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MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Breast cancer: An Overview

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Abstract

Breast cancer is a prevailing disease worldwide that requires effective and rational therapy. For this purpose, the use of various treatment modalities should be optimized according to the stage of disease and the risk: benefit ratio of the therapeutic agents employed in the patients. Although the therapies involved provide reduction in morbidity and mortality rates, monitoring is required to combat the resulting adverse drug reactions. This review would be helpful for healthcare professionals to address the multi factorial disease in accordance with its occurrence thereby providing rationalized therapy to the patients.

Keywords: Breast cancer; Chemotherapy; Endocrine therapy; Adjuvant therapy.

1. Introduction

Cancer is considered as a complex disease, which includes the changes in cell physiology, which ultimately lead to malignant tumors (Seyfried and Shelton, 2010). Cancer can result from abnormal differentiation of any of the different types of cells in the body, so there are hundreds of the same types of cancers which can differ substantially in their behavior and response to treatment. Cancer for humanity is the most complex disease faced today, as for more than 200 forms of cancer exists right now with different kinds of profiles that need unique treatment strategies (Hanahan, 2000). According to the International Agency for Research on Cancer (IARC), in KSA BC cases were 3629 (2018) 30% of all cancers in female this present is more than the average worldwide estimate of 24.2% indicating a major health burden in KSA. Breast cancer (BC) is a common disease around the world which leads to death by carcinoma. It is considered the most commonly diagnosed cancer in women in the USA. According to the latest report of Saudi Cancer Registry (SCR), more than one thousand and half female breast cancer cases were diagnosed in 2011 out of about 6000 new cancer cases in females reported in the same year. With about thirty percent of cancer cases, that means breast cancer is the highest among females in the Saudi Arabia (Cancer Incidence Report, 2011).

BC is not one disease, with biologically different characters with unique pathological and clinical symptoms. It is a heterogeneous entity of many subtypes that vary in development and therapy response (Safaei et al, 2013). BC is a malignant cancer which begins in the breast cells. It turns malignant when cancer cells grow without regulation and become able to spread or metastasize to the other tissues of the body (American Cancer Society, 2014).

2. Histology of the breast

The breast is a bilateral organ which changes dramatically in the human female regarding the size and shape, and have different functions all related to puberty, infant growth, pregnancy, post-menopausal regression and lactation. The human breast development is a progressive process began from embryonic life. About 15-25 lactiferous ducts are contained in the breast, and start at the nipple, branch into small ducts and end in the terminal duct lobule, which is formed of a terminal duct and many small ductulus. The ducts and ductulus are lined by an inner layer of cuboidal to columnar epithelial cells and an external layer of myoepithelial cells. The connective tissue in the lobule is formed of fibroblasts in a background of collagen and acid mucins, with histiocytes and occasional lymphocytes. The interlobular stroma is hypocellular and contain of fibroadipose tissue **(Vorherr, 2012).**

The epithelium and lobular stroma response to hormones. A marked proliferation of ductules isdeveloped during pregnancy, leading to very large lobules, and the epithelial cells have cytoplasm filled with secretory vacuoles **(Ramsay et al., 2005). (Figure 1)**

Luminal (epithelial) cells Columnar: cuboidal epithelium, may be pseudostratified (extralobular): the inner layer of bilayered ductal lobular system. Myoepithelial: the outer layer resting on a basement membrane **(Salapathi, 2011).**

Basement membrane: Partiallycovered only by contractile meshwork. Surrounds mammary ducts, ductules and acini.Has type IV collagen and laminin. Differentiate the ductal system from the stroma.Transgression of the basement membrane and myoepithelial layer by cancer cells defines invasive carcinoma in the setting of DCIS.Some kinds of invasive carcinoma may demonstrate basement membrane substances by definitedyes **(Salapathi, 2011).**

Breast cancer etiology causes and incidence

Breast cancer always arises in either the ducts or lobes. Most of invasive breast cancers start in the ducts, with complex network of channels works to transport milk from the lobules to the nipple. This type called ductal breast cancer

Breast cancers originate from the breast epithelial cells. According to a histological study, the breast epithelium is formed of a simple bilayer of inner luminal cells which produce milk in the breast, with an outer layer of myoepithelial cells that inject the milk **(Heffernan, 2018). (Figure 2)**

Further study of the cells in the breast reach for conclusion that many breast tumors start at the point between the terminal duct, and lobule the terminal units of the ductal lobular. Researchers have identified many causes of breast cancer as hormonal, lifestyle and environmental factors that can play role in having breast cancer.

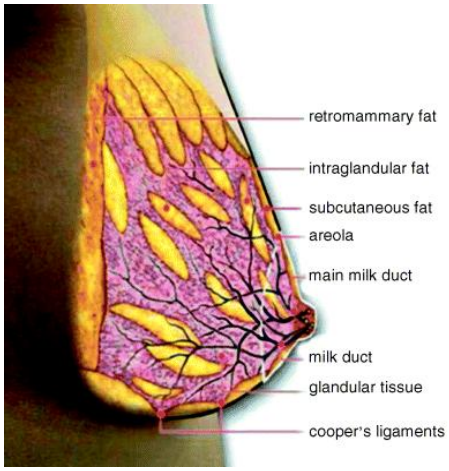

Figure 1 - Milk duct system and distribution of different tissues within the breast (Ramsay et al., 2005)

It's not known why some people without risk factors develop cancer, while others with risk factors never develop cancer. It's proposed that breast cancer is due to a complicated interaction of human genetics surrounding environment **(Negrei and Galateanu, 2019)**. Researchers concluded that there are number of mutated genes that can elevate the probability of breast cancer, gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). The two genes are increasing the risk for breast cancer **(King etal.,2003).**

As some genetic factors play the role in causing breast cancer, many women having breast cancer do not have a clearly identifiable risk profile **(Harris, 2012)**. In fact, it is only 5–10% of breast cancer causes are mutations in inherited high penetrance genes **(Chang-Claude, 2001).**

Other factors are personal, family breast cancer history, age, hormonal factors and reproductive factors (i.e., early menarche, first pregnancy at late age, pregnancies number are small, short periods of breastfeeding, or no breastfeeding at all and a delayed menopause) **(Lauby-Secretan,2015).**

Breast cancer symptoms and signs

Breast Lump is the common presenting symptom among females with breast cancer and has high predictive value for malignancy.

The main manifestation of breast cancer collected from Cancer research UK (2014):

- Presence in one or both breasts of one or more "hard masses" lumps of any shape, size, and texture, with smooth or rough margins.
- Inflammation of the entire breast, or parts of it.
- Change of the breast skin: redness, noticeable depressions or thickening.
- Prolonged pain in one or both breasts, the cause of which is not clear (in many cases, breast cancer develops painlessly).
- Nipple retraction.
- The appearance of sores on the nipple and if there I any redness or peeling **(CR-UK, 2014).**

The specific symptoms of invasive breast cancer include: Itchy or irritation of the breasts, breast color change, increasing of breast shape or size, feeling of hard, warm or tender during touch. Flaking or peeling of the nipple skin, thickening of breast or the presence of a breast lump, change the color to red or pitting of the breast skin (Union for international cancer control 2013).

BC risk factors and genomic instability

The associated factors with breast cancer, either positively or negatively, are changed for female who are diagnosed prior the age of forty **(Althuis et al., 2003).** In general the risk factors in females include history of cancer; family or personal, African ancestry or Ashkenazi Jewish, age (fifty five or older), early menstrual cycle (younger than twelve), late menopause (fifty five or older), late 1st pregnancy after thirty or never pregnant, hormone treatment , obesity (only for post-menopausal breast cancer), consuming alcohol, no physical activity,

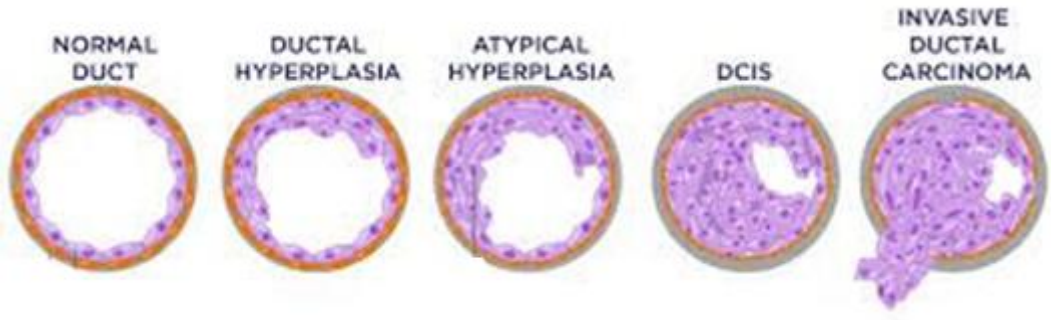

Figure 2: Diagram shows changes in cell structure and cellular activity

ionizing radiation exposure, genetic factors and dense breasts or atypical hyperplasia of breasts and genetic factors. The interference of smoking, diet, stress, weight at birth, diethylstilbestrol (DES) exposure, and the association of benign breast conditions with high breast cancer risk requires many researches.

Moreover, having many children and breastfeeding protect against the development of breast cancer. Using the healthy and good lifestyle early may participate in lowering the breast cancer development **(Torre et al.,2015).**

Breast cancer diagnosis and staging

Staging function is to anatomically grouping cases to determine the therapy and improvement. Precise staging is important to compare the results of therapies among the studies **(Edge et al., 2010)**. The Union for international cancer control (UICC) published in 1960 the Tumor-Node-Metastasis (TNM) staging system which was created for BC. The system of staging was revised and updated in the sixties and the edition number seven was published in 2009.By the TNMUICC classification, the classification of cancers is divided into (T1, T2, etc.) which is regarding to the size, but with no real logic to the categories. This method was reasonable from sixty years when the first TNM classification was developed **(Arnone et al., 2010)**. Problem of the old classification is that it does not make full use of the information collected by the modern diagnostic methods that identify small tumors. The classification of T1 category is for tumors that start from a few millimeters up to 2 cm. The T1 subcategories are (T1a, 1–5 mm; T1b, 6–10 mm; and T1c 11– 20 mm), which are arbitrary and needlessly complex. For the T2 classification is for 2.1 to 5 cm, consider diameter rather than volume. The classification includes a tumor of 2.1 cm diameter would have a volume 4.5 ml and a 5 cm cancer would have volume of about 60 ml. The prognosis difference between the two masses is high **(Arnone et al., 2010).**

In 2018, the American Joint Committee on Cancer (AJCC) developed the breast cancer staging guidelines to add other cancer characteristics to the T, N, and M system to determine a cancer's stage: **(breastcancer.org, 2019).**

- Tumor grade: to measure the similarity between the cancer cells and normal cells
- Estrogen and progesterone receptor status: If there are estrogen and progesterone hormonal receptors on the cancer cells.
- *HER2* status: Is there over expression of *HER2* protein?
- Oncotype DX: If the cancer is estrogen-receptor-positive, *HER2*-negative, and there is no cancer in the lymph nodes

The stages recognized today are as the following according to the NCCN clinical practice guideline for the year 2018 guide:

Stage 0 is describing the state of non-invasive breast cancers, such as Ductal carcinoma in situ (DCIS).

Stage I indicates invasive breast cancer, Stage I is divided into subcategories IA and IB. IA is up to 2 centimeters and IB greater than 0.2 mm but not larger than 2 mm. Stage II is divided into subcategories IIA and IIB. Stage IIA when no tumor can be found in the breast, but cancer (greater than 2 mm) is found in 1 to 3 axillary lymph nodes. Also, it used when 2 centimeters (cm) or smaller found and spread to the axillary lymph nodes. stage IIB indicates invasive breast cancer when the tumor is more than 2 cm but no less than 5 cm; small groups of breast cancer cells more than 0.2 mm but not more than 2 mm — are found in the lymph nodes or the tumor is more than 2 cm but no more than 5 cm. Stage III is divided into IIIA, IIIB, and IIIC n which stage IIIA is for when cancer is present in 4 to 9 axillary lymph nodes or in the lymph nodes near the breastbone, and it describes the tumor is more than 5 cm; small groups of breast cancer cells (more than 0.2 mm but not more than 2 mm) are present in the lymph nodes. Stage IIIB describes the breast cancer and a tumor that have any size but has spread to the chest wall and/or skin of the breast with clear swelling or an ulcer and it might spread up to 9 axillary lymph nodes. Stage IIIC indicates tumor has spread to 10 or more axillary lymph nodes and cancer has spread to lymph nodes above or below the collarbone. Stage IV occurs when the breast cancer which has spread beyond the breast and nearby lymph nodes to other organs of the body (NCCN,2018).

Breast cancer treatment strategies

Combination of treatments or single treatment is used for breast cancer as it depends on the situation. The most used way for treatment of breast cancer is lumpectomy surgery with axillary node removal and modified radical mastectomy which include

removal of the tumor mass, with a clear margin of normal breast surrounding the tumor, including lymph nodes under the arm. This means breast mastectomy, the underlying pectoral fascia, and some of the axillary nodes **(Harris et al., 1997).**

In other treatment radiation is considered as another option which is used more often now. In early stages of the application of surgical examination and lumpectomy of the axillary lymph glands. In the localized larger cancers, the involved parts may be irradiated after surgical treatment. Complications of the therapy can appear because of the spread of cancer to a distant site can be treated with radiation. In these cases, drug or hormone therapy may be given as well. The current gold standard treatment is complex physiotherapy (CP), a combination of care for the skin, manual lymph drainage (MLD), compressive elastic and inelastic bandaging, and myolympho kinetic exercises **(Bosman, 2010).**

X-ray destruction or surgical elimination of the hormones producing organs (such as the ovary or adrenal gland) will decrease the distinct hormones level inside the body. Now there are drugs which opposite the action of distinct hormones. In the other hand tumor depression can be achieved by increasing the level of other hormones by giving them in the form of drugs **(Harris et al.,2012).**

Treatment of breast cancer therapy by class

Treatment plan for breast carcinoma can be outlined by organized screening and identification of the ailment **(Geay, 2013).** The choice of therapy for breast carcinoma must outweigh benefits over risks **(Maughan et ql., 2010)**; the dose, dosing plan and response of the therapeutic agents used for treatment should be monitored through regular follow ups. The therapeutic agents used for breast cancer treatment cause adverse drug reactions in addition to their therapeutic outcomes and such adverse reactions discourage patient adherence to the therapy; hence, the pre- and post- treatments to cope such indications must be in line with the standard treatment recommendations **(Jose & Rao, 2006).** Various classes of therapeutic agents are employed for breast cancer treatment:

a. Alkylating agent: cyclophosphamide (nitrogen mustard)

b. Anti-metabolite: methotrexate (folic acid analogue), 5-fluorouracil & capacitabine (pyramidine analogues)

c. Natural product: vinorelbine (vinca alkaloid), paclitaxel (taxane), doxorubicin (antibiotic)

d. Hormone and antagonist: tamoxifen (anti estrogen), letrozole & anastrazole (aromatase inhibitors)

e. Miscellaneous: trastuzumab (monoclonal antibody), lapatinib (Protein tyrosine kinase inhibitor) **(Anjum et ql., 2017).**

Endocrine treatment

Tamoxifen is a selective estrogen receptor modulator (SERM) that binds to Estrogen Receptor and has mixed agonist and antagonist features i.e its principal mechanism of action is facilitated by its binding to the estrogen receptor and inhibition of the proliferative activities of estrogen on mammary epithelium; Tamoxifen 20 mg tablets are established as gold standard for breast cancer therapy. Reports have shown that with use of Tamoxifen, irrespective of menopausal or lymph node status, risk of ER+ breast cancer recurrence is reduced to 50% and also there is about 28% decrease in morbidity rates. On the contrary, it has been found that the endocrine treatments like Tamoxifen itself might intensify the xenoestrogens agonistic effects on transmuted Estrogen Receptors that are linked to drug resistance and refractoriness **(Anjum et ql., 2017).**

Aromatase is the chief estrogen source in postmenopausal females. As a substitute to Tamoxifen in postmenopausal women, (especially in ER+ breast cancer), third generation aromatase inhibitors i.e. letrozole, anastrozole and exemestane, are generally used. These agents are nonsteroidal that reversibly inhibit aromatase enzyme which transforms androstenedione into esterone and testosterone to estrogen. The drugs have exhibited enhanced positive results in the postmenopausal females and they also have a better body tolerance than preceding hormonal treatments **(Waldman & Terzic, 2009)**.

Chemotherapeutic agents

Some of the most common regimens employed in breast cancer are discussed as follows. Cyclophosphamide averts the DNA replication and

cell division and is employed for the treating breast cancer metastasis. This pro drug transforms into active form via hepatic intracellular enzymes to active metabolites (i.e. 4 hydroxy cyclophosphamide, aldophosphamide, acrolein and phosphor amide mustard) **(Anjum et ql., 2017).** The drug has been used generally as an adjuvant therapy in combination regime of CMF or with an anthracycline for treatment of breast cancer.

Platinum compounds like Carboplatin and cisplatin are employed against several cancers and are employed as monotherapy or in combination regimen to treat breast cancer **(Waldman & Terzic, 2009)**.

The influence of platinum compounds on DNA conformation and stability has been studied and a number of platinum- DNA adducts have been known in vivo and in vitro. Earliest investigations have quantified the influence of these dissimilar lesions on replication of DNA, their ability to bring in mutations and their susceptibility to DNA repair procedures. Further damage to DNA may be generated by platinum (IV) compounds, possibly through their decline by the cell to platinum (II) compounds. About 20-35% patients of Metastatic Breast Cancer under mono therapy had been found responding to carboplatin therapy. Gemcitabine and Taxanes are the drugs that are used generally in combination with Platinum compounds **(Perez et al., 2005; Burch et al., 2005).**

Paclitaxel and Docetaxel are the most commonly employed taxanes that cause mitotic arrest by stabilizing cellular microtubule elements. These agents have been used either as mono therapy or in combination schedule. A weekly management schedule of these agents has been reported to be well tolerated with little toxicity in breast cancer **(Sparano, 2000; Burstein et al., 2000; Eniu 2005).**

Anthracyclines like Doxorubicin and Epirubicin (anthracyclines) are broadly used in the combination regimen (i.e. FAC, AC, TAC) to treat breast cancer. Several mechanisms have been suggested for elucidating the cytostatic and cytotoxic activities of anthracyclines i.e. these comprise of free radical development, lipid peroxidation, and direct effects of membrane. Among all the mechanisms, the best described are the interactions with the DNA itself or DNA-topoisomerase II complex through intercalation or covalent bonding and base amendments, which cause instabilities in DNA replication and transcription, and then the initiation of repair of DNA or apoptotic cell death **(Szuławska & Czyz, 2006).**

Despite of the toxicities, the multi drug combination regimens have proven efficacy for breast cancer **(Waldman & Terzic, 2009).**

Capecitabine is an oral pro-drug of fluoropyrimidine that transforms into 5-FU by thymidine phosphorylase enzyme rendering similar effects as those of 5-FU upon infusion. It is having been used next to use of taxanes for treatment of progressing Metastatic Breast Cancer **(Blum et al., 2001)**.

Gemcitabine (or difluoro deoxy cytidine) is a pyrimidine nucleotide that blocks RNA synthesis and DNA replication and is applied for treating several types of cancers i.e. cancer of lung, bladder, breast, etc. Gemcitabine is well tolerated upon weekly IV injection **(Waldman & Terzic, 2009).**

References

Althuis, M. D., Brogan, D. D., Coates, R. J., Daling, J. R., Gammon, M. D., Malone, K. E., ... & Brinton, L. A. (2003). Breast cancers among very young premenopausal women (United States). Cancer Causes & Control, 14(2), 151-160.

Anjum, F., Razvi, N., & Masood, M. A. (2017). Breast cancer therapy: a mini review. MOJ Drug Des Develop Ther, 1(2), 00006.

Arnone, P., Zurrida, S., Viale, G., Dellapasqua, S., Montagna, E., Arnaboldi, P., ... & Veronesi, U. (2010). The TNM classification of breast cancer: need for change. Updates in surgery, 62(2), 75-81.

Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, et al. (2001) Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 92(7): 1759-1768.

Bosman, J., & Piller, N. (2010). Lymph taping and seroma formation post breast cancer. J Lymphoedema, 5(2), 1-7.

Breast Cancer Overview (2014). American Cancer Society

Burch PA, Mailliard JA, Hillman DW, Perez EA, Krook JE, et al. (2005) Phase II study of gemcitabine plus cisplatin in patients with metastatic breast cancer: a North Central Cancer Treatment Group Trial. Am J Clin Oncol 28(2): 195-200.

Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, et al. (2000) Docetaxel administered on a weekly basis for metastatic breast cancer. J Clin Oncol 18(6): 1212-1219.

Cancer Incidence Report (2011). Saudi Cancer Registry

Chang-Claude, J. (2001). Inherited genetic susceptibility to breast cancer. IARC scientific publications, 154, 177-190.

CR-UK, C. I. U. (2014). Cancer Research UK 2011.

Edge, S. B., Byrd, D. R., Compton, C. C., Fritz, A. G., Greene, F. L., Trotti, A. A. J. C. C., & American Joint Committee on Cancer. (2010). Cancer staging manual. American Joint Committee on Cancer (AJCC). 7th ed. New York: Springer, 73, 74.

Eniu A, Palmieri FM, Perez EA (2005) Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. Oncologist 10(9): 665-685.

Geay JF (2013) Physiopathology, diagnosis and treatment of breast cancer. Soins (776): 25-29.

Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. cell, 100(1), 57-70.

Harris, J. R., Lippman, M. E., Osborne, C. K., & Morrow, M. (2012). Diseases of the Breast. Lippincott Williams & Wilkins.

Harris, J. R., Lippman, M. E., Osborne, C. K., & Morrow, M. (2012). Diseases of the Breast. Lippincott Williams & Wilkins.

Heffernan M. (2018). Breast Cancer Histology, Mammography, and Litigation. Margot Heffernan research.

Jose J, Rao PG (2006) Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 54(3): 226-233.

King, M. C., Marks, J. H., & Mandell, J. B. (2003). Breast and ovarian cancer risks due to inherited mutations in BRCA1 and

BRCA2. Science, 302(5645), 643-646.

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Benbrahim-Tallaa, L., Bouvard, V., Bianchini, F., & Straif, K. (2015). Breast-cancer screening—viewpoint of the IARC Working Group. New England journal of medicine, 372(24), 2353-2358.

Maughan KL, Lutterbie MA, Ham PS (2010) Treatment of breast cancer. Am Fam Physician 81(11): 1339-1346.

Negrei, C., & Galateanu, B. (2019). Risk Factors as Biomarkers of Susceptibility in Breast Cancer. In Biomarkers in Toxicology (pp. 841-853). Academic Press.

Perez EA, Suman VJ, Rowland KM, Ingle JN, Salim M, et al. (2005) Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. Clin Breast Cancer 6(5): 425-432.

Ramsay, D. T., Kent, J. C., Hartmann, R. A., & Hartmann, P. E. (2005). Anatomy of the lactating human breast redefined with ultrasound imaging. Journal of anatomy, 206(6), 525-534.

Salapathi, S. (2011). Histopathological study of salivary gland tumours (Doctoral dissertation, rguhs).

Seyfried, T. N., & Shelton, L. M. (2010). Cancer as a metabolic disease. Nutrition & metabolism, 7(1), 7.

Sparano JA (2000) Taxanes for breast cancer: an evidence-based review of randomized phase II and phase III trials. Clin Breast Cancer 1(1): 32-40.

Szuławska A, Czyz M (2006) Molecular mechanisms of anthracyclines action. Postepy Hig Med Dosw (Online) 60: 78-100.

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. CA: a cancer journal for clinicians, 65(2), 87-108.

Union for international cancer control 2015

Vorherr, H. (2012). The breast: morphology,

physiology, and lactation. Elsevier.

Waldman SA, Terzic A (2009) Pharmacology and therapeutics: principles to practice, Elsevier, Canada, pp. 1536.

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www.nccn.org