Hindawi
International Journal of Clinical Practice
Volume 2024, Article ID 5132916, 9 pages
https://doi.org/10.1155/2024/5132916

Research Article

Vitreoretinal Traction Syndrome, Nitrituria and Human Epidermal Growth Factor Receptor Negative Might Occur in the Aromatase-Inhibitor Anastrozole Treatment

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Received 30 December 2023; Revised 1 April 2024; Accepted 10 April 2024; Published 10 May 2024

Academic Editor: Bing Niu

Background. Anastrozole has been approved for treatment of hormone receptor-positive advanced or metastatic breast cancer by FDA. This study was to assess Anastrozole-related adverse events (AEs) of real-world through data mining of the US Food and drug administration adverse event reporting system (FAERS). *Methods*. Four different disproportionality analyses, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN) and the multiitem gamma Poisson shrinker (MGPS) algorithms were employed to quantify the signals of Anastrozole-associated AEs. *Results*. A total 25 system organ class (SOCs) and 300 significant disproportionality Preferred Terms (PTs) were found in this study. The top 5 most significant SOCs were Eye disorders, renal and urinary disorders, respiratory, thoracic and mediastinal disorders, investigations, and cardiac disorders. Unexpected significant AEs was vitreoretinal traction syndrome (ROR = 1108.22, PRR = 1103.98, IC025 = 9.51, EBGM05 = 389.98), nitrituria (ROR = 3561.82, PRR = 3557.28, IC025 = 10.38, EBGM05 = 318.83) and human epidermal growth factor receptor negative (ROR = 675.04, PRR = 674.01, IC025 = 9, EBGM05 = 204.57). *Conclusion*. The Unexpected significant AEs associated with anastrozole were identified in this study, warrants urgent clarification through additional prospective studies.

1. Introduction

Breast cancer is the most commonly diagnosed cancer and the primary cause of cancer-related deaths among women worldwide, approximately 75% are hormone receptor positive and HER2 negative [1, 2]. The therapeutic prevention of early-stage cancer focuses on selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene, which have anti-estrogenic effects on the breast and agonistic or antagonistic effects on other organs. Prolonged treatment with anastrozole may be a treatment option for postmenopausal women with hormone receptor-positive breast cancer [3]. However, it is important to note that drug-related adverse events are often associated with a negative impact on patients' quality of life, leading to compromised treatment adherence and a significant proportion of patients prematurely discontinuing treatment, resulting in worse outcomes [4].

The FAERS database was designed to support post-marketing safety surveillance for all approved drugs and therapeutic biological products. Based on FAERS database and other spontaneous reporting systems, many real-world, retrospective pharmacovigilance study have been performed to explore new more drug situation, representing an attractive source of pharmacovigilance data for early detection and timely characterization of unexpected toxicities [5, 6].

In this study, we used the real-world data of the US Food and Drug Administration Adverse Event Reporting System

(FAERS) to assess anastrozole-related adverse events (AEs) *n* the postmarketing setting. It was found three new potential AEs of anastrozole, which deserves urgent clarification by means of further prospective studies.

2. Methods

2.1. Data Source. FAERS permits the reporting of arbitrary drug names, therefore, drug names were classified into generic name (Anastrozole) including trade name (Arimidex).

2.2. Study Design. All individual AEs based on Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and Preferred Terms (PTs) level recorded on Anastrozole reports were identified to describe the spectrum of toxicities. After removing duplicates based on the primary ID of each case, anastrozole-related AEs were compared against all other drugs from the 2013 Q1 to 2022 Q4. The workflow was showed in Figure 1.

2.3. Data Mining Algorithm. Disproportionality analysis, which was considered to play part in pharmacovigilance study, compared the potential signals between specific study drug and all other drugs. In our study, four different disproportionality approaches were performed to increase consistency and robustness of findings. Reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) algorithms were employed to quantity signals of anastrozole-related AEs [7, 8].

2.4. Statistical Analysis. All data processing and statistical analyses were performed using MYSQL 8.0, Navicat Premium 15, Microsoft Excel 2019 and the GraphPad Prism 8 (GraphPad Software, CA, USA). When at least one of the four disproportionality methods for a given AE met the criteria for statistical significance, AE signals was considered. The equations and criteria for the four algorithms were described in Table 1. The value (a value, *b* value, *c* value, *d* value) of PTs and SOCs were showed in Tables S1 and S2. The ROR was deemed statistically significant if the lower limit of the CI is >1; for IC, when the lower limit of CI of the IC is >0, $N \geq 3$. The significance criteria of PRR was PRR ≥ 2, $\chi^2 \geq 4$, $N \geq 3$; for BCPNN and MGPS, significance criterion was the lower limit of 95% CI of the IC > 0 and EBGM05 > 2 respectively. Proportions were compared using chi-square (χ^2) tests. Generally, the higher the value of the four parameters, the stronger the signal appeared to be. To increase the robustness of findings and reduce the likelihood of false positives, in this study, we chose AE signals that simultaneously met the above four algorithm standards for research. The novelty/unexpectedness signals were defined as any significant AE discovered which was not listed in the instructions/product label. For each SOC, a rank-sum approach was implemented, sum up the ranks obtained from each of the four analysis methods. Then rank the SOCs again based on their cumulative rank sums to identify the most significant SOC [9, 10].

3. Results

3.1. Description of Anastrozole AEs. During the study period, 3917 spontaneous reports on Anastrozole were collected from the FAERS database after the exclusion of duplicates. The clinical characteristics of events with Anastrozole are described in Table 2. Among all AEs, most patients aged 50–79 years in the known-age number of reports (45.11%). Most reports (1962 [50.09%]) came from North America, with the US as the most common notifying country with 1647 (42.05%) reports. Secondly, European was responsible for 607 (15.5%) cases, and 276 (7.05%) reports were registered by Japan. The AEs of Anastrozole occurred more commonly in females (85.93%) than in males (4.08%), which was consistent with the indications of Anastrozole mainly for breast cancer. Serious outcomes were found in 1106 (28.24%) of the reports. The most frequent serious outcome within these cases was hospitalization 636 (16.24%). Risk to life was notified in 358 (1.8%) of the reports, death in 222 (5.67%), disability in 136 (3.47%), and life-threatening in 112 (2.86%).

3.2. Signal Detection. A total of 25 significant disproportionality SOCs conforming to the four algorithms simultaneously were shown in Table 3. Statistically, we found that Anastrozole-induced AEs occurrence targeted 25 organ systems. The most frequently reported SOCs is Musculoskeletal and connective tissue disorders ($N = 1319$, 33.7%), the package insert includes these adverse reactions, and our results precisely support this point. The top five significant SOCs which ranked by the cumulative rank sums were Eye disorders (SOC:10015919), Renal and urinary disorders (SOC: 10038359), Respiratory, thoracic and mediastinal disorders(SOC: 10038738), Investigations(SOC: 10022891) and Cardiac disorders (SOC: 10007541).

A total of 300 significant disproportionality PTs were shown in Table S1, and the top 40 were shown in Table 4. For 300 different AEs, at least 4 reports were recorded. The most frequently reported AEs were metastases to bone ($N = 143$, 3.6%). Some AEs of bone and joint system in our results, such as clustering or trigger finger, dupuytren's contract, vertebral, column and mass joint neoplasty, have been included in the instructions of anastrozole, also pseudovirosis, labile hypertension and other PTs. These data are consistent with routine clinical observations and suggest the importance of pharmacovigilance [11–14]. Notably, unexcepted significant AEs was vitreoretinal traction syndrome (ROR = 1108.22, PRR = 1103.98, IC025 = 9.51, EBGM05 = 389.98), nitrituria (ROR = 3561.82, PRR = 3557.28, IC025 = 10.38, EBGM05 = 318.83) and human epidermal growth factor receptor negative (ROR = 675.04, PRR = 674.01, IC025 = 9, EBGM05 = 204.57). Safety signals were detected for a large number of AEs, such as nitrituria (ROR = 3561.82, lower limit of 95% CI = 850.91; IC = 10.38, lower limit of 95%

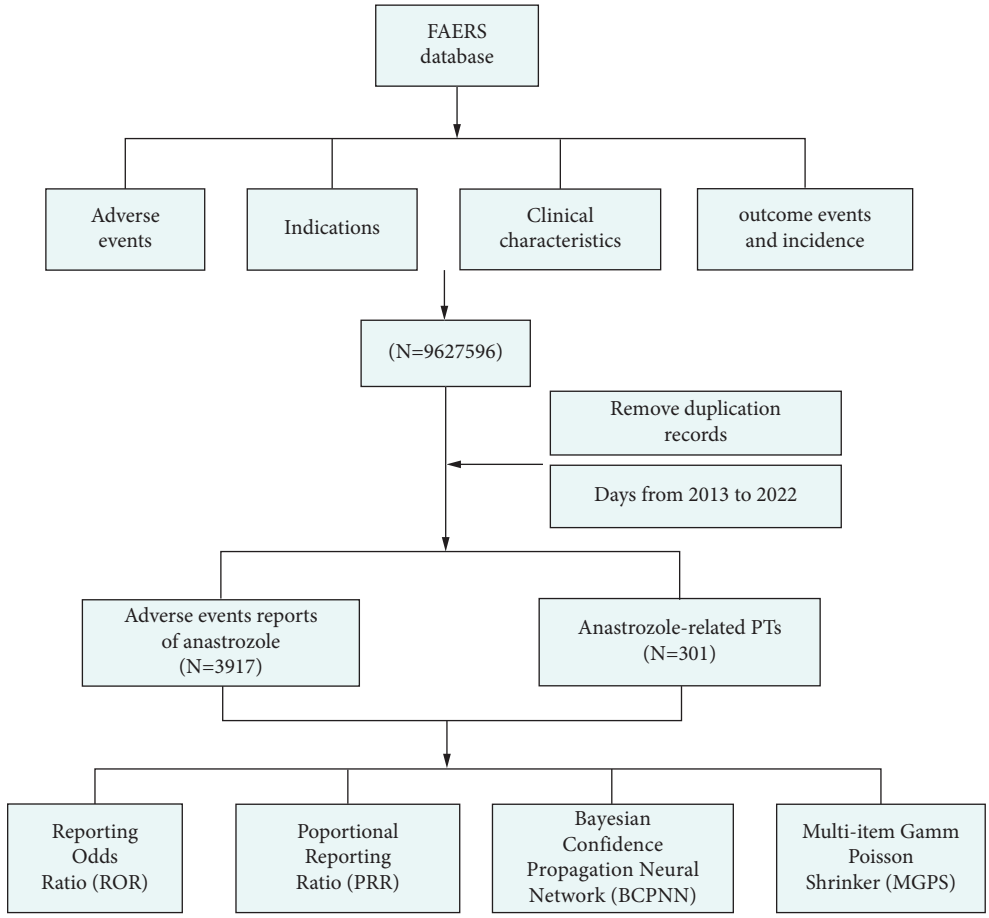

Figure 1: The flow diagram of selecting Anastrozole-related AEs from FAERS database.

CI = 6.97), vitreoretinal traction syndrome (ROR = 1108.22, lower limit of 95% CI = 593.69; IC = 9.51, lower limit of 95% CI = 7.63), leiomyosarcoma recurrent (ROR = 949.58, lower limit of 95% CI = 292.32; IC = 9.36, lower limit of 95% CI = 6.11).

4. Discussion

4.1. Main Interpretation. FAERS is a well-known publicly available postmarketing safety surveillance database for collecting AEs reports. Using FARES database, in previous study, Qilin Zhang et al. found new and unexpected AEs signals for olaparib, Yingjie Wang et al. found safety signals between the use of baricitinib and an increased risk of infection and thrombotic events [15, 16].

In this study, we comprehensively collected and evaluated the postmarketing safety of anastrozole in terms of pharmacovigilance on the basis of the largest samples of real-world data until recently. As showed in Figure 1. In order to reduce biases, we first implemented strict quality control on the data, and then evaluated it using four different disproportionate methods. Notably, previous studies have generally used one or two disproportionate analysis methods for analysis, large concordance was demonstrated between disproportionality measures (ROR) and relative risks emerged in formal analytical studies for a set of known AEs, thus providing a rough indication of the clinical significance of the signal strength [17]. To increase the robustness of findings and reduce the likelihood of false positives, we used four different approaches for signal detection, In our study, four methods were used for signal detection, and when the four disproportionality measures for a given AE met the aforementioned criteria for statistical significance a safety signal for the AE was considered.

Neoplasms remain the main killer worldwide [18, 19], among which, breast cancer is one mainly in women [20, 21]. It was reported that approximately 10% breast cancer patients experienced serious AEs considered causally related to anastrozole, common adverse reactions include the following: hot flashes, asthenia, joint disorders such as arthritis or arthralgia, osteoporosis, fractures, bone pain, back pain, vaginal dryness, dyspareunia, sexual dysfunction, uterine atrophy, hypertension, hyperlipidemia, hypercholesterolemia, thromboembolic disease, cardiac and cerebrovascular events, insomnia, nausea [11–14]. These adverse events also detected in our study. Disproportionality analysis indicated that the significant signals at the system organ level were Eye disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders, Investigations and Cardiac disorders. Estrogen receptor-positive, HER2-negative breast cancer is the most common subtype among patients diagnosed with advanced breast cancer, and hormone therapy

Table 1: Four major algorithms in this study to assess potential associations between anastrozole and AEs.

Algorithms	Equation	Criterion
ROR	$ROR = ad/b/c$, 95% $CI = e^{\ln(ROR) \pm 1.96\,(1/a+1/b+1/c+1/d)^{0.5}}$	Lower limit of 95% CI > 1, $N \geq 3$
PRR	$PRR = a\ (c+d)/c/(a+b)$, $\chi^2 = [(ad-bc)^2](a+b+c+d)/[(a+b)\ (c+d)\ (a+c)\ (b+d)]$	$PRR \geq 2$, $\chi^2 \geq 4$, $N \geq 3$
BCPNN	$IC = \log_2 a\ (a+b+c+d)/[(a+c)\ (a+b)]$, 95% $CI = E\ (IC) \pm 2V\ (IC)^{0.5}$	IC025 > 0
MGPS	$EBGM = a(a+b+c+d)/(a+c)/(a+b)$, 95% $CI = e^{\ln(EBGM) \pm 1.96\,(1/a+1/b+1/c+1/d)^{0.5}}$	EBGM05 > 2

Notes: a: target AEs of Anastrozole; b: non-target-AEs of Anastrozole; c: target AEs of non-Anastrozole; d: non-target AEs of non-Anastrozole. Abbreviations: 95% CI, 95% confidence interval; N, the number of reports; χ^2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E (IC), the IC expectations; V (IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

Table 2: The features of reports associated with Anastrozole from the 2013 Q1 to 2022 Q4.

	Anastrozole	
	Counts	Percentages (%)
Number of events	3917	
Gender		
Male	160	4.08
Female	3366	85.93
Unknown	391	9.98
Age		
<20	40	1.02
20–29	10	0.26
30–39	52	1.33
40–49	155	3.96
50–59	476	12.15
60–69	752	19.20
70–79	539	13.76
>80	238	6.08
Unknown	1655	42.25
Reported countries (the top ranked)		
US (United States)	1647	42.05
UK (United Kingdom)	365	9.32
CA (Canada)	315	8.04
JP (Japan)	276	7.05
DE (Germany)	242	6.18
Serious outcomes		
Hospitalization	636	16.24
Death	222	5.67
Disability	136	3.47
Life-threatening	112	2.86

is typically the first-line treatment choice for these patients [22]. Although this disease is incurable in the long term, advanced tumors can be controlled through long-term continuous treatment, which includes the combination of aromatase inhibitors and cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors [23–25].

The long-term continuous use of common aromatase inhibitors like anastrozole necessitates more attention to their associated adverse events. Previous randomized controlled trials comparing extended aromatase inhibitor therapy with placebo or no treatment have shown an increased risk of fractures and strokes and suggested an increase in cardiovascular events [26]. This is consistent with the findings of this study, where musculoskeletal and connective tissue disorders were the most frequently reported adverse events, aligning with the drug label and clinical safety data. It to some extent indicates the reliability of our study methodology and results. In addition to the adverse events identified in the drug label, it is worth noting that vitreomacular traction syndrome (VMT), nitrites in urine, and human epidermal growth factor receptor negativity were the top three most common adverse events according to the empirical Bayesian geometric mean method. Importantly, these three events are newly discovered and classified as anastrozole-related adverse events.

The visual impairments caused by aromatase inhibitors may have been underestimated. Previous studies on their association with anastrozole are scarce and mostly consist of case reports, with dry eye syndrome being a common manifestation, as also reflected in the drug label [27]. As anastrozole lowers estrogen levels, some research believe that its use may increase the risk of VMT [28]. A clinical study found that anastrozole causes elevated Vitreoretinal traction at the fovea [29]. Another study lately using FARES database to discuss adverse events of aromatase inhibitors also concluded that VMT was an adverse event of aromatase inhibitors [30]. In our analysis, VMT was identified as one of the significant adverse events. It suggests the need to reconsider the adverse events associated with anastrozole and update its drug label accordingly. These evidences also showed that our conclusion is credible, further, our study calls on clinical doctors, especially oncologists- and ophthalmologists, to remain vigilant about patients receiving aromatase inhibitors, especially anastrozole, so that they can provide timely intervention measures to allow further eye diseases.

Furthermore, most patients eventually experience disease progression on this first-line therapy if they initially respond to endocrine therapy or undergoes adjuvant endocrine treatment, and subsequent endocrine-based treatments and chemotherapy have lower efficacy and greater challenges in terms of tolerability. In cases of tumor progression or recurrence, a second-line endocrine therapy may provide additional benefits. Therefore, it is important to be vigilant about potential adverse events when using endocrine medications in clinical practice. In our findings, adverse events included HER2-negative cases, which may indicate low treatment efficacy or further promotion of the phenotypic progression of breast cancer. This suggests that gaining further understanding of its adverse events could serve as a starting point for targeted improvements in its therapeutic effectiveness. On another note, urinary tract infections are often observed with other hormonal therapies, such as tamoxifen, but have not been reported with the use of anastrozole [31]. This indicates the need for ongoing monitoring of anastrozole's impact on the urinary system.

Table 3: Signal strength of AEs of Anastrozole at the System Organ Class (SOC) level in FAERS source ranked by rank-sum approch.

SOC code	SOC	Case reports	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
10015919	Eye disorders	102	9.91 (8.14–12.07)	9.68 (7.99–11.73)	792.55	3.27 (2.62)	9.64 (7.92)
10038359	Renal and urinary disorders	51	9.52 (7.22–12.56)	9.41 (7.16–12.37)	382.33	3.23 (2.33)	9.38 (7.11)
10038738	Respiratory, thoracic and mediastinal disorders	194	9.66 (8.36–11.17)	9.23 (8.05–10.6)	1425.97	3.2 (2.72)	9.2 (7.96)
10022891	Investigations	285	9.64 (8.55–10.88)	9.01 (8.06–10.08)	2038.44	3.17 (2.76)	8.98 (7.96)
10007541	Cardiac disorders	79	8.78 (7.02–10.97)	8.62 (6.93–10.73)	531.28	3.1 (2.37)	8.59 (6.87)
10029205	Nervous system disorders	172	8.78 (7.53–10.23)	8.44 (7.29–9.77)	1129.14	3.07 (2.56)	8.41 (7.21)
10027433	Metabolism and nutrition disorders	116	7.7 (6.4–9.27)	7.51 (6.27–8.98)	654.37	2.9 (2.29)	7.48 (6.22)
10005329	Blood and lymphatic system disorders	402	7.99 (7.21–8.86)	7.27 (6.63–7.98)	2199.15	2.86 (2.51)	7.25 (6.54)
10028395	Musculoskeletal and connective tissue disorders	1319	10.16 (9.51–10.85)	7.07 (6.77–7.39)	7200.15	2.82 (2.61)	7.05 (6.6)
10018065	General disorders and administration site conditions	425	7.78 (7.03–8.6)	7.04 (6.44–7.7)	2230	2.81 (2.48)	7.02 (6.35)
10021428	Immune system disorders	147	6.68 (5.67–7.88)	6.47 (5.52–7.58)	681.73	2.69 (2.14)	6.45 (5.47)
10040785	Skin and subcutaneous tissue disorders	293	5.19 (4.61–5.85)	4.88 (4.37–5.45)	915.49	2.28 (1.89)	4.87 (4.32)
10037175	Psychiatric disorders	339	3.36 (3.01–3.76)	3.16 (2.85–3.5)	513.13	1.66 (1.29)	3.15 (2.82)
10017947	Gastrointestinal disorders	119	4.94 (4.12–5.93)	4.82 (4.04–5.76)	362.08	2.27 (1.66)	4.81 (4.01)
10077536	Product issues	39	3.12 (2.28–4.28)	3.1 (2.27–4.24)	55.71	1.63 (0.61)	3.1 (2.26)
10014698	Endocrine disorders	27	25.51 (17.43–37.33)	25.34 (17.36–36.99)	624.07	4.65 (3.43)	25.06 (17.12)
10010331	Congenital, familial and genetic disorders	18	24.64 (15.47–39.26)	24.53 (15.43–39)	401.79	4.6 (3.14)	24.27 (15.23)
10021881	Infections and infestations	20	23.49 (15.1–36.54)	23.38 (15.06–36.28)	423.86	4.53 (3.14)	23.14 (14.87)
10041244	Social circumstances	7	18.68 (8.87–39.34)	18.65 (8.87–39.23)	115.94	4.21 (2.04)	18.5 (8.78)
10047065	Vascular disorders	75	18.93 (15.05–23.82)	18.59 (14.84–23.28)	1238.78	4.2 (3.45)	18.44 (14.66)
10013993	Ear and labyrinth disorders	15	17.35 (10.43–28.87)	17.29 (10.41–28.71)	228.37	4.1 (2.52)	17.16 (10.31)
10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	511	17.38 (15.83–19.08)	15.24 (14.05–16.53)	6810.14	3.92 (3.61)	15.14 (13.79)
10022117	Injury, poisoning and procedural complications	93	15.04 (12.24–18.49)	14.71 (12.02–17.99)	1182.03	3.87 (3.19)	14.62 (11.89)
10019805	Hepatobiliary disorders	219	12.46 (10.87–14.29)	11.82 (10.39–13.45)	2167.62	3.56 (3.1)	11.76 (10.26)
10038604	Reproductive system and breast disorders	491	12.06 (10.97–13.25)	10.67 (9.82–11.59)	4332.55	3.41 (3.09)	10.62 (9.66)

Table 4: The excerpted 40 signal strength of AEs of Anastrozole at preferred terms (PTs) level (Complete table contents were showed in Table S1).

Preferred terms (PTs)	SOC	Case reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Vitreoretinal traction syndrome	Eye disorders	15	1108.22 (593.69–2068.67)	1103.98 (592.36–2057.51)	9.51 (7.63)	727.97 (389.98)
Nitrituria	Renal and urinary disorders	5	3561.82 (850.91–14909.47)	3557.28 (850.4–14880.23)	10.38 (6.97)	1334.6 (318.83)
Human epidermal growth factor receptor negative	Investigations	6	675.04 (269.45–1691.15)	674.01 (269.33–1686.76)	9 (6.34)	512.49 (204.57)
Leiomyosarcoma recurrent	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	949.58 (292.3–3084.81)	948.61 (292.25–3079.1)	9.36 (6.11)	657.04 (202.25)
Progesterone receptor assay positive	Investigations	6	534.41 (218.33–1308.09)	533.59 (218.23–1304.66)	8.74 (6.13)	427.07 (174.48)
Oestrogen receptor assay positive	Investigations	6	400.81 (167.5–959.11)	400.19 (167.43–956.56)	8.4 (5.85)	337.16 (140.9)
hER2 negative breast cancer	Reproductive system and breast disorders	4	502.72 (169.08–1494.71)	502.2 (169.06–1491.84)	8.67 (5.63)	406.74 (136.8)
Anhidrosis	Skin and subcutaneous tissue disorders	13	257.77 (144.87–458.66)	256.91 (144.63–456.36)	7.84 (6.06)	229.42 (128.93)
Breast cancer recurrent	Reproductive system and breast disorders	64	165.3 (127.95–213.56)	162.62 (126.37–209.27)	7.24 (6.4)	151.18 (117.02)
Pseudocirrhosis	Hepatobiliary disorders	16	201.7 (120.7–337.07)	200.88 (120.44–335.06)	7.52 (5.91)	183.69 (109.92)
Tongue cancer metastatic	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	341.85 (118.91–982.72)	341.5 (118.9–980.8)	8.2 (5.26)	294.53 (102.46)
Oestradiol increased	Investigations	9	218.79 (110.11–434.74)	218.29 (110.01–433.12)	7.63 (5.56)	198.13 (99.71)
Joint neoplasm	Musculoskeletal and connective tissue disorders	4	316.52 (110.7–905.02)	316.2 (110.69–903.25)	8.11 (5.19)	275.53 (96.37)
Pelvic organ prolapse	Reproductive system and breast disorders	6	233.19 (100.34–541.93)	232.84 (100.31–540.48)	7.71 (5.26)	210.04 (90.38)
Soft tissue neoplasm	Musculoskeletal and connective tissue disorders	5	254.41 (100.6–643.38)	254.09 (100.58–641.89)	7.83 (5.18)	227.17 (89.83)
Carbohydrate antigen 15-3 increased	Investigations	15	163.14 (96.42–276.03)	162.51 (96.23–274.46)	7.24 (5.6)	151.09 (89.29)
Trigger finger	Musculoskeletal and connective tissue disorders	58	124.64 (95.48–162.71)	122.81 (94.43–159.72)	6.86 (5.99)	116.18 (89)
Vascular compression	Vascular disorders	9	179.94 (91.07–355.52)	179.53 (90.99–354.2)	7.37 (5.32)	165.67 (83.85)
Metastatic uterine cancer	Reproductive system and breast disorders	4	230.98 (82.29–648.34)	230.74 (82.28–647.06)	7.7 (4.84)	208.33 (74.22)
Metastases to thorax	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	171.01 (74.41–393.02)	170.75 (74.38–391.96)	7.31 (4.89)	158.18 (68.82)

Table 4: Continued.

Preferred terms (PTs)	SOC	Case reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Vertebral column mass	Musculoskeletal and connective tissue disorders	6	162.35 (70.75–372.54)	162.1 (70.73–371.54)	7.24 (4.83)	150.73 (65.69)
Metastases to chest wall	Musculoskeletal and connective tissue disorders	8	140.24 (68.54–286.97)	139.96 (68.49–286)	7.04 (4.9)	131.41 (64.22)
Autoimmune pancreatitis	Immune system disorders	10	127.37 (67.24–241.25)	127.05 (67.18–240.27)	6.91 (4.97)	119.96 (63.33)
pIK3CA-activated mutation	Congenital, familial and genetic disorders	7	132.45 (61.69–284.37)	132.22 (61.66–283.5)	6.96 (4.71)	124.56 (58.02)
Metastases to abdominal wall	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	150.5 (60.74–372.92)	150.31 (60.72–372.05)	7.13 (4.56)	140.48 (56.69)
Resorption bone increased	Metabolism and nutrition disorders	6	128.26 (56.24–292.5)	128.06 (56.22–291.7)	6.92 (4.53)	120.87 (53)
Breast cancer metastatic	Reproductive system and breast disorders	94	67.75 (55.04–83.39)	66.15 (54–81.03)	6 (5.32)	64.19 (52.15)
Diabetic hyperosmolar coma	Endocrine disorders	6	124.52 (54.64–283.78)	124.33 (54.62–283.02)	6.88 (4.49)	117.54 (51.58)
Metastases to bone	Musculoskeletal and connective tissue disorders	143	63.74 (53.81–75.5)	61.45 (52.19–72.35)	5.9 (5.34)	59.76 (50.45)
Cystoid macular oedema	Injury, poisoning and procedural complications	28	74.95 (51.35–109.39)	74.42 (51.13–108.34)	6.17 (4.96)	71.95 (49.3)
Metastases to lymph nodes	Blood and lymphatic system disorders	54	65.42 (49.81–85.92)	64.53 (49.32–84.44)	5.97 (5.08)	62.67 (47.72)
Labile hypertension	Vascular disorders	4	135.65 (49.35–372.87)	135.51 (49.35–372.12)	6.99 (4.21)	127.48 (46.38)
Vitreous adhesions	Eye disorders	3	160.2 (49.54–518.07)	160.08 (49.54–517.24)	7.22 (4.13)	148.98 (46.07)
dupuytren's contracture	Musculoskeletal and connective tissue disorders	11	86.56 (47.33–158.29)	86.32 (47.28–157.59)	6.38 (4.53)	83 (45.39)
Clubbing	Cardiac disorders	6	107.78 (47.44–244.88)	107.61 (47.42–244.22)	6.68 (4.31)	102.5 (45.11)
Hyperparathyroidism primary	Metabolism and nutrition disorders	5	114.9 (46.7–282.69)	114.75 (46.69–282.03)	6.77 (4.22)	108.95 (44.28)
Lichen sclerosus	Skin and subcutaneous tissue disorders	7	91.82 (43.06–195.79)	91.66 (43.04–195.19)	6.46 (4.24)	87.93 (41.24)
Metastases to breast	Reproductive system and breast disorders	5	104.76 (42.66–257.23)	104.63 (42.66–256.62)	6.64 (4.1)	99.78 (40.64)
Hormone receptor positive breast cancer	Reproductive system and breast disorders	6	91.61 (40.44–207.53)	91.47 (40.43–206.97)	6.46 (4.1)	87.75 (38.74)
Retroperitoneal fibrosis	Immune system disorders	7	83.61 (39.27–178.04)	83.47 (39.25–177.5)	6.33 (4.11)	80.36 (37.74)

However, it is worth noting that the drug label and previous studies have reported adverse events such as vaginal discharge, which may not directly indicate urinary tract infections but do not exclude the possibility of accompanying or secondary infections [31]. Endocrine medications used for uterine smooth muscle tumor include aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), progestins, and gonadotropin-releasing hormone agonists (GnRH-a). There have been studies suggesting a potential promotion of uterine sarcoma development with SERMs, such as tamoxifen, which may be similar to the potential promotion of smooth muscle tumor development with anastrozole.

Our study found adverse events consistent with the instructions, and also found some unexpected adverse events. These adverse events may be rare, but they do exist, such as VMT. Previous studies confirmed the reliability of our conclusion, indicating that anastrozole does cause VMT, but like other AEs we found, it does not appear in the instructions. On the one hand, it reminds clinicians, especially oncologists, ophthalmologists and nephrologist to be vigilant against the occurrence of those AEs Aforementioned when using anastrozole. On the other hand, our study could provide valuable evidence for further studies and clinical practice of anastrozole. Prospective clinical studies are still needed to confirm the causal relationship between them. Finally, whether to remind FDA to supplement more clinical evidence to supplement and improve the instructions and warnings of drugs. Our study could provide valuable evidence for Furthermore studies and clinical practice of anastrozole.

However, the specific mechanisms underlying these three adverse events are currently unclear. While there are case reports or other indirect evidence suggesting possible correlations, we did not find direct evidence reported in the literature. Therefore, further clinical research is needed to understand the pathogenesis of these adverse events.

4.2. Limitations. Although the data mining techniques used in this study have many advantages and have resulted in valuable results, it is inevitable to consider some limitations when interpreting our results.

Firstly, due to the spontaneous nature of the FAERS database, the quality of reports varies, such as report bias caused by duplicate reports. Although we have implemented quality control, there are still some confounding factors such as age, dosage, drug interactions, comorbidities, or other factors that may affect adverse events that are difficult to control.

Secondly, the impact of the disease itself on AE signals is ignored, and we are unable to establish a causal relationship between anastrozole and AE based on database information.

Thirdly, due to the fact that the FAERS database only calculates adverse reaction reports of anastrozole and does not include all reports of anastrozole use, the number of patients treated with anastrozole is still unclear, so the exact incidence rate of each AE cannot be determined.

However, our study quantified the potential risk of adverse events through a large amount of data science and systematic analysis, and comprehensively characterized the occurrence of anastrozole AEs. In particular, the identification of new serious and unexpected adverse event signals provides evidence for further research and clinical trials of anastrozole [32, 33].

4.3. Conclusion. In conclusion, this present study scientifically and systematically quantified the potential risks and safety signal spectrum with anastrozole treatment using pharmacovigilance analysis of FAERS database. Unexcepted AEs as vitreomacular traction syndrome (VMT), nitrites in urine, and human epidermal growth factor receptor negativity might occur, which warrants urgent clarification through additional prospective studies.

Data Availability

Publicly available datasets were analyzed in this study. The data can be found in https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDEFAERS.html.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors have read and approved the final version of the manuscript. J.L. and B.Z. proposed the idea, performed data analyses, and drafted the manuscript. JB.W. checked the integrity and plausibility of data analysis. YQ.Z revised the manuscript and was responsible for the integrity of data acquisition and statistical analyses. Jie Li, Bin Zhao, YongQing Zhu, and Jibiao Wu contributed equally to this work. Jie Li and Bin Zhao contributed equally and are the co-first author.

Acknowledgments

We thanked Home for Researcher for language editing service.

Supplementary Materials

Supplementary 1. Table S1: The signal strength of AEs of Anastrozole at preferred terms level ranked by EBGM in FDA Adverse Event Reporting System (FAERS) source. Supplementary 2. Table S2: The value (*a* value, *b* value, *c* value, *d* value) of SOCs. (*Supplementary Materials*)

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