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Roles of androgens in the development, growth, and carcinogenesis of the mammary gland

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Abstract

Androgens influence the development and growth of the mammary gland in women. Treatment of animals and cultured cells with androgens has either inhibitory or stimulatory effects on the proliferation of mammary epithelia and cancer cells; the mechanisms for these dual functions are still not very clear and are discussed in this review. Epidemiological data suggest that, similar to increased estrogens, elevated androgens in serum may be associated with the development of breast cancer. Experiments in rodents have also shown that simultaneous treatment of androgen and estrogen synergizes for mammary gland carcinogenesis. Similar synergistic effects of both hormones have been observed for carcinogenesis of the uterine myometrium of female animals and for carcinogenesis of the prostate and deferens of males. There are also clinical and experimental indications for a possible association of elevated levels of both androgens and estrogens with the development of ovarian and endometrial cancers. A hypothesis is thus proposed that concomitant elevation in both androgens and estrogens may confer a greater risk for tumorigenesis of the mammary gland, and probably other female reproductive tissues than an elevation of each hormone alone. © 2002 Published by Elsevier Science Ltd.

Keywords: Premenopause; Postmenopause; Androgens; Estrogens

1. Introduction

Similar to estrogens, androgens influence the functions of many organs in women, such as the hypothalamus-pituitary-ovary axis, mammary gland, uterus, bone, cardiovascular system, etc. [1,2]. Data accumulated, especially during the recent years, have increased the attention to the adverse impact of subnormal levels of androgens on women's health. This raised attention has in turn led to an increase in the use of androgens to correct various clinical symptoms caused by androgen deficiency [1–3]. On the other hand, many lines of evidence have also shown that supernormal levels of androgens may also have adverse effects on the female reproductive system, including abnormal growth and possibly tumorigenecity [4,5]. This latter aspect has commanded much less wariness in the past and should be further studied, particularly because of the increasing use of androgens for various therapeutic purposes in women. This review summarizes mainly the experimental and clinical data on the effects of elevated androgens on the mammary gland, although data on the ovary and uterus are also discussed.

2. Uses of androgens in women

In clinics, many women, both before and after menopause, may have symptoms of androgen deficiency [1,2,6], including unexplained fatigue, lack of well-being, and diminished libido, although these syndromes are not specific for androgen deficiency. Androgens are often prescribed to correct the deficiency [2]. Androgens are also included in certain regimens of hormone replacement therapy for some postmenopausal women to improve their sexuality [7–11]. The additional androgen in hormone replacement therapy is even more important for the women who have received bilateral oophorectomy for any therapeutic reasons, because ovaries provide approximately half of the circulating testosterone (T) in premenopausal women [12,13]. Bone loss in both premenopausal and postmenopausal women has been reported to be associated with lower levels of total and free T [14]. In female monkeys and rats, T treatment results in increases in intrinsic bone strength and resistance to mechanical stress, as well as increases in bone mineral density, bone torsional rigidity and bending stiffness [15,16]. Treatment with androgen plus estrogen has been reported to have a better effect than estrogen alone to prevent bone loss in women, female monkeys and rats [13,15–17].

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Androgens alone may promote atherosclerosis, which was once a concern for using androgens for cardiovascular aspects in women. However, recent findings indicate that combined androgens and estrogens have the opposite effect on the arterial wall, as androgens help maintain vasodilation [2,18,19]. These new findings support the use of combined estrogen and androgen in postmenopausal women from the cardiovascular consideration [19]. Moreover, women are much more predisposed than men to the development of autoimmune diseases, indicating a prophylactic role of androgens for these conditions [20,21]. Laboratory experiments reveal that androgens suppress both cell-mediated and humeral immune responses [2,20,21]. Treatment of postmenopausal women with T or dehydroepiandrosterone (DHEA) has been reported to improve the symptoms of rheumatoid arthritis [22].

Other potential indications for therapeutic uses of androgens in women include postmenopausal loss of muscle mass, management of wasting in HIV infection, and premenstrual syndrome [1,2,13]. Probably the more problematic use of androgens in women is for female-to-male transsexuals, because the doses of androgens prescribed for this purpose are usually higher and the treatment periods are much longer, compared to other therapeutic uses mentioned above. In addition, androgen abuse also occurs occasionally among some female athletes; these supernormal levels of androgens may cause adverse effects as well [23].

3. Role of androgens in the development and growth of the mammary gland in rodents

All newborn rats and mice have female-type of mammary glands, regardless of their genetic sex [24–27]. Male mice and rats lack nipples and their mammary glands are not connected to the skin [24–28]. Gonadectomy at an early age [25,26,29] or treatment with an androgen inhibitor during pregnancy [30] prevents the destruction of the primary duct in the fetal male mouse, leaving the primary duct and the glands connected to the skin in the adults. Conversely, female offspring of rats receiving T during pregnancy show abnormal development of nipples [31,32]. Androgens administered during early pregnancy of rats and mice prevent the formation of the mammary anlagen in the fetus, while injection of androgens into rats and mice during late pregnancy masculinizes the rudiments of mammary glands in the female offspring, with postnatal hypertrophy seen in some glands [33,34]. These prenatal masculinizing effects can be reversed by injection of the mother with antiandrogens [34,35]. When explanted in vitro and protected from androgenic influences, the mammary gland rudiments isolated from a 13-day-old male rat develop into a female-type gland [36]. Conversely, when female rudiments are cultured either together with testicular explants or in the presence of T, they become the male type [25,33]. All these data demonstrate that the environment of sex hormones during pregnancy and neonatal life determines the pattern of the mammary gland in adult life, regardless of the genetic sex. The influence of T on the mammary rudiment is more pronounced during the earlier fetal stage and involves not only the mammary epithelium but also stromal–epithelial interactions [37–41]. After 15 days following conception, the rudiment becomes less sensitive [36,42], but androgens can still inhibit the growth and the development of the mammary gland in later life [29,43]. Short-term, low doses of several forms of androgens have been shown to inhibit the estrogen-induced proliferation of the mammary epithelial cells in female rats, mice and monkeys during adulthood [44–46]. Similar inhibitory effects are also observed in cell or tissue culture [47,48].

In conflict with the above-described inhibitory effects of androgens, many references since 1936 have also shown that administration of androgens, usually at moderate to high doses, stimulates lobule-alveolar development and milk secretion in the mammary glands of female rats with an intact pituitary gland [49–54]. In male rats, this effect is much less pronounced; male rats receiving testosterone propionate (TP) develop mainly aprocrine metaplasia, with the appearance of a large number of apoptotic cells [55]. However, large doses of TP given for long periods induce cystic formations of the mammary epithelia in the rat, and males seem to be more susceptible than females to this effect [49,51]. In contrast, female rats are more susceptible than males to the cyst induction by estrogens [49]. The growth stimulation can also be observed in cultured cells from normal, atypically hyperplastic, and malignant mammary epithelia [56,57]. These effects of androgens both in vivo and in vitro may not be exerted via enzymatic conversion of androgens to estrogens, since an estrogen receptor antagonist cannot block the lobular-alveolar induction by T, dehydrotestosterone (DHT), or DHEA, and since DHT is a non-aromatizable androgen [52,56]. In addition, androgens have also been shown to inhibit differentiation of mammary glands in vitro [52,58], which may not be surprising, as growth stimulation is usually coupled by differentiation inhibition.

In hypophysectomized female rats, T induces a thickening and dilation of the mammary duct systems by proliferation and hypertrophy of the ductal epithelium, without lobule-alveolar formation [49]. Addition of growth hormone restores the induction of lobule-alveolar development by T in hypophysectomized rats, indicating that growth hormone is the major pituitary hormone required for facilitating the effects of androgen on lobular-alveolar induction [49].

4. Role of androgens during adulthood on mammary tumor development and growth

Mammary carcinogens such as 7,12-dimethylbenz[a] anthracene (DMBA), 3-methylcholanthrene (MCA) and methylnitrosourea (MNU) induce mammary tumors at an incidence of virtually 100% in female rats and mice but at virtually 0% in males, if they were given at a single

dose [59]. Dao and Greiner showed that in the rat, the incidences of DMBA-induced mammary carcinomas in non-castrated males, castrated males, non-castrated males receiving an ovarian graft, and castrated males receiving an ovarian graft were 0, 14, 16 and 66%, respectively [60]. These data, together with many others, indicate that endogenous androgens may be prophylactic against DMBA-induced mammary carcinogenesis, while ovarian hormones are promotional [59–61]. On the other hand, Yoshida et al. showed that multiple, biweekly intragastric intubations of DMBA-induced mammary carcinomas in 100% of male and 84% of female rats that were gonadectomized at 27 days of age [62]. These results suggest a likely possibility that the cancer prophylaxis by androgens may be overridden by multiple doses of DMBA. Administration of DHEA to ovariectomized rats inhibits the growth of tumor xenografts formed by the human breast cancer cell line ZR-75-1 [63]. Various forms of androgens given to adult female rats inhibit mammary tumor induction by DMBA, MNU, or several types of estrogens [53,54,59,61,64–68]. Several forms of androgens given to adult female rats bearing palpable mammary tumors induced by chemical carcinogens cause regression of the tumors, although the regression may be incomplete in some cases [54,59,68–71]. Administration of T increases the latency of mammary tumor induction by estrogen when given before the tumor formation [72]. The T also causes tumor regression when given to the rats bearing estrogen-induced mammary tumors, but the regression is only temporary, and the tumors will later become refractory to the androgen, if the animals continue receiving estrogen [72,73].

It has been shown in several experiments that while most chemical- or estrogen-induced mammary tumors respond to androgen administration with regression, there are always a few tumors showing a stimulatory response [59,73,74]. Notably, several studies have shown that administration of different forms of androgens at moderate or high doses to rats bearing chemical-induced mammary tumors enhances the tumor growth [59,75–77]. In addition, androgen treatment plus ovariectomy is less inhibitory than ovariectomy alone for the growth of DMBA-induced mammary carcinomas, indicating that androgens may counteract the inhibitory effect of ovariectomy [78]. Boccuzzi et al. also show that DHEA stimulates the growth of the DMBA-induced mammary tumors in ovariectomized rats, although in their experiments DHEA inhibits the tumor growth in ovarian-intact rats [79]. The mechanisms for these stimulatory effects of androgens still remain unknown, although the phenomenon has been discerned for a few decades. The conjecture that conversion of androgens to estrogens accounts for the stimulatory response is certainly possible, but this may not be the dominant event, as it does not explain why in many other experiments androgens are inhibitory rather than stimulatory, as described in the above paragraph. Clinically, treatment of breast cancer patents with androgens has occasionally been observed to exacerbate the tumor as well [74,80].

5. Role of prenatal and neonatal androgens in mammary gland carcinogenesis during adulthood of rodents

Both rats and mice of either sex exposed to sex steroids in utero or the neonatal period exhibit permanent functional alterations in the endocrine and reproductive systems [81–86]. These animals have also been shown to develop dysplasia and neoplasia in vaginal and endometrial epithelia, as well as in mammary glands in certain strains of mice [83,86–89]. Female rats neonatally exposed to a single dose of TP show a significantly lower mitotic rate of the mammary epithelia during adulthood [90]. However, treatment of these neonatally androgenized female rats with DMBA at the age of 52 days induces a higher mitotic rate of the mammary epithelia before the tumor formation, compared to the non-androgenized counterparts [90].

Male and female mice neonatally exposed to either E2 or T exhibit increased incidences of mammary dysplastic lesions and carcinomas following their infection with mouse mammary tumor virus (MMTV) or their exposure to DMBA during adulthood; neonatal androgenization is more potent than neonatal estrogenization for this effect [86,91]. However, the influence of neonatal androgenization in DMBA-induced mammary carcinogenesis may be different in the rat. Some reports show that neonatal androgenization of female rats actually suppresses the induction of mammary adenocarcinomas by DMBA, while it induces mammary dysplasia, a lesion that is borderline between benign and malignant [92–97]. While some other studies in the rat confirm the increased induction of dysplastic lesions or adenofibromas (a benign form of tumor), they do not show a pronounced change in the incidence of the malignant tumors [86,90]. The reason for this species difference still remains unknown.

Verhoeven et al. performed gonadectomy to neonatal male and female rats and immediately treated some of the animals with a single dose of T or E2 [98]. These animals did not show significant change in the incidence of DMBA-induced mammary carcinomas, compared to the gonadectomized rats without treatment of T or E2. Thus, it seems that the effect of neonatal androgenization or estrogenization on the induction of mammary carcinomas by DMBA may require intact gonads during neonatal life [94,99,100]. Christakos et al. showed that DMBA given at the age of 55 days failed to induce mammary tumors in neonatally androgenized and ovariectomized rats, but induced the tumors in neonatally androgenized, ovary-intact rats with a longer latent period compared to non-androgenized, ovarian-intact controls, again showing an inhibitory role of neonatal androgenization and a dependence on the ovary. Yoshida et al. confirmed these findings of Christakos et al. and further showed that injection of progesterone restored tumor induction in ovariectomized rats [99], thus pointing to progesterone as the hormone responsible for the ovarian dependence.

Yoshida and Fukunishi [101] treated neonatally androgenized female rats with a single dose of DMBA at the

age of 50 days, and performed ovariectomy on one-half of the rats 28 days after dosing, with or without simultaneous administration of E2 or progesterone. While about 90% of the androgenized, ovarian-intact rats develop mammary dysplasia (mastopathia cystica), only 4% of androgenized, ovariectomized rats develop the dysplasia. Dysplasia developed at 96% incidence in the rats receiving ovariectomy plus E2, in strong contrast to its 0% incidence in the rats receiving ovariectomy plus progesterone. These data suggest that in neonatally androgenized female rats, development of dysplasia is dependent on estrogen, while progesterone may be either ineffective or inhibitory, in conflict with the progesterone dependence of the effects of neonatal androgenization on malignant carcinoma induction by DMBA. The reason for this conflict is currently unknown. Since various progestins are known to have variable degrees of androgenic effects [76,102–105], it cannot be excluded that the diverse effects of progesterone reflect the possibility that normal, benign, and malignant mammary tissues may have differential responses to the progestational and androgenic effects of progesterone.

Although both neonatal estrogenization and androgenization depress ovarian functions, only neonatal androgenization has been shown to induce lactational alterations in female rats, suggesting the involvement of prolactin [49–51]. Indeed, increased levels of circulating prolactin have been reported in neonatally androgenized female mice and rats [94,106]. Prolactin is considered to be responsible for the ovarian dependence of the effects of neonatal androgenization on DMBA-induced mammary carcinogenesis as well [94,106], since secretion of prolactin by the pituitary is controlled by the ovary. This consideration gains support from the fact that prolactin exerts a considerable influence on chemically induced mammary carcinogenesis [107–109]. Moreover, several in vitro studies also show that androgens induce expression of the prolactin receptor [110] as well as stimulate expression and secretion of prolactin in uterine stromal cells [111]. Thus, the lactational alterations in neonatally androgenized female rats may be due to increased function of prolactin–prolactin receptor signaling.

6. Indications for an association of androgens with breast cancer in women

Serum T concentration is 10 times higher than that of E2 in women [112,113]. Both normal and cancerous breast tissues contain and produce several forms of androgens as well [114–123]. Androgen receptor (AR) is expressed in normal mammary epithelial and stromal cells [124,125]. Many pathologic studies have also demonstrated that over 70% of human breast cancer biopsies from untreated women are positive for AR; the percentages are usually higher than, or equal high to, the percentages of ER and PR positivity [126–135]. These facts provide the basis for a direct AR-mediated action of androgens in the normal and malignant breast tissues. On the other hand, several key enzymes responsible for metabolic conversions of various forms of androgens to estrogens have also been detected at significant amounts in the tissues of normal breast and breast cancer [122,136–141], which provides the basis for the local biotransformation of androgens to estrogens, resulting in estrogen excess [4,119,140,142–147]. Currently it still unclear whether the direct, androgenic function, or the indirect, estrogenic function is the major mechanism used by androgens to influence the growth of the mammary gland and mammary carcinoma.

Many references have documented higher T levels in urine and blood of pre- and post-menopausal breast cancer patients, with or without a concurrent increase in circulating levels of estrogens, compared to the normal women at the same age [135,141,148–169]. However, some other studies show that the increased T occurs only in postmenopausal women with breast cancer, not in the premenopausal ones [170–172]. According to the estimation of Secreto and Zumoff [160] and Secreto et al. [165], about 60% of women with breast cancer show some degree of hypertestosteronemia, and ovariectomy eliminates the T excess, indicating its ovarian origin [160,173–175]. Grattarola found that 40% of breast cancer patients had simple proliferative endometrium, and 43% had hyperplastic or atypical endometrium, virtually pathognomonic for chronic anovulation [176]. It is likely that the hypertestosteronemic and anovulatory populations may be the coincident [160]. Therefore, T excess is likely to be generated from the hyperplastic interestitial cells of the ovary [177], a thought supported by the studies showing that chronic anovulation syndrome is a major risk factor for postmenopausal breast cancer [160,178]. A very high incidence of anovulation in premenopausal breast cancer patients has also been reported [179], although some other studies fail to find a significant association between polycystic ovary syndrome, which is defined by clinical features of anovulation and hyperandrogenism [180], and the risk of premenopausal breast cancer [181,182]. In some women originally exhibiting T excess, T level is increased again after the ovariectomy; suppression of the adrenal cortex by dexamethasone treatment eliminates the recurrence of T elevation, suggesting that biotransformation of adrenal androgens to T may account for the recurrence [160,173,174,183]. Recent studies not only confirm the strong association of elevated serum concentrations of both E2 and T with increased risk of breast cancer, but further show that the association of free T levels to breast cancer is independent of bioavailable estradiol levels [184,185]. Thus, the mechanism for the association of elevated T with breast cancer seems not as simple as conversion of T to E2.

While the association of T with breast cancer seems to be clear, the relationship between adrenal androgens and breast cancer is still confusing [76,79,170,172,179,186–188]. DHEA, DHEA sulfate (DHEAS), and Adiol (5-androstene-3β,17β-diol) of adrenal origin have all been detected at high amounts in normal breast tissue and in breast cancer [87,115,116,119,179]. Postmenopausal breast cancer

patients have been shown to exhibit supranormal plasma levels of DHEA and DHEAS [160,179,187]. Moreover, elevated plasma levels of DHEA have been found in women who subsequently developed postmenopausal breast cancer [150,162,169]. These data imply that similar to T, elevated adrenal androgens may be associated with breast cancer development, as well. Conversely, however, a low urinary excretion of DHEA metabolites has been reported in women who subsequently develop breast cancer, in women with breast cancer, and in women with high risk of the cancer recurrence after mastectomy [160,179,187]. Subnormal plasma levels of DHEA and DHEAS have also been reported in early, as well as advanced breast cancer patients, especially in premenopausal cancer patients [170,171]. These data suggest that higher levels of adrenal androgens may be prophylactic for the development, progression, and reoccurrence of breast cancer.

In cell culture, T and several forms of adrenal androgens have been shown to inhibit growth of many cell lines of breast epithelium or cancer [44,74,134,188–191] but to stimulate growth of several other cell lines [56,192–196]. It has been suggested that androgens stimulate growth of malignant cells more frequently than growth of non-malignant cells, whereas estrogen show an opposite effect [57]. At least for some of the mammary epithelial cell lines, non-aromatizable androgens DHT and 3-α-diol can also stimulate the growth, and estrogen receptor (ER) antagonists cannot block this stimulation. These results suggest that the growth stimulation may not be occurring due to conversion of androgens to estrogens and may not involve ER [56]. Nevertheless, androgens have been shown in many other experiments to exert their effects by binding directly to the estrogen receptor α (ERα) rather than the AR to promote cell proliferation [192,196–199]; in this situation, androgens actually function as estrogens and exert estrogenic effects. Currently, it is still mechanistically unclear how androgens exhibit different roles in the growth of these cells.

7. Synergy between androgens and estrogens in the tumorigenecity of mammary gland and other organs

In a series of publications since 1950, Kirkman and coworkers have described that simultaneous administration of estrogens and androgens to Syrian hamsters effectively induces lieomyomas and lieomyosarcomas in the uterus of females and in the epididymal tail and adjacent ductus deferens of males [200–209]. The female animals also exhibit extensive endometrial hyperplasia [201]. The hamsters receiving either estrogen or androgen alone do not develop these tumors, at least at the same time period, although androgen-treated animals develop papillary adenoma of uterus occasionally [202]. Simultaneous administration of androgen and estrogen to Syrian hamsters of either sex also induces malignant basal cell chaetepithelioma in the flank organs (scent glands) of the skin; this organ consists of many large sebaceous glands, hair follicles, and baskets of melanocytes around the growth cycles of the hair follicles [202,207,209–211]. Androgen is responsible for the early development of the chaetepithelioma but both androgen and estrogen are required for its unlimited growth as a definitive neoplasm.

Noble and coworkers described in a conference abstract in 1976 that, although Nb rats were relatively insensitive to estrogen-induced mammary carcinogenesis [212], male and female Nb rats receiving subcutaneous implants of both estrone and TP pellets developed mammary carcinomas in approximately 50–60% of the animals [213,214]. Noble and coworkers also mentioned that estrone treatment of female Nb rats produced mammary carcinomas only when begun in immature rats, whereas combined treatment with both hormones produced carcinomas in rats of any age [212,215,216]. The mammary tumors induced by estrogen or by both estrogen and androgen were transplantable and dependent on estrogen or androgen [217,218]. Although Noble had not published any full report on this rat model of mammary carcinogenesis, he established a prostate carcinogenesis model in male Nb rats by using both TP and estrone pellets [219,220]. According to Noble, administration of TP alone induced prostate cancer at approximately 20% incidence following over one year of treatment [219]. Simultaneous administration of both TP and estrone did not change the incidence of the tumors but shortened their latent period [219,220]. Initial androgen treatment followed by estrogen was the most effective, inducing cancer at about 50% incidence. The prostate tumors induced by both hormones were transplantable [215,216,219,220].

Unaware of Noble's earlier work, Liao et al. [55] and Xie et al. [221–224] independently reported similar findings recently, showing that simultaneous administration of TP and E2 (or E2 benzoate in the studies of Xie et al.) induced invasive mammary adenocarcinomas in male and female Nb rats, at virtually 100% incidence, 5–6 months following the hormonal treatment. At this time point rats receiving estrogen alone developed only hyperplasia, without tumor formation. Androgen alone does not induce obvious outgrowth of the mammary epithelia at the dose used in these Nb rat models, and therefore is likely to function as a promotional agent for estrogen-induced carcinogenesis. One should not be too surprised by these findings in the Nb rat, since the mammary gland shares the same embryonic origin with the sebaceous gland, the major component of the flank organ in the skin of hamsters, which was shown by Kikman and coworkers to develop epitheliomas upon combined treatment of androgen and estrogen [207,210,211]. However, these experimental results in Nb rats raise a concern as to whether a similar synergy between estrogens and androgens also occurs during breast tumorigenesis in humans. Since the literature about whether elevated estrogens are a risk factor of breast cancer has always been inconsistent [4,225–227], it would be an intriguing question as to whether it is the concurrent elevation of both estrogen and androgen,

but not each hormone alone, that is a risk factor of breast cancer.

Male-to-female transsexual patients need to receive estrogen therapy to become phenotypic females, and thus exhibit a unique endocrine situation of higher androgen levels than genetic females and higher estrogen levels than genetic males. Cases of the development of mammary cysts, fibroadenomas, and breast cancers have been reported in these transsexuals [228–230]. On the other hand, female-to-male transsexuals need to receive androgens to become phenotypic males while retaining ovaries, which results in higher androgen levels than genetic females and higher estrogen levels than genetic males [131,231,232]. Actually, the female-to-male transsexuals receiving androgen therapy exhibit increases not only in circulating T but also in circulating estrone and E2 [233–235], compared to normal women. This unique endocrine situation may make these female-to-male transsexuals a good population for the study of the possible synergistic tumorigenecity of abnormal estrogen and androgen in women. Unfortunately, so far, there have only been several studies and case reports on the observations of breast tissue collected at mammoplasty of female-to-male transsexuals [236–239]. In these studies, cystic formation and apocrine metaplasia are the major morphologic findings, while no pronounced hyperplasia nor dysplasia of the mammary epithelia is observed. However, the majority of the cases in these studies received androgen treatment for only one to several years, which is a too short a period relative to the life span in women, considering the fact that hormonal carcinogenesis in experimental animals usually takes one-fourth or more of the life span [55,221]. In addition, many patients in these studies had stopped use of androgens prior to their mammoplasty. Therefore, it remains unknown whether a longer androgen therapy in female-to-male transsexuals associates with neoplastic growth of their mammary glands.

There are also indications for a possible synergistic role of estrogens and androgens in the tumor development of other female reproductive organs. It has been well known that the development of ovarian cysts is associated with elevated levels of circulating T [131,232,240–242]. Since ovarian cysts have a higher risk to progress into ovarian cancer [243–245], elevated androgens may be interrelated to the ovarian cancer development [246–248]. This hypothesis is supported by the facts that AR is expressed in normal ovaries and in most ovarian cancer biopsies [249–252]. Because elevated estrogens have been associated with an increased risk of ovarian cancer [246,247,253], it cannot be excluded that increased estrogen and androgens may actually play a combined role. In line with this consideration, a pronounced increase in the development of polycystic ovarian disease has been documented in the literature for the female-to-male transsexuals, and cases of ovarian cancer have been reported in these transsexuals as well [131,241,254–258].

Elevations in circulating T are associated with the occurrence of endometrial hyperplasia and squamous metaplasia [178,246,259–261]. Since the androgen concentrations in uterine tissue are even higher than the concentrations in the serum [123,262], a direct role of androgens in the uterus is very likely. Supports to this thought are the facts that AR is expressed in significant amounts in endometrium and stroma of normal uterus and in endometrial cancer [134,249,251,263]. Moverover, increased androgenic activity has also been observed in well-differentiated endometrial adenocarcinomas [264]. All these data provide the cellular basis for a direct action of androgens in these normal and malignant uterine tissues.

Cases of endometrial cancer and uterine leiomyomas have been reported in women with hirsutism, usually caused by adrenal disfunction [265–267]. Women with a history of exposure to diethylstilbestrol (DES) in utero, so-called DES daughters, also exhibit an elevated level of ciruculating T [268] and an increase in the frequency of hirsutism [269]. Proliferative endometrium has been observed in the majority of the female-to-male transsexuals receiving androgen therapy, with cystic hyperplasia in some cases [241,256,257]. In line with these clinical data, female mice exposed in utero to DES, a treatment which has been shown to increase circulating T [270], develop uterine adenocarcinomas [84,268,270–276]. Treatment of ovariectomized female rats with T markedly increases the height of the luminal epithelium of the uterus [277] and induces marked endometrial metaplasia and hyperplasia [261]. All of these clinical and experimental results indicate an association of elevated androgens with endometrial outgrowth and cancer. Since elevated estrogens have been associated with the hyperplasia and neoplasia in the uterine endometrium as well [123,246,278–283], it is possible that increased estrogens and androgens may actually play a combined role. Actually, in female Syrian hamsters treated with estrogen and androgen, but not either hormone alone, uterine carcinomas were occasionally discerned, together with cystic glandular hyperplasia of endometrium [208,209]. Xie et al. also observed a uterine carcinoma in one female Nb rat receiving both hormones, although it was suspected to be a metastasis from the mammary tumors [221].

8. Possible mechanisms for the roles of androgens in the female reproductive organs

The mechanism accepted by most investigators for the growth-stimulatory action of androgens in mammary epithelia and breast cancer is that androgens serve as precursors for biotransformation to estrogens, resulting in estrogen excess. This mechanism certainly exists and plays certain roles, as described earlier. However, it does not explain the growth inhibition by androgens observed in many other situations, and therefore may not be the dominant mechanism, at least in certain circumstances.

It has been proposed for many years that low levels of adrenal androgens may promote breast cancer and higher levels may prevent it [187]. Adrenal androgens are postu-

lated to have two primary effects on mammary tumor cells [76,179,186,188]: (1) In the absence of estrogens, they stimulate growth of breast cancer cells via binding to ERα; this effect can be blocked by treatment with antiestrogen. (2) In the presence of estrogens; they act as antiestrogens to inhibit estrogen stimulation of growth of breast cancer cells, this effect is exerted via AR and can be blocked by antiandrogens [179,189,284]. According to these hypotheses, in those who have low circulating estrogens, such as most postmenopausal women, androgens may be growth stimulatory for mammary epithelial or cancer cells by direct binding to ERα to mediate estrogenic functions. This line of thinking obtains supports from the in vitro observations that androgens, especially those of adrenal origin, indeed are capable of binding to ERα, although the binding affinities are much lower, compared to estrogens [186,192,196–199]. On the other hand, in those who have relatively high circulating estrogens, such as most premenopausal women, androgens may exert mainly antiestrogenic effects via binding to AR, suppressing estrogen stimulation of the growth of mammary epithelial or cancer cells. Down regulation of the expression of ERα and progesterone receptor (PR) may be one of the mechanisms for androgens to achieve this effect [76,188,285].

It is a well-known phenomenon that most androgens have various abilities of binding to PR to mediate progestational functions [76,286]. Since progesterone has a complicated influence on the mammary epithelia, including both growth stimulation and inhibition [287], it remains possible that the reported dual functions of androgens may actually be a reflection of their progestational effects. In addition, androgens have been shown to stimulate expression and secretion of prolactin from uterine stromal cells [111] and to induce expression of the prolactin receptor in human breast cancer cells [110]. Neonatal androgenization also increases the secretion of prolactin from pituitary during adulthood [94,106]. Therefore, the effects of androgens may also be a result of increased function of prolactin–prolactin receptor signaling.

The AR gene contains a highly polymorphic CAG trinucleotide repeat, which encodes glutamines, in its first exon. The length of the CAG repeat is inversely associated with the degree of transcriptional activity of AR [288]. In a recent report [289], ovarian cancer patients who carried a short CAG repeat allele of AR was diagnosed on average of 7.2 years earlier than those patients who did not carry a short allele, indicting that a stronger AR activity might be associated with ovarian cancer development. On the other hand, in women who inherit a germline mutation in the *BRCA1* gene, those who carry more CAG repeats in at least one AR allele have a higher risk of breast cancer development than those who carry less CAG repeats [290,291]. Since BRCA1 protein is an AR coactivator that binds to AR and enhances AR signaling [292], it is possible that in BRCA1 carriers, androgens may act via AR to inhibit the development of breast cancer, although it may not be the case in non-BRCA1 carriers.

Another mechanism, which also involves an AR-coactivator but not androgens per se, is that in the presence of the AR coactivator ARA_{70}, E_2 (but not DES) is capable of binding to AR and activating AR transcriptional activities in some human prostate cancer cells [293,294]. Evidence has also been shown that this mechanism may be involved in the development of the male reproductive system as well [293]. Thus, the natural estrogen can also function as an androgen to be a natural ligand of AR under certain, yet undefined, conditions. It is currently unknown whether such ARA_{70}-mediated activation of AR transcriptional activities by E_2 also occurs in the normal and malignant tissues of the mammary gland and other female reproductive organs, although ARA_{70} expression has recently been shown to be activated in human ovarian cancer [295].

In summary, androgens of both ovarian and adrenal origins have been shown, both in animals and in cultured cells, to either stimulate or inhibit growth of the mammary gland and breast cancer. There are at least six possible mechanisms for androgens to accomplish these functions: (1) Androgens serve as estrogen precursors and are converted to estrogens. (2) Androgens exert estrogenic effects by directly binding to ERα; adrenal androgens have higher affinities for ERα than T and DHT, and therefore are more potent in this function. (3) Androgens exert androgenic effects by directly binding to AR. (4) Androgens may bind to PR and exert progestational effects. (5) Androgens may stimulate the expression of prolactin and prolactin receptors, playing the functions of prolactin. (6) In the cases of BRCA1 carriers, androgens may act via AR–BRCA1 complex to inhibit the development of breast cancer; this mechanism, if it really exists, is affected by the length of the CAG repeat in the AR gene.

9. Perspectives

Many references described in this review seem to lead us to a hypothesis that increased androgens and estrogens may be synergistic in tumorigenecity of several tissues of the reproductive systems. So far, this hypothesis has received experimental evidence in rodents for tumorigenesis in the prostate, epidimis, uterine myometrium, and mammary gland, as described earlier, while direct experimental evidence for tumorigenesis in the ovary and endometrium is still lacking. Attempts have been made to use either estrogen or androgen alone, but not in combination, in the induction of ovarian cancer and endometrial cancer [207,274,296–301]. The results of uterine carcinogenesis by either estrogen [274,275,297,300] or androgen [296,301] have been satisfactory, at least in certain strains of mice. Combined treatment of DMBA and T, but not each alone, has also been shown to effectively induce endometrial cancer in female rats [302]. However, estrogen- or androgen-induced ovarian tumorigenesis has so far resulted mainly in benign epithelial neoplasms, at least in guinea pigs [298,299]. It would be intriguing to see whether combinations of androgen and

estrogen at certain doses and ratios are capable of inducing tumors of the ovary and endometrium at high incidences, and which forms of androgens and estrogens are more potent than the others for tumorigenecity. It is possible that even if androgens and estrogens are eventually shown to be indeed synergistic for tumorigenecity of many reproductive organs, including the ovary and endometrium, the optimal doses of each hormone and the ratios between the two hormones may be tissue specific. Different forms of androgens and estrogens may show different tumorigenic potencies for different tissues or organs. Each specific target tissue may have its own optimal form of androgen and estrogen and its most optimal ratio of the two hormones for tumorigenecity. This may explain the observation that uterine carcinomas develop only occasionally in the female Syrian hamsters [208,209] and Nb rats [221] treated for other purposes with both estrogen and androgen.

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