

Drug Insight: breast cancer prevention and tissue-targeted hormone replacement therapy

Fernand Labrie

SUMMARY

The first-generation selective estrogen receptor modulator (SERM) tamoxifen has been the mainstream hormone therapy in breast cancer. Tamoxifen benefits all stages of the disease, but its use increases the risk of uterine cancer and thromboembolic events and it can only be administered for 5 years. Aromatase inhibitors are superior to tamoxifen at advanced stages of disease and as adjuvants; however, because they increase fractures, aromatase inhibitors are unlikely to be used to prevent disease. Raloxifene, a second-generation SERM, leads, like tamoxifen, to approximately 50% fewer cases of invasive breast cancer in high risk women, with a lower incidence of thromboembolic events. Several other SERMs are in development to improve tissue specificity, efficacy and tolerance. Raloxifene shows protection against vertebral fractures similar to bisphosphonates; however, no significant effect has been observed on nonvertebral fractures. Many SERMs are in development for prevention and treatment of osteoporosis. As breast cancer metastasizes early and advanced disease cannot be cured, prevention is essential. To avoid the concerns about the use of traditional hormone replacement therapy, dehydroepiandrosterone—a tissue-targeted precursor of sex steroid formation—offers hope of a physiological tissue-targeted hormone replacement that, combined with a SERM, would simultaneously prevent breast and uterine cancer.

KEYWORDS breast cancer, dehydroepiandrosterone, selective estrogen receptor modulators, tissue-targeted hormone replacement therapy

REVIEW CRITERIA

The literature search included publications on SERMs, breast cancer, aromatase inhibitors, osteoporosis and hormone replacement therapy for the past 10 years. The number of references cited has been restricted because of space limitations.

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INTRODUCTION

Breast cancer is the most-frequently diagnosed cancer and the second-commonest cause of death from cancer in women;¹ thus, it is the most feared disease in women. It is encouraging that a significant decrease in breast cancer deaths has been observed during the past 20 years.² Breast cancer has, however, already spread as micrometastases in approximately 50% of cases at the time of diagnosis, as shown by the rate of recurrence of cancer after surgery for localized disease.^{3,4} It is unlikely that improvements in the treatment of advanced disease will permit a cure in the foreseeable future. An efficient and well-tolerated strategy for breast cancer prevention is therefore an urgent need.

As women now spend half of their adult lifetime postmenopausal, a safe alternative to traditional hormone replacement therapy (HRT) is required that would be devoid of the increased risk of breast cancer incidence found in the Women's Health Initiative (WHI)⁵ and the Million Women Study.⁶ The rapid fall in circulating estradiol at menopause, coupled with the demonstrated beneficial effects of exogenous estrogens on menopausal symptoms⁷ and bone resorption^{4,5} has focused most of the efforts of HRT on estrogens as well as on combinations of estrogen and progestin (i.e. traditional HRT), without taking into account the potential role of androgens.

Here I discuss the relative merits of the compounds currently used for the treatment and/or prevention of breast cancer—namely tamoxifen, raloxifene (Evista®; Eli Lilly and Company, Indianapolis, IN), fulvestrant, and aromatase inhibitors—as well as the potential of the selective estrogen receptor modulators (SERMs) under development. Concerning the menopause, perhaps the best hope of realizing the objective of providing estrogens and androgens targeted to the tissues needing these hormones, and at the appropriate level, is to combine a highly specific SERM with dehydroepiandrosterone (DHEA), a compound converted into androgens and/or estrogens only in some tissues. Such targeting would avoid exposure of the other tissues to sex

steroids and avoid the negative effects found in the WHI⁵ and Million Women⁶ studies. The combination of a SERM plus DHEA could lower the risk of breast and uterine cancer while potentially providing combined benefits on bone, adipose tissue, glucose and insulin metabolism, cholesterol levels, muscle, vagina and skin.

SERMS USED AGAINST BREAST CANCER: TAMOXIFEN AND RALOXIFENE

SERMs are compounds that exert various levels of antiestrogenic activity in the breast and uterus while showing variable estrogenic effects in other tissues. These tissue-specific effects depend upon the level of interaction of the co-activators and co-repressors and other associated proteins with the estrogen receptor, which shows a unique three-dimensional structure induced by each SERM. Some SERMs, for example acolbifene, induce conformational changes that block both AF-1 (activation function 1) and AF-2 sites on the estrogen receptor, whereas tamoxifen blocks only AF-2.⁸

Tamoxifen has been shown to improve survival at all stages of breast cancer. In fact, allocation of adjuvant tamoxifen for about 5 years reduces the annual breast cancer death rate by 31% in women who have cancers expressing the estrogen receptor.⁴

Concerning prevention, tamoxifen is the only FDA-approved drug for breast cancer risk reduction in women. In the Study of Tamoxifen and Raloxifene (STAR) trial, the risk of breast cancer when taking either drug was reduced by approximately 50% for invasive breast cancer; raloxifene was less effective for noninvasive cancer.⁹ In the Raloxifene Use for The Heart (RUTH) trial, the risk of invasive breast cancer was reduced by 44% in women taking raloxifene (1.2 per 1,000 woman-years).¹⁰ In that study, the risk of fatal stroke was increased by 49% (0.7 per 1,000 woman-years) whereas the risk of clinical fractures was reduced by 35% (1.3 per 1,000 woman-years). It has recently been suggested that the mortality benefit from tamoxifen used as a preventive agent might only apply to women at very high risk of breast cancer.¹¹

Despite approval by the US FDA and endorsement by the American Society of Clinical Oncology, only 5–30% of high-risk women agree to take tamoxifen as a preventive agent¹² because of the reported side effects, namely endometrial cancer, thromboembolic events, and hot flashes.¹³

It should be mentioned that half of breast cancers are not prevented or delayed by tamoxifen or raloxifene.⁹ The objective of developing new SERMs is, therefore, to increase the benefit to risk ratio observed with tamoxifen and raloxifene. It is important to recognize that all SERMs are different and that the data obtained with tamoxifen or raloxifene cannot be extrapolated to other SERMs in development.

AROMATASE INHIBITORS USED AGAINST BREAST CANCER

Aromatase inhibitors are compounds that inhibit the transformation of androstenedione and testosterone into estrone and estradiol, respectively. Two classes of aromatase inhibitors, namely steroidal (e.g. exemestane) and nonsteroidal (e.g. anastrozole [Arimidex®, AstraZeneca, Wilmington, DE] and letrozole), are now available. Aromatase inhibitors are more effective than tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer¹⁴ or as adjuvant therapy in preventing recurrence of the disease;¹⁵ however, the long-term effects of aromatase inhibitors remain to be evaluated, especially in the context of prevention.

It should also be mentioned that aromatase inhibitors do not inhibit the formation of the estrogen androst-5-ene 3 β , 17 β -diol (5-diol; Figure 1), a steroid present in the blood of women at concentrations found to be stimulatory for the proliferation of human breast cancer cells as well as normal estrogen-sensitive tissues.¹⁶ The results of the Arimidex®, Tamoxifen, Alone or in Combination (ATAC) trial¹⁷ might suggest that the effect of 5-diol is minimal or at least inferior to the intrinsic estrogenic activity of tamoxifen.

A STEROIDAL ANTIESTROGEN USED AGAINST BREAST CANCER

Fulvestrant, a steroidal 'pure' antiestrogen (i.e. it is free of any estrogen-like activity in the absence of estrogens), exerts its action by blocking the binding of estrogens to the estrogen receptor in all tissues, thereby causing generalized estrogen deprivation. At the dose used, fulvestrant has been shown to be equivalent to tamoxifen as a primary treatment of advanced breast cancer.¹⁸ On the other hand, fulvestrant has shown no difference in median time to progression compared with anastrozole in patients who had progressed despite prior endocrine therapy.¹⁹ Encouraging results have also been observed with fulvestrant in patients with

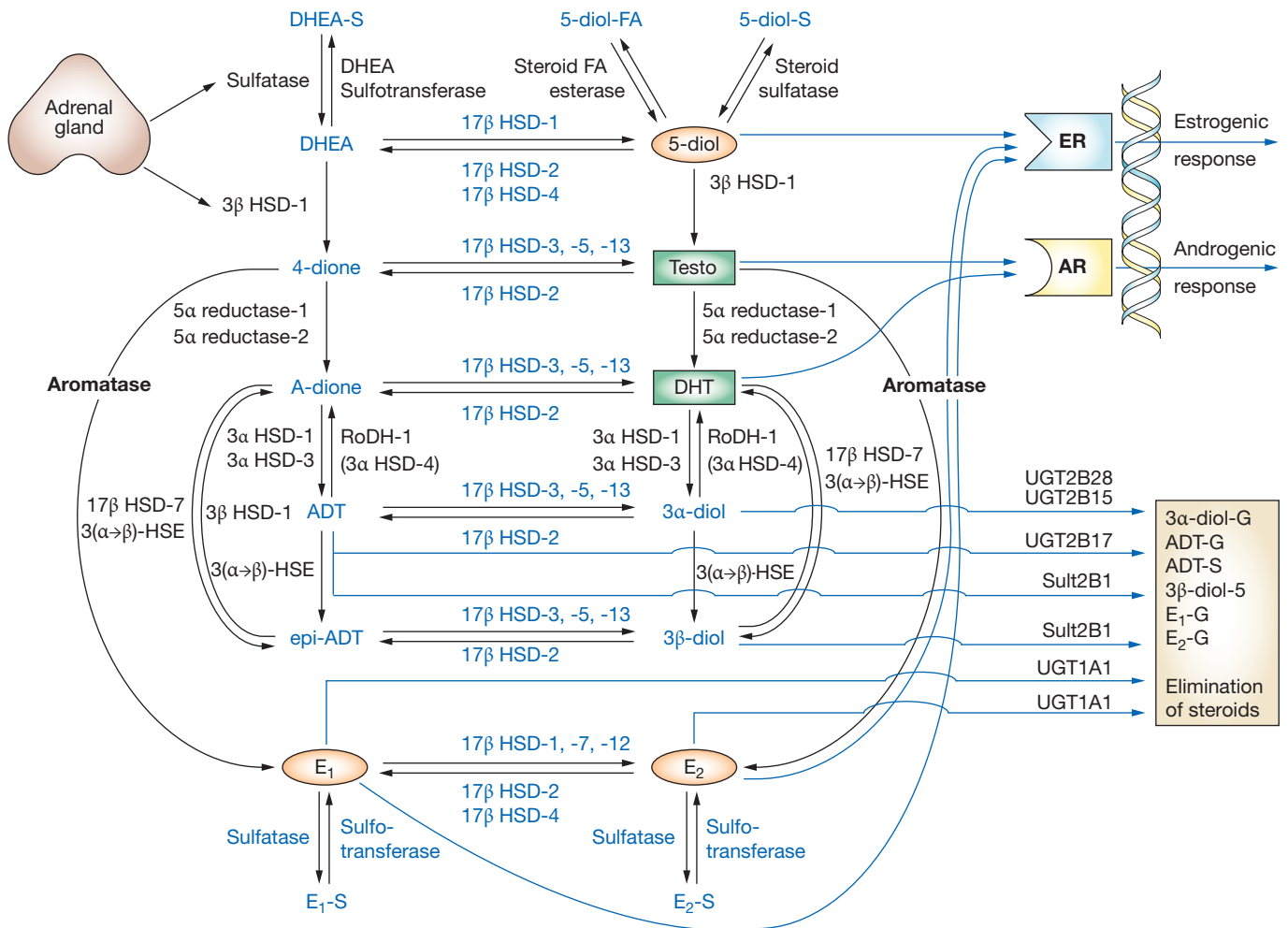


Figure 1 Human steroidogenic and steroid-inactivating enzymes in peripheral intracrine tissues. The adrenal glands produce DHEA and DHEA-S, which are transported in the general circulation to reach peripheral target tissues where they are converted into estrogens and/or androgens, depending upon the enzymatic machinery present in each tissue. The active hormones made locally are the estrogens E₂ and 5-diol and the androgens testosterone and DHT. The estrogens act via the ER whereas the androgens act via the AR to exert their specific effects. The pathways leading to hormone inactivation are also shown. Abbreviations: 3α HSD-1, 3α-hydroxysteroid dehydrogenase type 1; 3α-diol, androstane-3α, 17β-diol; 3α-diol-G, androstane-3α, 17β-diol glucuronide; 3α-diol-S, androstane-3α, 17β-diol sulfate; 3β HSD-1, 3β-hydroxysteroid dehydrogenase type 1; 3β-diol, androstane-3β, 17β-diol; 3(α→β)-HSE, 3(α→β) hydroxysteroid epimerase; 4-dione, 4-androstenedione; 5-diol, androst-5-ene 3β, 17β-diol; 5-diol-FA, 5-diol fatty acid; 5-diol-S, 5-diol sulfate; 17β HSD-1, 17β-hydroxysteroid dehydrogenase type 1; A-dione, androstenedione; ADT, androsterone; ADT-G, androsterone glucuronide; ADT-S, androsterone sulfate; AR, androgen receptor; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydroxytestosterone; E₁, estrone; E₁-G, estrone glucuronide; E₁-S, estrone sulfate; E₂, estradiol; E₂-G, estradiol glucuronide; E₂-S, estradiol sulfate; epi-ADT, epiandrosterone; ER, estrogen receptor; FA, fatty acid; RoDH-1, Ro dehydrogenase type 1; Sult2B1, sulfotransferase 2B1; Testo, testosterone; UGT2B28, uridine glucuronosyl transferase 2B28.

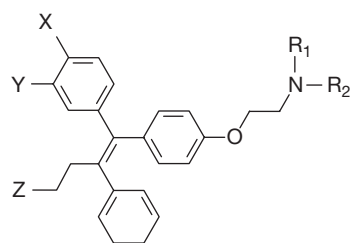
progressive disease who were under treatment with aromatase inhibitors.²⁰

A TUMORICIDAL SERM BEING DEVELOPED AGAINST BREAST CANCER

One SERM in development against breast cancer is acolbifene (Figure 2). Possibly the most significant characteristic of acolbifene is that it

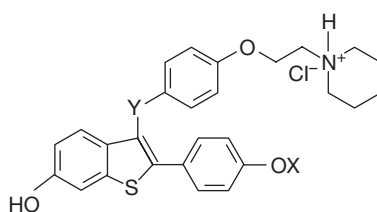
causes the disappearance or cure of 60% of human breast tumors in genetically immunodeficient mice.²¹ The tumoricidal action of acolbifene is a new paradigm of hormonal therapy. As a possible explanation, acolbifene is more potent than any of the available antiestrogens and SERMs in inhibiting the stimulatory effect of estrogens on the proliferation of human breast

Triphenylethylenes



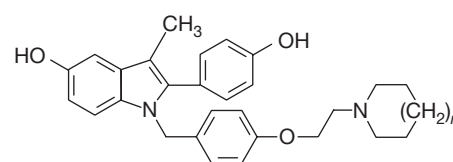
Tamoxifen	X=Y=Z=H, R ₁ =R ₂ =CH ₃
Droloxifene	X=H, Y=OH, Z=H, R ₁ =R ₂ =CH ₃
Toremifene	X=Y=H, Z=Cl, R ₁ =R ₂ =CH ₃
Idoxifene	X=I, Y=Z=H, R ₁ , R ₂ =C ₄ H ₈

Benzothiophenes



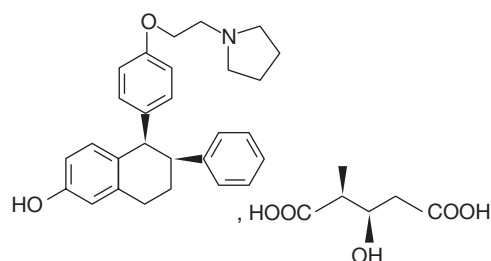
Raloxifene	X=H, Y=-CO-
Arzoxifene	X=CH ₃ , Y=-O-

Indoles



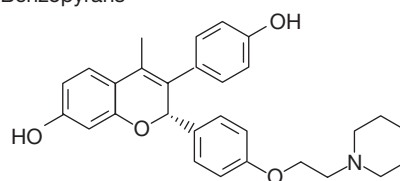
Pipendoxifene	(ERA 923) n = 1
Bazedoxifene	(TSE 424) n = 2

Naphthalenols



Lasofoxifene

Benzopyrans



Acolbifene

Figure 2 Structure of selective estrogen receptor modulators in current use or in development for osteoporosis or breast cancer. The number of carbons in the chain is indicated by “n = 1” or “n = 2”.

cancer cells *in vitro*.⁸ Similarly, among seven tested antiestrogens, acolbifene was the most potent inhibitor of the stimulatory effect of estrogens on the growth of human breast cancer tumors in nude mice.²² In addition, whereas resistance to treatment is a major problem of cancer therapy, no resistance is observed with acolbifene in human breast cancer tumors in nude mice.²³

Concerning the effect on the uterus, acolbifene possesses no estrogenic activity *in vitro* in human Ishikawa endometrial carcinoma cells, whereas all other SERMs tested stimulate alkaline phosphatase, encoded by a well-recognized estrogen-sensitive gene in uterine cells.²⁴ Data from two clinical trials—one phase II²⁵ and one phase III (Labrie F, unpublished data)—in advanced breast cancer patients who had progressed despite tamoxifen therapy showed that acolbifene induces a positive response in a significant proportion of patients, thus indicating that acolbifene is active after tamoxifen failure.

SERMS AND CARDIOVASCULAR EVENTS

When the overall safety was analyzed in the Multiple Outcomes of Raloxifene Evaluation (MORE) study by adding the arterial and venous events, raloxifene had no significant effect when all women are considered but it significantly decreased (by 37%; $P < 0.05$ versus placebo) the events in high-risk women.²⁶ In the RUTH trial involving women with, or at risk of, heart disease, the risk of breast cancer was reduced by 44% (1.2 per 1,000 woman-years) and the risk of clinical vertebral fractures was reduced by 35% (1.3 per 1,000 woman-years) in women who received raloxifene compared with placebo.¹⁰ Although there was no significant effect on the risk of primary coronary events, there was a 49% increased risk of fatal stroke (0.7 per 1,000 woman-years) and a 44% increased risk of venous thromboembolism (1.2 per 1,000 woman-years) in women who received raloxifene. No differences were found for ischemic heart disease events and for strokes in the women who received tamoxifen or raloxifene, whereas there were fewer

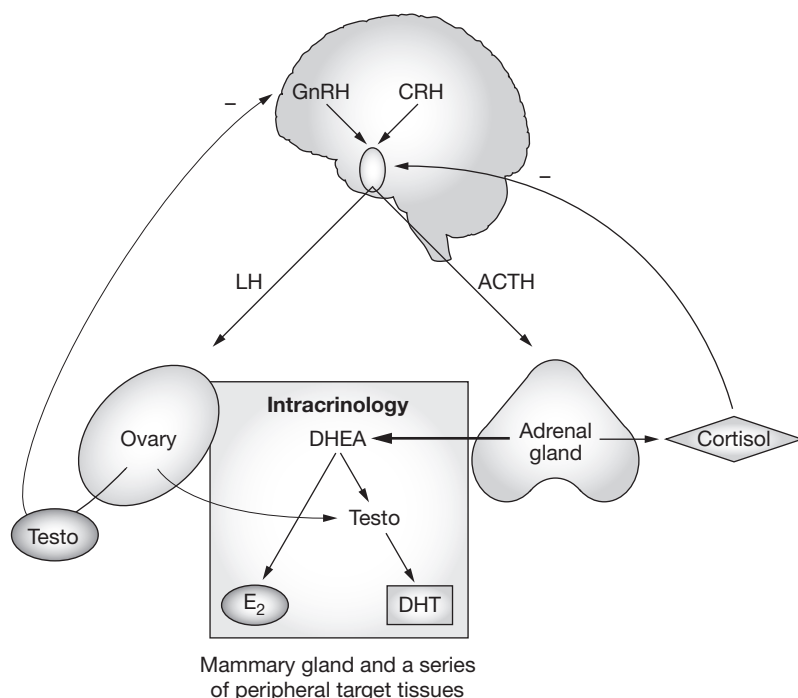


Figure 3 Schematic representation of the role of ovarian and adrenal sources of sex steroids in postmenopausal women. After the menopause, the secretion of E_2 by the ovaries ceases, and then all estrogens and nearly all androgens are made locally in peripheral, target intracrine tissues. The postmenopausal ovary secretes small amounts of testosterone directly into the circulation, where it has an inhibitory effect (–) on GnRH secretion in the brain. Conversely, the adrenal glands—as well as secreting cortisol that decreases CRH secretion, which otherwise stimulates ACTH levels—secrete large amounts of DHEA; this is converted in specific target tissues into androgens and/or estrogens via the process of intracrinology. Only small amounts of these peripherally made sex steroids diffuse into the circulation.²⁷ Abbreviations: ACTH, adrenocorticotropic; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; E_2 , estradiol; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; Testo, testosterone.

thromboembolic events and cataracts in the raloxifene-treated group.⁹

INTRACRINOLOGY AND DECLINING DHEA AND ANDROGENS AS WOMEN AGE

After the menopause, the adrenal glands become the almost exclusive source of sex steroids through the secretion of DHEA, which is transformed into sex steroids in a tissue-specific fashion²⁷ (Figure 3); DHEA levels, however, begin to decline by the age of 30 years (Figure 4) and a 60% decrease of serum DHEA as well as total androgens is already reached at the time of menopause.²⁸

With the serum concentrations of the metabolites androsterone glucuronide and androstane-3 α , 17 β -diol glucuronide as indicators, total androgen

levels in women at the ages of 55–65 years are 60% lower than the values found in women aged 30–35 years.²⁸ It is important to mention that large amounts of androgens are nevertheless present in women: they have at least 50% of the androgens present in men.²⁷ Such data strongly suggest that androgens have a major but so-far-underestimated physiological role in women. It is also important to note that recent data have shown that following administration of DHEA, the changes in serum DHEA observed are approximately double the ‘true’ changes (‘true changes’ here meaning the formation of active androgens); this effect is even more pronounced when comparing serum levels of DHEA with ‘true’ levels of estrogens (Labrie F *et al.*, unpublished data). This observation is of major importance in analyzing the data from DHEA studies where, most often, the dose of DHEA used is too low compared with the targeted physiological levels.

ANDROGENS AND THE NORMAL MAMMARY GLAND

Women with elevated androgen levels, whether endogenous or exogenous, experience breast atrophy consistent with the notion that androgens, *per se*, are antiproliferative for the breast.²⁹ Another strong argument against a potential positive correlation between androgen levels and breast cancer is provided by polycystic ovary syndrome, a situation characterized by an androgen excess in which the risk of breast cancer is not increased or is even decreased despite hyperandrogenism, with a relative risk of breast cancer decreased to 0.52.^{29,30}

The best demonstration of the role of endogenous androgens on the proliferation of the normal epithelial cells of the mammary gland has been obtained in the Rhesus monkey, where physiological levels of exogenous testosterone completely blocked the stimulatory effect of estradiol on mammary cell proliferation.³¹ It is worth mentioning that female athletes as well as transsexuals taking androgens show atrophy of breast glandular tissue.^{27,31}

ANDROGENS, DHEA AND BREAST CANCER

All the clinical and most preclinical data show that the administration of androgens inhibits proliferation of the normal mammary gland and breast cancer.^{32,33} The first observation of an inhibitory effect of androgens in women with breast cancer was made by Ulrich.³³ In fact, as reviewed by Labrie *et al.*,³² a series of clinical

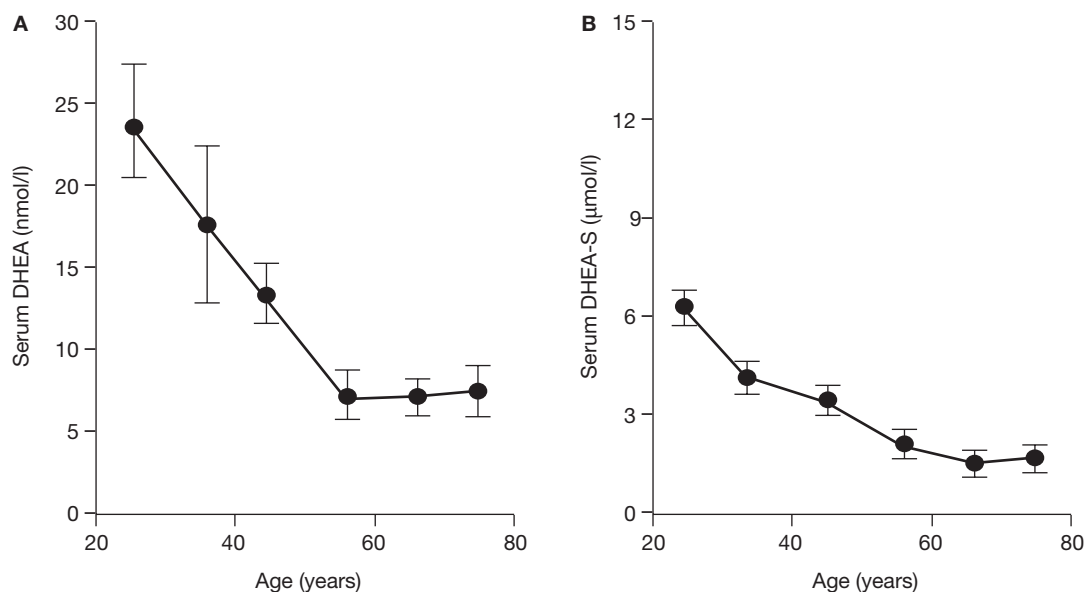


Figure 4 Effect of age on DHEA and DHEA-S levels in women. The graph shows the means \pm SEM for serum concentrations of (A) DHEA and (B) DHEA-S in women aged 20–80 years.²⁷ Abbreviations: DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate.

observations have shown that androgens such as testosterone, calusterone and anabolic steroids have an efficacy comparable to that achieved with other types of endocrine manipulations; however, because of its virilizing effects, androgen therapy has been replaced by tamoxifen, a better-tolerated compound. Nevertheless, androgens and DHEA, acting through the androgen receptor, have been shown in the vast majority of studies to inhibit estrogen-stimulated proliferation of human breast cancer cell lines.³²

As a strong correlation between the serum levels of estradiol and all other steroids is well known, and estradiol is recognized as a strong stimulator of breast cancer, it is difficult to assess the potential role of hormones other than estrogens in breast cancer risk. The majority of epidemiological studies performed in premenopausal women have found no correlation, or a negative correlation, between serum testosterone levels and risk of breast cancer.³⁴ On the other hand, epidemiological data in postmenopausal women have provided equivocal evidence: no association, a tendency for decreased risk of breast cancer or, more frequently, an association of high serum estradiol, testosterone or DHEA with high risk of breast cancer.^{35–38} It should, however, be noted that recent epidemiological data from 29 breast cancer cases have suggested a greater

risk of breast cancer when taking estrogen plus testosterone therapy compared with estrogen therapy alone; in this study, all subjects had used previous hormonal therapy.³⁹

In addition to the unavoidable physiological arguments clearly showing that serum testosterone is not a valid parameter of androgenic activity in women,²⁸ epidemiological studies have generally used unreliable and insensitive radioimmunoassays to measure the low levels of testosterone present in women. Moreover, comparison of testosterone levels in breast cancer tissue compared with plasma revealed ratios ranging from 0.05 to 5.00 (a 100-fold variation).⁴⁰ Such data clearly indicate the lack of reliability of measurement of serum testosterone with the objective of correlating with testosterone activity within tissues. These studies also did not take into account the marked diurnal variations of steroid levels and the previous history of hormone replacement therapy.

SERMS AND OSTEOPOROSIS

The US Surgeon General's report on bone health and osteoporosis⁴¹ estimates that more than 12 million women and men over 50 years old will have osteoporosis in the US by 2010, increasing to 14 million by 2020. Among women aged over 50 years, the lifetime risk of fracture is 40%, whereas it is 13% in men aged over

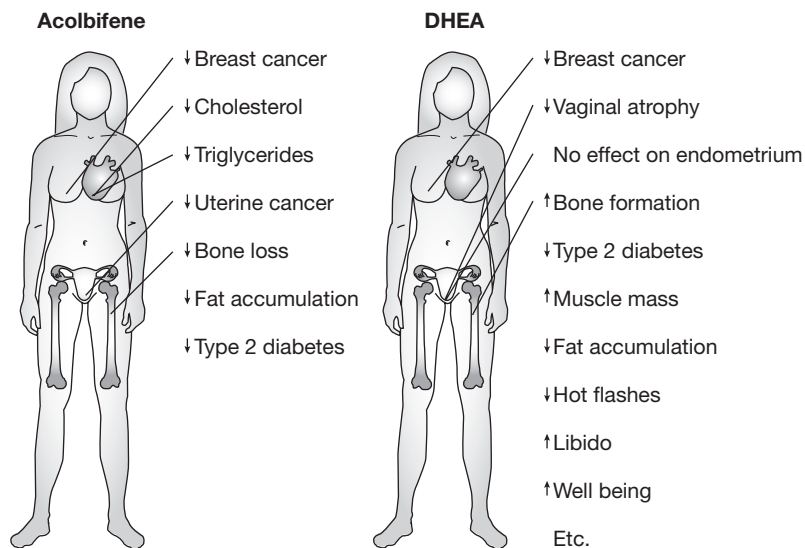


Figure 5 Schematic representation of the effects expected from the combination of a specific estrogen receptor modulator (acolibifene) and DHEA. The specific estrogen receptor modulator that is used should prevent breast and uterine cancer, whereas DHEA should replace the loss of sex steroids in postmenopausal women in the appropriate target tissues. Tissue-specific hormone replacement therapy avoids exposure of the other tissues to sex steroids, thus eliminating the negative effects observed in the Women’s Health Initiative⁵ and Million Women⁶ studies. Abbreviation: DHEA, dehydroepiandrosterone.

50 years. Osteoporosis and fractures are, therefore, a major health issue growing with the aging of the population.

Tamoxifen is the first SERM shown to decrease osteoporotic bone fractures.⁴² Among the SERMs in development for osteoporosis or breast cancer (Figure 2), all show beneficial effects on bone loss, at least at the preclinical level. Arzoxifene and bazedoxifene are at various stages of clinical development for the prevention and/or treatment of osteoporosis or for the prevention of osteoporotic fractures. Although the action of each SERM on other systems, especially on the breast and uterus, must be evaluated carefully, it is likely that prevention of bone loss can be achieved with each of these compounds. One must, however, choose the SERM(s) showing pure antagonistic activity in the mammary gland and uterus. Acolbifene has been found to be 10 times more potent than raloxifene on BMD in the rat.⁸

In common with the bisphosphonate alendronate, raloxifene prevents new vertebral fractures effectively in postmenopausal osteoporotic women;⁴³ however, a protective effect of raloxifene on nonvertebral fractures has not yet been demonstrated. Although the suppressive

effect of raloxifene on bone turnover or loss of BMD is lower than that of alendronate,⁴⁴ the effect of raloxifene on vertebral fractures is comparable.

As demonstrated following the end of the MORE study up to the beginning of the Continuing Outcomes Relevant to Evista® (CORE) study, BMD decreases upon cessation of raloxifene therapy, thus indicating the need for continuing raloxifene therapy. Similar findings have been observed following discontinuation of hormone therapy or bisphosphonate administration. In a study where postmenopausal women with osteoporosis treated with alendronate for an average of 43 months were randomized to continue on alendronate or to receive placebo or raloxifene,⁴⁵ the same effect (i.e. no decrease in BMD) was observed with alendronate and raloxifene on BMD of the lumbar spine and femur 24 months later.

SERMS PLUS DHEA—TISSUE-TARGETED HORMONE REPLACEMENT THERAPY

DHEA is known to prevent the development and to inhibit the growth of dimethylbenz(a) anthracene-induced mammary tumors in the rat.³² DHEA, in addition, inhibits the growth of human breast cancer xenografts in nude mice.³² Thus, in contrast to estrogens and progestins, which exert stimulatory effects, DHEA is expected—as demonstrated in the majority of human breast cancer cell lines—to inhibit both the development and growth of breast cancer in women.

To avoid the problems illustrated by the WHI study⁵ using traditional HRT, it seems logical to use a tissue-specific antiestrogenic or estrogenic (depending on the tissue) compound (SERM) combined with a tissue-targeted androgenic and estrogenic replacement therapy at perimenopause and postmenopause. This strategy could be the best or possibly the only way to maintain a physiological balance between androgens and estrogens in each cell of each tissue and simultaneously prevent breast and uterine cancer. Such an objective can feasibly be met by combining a SERM with DHEA.^{27,32}

Whereas SERMs have effects in the bone limited to the inhibition of bone resorption, DHEA stimulates bone formation through its androgenic or anabolic component^{46,47} (an effect not achieved with SERMs, bisphosphonates, estrogens or calcitonin, which only decrease the rate of bone resorption). In fact,

Table 1 Observed or expected effects of a SERM or DHEA alone, and their combination.

Feature	Effect of DHEA	Effect of SERM	Anticipated effect of combination of DHEA plus SERM
Bone density	Beneficial ^{46,47}	Beneficial ^{43,45}	Beneficial
Cholesterol	None ^{27,47}	Beneficial ^{43,45}	Beneficial
Hot flashes	Beneficial ⁵⁵	To be determined	To be determined
Breast cancer	Beneficial ³²	Beneficial ^{21–23,25}	Beneficial
Endometrial hyperplasia	None ⁴⁷	Beneficial ²⁴	Beneficial
Uterine bleeding	None ⁴⁷	Beneficial ²⁴	Beneficial
Thromboembolic events	To be determined	To be determined	To be determined
Vaginal atrophy	Beneficial ⁴⁷	To be determined	Beneficial
Type 2 diabetes	Beneficial ⁴⁸	Beneficial ⁸	Beneficial
Fat accumulation	Beneficial ^{48,49}	Beneficial ⁸	Beneficial
Muscle mass	Beneficial ⁵⁰	None	Beneficial

Abbreviations: DHEA, dehydroepiandrosterone; SERM, selective estrogen receptor modulator.

these antiresorptive therapies do not improve all the characteristics of normal bone, especially the microarchitecture. Whereas the high potency of acolbifene (10-fold higher than raloxifene) on bone has been demonstrated at the preclinical level,⁸ treatment with DHEA has already been observed to increase bone formation in postmenopausal women through an anabolic action.⁴⁷

In addition to an increase in bone formation, DHEA has been shown in postmenopausal women to stimulate vaginal maturation, decrease adiposity and decrease serum glucose and insulin levels. The effect of DHEA on fat and glucose metabolism described in some studies^{48–50} has not been found in others.^{51,52} It is also possible that SERMs could exert additional beneficial effects in postmenopausal women. In fact, preclinical data obtained with acolbifene include the following beneficial effects: lowered cholesterol and triglyceride levels, reduced fat accumulation and improved insulin sensitivity⁸ (Figure 5).

CONCLUSIONS

Detailed analysis of gene-expression profiles has shown that the ability to metastasize to distant sites and thereby become resistant to treatment is an early and inherent genetic property of breast cancer.⁵³ Unfortunately, such a capacity to metastasize early is reflected by the fact that approximately 50% of breast cancers are already present as micrometastases at time

of diagnosis.^{3,4} Such observations indicate the major importance, or even the necessity, of preventing the development of the disease, which becomes impossible to cure when the advanced stage has been reached.

The generalized estrogen ablation caused by aromatase inhibitors is unlikely to be acceptable for the prevention of breast cancer. It therefore seems reasonable to devote major efforts to develop a SERM that has potent and pure anti-estrogenic activity in the mammary gland and uterus while exerting beneficial or estrogen-like effects in other tissues of importance for women's health, especially the bones, adipose tissue, and glucose metabolism.

Although recognizing the need for a SERM to prevent breast and uterine cancer, it is clear that a SERM alone will not meet all the needs of women at menopause. It seems important, therefore, to develop an approach that takes into account the major decrease in both androgens and estrogens in postmenopausal women. From our current knowledge, DHEA—a tissue-specific precursor of both androgens and estrogens²⁷—seems an attractive solution. In fact, estrogen formation from DHEA in peripheral tissues should not be a problem because, as already well demonstrated, acolbifene can efficiently block the effect of estrogens in peripheral tissues,⁵⁴ thus strongly supporting the proposed combination approach.

When considering a global view of women's health at the menopause, I feel that the increased

understanding of androgen and estrogen formation and action in peripheral target tissues (i.e. intracrinology²⁷)—as well as our recent observations indicating the predominant role of androgens over that of estrogens in the prevention of bone loss after ovariectomy in the rat⁴⁶ and the observation of a stimulatory action of DHEA on BMD in postmenopausal women^{27,47,51,52}—has paved the way for potentially highly significant progress in the field of sex steroid replacement therapy at the menopause.

The tissue-targeted hormone replacement therapy achieved with the combination of a SERM plus DHEA (Figure 5) could also help controlling hot flashes, through the androgenic effect of DHEA, while preventing breast cancer, uterine cancer, ovarian cancer, bone and muscle loss as well as decreasing fat accumulation, type 2 diabetes and serum cholesterol (Table 1). The objective is to develop a tissue-targeted HRT—using acolbifene or another SERM having equivalent characteristics combined with DHEA—to provide sex-steroid replacement therapy only in the tissues that possess physiological levels of the steroid-forming enzymes able to provide tissue-targeted physiological hormone replacement for the tissues in need of these hormones while avoiding exposure of the other tissues and the associated side effects found in the WHI and Million Women studies.

KEY POINTS

- The selective estrogen receptor modulator (SERM) tamoxifen blocks estrogen action and prolongs survival in breast cancer
- New SERMs have more potent activity in the mammary gland and at least one does not stimulate the uterus, reducing the risk of uterine cancer
- The best hope of decreasing death from breast cancer is prevention of the disease, thereby avoiding micrometastases
- Dehydroepiandrosterone (DHEA) is the precursor component of tissue-specific hormone replacement therapy (HRT) and avoids exposure of other tissues as found with traditional HRT
- DHEA allows compensation for the loss of androgens at menopause exclusively in the tissues that need them
- The addition of a highly specific SERM to DHEA might offer the best hope to prevent breast and uterine cancer and to replace traditional HRT, thereby meeting many other needs of women after the menopause

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Competing interests

F Labrie has declared an association with the following organization: Endorecherche. See the article online for full details of the relationship.