Some Aspects of the Endocrine Profile and Management of Hormone-Dependent Male Breast Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify some differences in the endocrine profiles of male and female breast cancer patients.
2. Describe the importance of the endocrine profile in the management of male breast cancer.
3. Assess different points of the endocrine profile for tailoring individual therapy.

ABSTRACT

The management of hormone-dependent male breast cancer is insufficiently understood by practicing oncologists. This article provides a review of the endocrine profile of male breast cancer, and outlines the differences between hormone-dependent female and male breast cancers. A concise review of the past, present, and possible future management of hormone-dependent male breast cancer is presented. For a better understanding of this disease, more information on the natural history and biological behaviors of patients with male breast cancer is needed. This could be accomplished by the development of a specific multi-institutional tumor registry and execution of prospective clinical trials. The Oncologist 2007;12:798–807

INTRODUCTION

In men, breasts are considered vestigial organs and are subject to similar disease processes to those observed in women, including breast cancer. In the U.S., male breast cancer accounts for <1% of all breast cancers and approximately 0.2% of all male cancers [1]. This differs from the incidence in some African countries, where the percentage of male breast cancer is much higher [2, 3]. The incidence of male breast cancer has remained relatively stable over the last several decades [4, 5]. However, a recent analysis of data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database from 1973–2002 (in 5-year increments) reported a 26% increase in the overall incidence rate of male breast cancer (including intraductal carcinomas), although the death rates have remained constant since 1975 [6]. Because of the low...
frequency of male breast cancer, the experience of individual oncologists or even academic centers is limited. Similarly, much of the information regarding the natural history and management of this neoplasm has been obtained from studies with small numbers of patients or by extrapolation from studies and experiences with female breast cancer. Several recent reviews on male breast cancer have summarized the epidemiology, clinical presentation, pathology, genetics, molecular markers, and treatments [4, 5, 7–13]. These reviews point out that, although there are similarities between female and male breast cancers, there are also distinct differences. Analysis of the SEER database revealed subtle differences in the age-specific breast cancer incidence rates between men and women. In women, the age-specific rates of estrogen receptor (ER)-negative breast cancer stop increasing at age 50, but rates of ER-positive cancer continue to increase after age 50. In men, the pattern of ER-negative tumors was less clear because of the small number of cases, but the incidence rate appeared to increase at all ages, although at a slower rate than ER-positive tumors [8, 14]. The age-specific incidence rate patterns, the unimodal age-frequency distribution, and the prognostic factor profile characteristics (low nuclear grade and hormone receptor positivity) of male breast cancers are almost superimposable on those of late-onset female breast cancer [9]. In addition, men tend to have a higher proportion of ER-positive tumors than women [10]. Among patients with known ER status, 90.6% of men and 76.0% of women had ER-positive tumors. There are two ERs in the superfamily of receptors for steroid hormones, ER-α and ER-β. These two receptors have both overlapping and distinct functions. ER-β is more frequently expressed in male than in female breast cancers [15]. Similarly, male breast cancer tumors are more likely to express the progesterone receptor (PgR) (81.2% versus 66.7%). The propensity for receptor positivity in men may be a result of the low level of circulating estrogen in the male system. This is similar to that observed in postmenopausal women, which has led to the speculation that receptor-positive breast cancers may result from aberrant steroid receptor upregulation and a consequent constitutive activation of downstream targets [15].

It is generally accepted that there are two major factors involved in the growth stimulation of both male and female ER-positive breast cancers—ER signaling and circulating estrogen. Both factors are specific targets of breast cancer treatment in both genders. Accordingly, downgrading, blocking, or destroying the ER is one type of targeted therapy in male breast cancer. The other type focuses on the inhibition of mechanisms involving estrogen production and release.

**HORMONE RECEPTORS**

The role of the ER protein was introduced in 1962 by Jensen and his associates and was rapidly translated to the clinic [16, 17]. It has become increasingly clear that ER-positive tumors exhibit substantial molecular, biologic, and clinical heterogeneity [18]. In addition, the function of the ER in men may be different from that in women. The role of ER-α and ER-β in male breast cancer has not been sufficiently investigated. There is some evidence that ER-β is an independent marker for favorable prognosis in ER-α-negative female breast cancer patients [19]. Because the level of ER-β is high in male breast cancer, this observation may lead to investigation of the effects of various combinations of ER-α and ER-β in tumors. The heterogeneity of the ER may be the reason for nonuniform responses to hormone therapy. The introduction of tamoxifen, a selective estrogen receptor modulator, revolutionized the management of ER-positive breast cancer in women, and this was extrapolated to male breast cancer. During the last several years, the role of the PgR has also been evaluated in female breast cancer. It has been reported that, in premenopausal women with breast cancer, the presence of strongly PgR-positive nuclei is a predictor of treatment response to tamoxifen [20]. Because in men pre- and postmenopausal status are indistinguishable, this information may be irrelevant in male breast cancer. In addition, in postmenopausal women with ER-positive and PgR-negative tumors, the PgR negativity is considered to be a marker for tamoxifen resistance [21]. However, a recent analysis of the Arimidex, Tamoxifen Alone or in Combination trial may not support this notion [22]. The significance of PgRs in male breast cancer is unknown. In light of the fact that male breast tumors are more likely to be ER positive and PgR positive, it is intuitive that these tumors would be more responsive to endocrine treatment and have a more favorable prognosis. Several investigators and large clinical trials clearly demonstrated that female breast cancer patients whose tumors express ER respond to endocrine manipulation [23–26]. Such a conclusion cannot be made with certainty from information obtained from small clinical trials and retrospective reviews in male breast cancer [7, 13, 27, 28]. The androgen receptor has been the subject of investigation in both female and male breast cancer, but the findings have not yet been translated to clinical use [29–31].

**ESTROGENS**

A substantial body of experimental, clinical, and epidemiological evidence supports the hypothesis that hormones, and particularly estrogens, play an important role in the development and growth of breast cancer. Results from the exogenous administration of estrogen and studies of estro-
gen metabolism have also been reported [32, 33]. Because estrogen plays an important role in the development of breast cancer in men (as in women), it would be useful to outline the production and sources of estrogen in men under normal and pathological conditions.

Of the average daily estradiol production of 45 μg in the normal man, 17 μg is derived from the aromatization of circulating testosterone, 22 μg is formed from the weak estrogen estrone, and the remaining 6 μg is secreted directly by the testes [34–36]. It is generally accepted that, in normal adult men, plasma androstenedione and testosterone are the quantitatively important prehormones of extraglandular estrone (E1) and 17β estradiol (E2) formation, respectively (Fig. 1).

There is convincing evidence that E2 and/or E1 extraglandularly produced, derived from their plasma precursors, can stimulate male breast growth [37]. Some factors such as aging, liver disease, obesity, and hyperthyroidism could increase the conversion of plasma androstenedione and testosterone into their respective estrogen products [38]. Alterations in androgen–estrogen physiology may result from metabolic aberrations such as increased testicular secretion of estrogen or increased conversion of plasma precursors to estrogens, decreased testosterone secretion, or a combination of two or more of these alterations [36]. These alterations may play an important role in the development of resistance to the hormonal manipulation of male breast cancer and should be considered during the design of a treatment plan. Consequently, it may be inappropriate to extrapolate the treatment principles established for female breast cancer to the management of male breast cancer. Elevated endogenous estrogen production is not regularly found in men with breast cancer, nor do we have sufficient information indicating that estrogen is metabolized differently in men [33, 39]. While the principal site of estrogen formation in the nonpregnant premenopausal woman is the ovary, the formation in men is considered mainly as extraglandular from peripheral aromatization of circulating androgens (Fig. 1). Only a small amount of estradiol (about 15%) is secreted directly by the testes [35]. Using radioimmunoassay, plasma estradiol levels in men are in the range of 0.5–20.5 pg/ml. However, the level of plasma estradiol in men is not always a good indicator of estradiol production rate, because of technical difficulties with accurately measuring the low levels normally present in men. Another possible cause for the inaccuracy could be the episodic secretion of estradiol observed in some individuals [36]. Aromatase (cytochrome P450 19) has strikingly different activities in men and women [40]. There is no standard tool for measuring the effect of aromatase inhibitors in female breast cancer that could be appropriately translated to male breast cancer management. However, anecdotal reports demonstrate the clinical efficacy of aromatase inhibitors in male breast cancer [41, 42].

**Basis for Endocrine Manipulation**

While the similarity for nonhormone-dependent tumors in both genders could be used for justification of chemotherapy as a treatment of choice for both the adjuvant and metastatic settings, the patterns of hormonal production and hormone dependency of breast cancer in women and men are different [10]. The cessation of the menstrual cycle in women clearly marks the changes in reproductive function associated with anatomical organ changes. The patterns of the production of hormones related to the growth and function of the breast change as well. This separates women into two major groups (pre- and postmenopausal), which plays an important role in the approach to breast cancer treatment. The response to chemotherapy in female breast cancer patients has been shown to be related to age and ER status. Allocation to 6 months of anthracycline-based chemotherapy reduces the annual breast cancer death rate by 38% for women <50 years of age and by 20% for those aged 50–69 years [43]. This difference can largely be explained by the menopausal status of the patient. Such separation does not exist in the male population. Patients with ER-negative breast cancer have been shown to have significantly better response rates to anthracycline-based chemotherapy, compared with ER-positive tumors [44]. Testosterone production in women before or after cessation of ovarian function appears to be similar. Men have a high total testosterone production until 70 years of age, but free testosterone decreases gradually to 40% compared with young men [45]. This represents the substrate for the extragonadal production of estrogen through aromatase activation. Thus, the amount of testosterone to be converted to estrogen by aromatase is much greater in men than in women regardless of their menstrual status. This may explain the differences in the approach and response observed using hormonal manipulation in the treatment of male and female breast cancers. There is limited information indicating that the pattern of estrogen metabolism is different in patients with male breast cancer compared with healthy men. In this population, there is much less estrogen conjugation and much more conversion to estradiol than in control subjects [33]. In another study, a small number of male breast cancer patients were examined for urinary estrogen excretion and were found to have significant increases in all three major metabolites [46]. It was also reported that serum estradiol and estrone levels were higher in male breast cancer patients than in the matched normal controls, but the androgen levels were not significantly different [47].
HORMONAL MANIPULATION IN THE CLINICAL SETTING

Limited experience with various endocrine manipulators, such as high doses of estrogen, gonadotropin-releasing hormone (GnRH) agonists, antiandrogens, androgens, progestogens, adrenal suppressors, and adrenocorticosteroids, has been reported [48–53]. Early clinical experience with this relatively rare disease provided further information regarding the efficacy of endocrine surgical ablation and separated patients into responders and nonresponders, which was related to the length of their survival [11, 54, 55]. Earlier response to castration enhances the probability of longer survival. In addition, some patients who fail orchiectomy respond to subsequent adrenalectomy or treatment with tamoxifen [56, 57]. What is the basis of response to surgical ablation and why don’t all patients respond?

The testis is the source of sperm and the steroid hormones that regulate male sexual life. Those functions are under a complex feedback control of the hypothalamic–pituitary system. Thus, the biosynthetic functions and regulatory features of the testis are similar to those of the ovary and adrenal glands (Fig. 2).

The testis consists of two components: (a) a system of tubules for the production and transport of sperm and (b) Leydig cells that lie between the tubules and produce androgenic steroids. Because the testis contains aromatase, the production of estradiol from testosterone probably takes place at this location.

The pathways of testosterone formation from cholesterol are well established (Fig. 1). Several other steroids, including estradiol, are synthesized within the Leydig cells, but their quantitative significance in the normal man is minor. Only 6 μg of estrogen is secreted directly by the testes [21].

**Figure 1.** Biosynthesis of estradiol in men. The total amount of estradiol in men is 45 μg daily—22 μg is formed from the weak estrogen estrone, 17 μg is derived from aromatization of circulating testosterone, and 6 μg is secreted directly by the testes [21].

**Figure 2.** Regulation of testosterone production by LH and FSH.

(+): indicates stimulation; (−): indicates feedback inhibition.

Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.
normal young men [36]. Testosterone secretion is regulated mainly by luteinizing hormone (LH), but follicle-stimulating hormone (FSH) may also augment testosterone secretion, possibly by regulating the number of LH receptors on the Leydig cell. LH levels appear to be sensitive to the feedback effects of testosterone, with complete suppression following the administration of large amounts of exogenous androgen. FSH appears to stimulate the aromatization of androgens to estradiol in Sertoli cells. GnRH stimulates LH and FSH synthesis and release. Plasma concentrations of testosterone and LH fluctuate, reflecting changes in secretory rates (Fig. 2).

What are the expected consequences after endocrine ablation of men with breast cancer? Removal of the testes results in a decrease in plasma testosterone, which depletes the amount of hormone needed in peripheral tissues for conversion to estradiol via aromatase reaction. In addition, it decreases the levels of estradiol to some extent, and the entire pathway of androgen formation in the testis is eliminated. Importantly, the response to antiestrogen therapy in orchietomized patients appears to be better than that in nonorchiectomy-treated controls [11, 54, 57, 58]. In a case series, administration of tamoxifen to orchietomized patients with male breast cancer produced better responses than in those with preserved testes. At the present time, orchietomy is not a first-line therapy in the adjuvant or metastatic settings, but it is still used by some physicians as salvage therapy.

With removal of both adrenal glands, the levels of dehydroepiandrosterone and its sulfate (quantitatively the major androgens secreted by the adrenal cortex) decrease. In addition, androstenedione and 11-hydroxyandrostenedione are suppressed. All these are considered weak androgens but are peripherally interconvertible with the more potent androgen testosterone. Thus, the depletion of adrenal androgens also depletes testosterone, which affects the production of estrogen via peripheral tissue aromatization (Fig. 1).

The removal of the adrenals also affects glucocorticoid and mineral-corticosteroid production. This ultimately affects the corticosteroid, mineral-corticosteroid, adrenocorticotropic hormone, and renin-angiotensin physiology and may result in adverse events during the postoperative period. As a result of the introduction of new agents, this procedure and medical adrenalectomy have been abandoned. There is less experience with hypophysectomy in male breast cancer and the reported results are from very small numbers of patients [59, 60]. Today this procedure is not used because of the introduction of new agents with predetermined targets that avoid the adverse effects of the procedure in the postoperative period. Essentially, hypophysectomy ablates the regulation and physiological effects of the various anterior pituitary hormones and the hormone production of the neurohypophysis. The main therapeutic effect in male breast cancer probably is a result of the decreased effects of LH and FSH, which consequently decrease the aromatization of androgen to estradiol.

**NEWER APPROACHES TO ENDOCRINE MANIPULATION**

In metastatic male breast cancer, tamoxifen has shown substantial activity as a single agent and has been considered as a preferred first-line treatment for some time [9, 12, 61, 62]. Unfortunately, there are no prospective randomized trials to evaluate the real response rates and to obtain complete information regarding the adverse reactions associated with the use of this antiestrogen in men. The adverse effects of tamoxifen in male breast cancer patients have not been adequately studied. In early case reports, tamoxifen appeared to be less toxic [57, 63]. However, in a recent telephone survey conducted in male breast cancer patients on tamoxifen, 25% of them discontinued the treatment because of side effects. Sexual dysfunction was the cause of discontinuation for the majority of these patients [64]. Uterine carcinogenicity, which is of great concern in women, does not exist in men. This makes tamoxifen substantially safer in men than in women. Hot flushes, the dominating adverse event in women, have a lower intensity in men with breast cancer [52, 58, 65, 66]. This difference may result from the lower levels of circulating estrogens in men than in women [15].

During the last two decades, the estrogen antagonist fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals, Wilmington, DE) has been introduced and approved by the U.S. Food and Drug Administration for the treatment of hormone receptor–positive metastatic breast cancer in postmenopausal women [67]. The target of this drug is the ER, but the mechanism of action differs substantially from that of tamoxifen and the aromatase inhibitors (Fig. 3). Fulvestrant is 7-α alkylamide derivative of estradiol and has estrogen antagonistic activity but does not possess estrogen agonist activity [68]. The drug competitively binds to and degrades (destroys) ERs in human breast cancer tissue (Fig. 3). It is effective in estrogen-sensitive and tamoxifen-resistant human breast cancer cell lines [68]. Fulvestrant binds equally to both ER-α and ER-β and has a long elimination half-life so that a monthly i.m. injection is sufficient to maintain steady-state plasma concentrations [69, 70]. The most common adverse effects involve the gastrointestinal tract and vasodilatation, but the drug is considered safe and the side effects are tolerable [67].
The efficacy of fulvestrant in premenopausal women with metastatic breast cancer has not been established. However, when the target for endocrine therapy (ER positivity) is present, there is no reason to believe that the drug will have different activity than that demonstrated in postmenopausal breast cancer patients. At this time, there is only anecdotal information in the available literature about the efficacy of fulvestrant in male breast cancer patients [71]. It is considered a pure antiestrogen and does not have the adverse effects of tamoxifen and the aromatase inhibitors. We believe that the use of fulvestrant in male breast cancer as a single agent or in combination with other biological agents should be investigated in the near future.

In contrast to tamoxifen and fulvestrant, the aromatase inhibitors markedly suppress estrogen levels in women by inhibiting the enzyme aromatase, which is responsible for the synthesis of estrogens from androgenic substrates (androstenedione to estrone and testosterone to estradiol) (Figs. 1 and 3). With the introduction of aromatase inhibitors for the treatment of postmenopausal women with breast cancer, these agents soon found a place in the treatment of male breast cancer as well [41, 42]. The presumption that the pattern of male breast cancer characteristics resembles those of their female counterparts in postmenopausal women was justification for the replacement of tamoxifen with aromatase inhibitors as a first-line preferred agent in male breast cancer. Another reason for this change was the toxicity profile of aromatase inhibitors, which showed fewer adverse events in women when compared with tamoxifen, with the exception of bone loss [72]. The limited experience with aromatase inhibitors in male breast cancer does not allow complete evaluation of the efficacy and toxicity of these agents in the management of this disease, and the effects in the bone in particular. Osteoporosis is a well-known consequence of menopause and is an adverse effect of aromatase inhibition therapy in women. Less familiar is male andropause, where the production of testosterone is less complete and more variable than the estrogen deficiency in postmenopausal women [40, 73]. The long-term toxic effects of these agents in male breast cancer have not been studied. At the present time, many oncologists use aromatase inhibitors as a preferred first-line agent for male breast cancer, whereas others still consider tamoxifen as the standard first-line treatment [12].

**FUTURE CONSIDERATIONS**

The hormonal milieu in patients with male breast cancer depends on age and testicular function. Since orchiectomy is not used as a primary therapy in the adjuvant and metastatic settings, the role of the hormonal production of the testis cannot be ignored. The extent of conversion of testosterone to estradiol via aromatase reaction and estrogen secretion from the testes cannot be determined accurately using the available laboratory methods. Thus, using a fixed dosage of aromatase inhibitors may not result in an optimal therapeutic response. Usually the total testosterone level in normal healthy men is quite stable between 15 and 70 years of age, but free testosterone levels vary in the aging male popula-

![Mechanisms of action of tamoxifen, aromatase inhibitors, and fulvestrant.](http://theoncologist.alphamedpress.org/Downloaded from http://theoncologist.alphamedpress.org)
...quality of life of medically castrated men should also be considered and evaluated appropriately. In addition, the lowering estrogen levels in men with breast cancer should not inhibit the sulfatase that is responsible for the production of estrone and estradiol from their circulating precursors (Fig. 3). Some monitoring tool would be important for individual tailoring of the aromatase inhibitor dose in male breast cancer patients. The role of secreted estrogen in noncastrated men with breast cancer requires evaluation as well. The secretion of estrogen by the testes comprises approximately 15% of the total estrogen production in healthy men [36]. The rest is extraglandular production and can be blocked by aromatase inhibitors, but testicular estrogen excretion may be sufficient to stimulate growth if residual or metastatic disease is present. Treatment with a combination of antiestrogens (tamoxifen) and an aromatase inhibitor did not result in superior activity over a single agent alone in women [72]. The combination of an aromatase inhibitor with a GnRH agonist may be important for premenopausal women with breast cancer, but in men it may not affect the testicular secretion of estrogen. However, response to this combination has been reported recently in two patients with male breast cancer, one of whom had previously failed a trial of either agent alone [74]. This option is under study by the Southwest Oncology Group (SWOG), protocol #S0511. The combination of a GnRH analogue plus an antiandrogen versus the analogue alone has also been studied in small numbers of patients with advanced male breast cancer [75]. No significant difference in response rates was observed, but some of the side effects substantially affected quality of life (loss of libido and impotence). No long-term observations were reported. Extreme estrogen depletion may lead to osteopenia or osteoporosis after prolonged administration of this combination [76]. The detrimental effect on the bones of further lowering estrogen levels in men with breast cancer should be considered and evaluated appropriately. In addition, the quality of life of medically castrated men should also be evaluated.

A combination of aromatase inhibitor or tamoxifen and an ER-degrading agent (fulvestrant) could also be appropriate. Fulvestrant has no effect on estrogen synthesis, but it destroys ERs in the tumor cell, thus blocking further proliferation and inhibiting tumor growth. We are not aware of any clinical study using fulvestrant and aromatase inhibitors in men. However, drug–drug interaction between these agents looks unlikely and their clinical use could be beneficial for male breast cancer patients. Promising preliminary preclinical information for this combination in a breast cancer cell line (MCF-7) in castrated nude mice is available and some clinical investigations are in progress [68, 69, 70]. On the basis of this information the SWOG is studying this option in male breast cancer—protocol #S0226.

Developing resistance to both tamoxifen and aromatase inhibitors is an important element of treatment failure. ERs can activate signaling pathways by genomic or nongenomic mechanisms [77]. Genomic activation is associated with transcription factors in the nucleus, whereas nongenomic activation relates to membrane-associated ERs that interact with growth factor receptors. Overexpression of the epidermal growth factor receptor (EGFR) (ErbB-1) and human epidermal growth factor receptor (HER-2) (ErbB-2) stimulates nongenomic activation in response to estrogen and tamoxifen. This bidirectional crosstalk could result in a positive feedback cycle of cell proliferation and survival. Clinical experience demonstrates that aromatase inhibitors are superior to tamoxifen in tumors with high levels of growth factor receptors [77]. This approach should be considered with caution, because it has been reported that aromatase inhibitors can induce an estrogen hypersensitive phenotype that could result in resistance and the stimulation of cancer cell growth [78].

This information opens up the possibility of ER-targeted therapies combined with inhibitors of EGFR and HER-2/neu signaling that may restore sensitivity to endocrine therapies. Clinical attempts to use these strategies in female breast cancer appear to be promising and translation to male breast cancer should be encouraged [79–81].

For several decades, clinical and basic science investigators have sought methods for identifying patients at low risk for disease recurrence. Some progress has been made in female breast cancer, which could be tested in male patients as well. There is a paucity of studies of gene expression or other biological markers, with the exception of hormone receptors, in male breast cancer. Limited information regarding genetic markers has been reported but the significance of those findings is unclear [30, 82–87]. Attempts to distinguish female from male breast cancer have been made using genetic mutations, immunophenotypic variations, or androgen receptors [86]. No conclusive results are available. With the rapid development of molecular biology, new therapeutic targets of cancer cells are emerging and new biological agents for the treatment of breast cancer have been introduced. The biological heterogeneity of breast cancer...
has therapeutic implications that have been demonstrated by the use of gene-expression profiling. Several predictors in female breast cancer have been introduced on the basis of this method [88]. Male breast cancer patients are excluded from such studies. Because the majority of the male patients have distinct biological markers, this population could be included in future clinical trials or the evaluation of molecular-expression profiles. Limited attempts in male breast cancer by some investigators are in progress, but no convincing information is present in the available literature regarding the molecular therapeutic approach.

**CONCLUSION**

An optimal therapy for the management of hormone-dependent male breast cancer has not been established. Because the vast majority of cases of male breast cancer are hormone dependent and resemble female postmenopausal breast cancer, using hormonal manipulations as optimal approaches to treatment is appropriate. During the last decade, we have learned more about the epidemiology, clinical presentation, pathology, genetics, molecular markers, and treatment of male breast cancer. The incidence of male breast cancer is increasing, which justifies clinical investigation with prospective studies. The notion that the small number of patients with male breast cancer does not allow the design of prospective studies may not be valid anymore. There are some examples of clinical trials that involved a small number of patients and short treatment time and still correctly predicted clinical outcome. This suggests that there is a clear need for prioritized approaches in the design of trials with hormone-dependent male breast cancer patients. Building a specially focused tumor registry and including male breast cancer patients in prospective randomized trials will allow investigators to obtain reliable information related to the therapeutic response and biology of male breast cancer.

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**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.

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**REFERENCES**


