Breast Cancer Research and Treatment (2019) 174:15–26
https://doi.org/10.1007/s10549-018-4996-3

REVIEW

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

Raquel N. Rozner[1] · Azael Freites-Martinez[1] · Jerry Shapiro[2] · Eliza B. Geer[3] · Shari Goldfarb[4] · Mario E. Lacouture[1]

Received: 30 July 2018 / Accepted: 24 August 2018 / Published online: 22 November 2018

Abstract

Purpose To provide dermatologists and oncologists with a foundation for practical understanding and uses of 5α-reductase inhibitors and spironolactone for breast cancer patients and survivors receiving endocrine therapies (ETs), 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. Forty-seven studies were included in this review.

Results There is no evidence of interactions between 5α-reductase inhibitors and spironolactone with ETs used in breast cancer. Sex hormone alteration with 5α-reductase inhibitor or spironolactone use is variable. Three randomized controlled trials, 1 case–control study, and 6 retrospective cohort studies, including 284 female patients, studied the effects of 5α-reductase inhibitors 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. Four retrospective cohort studies, 1 case study, and 1 double-blinded crossover study, including 95 female patients, assessed the effect of spironolactone 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 5α-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 5α-reductase inhibitors has not been studied.

Conclusions Most patients did not show increased estrogen levels with spironolactone and there were 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 5α-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 US 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

✉ Mario E. Lacouture
lacoutum@mskcc.org

1 Department of Dermatology, Memorial Sloan-Kettering Cancer Center, 16 East 60th Street, Suite 407, 4th Floor, New York, NY 10022, USA

2 The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY, USA

3 Multidisciplinary Pituitary and Skull Base Tumor Center, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

4 Breast Medicine Service, Memorial Sloan Kettering Cancer Center, and Department of Medicine, Weill Cornell Medical College, New York, NY, USA

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 1.25 to 5 mg daily [33] has 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 5α-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 [35], whereas dihydrotestosterone (DHT) is responsible for transforming large, terminal hair follicles into miniaturized hair follicles [36, 37], causing 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 (ER) stimulation prolongs the duration of anagen in human scalp hair follicles [40, 41], antagonizing signaling through ERs 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 (ER 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 ERs, ERα and ERβ, found in the mammary gland, activating cell growth. ERα 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 ER modulators (SERMs) act as estrogen agonists on bone, liver, and the cardiovascular system, and as estrogen antagonists on the breast, but the effects of each SERM depend on where it is metabolized [46]. The binding of tamoxifen to ERα blocks breast cancer proliferation. AIs, notably anastrozole and letrozole, are first line anti-estrogen 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 post-menopausal women with advanced breast cancer [51]. GnRH agonists, such as leuprolide, have also been used in pre-menopausal women to suppress ovarian production of estrogen (Table 1).

Table 1 Endocrine agents examined

Classes	Drug names
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

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

Finasteride and dutasteride exert their effects via competitive inhibition of type 2 5α-reductase, blocking the conversion of testosterone to DHT [29]. DHT binds to androgen receptors on the scalp and results in miniaturized follicles [52, 53]. 5α-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 5α-reductase inhibitors is generally not seen, except for variability in serum testosterone levels. The efficacy of finasteride has been assessed 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 5α-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 overall risk of prostate cancer by 25% in 597 men receiving finasteride versus 676 receiving placebo (OR, 0.97; 95% CI, 0.91–1.04), despite high-grade prostate cancer being more common in the finasteride treatment group (OR, 1.00; 95% CI, 0.93–1.09) [73].

There are limited data on the use of finasteride and risk of male breast cancer. Two case–control reports, including 300–400 cases compared to approximately 4000 and 6800 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 non-users [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

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 ($n=10$)	5 mg daily (3 mo) ($n=10$)	NC ($n=10$)	I (total T); NC (free T) ($n=10$) ($p<0.001$)	N/A	NC ($n=10$)
Moghetti (1994) [29]	IH ($n=17$)	5 mg daily (6 mo) ($n=12$, 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 (9 mo) ($n=9$)	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 (6 mo) ($n=9$)	N/A	I (total T, 3 mo) by 85%($p=0.001$); NC (total T, 6 mo) ($n=9$)	N/A	D (3 mo) by 30%; ($p=0.008$) NC (6 mo) ($n=9$)
Castello (1996) [31]	IH ($n=14$)	5 mg daily (12 mo) ($n=14$)	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 (6 mo) ($n=25$)	N/A	NC (total T) ($n=25$)	NC ($n=25$)	NC ($n=25$)
Faloia (1998) [63]	IH ($n=27$)	5 mg daily (6 mo) ($n=14$ 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 (9 mo) ($n=21$)	N/A	NC ($n=21$)	N/A	NC ($n=21$)
Fruzzetti (1999) [60]	IH ($n=16$) Hyperandrogenism ($n=29$)	5 mg daily (12 mo) ($n=14$)	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 (12 mo) ($n=55$)	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 (12 mo) ($n=35$)	I ($n=35$) ($p<0.001$ at 12 mo; $p<0.005$ at 6 mo)	NC ($n=35$)	N/A	D ($n=35$) ($p<0.01$)
Venturoli (1999) [32]	IH ($n=15$)	5 mg daily (12 mo) ($n=15$)	D (360 da) ($n=15$) ($p<0.001$)	I (total T $p<0.05$, free T, $p<0.001$) ($n=15$)	N/A	D ($n=15$) ($p<0.01$)
Moghetti (2000) [61]	IH ($n=10$)	5 mg daily (6 mo) ($n=10$)	N/A	NC (free T) ($n=10$)	N/A	NC ($n=10$)
Bayhan (2000) [57]	IH ($n=30$)	5 mg daily (6 mo) ($n=30$)	NC ($n=30$)	D (total T, free T) ($n=30$)	N/A	NC ($n=30$)
Muderris (2000) [67]	IH ($n=35$)	5 mg daily (12 mo) ($n=35$)	I ($n=35$) ($p<0.01$)	NC ($n=35$)	N/A	D ($n=35$) ($p<0.01$)
Bayram (2002) [58]	IH ($n=56$)	2.5 mg ($n=29$); 5 mg ($n=27$) daily (12 mo)	NC (2.5 mg) ($n=29$); I (5 mg) ($n=27$) ($p<0.02$ at 6 mo, $p<0.0001$ at 12 mo)	NC ($n=56$)	N/A	NC ($n=56$)
Lumachi (2003) [96]	IH ($n=13$)	5 mg daily (12 mo) ($n=13$)	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 (6 mo) ($n=12$)	N/A	NC (total T) ($n=12$)	N/A	N/A
Bayram (2003) [66]	IH ($n=29$)	2.5 mg daily (12 mo) ($n=29$)	NC ($n=29$)	NC ($n=29$)	NC ($n=29$)	NC ($n=29$)
Beigi (2004) [62]	PCOS ($n=29$) IH ($n=11$)	5 mg daily (9 mo) ($n=20$)	N/A	I (total T); NC (free T) ($n=20$)	N/A	NC ($n=20$)

Table 2 (continued)

First author (year)	Diagnosis (total *n*)	Dose/duration of finasteride (*n*)	Effect on hormone levels			
			Estradiol (*n*)	Testosterone (*n*)	Androstenedione (*n*)	DHEA-S (*n*)
Tartagni (2004) [59]	IH ($n=22$) PCOS ($n=17$)	2.5 mg ($n=19$) daily or every 3 days ($n=19$) (10 mo)	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 $n=29$)	2.5 mg ($n=96$) 5 mg ($n=389$) 7.5 mg ($n=9$)	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 ($n=94$)

n Number of patients, *IH* idiopathic hirsutism, *I* increase, *NC* no change, *D* decrease, *N/A* not available, *mo* months, *da* days

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 1007 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 1007 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 are 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 four 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

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 QID (5 da), 50 mg QID (4 mo) ($n=1$)	D($n=1$)	D ($n=1$)	N/A	N/A
Smals (1979) [91]	HTN ($n=6$)	100 mg spironolactone (4 wks) ($n=6$)	NC ($n=6$)	NC ($n=6$)	N/A	N/A
Boisselle (1979) [85]	Healthy ($n=10$) IH ($n=6$)	25 mg BID (6 mo) ($n=16$)	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 (6 mo) ($n=25$) ($p<0.01$) D ($n=5$)	D (6–9 mo) 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 (3 mo) ($n=34$)	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(3 mo)	N/A	D (total T, both cohorts) ($n=30$) ($p<0.05$)	D ($n=15$, 200 mg cohort only) ($p<0.05$)	NC ($n=30$)
Dorrington-Ward (1985) [90]	IH ($n=9$)	75 mg BID (12 mo) after 2 mo placebo ($n=9$)	N/A	D by 47% at 7 mo till 12 mo ($n=9$) ($p<0.001$)	N/A	N/A
Siegberg (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 (6 mo) ($n=5$)	N/A	NC ($n=5$)	N/A	NC ($n=5$)
Erenus (1997) [93]	H ($n=20$)	100 mg daily 6 mo ($n=11$) 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 (12 mo) ($n=21$)	N/A	NC ($n=21$)	NC ($n=21$)	N/A
Moghetti (2000) [61]	IH ($n=10$)	100 mg daily (6 mo) ($n=10$)	N/A	NC ($n=10$)	N/A	NC ($n=10$)
Sert (2003) [95]	IH ($n=22$)	100 mg daily (12 mo) ($n=22$)	N/A	NC ($n=22$)	N/A	NC ($n=22$)
Lumachi (2003) [96]	IH ($n=15$)	100 mg daily (12 mo) ($n=15$)	N/A	NC ($n=15$)	NC ($n=15$)	NC ($n=15$)
Kelestimur (2004) [97]	IH ($n=54$)	100 mg daily (12 mo) ($n=32$); 100 mg daily + F 5 mg/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 ($n=24$) ($p<0.05$)

Table 3 (continued)

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*)
Ganie (2013) [84]	PCOS ($n=113$)	50 mg daily (6 mo) ($n=51$) versus 50 mg daily + metformin 100 mg/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 ($n=24$) Acne ($n=35$) Healthy ($n=10$) HTN ($n=7$)	50 mg ($n=129$) 100 mg ($n=267$) 150 mg ($n=13$) 200 mg ($n=82$)	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 ($n=58$)

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

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 1007 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 (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 **(2013)** [80]	2.3 million women in Denmark from 1995 to 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 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 ($p_{trend}=0.06$) ≥ 3 years of exposure to spironolactone, IRR 1.25 (1.06–1.47)

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

breast cancer who had pCIA, no AEs or tumor recurrence were reported [14].

5α-Reductase inhibitors and spironolactone as off-label systemic therapies for female AGA

The available FDA-approved treatments for male AGA 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 to 200 mg daily for greater than 20 years with a good long-term safety profile [20, 106, 107]. Despite no randomized controlled trials (RCTs) testing spironolactone for female AGA, it has had promising results. Higher doses of spironolactone, typically 200 mg 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 100 mg 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 the anti-androgen effect of spironolactone 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. Anti-androgen 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 AGA in males, attributed to lower levels of 5α-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 2.5 mg or 5 mg per day, 48 (47%) reported improvement and 54 (53%) reported stabilization in symptoms. Conversely, a review including 47 RCTs found finasteride failed to display higher efficacy over placebo (RR 0.95; 95% CI 0.66–1.37) [18]. Data on the effects of finasteride 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 1 mg daily was studied in 137 pre-menopausal women without elevated levels of androgens, no improvement in alopecia was noted, after 1 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].

The efficacy of finasteride 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, AGA, 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, the safety profile of finasteride 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 long-term 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.

Funding This study was supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748. This research was additionally funded in part by Beca Excelencia Fundación Piel Sana (Dr. Freites-Martinez) and the RJR Grant. The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest with regard to the preparation of this manuscript.

Disclosures Mario E. Lacouture has no relevant conflicts of interest with regard to preparation of this manuscript. He has served as consultant for Legacy, Adgero, Debiopharm,Galderma, Johnson and Johnson, Novocure Inc., Merck, Helsinn, Janssen, Menlo Ther, Novartis, Roche, Abbvie, Boehringer Ingelheim, Amgen, E.R. Squibb & Sons, EMD Serono, Genentech, Seattle Genetics, Bayer, Manner SAS, Lutris, Paxman Coolers, Pfizer, Bristol-Myers Squibb, Silk Therapeutics, Foamix, and Medische Voet. He has received research funding from GSK, Novartis, Veloce, US Biotest, Berg, Bristol-Myers Squibb. Eliza B. Geer has no relevant conflicts of interest with regard to preparation of this manuscript. She has served as the principal investigator of research grants to MSKCC from Novartis, Strongbridge, Chiasma, and IONIS and has received occasional consulting honoraria from Novartis, Strongbridge, Corcept, and Pfizer. Jerry Shapiro has no relevant conflicts of interest with regard to preparation of this manuscript. He has served as a consultant for Aclaris, Samumed, Incyte, Replicel Life Sciences, and Shook, Hardy, Bacon LLP who represent Sanofi Aventis US LLC.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. World Health Organization. WHO | breast cancer: prevention and control. http://www.who.int/cancer/detection/breastcancer/en/. Accessed 26 Nov 2017
2. Siegel RL, Miller KD, Jemal A. Cancer statistics (2018) CA Cancer J Clin 2018 68(1):7–30. https://doi.org/10.3322/caac.21442
3. Moscetti L, Agnese Fabbri M, Sperduti I et al (2015) Adjuvant aromatase inhibitor therapy in early breast cancer: what factors lead patients to discontinue treatment? Tumori 101(5):469. https://doi.org/10.5301/tj.5000376
4. Saggar V, Wu S, Dickler MN, Lacouture ME (2013) Alopecia with endocrine therapies in patients with cancer. Oncologist 18(10):1126–1134. https://doi.org/10.1634/theoncologist.2013-0193. Epub 13 Sep 2013
5. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med 348(24):2431–2442. https://doi.org/10.1056/NEJMra023246. Accessed 6 April 2018
6. Freites-Martinez A, Shapiro J, van den Hurk C, et al (2018) CME part 2: hair disorders in cancer survivors persistent chemotherapy-induced alopecia, persistent radiotherapy-induced alopecia, and hair growth disorders related to endocrine therapy or cancer surgery. J Am Acad Dermatol. https://doi.org/10.1016/j.jaad.2018.03.056
7. Freites-Martinez A, Shapiro J, Chan D et al (2018) Endocrine therapy-induced alopecia in patients with breast cancer. JAMA Dermatol. https://doi.org/10.1001/jamadermatol.2018.0454
8. Bourgeois H, Kerbrat P, Combe M et al (2010) Long term persistent alopecia and suboptimal hair regrowth after adjuvant chemotherapy for breast cancer: alert for an emerging side effect: French ALOPERS Observatory. Ann Oncol 21:83–84
9. Kang D, Kim IR, Lee D et al (2017) Incidence of permanent chemotherapy-induced alopecia among breast cancer patients: a five-year prospective cohort study. Ann Oncol 28:22
10. Kim S, Park H, Kim J et al (2016) Irreversible chemotherapy-induced alopecia in breast cancer patient. Cancer Res. https://doi.org/10.1158/1538-7445.SABCS15-P1-15-04
11. Masidonski P (2009) Permanent alopecia in women being treated for breast cancer. Clin J Oncol Nurs 13(1):13–15. https://doi.org/10.1188/09.CJON.13-14
12. Bertrand M, Mailliez A, Vercambre S, Kotecki N, Mortier L, Bonneterre J(2013) Permanent chemotherapy induced alopecia in early breast cancer patients after (neo)adjuvant chemotherapy: long term follow up. Cancer Res. https://doi.org/10.1158/0008-5472.SABCS13-P3-09-15
13. Fonia A, Cota C, Setterfield JF, Goldberg LJ, Fenton DA, Stefanato CM (2017) Permanent alopecia in patients with breast cancer after taxane chemotherapy and adjuvant hormonal therapy: clinicopathologic findings in a cohort of 10 patients. J Am Acad Dermatol 76(5):948–957. https://doi.org/10.1016/j.jaad.2016.12.027
14. Kluger N, Jacot W, Frouin E et al (2012) Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. Ann Oncol 23(11):2879–2884. https://doi.org/10.1093/annonc/mds095. Epub 9 May 2012
15. Thorp N, Swift F, Arundell D, Wong H (2015) Long term hair loss in patients with early breast cancer receiving docetaxel chemotherapy. Cancer Res. https://doi.org/10.1158/1538-7445.SABCS14-P5-17-04
16. Otberg N, Shapiro J (2012) Chapter 88. Hair growth disorders. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K (eds) Fitzpatrick's dermatology in general medicine, 8th edn. The McGraw-Hill Companies, New York. http://accessmedicine.mhmedical.com/content.aspx?aid=56049509. Accessed 25 March 2018
17. Sinclair R, Wewerinke M, Jolley D (2005) Treatment of female pattern hair loss with oral antiandrogens. Br J Dermatol 152(3):466–473. https://doi.org/10.1111/j.1365-2133.2005.06218.x
18. van Zuuren EJ, Fedorowicz Z (2017) Interventions for female pattern hair loss. JAMA Dermatol 153(3):329–330. https://doi.org/10.1001/jamadermatol.2016.5790
19. Clinical efficacy of oral administration of finasteride at a dose of 2.5 mg/day in women with female pattern hair loss (2018). Dermatol Ther 31(2):e12588. https://doi.org/10.1111/dth.12588
20. Camacho-Martinez F (2009) Hair loss in women. Semin Cutan Med Surg 28(1):19–32. https://doi.org/10.1016/j.sder.2009.01.001
21. Trüeb RM (2004) Finasteride treatment of patterned hair loss in normoandrogenic postmenopausal women. Dermatology 209(3):202–207. https://doi.org/10.1159/000079890. Accessed 20 March 2018
22. Seale LR, Eglini AN, McMichael AJ (2016) Side effects related to 5 α-reductase inhibitor treatment of hair loss in women: a review. J Drugs Dermatol 15(4):414–419

23. Gupta AK, Charrette A (2014) The efficacy and safety of 5α-reductase inhibitors in androgenetic alopecia: a network meta-analysis and benefit-risk assessment of finasteride and dutasteride. J Dermatol Treat 25(2):156–161. https://doi.org/10.3109/09546634.2013.813011. Accessed 26 March 2018
24. Boychenko O, Bernstein RM, Schweiger ES (2012) Finasteride in the treatment of female pattern (androgenic) alopecia: a case report and review of the literature. Cutis 90(2):73–76
25. Yeon JH, Jung JY, Choi JW et al (2011) 5 mg/day finasteride treatment for normoandrogenic asian women with female pattern hair loss. J Eur Acad Dermatol Venereol 25(2):211–214. https://doi.org/10.1111/j.1468-3083.2010.03758.x. Accessed 26 March 2018
26. Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt G (2010) Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. Arch Dermatol 146(10):1141–1150. https://doi.org/10.1001/archdermatol.2010.256. Accessed 26 March 2018
27. Iorizzo M, Vincenzi C, Voudouris S, Piraccini BM, Tosti A (2006) Finasteride treatment of female pattern hair loss. Arch Dermatol 142(3):298–302. https://doi.org/10.1001/archderm.142.3.298. Accessed 26 March 2018
28. Price VH, Roberts JL, Hordinsky M et al (2000) Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol 43(5 Pt 1):768–776. https://doi.org/10.1067/mjd.2000.107953. Accessed 20 March 2018
29. Moghetti P, Castello R, Magnani CM et al (1994) Clinical and hormonal effects of the 5 alpha-reductase inhibitor finasteride in idiopathic hirsutism. J Clin Endocrinol Metab 79(4):1115–1121. https://doi.org/10.1210/jcem.79.4.7962284. Accessed 11 April 2018
30. Wong IL, Morris RS, Chang L, Spahn MA, Stanczyk FZ, Lobo RA (1995) A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women. J Clin Endocrinol Metab 80(1):233–238. https://doi.org/10.1210/jcem.80.1.7829618
31. Castello R, Tosi F, Perrone F, Negri C, Muggeo M, Moghetti P (1996) Outcome of long-term treatment with the 5 alpha-reductase inhibitor finasteride in idiopathic hirsutism: clinical and hormonal effects during a 1-year course of therapy and 1-year follow-up. Fertil Steril 66(5):734–740. http://www.ncbi.nlm.nih.gov/pubmed/8893676
32. Venturoli S, Marescalchi O, Colombo FM et al (1999) A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. J Clin Endocrinol Metab 84(4):1304–1310. https://doi.org/10.1210/jcem.84.4.5591
33. Shum KW, Cullen DR, Messenger AG (2002) Hair loss in women with hyperandrogenism: four cases responding to finasteride. J Am Acad Dermatol 47(5):733–739
34. Somani N (2014) Hirsutism: an evidence-based treatment update. Am J Clin Dermatol 15(3):247–267. https://doi.org/10.1007/s40257-014-0078-4
35. Rossi A, Iorio A, Scali E et al (2013) Aromatase inhibitors induce 'male pattern hair loss' in women? Ann Oncol Off J Eur Soc Med Oncol 24(6):1710. https://doi.org/10.1093/annonc/mdt170
36. Price VH (1975) Testosterone metabolism in the skin. A review of its function in androgenetic alopecia, acne vulgaris, and idiopathic hirsutism including recent studies with antiandrogens. Arch Dermatol 111(11):1496–1502
37. Kaufman KD (1996) Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol Clin 14(4):697–711
38. Price VH (1999) Treatment of hair loss. N Engl J Med 341(13):964–973. https://doi.org/10.1056/NEJM199909233411307. Accessed 19 March 2018
39. Vexiau P, Chaspoux C, Boudou P et al (2000) Role of androgens in female-pattern androgenetic alopecia, either alone or associated with other symptoms of hyperandrogenism. Arch Dermatol Res 292(12):598–604
40. Ohnemus U, Uenalan M, Inzunza J, Gustafsson J, Paus R (2006) The hair follicle as an estrogen target and source. Endocr Rev 27(6):677–706. https://doi.org/10.1210/er.2006-0020. Accessed 31 May 2018
41. Conrad F, Ohnemus U, Bodo E et al (2005) Substantial sex-dependent differences in the response of human scalp hair follicles to estrogen stimulation in vitro advocate gender-tailored management of female versus male pattern balding. J Investig Dermatol Symp Proc 10(3):243–246. https://doi.org/10.1111/j.1087-0024.2005.10115.x.Accessed 31 May 2018
42. Langan EA, Paus R (2010) Female pattern hair loss: beyond an androgenic aetiology? Br J Dermatol 163(5):1142. https://doi.org/10.1111/j.1365-2133.2010.09955.x. Accessed 31 May 2018
43. Bickenbach KA, Jaskowiak N (2006) Aromatase inhibitors: an overview for surgeons. J Am Coll Surg 203(3):376–389. https://doi.org/10.1016/j.jamcollsurg.2006.05.291. Accessed 19 March 2018
44. Yu H, Shu X, Shi R et al (2003) Plasma sex steroid hormones and breast cancer risk in Chinese women. Int J Cancer 105(1):92–97. https://doi.org/10.1002/ijc.11034. Accessed 19 March 2018
45. Del Re M, Michelucci A, Simi P, Danesi R (2012) Pharmacogenetics of anti-estrogen treatment of breast cancer. Cancer Treat Rev 38(5):442–450. https://doi.org/10.1016/j.ctrv.2011.08.003
46. Boutin JA (1994) Tyrosine protein kinase inhibition and cancer. Int J Biochem 26(10–11):1203–1226
47. Fortunati N (1999) Sex hormone-binding globulin: not only a transport protein. What news is around the corner? J Endocrinol Investig 22(3):223–234. https://doi.org/10.1007/BF03343547. Accessed 19 March 2018
48. Yip L, Zaloumis S, Irwin D et al (2009) Gene-wide association study between the aromatase gene (CYP19A1) and female pattern hair loss. Br J Dermatol 161(2):289–294. https://doi.org/10.1111/j.1365-2133.2009.09186.x. Accessed 20 March 2018
49. Yip L, Rufaut N, Sinclair R (2011) Role of genetics and sex steroid hormones in male androgenetic alopecia and female pattern hair loss: an update of what we now know. Australas J Dermatol 52(2):81–88. https://doi.org/10.1111/j.1440-0960.2011.00745.x. Accessed 20 March 2018
50. Mirmirani P (2011) Hormonal changes in menopause: do they contribute to a 'midlife hair crisis' in women? Br J Dermatol 165(Suppl 3):7–11. https://doi.org/10.1111/j.1365-2133.2011.10629.x. Accessed 20 March 2018
51. Neven P, Paridaens R, Pelgrims G et al (2008) Fulvestrant (faslodex) in advanced breast cancer: clinical experience from a Belgian Cooperative Study. Breast Cancer Res Treat 109(1):59–65. https://doi.org/10.1007/s10549-007-9628-2. Accessed 19 March 2018
52. Atanaskova Mesinkovska N, Bergfeld WF (2013) Hair: what is new in diagnosis and management? Female pattern hair loss update: diagnosis and treatment. Dermatol Clin 31(1):119–127. https://doi.org/10.1016/j.det.2012.08.005. Accessed 20 March 2018
53. Gallicchio L, Calhoun C, Helzlsouer KJ (2013) Aromatase inhibitor therapy and hair loss among breast cancer survivors. Breast Cancer Res Treat 142(2):435–443. https://doi.org/10.1007/s10549-013-2744-2. Accessed 19 March 2018
54. Futterweit W, Dunaif A, Yeh HC, Kingsley P (1988) The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. J Am Acad Dermatol 19(5 Pt 1):831–836
55. Fruzzetti F, de Lorenzo D, Parrini D, Ricci C (1994) Effects of finasteride, a 5 alpha-reductase inhibitor, on circulating androgens and gonadotropin secretion in hirsute women. J Clin

Endocrinol Metab 79(3):831–835. https://doi.org/10.1210/jcem.79.3.8077369
56. Ciotta L, Cianci A, Calogero AE et al (1995) Clinical and endocrine effects of finasteride, a 5 alpha-reductase inhibitor, in women with idiopathic hirsutism. Fertil Steril 64(2):299–306. http://www.ncbi.nlm.nih.gov/pubmed/7615107
57. Bayhan G, Bahceci M, Demirkol T, Ertem M, Yalinkaya A, Erden AC (2000) A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. Clin Exp Obstet Gynecol 27(3–4):203–206. http://www.ncbi.nlm.nih.gov/pubmed/11214952
58. Bayram F, Muderris II, Guven M, Kelestimur F (2002) Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. Eur J Endocrinol 147(4):467–471. http://www.ncbi.nlm.nih.gov/pubmed/12370107
59. Tartagni M, Schonauer MM, Cicinelli E et al (2004) Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. Fertil Steril 82(3):752–755. https://doi.org/10.1016/j.fertnstert.2004.02.118
60. Fruzzetti F, Bersi C, Parrini D, Ricci C, Genazzani AR (1999) Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. Fertil Steril 71(3):445–451. http://www.ncbi.nlm.nih.gov/pubmed/10065780
61. Moghetti P, Tosi F, Tosti A et al (2000) Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab 85(1):89–94. https://doi.org/10.1210/jcem.85.1.6245
62. Beigi A, Sobhi A, Zarrinkoub F (2004) Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. Int J Gynaecol Obstet 87(1):29–33. https://doi.org/10.1016/j.ijgo.2004.06.003
63. Faloia E, Filipponi S, Mancini V, Di Marco S, Mantero F (1998) Effect of finasteride in idiopathic hirsutism. J Endocrinol Investig 21(10):694–698. https://doi.org/10.1007/BF03350800
64. Sahin Y, Bayram F, Kelestimur F, Muderris I (1998) Comparison of cyproterone acetate plus ethinyl estradiol and finasteride in the treatment of hirsutism. J Endocrinol Investig 21(6):348–352. https://doi.org/10.1007/BF03350769
65. Bayram F, Muderris II, Sahin Y, Kelestimur F (1999) Finasteride treatment for one year in 35 hirsute patients. Exp Clin Endocrinol Diabetes 107(3):195–197. https://doi.org/10.1055/s-0029-1212097
66. Bayram F, Müderris I, Güven M, Ozçelik B, Keleştimur F (2003) Low-dose (2.5 mg/day) finasteride treatment in hirsutism. Gynecol Endocrinol 17(5):419–422
67. Muderris II, Bayram F, Guven M (2000) A prospective, randomized trial comparing flutamide (250 mg/day) and finasteride (5 mg/day) in the treatment of hirsutism. Fertil Steril 73(5):984–987. http://www.ncbi.nlm.nih.gov/pubmed/10785225
68. Lakryc EM, Motta EL, Soares Jr JM, Haidar MA, de Lima GR, Baracat EC (2003) The benefits of finasteride for hirsute women with polycystic ovary syndrome or idiopathic hirsutism. Gynecol Endocrinol 17(1):57–63. http://www.ncbi.nlm.nih.gov/pubmed/12724020
69. Falsetti L, Gambera A, Legrenzi L, Iacobello C, Bugari G (1999) Comparison of finasteride versus flutamide in the treatment of hirsutism. Eur J Endocrinol 141(4):361–367. http://www.ncbi.nlm.nih.gov/pubmed/10526249
70. Olsen EA, Hordinsky M, Whiting D et al (2006) The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol 55(6):1014–1023. https://doi.org/10.1016/j.jaad.2006.05.007
71. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G (2002) Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 60(3):434–441
72. Drake L, Hordinsky M, Fiedler V et al (1999) The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol 41(4):550–554
73. Chau CH, Price DK, Till C et al (2015) Finasteride concentrations and prostate cancer risk: results from the prostate cancer prevention trial. PLoS ONE 10(5):e0126672. http://www.ncbi.nlm.nih.gov/pubmed/25955319
74. Duijnhoven RG, Straus SM, Souverein PC et al (2014) Long-term use of 5alpha-reductase inhibitors and the risk of male breast cancer. Cancer Causes Control 25(11):1577–1582. https://doi.org/10.1007/s10552-014-0455-6. Epub 19 Aug 2014
75. Bird ST, Brophy JM, Hartzema AG, Delaney JA, Etminan M (2013) Male breast cancer and 5alpha-reductase inhibitors finasteride and dutasteride. J Urol 190(5):1811–1814. https://doi.org/10.1016/j.juro.2013.04.132. Epub 9 May 2013
76. Meijer M, Thygesen LC, Green A et al (2018) Finasteride treatment and male breast cancer: a register-based cohort study in four Nordic countries. Cancer Med 7(1):254–260. https://doi.org/10.1002/cam4.1273
77. Gardiner P, Schrode K, Quinlan D et al (1989) Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. J Clin Pharmacol 29(4):342–347
78. Li CI, Malone KE, Weiss NS, Boudreau DM, Cushing-Haugen K, Daling JR (2003) Relation between use of antihypertensive medications and risk of breast carcinoma among women ages 65–79 years. Cancer 98(7):1504–1513. https://doi.org/10.1002/cncr.11663
79. Fryzek JP, Poulsen AH, Lipworth L et al (2006) A cohort study of antihypertensive medication use and breast cancer among Danish women. Breast Cancer Res Treat 97(3):231–236. https://doi.org/10.1007/s10549-005-9091-x. Accessed 24 March 2018
80. Biggar RJ, Andersen EW, Wohlfahrt J, Melbye M (2013) Spironolactone use and the risk of breast and gynecologic cancers. Cancer Epidemiol 37(6):870–875. https://doi.org/10.1016/j.canep.2013.10.004. Epub 1 Nov 2013
81. Mackenzie IS, Macdonald TM, Thompson A, Morant S, Wei L (2012) Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. BMJ 345:e4447
82. Mackenzie IS, Morant SV, Wei L, Thompson AM, MacDonald TM (2017) Spironolactone use and risk of incident cancers: a retrospective, matched cohort study. Br J Clin Pharmacol 83(3):653–663. https://doi.org/10.1111/bcp.13152. Accessed 17 March 2018
83. Ober KP, Hennessy JF (1978) Spironolactone therapy for hirsutism in a hyperandrogenic woman. Ann Intern Med 89(5):643–644. http://www.ncbi.nlm.nih.gov/pubmed/717935
84. Ganie MA, Khurana ML, Nisar S et al (2013) Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. J Clin Endocrinol Metab 98(9):3599–3607. https://doi.org/10.1210/jc.2013-1040. Epub 11 July 2013
85. Boisselle A, Tremblay RR (1979) New therapeutic approach to the hirsute patient. Fertil Steril 32(3):276–279. http://www.ncbi.nlm.nih.gov/pubmed/488407
86. Cumming DC, Yang JC, Rebar RW, Yen SS (1982) Treatment of hirsutism with spironolactone. JAMA 247(9):1295–1298. http://www.ncbi.nlm.nih.gov/pubmed/7199587

87. Milewicz A, Silber D, Kirschner MA (1983) Therapeutic effects of spironolactone in polycystic ovary syndrome. Obstet Gynecol 61(4):429–432. http://www.ncbi.nlm.nih.gov/pubmed/6828272
88. Lobo RA, Shoupe D, Serafini P, Brinton D, Horton R (1985) The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. Fertil Steril 43(2):200–205. http://www.ncbi.nlm.nih.gov/pubmed/3967781
89. Shapiro G, Evron S (1980) A novel use of spironolactone: treatment of hirsutism. J Clin Endocrinol Metab 51(3):429–432. https://doi.org/10.1210/jcem-51-3-429
90. Dorrington-Ward P, McCartney AC, Holland S et al (1985) The effect of spironolactone on hirsutism and female androgen metabolism. Clin Endocrinol (Oxf) 23(2):161–167. http://www.ncbi.nlm.nih.gov/pubmed/4053414
91. Smals AG, Kloppenborg PW, Hoefnagels WH, Drayer JI (1979) Pituitary–thyroid function in spironolactone treated hypertensive women. Acta Endocrinol 90(4):577–584. http://www.ncbi.nlm.nih.gov/pubmed/107696
92. Siegberg R, Ylostalo P, Laatikainen T, Pelkonen R, Stenman UH (1987) Endocrine and clinical effects of spironolactone in female hyperandrogenism. Arch Gynecol 240(2):67–73. http://www.ncbi.nlm.nih.gov/pubmed/3566358
93. Erenus M, Yucelten D, Durmusoglu F, Gurbuz O (1997) Comparison of finasteride versus spironolactone in the treatment of idiopathic hirsutism. Fertil Steril 68(6):1000–1003. http://www.ncbi.nlm.nih.gov/pubmed/9418687
94. Spritzer PM, Lisboa KO, Mattiello S, Lhullier F (2000) Spironolactone as a single agent for long-term therapy of hirsute patients. Clin Endocrinol (Oxf) 52(5):587–594. http://www.ncbi.nlm.nih.gov/pubmed/10792338
95. Sert M, Tetiker T, Kirim S (2003) Comparison of the efficiency of anti-androgenic regimens consisting of spironolactone, Diane 35, and cyproterone acetate in hirsutism. Acta Med Okayama 57(2):73–76. http://www.ncbi.nlm.nih.gov/pubmed/12866746
96. Lumachi F, Rondinone R (2003) Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. Fertil Steril 79(4):942–946. http://www.ncbi.nlm.nih.gov/pubmed/12749435
97. Kelestimur F, Everest H, Unluhizarci K, Bayram F, Sahin Y (2004) A comparison between spironolactone and spironolactone plus finasteride in the treatment of hirsutism. Eur J Endocrinol 150(3):351–354. http://www.ncbi.nlm.nih.gov/pubmed/15012621
98. Yemisci A, Gorgulu A, Piskin S (2005) Effects and side-effects of spironolactone therapy in women with acne. J Eur Acad Dermatol Venereol 19(2):163–166. https://doi.org/10.1111/j.1468-3083.2005.01072.x
99. Some thyrotropic agents (2001) IARC monographs on the evaluation of carcinogenic risks to humans, No. 79, p 725
100. Duvic M, Lemak NA, Valero V et al (1996) A randomized trial of minoxidil in chemotherapy-induced alopecia. J Am Acad Dermatol 35(1):74–78. https://doi.org/10.1016/S0190-9622(96)90500-9
101. Rodriguez R, Machiavelli M, Leone B et al (1994) Minoxidil (mx) as a prophylaxis of doxorubicin-induced alopecia. Ann Oncol 5(8):769–770. http://www.ncbi.nlm.nih.gov/pubmed/7826913
102. Uno H, Cappas A, Brigham P (1987) Action of topical minoxidil in the bald stump-tailed macaque. J Am Acad Dermatol 16(3 Pt 2):657–668
103. Hsu C, Liu J, Lin A, Yang C, Chung W, Wu W (2014) Minoxidil may suppress androgen receptor-related functions. OncoTarget 5(8):2187–2197. https://doi.org/10.18632/oncotarget.1886. Accessed 7 April 2018
104. Buhl AE, Waldon DJ, Kawabe TT, Holland JM (1989) Minoxidil stimulates mouse vibrissae follicles in organ culture. J Investig Dermatol 92(3):315–320
105. Buhl AE (1991) Minoxidil's action in hair follicles. J Investig Dermatol 96(5):74S
106. Burke BM, Cunliffe WJ (1985) Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. Br J Dermatol 112(1):124–125. http://www.ncbi.nlm.nih.gov/pubmed/3155956
107. Rathnayake D, Sinclair R (2010) Innovative use of spironolactone as an antiandrogen in the treatment of female pattern hair loss. Dermatol Clin 28(3):611–618. https://doi.org/10.1016/j.det.2010.03.011
108. Sawaya ME, Price VH (1997) Different levels of 5alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J Investig Dermatol 109(3):296–300. Accessed 19 March 2018
109. Tolino A, Petrone A, Sarnacchiaro F et al (1996) Finasteride in the treatment of hirsutism: new therapeutic perspectives. Fertil Steril 66(1):61–65. http://www.ncbi.nlm.nih.gov/pubmed/8752612