Spironolactone use does not increase the risk of female breast cancer recurrence: A retrospective analysis

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Background: Spironolactone is used off-label for androgenic alopecia because of its ability to arrest hair loss progression and long-term safety profile. However, little is known about the safety of spironolactone in breast cancer (BC) survivors. Because spironolactone has estrogenic effects, there is a theoretical risk for BC recurrence. Given that spironolactone is an important tool in the treatment of alopecia, we investigated whether spironolactone increased risk for BC recurrence.

Objective: To determine whether spironolactone is associated with increased BC recurrence.

Methods: A retrospective analysis was conducted using the Humana Insurance database. Patients with a history of BC were identified using International Classification of Diseases codes, stratified by spironolactone prescription, and also matched 1:1 using propensity score analysis. Patient characteristics and cancer recurrence rates between both cohorts were compared and analyzed.

Results: BC recurrence developed in 123 patients (16.5%) who were prescribed spironolactone compared with 3649 patients (12.8%) who developed BC recurrence without spironolactone prescribed (P = .004). After propensity matching, adjusted Cox regression analysis showed no association between spironolactone and increased BC recurrence (adjusted hazard ratio, 0.966; 95% confidence interval, 0.807-1.156; P = .953).

Limitations: Retrospective study.

Conclusion: Spironolactone was not independently associated with increased BC recurrence and may be considered for the treatment of alopecia in BC survivors. (J Am Acad Dermatol 2020;83:1021-7.)

Key words: androgenic alopecia; breast cancer recurrence; spironolactone; female patterned hair loss.

Androgens contribute significantly to the pathogenesis of female patterned hair loss (FPHL) and can have a detrimental impact on women's quality of life psychologically.[1] Currently, topical minoxidil is approved by the United States Food and Drug Administration for the treatment of FPHL. However, antiandrogen medications, such as cyproterone acetate, flutamide, and spironolactone, have been used for the treatment of FPHL off-label.

In particular, spironolactone is a potassium-sparing diuretic that competitively blocks aldosterone from

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binding to aldosterone-dependent sodium channels and is Food and Drug Administration approved for treating hypertension.[1,2] However, spironolactone is used off-label for androgenic alopecia because of its ability to arrest hair loss progression and long-term safety profile.[2] Spironolactone binds to androgen receptors causing competitive inhibition of androgens.

Although spironolactone has a well-established long-term safety profile, there is a theoretical risk for spironolactone influencing the risk of certain cancers, particularly breast cancer (BC), because of its antiandrogen and progesteronic effects.[3] Previous retrospective studies found that spironolactone was not associated with increased risk of primary malignancy development.[3-5] Biggar et al[5] retrospectively studied 2.3 million women from 1995 to 2010 and observed no increased risk of breast, ovarian, uterine, or cervical cancer with spironolactone use, which further strengthens spironolactone's safety profile.[2] In addition, the International Agency for Research on Cancer concluded there was a lack of evidence to support the carcinogenicity of spironolactone in humans.[6]

CAPSULE SUMMARY

- Spironolactone has a good long-term safety profile and has not been shown to increase the risk of developing cancer.
- Spironolactone may be a viable treatment option for alopecia in women who are under breast cancer remission and is not associated with an increased risk for breast cancer recurrence.

Little is known, however, about the safety and use of spironolactone for alopecia or other indications in BC survivors who are free of disease because the use of spironolactone in patients with a known history of BC is highly discouraged by providers due to concern for BC recurrence.[7,8] Management of alopecia for cancer survivors is based on small studies and expert opinion. There are no current Food and Drug Administration-approved therapies for endocrine therapy–induced alopecia or persistent chemotherapy-induced alopecia.[7] Many studies in the literature show improvement of alopecia with the use of topical minoxidil.[7] However, the adverse events of spironolactone have not been assessed in long-term (>12 months) controlled studies, and there is also a lack of treatment options available for cancer survivors who respond poorly to monotherapy with topical minoxidil.

We hypothesized that spironolactone would not increase the risk of BC recurrence. We sought to determine whether association exists between spironolactone use and cancer recurrence. Given that spironolactone is an important treatment for hair loss in BC survivors, the current study investigated the impact of spironolactone use on BC recurrence.

MATERIAL AND METHODS

Data source

Data were collected from the Humana Insurance database. The data contained from the database were deidentified, and no attempts were made to identify patients. In addition, all sample sizes between 1 and 10 subjects were reported as "-1" to prevent identification of patients. Patients were selected using the claims-based International Classification of Diseases, Ninth and 10th Revision (ICD-9 and ICD-10).

Power calculation

An a priori power analysis was performed to estimate the minimal number of patients needed to appropriately power this study. Data from previous studies show the minimum BC recurrence rate is 10.4%.[9,10] On the basis of previous literature from estrogen hormone replacement therapy studies, estrogen hormone replacement therapy may increase the risk of BC recurrence by 120% in BC survivors compared with no estrogen hormone therapy.[10] To appropriately power (≥0.8) for BC recurrence, the current study required a minimum sample size of 60 patients with history of BC prescribed spironolactone and 60 patients not prescribed spironolactone with $\alpha = 0.05$ and $\beta = 0.80$.

Study population

Personal history of BC was identified using ICD-9 and ICD-10 codes from years 2005 to 2017 (Table I). Personal history of a malignant neoplasm of the breast was defined as a person with BC remission. Male patients were excluded. In a previous data validation audit by BlueCross BlueShield insurance, physicians were found to document and claim for both current active cancer disease and previous history of cancer.[11] To minimize the bias from patients with clear remission of their cancer, patients who also had a concomitant active diagnosis for BC or any other primary or secondary malignancies were additionally excluded. Lastly, patients with an inactive, noncontinuous insurance policy were excluded.

Each group was stratified by spironolactone use, as defined by the presence or absence of a filled prescription for spironolactone. Demographics, including age and duration of spironolactone use, were recorded. Comorbidities pertaining to

Abbreviations used:

BC: breast cancer
CI: confidence interval
FPHL: female patterned hair loss
HR: hazard ratio
ICD: International Classification of Diseases

spironolactone usage, such as alopecia, acne vulgaris, hirsutism, hypertension, congestive heart failure, primary hyperaldosteronism, nephrotic syndrome, and ascites, and substance use history were assessed (Table I).[12,13] Alopecia was defined as having alopecia areata or androgenic alopecia. Primary aldosteronism was defined as having Conn syndrome. Ascites was defined as having nonmalignant accumulation of fluid in the peritoneal cavity. Hypertension, congestive heart failure, alcohol abuse, and drug abuse were defined by a list of ICD coding algorithms found from the Elixhauser comorbidity scores provided by Quan and colleagues.[14] Spironolactone use was identified using drug codes. Recurrent BC was examined among patients who had a continuous health insurance plan for 2 years after a diagnosis for a personal history of cancer was made since the highest risk for BC recurrence (15.2%) is between years 1 and 2.[9]

Table I. International Classification of Diseases Ninth and 10th Revision (*ICD-9* and *ICD-10*) codes of cohort groups and outcomes

ICD names (Cohort)	ICD-9	ICD-10
Personal history of malignant neoplasm of breast	V10.3	Z85.3
ICD disease names		
Alopecia	704.xx	L63.8, L63.9, L64.8, L63.9
Acne vulgaris	706.1	L70.0
Hirsutism	704.1	L68.0
Hypertension*	N/A	N/A
Congestive heart failure*	N/A	N/A
Conn syndrome	255.12	E26.01
Nephrotic syndrome	581.xx	N04.xx
Nonmalignant ascites	789.59	R18.8
Alcohol abuse*	N/A	N/A
Smoking	305.1	F17.200
Illicit drugs*	292.x, 304.x, 305.2-305.9, V65.42	F11.x-F16.x, F18.x, F19.x, Z71.5. Z72.2
Malignant neoplasm of female breast	174.x	C50.x

*Codes followed using Elixhauser comorbidity score.[14]

Statistical analysis

A priori power analysis was performed using G*power 3.1 software (G*Power, Düsseldorf, Germany) to power a study with an α-value of 0.05 and a power ($1-\beta$) of 0.8.[15] Patients with and without spironolactone were matched 1:1 using propensity score analysis. Variables used for the propensity match to model the probability of using spironolactone included age, alopecia, acne vulgaris, hirsutism, hypertension, congestive heart failure, primary hyperaldosteronism, nephrotic syndrome, nonmalignant ascites, smoking, alcohol abuse, and illicit drug abuse (Table II). Univariate and multivariate analyses were performed using R software (The R Foundation for Statistical Computing, Vienna, Austria). Analysis with χ^2 or one-way analysis of variance was performed when appropriate. Cox proportional hazard regression analysis was performed to adjust for rates of BC recurrences within the next 2 years after cancer remission. In the Cox regression analysis, all propensity-matching variables enlisted above and insurance status were included in our models. Schoenfeld residuals were used to assess the validity of the Cox proportional hazard regression model. Median survival time was also assessed with the Cox proportional hazard model. A P value of $<.05$ was considered statistically significant.

RESULTS

Prepropensity patient characteristics

Overall, 207,588 patients with history of BC were identified (Table III). Of those patients, 29,146 patients with history of BC had active insurance for 2 years, were female, and had no currently active primary or secondary cancer (Fig 1). A total of 746 patients (2.6%) with a history of BC were prescribed spironolactone. Of 746 patients, 733 patients were prescribed spironolactone for a duration of less than 1 year, and 13 patients were prescribed spironolactone for a duration of up to 2 years. Although most patients in spironolactone and nonspironolactone cohorts were between 70 and 79 years old, spironolactone-prescribed patients were older than nonspironolactone patients ($P = .019$; Table III).

Overall, spironolactone-prescribed patients had more comorbidities than nonspironolactone patients (Table III). Most patients in both cohorts had cardiovascular comorbidities, specifically hypertension being the most frequent. No patients had primary aldosteronism. Spironolactone-prescribed patients had higher rates of alopecia ($P = .009$), acne vulgaris ($P = .015$), hirsutism ($P = .001$),

Table II. Propensity match balancing analysis

Variable	Spironolactone cohort covariate weights	No spironolactone cohort (prematch → match) covariate weights
Age, years old		
20-24	0.000	0.0003 → 0.000
25-29	0.000	0.0006 → 0.000
30-34	0.000	0.0011 → 0.000
35-39	0.004	0.0034 → 0.004
40-44	0.003	0.0082 → 0.001
45-49	0.013	0.0149 → 0.011
50-54	0.032	0.0321 → 0.029
55-59	0.040	0.0580 → 0.040
60-64	0.120	0.0842→ 0.118
65-69	0.216	0.2362→ 0.215
70-74	0.203	0.2211→ 0.207
75-79	0.171	0.1574 → 0.174
80-84	0.118	0.0994 → 0.123
85-89	0.044	0.0544 → 0.044
≥90	0.036	0.0286 → 0.035
Alopecia	0.033	0.0193 → 0.036
Acne vulgaris	0.028	0.0160 → 0.021
Hirsutism	0.011	0.0029 → 0.008
Hypertension	0.7784	0.6028 → 0.784
Congestive heart failure	0.5260	0.1408 → 0.531
Conn syndrome	0.0000	0.0000 → 0.000
Nephrotic syndrome	0.0040	0.0459 → 0.005
Nonmalignant ascites	0.0694	0.0121 → 0.067
Alcohol abuse	0.0160	0.0113 → 0.017
Smoking	0.1268	0.1037 → 0.123
Illicit drugs	0.0734	0.0495 → 0.068
Intercept	0.0631	0.0247 → 0.063

hypertension ($P < .001$), congestive heart failure ($P < .001$), and ascites ($P < .001$).

Propensity-matched patient characteristics

A summary of the propensity score balancing is provided in Table II. After matching, the cohorts demonstrated no significant differences in demographics, comorbidities, and substance history (Table III).

Prepropensity BC recurrence

In the prepropensity univariate model, BC recurred within 2 years in 123 of the patients prescribed spironolactone (16.5%) compared with 3649 patients (12.8%) who were not prescribed spironolactone (χ^2, $P = .005$; Table III). However, in prepropensity multivariate Cox proportional hazard regression models, spironolactone was not associated with BC recurrence (adjusted hazard ratio [HR], 1.081; 95% confidence interval [CI], 0.953-1.227; $P = .227$; Table IV).

In addition, prepropensity multivariate Cox proportional hazard regression models that adjusted for age, spironolactone, alopecia, acne vulgaris, hirsutism, hypertension, congestive heart failure, primary aldosteronism, nephrotic syndrome, ascites, alcohol abuse, smoking, illicit drug abuse, and insurance plan showed no association between spironolactone and an increased BC recurrence rate (adjusted HR, 1.045; 95% CI, 0.918-1.189; $P = .507$; Table IV). Hypertension (adjusted HR, 1.157; 95% CI, 1.103-1.213; $P < .001$) and alcohol abuse (adjusted HR, 1.296; 95% CI, 1.081-1.554; $P = .005$) were factors associated with increased BC recurrence. Commercially insured patients had increased BC recurrence compared with Medicare patients (adjusted HR, 1.192; 95% CI, 1.093-1.299; $P < .001$). Median survival time was not determined in the prepropensity Cox proportional hazard regression model because the HRs did not reach to 0.50 (HR, 0.469; 646 days).

Propensity matched-adjusted BC recurrence

Univariate analysis of propensity-matched cohorts showed that spironolactone was not associated with increased BC recurrence (χ^2, $P = .779$; Table III). Similarly, multivariate Cox proportion hazard regression models showed no association between spironolactone and increased BC recurrence (adjusted HR, 0.966; 95% CI, 0.807-1.156; $P = .953$; Table IV). Acne vulgaris was inversely associated with increased BC recurrence (adjusted HR, 0.375; 95% CI 0.163-0.867; $P = .022$), whereas alcohol abuse was associated with increased BC recurrence, similar to prematched models (adjusted HR, 2.304; 95% CI, 1.324-4.008; $P = .003$). Median survival was not determined in the propensity-matched Cox proportional hazard regression model because the HRs did not reach 0.50 (HR, 0.491; 549 days).

DISCUSSION

This study retrospectively determined the impact of spironolactone on BC recurrence rates among female patients with history of BC in the Humana Insurance database. In both unmatched and propensity-matched cohorts, we were unable to determine an association between spironolactone and increased BC recurrence after adjusting for confounders. To our knowledge, this is the first large-scale population study in the United States to assess the effects of spironolactone in BC survivors.

Table III. Demographics of patients with personal history of breast cancer

	Full cohort			Matched cohort		
Patient characteristics	**Sp (n = 746), %**	**No Sp (n = 28,400), %**	***P* value***	**Sp (n = 746), %**	**No Sp (n = 746), %**	***P* value**
Age, years old			**.019**			.955
<50	0.5	2.8		0.5	2.0	
50-59	7.2	8.9		7.2	7.0	
60-69	33.6	31.5		33.6	32.9	
70-79	38.2	38.4		38.2	37.5	
≥80	20.5	18.4		20.5	20.6	
Alopecia	3.4	1.9	**.009**	3.4	3.6	.888
Acne vulgaris	2.8	1.6	**.015**	2.8	2.1	.506
Hirsutism	1.1	0.3	**.001**	1.1	0.4	.130
Hypertension	78.2	60.3	**<.001**	78.2	78.7	.851
CHF	52.8	14.1	**<.001**	52.8	53.4	.877
Conn syndrome	0	0	N/A	0	0	N/A
Nephrotic syndrome	0.4	0.2	.483	0.4	0.1	.317
Nonmalignant ascites	7.0	1.2	**<.001**	7.0	6.7	.918
Alcohol abuse	1.6	1.1	.305	1.6	1.7	>.99
Smoking	12.7	10.4	**.047**	12.7	12.3	.876
Illicit drugs	7.4	5.0	**.004**	7.4	6.8	.762
BC recurrence	16.5	12.8	**.005**	16.5	15.8	.779

BC, Breast cancer; *CHF*, congestive heart failure; *N/A*, not applicable; *Sp*, spironolactone.
*Bold *P* values are statistically significant ($P < .05$).

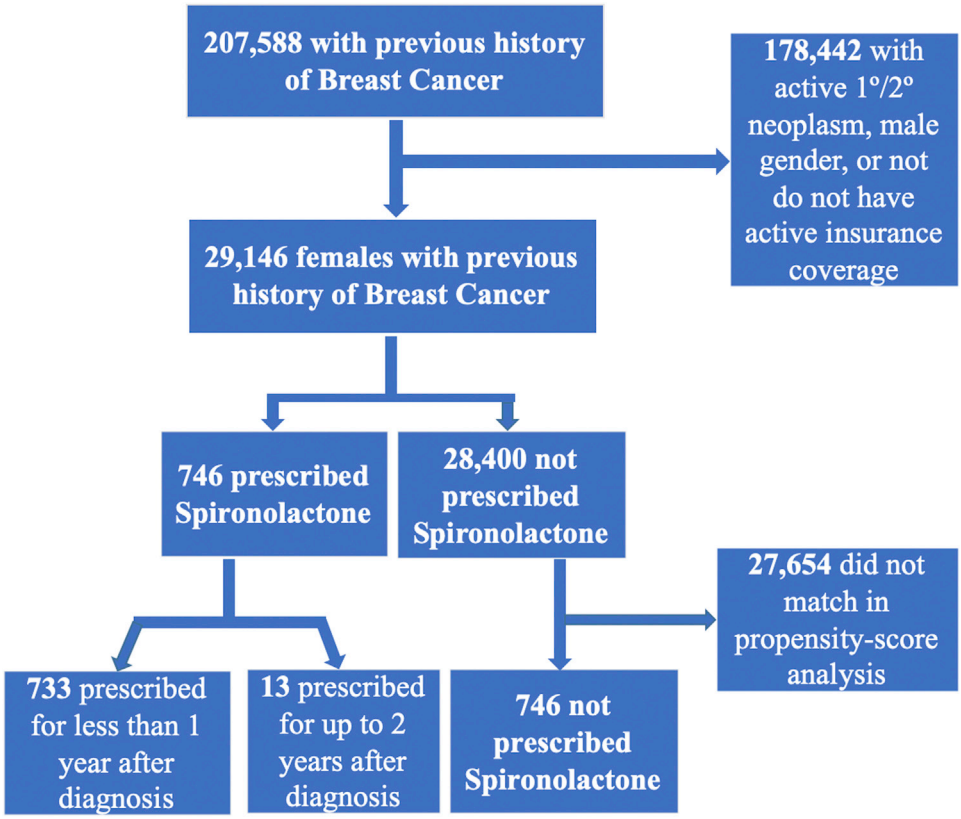

Fig 1. Flow diagram of exclusion criteria.

Table IV. Multivariate Cox proportional hazard regression analysis of the impact of spironolactone on breast cancer (*BC*) recurrence in 2 years according to each prognostic factor

Characteristics	HR	95% CI	*P* value*
Unadjusted (univariate) prematch BC recurrence analysis			
Spironolactone	1.08	0.95-1.23	.227
Adjusted prematch BC recurrence analysis			
Spironolactone	1.05	0.92-1.19	.507
Hypertension	1.16	1.10-1.21	**<.001**
Alcohol abuse	1.30	1.08-1.55	**.005**
Adjusted postmatch BC recurrence analysis			
Spironolactone	0.97	0.81-1.16	.953
Acne vulgaris	0.38	0.16-0.87	**.022**
Alcohol abuse	2.30	1.32-4.01	**.003**

CI, Confidence interval; *HR*, hazard ratio.
*Bold *P* values indicate statistical significance ($P < .05$).

BC recurrence develops during follow-up in approximately 30% of patients who are disease-free after BC, and 70% of BCs are estrogen-sensitive, progesterone-sensitive, or both, which makes the current's findings important for determining the viability of spironolactone in the treatment of FPHL in BC survivors.[9,16] In the present study, the recurrence rate for the spironolactone-prescribed cohort was 16.5%, which is within the range of expected BC recurrence rates with the use of oral hormone replacement therapy, and the recurrence rate of the nonprescribed cohort was also within the range of expected BC recurrences within 1 to 2 years.[9,10] However, despite the proestrogen effects of spironolactone, BC recurrence rates were unaffected, which further supports spironolactone's safety profile and reaffirms the International Agency for Research on Cancer's position that spironolactone does not cause carcinogenicity.[3,7,8]

Few studies report on patients with previous history of BC on spironolactone.[17] Kluger et al[17] conducted a prospective study that contained 1 patient with BC who was being treated with spironolactone at a dosage of 150 mg daily for 3 months and did not report any tumor recurrence during follow-up. Mackenzie et al[8] performed a matched-cohort retrospective study on 1340 BC survivors that assessed the impact of spironolactone on BC recurrence that showed no increase in recurrence rates, but the study had limitations because they could not differentiate true BC recurrence from repeat reporting of previous BC, whereas our study was able to differentiate these 2 entities.

The evidence to support or refute the association between alcohol and BC recurrence is variable even though there is a general consensus that alcohol is associated with risk for BC.[18] Our results show that alcohol abuse is associated with increased risk of BC recurrence, which is consistent with previous studies.[19] Kwan et al[19] showed that heavy alcohol drinking was associated with a 19% risk for breast cancer recurrence. Ethanol has been shown to interfere with antioxidative defense systems, increase estrogen levels through activation of the CYP19 enzyme induction, and downregulate *BRCA1*, a key tumor suppressor gene for the suppression of BC tumorigenesis.[18] However, other studies report that heavy drinking leads to increased BC-free survival.[20] Given that alcohol is associated with increased estrogen production, providers should generally counsel BC patients to abstain from alcohol when being on spironolactone for alopecia treatment.

There is concern among providers for the use of spironolactone in patients with previous BC because of its proestrogenic effects.[8] Estrogen signaling induces cell proliferation and causes genetic alterations, including aneuploidy.[18] However, there are inconsistent data with spironolactone affecting serum hormone levels, including estradiol, in normal patients.[7] Rozner et al[7] concluded in their literature review that there were no significant changes in serum estradiol levels. More uniform studies need to be performed to obtain consistent data needed to determine whether patients with BC would have increased serum estradiol levels compared with healthy patients when taking spironolactone.

This study has several limitations. Given that spironolactone is a long-term medication, the current study only examined 2 years of data surveillance.[1,2] Data with a longer surveillance time would be required to assess 5- or 10-year cancer recurrence risk. Also, the current study only looked at the frequency of spironolactone prescriptions filled and did not know whether the patient was physically compliant with the medication or even whether she received the medication. Additionally, spironolactone dosage was not assessed.

Another limitation is that validation studies have not been previously done for validating personal history of malignant neoplasm ICD-9 and ICD-10 codes for BC. Therefore, how predictive these ICD codes are at capturing the true population is not clear. However, after appropriately powering the study, reducing the number of patients with an

unclear status of their BC and having prior validation studies allowing us to reliably identify patients that had BC recurrence, we felt that we performed our best at decreasing bias.[21] Even with safeguards placed, coding errors can still be possible, however rare, in an insurance database. The Medicare database, for example, may have up to 1.3% coding errors in its database.[6] Despite these concerns for potential coding error, we are confident that we were able to minimize the selective bias as best we could. Lastly, this study may not entirely reflect the whole population given that this current study only observed patients from a particular database.

CONCLUSION

Spironolactone was found to not be associated with increased risk for BC recurrence, whereas alcohol was associated with increased BC recurrence. Spironolactone may be an additional option for the treatment of alopecia in female BC survivors who are disease-free. Future prospective studies or clinical trials may be performed to assess the efficacy and safety of spironolactone in patients who have cancer remission to confirm our findings. In addition, validation studies of ICD-9 and ICD-10 codes of personal history of malignant neoplasm should be performed.

REFERENCES

1. Rathnayake D, Sinclair R. Innovative use of spironolactone as an antiandrogen in the treatment of female pattern hair loss. *Dermatol Clin*. 2010;28(3):611-618.
2. Levy LL, Emer JJ. Female pattern alopecia: current perspectives. *Int J Womens Health*. 2013;5:541-546.
3. Mackenzie IS, Morant S, Wei L, et al. Spironolactone use and risk of incident cancers: a retrospective, matched cohort study. *Br J Clin Pharmacol*. 2016;83(3):653-663.
4. Almukhtar R. Spironolactone use and the risk of breast cancer. *J Am Acad Dermatol*. 2016;24(5, Supplement 1):AB72.
5. Biggar RJ, Andersen EW, Wohlfahrt J, et al. Spironolactone use and the risk of breast and gynecologic cancers. *Cancer Epidemiol*. 2013;37(6):870-875.
6. World Health Organization. International Agency for Research on Cancer Some thyrotropic agents. IARC Monographs on the Evaluation of Carcinogenic Risks to humans. Volume 79: Some Thyrotropic Agents. 2001. Available at: http://monographs.iarc.fr/wp-content/uploads/2018/06/mono79.pdf. Accessed February 20, 2020.
7. Rozner RN, Freites-Martinez A, Shapiro J, et al. Safety of 5α-reductase inhibitors and spironolactone in breast cancer patients receiving endocrine therapies. *Breast Cancer Res Treat*. 2019;174(1):15-26.
8. Mackenzie IS, Macdonald TM, Thompson A, et al. Spironolactone and the risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. *BMJ*. 2012;345:e4447.
9. Colleoni M, Sun Z, Karen N, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the International Breast Cancer Study Group Trials I to V. *J Clin Oncol*. 2016;34(19):927-935.
10. Lupo M, Dains JE, Madsen LT. Hormone replacement therapy: an increased risk of recurrence and mortality for breast cancer patients? *J Adv Pract Oncol*. 2015;6(4):322-330.
11. BlueCross BlueShield of Alabama. Coding Neoplasms. Available at: https://providers.bcbsal.org/portal/documents/10226/306297/Coding+Neoplasms+%28Cancer%29/1c52e9bd-7ac8-4ca0-a4a4-4238a15ef0a6. Accessed December 25, 2019.
12. Funder JW. Spironolactone in cardiovascular disease: an expanding universe? *F1000Res*. 2017;6:1738.
13. Charny JW, Choi JK, James WD. Spironolactone for the treatment of acne in women, a retrospective study of 110 patients. *Int J Womens Dermatol*. 2017;3(2):111-115.
14. Quan H, Sundarajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
15. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175-191.
16. Brufsky AM, Dickler MN. Estrogen receptor-positive breast cancer: exploiting signaling pathways implicated in endocrine resistance. *Oncologist*. 2018;23(5):528-539.
17. Kluger N, Jacot W, Frouin E, et al. Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Ann Oncol*. 2012;23(11):2879-2884.
18. McDonald J, Goyal A, Terry MB. Alcohol intake and breast cancer risk: weighing the overall evidence. *Curr Breast Cancer Rep*. 2013;5(3). https://doi.org/10.1007/s12609-013-0114z.
19. Kwan ML, Chen WY, Flatt SW, et al. Postdiagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. *Cancer Epidemol Biomarkers Prev*. 2013;22(1):32-41.
20. Kowalksi A, Striley CW, Varma DS, et al. Interactions between alcohol consumption and adjuvant hormone therapy in relation to breast cancer-free survival. *J Breast Cancer*. 2018;21(2):158-164.
21. Abraha I, Serraino D, Giovannini G, et al. Validity of ICD-9-CM codes for breast, lung, and colorectal cancers in three Italian administrative healthcare databases: a diagnostic accuracy study protocol. *BMJ Open*. 2016;6(3):e010547.