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The RESILIENT Study: A Retrospective, Descriptive, Correlational Investigation of Correlates of Oral Endocrine Therapy Adherence in Older Women With Breast Cancer

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ABSTRACT

Background: Breast cancer is the most prevalent and costly cancer. Oral endocrine therapy (OET) improves survival rates and quality of life while reducing recurrence, mortality, morbidity, and medical costs. However, adherence to OET is challenging because OET is prescribed for 5–10 years. Determinants of OET nonadherence (NA) among women aged 65 and older remain poorly characterized. Existing studies are limited, often focusing on small, single-site samples and focusing on patient-level rather than multi-level determinants. Despite the unique needs of older women, research on OET-NA remains scarce.

Objective: This study identified multi-level determinants of OET-NA in older women using ecological systems theory and the World Health Organization's five-dimension model.

Methods: A descriptive, correlational secondary data analysis was conducted using the 2019 Surveillance-Epidemiology-End-Results (SEER) Medicare database, which includes more than 9 million cancer cases in the United States.

Result: OET-NA was significantly affected by (a) patient-related factors of ethnicity (i.e., Black [AOR 1.55; 95% CI 1.34–1.78; $p < 0.001$]) and psychological issues (i.e., depression [OR 1.40; 95% CI 1.27–1.54; $p < 0.001$]), (b) socioeconomic-related factors of marital status (i.e., divorced [OR 1.17; 95% CI 1.04–1.32; $p \leq 0.01$]), and lifestyle (i.e., tobacco use [OR 1.41; 95% CI 1.22–1.63; $p < 0.001$]), (c) therapy-related factors of switching OET medications (OR 2.72; 95% CI 2.41–3.07; $p < 0.001$), (d) condition-related factors of comorbidities (i.e., obesity [OR 1.13; 95% CI 1.03–1.23; $p < 0.01$]), and (e) characteristics of the healthcare team and health system-related factors (i.e., group practice type [OR 1.26; 95% CI 1.01–1.56; $p < 0.05$]).

Conclusion: OET-NA was associated with multi-level determinants, including being Black, having depression, being divorced, using tobacco, switching OET medications, having obesity, and receiving care in group practices. Identifying these determinants is a critical first step toward developing and testing interventions to improve OET-NA and enhance survival and quality of life.

1 | Introduction

In the United States, breast cancer is the most prevalent cancer among females and is the second-leading cause of all cancer deaths, with 268,600 new cases and 41,760 deaths in 2019, despite prescribed therapy [1, 2]. More than 1.7 million people are diagnosed and treated for breast cancer each year worldwide [3, 4]. However, only 41%–72% of breast cancer patients fully adhere to their prescribed oral endocrine therapy (OET) [5]. These treatments not only improve survival rates but also enhance the

quality of life (QOL) for cancer patients. Nevertheless, patients often struggle with nonadherence (NA) to OET due to various challenges [6].

The risk of developing breast cancer increases with age [7], and mortality rates are higher for women over the age of 65 years [8]. Accelerated aging in breast cancer survivors is also linked to increased mortality [9]. Older women face adherence challenges due to physical functioning, side effects, drug–drug interactions, cognitive effects, psychological status, altered nutritional status, limited knowledge of medication regimens, and financial issues [10]. According to the Surveillance Epidemiology and End Results (SEER) registry and Breast Cancer Research Foundation (BCRF), the median age at breast cancer diagnosis was 62, and more than 20% of newly diagnosed women were older than 70 years in 2021. As the general population ages, breast cancer cases will double by 2030 in the United States, and women over 70 years old will comprise a significant portion of this population [11]. Medication-NA affects approximately 50% of older adults, leading to poorer health outcomes and increasing healthcare costs, estimated at $100–$300 billion annually [12]. Despite these consequences, medication-NA remains a persistent challenge [13].

The pathophysiology of breast cancer in older adults is characterized by nearly 80% of estrogen-positive (ER+) tumors and a higher prevalence of luminal A subtypes—tumors that are ER+ and progesterone-positive (PR+), and negative for human epidermal growth factor receptor 2 (HER2) [14–16]. This suggests that OET is an effective treatment for older populations. In this study, OET included both tamoxifen and aromatase inhibitors (AIs), specifically anastrozole, exemestane, and letrozole [17]. OET is standard therapy for ER+ breast cancer and works by blocking hormone receptors that fuel cancer growth [18, 19].

Despite the effectiveness of OET, a recent report indicated that 70% of breast cancer patients discontinued their recommended OET regimen before completing the full 5 years [20]. Older women who struggle with OET-NA face diminished QOL and increased recurrence rates and mortality. More recently, trials have suggested that OET should be administered for 10 years rather than 5 years [19]. This new recommendation raises even more concern about OET-NA since it doubles the duration of medication use and increases the difficulty of monitoring patients' self-administration of medications. The risk of breast cancer recurrence is 1.44 times higher for OET non-adherent patients than for adherent patients [21]. Low adherence to OET is associated with a 30% increase in mortality due to cancer recurrence [22–24]. These statistics highlight the critical need to address barriers to OET-NA in older women to improve long-term outcomes and survival rates. Moreover, the patient-managed nature of OET often leaves older breast cancer patients struggling with medication-NA. Few studies delve into the determinants of OET-NA and explore why older breast cancer patients struggle to consistently take OET, despite the increased risk of undertreatment linked to poor outcomes [25].

Increased medical costs have become a growing problem in the breast cancer population as the number of older breast cancer patients continues to rise in the U.S. Due to the high percentage of breast cancer patients on Medicare, this has led to a greater cost burden on the U.S. government, with projected costs of $20.5 billion for breast cancer care alone in 2020 [26]. Older adults with breast cancer are already considered a high-risk population due to their increased vulnerability to drug-related problems stemming from age-related changes in (a) pharmacokinetics and pharmacodynamics (the physiologic effects of a drug); (b) high prevalence of cognitive and functional impairment; and (c) increased cost burden of service use across settings and treatment complexity [27–31]. These age-related changes contribute to the rising cost of care, which can lead to OET-NA and place an overall strain on the healthcare system [22–24, 32, 33].

Most existing research has been conducted in the U.S. and Europe, using single-site samples ($N = 100$–2000) from small single-sites (e.g., clinics and hospitals). Similarly, many retrospective studies examining medication-NA have utilized relatively small electronic databases with sample sizes of fewer than 10,000 individuals globally [20, 24, 34–37]. This trend is also consistent with studies focused on older women with breast cancer in the U.S. Moreover, few studies have been conducted with diverse samples (i.e., including various races, ethnicities, genders, age groups, etc.), with minimal numbers of older American women with breast cancer, even though they are a high-risk population [10]. These findings emphasize the value of future research examining OET-NA across diverse populations, with larger sample sizes and in multi-site settings. The purpose of this study is to identify the determinants of OET-NA among older women with breast cancer by using the SEER-Medicare dataset.

1.1 | Theoretical Frameworks

This study utilized two theoretical frameworks: (a) Bronfenbrenner's ecological system theory (EST) and (b) the five-dimension model (FDM) for medication adherence, which was developed by the World Health Organization (WHO) [38]. The FDM focuses on medication-NA issues; however, this model includes a critical backbone of ecological perspectives.

Bronfenbrenner identified variables for systems thinking at multiple levels: individual-, micro-, meso-, exo-, macro-, and chrono-system levels [39–41]. The micro-system shows interpersonal relationships within an environmental context [39, 42]. The microsystem involves direct interpersonal relationships such as a patient's family and peer group [39]. The meso-system addresses the connection between environmental settings [39, 42]. The mesosystem describes the interactions between microsystems that contribute to healthy behaviors such as medication adherence [39]. The exo-system describes the indirect environmental settings that exert influence without active patient engagement [39]. The macro-system refers to broader systems that include culture or subculture such as the economic, social, education, healthcare, legal, and political systems [39, 43]. At last, the chrono-system encompasses changes over time that affect an individual's development including life transitions such as marriage, divorce, school entry, and relocation [41]. Bronfenbrenner added the individual-level concept in 1983. The individual level is considered to be a patient-centered system that includes demographics, knowledge, self-efficacy, and medication beliefs [40, 42]. Because of its multi-system emphasis, Bronfenbrenner's

EST has been frequently used in public health interventions and health promotion efforts to improve health outcomes [44].

The FDM considers patient-related, socio-economic, therapy-related, condition-related, and health care team/system-related factors [38]. In the WHO's five-dimension model, (a) patient-related factors include a patient's knowledge, attitude, self-efficacy, beliefs on treatment efficacy, and perceived barriers to adherence; (b) social and economic-related factors include social networks, family functioning, and the cost of medication; (c) therapy-related factors include side effects of the regimen, duration of treatment, and dose complexity; (d) condition-related factors involve comorbidities, depression, and other psychiatric diagnoses such as substance abuse; and (e) health care team/system-related factors consider the knowledge of health care professionals and the relationship between the patient and their health care team [38].

Both theoretical frameworks support investigating medication-NA issues effectively, as they are influenced by multiple factors—including a patient's social environment of family, friends, and community—where these factors can also exert influence simultaneously and reciprocally [45]. For example, the patient's depression (micro-system) may decrease adherence, worsening their prognosis and causing a financial burden (exo-system), which in turn heightens psychological distress (individual level), creating a cycle of non-adherence across multiple levels of Bronfenbrenner's ecological framework.

1.2 | Purpose and Research Questions

The purpose of this study was to identify multi-level determinants of OET-NA by using the SEER-Medicare dataset from 2019. The research question guiding this study was: what are the multi-level determinants that influence OET-NA in women aged 65 and older with breast cancer?

2 | Materials and Methods

2.1 | SEER Medicare Database

The SEER program, a clinical database funded by the U.S. National Cancer Institute (NCI), collects data on cancer incidence and survival from U.S. cancer registries [46]. The SEER registry contains more than 9 million cancer cases with over 470,000 new cases added to the database every year [47]. The SEER-Medicare data comply with the Health Insurance Portability and Accountability Act (HIPAA) requirements including the requirement for an investigator's signed data use agreement [46]. This study was reviewed and approved by the University of Missouri-Kansas City (UMKC) IRB under protocol 2061023, in accordance with ethical guidelines for secondary data analysis. The SEER database has been linked to Medicare data that includes (a) claims-based measures of comorbidities, (b) screenings and evaluation tests, and (c) detailed treatment and outcomes data, through collaboration among the NCI, SEER registry, and the Centers for Medicare and Medicaid Services (CMS) [48]. SEER-Medicare includes data from various populations to address health disparities, quality of care, and treatment costs in oncologic diseases [47]. Nonetheless, the SEER-Medicare database is among the most comprehensive cancer databases available, offering the closest representation of the U.S. cancer population, including diverse ethnic groups, in a large-scale dataset with yearly follow-up.

A total of six SEER database component files were utilized to conduct this study: (a) the Master Beneficiary Summary File (MBSF) Chronic Conditions database, (b) the MBSF other chronic condition database, (c) the National Claims History (NCH) database, (d) the Medicare Part D Medication Therapy (PDEMTM) database, (e) the Medicare Part D Event and Drug Characteristics (PDESAF) database, and (f) the SEER Cancer Registry database [46].

2.2 | Methods

This study is a retrospective, descriptive, correlational study that investigates the multilevel determinants influencing OET-NA in older women with breast cancer. It utilizes secondary data analysis of the SEER-Medicare database, focusing on OET-NA recorded in 2019 [46].

2.2.1 | Inclusion Criteria

The stepwise cohort selection included: (a) women, (b) Age 65 or older, (c) who were enrolled in Medicare Part D, (d) diagnosed with breast cancer Stages I–III using ICD-9 code 174 (10 codes) and ICD-10 code C50 (female, 36 codes) from 2019 for OET-NA determinants, and (e) filed a prescription for one of the following oral medications: tamoxifen, anastrozole, exemestane, or letrozole.

2.2.2 | Participants

The study participants were identified consecutively from the 2019 SEER-Medicare medication database (PDESAF) using this study's inclusion criteria to obtain pertinent medication adherence data. The sub-sampling process is outlined in Figure 1. After reviewing all 141,457 patient IDs for the dependent variable, patient information was matched from the "PDESAF Extracted" database to the other databases by referencing the patient IDs to find matches. Figure 2 shows the patient overlap between "PDESAF Extracted" and each of the five databases used in this study. Information was found for 141,455 patients in the MBSF OTH CC database that had corresponding patient IDs in our dependent variable PDESAF Extracted database ($n = 141,457$) after checking for duplicate patient information. Each database had matching patient IDs, yielding 141,454 patients in the MBSF CC database, 141,454 in the SEER CANCER database, 11,443 in the PDEMTM database, and 84,269 in the NCH database, respectively (Figure 2).

2.2.3 | Outcome Variables

2.2.3.1 | OET Non-Adherence (NA). The primary outcome variable was OET-NA, calculated as the proportion

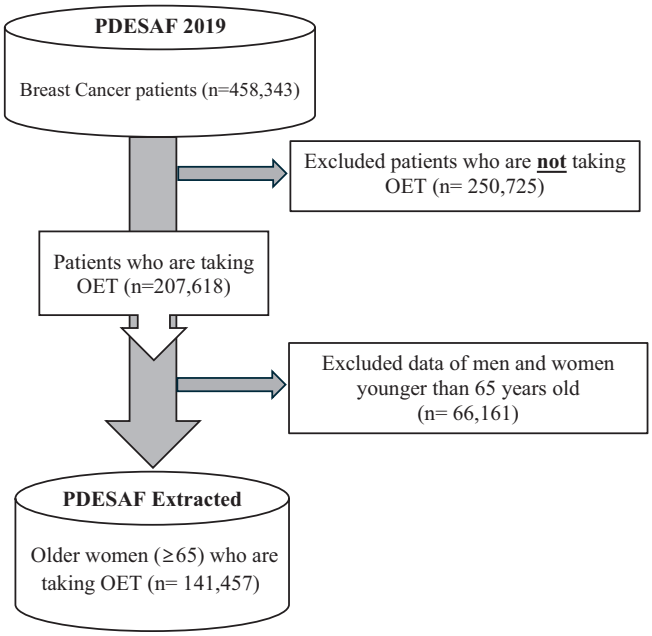

FIGURE 1 | Sample extraction diagram.

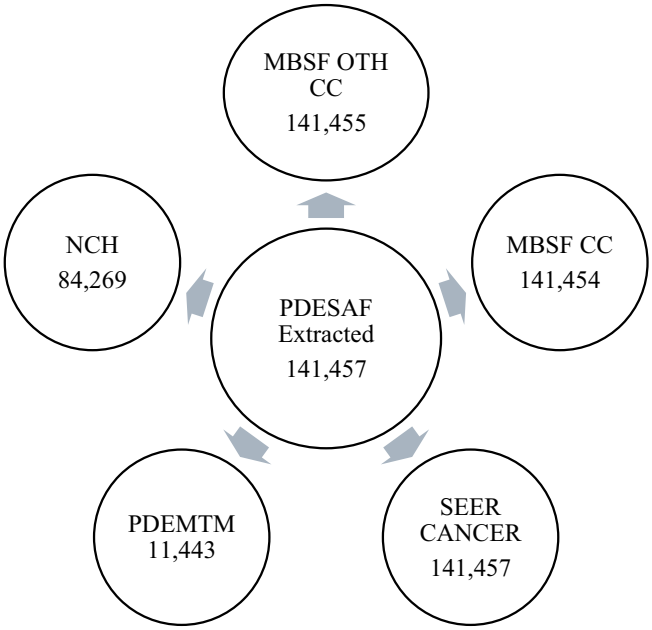

FIGURE 2 | Relevant patient count in linked databases.

of days covered (PDC) [49]. The "Part D Event (PDE) file with appended drug characteristics" was used to identify medication refill data. The PDC was the number of days covered by a prescription drug divided by the total number of days in an observation window [50]. The total "days supply" in the PDE file was divided by the total number of days in the observation period. PDC was calculated similarly to Medication Possession Ratio (MPR) but removed overlapping refill days to avoid inflating coverage. As shown in Figure 3, this correction prevents overestimation from early refills, making PDC a more accurate and preferred adherence measure compared to MPR. A patient with OET-NA was identified based on the PDC data using the common cut-point of < 80% PDC (non-adherent) versus ≥ 80% PDC (adherent) [51, 52].

2.2.4 | Descriptive Statistics Variables

A. Patient-related variables
- *Age*: The patient's age at the time of cancer diagnosis, categorized as 65–74, 75–84, 85–99, or unknown.
- *Race*: Race was categorized by SEER Race1 code as White (reference category), Black, American Indian/Alaska Native, Asian/Pacific Islander, and Other [53–61].
- *Psychological factors*: Depression and anxiety were identified as key psychological factors associated with medication-NA among breast cancer patients [59, 62–66]. Patients without depression and anxiety were used as the reference group.

B. Socioeconomic-related variables
- *Lifestyle factors*: Lifestyle factors included alcohol, drug, and tobacco use, which are frequently identified as determinants of medication-NA [67–69]. Patients without these conditions were used as the reference group.
- *Living status*: Residence was categorized as metropolitan (reference category), urban, or rural. This variable has been associated with health disparities across various diseases including breast cancer [69–74].
- *Marital status at diagnosis (socioeconomic-related variable)*: Marital status was recorded as single (never married), married (including common-law) (reference category), separated, divorced, widowed, or unmarried/domestic partner (same or opposite sex, unregistered) [60, 75–79].

C. Therapy-related variables
- Medications: OET medications included tamoxifen, anastrozole, letrozole, and exemestane.
- Switch medication status: This variable indicated whether a patient switched between OET medications [24, 66, 80]. Possible values were (a) prescribed medication was changed or (b) prescribed medication was not changed (reference group).

D. Condition-related variables
- *Comorbidities*: Key comorbidities included hyperlipidemia, hypertension, obesity, and osteoporosis. These conditions were selected based on their significance in univariate analyses and their recognized importance across chronic diseases [63, 66, 70, 74, 81, 82]. Patients with these comorbidities served as the reference group to allow for a robust comparison of their effects on OET-NA in the multivariate analysis.
- *Stage of cancer*: Cancer stage was defined as follows:
  - –. Stage 0 (carcinoma in situ): Abnormal cells not yet spread to nearby tissues.
  - –. Stage I (early stage): Cancer localized to a small area.
  - –. Stage II (localized): Tumor 20–50 mm with limited lymph node involvement, or > 50 mm with none.
  - –. Stage III (regional): Tumor > 50 mm with regional lymph node involvement.
  - –. Stage IV (distant): Cancer spread to distant organs.

E. Health care team/systems-related variables
- *Health care team practice characteristics*: Practice type was categorized as (a) group practitioners in a clinic,

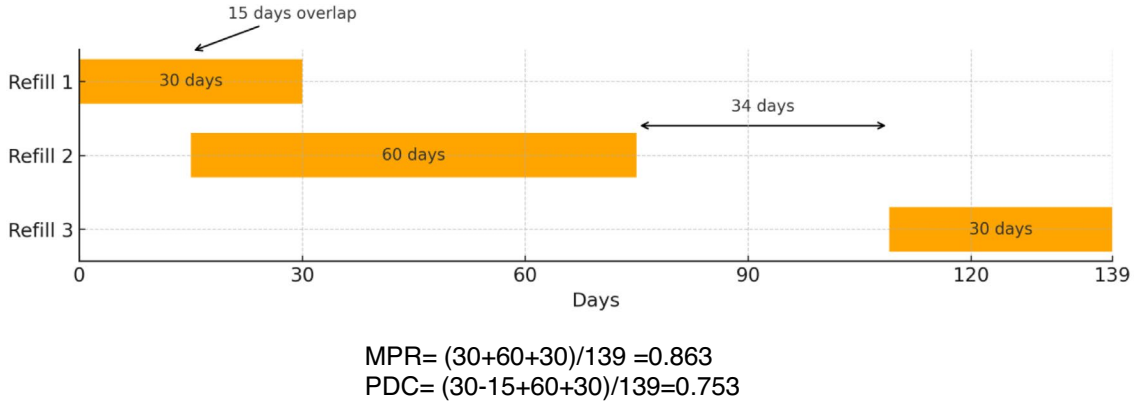

FIGURE 3 | MPR and PDC calculation example MPR = (30 + 60 + 30)/139 = 0.863.

(b) solo practitioners (reference category), or (c) institutional providers who share patients. Previous research suggests that having multiple providers may increase medication-NA due to reduced continuity of care [75, 80, 83–86].

- *Insurance subject to deductible*: Insurance status was classified as (a) health care services subject to deductible (reference category) or (b) not subject to deductible. Patients whose services were subject to a deductible may face greater out-of-pocket costs, potentially increasing financial barriers to OET adherence [24, 55, 57, 59, 87].

3 | Data Analysis

Descriptive statistics were used to interpret demographic data including patient age groups, race, and marital status. Univariate and multivariate binary logistic regression analyses were conducted to examine the relationship between multilevel determinants and OET-NA, with an alpha level of 0.05. The adjusted odds ratios (AORs) and their corresponding confidence intervals (CIs) were calculated using logistic regression.

Because the six component datasets within SEER–Medicare are structurally disconnected and not stored in a unified relational format, a MongoDB database was used in conjunction with C++ and Python (version 3.11.4) to link and organize all data. Data were managed using the Python library Statsmodels (version 0.14.0). We used only records with complete data for all variables in a given analysis, rather than imputing missing values. Since our data analysis program operated exclusively on complete datasets for specific determinants and did not perform any imputations for missing values. We applied a last-observation-carried-forward (LOCF) approach when multiple entries were present, retaining the most recent value for analysis. LOCF is a commonly recommended preprocessing strategy in large observational datasets when the goal is to use a single, consistent observation per individual without performing imputation [88]. Because records with missing data were excluded during analysis, Table S1 has been added to summarize the full database, to uncover any potential bias introduced by this exclusion process. This table details the dataset after applying inclusion criteria, and the final multivariate analytic sample. Table S1 demonstrates that patterns of missingness across demographic and clinical variables were similar between the full dataset and the analytic sample, indicating that missingness was largely random.

Univariate adherence analyses produced results consistent with the multivariate model, with negligible differences ($p < 0.005$), confirming that missingness did not bias the findings and that the analytic cohort remained representative of the original population. All samples used in each analytic stage were proportionally and randomly selected, with missing data systematically removed as documented in Table S1.

4 | Results

4.1 | Demographics of Study Samples

Demographics are presented in Table 1. Multivariate analysis results are presented in Table 2. Univariate analyses of patient-related, condition-related, therapy-related, social/economic-related, and healthcare team/system-related variables are available in the Figures S1–S7. The database initially contained 458,343 breast cancer patients in 2019. After excluding those not taking oral endocrine therapy (OET), 207,618 patients remained (Figure 2). After applying the study's inclusion criteria, the dataset was further refined to 141,457 older women (≥ 65 years) on OET in 2019. The mean age was 73.16 years. Most patients were White (83.33%), married (29.94%), and living in a metropolitan area (88.57%). The majority of breast cancers were Stage I at first diagnosis (65.36%) and patients received AIs medications such as anastrozole (55.32%), exemestane (6.83%), and letrozole (23.92%). Approximately 25% of patients were diagnosed between 2010 and 2014, while the remaining 75% were diagnosed between 2015 and 2019.

4.2 | Multi-Level Determinants Influencing OET-NA

Table 2 and Figure 4 present the multilevel logistic regression analysis, which modeled the determinants of OET-NA among

TABLE 1 | Demographics of 2019 breast cancer patients taking OET medications ($N = 141,457$).

Demographics	Count	Percentage (%)
Race		
White	117,873	83.33
Black	13,852	9.79
American Indian/Alaska Native	459	0.32
Asian or Pacific Islander	8238	5.82
Unknown	1035	0.73
Age		
Mean age (min/max/σ)	73.16 (65/99/6.42)	
65–74	92,044	65.07
75–84	40,338	28.52
85–99	9046	6.39
Unknown	29	0.02
Cancer stage		
Stage I	92,450	65.36
Stage II	29,971	21.19
Stage III	4909	3.47
Stage IV	2416	1.71
Unknown	11,711	8.28
Marital status at diagnosis		
Single (never married)	9104	6.44
Married (including common law)	42,354	29.94
Separated	572	0.4
Divorced	9923	7.01
Widowed	19,487	13.78
Unknown	60,017	42.43
Year of diagnosis for 2019 cancer patients		
2010	2616	1.85
2011	3839	2.71
2012	5101	3.61
2013	8137	5.75
2014	14,838	10.49
2015	17,790	12.58
2016	20,008	14.14
2017	22,567	14.39
2018	26,205	18.53
2019	20,356	14.39
Unknown	0	0
Rural urban status		
Metro area (more than 250,000 populations)	125,289	88.57
Urban area (more than 2500 populations)	14,668	10.37
Rural area (less than 2500 populations)	1495	1.06
Unknown	0	0.00
Switch medication status		
Prescribed medication was changed	7607	5.38
Prescribed medication was not changed	133,850	94.62
OET medication		
Anastrozole	78,256	55.32
Exmestane	9663	6.83
Letrozole	33,864	23.92
Tamoxifen	19,674	13.91

older women with breast cancer. This analysis included 35,326 patients, as detailed in Table S1, yielding a pseudo-R-squared of 0.02—a value commonly observed in healthcare and social science research, given the complex, multifaceted influences on patient behavior [89–91]. The OET-NA rate in this sample was 6.35%.

Regarding race category, Black patients showed a higher likelihood of OET-NA, with an AOR of 1.55 (95% CI 1.34–1.78; $p < 0.001$). Regarding obesity, patients classified as obese had an increased risk of OET-NA (AOR 1.13; 95% CI 1.03–1.23; $p = 0.007$). For cancer stage, patients diagnosed with Stage II cancer were more likely to be non-adherent (AOR 1.12; 95% CI 1.02–1.22; $p = 0.013$). Alcohol use also contributed to higher OET-NA risk (AOR 1.40; 95% CI 1.10–1.93; $p = 0.043$), as did tobacco use (AOR 1.41; 95% CI 1.22–1.63; $p < 0.001$). Marital status was another factor, where single (AOR 1.15; 95% CI 1.01–1.30; $p = 0.032$) and divorced (AOR 1.17; 95% CI 1.04–1.32; $p = 0.01$) patients exhibited higher OET-NA. Those who had switched OET medications also demonstrated increased non-adherence (AOR 2.72; 95% CI 2.41–3.07; $p < 0.001$). Patients with multiple healthcare providers were also more likely to be non-adherent (AOR 1.26; 95% CI 1.01–1.56; $p < 0.001$). Finally, a diagnosis of depression was a significant predictor of OET-NA (AOR 1.40; 95% CI 1.27–1.54; $p < 0.001$).

TABLE 2 | Analysis to explore joint influences of multi-level determinants.

Variables			Multivariate analysis			
			Odd ratio	Lower 95% CI	Upper 95% CI	*p*
Patient-related variables	Race/ethnicity	White	—	—	—	—
		Black	1.55	1.34	1.78	<0.001
		American Indian/ Alaska Native	1.38	0.80	2.38	0.25
		Asian or Pacific Islander	0.94	0.78	1.12	0.47
	Psychological factors	Anxiety (Y)	1.08	0.98	1.19	0.10
		Anxiety (N)	—	—	—	—
		Depression (Y)	1.40	1.27	1.54	<0.001
		Depression (N)	—	—	—	—
Socioeconomic related variables	Marriage status	Single	1.15	1.01	1.30	0.03
		Married	—	—	—	—
		Separated	1.41	0.91	2.18	0.13
		Divorced	1.17	1.04	1.32	0.01
		Widowed	1.07	0.97	1.18	0.16
	Lifestyle factor	Alcohol (Y)	1.40	1.01	1.93	0.04
		Alcohol (N)	—	—	—	—
		Drug (Y)	1.18	0.94	1.49	0.15
		Drug (N)	—	—	—	—
		Tobacco (Y)	1.41	1.22	1.63	<0.001
		Tobacco (N)	—	—	—	—
	Living status	Metro area	—	—	—	—
		Urban area	0.98	0.88	1.10	0.77
		Rural area	1.07	0.81	1.42	0.64
Condition-related variables	Disease characteristics	Stage I	—	—	—	—
		Stage II	1.12	1.02	1.22	0.01
		Stage III	1.03	0.85	1.25	0.74
		Stage IV	1.28	0.90	1.83	0.17
	Comorbidities	Hyperlipidemia (Y)	—	—	—	—
		Hyperlipidemia (N)	1.04	0.96	1.13	0.38
		Hypertension (Y)	—	—	—	—
		Hypertension (N)	1.00	0.91	1.09	0.95
		Obesity (Y)	1.13	1.03	1.23	0.01
		Obesity (N)	—	—	—	—
		Osteoporosis (Y)	1.07	0.97	1.17	0.16
		Osteoporosis (N)	—	—	—	—

(Continues)

TABLE 2 | (Continued)

Variables			Multivariate analysis			
			Odd ratio	Lower 95% CI	Upper 95% CI	*p*
Therapy-related variables	Medication regimen	OET medication switched (Y)	2.72	2.41	3.07	<0.001
		OET medication switched (N)	—	—	—	—
Health care team/system-related variables	Healthcare team practice characteristics	Solo partitioner	—	—	—	—
		Group partitioner	0.97	0.87	1.07	0.53
		Institution providers (share patients)	1.26	1.01	1.56	0.037
	Healthcare system characteristics	Health care service subject to deductible (Y)	1.15	0.94	1.40	0.17
		Health care service subject to deductible (N)	—	—	—	—

Abbreviation: CMR, comprehensive medication review.

5 | Discussion

The demographic and clinical variable patterns in our results align with trends documented in SEER–Medicare studies from other years [92–95]. With the high impact of OET-NA on decreased survival and worse QOL outcomes, this study aimed to assess determinants of OET-NA from a large-scale United States database of older women who had been diagnosed with cancer. The findings suggest that OET-NA is closely related to cancer survivors' health and environmental contexts, with several determinants that may serve as targets for future interventions to reduce OET-NA. We compared our overall findings with prior breast cancer and chronic disease studies (Table 3), and we also reviewed the major patient, socioeconomic, therapy, condition, and health system factors related to OET-NA.

5.1 | Patient-Related Determinants

Ethnicity and psychological factors were significant patient-related variables associated with OET-NA. Black patients were significantly more likely to be non-adherent to their OET regimen than White and Asian patients. These results were consistent with other breast cancer studies focused on older women [66, 93]. Other breast cancer studies reported that non-White patients generally had higher rates of OET-NA and overall medication non-adherence, but few studies specifically identified patients who identified as Black [55, 60, 61, 96]. Future interventions to improve adherence to OET will need to tailor care opportunities to communities with a high prevalence of Black breast cancer survivors.

The univariate analysis indicated that psychological factors, including psychiatric symptoms, cognitive issues, and decreased sensory or motor function, were associated with a higher likelihood of OET-NA, consistent with previous studies [22, 66, 85, 86, 97–100]. Similar patterns were observed in both univariate and multivariate models. In particular, anxiety and depression emerged as significant determinants of OET-NA in the multivariate analysis, as supported by prior research [59, 66]. Notably, depression was a stronger predictor of OET-NA than anxiety among older women with breast cancer. Previous studies rarely included participants with psychological disorders such as attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder. In this study, both ADHD and bipolar disorder were identified as determinants of OET-NA, an under-researched area within oncology and other chronic disease studies. Some studies have found that bipolar disorder is associated with OET-NA [93], while others, using smaller samples, did not observe this relationship [101]. Additionally, ADHD is known to impair medication adherence, and it often co-occurs with other psychological conditions such as anxiety and depression, which may further compound NA [102].

A diagnosis of Alzheimer's disease was one of the strongest predictors for OET-NA, which has also been correlated with medication-NA in prior breast cancer and chronic disease studies [66, 103]. Individuals with cognitive issues often experience forgetfulness [71, 104, 105], limited health literacy [67], and other dementia-related challenges that impact medication-NA [105, 106].

Hearing and mobility impairments were also identified as determinants of OET-NA in the univariate findings; however, these specific impairments remain under-investigated in breast cancer and chronic disease populations. Older patients have a higher risk of medication-NA due to decreased dexterity, mobility, hearing, and vision [107]. Unfortunately, these impairments are often overlooked in research due to sampling limitations, thereby reducing understanding of their potential impact [108]. Some prior studies have examined the severity of impairment and the complexity of self-management tasks as factors influencing medication-NA [109]. Evidence suggests that greater impairment severity is positively associated with

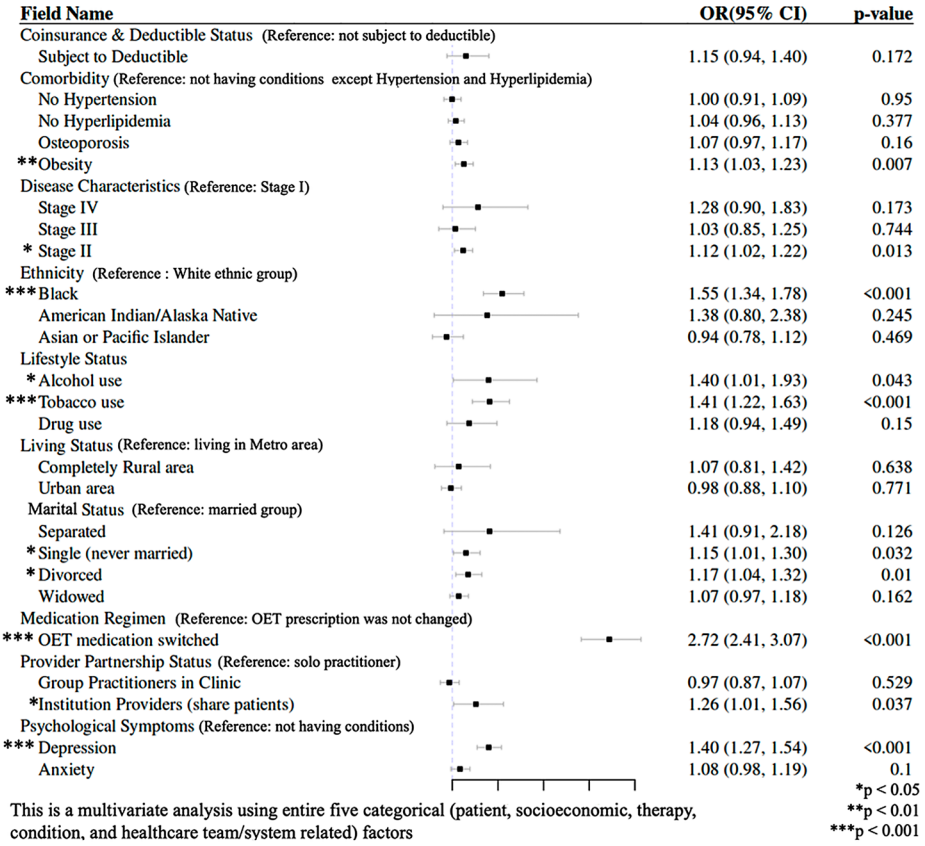

FIGURE 4 | Analysis to explore joint influences of multi-level determinan.

TABLE 3 | Patient-related discussion.

Patient-related	Our findings	Breast cancer	Chronic disease
Cognitive issues	Alzheimer's (dementia) disease (OR 1.49) (Reference: Not having these conditions)	Dementia	Forgetfulness Knowledge issues Dementia disease
Decreased sensor/motor skills	Hearing impairment (OR 1.12) Mobility impairment (OR 1.24) (Reference: Not having these conditions)	—	—
Ethnicity	*Black (OR 1.57) (Reference: White)	Black, not being White	Not being White
Psychological disease	ADHD (OR 1.46) Bipolar disorder (OR 1.25) (Reference: Not having these conditions)	Bipolar (protective for OET-NA)	Bipolar
Psychological symptoms	Anxiety (OR 1.08) *Depression (OR 1.33) (Reference: Not having these conditions)	Anxiety and depression	Anxiety and depression

*These variables had the same trends in Figure 4 multivariate analysis.

medication-NA. For example, cognitive impairment, such as dementia, can reduce older adults' medication management skills by affecting their ability to plan, organize, and execute tasks [109]. However, those studies are often limited by small sample sizes and subjective designs that rely on healthcare professionals to observe and report medication-taking behaviors.

TABLE 4 | Socioeconomic-related discussion.

Socioeconomic-related	Our findings	Breast cancer	Chronic disease
Marital status	*Single (OR 1.22), separated (OR 1.54) *Divorced (OR 1.28), widowed (OR 1.12)	Single, divorced, widowed	Non-married or no cohabitation status
Lifestyle factor	*Alcohol use (OR 1.67), opioid drug use (OR 1.85) *Tobacco use (OR 1.48)	Smoker (vs. never smoked) 5	Alcohol and drug use

*These variables had the same trends in Figure 4 multivariate analysis.

TABLE 5 | Therapy-related discussion.

Therapy-related	Our findings	Breast cancer	Chronic disease
Lifestyle factor	*OET prescribed medication is switched (OR 2.65)	Switching medications	Switching medications (only found in cancer)

*These variables had the same trends in Figure 4 multivariate analysis.

5.2 | Socioeconomic-Related Determinants

Socioeconomic-related factors associated with OET-NA were consistent with previous studies (in Table 4) [33, 38, 77, 79, 110, 111]. Patients who were not married and those with lifestyles involving drugs, alcohol, and/or tobacco use showed a higher risk of OET-NA, consistent with previous literature [60, 66, 82, 106]. Married patients demonstrated better OET adherence than non-married individuals (including those who were single, separated, divorced, or widowed). Most literature on medication-NA suggests that spousal support plays a key role in promoting adherence through social and emotional reinforcement [55, 59, 63, 70, 112]. These findings also align with the psychological factors identified in the individual-level analysis. For example, Xu and Wang reported higher levels of depression and anxiety among divorced breast cancer patients, which may further compound the absence of spousal support [113]. Moreover, recent systematic reviews have shown that medication-NA is strongly associated with the non-married status in chronic disease populations [114]. Patients with lifestyles involving alcohol, drug, or tobacco use also demonstrated higher rates of OET-NA in the individual-level related factor analysis [37].

5.3 | Therapy-Related Determinants

Therapy-related factors, including switching OET medications, were positively correlated with OET-NA. Previous studies have found that modifying a patient's prescribed regimen has the greatest impact on OET-NA (Table 5) [24, 38, 60, 62, 66, 68, 70, 115]. Several prior studies have identified medication switching as a risk factor for medication-NA, though most focused exclusively on breast cancer or other cancer treatments [66, 67]. Medication switching is often driven by patients' efforts to avoid side effects from their current OET medication, which may have already contributed to OET-NA. Specifically, multiple studies have highlighted treatment-related side effects as significant determinants of medication-NA among cancer patients [116] and those with other chronic diseases [62, 70]. Interestingly, these adverse effects can also lead to drug therapy problems, further complicating adherence.

5.4 | Condition-Related Determinants

Condition-related factors included disease characteristics and comorbidities in both univariate and multivariate analyses. Comorbidities were all positively related with medication-NA across various chronic disease populations [33, 38, 66, 92, 111, 117–122]. Moreover, some studies have revealed that patients with Stage II and IV cancer were more likely to exhibit OET-NA compared to those with Stage I cancer. Numerous studies have identified determinants of OET-NA at both early and advanced stages of breast cancer, reporting similar patterns [66, 93, 94, 118, 122].

Almost all comorbidities were risk factors for OET-NA; however, obesity emerged as a particularly significant determinant in both the comorbidity analysis (Table 6) and multilevel determinants analysis (Table 2). In the comorbidity analysis, patients with hip fractures had the highest OET-NA rates—approximately twice those of other groups. Cardiovascular and cardiopulmonary conditions also posed elevated risks, including acute myocardial infarction (AMI), chronic heart failure, chronic obstructive pulmonary disease, and peripheral vascular disease. Specifically, about 40% of AMI patients were more likely to be OET-NA than those without this condition. Interestingly, patients without hypertension or hyperlipidemia exhibited higher OET-NA than those diagnosed with those conditions. This pattern may be influenced by the fact that a majority of breast cancer patients (over 60%) have hypertension and hyperlipidemia. Other comorbidities were associated with a modest 10%–30% increase in the likelihood of OET-NA.

These comorbidity findings were consistent with prior breast cancer studies that examined factors such as obesity and

TABLE 6 | Condition-related discussion.

Condition-related	Our findings	Breast cancer	Chronic disease
Disease characteristic	*Stage II (OR 1.10) Stage IV (OR 1.38) (Reference: Stage I)	Stage IV, earlier stage (I or II)	—
Comorbidity	AMI (OR 1.38), PVD (OR 1.19), *obesity (OR 1.10), migraine (OR 1.20), liver disease (OR 1.12), no HTN (OR 1.08), no HLD (OR 1.09), fibromyalgia (OR 1.20), epilepsy (OR 1.52), diabetes (OR 1.08), COPD (OR 1.20), CHF (OR 1.13), anemia (OR 1.15), hip fracture (OR 2.21) Ulcers (OR 1.44)	Overweight or obese No HTN Cardiopulmonary comorbidities	CVD-risk (CAD, HTN, diabetes, and HLD)

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, congested heart failure; CVD, cardiovascular disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; HLD, hyperlipidemia; HTN, hypertension; PVD, peripheral vascular disease.
*These variables had the same trends in Figure 4 multivariate analysis.

TABLE 7 | Healthcare team/system-related discussion.

Healthcare team/ system-related	Our findings	Breast cancer	Chronic disease
Healthcare team characteristics	*Institution provider (shares patients) (OR 1.54) (Reference: solo practitioner)	—	Increased complexity in the provider team (only found in cancer study)
Healthcare system characteristics	Subject to deductible (OR 1.25) Coinsurance $20–40 (OR 1.31) Coinsurance $20–40 (OR 1.17) (Reference: having no coinsurance payments group variables, and not subject to deductible)	Increased out-of-pocket	Insurance types, increased coinsurance, copayments, deductibles or caps

*These variables had the same trends in Figure 4 multivariate analysis.

cardiopulmonary disease risk [66], and the absence of hypertension [37]. Several previous studies have also emphasized that cardiovascular disease (CVD), diabetes, and hyperlipidemia are among the most common comorbidities observed in cancer populations [123, 124]. Patients with CVD or CVD-related risk factors (i.e., diabetes, hypertension, and hyperlipidemia) generally demonstrated higher rates of medication-NA [124]. In breast cancer specifically, osteoporosis represents another important comorbidity because OET increases the risk of bone loss and may exacerbate osteoporosis [125]. In this study, no significant association was found between OET-NA and osteoporosis. Several studies have similarly reported that increased CVD risk is associated with OET-NA, potentially due to the medication's effects on gynecologic and hormonal pathways [66, 81, 103].

5.5 | Health Care Team/System-Related Determinants

Among the health care team/system-related factors examined (Table 7), the number of providers involved in a patient's care and insurance type were significantly associated with OET-NA [33, 38, 81, 84, 111, 117, 126–129]. Patients who received care from multiple providers exhibited an increased risk of OET-NA. The provider partnership was assessed to determine whether patients were treated by multiple providers (e.g., within the same group practice or institution) and how this influenced adherence. A positive correlation was observed between inconsistent continuity of care (i.e., when patients did not regularly see the same provider) and higher OET-NA rates. This underexplored risk factor may stem from the increased communication burden among providers involved in shared care [80, 130]. Patients with chronic diseases, including cancer, often report feeling unable to discuss medication concerns due to a limited trust-based relationships with their providers [84, 128]. Lower levels of patient-provider trust may arise from inconsistent interactions, hindering the development of stable therapeutic relationships. This important issue remains understudied due to challenges in objectively assessing patient–provider dynamics and the reliance on small or subjective adherence studies.

Regarding healthcare system characteristics, our results indicated that Medicare insurance was associated with OET-NA, consistent with findings from other breast cancer and chronic disease studies [59]. Previous research suggests that insurance type and age can significantly influence adherence, particularly during periods of healthcare disruption such as the COVID-19 pandemic [131]. For instance, pharmacy home or

mail-order delivery options may enhance adherence by improving medication access, which could partially explain the observed patterns. Although our study did not directly examine these factors, future research should further explore these relationships.

Financial burden may also contribute to OET-NA, as patients with Medicare or private insurance may face high co-payments and out-of-pocket costs [59, 66, 81, 117]. Coinsurance, which is defined as the percentage of healthcare costs paid by the patient [132], was not fully captured in our dataset because secondary insurance information was unavailable. Patients with lower coinsurance may lack supplemental insurance, but additional data are needed to confirm this association. Furthermore, OET-NA patients were more likely to meet their deductible before Medicare coverage began, suggesting potential cost-related barriers to coverage. No statistically significant relationships were found for coinsurance variables in the NCH database; however, these system-level factors may still influence OET-NA. Previous studies have reported modest positive associations between these variables and OET-NA, though most used relatively small samples (fewer than 1000 participants) [61, 115, 133, 134].

5.6 | Perspectives on All Determinants

Although many prior studies have examined individual factors in isolation, this analysis evaluated how multiple variables interact to influence patients' overall risk of OET-NA. Consistent patterns of OET-NA were observed in both univariate and multivariate models. Notably, the multivariate analysis identified several key determinants when considered collectively, including obesity, Stage II cancer, Black ethnicity, alcohol or tobacco use, divorced marital status, switching OET medications, multiple healthcare providers, and depression.

This trend was particularly evident among the American Indian/Alaska Native group (0.32%) and those residing in rural areas (1.06%), where small sample sizes contributed to greater variability across certain variables. The combination of these demographic and geographic limitations may have amplified the observed effects of key determinants, leading to larger disparities in outcomes. Many clinical studies with low pseudo-R^2 values prioritize statistical significance ($p < 0.05$) over model fit, due to sample-size constraints [89, 90]. Even though some categories in our analysis had relatively small sample sizes, it is critical to include them when results were statistically significant (i.e., therapy-related and healthcare team/system-related determinants), since these factors have been less explored in previous literature. For this reason, the findings should be interpreted with caution and not generalized to all populations.

Of particular note, switching OET medications emerged as a strong predictor of OET-NA, with its effect becoming more pronounced when evaluated in conjunction with other variables. This may be attributable to medication-related side effects that disrupt adherence, underscoring the need for patients to establish new routines or consider underlying pharmacogenetic factors that influence medication tolerance and sensitivity [135].

5.7 | Strengths

This study has several notable strengths. First, the demographic characteristics of the study sample closely align with national U.S. breast cancer demographics. For example, national data indicate that 60.43% of breast cancer patients are Non-Hispanic White, 13.70% are Non-Hispanic African American, 6.70% are Non-Hispanic Asian or Pacific Islander, and 18.33% are Hispanic [136]. Our sample's ethnic composition closely reflects national patterns, with slightly higher representation among minority groups. Second, this is the first study to use a large national dataset to provide a comprehensive understanding of OET-NA. Smaller sample sizes in prior research often present computational challenges, such as an imbalance between outcome and non-outcome events, which are more difficult to correct in limited datasets [137]. Third, this study integrates multilevel determinants grounded in established theoretical frameworks, enabling a more holistic understanding of OET-NA. Finally, a major strength is our use of a Python–MongoDB logistic regression pipeline as an innovative first step toward machine learning (ML), leveraging NoSQL's scalability to analyze large, complex datasets. It is widely used to identify influential features, evaluate data structure, and validate analytic pipelines before applying more complex algorithms—providing a stable foundation before moving into advanced ML methods [138]. To our knowledge, no prior nursing science studies have applied these advanced computational methods to examine OET-NA, highlighting the innovative strength of our analytic approach.

5.8 | Limitations

Although this study leverages a large dataset to address prior research gaps, certain groups remain underrepresented, and their related social determinants are unknown, suggesting that large-scale studies may overlook variables specific to smaller populations. In SEER-Medicare, race was categorized as White, Black, American Indian/Alaska Native, Asian/Pacific Islander, and Other; however, Hispanic origin was classified separately as an ethnicity rather than a race, limiting our ability to analyze Hispanics individuals as a distinct group. Moreover, while the SEER-Medicare database provides extensive clinical and demographic information, it lacks direct measures of key social determinants of health (SDOH)—such as transportation access, health literacy, food insecurity, and pharmacy availability—that are known to affect medication-NA. The higher rates of OET-NA observed among Black women and socioeconomically disadvantaged populations in this study may therefore reflect, in part, the influence of unmeasured SDOH rather than clinical or treatment-related factors alone. Future research that integrates SDOH measures and examines trends across different ethnic groups is needed to generate more precise and equitable insights into OET-NA among diverse populations.

Second, the findings may not be generalizable to patients not enrolled in Medicare Part D. Because not all individuals use Medicare services, the results may not fully represent the broader population. According to the U.S. Department of Health

and Human Services, 74% of the 63 million Medicare beneficiaries were enrolled in Medicare Part D in 2019 [139].

Third, missing data may introduce bias into the multivariate analysis, particularly for variables such as marital status, therapy combinations, and insurance claims linked to prescriptions because high levels of missingness can compromise model integrity and distort parameter estimates [19]. To safeguard analytical validity, we conducted a completeness assessment rather than applying imputation. This evaluation was performed on the full database, and all cases with missing or unknown values were systematically excluded prior to analysis. As detailed in Table S1, the proportional distributions of demographic and clinical variables remained consistent across the full database, the inclusion-criteria dataset, and the final multivariate analytic sample. This stability indicates that the analytic cohort is representative of the broader population and that the removal of incomplete records did not distort the underlying data structure. These findings confirm that listwise exclusion of missing data did not introduce bias into the analytic process and that the final cohort preserves the population's original characteristics.

Fourth, unmeasured confounders may have influenced the findings. The SEER-Medicare data often underreport conditions like obesity, substance use disorders, and mental illnesses due to the limitations of claims-based reporting [140, 141]. Additionally, the episodic and billing-oriented structure of SEER-Medicare data limits the ability to conduct comprehensive analyses, thereby limiting its application in holistic health research [19, 142]. The cost structure within the NCH database is complex because data are presented in aggregated form. For example, "beneficiary responsibility" includes copayments, deductibles, and coinsurance, whereas "out-of-pocket" costs represent actual amounts paid after supplemental insurance or assistance programs are considered [143]. These records do not fully reflect patients' true expenditures or payment methods [140].

Furthermore, comorbidities were identified within the year preceding the cancer diagnosis, requiring continuous healthcare plan enrollment to ensure accurate documentation. This approach enhances the completeness of patients' comorbidity profiles but may lead to underestimation if lapses in enrollment occur, potentially affecting the interpretation of their influence on outcomes.

Additionally, this study did not examine the initiation, implementation, and discontinuation phases of medication adherence [144]. Although this was beyond the current research question, future work could benefit from identifying which adherence phase contributes most to OET-NA.

At last, prescription refill data serve as an indirect measure of adherence and cannot accurately capture real-time medication administration [145]. One major limitation of this method is the assumption that refilling a prescription equates to medication intake [146]. Refilling occurs before consumption and does not confirm that the medication was taken as prescribed [147]. This approach also overlooks partial medication-NA during the refill period, thereby limiting the precision of adherence assessment.

6 | Conclusion

This study identified that race, marital status, lifestyle factors (such as drug and tobacco use), changes in prescribed medication, having psychological symptoms and disorders, cognitive issues, comorbidities, drug therapy problems, and insurance factors significantly affected OET-NA among breast cancer patients, consistent with findings from prior studies. Our results confirm previous literature that was conducted with smaller samples of breast cancer patients. Because this study utilized a much larger dataset, the findings are more generalizable than those from prior research.

The results also demonstrated that the determinants of medication-NA among breast cancer patients differ from those observed in other chronic diseases. This highlights the importance of examining disease-specific factors and implementing tailored clinical interventions to improve medication adherence. This study is particularly valuable because it identifies the most influential determinants, offering a foundation for developing predictive models to guide personalized, high-impact interventions. Future studies should further investigate how these determinants interact and vary across the initiation, implementation, and discontinuation phases of medication adherence—to enhance understanding of OET-NA.

These findings suggest that enhanced clinical management and structured follow-up after OET medication changes may improve adherence and treatment continuity among breast cancer patients.

Ultimately, this study advances the scientific understanding of medication-NA by integrating large-scale data analytics with established theoretical frameworks, thereby providing an evidence-based foundation for precision interventions aimed at improving adherence and long-term outcomes among women with breast cancer.

Author Contributions

Sunny Y. Ruggeri: conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, visualization, writing – review and editing, software, formal analysis, project administration, data curation. **Cynthia L. Russell Lippincott:** conceptualization, supervision, writing – review and editing, methodology, data curation, investigation. **Gregory L. Alexander:** writing – review and editing, validation, supervision, resources. **Rebecca J. Bartlett Ellis:** supervision, validation, writing – review and editing, resources. **Steven R. Chesnut:** supervision, resources, methodology, validation, writing – review and editing, visualization, formal analysis. **Lori A. Erickson:** writing – review and editing, validation, supervision, resources.

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Disclosure

The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

Ethics Statement

This study adheres to strict ethical standards, protecting patient privacy, ensuring data accuracy, reducing bias, and complying with IRB and SEER-Medicare research guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in SEER-Medicare at https://healthcaredelivery.cancer.gov/seermedicare/overview/.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** cam471925-sup-0001-FiguresS1-S7.docx. **Figure S2:** cam471925-sup-0001-FiguresS1-S7.docx. **Figure S3:** cam471925-sup-0001-FiguresS1-S7.docx. **Figure S4:** cam471925-sup-0001-FiguresS1-S7.docx.**FigureS5:**cam471925-sup-0001-FiguresS1-S7.docx. **Figure S6:** cam471925-sup-0001-FiguresS1-S7.docx. **Figure S7:** cam471925-sup-0001-FiguresS1-S7.docx. **Table S1:** cam471925-sup-0002-TableS1.docx.