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ORIGINAL STUDY

Comparative safety of conjugated estrogens/bazedoxifene versus estrogen/progestin combination hormone therapy among women in the United States: a multidatabase cohort study

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Abstract

Objective: To assess the risk of select safety outcomes including endometrial cancer, endometrial hyperplasia, and breast cancer among women using conjugated estrogens/bazedoxifene (CE/BZA) as compared with estrogen/progestin combination hormone therapy (EP).

Methods: We conducted a new-user cohort study in five US healthcare claims databases representing more than 92 million women. We included CE/BZA or EP new users from May 1, 2014, to August 30, 2019. EP users were propensity score (PS) matched to users of CE/BZA. Incidence of endometrial cancer, endometrial hyperplasia, breast cancer, and eight additional cancer and cardiovascular outcomes were ascertained using claims-based algorithms. Rate ratios (RR) and differences pooled across databases were estimated using random-effects models.

Results: The study population included 10,596 CE/BZA and 33,818 PS-matched EP new users. Rates of endometrial cancer and endometrial hyperplasia were slightly higher among CE/BZA users (1.6 and 0.4 additional cases per 10,000 person-years), although precision was limited because of small numbers of cases (endometrial cancer: RR, 1.50 [95% confidence interval {CI}, 0.79-2.88]; endometrial hyperplasia: RR, 1.69 [95% CI, 0.51-5.61]). Breast cancer incidence was lower in CE/BZA users (9.1 fewer cases per 10,000 person-years; RR, 0.79; 95% CI, 0.58-1.05). Rates of other outcomes were slightly higher among CE/BZA users, but with confidence intervals compatible with a wider range of possible associations.

Conclusions: CE/BZA users might experience slightly higher rates of endometrial cancer and endometrial hyperplasia, and a lower rate of breast cancer, than EP users in the first years of use.

Key Words: Bazedoxifene – Breast cancer – Endometrial cancer – Estrogen – Hormone therapy – Multidatabase study.

lthough hormone therapy is frequently used to treat vasomotor symptoms of menopause, it is not without other potential implications to public health.[1] Among women with a uterus, the use of estrogen by itself increases the incidence of endometrial cancer.[2] This increase in risk is typically mitigated by the addition of progestin to "oppose" the estrogen, but the addition of progestin seems to increase the risk of breast cancer relative to placebo or taking estrogen therapy.[3-5] Other molecular entities could be considered for the purpose of estrogen opposition that may not have this undesired effect. For example, it is possible that using a selective estrogen receptor modulator (SERM) instead of progestin to oppose estrogen could mitigate the increased risk of endometrial cancer associated with estrogen therapy without increasing the risk of breast cancer.[6-8]

Bazedoxifene (BZA) is a SERM that was developed as an estrogen antagonist in breast and endometrial tissue.[6] Combined with conjugated estrogens (CE/BZA), it is the first approved hormone therapy to pair estrogen with a SERM for the treatment of the vasomotor symptoms associated with menopause. In 2013, oral CE/BZA (Duavee) was approved in the United States for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis[9] in women with a uterus.[10] In 2014, oral CE/BZA (Duavive) was authorized throughout the European Union for the treatment of menopause-associated symptoms in women with a uterus.[11] Uptake of CE/BZA in Europe has been low,[12] with most women exposed to CE/BZA located in the United States.

Evidence regarding the safety of CE/BZA is limited to preclinical studies and clinical trials, principally five clinical trials known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials.[13-16] Because of their small sizes, the SMART trials were, however, not informative regarding endometrial outcomes or breast cancer risk. Preliminary evidence suggests, however, a potential for CE/BZA to reduce breast cancer risk factors such as breast density and biomarkers including insulin-like growth factor and serum progesterone.[16,17]

No studies have compared the rates of endometrial outcomes and breast cancer between CE/BZA and estrogen-progestin therapy (EP) users. Although a randomized controlled trial is the ideal approach to assess causal relationships, these outcomes could not be readily assessed using a trial design because of their infrequency. To assess these and other safety outcomes, the European Medicines Agency designated a noninterventional, Post-Authorization Safety Study to examine the real-world safety of CE/BZA.[18] To fulfill this Post-Authorization Safety Study commitment, we used data from five, large, US healthcare claims databases containing more than 92 million women between 2014 and 2019. Because uptake of this new drug combination was low in Europe,[12] these US databases likely contain a majority of the women exposed to this new treatment.

METHODS

Study design

We performed a propensity score (PS)–matched, new-user, active comparator cohort study in five US claims databases and integrated results using meta-analyses. Approval of the study protocol (Protocol Number: B2311060) was granted by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. The study protocol is publicly accessible through the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's European Union electronic Register of Post-Authorisation Studies (Register Number: EUPAS11599).[18]

Data sources

The study included five US health insurance claims databases: research portion of Aetna's Sentinel Common Data Model (maintained by CVS Health Clinical Trial Services), HealthCore Integrated Research Database (HIRD), MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases, MarketScan Medicaid, and Optum Research Database (ORD). Each database captures the healthcare experience of persons from across the United States who are covered by commercial or public health insurance (Table 1). These data include individuals' health insurance claims and enrollment information.

Study population

The study population included female health plan enrollees of any age with medical and pharmacy coverage and at least 12 months of continuous health plan enrollment before their first (index) dispensing of CE/BZA or EP in the database. Women were included if they initiated CE/BZA or EP during the study period from May 1, 2014, to August 30, 2019 (or end of data availability, if earlier). We excluded women with a history of hysterectomy; cancer diagnoses (other than nonmelanoma skin cancer); previous dispensings of CE/BZA, EP, or unopposed estrogen; or simultaneous dispensings of both CE/BZA and EP on the index date (Supplemental Digital Content [SDC] Tables 1 and 2, http://links.lww.com/MENO/B148).

For the analyses of endometrial hyperplasia, women diagnosed with endometrial hyperplasia in the 12 months before initiating CE/BZA or EP were excluded. For analyses of cardiovascular outcomes, women with any cardiovascular diagnosis (SDC Table 3, http://links.lww.com/MENO/B148) in the 6 months before initiating CE/BZA or EP were excluded. For the analyses of ovarian cancer, women with a history of bilateral oophorectomy were excluded.

Exposures

Women were considered exposed to CE/BZA if they had at least one pharmacy claim with a National Drug Code for CE/BZA (SDC Table 1, http://links.lww.com/MENO/B148). Women were considered exposed to EP if they had at least one pharmacy claim for oral, topical, or transdermal EP (SDC Table 1, http://links.lww.com/MENO/B148). Eligible EP drugs included CE/medroxyprogesterone acetate, estradiol and norethindrone acetate, norethindrone acetate-ethinyl estradiol, estradiol/drospirenone, estradiol/levonorgestrel, and estradiol/norgestimate (SDC Table 1, http://links.lww.com/MENO/B148). The index date for each woman was their first (index) exposure (CE/BZA or EP) recorded in the database during the intake period.

Database	Payor or servicer	Includes Medicare plans?	Data availability	Females with enrollment in study period[a]
CVSH CTS/Aetna's SCDM[b]	Private (Aetna)	Advantage	01/2008-08/2019	5,841,695
HIRD	Private (Anthem)	Advantage	01/2006-08/2019	19,045,398
MarketScan CCAE-MDCR	Private (mixed, ES)	Supplemental	01/2013-07/2019	41,224,183
MarketScan Medicaid	Public (Medicaid)	Yes	01/2013-12/2018	10,859,907
ORD	Private[c]	No	05/2011-08/2019	15,451,242

CCAE-MDCR, MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases; CVSH CTS, CVS Health Clinical Trial Services; ES, employer-sponsored; HIRD, HealthCore Integrated Research Database; ORD, Optum Research Database; SCDM, Sentinel Common Data Model.
[a]The study period began May 1, 2014, and ended on the final date of data availability for the respective database.
[b]Maintained by CVSH CTS.
[c]A large US health plan affiliated with Optum.

Outcomes

Endometrial cancer and endometrial hyperplasia cases were identified using algorithms developed and validated in EP users in the HIRD.[19,20] Endometrial cancer was identified by the presence of at least one inpatient hospitalization with a principal diagnosis of endometrial cancer or more than two outpatient or emergency department visits on different dates with an endometrial cancer diagnosis in any position. The endometrial cancer algorithm had a positive predictive value of 91% (95% confidence interval [CI], 87%-94%).[20] Endometrial hyperplasia was identified using a predictive model algorithm with a positive predictive value of 80% (95% CI, 77%-88%) in the HIRD.[18]

Venous thromboembolism (VTE) cases were identified by the presence of at least one inpatient hospitalization with a principal diagnosis of VTE (SDC Table 4, http://links.lww.com/MENO/B148). Myocardial infarction and stroke/transient ischemic attack (TIA) cases were identified by the presence of either (*a*) at least one inpatient hospitalization with a principal diagnosis for the condition with a length of stay of at least 3 days, (*b*) at least one inpatient hospitalization with a principal diagnosis for the condition and a discharge status of death, or (*c*) at least one emergency department visit with a principal diagnosis code for the condition (SDC Table 4, http://links.lww.com/MENO/B148).

Other cancer outcomes required either (*a*) at least one inpatient hospitalization with a principal diagnosis of the cancer under study (for breast cancer, could be a secondary diagnosis) or (*b*) at least two outpatient or emergency department visits on different dates with the relevant diagnosis in any position (SDC Table 4, http://links.lww.com/MENO/B148).

Covariates

Covariates were identified on or before the index date and included age, sex, geographic region, total time enrolled in health plan, calendar year of index date, cardiovascular, cerebrovascular, or coronary heart disease (in the 183 d before and including index date), prespecified comorbidities and medications (in the 365 d before and including the index date; SDC Tables 5 and 6, http://links.lww.com/MENO/B148), and the 25 most common comorbidities and procedures within each database's prematched study population. For the 25 most common comorbidities and procedures, categories were created using the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project's Clinical Classification Software.[21] The Clinical Classification Software groups *International Classification of Diseases, Ninth and Tenth Revisions*, *Current Procedural Terminology (CPT)*, and *Healthcare Common Procedure Coding System (HCPCS)* codes into broader clinically meaningful categories.[21]

Endometrial hyperplasia during the baseline (preindex) period was treated as a covariate in all analyses, except analyses of endometrial hyperplasia for which women with endometrial hyperplasia in the 365 days before and including the index date were excluded. When treated as a covariate or exclusion criterion (as opposed to an outcome), endometrial hyperplasia was defined by a diagnosis code for endometrial hyperplasia on any claim in any position.

The ORD included the following additional covariates on or before the index date: any emergency department visit (yes/no), time from the start of study period (May 1, 2014) to index date, number of three-digit diagnosis codes, number of inpatient stays, number of procedures, number of unique procedures, number of drugs dispensed, number of physician visits, and total healthcare costs.

Follow-up

Follow-up for each woman began on the day after the index date and continued until the earliest of death, disenrollment, the end of the available data period (Table 1), hysterectomy, treatment switch (defined as EP to CE/BZA or CE/BZA to EP, while switching among EP drugs was permitted), or occurrence of the outcome. For noncancer outcomes (ie, endometrial hyperplasia, VTE, myocardial infarction, and stroke/TIA), follow-up was also censored by any cancer diagnosis or end of current treatment episode, and women could contribute more than one treatment episode. Treatment episodes for noncancer outcomes were constructed by concatenating consecutive dispensing days' supplies, that is, fill date + days' supply, allowing for treatment gaps of 30 days (ORD allowed for up to 32 d). If a woman had a dispensing of the same study drug type (ie, CE/BZA or EP) that occurred before the end of a treatment episode, the treatment episode was extended by the number of overlapping days (ie, stockpiling was assumed).

Statistical analysis

PS (ie, the probability of receiving CE/BZA vs EP) was estimated using logistic regression models including all covariates (see Covariates). Positivity[22] was assessed by comparing distributions of PS in each treatment group to visually assess the extent of nonoverlap. Women exposed to EP were matched without replacement by PS to women exposed to CE/BZA.

Matching was tailored to the needs of each database per the number and characteristics of women in each treatment group. Absolute standardized differences were computed to assess covariate balance.[23,24]

Incidence rates (IR) for each outcome were calculated for each treatment group by database. Incidence rate ratios (RR) for each outcome were calculated with EP users as the referent.

The DerSimonian and Laird random-effects model[25] was used to pool the estimates for IR and RR across databases. The Cochran Q test and I^2 values were used to assess heterogeneity of results between databases. P value functions were constructed for the pooled endometrial and breast cancer RRs. These functions simultaneously convey the precision of effect estimates and the consistency of the data with various magnitudes of hypothetical effect.[26]

To account for endometrial and breast cancers that may have had onset before initiating CE/BZA or EP exposure, and to account for potential latency between exposure and risk period, we implemented a sensitivity analysis in three databases (HIRD, MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases, and MarketScan Medicaid) in which follow-up began 6 months after first exposure to CE/BZA or EP. Effect estimates were then pooled across these three databases.

Data management and analysis took place in 2019 to 2020 using Statistical Analysis System (SAS) Enterprise Guide version 7.15 (SAS Institute, Cary, NC) and SAS 9.4 (SAS Institute Inc., Cary, NC) and were completed by HealthCore (HIRD and MarketScan databases), Pfizer (data management for MarketScan databases only, with data extraction code authored by HealthCore), Optum (ORD), and CVS Health Clinical Trial Services (as Healthagen). Pooled analyses were completed by HealthCore using the *metafor* package in R.[27,28]

RESULTS

Participant characteristics

There were 92,422,425 women with health plan enrollment across the five databases during the study period. We identified 10,603 CE/BZA and 94,531 EP new users meeting the study entry criteria. Of these, 10,596 CE/BZA and 33,818 EP new users were included after PS matching (Table 2). In each database, demographic and clinical covariates were balanced between CE/BZA and EP users in the matched population (SDC Table 7, http://links.lww.com/MENO/B148). Treatment duration by treatment group and study database is shown in SDC Table 8, http://links.lww.com/MENO/B148, and was slightly longer in the CE/BZA group in most databases. Average follow-up time for cancer outcomes was approximately 22 months, and average follow-up time for endometrial hyperplasia and cardiovascular outcomes was 10 to 11 months (SDC Table 9, http://links.lww.com/MENO/B148).

Pooled comparative findings

Pooled comparative findings are presented in Figure 1 and Table 3. For all pooled RR values, the P value for the Cochrane Q test was greater than 0.1, and I^2 was 0%, with the exception of

endometrial hyperplasia, which showed greater heterogeneity than other outcomes (Table 3).

A total of 39 endometrial cancer cases occurred in 82,458 person-years of follow-up. The IR of endometrial cancer was slightly higher (1.6 additional cases per 10,000 person-years) in the CE/BZA users than in EP users (5.2 vs 3.6 per 10,000 person-years; RR, 1.50; 95% CI, 0.79-2.88; Fig. 1; Table 3). A total of 48 endometrial hyperplasia cases occurred in 38,770 person-years of follow-up. The IR of endometrial hyperplasia was similar, although also slightly higher (0.4 additional cases per 10,000 person-years) in the CE/BZA users than in EP users (11 vs 10.6 per 10,000 person-years; RR, 1.69; 95% CI, 0.51-5.61), although with greater uncertainty due to variation among data sources.

Rates and RRs for additional outcomes are shown in Table 3. The most precise result for a specific outcome was the effect estimate for breast cancer. A total of 286 breast cancer cases occurred in 82,047 person-years of follow-up. The breast cancer IR was lower (9.1 fewer cases per 10,000 person-years) in the CE/BZA users than in EP users (27.2 vs 36.3 per 10,000 person-years; RR, 0.79; 95% CI, 0.58-1.05; Fig. 1; Table 3).

The P value functions show the range of estimates compatible with the data (Fig. 1), indicating greater precision for the breast cancer RR. The P value functions for endometrial cancer and hyperplasia are shifted to the right and wider than the P value function for breast cancer, which is shifted to the left of the null.

After applying a 6-month lag period for endometrial and breast cancers, pooled RRs were 1.88 (95% CI, 0.90-3.91; Q = 0.6; I^2 = 0%) for endometrial cancer and 0.65 (95% CI, 0.44-0.97; Q = 0.8; I^2 = 0%) for breast cancer in three databases.

Effect estimates for extrauterine outcomes with similar precision to endometrial cancer were thyroid cancer (RR, 1.5; 95% CI, 0.8-2.9), gastrointestinal cancer (RR, 0.8; 95% CI, 0.4-1.5), and stroke (RR, 1.2; 95% CI, 0.7-2.1). The remaining outcomes showed slightly higher rates for CE/BZA but were less precise.

DISCUSSION

We assessed safety outcomes among women initiating CE/BZA for hormone therapy across five large US healthcare databases with a collective 92 million women. Rates of endometrial hyperplasia and endometrial cancer were slightly higher in women who used CE/BZA than in women who used EP, although precision was limited because of small numbers of cases. Breast cancer rates were lower in women who used CE/BZA than in women who used EP, suggesting that the use of BZA for estrogen opposition does not increase breast cancer risk as progestin may be known for.[3-5] Among other outcomes, rates of thyroid cancer, ovarian cancer, and stroke/TIA were higher (albeit imprecisely so) in CE/BZA users, although these results are not strongly supported by other literature, and further study would be valuable. Similarly, the results for the remaining outcomes are less precise and are consistent with both potentially important increased and decreased rates comparing CE/BZA with EP.

Previous trials suggest a potential for CE/BZA to reduce risk factors of breast cancer, such as breast density, insulin-like

TABLE 2. *US Food and Drug Administration–approved combination hormone therapy products available by prescription in the United States, by estrogen and progestin type, and distribution of index medication in propensity score–matched new user population across five databases*

Commercial name	Estrogen type	Progestin type	Route	Initial US approval[a]	n (%)[b]
Duavee	CE	N/A[c]	Pill	2013	10,596 (24)
All EP	—	—	—	—	33,818 (76)
Prempro & Premphase	CE	MPA	Pill	1995	12,403 (28)
Activella	Estradiol	Norethindrone acetate	Pill	1998	10,757 (24)
Combipatch	Estradiol	Norethindrone acetate	Patch	1998	5,030 (11)
Femhrt	Ethinyl estradiol	Norethindrone acetate	Pill	1999	3,239 (7)
Angeliq	Estradiol	Drospirenone	Pill	2005	333 (1)
Climara Pro	Estradiol	Levonorgestrel	Patch	2003	2,022 (5)
Prefest	Estradiol	Norgestimate	Pill	1999	40 (0)

CE, conjugated estrogens; EP, estrogen-progestin hormone therapy; MPA, medroxyprogesterone acetate; *n*, number; N/A, not applicable.
[a]Source: https://www.accessdata.fda.gov/scripts/cder/daf/.
[b]Participants in the EP group could have more than one EP type as their index medication. This was the case for *n* = 6 participants (0.01%).
[c]Bazedoxifene instead of progestin.

growth factor, and serum progesterone.[16,17] The results reported here for breast cancer incidence are consistent with results for surrogate endpoints in the aforementioned clinical trials as well as the protective effects of two other SERMS (raloxifene and tamoxifen) approved in the United States for the prevention of breast cancer in high-risk women.[6]

Although a randomized controlled trial is the ideal approach to assess causal relationships, these outcomes could not be readily assessed using a trial design because of their infrequency. Even observational studies in large databases are challenged to assemble large populations to study rare outcomes among users of uncommon medications. We used data from 92 million women across five US health insurance claims databases to examine the rates of safety outcomes among new CE/BZA and EP users, likely including most of the women exposed to CE/BZA to date. Despite these efforts, effects are estimated with less precision than we would like. To assess random error, we present *P* value functions that show the compatibility of the results across a wide range of hypothetical effect sizes for endometrial outcomes and breast cancer (Fig. 1). This strategy avoids dichotomizing contin-

FIG. 1. *P* value functions of RRs for EC, EH, and breast cancer. This plot displays all *P* values for a range of possible RRs. The probabilities shown are for the observed data given each hypothesized RR. The axis values of this plot can be used to infer confidence limits at varying levels of confidence. For example, *x* axis values at the 0.05 level of the *y* axis represent the 95% confidence interval limits. Similarly, the *x* axis values at the 0.10 level of the *y* axis represent the 90% confidence interval limits. The peak of each curve represents the study point estimate (rate ratio). The two-sided null hypothesis *P* value (familiar for its common use in statistical significance testing) is the *y* axis value at which the *x* axis value is 1 (eg, *P* ~ 0.10 for breast cancer). CE/BZA, conjugated estrogens/bazedoxifene; EC, endometrial cancer; EH, endometrial hyperplasia; EP, estrogen-progestin hormone therapy; RR, incidence rate ratio.

uous *P* values or confidence intervals into regions of "statistically significant" and "not statistically significant" that has resulted in researchers overlooking potentially important public health effects that were not "statistically significant."[29] Instead, the degree of support for possible effect sizes is considered quantitatively and in light of additional, contextualizing evidence. The data used represent the largest study available at this time, included most of the relevant population, and demonstrated a plausible and potentially important effect on breast cancer, the most common cancer among women worldwide.[30]

There are several important limitations to this study. Because the safety outcomes of interest and the exposure are uncommon, we pooled findings from five large US health insurance claims databases representing 10,596 new users of CE/BZA and 33,818 new users of EP. Doing so enabled us to include most study-eligible CE/BZA users in the United States during the study period.[12] Despite pooling results from these large databases, interpretation is challenging because of few outcome cases and the limited precision of our estimates, and the variation among databases for some estimates.

Because average durations of use tended to be brief and follow-up times were 2 years or less for all outcomes, these data do not address possible long-term effects of CE/BZA versus EP. Important effects may still occur in the short term because of the promotion of growth in undetected existing tumor cells.[31,32] After taking possible latency into account and removing cases that were diagnosed in the first 6 months of follow-up, the effect estimates for breast cancer and endometrial cancer both increased in absolute magnitude; the estimate for breast cancer was more strongly protective, whereas the effect estimate for endometrial cancer increased.

This study did not estimate effects according to duration of use, EP formulation, dose, route of administration, or time since menopause, which may affect the incidence of the studied outcomes.[33,34] The study compares the effects of substituting BZA for progestin in commonly used hormone therapy and cannot assess individual contributions of each drug or how CE/BZA would compare with CE without progestin. Sample size was insufficient to compare CE/BZA with any particular estrogen dose or formulation.
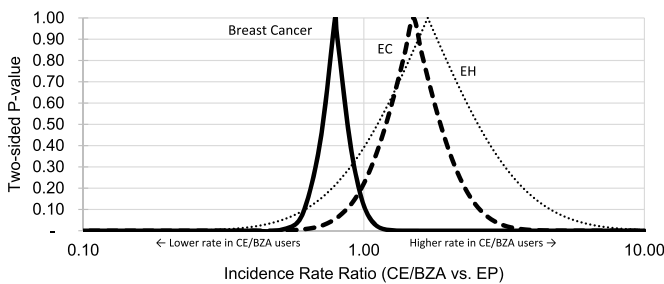
TABLE 3. *Pooled random-effects IR and RR for cancer and cardiovascular outcomes in new users of CE/BZA and new users of EP*

	CE/BZA (n = 10,596)					EP (n = 33,818)					CE/BZA vs EP (ref)		
	Cases	PY	IRp (95% CI)[a]	Q	I[2b]	Cases	PY	IRp (95% CI)[a]	Q	I[2b]	RRp (95% CI)	Q	I[2b]
Endometrial outcomes													
Endometrial cancer	12	19,704	5.2 (2.0-8.4)	3.3	0	27	62,754	3.6 (1.1-6.1)	8.5	52.6	1.5 (0.8-2.9)	0.6	0
Endometrial hyperplasia[d]	14	9,689	11.0 (1.8-20.2)	5.9	31.8	34	29,081	10.6 (6.1-15.1)	4.8	15.7	1.7 (0.5-5.6)	8.2	51.3
Extrauterine outcomes													
Any cancer[c]	140	19,487	71.6 (59.7-83.5)	1	0	478	62,066	76.7 (69.8-83.6)	2.1	0	0.9 (0.8-1.1)	0.5	0
Breast cancer	55	19,625	27.2 (19.9-34.5)	2.1	0	231	62,422	36.3 (30.4-42.2)	5	20.5	0.8 (0.6-1.1)	3.5	0
Ovarian cancer	5	19,693	2.1 (0.1-4.1)	1.8	0	10	62,741	1.6 (0.6-2.6)	1.1	0	1.9 (0.7-5.5)	2.5	0
Thyroid cancer	13	19,677	5.9 (2.5-9.2)	2.5	0	30	62,717	4.7 (3.0-6.3)	1.8	0	1.5 (0.8-2.9)	1.9	0
Renal cancer or adenoma	1	19,707	0.7 (0.0-1.9)	1.6	0	8	62,756	0.9 (0.2-1.7)	2.7	0	1.1 (0.3-4.0)	0.9	0
GI cancer	11	19,702	4.9 (1.8-8.1)	1.8	0	48	62,712	7.5 (5.4-9.7)	1.2	0	0.8 (0.4-1.5)	1.9	0
VTE[d]	4	9,725	3.3 (0.0-6.8)	2.3	0	13	29,188	3.6 (0.7-6.5)	5.4	26.2	1.3 (0.5-3.5)	1.4	0
Myocardial Infarction[d]	3	9,353	3.9 (0.0-7.9)	0.8	0	11	27,966	3.3 (1.2-5.4)	2.8	0	1.2 (0.4-3.8)	1.6	0
Stroke/TIA[d]	15	9,348	14.0 (1.0-27.1)	7.7	48.2	41	27,954	13.4 (7.1-19.6)	6.2	34.9	1.2 (0.7-2.1)	1.6	0

CE/BZA, conjugated estrogens/bazedoxifene; CI, confidence interval; EP, estrogen-progestin hormone therapy; GI, gastrointestinal; IR, incidence rate; IRp, pooled incidence rate; n, number; PY, person-years; RR, incidence rate ratio; RRp, pooled incidence rate ratio; ref, referent; TIA, transient ischemic attack; VTE, venous thromboembolism.
[a]Per 10,000 PY. IR values were pooled independently from RR values; as a result, the CE/BZA IRp divided by the EP IRp may not equate to the RRp.
[b]Displayed as %.
[c]Any cancer except nonmelanoma skin cancer.
[d]Noncancer outcomes were censored by the end of current treatment episode.

Results from administrative claims databases can be affected by outcome misclassification. We used validated algorithms for the endometrial cancer and endometrial hyperplasia outcomes,[19,20] but claims-based algorithms do not guarantee accurate case ascertainment. In terms of potential bias, the main concern is the extent to which misclassification errors might differ between treatment groups.[35] The comparison groups in this study were, however, treated for a common indication, and users were propensity score matched to produce balance between the two groups for potential confounding factors including age, geographic region, medications filled, and comorbidities. Furthermore, screenings for endometrial cancer and breast cancer are typically performed as part of routine preventive care in this population, and baseline mammogram frequency was balanced between the treatment groups after propensity score matching.

As a claims database analysis, this real-world study reflects actual practice and could not conduct baseline imaging or biopsies to ensure that no cancer or hyperplasia existed before treatment initiation. In lieu of this, we examined healthcare claims to identify existing diagnosed malignancy or hyperplasia before treatment initiation and excluded those women from the corresponding analyses as described earlier.

Drug exposure was based on insurance claims for drug dispensings; medication use from drug samples or self-paid fills was not included. In addition, length of treatment episode was based on the days' supply accompanying each medication dispensing, and it is possible that some women took the drug differently from prescribed or not at all.

CONCLUSIONS

In summary, the results of this multidatabase study suggest that users of CE/BZA might experience slightly higher rates of endometrial cancer and endometrial hyperplasia and a lower rate of breast cancer than estrogen/progestin users, providing another option for women considering hormone therapy for vasomotor symptoms of menopause.

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