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Safety of 5 α -reductase inhibitors and spironolactone in breast cancer patients receiving endocrine therapies

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Abstract

Purpose: To provide dermatologists and oncologists with a foundation for practical understanding and uses of 5 α -reductase inhibitors and spironolactone for breast cancer patients and survivors receiving endocrine therapies, including the effect of these treatments on sex hormone levels, any reported drug interactions, and any risk of malignancy.

Methods: All published studies from January 1978 through April 2018 were considered, using databases such as PubMed, Google Scholar, and Science Direct. 47 studies were included in this review.

Results: There is no evidence of interactions between 5 α -reductase inhibitors and spironolactone with endocrine therapies used in breast cancer. Sex hormone alteration with 5 α -reductase inhibitor or spironolactone use is variable. 3 randomized controlled trials, 1 case control study, and 6 retrospective cohort studies, including 284 female patients, studied 5 α -reductase inhibitors' effects on serum estrogen levels. Levels were increased in 97 of 284 (34%) patients, decreased in 15 of 284 (5.3%) patients, and unchanged in 162 of 284 (57%) patients. 4 retrospective cohort studies, 1 case study, and 1 double-blinded crossover study, including 95 female patients, assessed spironolactone's effect on estrogen levels. Levels were increased in 25 of 95 (26%) patients, decreased in 6 of 95 (6.3%) patients, and unchanged in 64 of 95 (67%) patients. Ultimately, most patients did not have a significant alteration in the level of estrogen when using 5 α -reductase inhibitors or spironolactone. No consistent evidence of increased risk of female breast cancer while on spironolactone was reported in 3 studies including 49,298 patients; the risk of breast cancer with the use of 5 α -reductase inhibitors has not been studied.

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Conclusions: Most patients did not show increased estrogen levels with spironolactone and there was no data suggesting increased risk of breast cancer. Based on hormonal and pharmacological activity, spironolactone may be considered for further research on alopecia and hirsutism in breast cancer patients.

Keywords

5 α -reductase inhibitors; spironolactone; female pattern hair loss; female breast cancer; endocrine therapy

INTRODUCTION

Breast cancer is the most common cancer in women [1]. Over 250,000 women in the United States are diagnosed with breast cancer each year [2]. Fortunately, systemic therapies, such as endocrine therapies (ETs), can improve these patient's lives' expectancy significantly, but are also associated with adverse events (AEs) related to estrogen deprivation [3], including hot flashes (40%), arthralgias and myalgias (21%), and alopecia (15–25%) [4,5].

Approximately 15–25% of women taking ETs will develop alopecia, similar to androgenetic alopecia [6]. ET-induced alopecia (EIA) is clinically characterized as a diffuse alopecia over the fronto-parietal area of the scalp, with or without frontal hairline recession; it is similar to female androgenetic alopecia (female AGA), has a substantial negative impact on quality of life [7], and can hinder patients' adherence to cancer therapies. In a systematic review including 13,415 women from 35 clinical trials, 4.4% developed EIA with the highest incidence in patients treated with tamoxifen (25.4%) [4].

Incomplete hair regrowth 6 months following chemotherapy completion in patients who received cytotoxic chemotherapy is defined as persistent chemotherapy-induced alopecia (pCIA) [8]. pCIA has a reported incidence of up to 30% [9] in women treated with taxane-based chemotherapy (paclitaxel and docetaxel) [8,10–13] and cyclophosphamide-based chemotherapy [11,14,15].

Management of pCIA and EIA in breast cancer survivors is mostly based on case reports and expert opinion. Consequently, there are currently no Food and Drug Administration (FDA) approved therapies for pCIA and EIA [16]. Improvement with topical minoxidil has been shown in case reports of pCIA [13,14] and in one uncontrolled study for EIA, where 37 of 46 patients (80%) had moderate to significant improvement [7]. Spironolactone has shown some efficacy in female AGA in a study on 80 non-cancer women, 44% experienced regrowth with oral spironolactone [17]. On the other hand, finasteride's efficacy remains controversial; both treatment successes and failures exist in the literature [18–28]. Improved hair growth at doses ranging from 1.25mg to 5mg daily [33] have been reported in both hyperandrogenic and normoandrogenic women with female AGA. Despite these findings, a review of 47 randomized trials found that there is low-quality evidence to support finasteride's efficacy over placebo in treating female AGA [18]. Finasteride has reportedly been successful in treating idiopathic hirsutism in several studies [29–32]. Despite moderate quality evidence favoring finasteride's efficacy over placebo, to treat hirsutism, still only a weak recommendation exists [34].

The goal of this review is to provide dermatologists and oncologists with a foundation for practical understanding and uses of 5 α -reductase inhibitors and spironolactone for EIA and pCIA among breast cancer patients and survivors receiving ETs, including the effect of these systemic alopecia therapies on sex hormone levels, any reported drug interactions, and any risk of malignancy and tumor recurrence.

Sex Hormones and Hair Cycle

Estrogen promotes hair growth and dictates hair loss [35], whereas dihydrotestosterone (DHT) is responsible for transforming large, terminal hair follicles into miniaturized hair follicles [36,37], causing female AGA. Sex hormone binding globulin (SHBG) may also serve a role in female AGA, as it is the major transport protein for circulating testosterone and estradiol. Elevated androgens, notably testosterone, DHT, and their precursors: dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione, block SHBG production, while estrogen increases SHBG synthesis. Total testosterone is normally bound to SHBG in the serum, whereas free testosterone is active in peripheral tissues and accounts for 2% of total testosterone [38]. Only free testosterone and estradiol are active in the body; therefore, SHBG levels have been reported inversely proportional to the degree of female AGA [39].

Since estrogen receptor stimulation prolongs the duration of anagen in human scalp hair follicles [40,41], antagonizing signaling through estrogen receptors is expected to shorten anagen, inducing premature hair follicle regression (catagen), and telogen effluvium. Since female AGA likely results not only from the undesired effects of androgen stimulation of hair follicles in androgen-sensitive skin regions, but also from a relative lack of hair follicle stimulation by estrogens [42], this may explain the similarities between EIA and female AGA treated with anti-estrogens.

Endocrine Therapies used in Breast Cancer

Breast cancers can be hormone responsive (estrogen receptor and/or progesterone receptor positive), human epidermal growth factor 2 (HER2) responsive, or triple negative for hormones or HER2. High levels of estrone and testosterone have been associated with an elevated risk of breast cancer [44]. B-estradiol (E2) works via binding to the estrogen receptors (ERs), ER α and ER β , found in the mammary gland, activating cell growth. ER α is present in about 40–70% of breast cancers and is thought to be predictive of ET responsiveness [45]. Approximately 2/3 (66%) of breast cancer cells express aromatase, which functions to convert androgens to aromatic estrogens [43].

Selective Estrogen Receptor Modulators (SERMs) act as estrogen agonists on bone, liver, and the cardiovascular system, and as estrogen antagonists on the breast, but each SERM's effects depend on where it is metabolized [46]. The binding of tamoxifen to ER α blocks breast cancer proliferation. AIs, notably anastrozole and letrozole, are first line antiestrogen agents of choice for post-menopausal women, by blocking estrogen production in peripheral tissues. Circulating estrogen competes with androgens for binding to SHBG, and it is postulated that SHBG synthesis reflects the estrogen/androgen balance [47]. AIs inhibit the enzyme aromatase, and can lead to increased testosterone and DHT, as well as decreased

estrogen in the scalp [48–50]. Lastly, fulvestrant is an estrogen antagonist used to treat postmenopausal women with advanced breast cancer [51]. GnRH agonists, such as leuprolide, have also been used in premenopausal women to suppress ovarian production of estrogen (Table 1).

5 α -reductase inhibitors used for alopecia (finasteride/dutasteride)

Finasteride and dutasteride exert their effects via competitive inhibition of type 2 5 α -reductase, blocking the conversion of testosterone to DHT [29]. DHT binds to androgen receptors on the scalp and results in miniaturized follicles [52,53]. 5 α -reductase inhibitors, theoretically, may increase serum total testosterone levels, leading to increased estrogen levels via aromatization. Hyperandrogenemia has been displayed in 82–87% women with female AGA exhibiting clinical signs of hirsutism [39,54]. However, anti-androgen therapy with finasteride has not been consistently successful in treating female AGA in normoandrogenic patients [39].

Safety—Finasteride is generally safe in women with female AGA based on several studies [20–28]. However, it has been associated with depression, reduced libido, and fetal teratogenicity, warranting its classification as an FDA pregnancy category X drug and is contraindicated in pregnant and reproductive age women [18].

Evidence of alterations in sexual hormones with 5 α -reductase inhibitors is generally not seen, except for variability in serum testosterone levels. Finasteride's efficacy has been tested in 21 studies including 394 women with idiopathic hirsutism, and 7 studies including 135 women with polycystic ovarian syndrome (PCOS), with no existing studies on female breast cancer patients taking finasteride. No change in serum levels of estrogen [29,55–59], free testosterone [29,55,56,60–62], or total testosterone [58,63–67] were demonstrated in 6 of 21 studies (29%) on hirsute women given finasteride (Table 2). Overall, out of 284 female patients included in table 2, 97 (34%) had an increase in serum estrogen level, 15 (5.3%) had a decrease in serum estrogen level, and 162 (57%) showed no significant change in serum estrogen level. Of note, none of the studies specified when in the menstrual cycle the estrogen level was drawn. Consequently, more than half of the patients did not experience a significant alteration in the level of serum estrogen, after taking 5 α -reductase inhibitors. Eleven of 21 (52%) studies reported no change in LH/FSH [32,55–58,61,65–69], and 12 of 21 (57%) reported no change in SHBG [32,55–60,62–64,66,69]. However, 8 of 21 (38%) studies reported an increase in total testosterone [29,31,32,55,56,60,62,69]. As expected, DHT was generally decreased with finasteride use in women with hirsutism, with as high as 90.2% serum DHT reduction from baseline, after 24 months of treatment [70–72].

To date, there is no established association between finasteride use and increased risk of prostate or male breast cancer. Finasteride demonstrated a reduction in the risk of prostate cancer by 25% in 597 men receiving finasteride, versus 676 receiving placebo, despite high-grade prostate cancer being more common in the finasteride treatment group [73].

There is limited data on the use of finasteride and risk of male breast cancer. Two case-control reports, including 300–400 cases compared to approximately 4,000 and 6,800 controls, resulted in no significant association between finasteride use and male breast

cancer [74,75]. However, in an epidemiologic study including 90,000 of 7.5 million men from Nordic countries, an increased incidence rate ratio of 1.44 was observed among finasteride users, compared to nonusers [76].

Spironolactone

Spironolactone acts as an aldosterone antagonist, but is also a peripheral anti-androgen, and is commonly used to treat heart failure and clinical signs of hyperandrogenism including hirsutism and alopecia. Unfortunately, the mechanism of action of spironolactone is not well understood [77]. Proposed mechanisms include direct inhibition of the mineralocorticoid receptor and action via active metabolites. Spironolactone also acts as an agonist on the progesterone receptor, yet is also an androgen receptor antagonist.

Safety—The link between spironolactone use and increased risk of breast and gynecologic cancer remains weak [78–81] (Table 4). However, it is hypothesized that spironolactone may increase levels of estrogen and cause an increased risk of hormone-responsive cancers such as breast and ovarian [82]. When spironolactone was studied in 28,000 cases versus 56,000 controls out of a total population of 1,290,625 women aged 55 or greater, no increased incidence of breast cancer was found [81]. Furthermore, no increased incidence in cancers could be concluded, when spironolactone was used in 74,272 patients matched 1:2 with unexposed controls. Out of the 74,272 women, 52,671 (71%) were incident users, with a median follow-up time of 11.3 years compared to 3.1 years for prevalent users [82]. Lastly, no statistically significant association between spironolactone exposure and increased incidence of breast cancer was observed in two case-control reports. One studied approximately 50,000 hypertensive women, treated with spironolactone and compared to placebo, [79] and the other studied 975 hypertensive women with breast cancer, compared to 1,007 hypertensive women without breast cancer [78].

The literature review supports that there is no significant change in serum androgens, estradiol, or LH/FSH (Table 3). A decrease in serum testosterone was found in 8 of 18 (44%) studies [83–90], whereas no change in serum testosterone was found in 10 of 18 (56%) studies [30,61,91–98]. No change in DHEA-S was reported in 9 of 18 (50%) studies [30,61,86,88,92,93,95–97], and a decrease in DHEA-S was observed in only 2 of 18 (11%) studies [87,98]. No change in androstenedione was reported in 3 of 18 (17%) studies [92,94,96], and a decrease in androstenedione was observed in 2 of 18 (11%) reports [87,88]. Out of the 95 patients included in table 3, 25 (26%) had an increase in serum estrogen level, 6 (6.3%) had a decrease in serum estrogen level, and 64 (67%) showed no significant change in serum estrogen level. Of note, none of the studies specified when in the menstrual cycle the estrogen level was drawn. Serum estradiol was unchanged in 3 of 18 (17%) studies [87,91,92] and decreased in one case report involving a woman with hirsutism, who experienced decreased estradiol and testosterone levels after taking spironolactone for 6 months [83]. Increased estradiol levels, no change in LH, and, oddly, a decrease in FSH and progesterone were reported in 25 of 30 hirsute women, after 6 months of spironolactone [89]. Hence, the majority of patients had no significant alteration in serum estrogen levels, after taking spironolactone. When spironolactone was studied in 975 women with breast cancer compared to 1,007 women receiving placebo, no increased incidence of

breast cancer was demonstrated [78]. Mackenzie et al published the largest trial to date including 1,290,625 women older than 55 years of age without breast cancer; where 28,032 were exposed to spironolactone versus 55,961 controls. This study found no association between spironolactone use and increased risk of incident breast cancer (HR 0.99, 95% CI 0.87–1.12) [81].

Currently, there is no data to support that spironolactone interacts with ETs used for breast cancer (Table 4), and spironolactone has not been linked to an increased incidence of breast cancer, based on 4 published large reports [14,74–76]. Additionally, the International Agency for Cancer Research deemed there to be a lack of adequate data to support carcinogenicity of spironolactone in humans [99]. Finally, when spironolactone was given to a patient with breast cancer who had pCIA, no AEs or tumor recurrence were reported [14].

5 α -reductase inhibitors and spironolactone as off-label systemic therapies for Female AGA

The available FDA-approved treatments for male androgenetic alopecia are finasteride and topical minoxidil, versus topical minoxidil only for female AGA [7,16,38]. Minoxidil will not be the focus of this review; however, it has an excellent safety profile without significant AEs, when tested in patients with female AGA. In fact, it showed a reduction in duration of CIA by roughly 40 days [100] but failed to prevent CIA [101]. Minoxidil's mechanism of action is not fully understood, but it reportedly induces hair growth via prolongation of the hair follicle cycle into the anagen phase [102] and suppression of androgen activity in the hair follicle [103]. Its hair growth promoting effects are reportedly unrelated to its effects on vasodilation and opening of the potassium channels [104,105]

Spironolactone has been used off label to treat female AGA at doses ranging from 5–200mg daily for greater than 20 years with a good long-term safety profile [20,106,107]. Despite no randomized controlled trials testing spironolactone for female AGA, it has had promising results. Higher doses of spironolactone, typically 200mg daily, may inhibit testosterone action and hence are used to reduce the effects of hyperandrogenism. Existing data include a range of doses, with 267/492 (54%) of patients taking 100mg spironolactone daily, which may not be sufficient to produce a significant anti-androgen effect. Notably, testosterone levels were unchanged in patients receiving both higher and lower doses of spironolactone, so the relationship between circulating testosterone concentrations and spironolactone's anti-androgen effect is unclear. In addition, previous trials have been short-term, with the longest study conducted for 12 months. To better assess the effect of spironolactone on serum hormone levels and their actions, longer studies comparing a range of spironolactone doses should be conducted, as clinical effects may require more than 12 months to manifest.

Dosage of finasteride, duration of therapy, or androgen levels at baseline may affect patient outcomes. Antiandrogen therapies, such as finasteride and dutasteride, have been used to treat female AGA when associated with elevated levels of androgens [20]. Female AGA is usually milder when compared to androgenetic alopecia in males, attributed to lower levels of 5 α -reductase and androgen receptors in the female scalp [108]. Although finasteride is not fully favorable to treat female AGA when minoxidil has failed, there have been multiple reports of improved hair growth with its use [20–28]. In a retrospective review on 136 women with female AGA, of which 102 received finasteride 2.5mg or 5mg per day, 48

(47%) reported improvement and 54 (53%) reported stabilization in symptoms. Conversely, a review including 47 randomized clinical trials (RCTs) found finasteride failed to display higher efficacy over placebo (RR, 0.95; 95% CI 0.66–1.37)[18]. Data on finasteride's effects on increasing hair count were variable, as 2 studies on 219 patients found no significant difference and 1 study on 12 patients concluded favorability of finasteride [18]. Finally, when finasteride 1mg daily was studied in 137 pre-menopausal women without elevated levels of androgens, no improvement in alopecia was noted, after one year of treatment [28].

Summary and key points

EIA is a known complication of ETs used to treat hormone-sensitive breast cancer, seen in approximately 15–25% of patients [6,7]. Patients with EIA experience a considerable negative emotional burden from their alopecia. Unfortunately, for those who respond poorly to topical minoxidil, second line therapies are limited. [7]

Finasteride's efficacy for female AGA remains controversial, despite its increased popularity in off-label use in treating female AGA, as both treatment failures and successes have been published. Our understanding of its use for female AGA is limited, as existing trial designs and data vary in dosage, duration of therapy, and conditions treated. The existing literature published on finasteride use in dermatology includes hirsutism, androgenetic alopecia, lichen planopilaris, and frontal fibrosing alopecia, with a wide range in treatment duration. No studies on female breast cancer patients given finasteride have been conducted, and results of finasteride exposure in male breast cancer patients cannot be applied to the female breast cancer population with EIA. Hence, finasteride's safety profile in the existing literature should not be extrapolated to all women with female AGA, or EIA, based on the inconsistent study designs and outcomes. A meta-analysis is near impossible to perform with the existing trial designs, and justifies why only short-term outcomes, up to 24 months, have been published. Therefore, finasteride should not be recommended for women with EIA until the implications of longterm use are understood, which require improved study protocols.

To date, no study has shown a significant increased risk of incident female breast cancer while using spironolactone. There are no controlled or long-term studies assessing AEs of spironolactone in female breast cancer patients or on any risk of breast cancer recurrence with the use of this systemic therapy for female AGA. The consequences of altered estrogen levels related to treatments also remains unclear. Despite documented treatment successes and failures with increased popularity of use, spironolactone has the potential to be used as relatively safe systemic treatment options for the management of EIA in female breast cancer patients and survivors on ET who respond poorly to monotherapy with topical minoxidil.

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Table 1.

Endocrine Agents Examined

Class	Drug name
Selective estrogen receptor modulators (SERMs)	Tamoxifen, toremifene, raloxifene
Aromatase inhibitors	Anastrozole, letrozole, exemestane
Estrogen receptor antagonist	Fulvestrant
Gonadotropin-releasing hormone agonist (GnRH agonist)	Leuprolide
Estrogen	Estradiol
Progestational agents	Megestrol, medroxyprogesterone acetate

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Table 2.

Studies assessing finasteride's effects on sex hormones

First Author (Year)	Diagnosis (Total n)	Dose/Duration of Finasteride (n)	Effect on Hormone Levels	Estradiol (n)	Testosterone (n)	Androstenedione (n)	DHEA-S (n)
Fruzzetti (1994) [55]	IH (n=10)	5mg DAILY (3mo) (n=10)	NC (n=10)		I (total T; NC (free T) (n=10) (p<0.001)	N/A	NC (n=10)
Moggetti (1994) [29]	IH (n=17)	5 mg DAILY (6mo) (n=12, finasteride only; n=5, finasteride + OCP)	NC (n=17)		I (total T) (n=12) (p<0.025); NC (free T) (n=5)	N/A	NC (n=17)
Ciotta (1995) [56]	IH (n=9)	7.5 mg DAILY (9mo) (n=9)	NC (n=9)		I(total T) (p<0.001); NC (free T) (n=9)	NC(n=9)	NC(n=9)
Wong (1995) [30]	IH (n=2) PCOS (n=7)	5 mg DAILY (6mo) (n=9)	N/A		I (total T, 3mo) by 85% (p=0.001); NC (total T, 6mo) (n=9)	N/A	D (3 mo) by 30%; (p=0.008) NC (6 mo) (n= 9)
Castello (1996) [31]	IH (n=14)	5 mg DAILY (12mo) (n=14)	N/A		I (total T) (n= 14) (p<0.05)	N/A	N/A
Tolino (1996) [109]	IH(n=10) PCOS(n=15)	5 mg DAILY (6mo) (n=25)	N/A		NC (total T) (n=25)	NC(n=25)	NC(n=25)
Faloia (1998) [63]	IH(n=27)	5 mg DAILY (6mo) (n= 14 finasteride only; n=13, finasteride + OCP)	N/A		NC (n= 27)	NC (n=27)	N/A
Sahin (1998) [64]	IH(n=21)	5 mg DAILY (9mo) (n=21)	N/A		NC (n=21)	N/A	NC (n=21)
Fruzzetti (1999) [60]	IH (n=16) Hyperandrogenism (n=29)	5mg DAILY (12mo) (n=14)	N/A		I (total T) (p<0.01); NC (free T) (n=14)	NC (n=14)	NC (n=14)
Falsetti (1999) [69]	IH (n=23) PCOS (n=32)	5 mg DAILY (12mo) (n=55)	N/A		I (total T) by 40% in PCOS, 60% in IH (p<0.001)	N/A	N/A
Bayram (1999) [65]	IH (n=14) PCOS (n=21)	5 mg DAILY (12mo) (n=35)	I (n=35) (p<0.001 at 12 mo; p<0.005 at 6mo)		NC (n=35)	N/A	D (n=35) (p<0.01)
Venturoli (1999) [32]	IH (n=15)	5 mg DAILY (12mo) (n=15)	D (360da) (n=15) (p<0.001)		I (total T p<0.05, free T, p<0.001) (n=15)	N/A	D(n=15) (p<0.01)
Moggetti (2000) [61]	IH (n=10)	5 mg DAILY (6mo) (n=10)	N/A		NC (free T)) (n=10)	N/A	NC(n=10)
Bayhan (2000) [57]	IH (n=30)	5 mg DAILY (6mo) (n=30)	NC (n=30)		D (total T, free T) (n=30)	N/A	NC (n=30)
Muderris (2000) [67]	IH (n=35)	5 mg DAILY (12mo) (n=35)	I(n=35) (p<0.01)		NC(n=35)	N/A	D(n=35) (p<0.01)
Bayram (2002) [58]	IH (n=56)	2.5mg (n=29); 5mg (n=27) DAILY (12mo)	NC(2.5mg) (n=29); I(5mg) (n=27) (p<0.02 at 6mo,		NC (n=56)	N/A	NC (n=56)

First Author (Year)	Diagnosis (Total n)	Dose/Duration of Finasteride (n)	Effect on Hormone Levels			
			Estradiol (n)	Testosterone (n)	Androstenedione (n)	DHEA-S (n)
			p<0.0001 at 12 mo)			
Lumachi (2003) [96]	IH (n=13)	5 mg DAILY (12mo) (n=13)	N/A	NC (free T) (n=13)	NC(n=13)	NC(n=13)
Lakryc (2003) [68]	IH(n=10) PCOS (n=14)	5 mg DAILY (6mo) (n=12)	N/A	NC (total T) (n=12)	N/A	N/A
Bayram (2003) [66]	IH (n=29)	2.5 mg DAILY (12mo) (n=29)	NC (n=29)	NC (n=29)	NC (n=29)	NC (n=29)
Beigi (2004) [62]	PCOS (n=29) IH (n=11)	5 mg DAILY (9mo) (n=20)	N/A	I (total T), NC (free T) (n=20)	N/A	NC(n=20)
Tartagni (2004) [59]	IH(n=22) PCOS (n=17)	2.5 mg(n=19) DAILY or every 3 days(n=19) (10mo)	NC (n=38)	NC (total T) (n=38) (P<0.001)	NC(n=38)	NC(n=38)
Systematic Review	IH (Total n=394) PCOS (total n=135) Hyperandrogenism (total n=29)	2.5mg (n=96) 5mg (n=389) 7.5mg (n=9)	NC (n=162) I (n=97) D(n=15)	NC (free T, n=81; total T n=287) I (n=103) D(n=30)	NC (n=155)	NC (n=301) D (n=94)

¹ Abbreviations: n, number of patients, IH, idiopathic hirsutism; I, increase; NC, no change; D, decrease; N/A, not available;mo, months;da, days

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Table 3.

Studies assessing Spironolactone's effects on sex hormones

First Author (Year)	Diagnosis (n)	Dosage and Duration of Therapy(n)	Effect on Estrogen (n)	Effect on Testosterone(n)	Effect on Androstenedione (n)	Effect on DHEA-S(n)
Ober (1978) [83]	IH, amenorrhea, HTN(n=1)	25 mg OID (5da), 50 mg QID(4mo) (n=1)	D(n=1)	D(n=1)	N/A	N/A
Smals (1979) [91]	HTN (n=6)	100 mg spironolactone (4wks) (n=6)	NC (n=6)	NC(n=6)	N/A	N/A
Boisselle (1979) [85]	Healthy (n=10); IH (n=6)	25 mg BID (6mo) (n=16)	N/A	D (n=16)	N/A	N/A
Shapiro (1980) [89]	IH (n=30)	100 mg BID (n=25), 150 mg BID (n=4), 100 mg DAILY (n=1) (3–13 mo)	I(6mo) (n=25) (p<0.01) D (n=5)	D (6–9mo) by about 80% (n=30) (p<0.01)	N/A	N/A
Cumming (1982) [86]	IH (n=10) PCOS (n=10)	100–200 mg DAILY (12 mo) (n=20)	N/A	D (n=20) (p<0.01)	N/A	NC(n=20)
Milewicz (1983) [87]	PCOS and hirsutism (n=34)	100 mg DAILY (3mo) (n=34)	NC (urine) (n=34)	D(n=34) (p<0.05)	D(n=34) (p<0.05)	D(n=34) (p<0.05)
Lobo (1985) [88]	IH (n=30)	100 mg (n=15) or 200 mg (n=15) DAILY(3mo)	N/A	D (total T, both cohorts) (n=30) (p<0.05)	D (n=15, 200mg cohort only) (p<0.05)	NC (n=30)
Dorrington-Ward (1985) [90]	IH (n=9)	75 mg BID (12mo) after 2mo placebo(n=9)	N/A	D by 47% at 7mo till 12 mo (n=9) (p<0.001)	N/A	N/A
Sieberg (1987) [92]	Hyperandrogenism (n=24)	100 mg DAILY (day 5–21 of menstrual cycle) for 3 mo(n=24)	NC(n=24)	NC(n=24)	NC(n=24)	NC(n=24)
Wong (1995) [30]	IH (n=5)	100 mg DAILY (6mo) (n=5)	N/A	NC(n=5)	N/A	NC(n=5)
Erenus (1997) [93]	H (n=20)	100 mg DAILY 6mo (n=11) or 9 mo (n=9)	N/A	NC (n=9)	N/A	NC(n=9)
Spritzer (2000) [94]	IH (n=11) PCOS (n=10)	200 mg DAILY, 20 d/mo (12mo) (n=21)	N/A	NC(n=21)	NC(n=21)	N/A
Moggetti (2000) [61]	IH (n=10)	100 mg DAILY (6mo) (n=10)	N/A	NC(n=10)	N/A	NC(n=10)
Sert (2003) [95]	IH (n=22)	100 mg DAILY (12mo) (n=22)	N/A	NC(n=22)	N/A	NC(n=22)
Lumachi (2003) [96]	IH (n=15)	100 mg DAILY (12mo) (n=15)	N/A	NC(n=15)	NC(n=15)	NC(n=15)
Kelestimur (2004) [97]	IH (n=54)	100 mg DAILY (12mo) (n=32); 100mg daily + F 5mg/day (n=33)	N/A	NC (n=32); I (free T) (n=33) (p<0.005)	N/A	NC (n=54)
Yemisci (2005) [98]	Acne (n=35)	100 mg DAILY (16 d/mo) 3 mo (n=35)	N/A	NC (n=35)	N/A	D (n=24) (p<0.05)
Ganie (2013) [84]	PCOS (n=113)	50mg DAILY (6mo) (n=51) vs 50mg daily + metformin 100mg/da (n=62)	N/A	D(n=51) (p=0.001); D (n=62) (p<0.05)	N/A	N/A
Systematic Review	IH (total n=223) PCOS (total n=167) Hyperandrogenism	50mg (n=129) 100mg (n=267)	NC (n=64) I (n=25) D(n=6)	NC(n=179) I (free T, n=33) D(n=253)	NC (n=60) D (n=49)	NC (n=189) D(n=58)

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First Author (Year)	Diagnosis (n)	Dosage and Duration of Therapy(n)	Effect on Estrogen (n)	Effect on Testosterone(n)	Effect on Androstenedione (n)	Effect on DHEA-S(n)
	(n=24) Acne (n=35) Healthy (n=10) HTN (n=7)	150mg (n=13) 200mg (n=82)				

Abbreviations: H, hirsutism; HTN., hypertension; n, number of patients, D, decrease; NC, no change; N/A, not available; mo, months; da, days; wks, weeks; QID, four times daily; BID, twice daily; PCOS, polycystic ovarian syndrome; F, finasteride

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Table 4.

List of studies examining spironolactone and risk of incident breast cancer, in patients with no prior history of disease.

First Author (Year)	Population Studied	Comments
Li (2003) [78]	Population based case-control study of women ages 65–79 years old; 975 women with invasive breast carcinoma compared to 1,007 controls.	CCB, thiazides, potassium sparing diuretics showed mild increased risk of breast cancer (OR 1.5; 95% CI 1.0–2.1; OR, 1.4; 95% CI, 1.1–1.8; and OR, 1.6; 95% CI, 1.2–2.1, respectively) Overall no trend appreciated in excess risk of breast cancer with increasing duration of use of anti-hypertensive medications.
Fryzek JP (2006) [79]	49,950 women in Denmark between 50 and 67 years of age; 19,284 exposed to anti-hypertensive medications versus 30,666 controls	No statistically significant association between spironolactone and increased breast cancer incidence (RR = 0.95; 95% CI = 0.81–1.10).
Mackenzie (2012) [81]	1,290,625 women older than 55 years of age without breast cancer from 1987 to 2010; 28,032 exposed to spironolactone versus 55,961 controls	In women greater than 55 years of age, there is no increased risk of incident breast cancer with spironolactone use (HR 0.99, 95% CI 0.87–1.12)
Biggar RJ (2013) [80]	2.3 million women in Denmark from 1995–2010; 1.3 million prescriptions for spironolactone (214,112 p-y in current users and 152,746 p-y in former users).	Increased risk of breast cancer risk among current and former users of spironolactone (IRR: 1.19; 95% CI: 1.12–1.27) and (1.13; 1.04–1.22) respectively. >1 year of exposure to spironolactone, IRR 1.09 (0.97–1.22). Risk increased with duration of exposure (ptrend = 0.06). >3 years of exposure to spironolactone, IRR 1.25 (1.06–1.47).

Abbreviations: OR, odds ratio; RR, relative risk; n= number of persons; n/a, not available; CI, confidence interval; p-y, person-years; IRR, incidence rate ratio; HR, hazard ratio