrine therapy in recurrent breast cancer[55]. Acquired tamoxifen

resistence is associated with an increase in EGFR numbers accompanied by loss of Estrogen Receptors (ER) and Progesterone Receptors (PGR)[56].

Insulin-like growth factors IGF1 and IGF2 are potent mitogens for breast cancer cells[57]. Apart from estrogens, they are the most powerful growth stimulators *in vitro*. The growth effects of both are mediated via IGF1 receptors, which have been demonstrated to be present in 67-93% of human breast cancers[58]. So far, no data are available on the relation between tumor IGF1R levels and response to therapy in patients with breast cancer. With respect to IGF2, it was suggested that its overexpression may be capable of mediating malignant progression in human breast cancer. The blockade by monoclonal antibodies of IGF1R and downregulation of IGF2 by tamoxifen or estrogens results in growth inhibition, suggesting that IGF2 expression is correlated to breast cancer growth and both IGF2 and IGF1 may be involved in hormone independence[59].

Breast cancer is termed a hormonally driven tumor. This indicates that the development and growth of the tumor is spurred by the body's hormones. The regression of an advanced mammary tumor following surgical castration of ovaries was observed as early as the end of nineteenth century. This fact indicated a dependance of tumor upon the presence of female sex hormones[60]. Such observations provided a base for the introduction of hormonal therapy in treatment of mammary cancer. The practice of castration was abolished with the development of a pharmacological alternatives introduced various anti-estrogenic drugs, the most popular of which is tamoxifen. In breast cancer it is the hormone estrogen that primarily drives its development and growth. On balance, estrogen is an enormously healthful hormone. Estrogen, beside its effects on the secondary sex characteristics in women, also has a variety of roles that promote health: it protects the heart, protects against bone loss by helping to absorb calcium from bloodstream, stimulates water retention and body oil lubrication, so the skin remains youthful. Recently, scientists proved that estrogen interacts with nerve growth factors to protect brain cells from degenerating.

When Elwood Jensen discovered the estrogen receptor-ER-α in 1958, for many years thereafter it was known as the classical receptor.

Jensen's explanation of the two steps mechanism of steroids hormones was confirmed by others' studies. This mechanism involves the activation of receptor proteins by the hormone estrogen and their subsequent binding to hormone response elements in target genes, thus regulating their expression.

In the late 1970's Jensen's discoveries led to the standard clinical procedure of analyzing the receptors on the breast tumor tissue to determine therapy choices. It was known that some breast cancers are hormonally driven, but only in approximately one-third of them does the depravation of estrogen lead to remission. Jensen's study proved that only patients whose cancers have substantial receptor levels benefit from treatment that reduces the amount of estrogen in the body.

The dogma that only one such receptor ER-alfa, existed was finally abolished by a Swedish group in 1996 by discovering receptor ER-β. Their studies proved the existence of two independant ER genes in the human[61,62]. This finding forced scientists to search for possible new treatment,some perhaps utilizing ER-α and ER-β-specific ligands.

Breast cells have receptors on their surface, each one capable of receiving a single message. Once the message is received, it is transmitted to the center-nucleus, where it is processed and then directed to a specific gene. However, sometimes cancer cells produce receptors that are abnormal and behave as if they've been stimulated by growth factors though none are present.

The steroid hormones (testosterone, estrone, progesterone, cortisol and aldosterone) all act on target cells by binding with them. They have a high affinity to a cytoplasmics receptors protein which forms with them a hormone-receptor complex. Consequently, a change in conformation of the receptor occurs, resulting in an activated complex which triggers an enhancement of genetic description. This initiates a spectrum of processes responsible for manifestation of hormonal responses.

When estrogen attaches to receptor, it directs the cell to carry out a task, such as ovulation, menstruation, pregnancy, or lactation. Estrogen's activity was one of the first examples of the critical process called cell signaling, the means by which all cells in the body receive orders, including orders to grow and divide.

Some, but not all, breast cancers cells carry estrogen receptors. When a breast cancer cells carries a receptor, the grow and divide message from an estrogen molecule can be crucial for its proliferation.

Estrogen Receptors (ER) status was the first of the biological markers to be studied.

About 40% of breast cancers in premenopausal women and 60% in postmenopausal women are ER positive. The original assay methods were biochemical, using a radioligand assay, but have now been replaced immunochemical assays using a monoclonal antibody raised against an ER-related protein[63].

It is recommended that all breast cancer patients have their ER status estimated and recorded. Tumors that are ER positive tend to be less life threatening than those that are ER negative, precisely because they respond to estrogen therapy. Natural products, such such as isoflavones from soy, which block estrogen receptors may emerge as obvious candidates for drug development.

Progesterone, the hormone that becomes active in the second half of the menstrual cycle, inhibits cell division in the uterus and breast and so is thought to counteract the stimulation of cell growth caused by estrogen.

Progesterone receptors depend upon an intact ER pathway in order to be expressed. Therefore their status tends to correlate with ER status. Patients with estrogen-positive tumors have between a 50 and 70% chance of responding to hormonal therapy and this increases to over 70% in patients whose tumors have both estrogen and progesterone receptors[63].

The major source of estrogen in premenopausal women is the ovaries. Levels of estrogen in postmenopausal women are much lower and their estrogen is synthesized peripherally from androstenodione which is produced in adrenal gland. Such estrogen is found principally in fat (including breast fat), but also in the skin, muscle and liver. The production of estrogen requires the presence of hormone aromatase.

Tamoxifen is a synthetic hormone which acts primarily by binding to the estrogen receptors. It is the most widely used hormonal treatment for breast cancer.

Studies done by Clark *et al*. showed the relationship between estrogen receptors, progesterone receptors and a variety of patient characteristics in 2,977 women with primary breast cancer[64]. Older women are were likely to be estrogen-receptor positive than younger women. When patient age and menopausal status were analyzed together age was found to be primary determinant of increased estrogen receptors concentrations. There appeared to be no correlation of progesterone receptors concentration with either age or menopausal status when these variables were analyzed separately. However, premenopausal women had higher progesterone concentrations than postmenopausal women when patients of the same age were compared, perhaps reflecting greater estrogen-mediated synthesis of progesterone receptors.

Further understanding of the action of hormones which positively affect the breast and consequently reduce the risk of malignant development will be the task of future research. The evidence shows that estrogen is the hormone most connected to breast cancer, enhancing proliferation more often and more rapidly than others. Thus, if a mutation, inherited or triggered by a carcinogen, lies embedded in the DNA, cancer cells are more likely to proliferate when high estrogen levels are present.

Perhaps blocking the action of estrogen by partially replacing it with less aggressive hormones such as phytoestrogenes derived from plants can slow down or stop the harmful effects of estrogenes exposure throughout life's cycles.

Recent studies have concentrated on the superfamily of growth factor receptor tyrosine kinases in order to understand the biochemistry of of human cancer. Protein kinases transfer phosphates from adenosine triphosphate (ATP) to other proteins.

The Epidermal Growth Factor (EGF) subfamily comprises the focus of research in laboratories worldwide. It includes the EGF receptor, the Neu tyrosine kinases (also known as Erb2 or HER2) the Erb3 (or HER3) protein and Erb4 (or HER4) protein.

The EGF receptor is highly overexpressed in some human tumors. Breast cancer cell lines express differing amounts of EGF receptors tyrosine kinases and Neu tyrosine kinases.

Epidermal Growth Factor Receptors (EGFR) is a cell membrane protein which is related to an oncogene product, v-erbB, originally named after the erythroblastic virus which causes cancer in chickens. Binding of its ligand, EGF, promotes the growth of cancer cells, including breast cancer cells, grown in culture.

ErbB2 or HER2 protein is a cell membrane receptor and is the product of the neu oncogene. It was discovered that this oncogene had not mutated like most others. Usually a mutation causes a gene to produce the normal protein, but in abnormally high amounts. This phenomenon is known in molecular biology as overexpression.

When the Neu gene is mutated and the protein overexpressed, the cell is overloaded with signals that cause it to grow out of control-to become cancerous. A typical breast cell carries about 50,000 HER2/neu receptors on the surface. When the gene is mutated, the number jumps to between 1 and 1, 5 million[65].

Just as certain breast and ovarian,cancer cells overexpress HER2/neu, cells in several types of cancer overexpress the EGF receptors.

The status of progesterone receptors always correlates with status of estrogen receptors with a given cells.

Steroid hormones are an important category of hormones involved in the growth regulation of breast cancer. Estradiol, a natural steroid, is one of the most powerful tumor growth stimulating factors. Still the mechanism of hormonal dependence in breast cancer is not completely understood[66].

Breast cancer patients having high levels of Estrogen Receptors (ER) and Progesterone Receptors (PR) receive more benefit from endocrine adjuvent therapy than patients with ER/PR negative breast cancer[67].

The rationale for endocrine therapy has been the reduction of estrogenic stimulation of cancer growth. Tamoxifen has been the principal agent used to block binding of estrogens to their receptors. In advanced breast cancer, activity of tamoxifen can be enhanced by use of prednisone[68].

The relative role of viruses in causing human breast cancer remains ambiguous, but recent studies have established some of their involvement. The natural history of spontaniously occuring cancer suggests a multistep process of cellular evolution repeated selection of rare, sensitive cells with some potential for growth advantage. Some observations suggest that a tumor virus acts as a cofactor in the multiple cellular oncogenes involved in the evolution of cancer. Viral cellular transformation is a heritable, stable change in the control of cell proliferation and differentiation.

The discovery that a particular virus MMTV (Mouse Mammary Tumor Virus), in a certain strain of mice was able to cause mammary tumors led to the question whether similar agent may play a role in human breast cancer[69]. Pogo's findings led to further investigation of viral particles of MMTV-like LTR seguences in human breast cancer and normal breast tissue. Tissue studied by Pogos group originated from highly invasive ductal carcinomas discarded surgically from tumors and from normal tissue during reductive mammoplasties, as a comparison. Detection of MMTV-like LTRs was positive in 41.5% of human breast cancers and in none of the normal tissue analysed[70].

The metastic process is inherently inefficient. Like many aspects of cancer, metastasis is a complicated and poorly understood process. The inefficiency of the metastatic process leads naturally to the question of whether metastasis is a random or a specific process. Clarke's study found that only a minority of breast cancer cells had the ability to form new tumors. After isolation from patients tumorigenic cells CD44 CD24 were identified. It was found that a few as 100 cells of this phenotype were able to form new tumors in mice. Tens of thousands of cells with alternate phenotypes failed to produce new tumors. Clarke determined that only one to fifteen% of breast cancer cells were capable of forming new malignant tumors[71].

Future studies will facilitate the elucidation of pathways that regulate the cells which determine tumor development and survival. Effective therapies could be based on such studies to target and eliminate all tumorigenic (tumor initiating) breast cancer cells.

The skeleton is the most common distant site to which breast cancer spreads (most frequently in the thoracic and lumbar spine). With advanced breast cancer, metastases to the bone can approximate 70% of cases[72].

Inoperable tumors are initially treated with systemic therapy-chemotherapy for premenopausal women and hormone (endocrine) therapy for postmenopausal women. Tamoxifen is the main agent for endocrine therapy[56]. Treatments for advanced breast cancer are not yet curative.

The majority of papers do not show an association between steroid receptor status and response to chemotherapy[73]. Improvements in cytotoxic chemotherapy concentrate on reduction of toxicity and the search for new, strong, selectively working bioactive agents.

Breast cancer is a complex disease with many molecular roads. A new way to find cancer genes is to know the signal transduction pathways to which they belong. Different pathways mean different proteins. Proteins implicated in breast cancer include receptors, growth factors, enzymes, cell cycle regulators and adhesion molecules. Perhaps proteomics will be the key in solving the cancer enigma.

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