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Testosterone for the Treatment of Mammary and Prostate Cancers: Historical Perspectives and New Directions

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1. Introduction

After lung cancer, breast cancer and prostate cancer are the two most common forms of cancer. Approximately 209,060 women were thought to have been diagnosed with breast cancer in the US in 2010, and 217,730 men with prostate cancer (National Cancer Institute, 2007). Furthermore, a total of 39,840 women and 32,050 men were expected to have died of breast or prostate cancer during this year (National Cancer Institute, 2007).

It has been known for some time that the sex hormones, estrogen and testosterone, play a major role in the etiology of breast and prostate cancer (Bonkhoff & Berges, 2009; Carruba, 2007; Dimitrakakis & Bondy, 2009; Folkerd & Dowsett, 2010; Ho, 2004; Mcleod, 2003; Meyer, 1955; Suzuki et al., 2010). However, determining their precise impact in these cancers has proved controversial, and theories of their involvement have been repeatedly revised with the emergence of new scientific evidence (Drewa & Chlosta, 2010; Jensen et al., 2010; Margo & Winn, 2006; Morgentaler, 2006). Because causation has often been assumed where in fact mere association exists, ineffective treatment strategies have frequently been adopted while potentially successful avenues have been neglected.

A key insight that was missing for many years was that testosterone and estrogen can be considered as two sides of a see-saw. In other words, manipulation of one has a direct effect upon the other (Ellem & Risbridger, 2010). This connection was realized with the discovery of aromatization (Santen et al., 2009), but unfortunately did not lead to the necessary re-examination of previous findings in the treatment of hormone-related cancers.

Despite enormous clinical and research efforts, hormonal treatments for advanced breast cancer and prostate cancer have not resulted in significant prolongation of survival over the last few decades. A comprehensive reassessment of prevailing hormonal treatment strategies and the scientific logic behind them is therefore long overdue.

The following chapter examines the role of testosterone and estrogen in breast and prostate cancer from an historical perspective, and suggests that a revised approach of combined therapies targeting multiple pathways in the hormonal cascade is required in order to lead to the meaningful hormonal manipulation of these cancers.

2. Estrogen and testosterone: a biological balancing act

Although people have been aware of the sex hormones since ancient times (Freeman et al., 2001), estrogen and testosterone were only isolated and fully characterized in the 1920s and

1930s. The structure of estrogen was the first to be determined when Adolf Butenandt and Edward Adelbert Doisy independently identified the chemical configuration in 1929 (Tata, 2005). Isolation of testosterone quickly followed in 1935 (David et al., 1935), and this was characterized and named once again by Butenandt (Butenandt & Hanisch, 1935).

New organic synthetic methods emerging during and after the 1930s created ready access to testosterone and estrogen and their derivatives, allowing a period of prolific research into the sex hormones in what has been termed 'The Golden Age of Steroid Chemistry' from the 1930s until the 1950s (Schwarz et al., 1999).

The studies conducted during this time began to reveal similarities between the androgens and estrogens, and it was speculated that it might be possible to convert the C19 androgens directly into C18 estrogens (Santen et al., 2009). Indeed, in 1934, the German-Jewish gynecologist Bernhard Zondek demonstrated remarkable early insight when he stated, '*the female hormone which is regularly present in the male organism represents a normal physiological product of the metabolism of the sex hormones, especially since – due to our present chemical knowledge – a conversion of the male hormone into the female one appears to be quite possible*' (Zondek et al., 1934). This speculation was further supported when the Austrian endocrinology pioneer Steinach and his colleague Kun showed enhanced estrogenic activity in the urine of men administered testosterone propionate (Steinach & Kun, 1937).

The crucial biochemical step in the conversion of testosterone to estradiol, the major estrogen present in humans, is the formation of an aromatic ring from the only unsaturated ring of testosterone (ring 'A', Figure 1). This process is known as 'aromatization'.

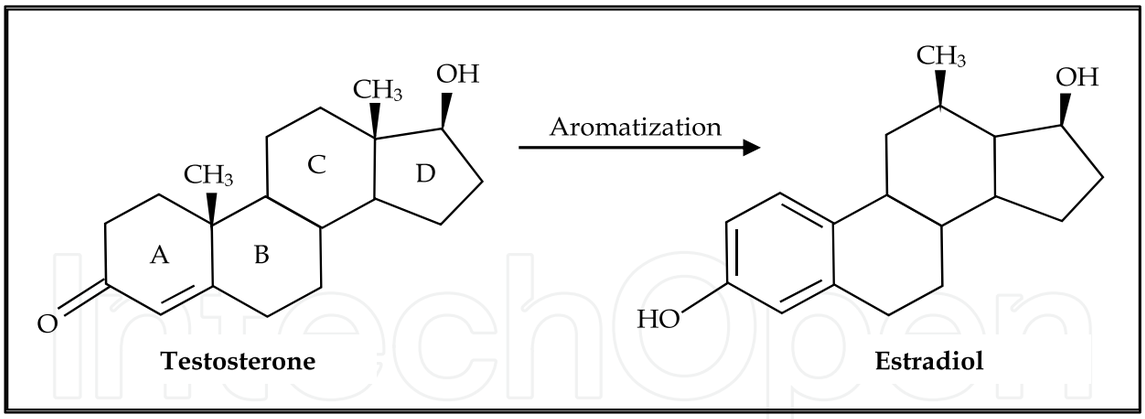

Fig. 1. Aromatization of testosterone to estradiol.

In 1955, a Swiss chemist named Meyer achieved this aromatization using bovine adrenal extracts (Meyer, 1955; Meyer et al., 1955). He recognized that this transformation was likely to be enzyme catalyzed, but the specific enzyme involved was not purified until the 1980s. The enzyme responsible for the aromatization of testosterone was ultimately found to be a member of the P450 cytochrome family of enzymes, and was named aromatase. Eventually, the full mechanism for the conversion of testosterone to estradiol was established (Figure 2).

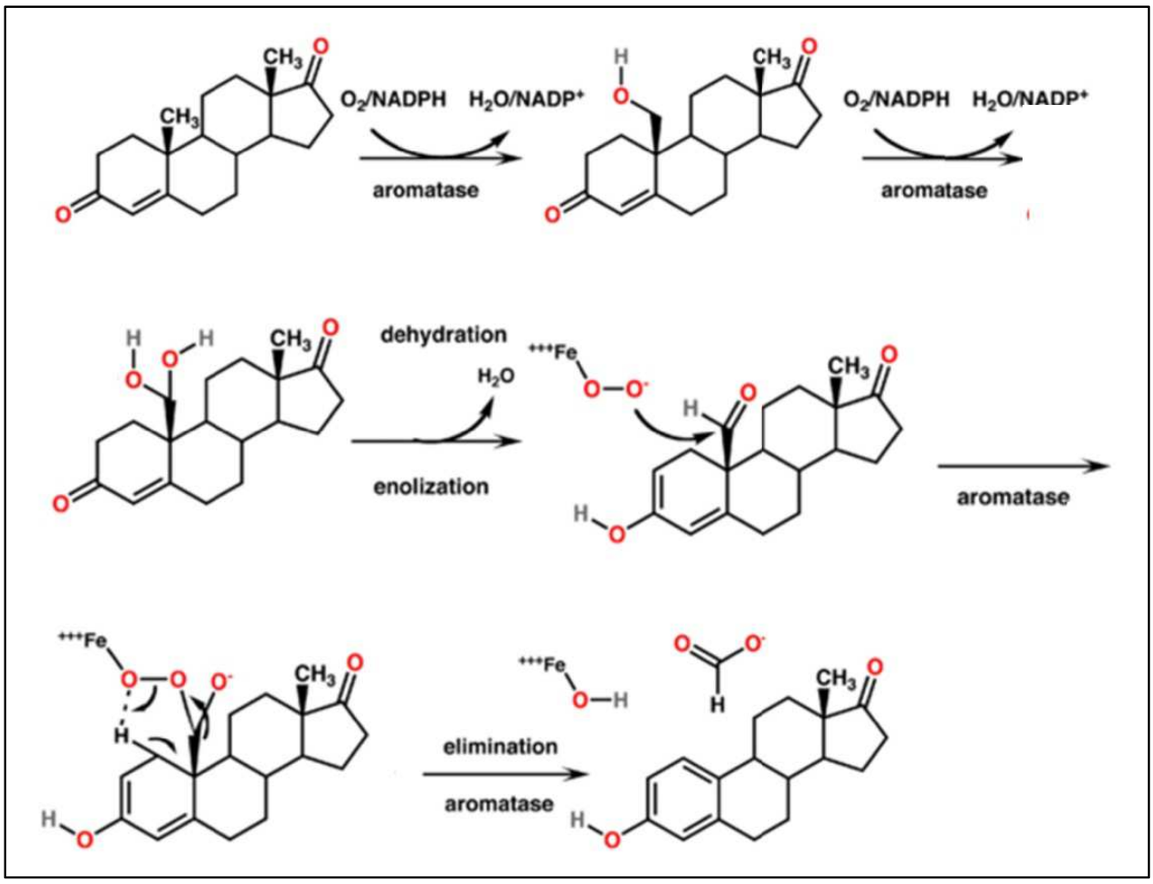

Fig. 2. Mechanism of action of aromatase in the conversion of testosterone to estradiol.

3. Hormonal manipulation in breast and prostate cancer: the controversy begins

3.1 Breast cancer

The first link between estrogen and breast cancer was observed in the late 1890s by a Scottish surgeon by the name of George Beatson (Mukherjee, 2011). Beatson had noticed that removal of the ovaries altered the capacity of cows to lactate, establishing for the first time a connection between breast and ovary. From this, he made the leap to speculate that removal of the ovaries in women with breast cancer may prove therapeutic. He successfully demonstrated the benefit of this intervention in a small group of his breast cancer patients when the tumors of three of his patients shrank dramatically following ovary removal (Beatson, 1896). Butenandt and Doisy's discovery of estrogen was still decades away and Beatson had no understanding of any mechanism for this effect. However, Beatson was convinced he had found a route to control breast cancer. When Beatson's experiments were repeated by others, around two thirds of breast cancer patients were found to benefit (Mukherjee, 2011). This was an important observation, the relevance of which would not become apparent for many years.

Despite its apparent success, removal of the ovaries was not considered a practical or viable treatment for breast cancer as it caused many side effects, including osteoporosis. The

alternative was to suppress estrogen pharmacologically, and it was found that this could be achieved by administering testosterone (Mukherjee, 2011). Testosterone soon became an important and effective treatment for breast cancer, and was used extensively between the 1930s and 1960s (Fels, 1944; Goldenberg, 1964; Segaloff et al., 1951, 1964). However, when raised blood and urine levels of testosterone were found in breast cancer patients, testosterone was assumed to be the cause and not a simple associated factor, and successful testosterone therapy was abandoned (Malarkey et al., 1977; Secreto et al., 1983). Subsequent discovery of the confusion between total and free testosterone levels came too late redress the error (Vitola & Zeĭkate, 1976).

In 1968, an American chemist named Elwood Jensen made an important discovery when he identified the estrogen receptor (ER) in the breast, and began to look for the same receptor in breast cancer cells. He found that some breast cancers expressed high levels of the estrogen receptor (ER-positive tumors), while others expressed low levels (ER-negative tumors) (Mukherjee, 2011). This finally provided an explanation for why only a proportion of the early breast cancer patients investigated around 70 years earlier had responded to complete ovary removal. Only ER-positive tumors responded to the resulting estrogen deprivation.

Following this discovery, efforts were directed towards strategies to block the estrogen receptor in breast cancer. The first nonsteroidal antiestrogen developed, MER-25, was only weakly active in large doses and caused severe central nervous system side effects (Gajdos & Jordan, 2002). However, an alternative was soon found, although through an indirect route. Tamoxifen (Figure 3) was originally developed in an attempt to create an estrogen stimulator which would be effective as a female contraceptive drug. However, tamoxifen was very quickly shown to induce ovulation in women instead, acting as a fertility agent rather than a contraceptive (Klopper & Hall, 1971). Instead of stimulating estrogen, tamoxifen was acting as an estrogen antagonist, turning off the estrogen signal in many tissues. As an estrogen antagonist was thought to have no possible clinical benefit, clinical development of tamoxifen was very nearly abandoned.

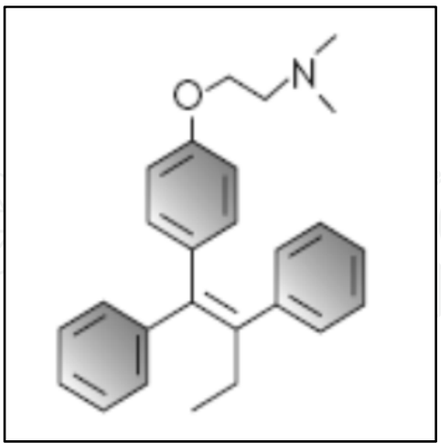

Fig. 3. Chemical structure of tamoxifen.

However, one chemist at ICI where tamoxifen had first been synthesized saw a possible connection between fertility drugs and cancer. Arthur Walpole had been intimately involved in the development of tamoxifen and knew of previous experiments of the sex hormones in prostate and breast cancer. Walpole wondered whether an estrogen antagonist

could have a role in ER-positive breast cancer (Furr & Jordan, 1984). Unlike MER-25, tamoxifen is a selective estrogen receptor modulator (SERM), which means it is a partial antagonist effective in only a number of sites, and has relatively low toxicity (Cole et al., 1971; Furr & Jordan, 1984). Tamoxifen therefore appeared to have the attributes of a potential chemotherapeutic candidate for breast cancer.

In collaboration with an oncologist from Manchester, a clinical trial of tamoxifen in 46 women with breast cancer was quickly designed. The results were astonishing. An almost immediate response was observed in ten patients in the trial, with tumors visibly shrinking in the breast, reductions in lung metastases, and a dramatic reduction in bone pain.

Tamoxifen was quickly discovered to improve survival of ER-positive breast cancer patients (Early Breast Cancer Trialists' Collaborative Group, 1998) and soon became a standard adjunctive therapy (Lerner & Jordan, 1990). Tamoxifen held the dominant position for treatment of ER-positive breast cancer for nearly three decades, although numerous other SERMs were also developed (Gajdos & Jordan, 2002). The reduction in the number of deaths from breast cancer in the Western world over recent decades can largely be attributed to tamoxifen therapy (Gajdos & Jordan, 2002; Gradishar, 2010; Hackshaw et al., 2011).

For many years, tamoxifen was considered to act exclusively through its anti-estrogen activity. However, recent evidence has emerged to suggest that its benefit in breast cancer may be due to the up-regulation of androgen receptors (Labrie et al., 2003; Somboonporn & Davis, 2004; Wierman et al., 2006; Zhou et al., 2000). Thus tamoxifen therapy represents an indirect return to the testosterone therapy which was abandoned during the 1950s.

To complete the circle, a review of studies of androgen therapy has recently suggested testosterone itself has a protective effect against breast cancer (Dimitrakakis & Bondy, 2009), while the role of estrogen in the development of breast cancer is now firmly established (Ekmektzoglou et al., 2009; Rana et al., 2010; Sonne-Hansen & Lykkesfeldt, 2005; Thijssen & Blankenstein, 1989).

3.2 Prostate cancer

Just as female hormones were known to control the growth of breast tissue, so it was speculated around the same time that the androgens were responsible for the control of prostate growth. In the 1920s and 1930s, experiments conducted by the urologist Charles Huggins working at the University of Chicago showed that surgical removal of dog testicles led to a dramatic reduction in prostate size, an effect that could be ameliorated by injecting purified exogenous testosterone (Mukherjee, 2011). Soon, Huggins and his colleague, Hodges, published a paper reporting that reducing testosterone levels through castration or estrogen therapy achieved regression of metastatic prostate cancer, while administration of exogenous testosterone resulted in growth of prostate cancer (Huggins & Hodges, 1941). This paper marked the beginning of the long association of testosterone with increased prostate cancer risk and progression, establishing the enduring perception of testosterone as ‘food for a hungry cancer’ (Morgentaler, 2006). From this time onwards, the presence of prostate cancer, or any prior history of prostate cancer, became an absolute contraindication for use of testosterone therapy.

In an attempt to achieve medical, rather than surgical, castration, estrogens began to be routinely administered to prostate cancer patients in an attempt to halt the production of testosterone. The first results with diethylstilbestrol (DES), a xenoestrogen, appeared extremely encouraging. Patients with aggressive prostate cancer treated with estrogen derivatives responded rapidly and markedly (Mukherjee, 2011).

Estrogen therapy was soon hailed as the salvation for prostate cancer. The reduced side effects achieved were considered particularly important as the current pharmaceutical model of cancer management involved increasingly aggressive cytotoxic drugs which took patients to the very limits of their tolerance. Although patients frequently relapsed, remission could often be achieved for several months. It seemed that prostate cancer would finally be beaten by hormonal manipulation through estrogen therapy.

Over time, new methods for restricting testosterone levels became common place, notably novel phytoestrogens (Castle & Thrasher, 2002; Morrissey & Watson, 2003) and synthetic estrogens (Kim et al., 2002). Yet decades of estrogen-based therapies and testosterone deprivation have failed to make a significant impact on survival and have resulted in significant toxicities.

Despite numerous studies investigating the proposed link between testosterone and prostate cancer, no direct correlation has in fact been found (Jannini et al., 2011; Morgentaler, 2006). Equally, low testosterone levels have not conclusively been linked with the absence of prostate cancer (Jannini et al., 2011; Morgentaler, 2006). For example, prostate biopsies in a study of hypogonadal men revealed prostate cancer in 14.3% of men (Morgentaler et al., 1996), comparable with the 15.2% found in the placebo arm of the Prostate Cancer Prevention Trial (Thompson et al., 2004). Of even greater concern, neither prostate specific antigen (PSA), prostate volume, nor cancer progression has been found to increase with increasing testosterone levels in men with untreated prostate cancer (Morgentaler et al., 2011). Interestingly, evidence is even emerging to show that patients with a lower serum testosterone level may have a higher risk of prostate cancer than patients with high serum testosterone (Shin et al., 2010).

Recent scrutiny of the seminal work conducted by Huggins and Hodges has revealed some fundamental flaws and methodological failings (Morgentaler, 2006). Perhaps the most damning criticism of the causative link between testosterone and prostate cancer comes from the observation that prostate cancer rates are lowest during the late teens and early 20s when testosterone levels are highest, and highest in old age when testosterone levels are at their lowest (Figure 4). If testosterone truly was a cause of prostate cancer, the reverse relationship would be expected.

Not only does it appear that testosterone should be exonerated from its role in causing prostate cancer, but evidence is emerging to suggest that it may actually be beneficial in managing the condition (Gardiner et al., 2009; Dorff & Vogelzang, 2011; Algarté-Génin et al., 2004). For example, two preliminary phase I studies have shown that high-dose exogenous testosterone therapy can safely be administered in patients with castrate-resistant metastatic prostate cancer (Szmulewitz et al., 2009; Morris et al., 2009). Some response in terms of PSA reduction was noted in these trials, but neither study was designed to investigate efficacy of this regimen. A larger, randomized trial is under way to further characterize efficacy and impact on quality of life measures more fully.

To complete the absolute reversal of the conventional dogma regarding the role of estrogen and testosterone in prostate cancer, there is also now considerable evidence to suggest that estrogens, once used to treat prostate cancer, actually contribute to the genesis of the disease (Bonkhoff & Berges, 2009; Carruba, 2007; Jensen et al., 2010; Prins & Korach, 2008; M Singh et al., 2008; P Singh et al., 2008; Wibowo et al., 2011)

In summary, after decades of research and contradictory claims it now seems that, contrary to the received wisdom, estrogen is a causative factor in breast and prostate cancer while

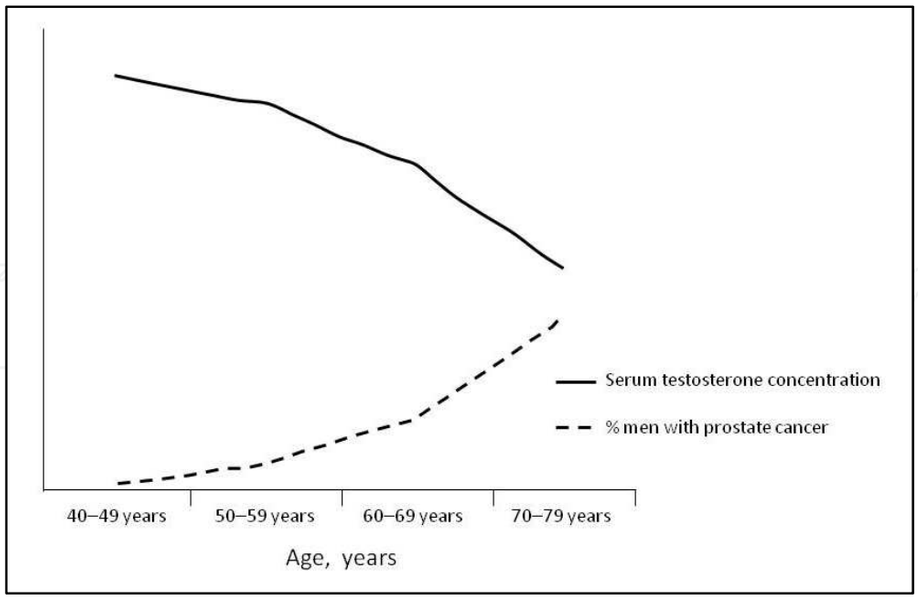

Fig. 4. Prostate cancer prevalence and testosterone levels with ageing. pCA: prostate cancer, T: testosterone. Reproduced from Morgentaler, 2006 with permission.

	Prostate cancer	**Breast cancer**
Estrogen	Causative	Causative
Testosterone	Protective	Protective

Table 1. Current understanding of the relationship between estrogen/testosterone and prostate/breast cancer.

testosterone actually offers protection against the conditions (Table 1). The concept of aromatization is the key to understanding the conflicting findings.

3.3 The importance of aromatization

From the earliest studies of the sex hormones, it was widely believed that estrogen was only formed in the ovaries and testosterone in the testes. However, research conducted during the 1970s demonstrated that aromatase was abundant in the adipose tissue of both men and women, demonstrating that the peripheral tissue is the major source of estrogen synthesis in men and postmenopausal women (Grodin et al., 1973; MacDonald et al., 1967; Santen et al., 2009).

The close connection between estrogen and testosterone in both men and women presented the possibility of fine-tuning the balance of the two hormones in the body. Scientists began to recognize the therapeutic potential of targeting aromatase to control the biosynthesis of estrogen, and started to develop selective aromatase inhibitors for therapeutic purposes (Barone et al., 1979; Santen et al., 2009; Thompson & Siiteri 1973, 1974).

Research conducted over recent years suggests that aromatase expression and activity in the breast and prostate may be up-regulated at the tumour site, resulting in an altered local hormonal environment and an increased estrogen/testosterone ratio (Ellem & Risbridger,

2010). This is thought to lead to proliferation of the tumor cells in both breast and prostate cancer through a positive feedback loop, established via paracrine and autocrine mechanisms leading to the continuing growth and development of the tumors (Simpson et al., 1997). Further research has suggested that estrogens are capable of inducing prostatic inflammation (Bianco et al., 2006), and this is likely to establish a cycle of increased aromatase, local estrogen activity and subsequently greater inflammation.

Development of inhibitors of the aromatase enzyme therefore represents a logical strategy for the management of hormonally-derived tumors. Aromatase inhibitors are currently used with great effect in the endocrine therapy of ER-positive breast cancer in postmenopausal women to counteract the local estrogens produced in the tumor and surrounding tissue which act as a stimulant for growth (Eisen et al., 2008; Ghosh et al., 2009). Their potential in male breast cancer is also being investigated and shows early promise (Doyen et al., 2010).

Aromatase inhibitors have advanced considerably since the first generation of agents was developed (Table 2). Third-generation aromatase inhibitors now used routinely (Bhatnagar, 2007).

Type	Generic	Dose	Selected brand names
First generation (non-selective)	Aminoglutethimide	250 mg	Cytadren®, Orimeten®
	Testolactone	50 mg	Fudestrin®, Teslac®
Second generation (selective)	Formestane	250 mg	Lentaron®
	Fadrozole	1 mg	Afema®
Third generation (selective)	Exemestane	25 mg	Aromasin®
	Anastrozole	1 mg	Arimidex®
	Letrozole	2.5 mg	Femara®
	Vorozole	2.5 mg	Rivizor®

Table 2. Aromatase inhibitors.

4. Applying current knowledge in future directions

After more than a century of research and controversy surrounding the hormonal treatment of breast and prostate cancer, some conclusions can finally be drawn. First, excessive estrogen levels can be implicated in both breast and prostate cancer, while testosterone appears to offer a protective effect. Second, aromatase inhibitors reduce the conversion of testosterone to estrogen, thus lowering levels of estrogen and increasing testosterone activity. Third, the SERM tamoxifen blocks estrogen activity and both directly and indirectly increases testosterone activity by up-regulating androgen receptors.

In view of these findings, the most rational approach to treatment of breast and prostate cancer would be to administer a combination of three drugs – tamoxifen, an aromatase inhibitor and testosterone. The combination of these three drugs would allow patients to greatly benefit from their synergistic effects in maintaining a desirable hormonal balance in the following way:

1. **Aromatase inhibitor** would allow both endogenous and exogenous testosterone levels to be maintained and estrogen levels to be reduced;

2. **Tamoxifen** would allow upregulation of androgen receptors and downregulation of estrogen receptors, thereby both increasing testosterone's action and ensuring further suppression of estrogen activity;
3. **Exogenous testosterone** in the presence of the aromatase inhibitor would allow increased testosterone levels whilst halting its aromatization to estrogen.

These effects are summarized in Figure 5.

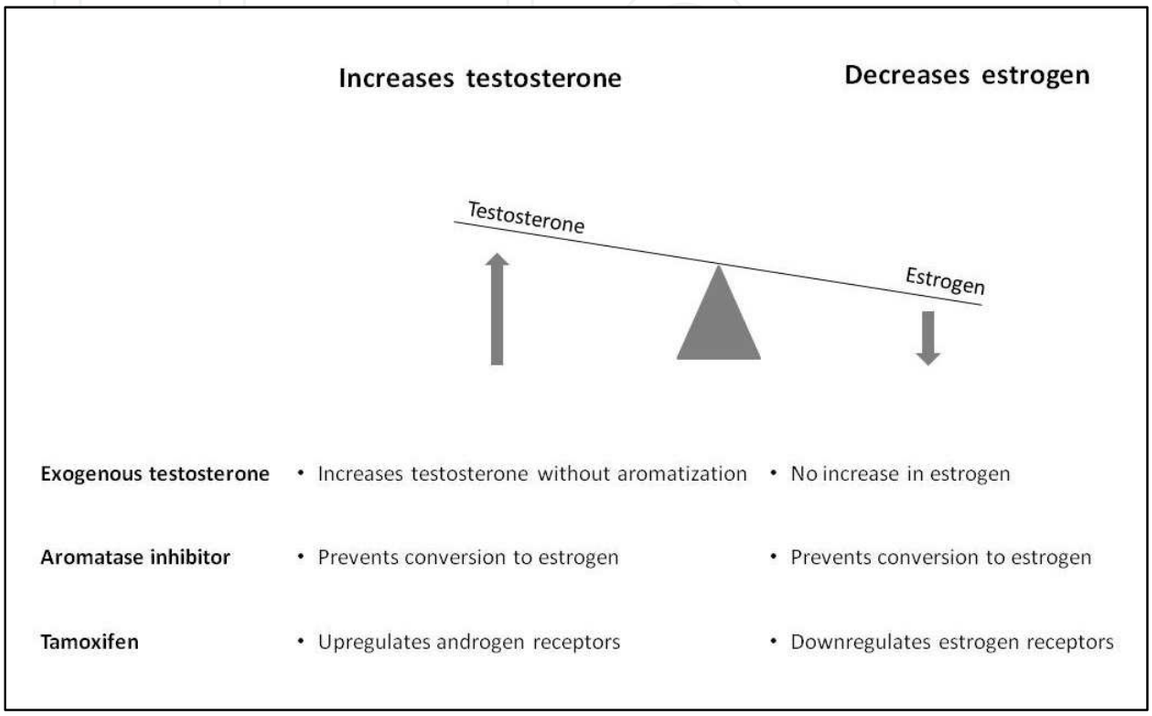

Fig. 5. Rationale for the combination of exogenous testosterone, an aromatase inhibitor, and tamoxifen for the treatment of breast or prostate cancer through elevation of testosterone and reduction of estrogen levels.

Considerable research efforts continue to be devoted to the development of new SERMs to improve upon tamoxifen (Clarke & Khosla, 2009; Silverman 2010). However, the now off-patent tamoxifen confers a significant advantage over newer drugs in being inexpensive and well-tolerated with a known side-effect profile. As well as an established role in the treatment and chemoprevention of hormone-related breast cancer, tamoxifen is also cardioprotective and increases bone mineral density, and appears to have other beneficial physiological effects (M Singh et al., 2008). Although usually prescribed at 20 mg daily, studies have revealed that tamoxifen may be as effective, and perhaps even more effective, at one-tenth the dose (Tormey et al., 1983). This is highly desirable as the risks associated with high dose tamoxifen include thrombo-embolism and uterine cancer.

Testosterone has been safely used for decades and its use does not require any regulatory approval. When used in combination with other drugs, it may have beneficial effects at much lower doses than usual. Ideally it would be possible to use at physiologic doses that would mean customizing the dose to each patient's individual requirement. This could be determined with comprehensive individual hormonal assessments.

There have been several clinical trials in the past 30 years demonstrating superior effects of combining a synthetic androgen with tamoxifen in treating advanced breast cancer over using tamoxifen alone (Ingle et al., 1991; Swain et al., 1988; Tormey et al., 1983), as well as preliminary research into thecombination of tamoxifen with an aromatase inhibitor (Coombes et al., 1982).

Combination therapy has been a common practice in the treatment of cancer for many years, and new combinations continue to be investigated (Lin et al., 2010). It is proposed here that hormonal therapy could also be used in combination in order to take advantage of the combined benefits of the drugs discussed above.

5. Conclusion

Despite considerable research, treatments for advanced breast cancer and prostate cancer have not resulted in significant prolongation of survival over recent years. A comprehensive reassessment of prevailing treatment strategies and the scientific logic behind them is long overdue.

New evidence discovered in the last few years concerning the role and interaction of tamoxifen, testosterone, and estrogen in these cancers is compelling. In the light of this new evidence a rigorous reinvestigation of the science and logic behind existing and long-abandoned therapies is now called for.

We propose that combination treatment with tamoxifen, an aromatase inhibitor, and testosterone may offer substantial survival benefits among patients with breast or prostate cancer. A formal investigation may reveal a significant benefit of this combination of treatments and provide an additional and effective treatment option for the improved management of patients with some of the most prevalent forms of cancer.

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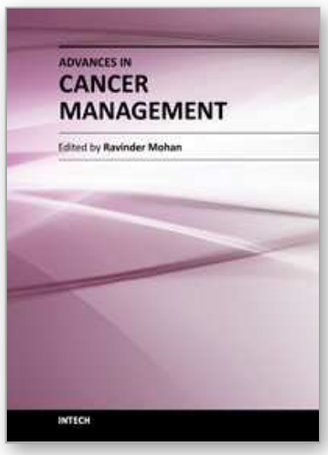

Advances in Cancer Management

Edited by Prof. Ravinder Mohan

ISBN 978-953-307-870-0
Hard cover, 278 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

Cancer is now the most common cause of death in the world. However, because of early diagnosis, better treatment, and advanced life expectancy, many cancer patients frequently live a long, happy, and healthy life after the diagnosis- and often live as long as patients who eventually do not die because of cancer. This book presents newer advances in diagnosis and treatment of specific cancers, an evidence-based and realistic approach to the selection of cancer treatment, and cutting-edge laboratory developments such as the use of the MALDI technique and computational methods that can be used to detect newer protein biomarkers of cancers in diagnosis and to evaluate the success of treatment.

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