Tamoxifen: The Ideal Post Operative Hormonal Therapy to Demote Ductal Carcinoma In Situ

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
August 2022

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

This study does not involve any human or animal trials.

Abstract/ Executive Summary

The most common cause of cancer among women is breast cancer, accounting for almost one in every ten new cases of cancer every year. Invasive lesions include ductal carcinoma (now called 'no special type' (NST)) as well as lobular carcinoma, both of which have preinvasive counterparts in the form of ductal carcinoma in situ along with lobular cancer in situ (or lobular neoplasia). DCIS normally has no outward signs or symptoms. Yet, a lump or discharge from the nipple might be observed in a few cases. Many classification systems have been created due to the microscopic heterogeneity of DCIS. This review was conducted to find out whether Tamoxifen is the ideal choice of therapy for post operative DCIS among other therapies.

Keywords: aromatase inhibitors; breast cancer; ductal carcinoma in situ; estrogen receptor positive; hormonal therapy; tamoxifen.

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List of Acronyms

CE	Contrast Enhanced
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Estrogen Receptor
DCIS	Ductal Carcinoma In Situ
HR	Hazard Ratio
LCIS	Lobular Carcinoma In Situ
MI	Microwave Imaging
MRI	Magnetic Resonance Imaging
NSABP	National Surgical Adjuvant Breast and Bowel Project
NST	No Special Type
PET	Positron Emission Tomography
PPAR	Peroxisome Proliferator-Activated Receptor
RBC	Red Blood Cells
RCT	Randomized Controlled Trials
RF	Radio Frequency
RR	Relative Risk

SD	Standard Deviation
SERM	Selective Estrogen-Receptor Modulator

Chapter 1

Introduction

1.1 Breast Cancer and Its Types

The main cause of cancer being diagnosed in women is breast cancer, responsible for higher than one in every ten new cancer cases being diagnosed each year. Worldwide, it has been the second main cause of death due to cancer among women after lung cancer. According to its anatomy, milk-producing glands have the location on the front of chest wall. Ligaments support them, which connect breasts to chest wall, lying on pectoralis major muscle. Around fifteen to twenty round lobes make up the breast. Fat covering these lobes determine the size and shape of breasts. Moreover, each lobe is made up of lobules that contain glands producing milk in response to hormone stimulation ("Breast Cancer - PubMed," n.d.).

This threatening cancer is a silent disease developing over time. Most patients find out about their condition though routine screenings. Others may exhibit a breast lump that was discovered by accident, a change in breast shape or size, or nipple discharge. Mastalgia, on the other hand, is a regular occurrence. Breast cancer must be diagnosed with physical exams, imaging (mainly mammography), and tissue biopsy. Chances of survival are higher with being able to detect earlier. Distant metastasis as well as a poor prognosis might occur due to the tumor's tendency of spreading hematologically and lymphatically ("Breast Cancer - PubMed," n.d.).

Breast cancer is said to be a heterogeneous condition on a molecular level. Over the period of last 10–15 years, the treatment approaches have changed with an aim to accommodate for this heterogeneity, having focus on more biologically-directed treatments as well as treatment de-escalation for reducing treatment side effects. Even after the inherent molecular heterogeneity that determines modern-day treatments, few characteristics, like the impact of locoregional

tumor burden or even metastatic patterns, impact therapy being similar. Early breast cancer is considered curable if it is contained within the breast or has only migrated to the axillary lymph nodes. Multimodal therapy advancements have elevated the probability of cure in 70–80 percent patients. Advanced or metastatic diseases, on the other hand, is thought to be untreatable with existing choices of therapy. In contrast, advanced breast cancer is a disease that is treatable having main goals of treatment being to extend longevity, also control symptoms with slightest toxicity that related to treatment for maintaining or elevating better quality of living (Harbeck et al., 2019).

Breast cancer is divided into two histological subtypes: Invasive lesions include ductal carcinoma (now known as 'no special type' (NST)) and lobular carcinoma; whose preinvasive counterparts are ductal carcinoma in situ and lobular carcinoma in situ (or lobular neoplasia), respectively. From the preinvasive, DCIS spreads through ducts and distorts ductal architecture, can advance to invasive cancer, and is unilateral, whereas lobular carcinoma in situ (LCIS) does not distort ductal architecture, might be bilateral, and is a risk factor rather than a precursor. On the other hand, among the invasive, ductal carcinoma no special type (NST) develops from DCIS, has a fibrous response to produce a mass, and metastasizes through lymphatics and blood, whereas lobular carcinoma is composed of isolated tumor cells (CDH1 mutations), has a minimal fibrous response, and spreads via viscera preferentially (Harbeck et al., 2019).

1.2 History

The Edwin Smith Surgical Papyrus (3,000-2,500 B.C.) is thought to have been written by Imhotep, contains genuine stories of breast cancer. Votive contributions in the shape of breasts at Greek temples that contained Asclepius, the god of medicine, show that a divinity was asked to bring cure from breast illnesses. The medical terms carcinoma (karkinoma), scirrhous (hard,

Greek skirros), and cacoethes (malignant illness, Greek kakoethes) all come from Hellenistic texts. Hippocrates' theory of humour imbalance as a cause of sickness (about 400 B.C.) and his classic depictions of the progressive breast cancer stages illustrates early hypotheses on cancer's etiology. In the first century A.D., Leonides of Alexandria, following Greek traditions, boldly and deftly outlined his technique to incision and cautery. His concept that a large margin of excision be left and that only small tumors be removed foreshadows the oncological principles of modern surgical treatment. Galen determined breast cancer as a systemic disease after relating it to the formation of black bile in blood in 200 A.D. The ancient physicians hypothesized that menstrual termination was cancer-related; as a matter of fact, it was most likely related to the linkage of cancer with old age. Galen disapproved of the use of ligatures and let surgical wounds to bleed naturally to clear off the black bile. He developed the term "crab" to describe the dilated veins spreading from the tumor. Albucasis was a proponent of using cautery in surgery. Using caustic pastes to obliterate the tumor and making it operable is similar to how chemotherapy is used now for large breast cancers. Henri de Mondeville, Guy de Chauliac and Albucasis developed unique equipment to assist through the quick removal of breast tumors (Ekmektzoglou, Xanthos, German, & Zografos, 2009).

1.3 Symptoms and Diagnosis

DCIS usually has no visible symptoms. In a few cases, however, a lump or discharge from the nipple may be discovered. In the long run, early cancer identification could significantly minimize fatality rates of breast cancer. During recent times, researchers have focused their efforts on developing biosensors that can diagnose breast cancer using several biomarkers. As a possible diagnostic tool, microwave imaging techniques have been extensively researched for breast cancer’s speedy and cost-efficient early-stage detection, in addition to biosensors and biomarkers. Currently, the standard technique for breast screening is mammography, however, in people below 40 as well as having dense breasts, it has

low effectiveness, has reduced sensitivity towards tumors that are small (being below 1 mm, roughly 100,000 cells), also provides no information about disease outcome eventually. Although contrast-enhanced (CE) digital mammography is more accurate than mammography and ultrasonography in dense breasts, it is not generally available because of its high cost and involvement of high radiation exposure. For mammography, ultrasound has been used as supplementary medical imaging tool. Magnetic resonance imaging (MRI) has the ability to detect minor lesions, which mammography is unable to detect otherwise; nonetheless, it is expensive and also possesses a low specificity, resulting in overdiagnosis. The most precise tool for visualizing the tumor spreading or how they are responding to therapy is positron emission tomography (PET). Lately, microwave imaging or MI methods have been proposed as a low-cost plus safe alternative to mammography for diagnosis of breast cancer. The MI theory development and implementation methods for laboratory conditions has received a lot of attention in recent years. In numerical as well as experimental settings, several MI techniques have been created and tested. According to recent clinical studies, researchers should focus more on developing MI prototypes for clinical use, particularly focusing radio frequency (RF) sensors plus sensor arrays having high frequency. In order to differentiate between cancerous and benign tissues, breast biopsies are often performed in addition to screening techniques, however this is an expensive procedure requiring trained personnel. Immunohistochemistry, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), as well as fluoroimmunoassay are all techniques based on biomarkers that can be used to diagnose breast cancer. Although biomarker-based methods are selective and sensitive, they have significant drawbacks, including being costly, lengthy, requiring trained personnel, and being in need of a sophisticated labeling process. Therefore, developing a highly sensitive, label-free method for quick diagnosis of breast cancer is critical (Wang, 2017).

1.4 Objective of Study

The aim of this study was to find out which choice of therapy would be the ideal post operative hormonal therapy to demote ductal carcinoma in situ.

Chapter 2

Methodology

To conduct this review paper, articles and research papers from high-impact factor journals relevant to the topic were used. Recent official reports and peer-reviewed journals were utilized for performing a comprehensive search. The data for this paper was collected using search engines like PubMed, Science Direct, Elsevier, Google Scholar, ResearchGate, etc. The journals after screening were narrowed down to taking data from relevant and most recent ones, which was within last five years. However, due to lack of information on certain topics, few articles were taken that got published earlier. All these were maintained to create a quality review of tamoxifen as the ideal post operative hormonal therapy to demote ductal carcinoma in situ.

Chapter 3

Pathology and Histological Grading of DCIS

3.1 Pathology and Histopathological Features

Because of the microscopic variability of DCIS, several classification systems have been developed. DCIS has traditionally been divided into subtypes according to the architectural pattern of the proliferation, including comedo, micropapillary, cribriform, solid, or mixed. This classification system gives some insight into possible progress of disease; for instance, micropapillary DCIS is more likely to be multiquadrant (about 71 percent) compared to comedo-type disease (about 8 percent). In certain studies, comedo-type DCIS presents more typically on mammography, but symptomatically, cribriform disease is detected more frequently. Unfortunately, this categorization system's reproducibility based on growth patterns only is an issue; lesions with a mixture of patterns are seen about twice as commonly (62 percent) compared to lesions with a single architecture (31.9 percent). Furthermore, even a single duct area may exhibit a difficult-to-categorize architectural pattern. Newer approaches are based often on nuclear grade, which is less frequently mixed (about 15.7 percent), with the luminal necrosis's presence or absence incorporated in some cases (Pinder, 2010). Malignant epithelial cells in breast ducts with no invasion or rupture of neither myoepithelial layer nor basement membrane characterize DCIS. DCIS has a wide range of histopathologic traits, including architectural subtype and nuclear grade, leading to a plethora of classification systems, from which none have been accepted universally. Micropapillary, cribriform, comedo, solid, and mixed are some of the architectural subtypes. For example, comedo lesions resemble plugged ducts having atypical cells as well as central necrosis. These subtypes might indicate information about DCIS's nature (Parikh, Chhor, & Mercado, 2018).

3.2 Grading

The European Guidelines' last edition recommended that DCIS be rated as low, moderate, and high. Some cases are classic examples of low and high-grade DCIS, which perhaps even inexperienced pathologists would be able to describe them correctly. However, certain examples are more difficult to grade. This has to do with the absence of uniformity in disease grading criteria (Cserni & Sejben, 2020).

Large, pleomorphic cells having many nucleoli that are prominent generate high-grade DCIS. The size of nuclei in comparison to surrounding normal cells, usually normal epithelial cells or even RBCs, can help with classification. Diameter of high-grade DCIS nuclei are often larger than 2.5 RBCs. Mitoses might be common. This DCIS grade has a solid architecture, prefers to not show cell polarization, and often has central necrosis either having microcalcification or even without it. However, comedo necrosis can appear associated with other architectural patterns (for example: cribriform DCIS). Even though the term "comedo DCIS" is often used in historical series, it does not give the lesion a particular architecture or grade. There is also no agreement in the literature about how much central necrosis is needed, hence reproducibility as a DCIS category is doubtful (Pinder, 2010).

Low-grade DCIS, on the other hand, is made up of uniformly spaced cells, small and regular, having round and monotonous nuclei. The diameter of them is usually 1.5–2 RBCs. The cells exhibit polarization and have distinct cell boundaries, around micropapillae or cribriform structures, for instance. Mitoses are uncommon, and chromatin is often finely scattered. Nucleoli are rarely observable (Pinder, 2010).

When a lesion cannot be classified as either high or low nuclear grade, it gets identified as intermediate-grade DCIS. Patterns of growth usually are solid or cribriform, having some degree of polarization. The nuclei have considerable pleomorphism, which is lesser than what

is found in high-grade cell disease, yet do not have the low-grade form's monotonous and uniformity of size and spacing (Pinder, 2010).

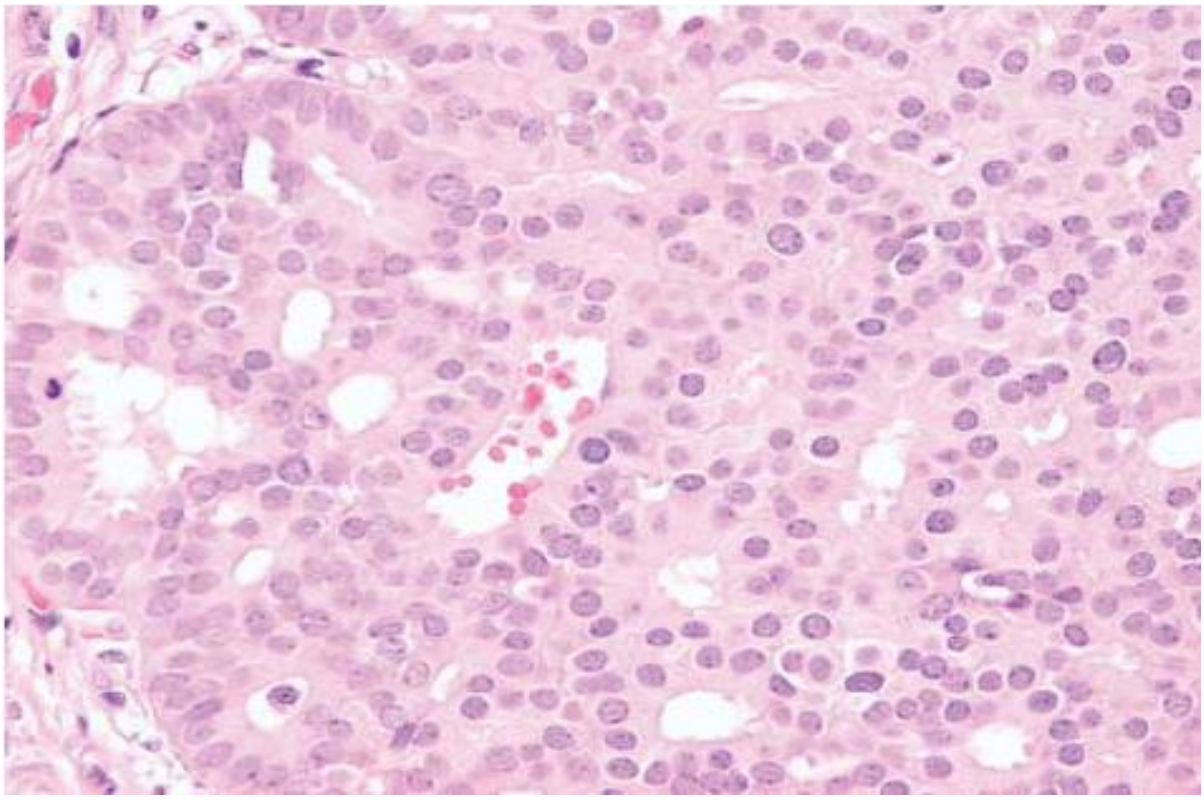

Figure 1: Cribriform architecture of low-grade DCIS. Mild pleomorphism can be distinguished by small nuclei (diameter about 1.5–2 erythrocytes), some of which have prominent nucleoli|("Low-Grade Ductal Carcinoma in Situ (DCIS) of Cribriform Architecture.... | Download Scientific Diagram," n.d.).

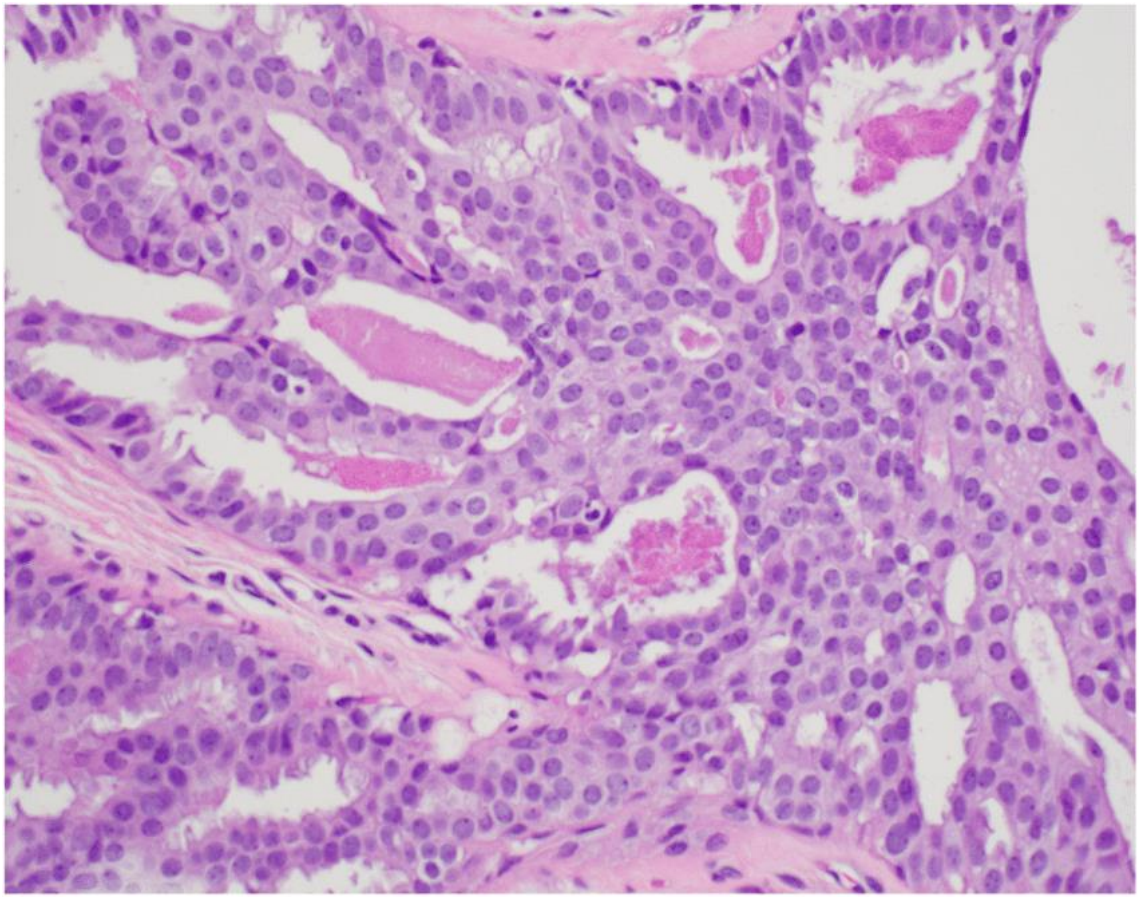

Figure 2: Intermediate-stage DCIS exhibiting mild - to - moderate pleomorphism and localized necrosis (40x) ("Ductal Carcinoma in Situ, Intermediate Grade with Mild to Moderate... | Download Scientific Diagram," n.d.).

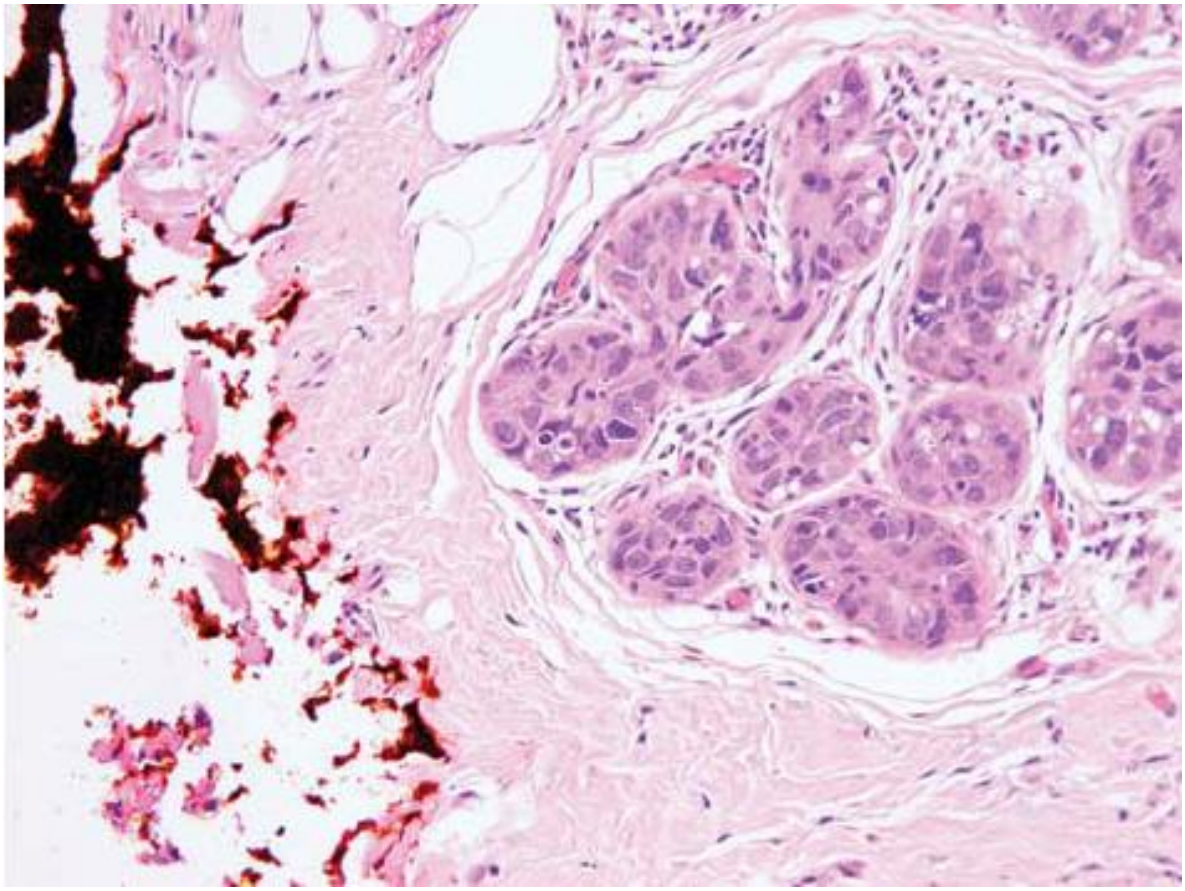

Figure 3: Cancerization of lobules below 1 mm from lateral border of the large local excision specimen above demonstrates high-grade DCIS (seen as the orange ink) ("High-Grade Ductal Carcinoma in Situ (DCIS) Seen as Cancerization of... | Download Scientific Diagram," n.d.).

Chapter 4

Post Operative Hormonal Therapies for DCIS

4.1 Need for Post Operative Hormonal Therapy

Adjuvant systemic therapy might be used following definitive surgical management to lower the local and distant recurrence risk. Adjuvant endocrine therapy with a selective estrogen-receptor modulator (SERM) like tamoxifen (Nolvadex), aromatase inhibitor like anastrozole (Arimidex), letrozole (Femara), or exemestane (Aromasin) is advised for at least 5 years upon local treatment of hormonal receptor–positive breast cancer, either having or not having chemotherapy. The endocrine therapy drugs are often chosen depending on menopausal status as well as side-effect profiles. For premenopausal women, aromatase inhibitors must be used with ovarian suppression. Adjuvant endocrine therapy is linked to a 50% decrease of breast cancer recurrence. Multigene assays like OncotypeDx or Mammaprint that are available commercially have showed efficacy in identifying prognostic and predictive benefits among both hormonal therapy and chemotherapy for breast cancer. The TAILORx trial's findings support the regular usage of multigene assays to identify patients with intermediate risk scores who can safely avoid chemotherapy (“Breast Cancer - an Overview | ScienceDirect Topics,” n.d.). Hormonal therapy is required for all hormonereceptor-positive breast cancer patients. It works for both adjuvant and metastatic cancers. Tamoxifen is the sole adjuvant hormone therapy that is active in both pre-menopause as well as post-menopause. The length of adjuvant treatment has an impact on disease-free survival, the likelihood of developing a contralateral breast cancer, and survival in general. Anastrozol, Letrozol, and Exemestan are aromatase inhibitors that are exclusively used post-menopause. Fulvestrant is used to treat recurrent disease either after or during Tamoxifen treatment (“Hormone Therapy in Breast Cancer,” n.d.).

4.2 Tamoxifen

Tamoxifen is a hormonal therapy for treating breast cancer that is estrogen receptor (ER) positive. It acts by binding to ER positive breast cancer. Tamoxifen as well as its metabolites like 4-hydroxyTamoxifen and endoxifen attach to nuclear estrogen receptors within estrogen-sensitive tissues, preventing estrogen to bind with its receptor. But there are reported side effects and although these side effects are uncommon, tamoxifen has been proven to raise risks of stroke, endometrial cancer, as well as venous thromboembolic events (Staley, McCallum, & Bruce, 2014).

Tamoxifen's role as an adjuvant therapy for invasive breast cancer is quite well established: following mastectomy, 5 years of adjuvant treatment reduces mortality rate, ipsilateral recurrence, as well as contralateral carcinoma among women who have cancers that are either ER positive or which have ER status that is uncertain. At surgery, individuals having node-positive disease at surgery have the most survival benefit, where absolute mortality reductions are 10.9 percent (SD 2.5) after 10 years in node-positive and 5.6 percent (SD 1.3) for node-negative disease (Staley et al., 2014).

In a fraction of DCIS tumors, cells express same estrogen receptors. Nearly half of the local recurrences be invasive instead of recurring DCIS, with low-grade DCIS retrospective studies showing that about 33 percent patients would have an invasive recurrence even after 2 decades of follow-up. One study looked at DCIS recurrences and found that 63 percent of them had the same histology and marker expression. This could point to a progressive, stepwise model of carcinogenesis, and as anti-cancer treatments are able to stop the process, adjuvant therapy in 'pre-malignant' phase is justified (Staley et al., 2014).

In a 2014 study, data had been extracted from randomized controlled trials (RCTs) on local DCIS recurrence, new invasive carcinoma, distant disease, mortality, as well as adverse

effects, comparing Tamoxifen with or without adjuvant radiotherapy post DCIS surgery, irrespective of the ER status. These results had been presented as relative risks (RRs) and also hazard ratios (HRs), having 95 percent confidence intervals (CIs) after performing meta-analysis by using fixed-effect model. The study included two RCTs with a total of 3375 women. Tamoxifen following DCIS surgery decreased ipsilateral (HR 0.75; 95 percent CI 0.61-0.92) as well as contralateral DCIS recurrence (RR 0.50; 95 percent CI 0.28-0.87). There was a decrease in contralateral invasive cancer (RR 0.57; 95 percent CI 0.39-0.83), with ipsilateral invasive cancer also on the decline (HR 0.79; 95 percent CI 0.62-1.01). 15 people needed to be treated with Tamoxifen for it to present protective effect against every breast event. In terms of all-cause mortality, there was no evidence of change (RR 1.11; 95% CI 0.89-1.39). Only one of the trials with 1799 patients which was conducted for a period over 163 months (median) had reported upon adverse events, without any significant event-rate difference between the Tamoxifen groups and placebo groups, however an insignificant trend toward higher endometrial cancer within Tamoxifen group occurred. Even though Tamoxifen following DCIS local excision, accompanied by adjuvant radiotherapy or not, lowered risks of recurrent DCIS, it caused no decrease in the all-cause mortality risk, according to this study (Staley et al., 2014).

4.3 Aromatase Inhibitors

Aromatase enzyme complex's cytochrome p-450 component, which is responsible for estrogen production's final step, is blocked by anti-aromatase agents. They can be divided into three groups: the first-generation drugs contain aminoglutethimide, the second-generation drugs contain formestane and fadrazole, and lastly, the third-generation drugs contain anastrozole, letrozole, and also exemestane. On the other hand, anti-aromatase agents also can be put into two groups: type I, as well as type II inhibitors. Aromatase inactivators contain a steroidal

structure that is like androgens and can irreversibly inactivate enzyme through blocking the substrate-binding site. Nonsteroidal Type II inhibitors have reversible action (Mokbel, 2002).

In the MA17 study, only one DCIS incident was there in contralateral breast of patients who were using letrozole against five being treated with placebo, which randomized participants to letrozole or placebo for up to 5 years. In this study, four patients on placebo experienced DCIS in conserved breast, but no one did in letrozole-treated group. As a result, we can see from the available clinical data showing aromatase inhibitors to likely seem effective among DCIS. A 14-day preoperative study was conducted with 206 invasive ER-positive women who were menopausal and had been randomly assigned for receiving 2.5mg letrozole or 1mg anastrozole. A histological review regarding this study found 27 patients who had 28 pairs of tumors. There was adequate ER positive DCIS in invasive carcinoma among them in initial core biopsy as well as subsequent surgery specimen for evaluating PgR activity plus proliferation. PgR expression was considerably decreased by both of the aromatase inhibitors in DCIS, and both of the medications greatly reduced proliferation. The decline in PgR in both invasive cancer and DCIS (Kappa=0.5; p=0.0013) and the decline in proliferation and both invasive and also in situ components were moderately correlated (correlation coefficient=0.68; $p<0.001$). According to this study, aromatase inhibitors were found to have a significant effect on DCIS, indicating that they are therapeutically effective in this condition (Dixon et al., 2007).

4.4 Tamoxifen As The Choice Of Therapy

DCIS is currently responsible for 20-30 percent of the new cases of breast cancer diagnoses, due to screening mammography's extensive use. Ipsilateral breast recurrence occurs in approximately 15 percent of women despite a combination of lumpectomy with radiation therapy for treatment, with invasive disease being harbored in half the recurrences. In addition, women receiving DCIS treatment had a chance of 6 percent to develop contralateral breast

cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 research, on randomizing over 1,800 women for a period of 5 years, who received breast-sparing operation as well as radiation for DCIS to adjuvant tamoxifen against placebo, was inspired by discovery which is adjuvant tamoxifen decreases local, regional, as well as distant diseases among women who were diagnosed having invasive breast cancer. After following up for 7 years, women using tamoxifen had a statistically significant 27 percent lower yearly incidence rate of all events that were related to breast cancer, including a 48 percent lower incidence rate of invasive breast cancer. Tamoxifen's benefit was limited to cancers that were ER-positive. In older women, however, adverse outcomes such as endometrial cancers, thromboembolic events, as well as cataracts occur more usually. Tamoxifen should therefore be explored as a supplement to treatment for women undergoing having breast-conserving surgery with DCIS that was ER-positive (Daly, 2006).

Over the course of its 40-year development, tamoxifen has become the most researched anticancer drug. The drug's success has been quantified so far as being an adjuvant therapy: long-term treatment with tamoxifen has saved 400 000 women’s lives having breast cancer. Most notably, tamoxifen development showed that specifically targeting the estrogen receptor provided a benefit to patients. As a result, the pharmaceutical industry in order to find medications that are more effective and safer, has increased its investment in research. This can be demonstrated with comparing the 1970 treatment options of advanced breast cancer, which was before tamoxifen was introduced (Figure 4) to 2005 treatment options for all breast cancer stages (Figure 5) (Jordan, 2007).

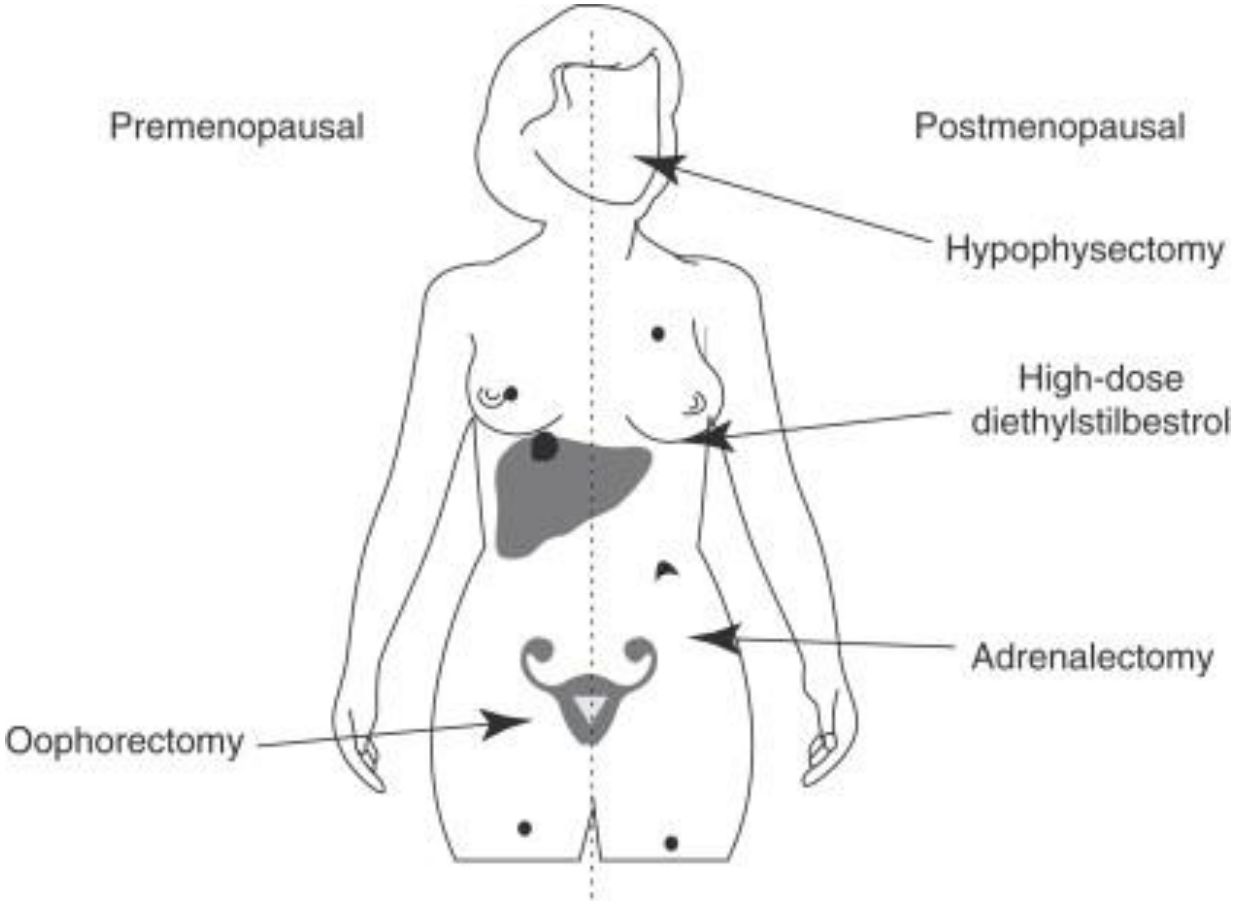

Figure 4: In the early 1970s, endocrine options for patients suffering from metastatic breast cancer were limited. Ablative surgery involves removing endocrine organs that release estrogenic hormones or precursors of them. Standard therapy for postmenopausal women included adding high doses of estrogens, androgens, or progestins (Jordan, 2007).

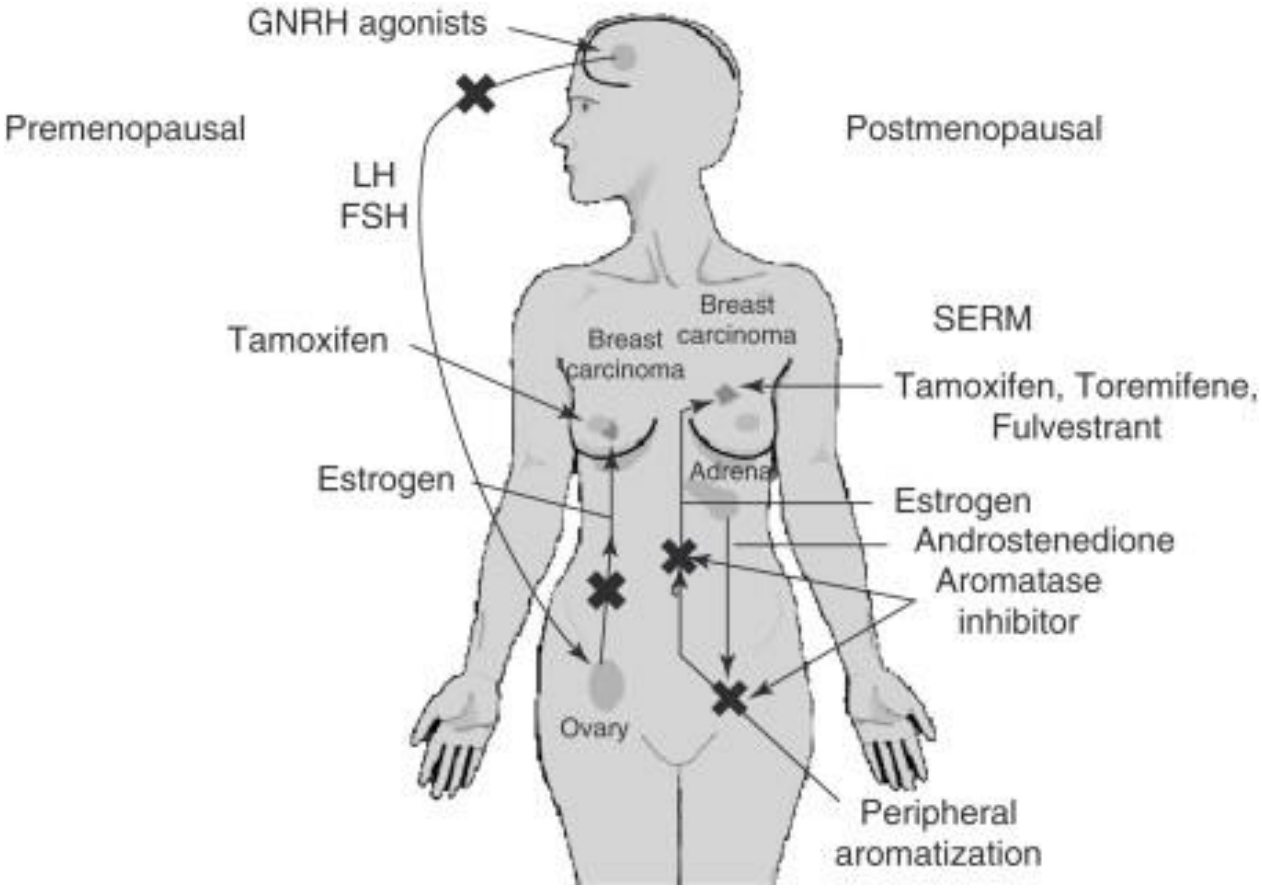

Figure 5: The current treatment options for preventing estrogen exposure as well as action in breast tumors. In all circumstances, ultimate goal is to prevent tumor cells from forming the estrogen–estrogen receptor complex. FSH stands for follicle-stimulating hormone (Jordan, 2007)

The therapeutic success of tamoxifen prompted a significant re-evaluation of aromatase enzyme-system inhibitors. To put it another way, prevent estrogens synthesis from androgen precursors. Early non - specific inhibitors, like aminoglutethimide, had a lot of side effects, particularly because they had to be co-administered with a glucocorticoid. During the 1970s, aminoglutethimide went out of fashion because preferred endocrine treatment of breast cancer was tamoxifen (Jordan, 2007).

Surprisingly, some researchers and clinicians believe tamoxifen will be continuing to play a role in the treatment of certain patients, and that will surely be a valuable treatment option among underdeveloped nations which are unable to afford costly treatments like with

aromatase inhibitors. It is also reasonable to argue that if tamoxifen research had not been pursued, pure antiestrogen fulvestrant would not be found during the early 1980s at ICI Pharmaceuticals Division. Tamoxifen is a pioneering but not perfect medicine, so it makes sense that work on other ways to treat breast cancer that target the estrogen receptor should have started in the 1980s in order to take advantage of tamoxifen's expanding clinical market. Example of skilled industry scientists' drug discovery can be seen by accidental discovery of pure antiestrogens, who discovered a new drug class, estrogen receptor down regulators, that are not only beneficial in clinic but also provide fresh insight on cancer cell regulatory processes. (Jordan, 2007)

Tamoxifen was the first SERM, and raloxifene, formerly a failed breast cancer medicine named keoxifene, would not be reinvented as a therapeutic as well as preventive for osteoporosis including breast and endometrial safety with no developing pharmaceutical database throughout the 1980s (Jordan, 2007).

The discovery of SERM activity in tamoxifen has paved the way for finding selective activity in all members of those in steroid hormone receptor superfamily. An enormous effort is being made in finding agonists and antagonists for receptors that are androgen, progesterone, glucocorticoid, thyroid hormone, as well as peroxisome proliferator-activated receptor, also known as PPAR (Jordan, 2007). The influence of tamoxifen upon healthcare, drug discovery, as well as cancer cell biology has been overwhelmingly positive, but the process has taken more than 40 years. (Jordan, 2007).

Tamoxifen is the most commonly recommended endocrine medication for breast cancer, having been used by over 7.5 million women in clinical trials. Tamoxifen possesses antiestrogenic as well as estrogenic activities. The antiestrogenic activity is believed to be responsible for its ability to prevent breast cancer, whereas the estrogenic activity is linked to improved bone mineral density and lipid profiles, as well as have a proliferative effect

on endometrium in certain women. Tamoxifen has a high tolerability profile and has shown to improve the overall as well as disease-free survival in breast cancer patients while also lowering contralateral breast cancer risk.

Endometrial cancer and its related illnesses are few of the only side effects associated with Tamoxifen. In breast cancer patients who has been treated with tamoxifen, the proven advantages that comes with tamoxifen vastly outweigh risks of endometrial cancer ("Risks and Benefits of Tamoxifen Therapy - PubMed," n.d.).

Chapter 5

Future Prospects

5.1 Future Prospects

Even though for patients having ER-positive breast cancer tamoxifen therapy is undeniably helpful, about one in three of these patients will either be unresponsive to the tamoxifen or end up developing resistance towards the drug. As a result, identifying novel, reliable, and also easily detectable biomarkers that indicate drug resistance is essential. A study involving 224 breast cancer patients, who were ER-positive, was conducted to investigate SOX2 and AGR2 biomarker expression in their tumor tissues, as well as the amount of AGR2 in their serum, for verifying those biomarkers as tamoxifen resistance's initial predictors. All patients primarily had their serum AGR2 levels measured by ELISA, having their breast cancer tissue be immunostained for SOX2 as well as AGR2. The patients were separated into three groups after 5 years of follow-up: group 1 had been sensitive to tamoxifen, while group 2 and group 3 had been resistance to tamoxifen. Groups 2 and 3 had significantly higher SOX2 and AGR2 biomarker expression plus serum AGR2 levels compared to group 1, however the link among Her2 neu expression as well as Ki67 index in all of the three groups were statistically insignificant. Decreased SOX2 and AGR2 expression, as well as lower AGR2 serum levels, were found to be related with a longer time to failure of tamoxifen therapy in the group 2 and group 3. The combined use of the examined markers had a validity with 100 percent sensitivity, 96 percent specificity, 96 percent PPV, and 100 percent NPV ($p < 0.001$; AUC: 0.984), as per the ROC curve. As a result, the combination of SOX2 and AGR2 biomarkers with a serum AGR2 assay shows promise for their future application among ER-positive breast cancer patients as predictive markers for early diagnosis of resistance towards tamoxifen (Zamzam, Abdelmonem Zamzam, Aboalsoud, & Harras, 2021).

5.2 Conclusion

Although breast cancer patients who are ER-positive find tamoxifen undeniably helpful, it has its own disadvantages and side effects. Even so it took a long time to achieve its expected benefits, tamoxifen's impact on drug research, healthcare as well as cancer cell related biology became largely favorable. With scopes of further research in this field, there is not only benefit of cure but also the combination between SOX2 and AGR2 biomarkers, as well as a serum AGR2 assay, offers promise for future application being predictive indicators for detecting tamoxifen’s resistance early in ER-positive cancers.

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