OPTIMIZING BREAST CANCER CARE: A MULTI-DATABASE EVALUATION OF ENDOCRINE THERAPY USE, OUTCOMES AND TELEHEALTH IMPACT

by

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(Under the Direction of Lorenzo Villa Zapata and Henry Young)

ABSTRACT

Optimal medication use is critical for effective disease management, ensuring patient safety, and maximizing treatment benefits. However, numerous challenges hinder optimal use in routine clinical practice, with low adherence levels being a persistent issue. Medication-taking behavior is a complex phenomenon influenced by a range of factors, including patient characteristics (e.g., age, race, and socioeconomic status), treatment-related attributes (e.g., dosage form, regimen complexity, and duration), and healthcare system factors. The relative impact of these factors varies depending on the patient's medical condition and treatment context.

In oncology, consistent adherence to treatment is essential for achieving favorable outcomes, preventing disease progression, and ultimately saving lives. Breast cancer is the most commonly diagnosed malignancy among women worldwide, and endocrine therapy has played a fundamental role in its treatment for decades. However, significant disparities in treatment adherence and outcomes continue to persist. Based on an extensive literature review and analyses of multiple data sources, this dissertation comprises three interrelated projects that evaluate real-world adherence patterns, clinical outcomes, and adverse events

associated with oral endocrine therapies, as well as assess the potential of telehealth as an intervention to improve breast cancer care.

The first project synthesizes evidence on endocrine therapy usage rates, effectiveness, side effects, and contributing factors among breast cancer patients in resource-limited settings. The second project examines the safety profile of endocrine therapies by analyzing reported adverse events in the FDA Adverse Event Reporting System (FAERS), highlighting risks that may affect medication adherence, impair quality of life, or pose life-threatening consequences. The third project uses administrative claims data to evaluate the impact of telehealth utilization on adherence to endocrine therapy, clinical outcomes, and healthcare expenditures in a commercially insured cohort of nonelderly women with breast cancer in the United States.

Collectively, these studies provide critical insights into the drivers of endocrine therapy nonadherence, associated patient outcomes, and safety concerns. Findings from this work inform future strategies aimed at improving breast cancer care, enhancing patient safety, and reducing health disparities across populations. Moreover, this dissertation underscores the promise of digital health interventions to strengthen healthcare delivery and promote patient-centered cancer management.

INDEX WORDS: Breast cancer; Endocrine therapy; Tamoxifen; Aromatase inhibitors; Real-world data; Adherence; Cancer recurrence; Survival rate; Clinical outcomes; Adverse drug reactions; Side effects; Safety; Telehealth; Digital health; Developing countries; FAERS database; Merative MarketScan; Meta-analysis; Disproportionality analysis; Generalized linear models

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DEDICATION

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

"And He found you lost and guided you." (Quran 93:7)

With profound gratitude, I dedicate this dissertation to **Allah**, whose infinite mercy and countless blessings have guided me through every step of this journey. Every challenge, moment of doubt, and success has been a testament to His divine wisdom and grace.

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CHAPTER 1

INTRODUCTION

Background

Breast cancer is the most prevalent cancer among women worldwide, with millions of new cases diagnosed annually.[1] In 2020, female breast cancer accounted for 12% of all cancer incidences, with approximately 2.3 million new cases reported globally and an estimated 300,000 in the United States (US) alone.[1,2] Beyond its significant mortality burden, reaching 685,000 deaths worldwide in 2020, breast cancer also imposes a substantial economic strain and is one of the most financially burdensome cancers, with healthcare costs that continue to rise.[3]

The significant burden of breast cancer has varied across nations, largely influenced by income levels. While incidence rates are the highest among women in high-income countries, mortality rates are disproportionately higher in low-income regions, particularly in Africa.[4] This disparity is primarily attributed to the widespread implementation of routine screening programs in high-income countries that have enabled more and earlier detection of the disease, better treatment outcomes, and lower mortality rates.[5,6]

To alleviate the burden of breast cancer, effective prevention and risk reduction strategies are critical. Modifying certain lifestyle behaviors, such as maintaining a healthy weight, avoiding smoking, and engaging in regular physical activity can lower the risk of developing the disease. However, some women remain at higher risk due to nonmodifiable factors which include aging, family history of breast cancer, inherited genetic mutations,

excessive radiation exposure, and the use of oral contraceptives or hormone therapy. Reproductive factors such as age at puberty, first pregnancy and menopause also contribute to breast cancer susceptibility.[7,4] Although some women may still develop breast cancer despite the absence of known risk factors or preventive measures, diagnosis of the disease at an early stage significantly improves cancer management especially with the availability of effective breast cancer treatments.[1]

Recent advances in breast cancer treatment have substantially improved cancer control and outcomes, achieving unprecedented survival rates. In the US, the total number of cancer survivors now exceeds 18 million, with female breast cancer ranking at the top of all cancer types with more than 4 million survivors.[8] The most appropriate therapeutic approach and its clinical benefits depend primarily on breast cancer subtype, stage at diagnosis, and individual patient characteristics.

Hormone receptor-positive (HR+) tumor is the most common subtype of breast cancer, comprising approximately 75% of all breast cancer cases in women.[9] The term HR+ breast cancer refers to tumors that express estrogen receptors (ER), progesterone receptors (PR), or both and depend on these hormones for growth.[10] Compared to other subtypes, such as triple-negative breast cancer, HR+ tumors tend to be less aggressive and are associated with a more favorable prognosis (at least initially).[9] Unless progressed to an advanced or metastatic stage, the early stages of HR+ breast cancer are highly curable with appropriate therapeutic interventions.

Treatment options for women with nonmetastatic HR+ breast cancer typically consist of surgical removal of the primary tumor and surrounding affected tissues, radiotherapy, chemotherapy (such as anthracyclines), and endocrine therapy. Surgery,

either in the form of lumpectomy or total mastectomy, as well as radiotherapy are central in controlling the tumor locally in and around the breast.[11] In addition to local treatment, systemic anticancer therapies, including chemotherapy and endocrine therapy play an important role in managing HR+ breast cancer. These treatments may be administered before surgery (neoadjuvant therapy) to reduce tumor size or after surgery (adjuvant therapy) to eliminate any remaining cancer cells and reduce the risk of recurrence and metastasis.[9]

Endocrine therapy is the current standard adjuvant treatment for all women with HR+ breast cancer and is considered one of the greatest clinical advancements in oncology over the past decades.[12] Tamoxifen (TAM, Nolvadex) was the first endocrine therapy approved by the US Food and Drug Administration (FDA) in the late 1970s, marking the beginning of hormone-based treatment strategies for breast cancer.[13] A newer generation of endocrine therapies, known as aromatase inhibitors (AIs), later gained FDA approval in the mid-1990s. These AIs include anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin).[13] The effectiveness of endocrine therapy in treating breast cancer is based on its ability to inhibit the growth of hormone-dependent cancer cells through different mechanisms. While TAM blocks estrogen effects on breast cancer cells, AIs suppress intrinsic estrogen production either temporarily (anastrozole and letrozole) or permanently (exemestane).[14]

Endocrine therapies are highly effective in reducing the risk of disease relapse and improving both disease-free and overall survival in patients with HR+ breast cancer. Recurrences may still occur years or even decades after treatment completion with a varying rate based on the initial tumor status.[15] To impart further protection particularly for

patients at high risk of relapse, experts have recently recommended extending the duration of endocrine therapy after surgery from the standard five years to ten years.[16,17] Although prolonged administration of oral adjuvant therapies has demonstrated favorable clinical outcomes, extending endocrine therapy also implies an increase in the occurrence of common and late-onset side effects which must be carefully considered.

Endocrine therapies are associated with a wide range of side effects that vary in intensity and severity, often impairing patients' quality of life and contributing to treatment discontinuation. As these therapies induce systemic estrogen deficiency or block its physiological effects, menopausal symptoms are common among breast cancer patients across all age groups. Frequently reported symptoms that interfere with daily functioning include hot flashes, night sweats, sleep disturbances or insomnia, vaginal dryness, mood swings, irritability, and depression.[18]

Like most anticancer medications, endocrine therapies are highly effective but can also be associated with serious toxicities that result in hospitalization or, in rare cases, death. The use of TAM has been linked to an increased risk of uterine cancer, thromboembolic events, and, to a lesser extent, cataract formation.[19] AIs primarily cause musculoskeletal complications (including arthralgia, muscle pain, and joint stiffness) which negatively impact physical function and often worsen with age, potentially progressing to osteoporosis or fractures.[20,21] Furthermore, growing concerns have emerged regarding AI-related fatal cardiovascular toxicities, such as heart failure.[22] Close monitoring of symptom burden and proactive management of side effects are essential to ensure patient safety, improve treatment tolerability and adherence, and ultimately enhance therapeutic outcomes.

Statement of overall problem

The long-term use of endocrine therapies in clinical practice has demonstrated value in preventing life-threatening disease recurrence and progression, improving disease-free survival, and potentially enhancing overall survival.[23] Despite these well-established clinical benefits and the critical importance of adherence for treatment success, nonadherence to endocrine therapy remains a persistent challenge among breast cancer survivors. The evolving landscape of oncology care, from clinic-based supervised injectable treatments to self-administered oral medications taken over extended periods, has redefined cancer as a chronic condition and introduced new complexities in long-term disease management.[24] Ensuring adequate adherence to oral anticancer agents and maintaining sustainable medication safety have become priorities in cancer survivorship, requiring continued support and the development of targeted intervention strategies.

Suboptimal medication adherence is influenced by a combination of factors related to the disease, the medication itself, the patient, and the broader healthcare system.[25] Among these factors, the frequent and often severe side effects of oral anticancer therapies represent a major barrier to long-term treatment tolerability and significantly impede consistent medication use.[26,27] Side effects related to endocrine therapy are among the most commonly reported reason for nonadherence and premature treatment discontinuation.[28–33] Therefore, the proactive prevention, early detection, and effective management of distressing symptoms are essential strategies for ameliorating patient discomfort, addressing intolerable side effects, and promoting proper adherence to therapy.[34]

The acute and long-term toxicities of cancer treatments are often poorly understood, inadequately studied, and underestimated. The systemic effects and cumulative burden of

prolonged therapy along with the severity of the underlying disease typically complicate the identification and timely management of adverse treatment events. Data on oncology medications safety from clinical trials (CTs) have inherent limitations, including the small number of participants, variability in treatment regimens (such as individualized tolerated dosing approaches), exclusion of certain patient populations (e.g., those with comorbidities or advanced disease), and relatively short follow-up periods.

Ongoing exploration of pharmacovigilance systems, even for long-established anticancer medications, is essential to advance the understanding and prediction of treatment potential risks. Adopting data from multiple sources can complement existing evidence and help bridge knowledge gaps especially on serious, rare, or long-term side effects that emerge over time. Comprehensive and accurate information on endocrine therapy complications can inform the development of effective mitigation strategies, improve patient quality of life, and support sustained medication adherence.

Cost is another well-recognized attribute that influences adherence to prescribed medications. In oncology, the financial aspect is unique and more complex. Expensive prices of cancer treatments limit their affordability and create barriers to equitable access and utilization of care.[35–37] Beyond the high cost of cancer medications, patients endure further expenses for pharmaceuticals and supplements needed to manage treatment-related side effects. Cancer care entails substantial expenditures on medical services, supportive care, indirect costs (e.g., reduced or lost work productivity), along with additional nonmedical costs (e.g., transportation and childcare during treatment or post-surgical recovery).[38] The resulting financial toxicity incorporates both patients and healthcare systems.

In 2020, national direct medical expenses for breast cancer management were the highest of all cancer types, totaling approximately $30 billion.[39] The average cost burden for a breast cancer patient during the initial year of treatment was $35,000 for disease-related medical services and $1,100 for oral prescription medications.[39] These costs decreased during the continuing care phase to an annual average of $3,500 and $830, respectively.[39] Cost-sharing is particularly burdensome for young breast cancer patients who are often ineligible for public insurance and face higher out-of-pocket (OOP) expenses.[40] Also, the financial impact of cancer and its treatment, including work absenteeism, changes in employment status, and other competing financial obligations, further contributes to the overall strain of the young population and exacerbates their inability to afford care.

To mitigate the financial burden of cancer treatment, many breast cancer patients may delay, skip doses, or even discontinue recommended medications. Rate of adherence to endocrine therapy is consistently low and tends to decline over time. On average, only about 66% of women with breast cancer adhere to endocrine therapy for the full recommended five-year duration, with the lowest adherence rates observed in the fifth year.[41] Furthermore, almost one-third of patients discontinue their endocrine therapy prematurely before the end of the treatment course.[41] High medication cost is a principal barrier to adherence.[42–44] Among breast cancer patients covered by prescription drug plans, the median annual OOP costs for endocrine therapy alone in 2011 were $804 for TAM and exceeded $2,200 for some AIs.[45]

While high medication costs are a known driver of poor adherence to cancer treatment, the relationship between cost and adherence is bidirectional. Nonadherence not

only compromises health outcomes for breast cancer patients but also results in substantial economic consequences. Suboptimal medication use undermines treatment effectiveness, leading to disease progression and increased clinical burden. From a financial perspective, nonadherence contributes significantly to rising healthcare expenditures, placing additional strain on already overwhelmed health systems, especially in the context of cancer care. In the US, medication nonadherence is estimated to account for billions of dollars in avoidable healthcare costs annually, even before considering indirect and nonmedical expenses.[46]

The costs associated with nonadherence vary across different conditions, with spending consistently higher at lower adherence levels; but the opposite applies to pharmacy costs.[47] In many chronic diseases, the increase in medication expenses among adherent patients is often offset by improved health outcomes, better prognosis, reduced complications, and lower overall healthcare utilization, resulting in net cost savings. However, in oncology, patients who adhere to medical care bear the dual burden of expensive anticancer treatments and the additional costs of managing treatment-related side effects which attenuate any financial savings. Meanwhile, nonadherent patients are more susceptible to disease progression that often requires more complex and costly treatment interventions, if any remain viable. From a healthcare system or provider perspective, the dilemma of patient nonadherence implies a waste of healthcare resources, billions of dollars in avoidable costs, and, more importantly, preventable losses of lives despite substantial investments in ensuring the quality and effectiveness of care.

The high prevalence of suboptimal adherence to endocrine therapy among breast cancer survivors in conjunction with the rising costs of cancer care heighten the need for a comprehensive cost containment strategy that optimizes therapeutic outcomes while

minimizing waste. Evaluating the economic impact and clinical value of these interventions, particularly among working-age breast cancer patients who are more vulnerable to financial hardships, can inform health policy decisions on potential strategies to alleviate the financial burden on cancer patients, and improve both adherence and long-term treatment success.

Given that the impact of cost on treatment interruptions or even complete discontinuation is common and of significant magnitude even in a wealthy country like the US,[48,49] these financial challenges are definitely more pronounced in countries with limited healthcare budgets and constrained resources. Notably, most studies on adherence to endocrine therapy have been conducted mainly among breast cancer patients in developed countries. Advanced healthcare systems with accessible essential treatments implement patient-centered care by systematically monitoring outcomes such as symptom distress and adherence, in order to ensure an efficient cancer care process and support high-quality survivorship for their populations.[50–52] In contrast, adherence to medication in less developed nations has received relatively little attention in the context of other unmet healthcare needs and competing priorities.

Concerns about patient safety and improper medication use in developing countries have been a critical issue due to the scarcity of health resources and limitations in pharmaceutical regulation.[53] Given the proven cost-effectiveness of endocrine therapies in basic healthcare systems and the observed low adherence rates among minority and low socioeconomic status populations in high-income countries,[54–57] investigating the usage patterns and experiences of underrepresented breast cancer patients in developing countries has become an increasingly important research focus. Nonadherence to these essential

medications may simply explain the persistent disparities in breast cancer outcomes across nations.

Purpose of the dissertation

Our long-term goal is to develop evidence-based strategies that promote optimal use of and adherence to therapeutic recommendations among cancer survivors, enhance patient safety and quality of life, and reduce the financial burden associated with cancer treatment. The primary objective of this dissertation was to systematically examine the use (specifically, the prevalence of medication nonadherence), safety, and clinical outcomes (cancer recurrence and survival) of endocrine therapy among breast cancer patients in developing countries. In addition, this work explored treatment-related side effects as a key driver of nonadherence and quantified the impact of digital health interventions on adherence and outcomes among women receiving endocrine therapy for breast cancer.

The specific aims of this dissertation are:

Specific aim 1: To comprehensively summarize the available evidence on the utilization patterns (adherence rates), side effects, and effectiveness of endocrine therapies among nonmetastatic breast cancer survivors in developing countries. Medication adherence and safety are underreported topics in resource-limited settings. It is necessary to consider how adherence is measured: subjectively (self-reported or perceived) or objectively (e.g., pill counts, pharmacy refills) as patient-reported measures often overestimate adherence.

Specific aim 2: To identify reported adverse events associated with endocrine therapies in female breast cancer cases within the FDA database and characterize them by frequency, severity, treatment agent, and reporter (patient or clinician).

Specific aim 3: To assess and compare the impact of telehealth services on adherence to endocrine therapy, cancer metastasis, and healthcare costs in a cohort of nonelderly women with nonmetastatic breast cancer using real-world data from the Merative MarketScan database. Differences in adherence, metastasis incidence, and healthcare costs between telehealth users and nonusers were examined. The financial implications were evaluated from the patient perspective. We hypothesize a positive correlation between telehealth utilization and an increase in adherence to endocrine therapy, as well as overall cost savings at the patient level.

CHAPTER 2

LITERATURE REVIEW

Factors affecting medication adherence

The intuitive quote, “Drugs don't work in patients who don't take them” (C. Everett Koop, 1985) highlights the critical role of patient adherence in the success of healthcare interventions. While recent advances in treatment and quality of care have the potential to improve disease management and outcomes, poor adherence to prescribed medications remains a significant challenge and has emerged as a pressing public health concern.

The efficacy and safety profiles of medications initially evaluated in CTs (the gold standard of drug assessment) often differ in magnitude or direction once the medication enters the market. This discrepancy arises, in part, because patients behave differently under the controlled conditions of CTs, which can create an overly favorable yet distorted representation of treatment effectiveness in real-world settings.[58] Researchers suggest that CT participants are often not fully representative of the general population, limiting the generalizability of trial findings.[59] They may also receive additional support, incentives, and monitoring that enhance adherence beyond what is typically observed in routine clinical practice. A meta-analysis of therapeutic agents for primary breast cancer prevention in over 21,000 high-risk women found substantial differences in medication uptake between trial settings and usual care, with significantly higher adherence estimates in CTs (25% versus 9%).[60]

The use of medications on a larger scale in routine clinical practice provides a more accurate reflection of patient adherence, rare and long-term treatment complications, and the true effectiveness of therapies over extended periods. Real-world data capture diverse patient experiences, including those of vulnerable populations with multiple comorbidities who are often excluded or underrepresented in CTs. As a result, health authorities and organizations are increasingly prioritizing the integration of real-world evidence to inform coverage decisions and gain a deeper understanding of the potential benefits and risks of medications.[61]

Multiple other factors could influence medication use and adherence, including patient-related aspects (e.g., age, race, and socioeconomic status), treatment-specific factors (e.g., dosage form, regimen complexity, and duration), and healthcare system-related elements (e.g., facilitators and barriers to access).[25] However, the impact of each factor on the complex phenomenon of medication adherence varies significantly depending on the patient's medical condition and treatment context.

Medication adherence among cancer patients and survivors

Cancer diagnosis is a profound health shock that imposes significant physical, mental, emotional, and social distress on patients, caregivers, and families. Toxicities associated with cancer treatments can further disrupt the patient's daily life, impair quality of life, and, in some cases, pose greater risks than the disease itself. For instance, cardiovascular complications, are a leading competing cause of death among survivors of urinary bladder, prostate, and breast cancer.[62] The extent of these adverse effects, as well as the overall benefits of treatment primarily depends on baseline clinical characteristics of patients. Effective management of underlying risk factors through consistent use of

preventive therapies and treatments is essential for improving cancer outcomes and preventing the development or progression of comorbid conditions.

Following cancer diagnosis trauma, healthcare priorities often shift more toward management of the emerging disease and patients' health behaviors (including medication adherence) change significantly. A recent systematic review of 21 studies found a deterioration in adherence to prescribed medications for hypertension, dyslipidemia, and diabetes from the point of cancer diagnosis through survivorship across various cancer types.[63]

In oncology, adherence to life-saving medications was expected to be high -- especially after the recent transition to the preferable and convenient orally administered formulations. Nonetheless, the reality mirrored that of noncancer medications. The nonadherence rate for oral anticancer therapies may be as high as 54%, with variations based on the type of medication, whether endocrine therapy, cytotoxic agents, or targeted therapies.[64]

Factors affecting adherence to endocrine therapy

Extensive research has demonstrated strong evidence on several barriers to adherence and long-term persistence with endocrine therapy. Principal deterrents include treatment-attributable side effects, poor healthcare provider-patient communication, negative treatment beliefs, low socioeconomic status, presence of multiple comorbidities, and high OOP costs.[65–68] Among these factors, adverse events of TAM and AIs are the most frequently cited reason for poor adherence and early discontinuation.[28–33] In the large randomized CT Breast International Group (BIG) 1-98, more than half of participants who

did not complete the full five-year course of assigned endocrine therapy discontinued treatment due to side effects, with an average treatment duration of 19 months.[69]

A novel analysis of messages content from an online breast cancer patient portal revealed that the likelihood of successfully completing the endocrine therapy regimen decreased by 20% when patients acknowledged adverse treatment effects.[70] Conversely, the likelihood increased by a similar margin when patients stated taking medications to manage treatment-related toxicities.[70] Similarly, an observational study examining factors that affect endocrine therapy duration in a cohort of federally insured women with breast cancer displayed a better treatment persistence among patients who concurrently filled prescriptions for medications likely to cope with side effects, especially during the first year of endocrine therapy.[71]

Continuous follow-up and open communication about bothersome symptoms with healthcare providers are essential for improving medication tolerability and adherence. Medical practitioners should proactively assess each patient's susceptibility to complications and provide comprehensive, accurate information on the benefits and potential harms of endocrine therapy to guide and support its appropriate use.[72] Effective patient-clinician interactions, including professional consultation and patient education, have been shown to significantly impact adherence to endocrine therapy.[66,67] Lack of necessary information about endocrine and supportive therapies, as well as limited understanding of treatment goals can lead to misconceptions and uncertainty about treatment outcomes, discouraging medication use. While perceived benefits of endocrine therapy are associated with increased adherence, gaps still exist in patients' understanding of certain treatment-related aspects.[65,73,74]

A series of studies have indicated several sociodemographic characteristics that can serve as predictors of patient adherence to endocrine therapy. Breast cancer survivors under 50 years old were less likely to fill prescriptions and adhere to treatment, with the lowest adherence rates observed in a subgroup of less privileged women.[75] An analysis of approximately 50,000 privately insured female breast cancer patients receiving endocrine therapy found better adherence among older women aged 50 to 69, residents of the Northeast region, and those without depression or other coexisting conditions.[42]

Beyond age, adherence to endocrine therapy also differs significantly by race where African American women, especially those living in rural areas, consistently show lower adherence rates than their White counterparts.[76–78] This racial disparity can be partially explained by a disproportionately higher burden of treatment-related side effects reported among African American patients in multiple studies.[76,56,79,80]

Adherence to endocrine therapy is also strongly linked to socioeconomic status. Patterns of delayed treatment initiation, poor adherence, and early discontinuation are routinely exhibited in low-income minority patients.[81] In a follow-up survey assessing endocrine therapy use among Black and White breast cancer patients over two years, suboptimal use was most prevalent in respondents with Black race, the youngest age stratum (under 45 years old), insured by Medicaid, and those earning less than $15,000 annually.[80] Similarly, a study by Farias et al. revealed that in a cohort of Medicaid-insured women, only one-third remained adherent to endocrine therapy over the recommended duration of five years.[82] Additionally, low levels of adherence to AIs were observed in a Texas-based sample of Latino breast cancer patients that had 58% of women earning less than $15,000 annually and over 40% attained middle school education at most.[57]

Logically, adherence declines further as treatment costs increase. A cohort study of privately insured women found a direct correlation between higher OOP payments and poor endocrine therapy adherence—patients with higher medication copayments were more likely to forgo filling their prescriptions or skip doses.[43] Conversely, lower copayments were significantly associated with improved long-term adherence. Among breast cancer patients who had commercial insurance, a low copay for all prescription medications ($11or less per month) was a strong indicator of treatment retention over a five-year period.[42] Similarly, a study using Medicare data on a diverse national cohort of elderly female breast cancer patients showed a significant reduction in adherence to TAM and AIs when the average monthly OOP medication cost exceeded $2.65.[44]

Cost-related barriers are particularly challenging for young breast cancer patients as they face higher cost-sharing requirements for cancer care than elderly patients covered by public insurance programs. Furthermore, with the financial strain of cancer and its treatment combined with its negative impact on work productivity and income, younger patient populations are more vulnerable to financial difficulties that hinder their ability to afford and adhere to treatment. A study by Zheng et al. on a nationally representative sample of cancer survivors recorded the intense economic burden among nonelderly patients (ages 18–64).[48] In a cohort of 2,494 female breast cancer patients under the age of 50, financial hardships, including income loss and unemployment were prevalent two years after diagnosis, especially among African American women.[83] As expected, cost was more frequently claimed as a reason for nonadherence to endocrine therapy among African American patients compared to White women (17% versus 7%).[80]

Cost remains a modifiable risk factor for nonadherence. Reducing the financial burden of treatment can help more women adhere to their treatment plans. The introduction of the generic version of branded AIs has largely lowered OOP costs for patients.[45,84,85] Users of lower-cost generics were more likely to be adherent and persistent compared to recipients of brand-name AI products, as demonstrated in Hershman et al.'s analysis of data for patients with primarily commercial insurance.[85] Additionally, studies have reported that the availability of generic AIs helped slow the decline in long-term adherence among elderly women who did not have a supplementary support for pharmaceuticals (e.g., copay reduction programs) and benefited from substantial cost reductions following the introduction of generics.[84,86]

Over the years, several national programs and policies have been implemented to make prescription medications more affordable to patients. One example of these initiatives is the subsidy program which provides additional coverage benefits for low-income Medicare enrollees. Studies have linked this program to a steady improvement in adherence to endocrine therapy among subsidized patients in comparison to those who were unsubsidized.[84,86] Another cost containment measure is the release of oral oncology parity laws in most states that were designed to specifically cap patient spending on oral anticancer medications. However, these laws have resulted in only modest reductions in OOP costs for endocrine therapy and, consequently, have had a limited effect on overall adherence.[87]

A comprehensive approach to enhancing adherence to endocrine therapy should integrate multiple underlying factors rather than addressing them in isolation. Given the complex and multidimensional nature of nonadherence, it is also imperative to consider

how these factors interact and influence patient behavior across different domains. Interventions at the healthcare system level are potentially the most effective in driving meaningful changes in adherence, ultimately optimizing treatment outcomes and improving patient care.

Importance of adherence to endocrine therapy (Consequences of nonadherence to endocrine therapy)

Findings from randomized trials and large observational studies emphasize the critical importance of adherence to both the dosage and duration of endocrine therapy in achieving its full therapeutic benefits. The BIG 1-98 randomized multisite CT reported that women who discontinued letrozole (an AI) early had a 45% worse five-year cancer-free survival rate compared to those who completed treatment.[69] Additionally, poorer health outcomes were observed among less adherent participants.[69] A recent systematic review of 12 cohort studies examining the clinical implications of endocrine therapy nonadherence identified a significant association between nonadherence and higher risks of disease recurrence, metastasis, and mortality.[23] Notably, maintaining consistent adherence throughout the course of endocrine therapy may help narrow, or even eliminate, the gap in breast cancer mortality between African American and White women.[82]

Besides its clinical significance, medication adherence has substantial economic implications for both patients and healthcare systems. In the US, the direct costs of nonadherence are estimated to be billions of dollars annually, mainly due to overutilization of healthcare services (particularly hospitalizations).[46] The financial burden of poor adherence is paramount in cancer care due to the severity of the disease. Cutler et al.

reported exceptionally high costs associated with nonadherence in cancer relative to other conditions, such as cardiovascular and respiratory diseases.[47]

Few studies have investigated the economic impact of nonadherence in breast cancer patients receiving endocrine therapy. A cost-effectiveness analysis of TAM adherence in a cohort of Scottish breast cancer patients showed that higher adherence was associated with a reduction in total expenses, from approximately £21,000 to £15,000.[88] Similarly, studies that were conducted in the US consistently revealed lower medical costs among adherent versus nonadherent women throughout the treatment period.[89,90] However, these savings were offset by a concomitant increase in pharmacy costs, resulting in no significant reduction in overall healthcare expenditures.[89,90] Notably, these studies primarily focused on elderly breast cancer patients who are already protected by federally funded insurance or were limited to nonelderly women within a cancer registry of a single state (i.e.; small in scale).

Awareness of the importance of adherence has informed the development and implementation of targeted interventions and public health initiatives. However, further research is needed to fully assess the effectiveness and economic impact of certain interventions, such as telehealth, using large, nationally representative samples of nonelderly women with breast cancer. Enhancing adherence among vulnerable subgroups can improve survival and quality of life while mitigating avoidable costs for both patients and healthcare systems. By integrating evidence-based strategies, healthcare systems can optimize treatment outcomes, minimize financial burden, and promote long-term adherence on a broader scale.

Particular importance of adherence to endocrine therapy in developing countries

The widespread issue of suboptimal medication adherence among breast cancer survivors in high-income countries and its severe medical and financial consequences suggests an even greater concern in developing nations. Globally, the burden of breast cancer is rapidly increasing, with millions of new cases being diagnosed every year as well as enormous numbers of deaths that combine with massive costs. Notably, cancer-related mortality varies significantly across countries, with higher death rates among women in low- and middle-income countries (LMICs) compared to their counterparts in Western countries.[4] For instance, among African women, only 59% of a population-based cohort survived beyond five years after a breast cancer diagnosis, with survival rates as low as 12% in Uganda and 40% in South Africa.[91] In contrast, the corresponding five-year overall survival rate for female breast cancer patients in the US has now surpassed 90%.[92]

To address the global disparity in breast cancer mortality, the World Health Organization (WHO) recently launched a collaborative initiative that involves multisectoral stakeholders from around the world.[93] The key approaches of the WHO-led Global Breast Cancer Initiative (GBCI) have mainly relied on: a) raising public awareness about breast cancer and the importance of treatment, b) promoting early and accurate diagnosis by healthcare providers, and c) provision of timely and comprehensive cancer management and survivorship care.[93]

Effective breast cancer management with timely and appropriate treatments is a primary determinant of survival outcomes. A large study among women in sub-Saharan Africa revealed that earlier diagnosis combined with multimodal therapeutic interventions (including both surgery and systemic therapy) contributed significantly to survival gains

and could collectively prevent 28% to 37% of breast cancer deaths in this disadvantaged region.[94] Similarly, the prevalent underutilization of breast cancer treatments by minority populations in the US partially explains the ongoing racial disparities in disease mortality across the country.[76,80,82]

Endocrine therapy is a cornerstone of systemic treatment for all women with HR+ breast cancer (75% of all breast cancer cases) in both the curative and palliative care settings.[9,12] In early-stage (nonmetastatic) disease, administration of adjuvant TAM and AIs alone or sequentially for five years has proven effective in improving disease control and reducing cancer mortality.[9,15,23] Despite their well-established survival benefits, maintaining adherence to recommended endocrine therapy remains a persistent medical challenge. While extensive research has thoroughly investigated patient attitudes and experiences with endocrine therapy in developed countries, data on adherence in LMICs-specific populations is limited.

In developing nations, the focus on ensuring access to essential cancer treatments has often given priority over monitoring medication adherence. The WHO has classified many conventional breast cancer treatments, including endocrine therapies, as essential medicines (i.e.; a priority for endorsement by national cancer programs).[95] However, country-specific factors such as cost and feasibility determine the final adoption and accessibility of cancer medications. While TAM has long been widely available in LMICs at little to no cost, access to the newer and more expensive AIs (particularly letrozole and anastrozole) has expanded significantly in recent years.[96–98]

The universal availability of endocrine therapies in developing countries reinforces the need to ensure their safe and appropriate use among vulnerable cancer patients.

Adherence to these effective treatments is crucial for optimizing health benefits and alleviating the intense global burden of breast cancer. Comprehensive data on endocrine therapy usage patterns, experienced side effects, and treatment responses across diverse breast cancer populations would help identify key areas for improving disease outcomes in LMICs.

Unique challenges for appropriate use of cancer medications in developing countries

Managing breast cancer in developing countries has been a persistent challenge for decades. Effective cancer care relies on advanced diagnostic technologies, costly infrastructure, highly trained healthcare professionals, intensive disease monitoring, expensive therapeutic interventions with significant risks, and prompt control of treatment-related toxicities. However, many LMICs face severe resource constraints, including a shortage of basic cancer care services, qualified specialists, essential treatments, and systems for tracking patient health.[5,6] In these challenging settings, healthcare systems struggle to combat a complex disease while also meeting the basic medical needs of their populations. As a result, breast cancer is often diagnosed at late stages, leading to high treatment failure rates and poor survival outcomes in less-developed nations.

In addition to the weak and overwhelmed cancer control programs, several unsafe healthcare practices and patient behaviors further complicate disease management in LMICs. Poor adherence to essential and sometimes life-saving medications is a common and evident issue in many developing nations. For instance, in Africa, where HIV remains a major public health concern, approximately 48% of adults with HIV were not fully adherent to antiretroviral therapy with 27% demonstrating inadequate adherence.[99]

Similarly, across 19 developing countries, the average rate of nonadherence to antihypertensive medications was 47%.[100]

The true extent of medication nonadherence in developing countries might be underestimated due to limited data on representative populations. In many low-income nations, issues related to patient adherence, treatment experiences, and health-related quality of life have traditionally received little attention. However, with the expanded availability of essential therapies in recent years and high rates of nonadherence worldwide, ensuring the appropriate use of medications in LMICs has become increasingly critical. Poor adherence not only exacerbates health risks but also adds substantial costs and complexity to already overwhelmed healthcare systems.

The rational use of therapeutics in developing countries is further complicated by the widespread practice of self-medication. Many prescription treatments, including anticancer drugs, are readily available over the counter, posing significant health risks. This issue is particularly concerning for patients with serious illnesses like cancer, who may lack adequate knowledge about their medications and use them without proper medical supervision or monitoring for potential adverse effects. Additionally, week surveillance systems for tracking medication exposure and outcomes underscore the urgent need for robust regulatory oversight to ensure the safe and appropriate use of anticancer therapies in developing countries.

CHAPTER 3

ADHERENCE, CLINICAL BENEFITS, AND ADVERSE EFFECTS OF ENDOCRINE THERAPIES AMONG WOMEN WITH NONMETASTATIC BREAST CANCER IN DEVELOPING COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS [1]

[1] Elshafie S, Trivedi R, Villa-Zapata LA, Tackett RL, Zaghloul IY, Young HN. Cancer. 2025 Jan 1;131(1): e35550. doi: 10.1002/cncr.35550. Reprinted here with permission of the publisher.

Abstract

Introduction: Despite significant advances in breast cancer control and survival with endocrine therapies (ETs), treatment utilization and outcomes in developing countries have not been adequately explored. This review evaluated ET adherence, potential benefits, and harms in populations across developing countries.

Methods: A literature search was conducted through August 2023 in five databases: PubMed, Cochrane Library, Web of Science, Global Health, and WHO Global Index Medicus. Retrieved records were screened to identify observational research presenting at least one outcome in women with non-metastatic breast cancer in developing countries who received ET (tamoxifen or aromatase inhibitors). A random effects model was used to compute the rates of adherence, discontinuation, adverse events (AEs), disease progression, and death.

Results: A total of 104 studies met the inclusion criteria. Risk of bias was low in most studies, and a large portion of the patients involved Asians. The overall heterogeneity between studies was partially attributed to variations in study design or outcome measurement method. Results showed a pooled adherence rate of 75% (95% CI: 67-81%) and a discontinuation rate of 16% (95% CI: 10-25%). Treatment side effects and young age consistently emerged as significant predictors of non-adherence. A wide range of AEs was identified in our analysis. The estimated average rates of cancer recurrence and mortality at 5-years were 16% and 8%, respectively.

Conclusion: Our findings underscore suboptimal ET use in developing countries and provide comprehensive insights into treatment experiences in the real-world setting.

Targeted strategies are warranted to enhance adherence and subsequently–optimize treatment benefits.

Introduction

The intuitive quote, “Drugs don't work in patients who don't take them” by C. Everett Koop reflects the complementary role of patients in the success of treatment strategies. Besides the medical importance of appropriate medication use, patient non-adherence to therapies has financial implications which are particularly severe in the field of oncology due to the life-threatening nature of cancer. Non-adherence to recommended medication regimens can undermine treatment benefits leading to cancer progression and costs that surpass those of many other diseases.[47] As the trend shifts from injectable anti-cancer agents in supervised settings to self-administered oral medications taken over prolonged periods,[24] ensuring patient adherence and maintaining medication safety have become pivotal aspects of managing cancer and supporting survivorship.

Breast cancer is the most prevalent type of cancer among women worldwide, yet its burden has varied significantly across regions with higher mortality rates observed in less-developed countries compared to western countries.[4] For example, only 59% of African women in a population-based cohort remained alive five years after breast cancer diagnosis.[91] Conversely, the five-year overall survival rate for female patients in the United States (US) has recently exceeded 90%.[101] This discrepancy in mortality is mainly attributed to unique and evolving challenges in developing countries, such as shortage of cancer care resources, limited access to essential medications, and inadequate systems for monitoring patients’ health.[5,6] As a result of these constraints, cancer programs are often weak and overwhelmed, and survival outcomes are jeopardized.

Timely access to comprehensive cancer therapies and their proper use are crucial for reducing the disease burden and improving patient outcomes. A large study among

women in sub-Saharan Africa showed that early cancer diagnosis and a multimodal treatment approach (involving surgery and systemic therapy) could prevent 28% to 37% of breast cancer deaths in this underserved region.[94] Furthermore, consistent adherence to breast cancer treatment protocols can narrow or even eliminate the gap in disease mortality between minorities and White American women.[76,80]

Endocrine therapies (ETs) serve a fundamental role in the systemic treatment of hormone-dependent breast tumors which account for the majority of breast cancer cases.[9] The World Health Organization (WHO) recognized ETs as a priority for integration in national medicines list, especially those indicated for curative purposes, including tamoxifen (TAM) and aromatase inhibitors (AIs).[95] While TAM has been widely available in developing countries, access to most AIs has expanded only in recent years.[96] In the early stages of breast cancer, administration of ET agents for at least 5 years following breast surgery has significantly improved disease control and decreased disease mortality.[9,15]

Despite the proven survival benefits of ETs, patterns of delayed treatment initiation, poor adherence, and early discontinuation are common and of significant magnitude.[102–104] For example, Hershman and colleagues reported non-adherence and discontinuation rates of over 50% and an associated increase in the risk of death within a cohort of US women with breast cancer.[104,105] Although extensive research has investigated non-adherence to ETs and related factors, the focus has predominantly been on affluent nations. Advanced healthcare systems in these countries implement patient-centered care with vigilance toward adherence and symptom distress to enhance the efficiency and quality of medical

services.[50–52] In contrast, medication use and safety in developing countries has received relatively less attention amid other unmet needs and competing priorities.

With concerns regarding adherence to ETs in developed countries and ET favorable effects on cancer treatment and survivor, the current study illuminates treatment use and outcomes among vulnerable cancer patients in developing countries settings where risks of unsafe and improper use of medications are evident.[53] This systematic review and meta-analysis evaluated ET utilization, side effects, treatment responses, and related factors among women with non-metastatic breast cancer in these regions.

Methods

Overview

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines;[106] a rigorous approach to systematically reviewing the use, complaints, and experiences with ETs in women with non-metastatic breast cancer in developing countries. The 2023 United Nations classification of countries by development status was used to identify eligible nations.[107] This classification was based on country basic economic condition and limited the 'developed countries' category to Australia, Canada, European countries (majority), Japan, New Zealand, and the US. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42023490977).

Search Strategy

A comprehensive literature search was executed through August 2023 across PubMed, Cochrane Library, Web of Science, Global Health (EBSCO), and WHO Global Index Medicus. The search string (Appendix A) was constructed by combining relevant

MeSH terms and cross-checked by an experienced librarian. Two researchers independently conducted the search without imposing restrictions on language, publication date or type and avoided using automation tools to preserve selection process integrity. Records from each database were compiled and managed in Zotero software. After the elimination of duplicate entries, each article was manually checked for eligibility against predefined criteria.

Inclusion and exclusion criteria

The full search results were screened to identify peer-reviewed observational research that provided original data on women with non-metastatic breast cancer in developing countries who received ET regimens (including TAM, anastrozole, letrozole, or exemestane). Non-metastatic condition was defined as stages 0-III at diagnosis, explicitly stated as non-metastatic or operable, or patients' receipt of ET post-curative breast surgery. All studies were required to report at least one of the following outcomes: medication use (initiation, adherence, discontinuation), treatment-related adverse events (AEs), and either disease-free or overall survival over time.

Excluded articles were clinical trials, studies that included men or patients with metastatic disease, and studies that assessed outcomes for all disease stages or across an entire world region without stratifying by cancer stage or country development. Non-empirical sources, including case reports, case series, reviews, commentaries, editorials, and conference abstracts were also excluded.

Data extraction

Two researchers independently screened the abstracts and full texts of retrieved studies to determine their eligibility and utilized professional translation services for non-

English articles. Upon reaching a consensus on the articles that met the inclusion criteria, both reviewers independently extracted data from each study while being blinded to each other's findings to minimize bias. Key characteristics and outcome measures were thoroughly documented and compared. Discrepancies were resolved through discussion or consultation with a third senior researcher. Data were systematically recorded in Microsoft Excel spreadsheets and subsequently analyzed with statistical software.

The data extraction covered key variables such as the first author's name, publication year, study design and location, enrollment period, cancer stage, the specific ET and its duration, prior treatment (surgery, radiation, chemotherapy), menopausal status, mean age, and number of patients. Outcome data were organized into three categories: usage, safety, and effectiveness. For ET use, details on usage phases, definitions and measurement methods, the number of patients who adhered to or discontinued ET early, and significant predictors of non-adherence were collected. Information related to safety and effectiveness involved AEs reported at least three times, AE data sources, proportions of women who experienced each event, and recurrence or death rates, along with factors significantly associated with these events.

Quality assessment

The Joanna Briggs Institute (JBI) critical appraisal checklists were used to assess the methodological quality of the included studies. These tools are widely recognized for their versatility in evaluating observational studies and address participants' selection, study setting, measurement of exposure and outcome, and statistical analysis.[108,109]

Two researchers performed the quality appraisal to minimize performance bias. Each checklist item was scored as 'yes', 'no' or 'unclear' based on whether the study

adequately fulfilled each domain. Items not relevant to most studies were omitted to maintain the checklists' applicability. At the individual study level, overall quality was rated as 'good', 'fair', or 'poor' indicating low, moderate, or high risk of bias that was determined by the number of criteria met: more than 6, between 5 and 6, or less than 5, respectively.

Data synthesis plan

Summary estimates were calculated with a random effects model to account for variance within and across studies. In this model, outcomes from eligible studies were pooled and analyzed as proportions of women who adhered to ET, discontinued treatment, experienced specific AEs, progressed in disease, or died from any cause, along with the corresponding 95% confidence intervals (CIs) (implying significance at a p-value ≤ 0.05). Findings were illustrated through forest plots to facilitate interpretation. Raw proportions and statistical transformations (logit, log, arcsine, and double arcsine) were applied to compute the overall effect metric, but results were reported solely from the method that generated the most stable variance.

The I^2 statistic was used to measure between-study heterogeneity and was classified as low (<35%), moderate (35%-70%), and high (>70%). However, it is important to acknowledge that the I^2 test may produce exaggerated values in meta-analyses of proportions warranting cautious interpretation.[110] To address data inconsistencies, prediction intervals that can accurately estimate the range of expected outcome were calculated.[111] In addition, influence and subgroup analyses were performed to elucidate key contributors to heterogeneity; considering variables such as study design, country income level or region, ET type, and outcome assessment methods. Publication bias was

qualitatively assessed rather than relying on conventional tests which demonstrated a limited utility for non-comparative studies.[110] All statistical analyses were carried out in R software version 4.3.2 utilizing the 'meta' package.

Results

Study selection

The literature search across five databases yielded 4,146 records. After removing duplicates and screening titles and abstracts, 272 articles were deemed potential candidates and underwent full-text review. Ultimately, 104 studies satisfied the inclusion criteria, and the remaining 168 reports were mainly excluded due to insufficient information on metastasis status, inclusion of patients in advanced cancer stages, or absence of relevant data. The search and selection process are visually depicted in the PRISMA flow diagram (Figure 1.1).

Characteristics of adherence studies

Table 1.1 summarizes data from 32 studies reporting a quantitative aspect of ET use: treatment initiation, daily adherence, and persistence over time.[112–143] The studies were predominantly conducted in middle-income countries, with fewer records from low-income nations. The Western Pacific region, as defined by the WHO, was the largest contributor to adherence research in developing countries. These observational studies were primarily cohort-based (n=23) or cross-sectional (n=9).

All participating women were diagnosed with non-metastatic breast cancer at stages 0 to III or had undergone curative breast surgery as a primary intervention. The patients' average age was 55 with a range from 36 to 77 years, indicating considerable variability in menopausal status upon study entry. Treatment regimens included TAM, AIs or both in

sequence. However, the duration of treatment and additional therapeutic modalities (e.g., radiotherapy, chemotherapy) were infrequently reported.

Patient adherence to ETs was primarily measured through pharmacy refill records, self-reporting, or both techniques. Only one study used a direct method (plasma medication concentration level) to assess adherence. The timeframes for adherence evaluation varied substantially from one month to five years. Discrepancies were also present across studies in the definition of adherence; however, a common threshold for adequate adherence was having 80% or more prescription coverage. Premature discontinuation was generally defined as treatment cessation before five years for reasons other than recurrence, metastasis, or death, with different durations of interruption specified.

Usage rate and correlates

The meta-analysis revealed a pooled adherence rate of 75% with a range between 67% and 81% ($I^2 = 99\%$), indicating an average non-adherence rate of 25%. The prediction interval (29 to 96%) suggested that future rates of non-adherence in similar cohorts could potentially exceed 70%. No significant differences were found in adherence rates based on country income level, region, study design, or ET regimen (all p-values > 0.05). However, the adherence measurement method (pharmacy refill data, patient reports, or both, medication level) significantly affected the summary rate (p-value < 0.0001). The lowest rate (44%) was observed when adherence was assessed directly by plasma concentration level while pooled adherence rates of 74% and 79% were observed with self-reporting and pharmacy record measures, respectively. In addition, 16% of women discontinued treatment early (95% CI: 10-25%, $I^2 = 99\%$). Figure 1.2 and Supplementary-Figure A (Appendix B) present rates for each outcome.

Several factors were recognized to significantly impact adherence to and persistence with ETs among developing countries population, including patient characteristics (age, employment status, residence, comorbid conditions (e.g., hypertension and HIV)), treatment elements (AEs, ET type and duration), and cancer correlates (tumor and nodal stage, type of breast surgery, receipt of radiotherapy or chemotherapy). Specific reasons and factors that were identified in each individual study are listed in Table 1.2. Notably, treatment-attributable side effects and younger age at diagnosis were the most frequently cited predictors of poor adherence and early discontinuation.

Assessment of adverse events

Twenty-two complications of ETs were consistently reported across 56 studies [120,121,124,126,129,131,133,134,137,139,141,144–187] with a single record from a low-income population.[188] The studies utilized cohort (n=42), cross-sectional (n=12), and case-control (n=2) designs. Sample sizes ranged from fewer than one hundred to over 47000, and the mean ages of women fell between 36 and 63 years. Tumors were either in situ or invasive without metastasis. Over 92% of the patients underwent surgical operations as the initial treatment for cancer. However, the receipt of chemotherapy in the neoadjuvant or adjuvant settings varied significantly between cohorts with percentages ranging from 0 to 100%.

Adverse effects of ETs involved musculoskeletal, gynecological, metabolic, psychological, cardiovascular, and ocular disorders which extended from mild to serious issues, such as secondary malignancies and fatal cardiac events. Safety data majorly came from medical records, claims databases, and patient reports, with few studies utilizing clinical examination and diagnostics in their data collection. Specific classes of side effects were associated with the type of ET received and patient's age at cancer diagnosis. Several

risk factors for AEs included previous chemotherapy, ovarian function suppression, transition into menopause and its duration, as well as elevated body fat or weight. Table 1.3 lists the specific risk factors that were associated with each event and summarizes the main pooled rates of ET safety outcomes.

In the analyses of AEs, I^2 values often exceeded 80%, and prediction intervals for estimates tended to be imprecise and unreliable primarily due to the small number of studies per event or the heterogeneity parameter. Notably, two studies with significant methodological concerns were identified as consistent outliers in influence analyses and excluded from meta-analyses where indicated.[141,148]

The most frequently reported AE was joint, muscle, or bone pain with a higher summary estimate found in cross-sectional studies (64%) than cohort studies (28%). Patients treated with AIs primarily experienced musculoskeletal discomfort at an overall rate of 60% compared with 36% for those treated with TAM. Patients on AIs exhibited about doubled risk of developing osteoporosis (15% versus 8%) and over six times the risk of bone fractures (4% versus 0.6%) compared to TAM users. Notably, the rates for both conditions were based exclusively on studies in Asian populations.

Hot flashes were the second most referenced side effect. The occurrence of hot flashes varied significantly by study design: approximately 75% of women in cross-sectional studies reported these symptoms while 12% of participants in cohort studies were noted during follow-up. When comparing ET types, TAM users generally experienced hot flashes more frequently than those on AIs.

Various gynecological problems have been typically attributed to TAM use. Uterine cancer, a serious but rare AE, occurred at a rate of 0.4% with a range from 0.3 to

0.7%. An abnormal thickening of the uterus was observed in 5% of TAM recipients (95% CI: 2-9%). Some women experienced lower-grade genital symptoms, including vaginal dryness, ovarian cysts, and, to lesser extent, vaginal bleeding. In addition, TAM administration following chemotherapy influenced the rate of chemotherapy-related amenorrhea in premenopausal women.

Our analysis of studies on metabolic dysfunctions associated with ETs revealed that 31% (95% CI: 22-41%) of patients (mainly on TAM) developed fatty liver disease. These therapies also tended to impact body fat leading to weight gain and altered lipid profiles. Sleep disturbances were observed in nearly half of women undergoing ET, while over 80% suffered from fatigue. Other complaints included headaches and, less commonly, nausea. Mood disorders, such as depression and anxiety were evident during treatment and affected more than one-third of the patients. Few studies showed the association of TAM with cataract formation resulting in an average incidence rate of 1% (95% CI: 0.1 to 17%).

Exposure to ETs has been related to cardiovascular complications, such as myocardial infarction, heart failure, and stroke, especially among Asian women. In this group, the overall prevalence of cardiac complaints was 58%, and incidence rate of major events was 6% (95% CI: 4-8%). Arterial or venous thromboses were primarily noted in TAM users with a combined incidence of 1% (95% CI: 0.8-2%). Forest plots in Supplementary-Figure B (Appendix B) display the pooled rates of selected safety outcomes.

Cancer recurrence and overall survival

Fifty observational studies investigated disease progression, mortality, or both among women with breast cancer who were undergoing ETs in developing countries.[116,119–121,123,127,129,132,135,137,138,140,141,144,145,148,149,151,153,156,163,175,188–215] The included studies

spanned numerous countries with a major portion of the patient population originating from the Western Pacific region. Women from low-income countries were notably underrepresented. The primary research design used was the longitudinal cohort. Patients received diverse treatments and had a mean age range of 42 to 64 years, except for one study that was limited to older women who averaged 77 years old.

The overall rate of any cancer recurrence during ET was 11% (95% CI: 8-15%), and the predicted values for new events was between 1% and 52%. No individual study significantly skewed the summary estimate, and subgroup analysis by treatment regimen revealed no significant differences (p-value = 0.067). However, the risk of relapse changed substantially over time (p-value < 0.0001) with recurrence rates of 4% after 3 years and rising to 16% through the 4th and 5th years of follow-up and averaging 10% through 12 years of follow-up. The detailed recurrence rates at specific time points are displayed in forest plots in Figure 1.3 (a-b) and Supplementary-Figure C (Appendix B).

The pooled mortality rate was 7% (95% CI: 5-10%), indicating that 7 out of every 100 women with breast cancer died from any cause during ET. The frequency of deaths did not vary significantly due to studies heterogeneity or between different treatment regimens with a p-value of 0.652. The risk of death increased slightly over time; the observed average mortality rates at 3-, 4-, and 5-years were 5%, 7%, and 8% respectively and reached 7% over 6 to 15 years of follow-up (Figure 1.4 (a-b) and Supplementary-Figure D Appendix B). All meta-analyses of effectiveness outcomes demonstrated I^2 values of over 80%.

Multiple factors were consistently associated with poor clinical outcomes in the current breast cancer cohort (Table 1.4). Age at diagnosis emerged as a strong independent

correlate to recurrence or mortality, yet the specific age groups at risk varied across studies. Other adverse prognostic indicators included not receiving ET (especially TAM), interruptions or discontinuations in treatment, lymph node involvement, high levels of Ki-67 biomarker, advanced disease stage, large tumor size, certain biological subtypes of breast cancer, type of breast surgery performed, and the CYP2D6 genotype in TAM users.

Evaluation of risk of bias

The quality assessment results based on the JBI tools are shown in Supplementary-Figure E (Appendix C). Out of 104 observational studies reviewed, over 75% were considered to apply good methodologies per appraisal criteria. However, 22 studies received a fair quality rating, and 2 were deemed of poor quality. The low ratings of domains originated mainly from concerns about the validity and reliability of outcome measurement methods, the ascertainment of treatment exposure, and the management of confounding factors. For cohort studies, additional potential sources of bias included incomplete follow-up, inadequate explanations for loss to follow-up, pre-existence of outcomes at baseline, and unreported follow-up durations.

Discussion

This study is the first to meta-analyze data related to adherence status, experiences of AEs, and the likelihood of cancer recurrence and survival during ET in developing nations. Based on heterogenous data with a low risk of bias, our systematically synthesized evidence indicates a prevalence of low rates of adherence to ETs among women with breast cancer in developing countries. Treatment side effects were consistently found to contribute to this issue and pose significant challenges ranging from mild impairments in women's quality of life to serious toxicities that can lead to hospitalization or death.

Furthermore, mortality rates were generally low in women treated with ET and adherence to treatment dosage and duration was correlated with a better disease prognosis.

Published records on treatment outcomes from low-income countries were notably scarce, while a large portion of the patient population consisted of Asian women from the Western pacific region. Each ET regimen presented unique AEs, yet they exhibited comparable levels of effectiveness and shared similar risks of treatment interruption. Overall, a high degree of heterogeneity was observed between studies; however, this is a common scenario in meta-analysis of single proportions.[110] Notably, some of the heterogeneity could be attributed to variations in study design or outcome assessment method.

Our observations of prevalent non-adherence practices to ETs align with the findings of a recent review focused on African women and a systematic review of 26 studies predominantly from developed countries.[102,216] However, observed value of adherence (75%) is much higher than expected with reported levels reaching 65% or less than 50% in developed nations.[103,104] Our estimated prediction interval suggests that adherence rates among patients in developing countries may potentially drop to 29%. One reason for this variability may be that the included studies largely relied on indirect methods for assessing adherence (such as pharmacy refill data and self-reporting) which usually provide less accurate and higher estimates of patients' adherence levels.[217] Breast cancer patients' use of ETs represents a multidimensional and complex phenomenon, particularly with the lack of a standardized threshold and method for measuring adherence. Self-reports are commonly recognized to overestimate adherence rates, and objective

indices based on dispensed prescriptions may not necessarily reflect the patient's actual consumption of the medication.[218]

Young age has been consistently identified as a risk factor for poor adherence to ETs. In a follow-up survey evaluating ET usage at 2 years within a sample of US women with breast cancer, the lowest levels of adherence were reported among the youngest respondents (below 45 years).[219] Conversely, older women (50 to 69 age group) from a large cohort of approximately 50,000 American breast cancer patients were more likely to fill and adhere to endocrine prescriptions over 5 years.[103] Low adherence rates among young women have been mainly driven by childbearing and fertility concerns.[220] In addition to age, intolerance of ETs has been a reliable predictor for both non-adherence and premature discontinuation, a consistent finding across more affluent nations.[221–224] In the US, a disproportionate burden of treatment side effects among African Americans has been identified as a remarkable contributor to the nationwide racial disparity in adherence to ETs.[76,80,225,226]

The safety of medications in less privileged context is a clinically salient area yet remains understudied. Identifying AEs associated with oral anti-cancer treatments is challenging and often complicated by the systemic effects of the cumulative doses of lengthy therapy as well as the pathophysiology of the underlying disease. Without sufficient data from representative populations, an accurate estimation of the risk of treatment harms is difficult. Close monitoring, early detection, and timely management of bothersome symptoms can alleviate patient distress, promote medication adherence, and ultimately achieve the full benefits of treatment. Studies have shown that a longer duration

of ET administration is possible when pharmaceuticals or supplements are used to mitigate side effects.[227,228]

Minimizing obstacles for ET utilization can significantly improve the survival rates of breast cancer patients and reduce avoidable costs given their documented cost-effectiveness even in basic healthcare systems.[229,230] A previous systematic review of 12 cohort studies highlighted a significant relationship between non-adherence to ETs and increased risks of disease recurrence, metastasis, and mortality outcomes.[23] In a large randomized trial, more than half of the trial participants did not complete their assigned 5 years of ETs due to side effects.[69] Women who were less adherent or who discontinued treatment early demonstrated inferior cancer-free survival rates.[69] Values of non-adherence and its detrimental clinical implications might be much worse in routine practice compared to trial settings.

The current study boasts several strengths, including adherence to the rigorous PRISMA guidelines. It stands as the first to offer comprehensive and detailed insights into multiple clinical aspects of ETs in women from developing countries, who are routinely underrepresented in medical literature. The study's large scale and the patient population diversity enhance the reliability and generalizability of the findings. Focusing exclusively on non-metastatic female patients minimizes the potential for biased or inflated outcome measures, given the aggressive and incurable nature of metastatic cancer stages. Additionally, a key strength is the emphasis on data derived from real-world conditions; observational studies provide a more accurate reflection of patient experiences, treatment challenges, and the genuine effectiveness of medications.

Despite its strengths, limitations of this study include the absence of a comparison group of individuals who did not use ET. Nevertheless, it still portrays patterns and trends from the existing literature to facilitate a better understanding of the usage, benefits and potential harms associated with these crucial medications. While the included studies spanned various regions, the predominance of Asian patients makes it challenging to draw definitive conclusions about certain outcomes in other parts of the world. Additionally, methodological differences in adherence measures across studies present another inherent challenge in this area of research. Some critical confounding variables, such as the administration of chemotherapy and treatment duration were infrequently reported limiting our ability to adjust for their potential effects.

Conclusion

In summary, this research underscores the problem of suboptimal adherence to and persistence with ET among women with non-metastatic breast cancer in developing countries and addresses significant knowledge gaps concerning the adverse effects experienced by patients in these settings. Future strategies to enhance ET adherence should focus on vulnerable groups and tackle modifiable deterrents, particularly treatment side effects, while carefully considering the feasibility and appropriateness of these approaches at the country level. Implementation of effective interventions and health policy measures that improve ET use is crucial in supporting breast cancer care and survivorship in developing countries.

Table 1.1: Summary of Key Characteristics of Studies on Endocrine Therapy Use

Study	Country	Study design	Patients [a]	Medication Use	Outcome definition	Measurement method
Nardin JM[112] (2020)	Brazil	Cohort	HR+ BC women (stage 0-II) receiving TAM	Adherence	High adherence: 'no' responses of all 4 questions of MMAS at 12 months	Self-reported
Cruz A[113] (2017)	Brazil	Cross-sectional	HR+ BC women (stage I-III) receiving TAM	Adherence	Fully adherent: 'no' responses of all 4 questions of MMAS	Self-reported
Brito C[114] (2014)	Brazil	Cohort	Women with curable BC (stage 0-II) receiving TAM or AI	Adherence	Adherent: MPR ≥ 80% over a median follow-up of about 3 years	Hospital databases & cancer register
Brito C[115] (2014)	Brazil	Cohort	Women with curable BC (stage 0-II) receiving TAM or AI	Discontinuation	Non-persistence: discontinuation of recommended ET for ≥ 60 days within 5 years	Hospital databases & cancer register
Tong Y[116] (2022)	China	Cohort	Women with HR+ invasive non-metastatic BC receiving AI	Adherence	Non-adherent: received treatment inconsistent with recommendations or spontaneously stopped treatment regardless of physician recommendation over a median follow-up of 50 months	Prescription records
Xu H[117] (2020)	China	Cross-sectional	Women with HR+ non-metastatic BC receiving TAM or AI	Adherence	High adherence: 'no' responses of all 4 questions of MMAS	Self-reported

				Discontinuation	no longer using ET & duration of use was < 5 years	
Gao P[118] (2018)	China	Cohort	Women with HR+ non-metastatic BC receiving TAM or AI	Discontinuation	Non-persistence: discontinuation of ET before 5 years without recurrence, metastasis or death	Self-reported
Xing P[119] (2017)	China	Cohort	Women with HR+ BC (stage I-III) who received TAM or AI	Initiation	Adherent: initiated ET	Self-reported
				Discontinuation	Non-persistence: cessation of ET within 5 years	
Gu R[120] (2012)	China	Cohort	Premenopausal women with HR+ BC (stage I-III) who received TAM for at least 1 year	Discontinuation	Stopped treatment within 5 years	Cancer registry
Quintero-Ortiz MA[121] (2022)	Colombia	Cohort	Women with HR+ BC (stage I-III) receiving TAM or AI	Discontinuation	Stopped ET within a median follow-up of 4 years	Institute database & EMRs
Zeeneldin AA[122] (2012)	Egypt	Cross-sectional	Pre & postmenopausal women with HR+ non-metastatic BC who received TAM or AI for at least 2 months	Adherence	Adherent: number of days receiving medications/total days ≥ 80% during Ramadan (lunar month)	Self-reported
Sella T[123] (2020)	Israel	Cohort	Women with HR+ non-metastatic BC receiving TAM or AI	Adherence	Adherent: PDC ≥ 80% over 5 years of follow-up	Health insurance claims database

				Discontinuation	Refill gap ≥ 6 months within 5 years	
Geffen DB[124] (2013)	Israel	Cohort	Mainly postmenopausal women with HR+ BC (stage I) who switched from TAM to AI	Discontinuation	Premature discontinuation of AI before the planned completion time	EMRs
Martinez-Cannon BA[125] (2021)	Mexico	Cross-sectional	BC women (stage 0-II) receiving TAM	Adherence	Adherent: taking medication regularly	Self-reported
					Adherent: MPR ≥ 80%	Dispensing data
Villarreal-Garza C[126] (2021)	Mexico	Cross-sectional	Premenopausal women with HR+ BC (stage 0-III) who received TAM or AI for 1-5 years	Adherence	Complete adherence: taking medication 100% of days during the last month	Self-reported
				Discontinuation	Treatment interruption for ≥ 2 consecutive months	
Khobrani A[127] (2022)	Saudi Arabia	Cohort	Pre & postmenopausal women with HR+ BC (stage I-III) receiving TAM or AI	Adherence	Adherent: PDC ≥ 0.8	Cancer registry & medical records
Elsamany SA[128] (2022)	Saudi Arabia	Cross-sectional	Pre & postmenopausal women with HR+ early BC who received TAM or AI for at least 2 years	Adherence	Adherent: taking ≥ 80% of prescribed doses of ET (no interruption, no missing pills on separate days or interruption < 1 week/month in total)	Self-reported

Tan EY[129] (2022)	Singapore	Cohort	Postmenopausal women with HR+ BC (stage I-III) receiving TAM or AI	Discontinuation	Premature discontinuation of ET before completing 5 years of treatment	——
Ali EE[130] (2017)	Singapore	Cross-sectional	BC women (stage 0-III) who received TAM or AI for at least 6 months	Adherence	High adherence: 'no' responses of all 4 questions of MMAS	Self-reported
					Adherent: no refill gap from the start to the most recent prescription received	Dispensing records
Ayeni OA[131] (2023)	South Africa	Cohort	Women with HR+ BC (stage I-III) who received TAM for at least 3 months	Adherence	Adherent: plasma TAM level ≥ 60 ng/mL after 3 months of daily TAM use and was measured after a median of 13 months since TAM initiation	Blood concentration level
Wasserman LJ[132] (2007)	South Africa	Cohort	Elderly (70+ years old) women with BC (stage 0-III) receiving TAM	Adherence	Compliance with TAM use was undefined but was evaluated over a mean follow-up of 62 months	Cancer database
Lee Y[133] (2019)	South Korea	Cohort	Women with HR+ BC who received TAM or AI for at least 1 year	Adherence	Non-adherent: medication coverage index < 3 years	Health insurance claims database
Yi M[134] (2018)	South Korea	Cross-sectional	Mainly postmenopausal women with non-metastatic BC who received TAM or AI for > 3 months	Adherence	Adherent: no experience of noncompliance to medication	Self-reported

Foerster M[135] (2022)	sub-Saharan African countries (Namibia, Nigeria, Uganda, South Africa & Zambia)	Cohort	Women with invasive non-metastatic BC who received TAM or AI	Initiation	Adherent: initiated ET after being indicated due to HR+ or unknown HR status over a median follow-up of 5 years	Medical records & self-reported
				Discontinuation	Treatment abandonment before 3 years	
Chan PW[136] (2021)	Taiwan	Cohort	Women with HR+ BC who underwent primary surgical operations and received TAM or AI	Adherence	Adherent: MPR ≥ 80% in the 1st year	Health insurance claims database
Chu SC[137] (2020)	Taiwan	Cohort	Women with non-metastatic BC who received TAM for at least 6 months	Adherence	Adherent: cDDD over period of follow-up ≥ 50% within 5 years	Health insurance claims database
Hsieh CJ[138] (2017)	Taiwan	Cohort	Women with non-metastatic BC receiving TAM	Adherence	Adherent: cDDD over period of follow-up ≥ 50% within a median follow-up of 4 years	Health insurance claims database
Hsieh KP[139] (2015)	Taiwan	Cohort	Women with non-metastatic BC who received TAM or AI for at least 29 days	Adherence	Adherent: MPR ≥ 80% over a median follow-up of 4 years	Health insurance claims database
Hsieh KP[140] (2014)	Taiwan	Cohort	BC women who underwent primary surgical operations and received TAM or AI for at least 12 months	Discontinuation	Non-persistence: refill gap > 180 days within a median follow-up of 5 years	Health insurance claims database

Uskent N[141] (2011)	Turkey	Cohort	Postmenopausal women with HR+ early BC (stage I or II) receiving AI (ANA)	Adherence	Adherent: very good treatment compliance over a median follow-up of 12 months	Self-reported
Camejo N[142] (2023)	Uruguay	Cross-sectional	Women with HR+ early BC (stage 0-III) receiving TAM or AI	Adherence	Adherent: MPR ≥ 0.8 within 2 years from the start of ET & correct MMAS responses	Pharmacy records & self-reported
Camejo-Martínez N[143] (2019)	Uruguay	Cohort	Mainly postmenopausal women with HR+ BC (stage 0-III) who received TAM, AI or both for 5 years	Adherence	Adherent: patient's willingness to take prescribed ET at the recommended dose and interval over 5 years	Medical records

[a] Patients listed are either the entire study cohort or a subset of it that met eligibility criteria

Abbreviations: AI (aromatase inhibitor), ANA (anastrozole), BC (breast cancer), cDDD (cumulative defined daily dose), EMRs (electronic medical records), ET (endocrine therapy), HR+ (hormone receptor-positive), MMAS (Morisky Medication Adherence Scale), MPR (medication possession ratio), PDC (proportion of days covered), TAM (tamoxifen)

Table 1.2: Risk Factors for Suboptimal Use (Non-Adherence or Discontinuation) of Endocrine Therapies

Study	Country	Identified factors
Nardin JM (2020)[112]	Brazil	* Younger age * Premenopausal status * Reporting adverse events
Cruz A (2017)[113]	Brazil	* Forgetfulness related reasons
Brito C (2014)[114,115]	Brazil	* More advanced disease stage (III and IV)
Xu H (2020)[117]	China	* Type of ET * Longer duration of ET * Side effects * Older age
Gao P (2018)[118]	China	* Adverse effects
Xing P (2017)[119]	China	* Older age (≥ 65) * Residence in suburban or rural areas * Advanced tumor or nodal stage * Not taking radiotherapy or chemotherapy * Type of ET
Gu R (2012)[120]	China	* Side effect related reasons
Quintero-Ortiz MA (2022)[121]	Colombia	* Health insurance related reasons * Adverse event related reasons
Sella T (2020)[123]	Israel	* Younger age (≤ 45) * Low body mass index (BMI) * Absence of comorbid hypertension
Geffen DB (2013)[124]	Israel	* Treatment-related toxicity (moderate to severe myalgias or arthralgias)
Villarreal-Garza C (2021)[126]	Mexico	* Being an employee or student * Having concerns about long-term ET use mainly due to fear of experiencing harmful effects * Experiencing >7 types of side effects
Elsamany SA (2022)[128]	Saudi Arabia	* Job status * Marital status * Residence location * Nodal stage
Tan EY (2022)[129]	Singapore	* Adverse effect related reasons

Ali EE (2017)[130]	Singapore	* Absence of comorbidities
Ayeni OA (2023)[131]	South Africa	* Positive HIV status
Yi M (2018)[134]	South Korea	* Rate of side effects (feeling increased pain after ET)
Foerster M (2022)[135]	sub-Saharan Africa	* Country of origin (Namibia, Nigeria, South Africa, Uganda or Zambia)
Hsieh KP (2015)[139]	Taiwan	* Younger age (< 50) * Type of breast surgery * Type of ET (TAM only) * Taking adjuvant chemotherapy
Hsieh KP (2014)[140]	Taiwan	* Younger age (< 50) * Type of breast surgery * Type of ET (AIs only or switching between ETs) * Taking adjuvant chemotherapy
Camejo N (2023)[142]	Uruguay	* Younger age * Being employed or self-employed while treated with AIs
Camejo-Martínez N (2019)[143]	Uruguay	* Type of ET * Adverse event related reasons

Abbreviations: ET (endocrine therapy), TAM (tamoxifen), AIs: (aromatase inhibitors)

Table 1.3: Key Findings and Risk Factors for Adverse Events Related to Endocrine Therapies

Adverse event	Rate [a] (95% CI)	Associated risk factors
Musculoskeletal disorders		
Musculoskeletal pain	By Design Cohort: 28% (14-46%) Cross-sectional: 64% (50-76%) By Regimen TAM alone: 36% (21-55%) AI alone: 60% (44-73%)	* Type of ET [134,154,183] * Age [134,155] * Genetic polymorphism [155,180] * Receiving chemotherapy [164,180] * Progesterone receptor expression [155] * Mode of menopause (Induced) [155] * Shorter duration since transition into menopause [155] * Time point since TAM initiation [164] * Bodily pain [179] * Poor physical well-being [179] * Receiving physiotherapy [179] * Presence of osteoarthritis [179] * Duration after menopause until starting ET [183]
Osteoporosis	By Regimen TAM alone: 8% (1-32%) AI alone: 15% (5-37%)	* Type of ET [166] * Age [166]
Fracture	By Regimen TAM alone: 0.6% (0.4-0.9%) AI alone: 4% (1-17%)	* Type of ET [154,166] * Age [166]
Vasomotor symptoms		
Hot flashes	By Design Cohort: 12% (3-38%) Cross-sectional: 76% (65-84%) By Regimen TAM alone: 43% (25-63%) AI alone: 17% (1-83%)	* Type of ET [126,134] * Age [134,155] * Ovarian function suppression [126] * Time point since TAM initiation [164] * Chemotherapy treatment prior to TAM [184] * Contraceptive therapy use [184]
Gynecological disorders		
Endometrial cancer	0.4% (0.3-0.7%)	* Age [137,163,176] * Using TAM [160]

Endometrial hyperplasia	TAM alone: 5% (2-9%)	* Type of ET [133]
Vaginal dryness	TAM alone: 19% (8-39%)	* Type of ET [126] * Ovarian function suppression [126] * Age [134]
Ovarian cyst	TAM alone: 12% (5-24%)	-
Vaginal bleeding	TAM alone: 4% (2-10%)	* Type of ET [133]
Chemotherapy-induced amenorrhea	TAM alone: 71% (43-89%)	* Age [158,172,173] * Chemotherapy regimen [172] * Using TAM [173]
Metabolic disorders		
Fatty liver	31% (22-41%)	* Triglycerides [149,156,157,168] * Body mass index (BMI) [149,168,169] * Low-density lipoprotein cholesterol [149,156] * High-density lipoprotein cholesterol [157,168] * Total cholesterol [169] * Ovarian function suppression [147] * Lymphatic metastasis [149] * Estrogen receptor positivity [149] * Alanine aminotransferase (ALT) [149] * Alanine aminotransferase (ALT) to aspartate aminotransferase (AST) ratio [168] * Being overweight [156] * High waist circumference [156] * High fasting blood sugar [157] * Using TAM [168] * Age [168]
Weight gain	17% (4-52%)	* Age [170] * Not using AI [170] * Body mass index (BMI) [170] * Chemotherapy with longer duration of TAM use [178]4/13/25 4:32:00 PM
Dyslipidemia	7% (0-60%)	* Postmenopausal status [146] * Age [147] * Ovarian function suppression [147] * Baseline low-density lipoprotein cholesterol [147]
General disorders		
Sleeping problems	48% (17-80%)	* Age [164]

		* Time point since TAM initiation [164]4/13/25 4:32:00 PM
Fatigue	83% (61-93%)	* Age [134] * Menopausal status [182] * Duration of ET [182] * Cancer stage [182] * Diet [182] 4/13/25 4:32:00 PM
Headache	23% (3-72%)	* Chemotherapy treatment prior to TAM [184]
Nausea	3% (1-8%)	-
Mood disorders		
Depression	36% (9-77%)	-
Anxiety	43% (14-77%)	-
Ocular disorders		
Cataract	TAM alone: 1% (0.1-17%)	* Age [161]
Cardiovascular disorders		
Cardiovascular events	By Design Cohort: 6% (4-8%) Cross-sectional: 58% (36-77%)	* Using TAM [174] * Age [175] * Presence of comorbidities [175]4/13/25 4:32:00 PM
Thromboses	TAM alone: 1% (0.8-2%)	-

[a] Values are expressed as pooled rates
Abbreviations: CI (confidence interval), ET (endocrine therapy), TAM (tamoxifen), AI (aromatase inhibitor)

Table 1.4: Risk Factors for Poor Prognosis (Recurrence or Death) during Endocrine Therapy

Study	Country	Identified correlates
Boucenna A (2022)[189]	Algeria	* CYP2D6 phenotype * Low endoxifen plasma level
Brito C (2016)[190]	Brazil	* More advanced disease stage (III and IV)
Ho SC (2021)[194]	China	* Not using TAM
Xing P (2017)[119]	China	* Type of breast surgery * Advanced tumor or nodal stage * Not treated with ET * Discontinuation of ET
Yan M (2017)[149]	China	* Tumor size * Lymphatic metastasis * Ki-67 value * Development of non-alcoholic fatty liver disease
Lei L (2016)[151]	China	* CYP2D6 genotype in patients < 40 years of age
Chow LW (1997)[192]	China	* Not treated with adjuvant TAM
Quintero-Ortiz MA (2022)[121]	Colombia	* Clinical stage * Biological subtype of breast cancer * Tumor size * Lymph node involvement * Discontinuation of adjuvant ET
Elzawahry HM (2013)[193]	Egypt	* Ki-67 value
Hathila TN (2015)[195]	India	* Not treated with TAM (due to HR- status)
Yadav B (2010)[196]	India	* Not treated with TAM * Younger age (< 65)
Raina V (2005)[197]	India	* Lymph node involvement
Taroeno-Hariadi K (2021)[156]	Indonesia	* Not developing non-alcoholic fatty liver disease * Higher histological grade (grade 3)
Choi YJ (2021)[201]	South Korea	* Not using TAM
Ahn SJ (2021)[202]	South Korea	* Older age * Higher body mass index (BMI) * Type of breast surgery * Not treated with ET
Lim ST (2020)[205]	South Korea	* Vitamin D deficiency
Hwang KT (2018)[203]	South Korea	* Not treated with TAM

Ahn SG (2014)[206]	South Korea	* Not treated with zoledronic acid
Park IH (2012)[208]	South Korea	* Nodal status * Ki-67 value * Progesterone receptor negativity * Human epithelial receptor 2 (HER2) positivity
Kim J (2012)[210]	South Korea	* Mammographic density change * Tumor size * Lymph node positivity * Ki-67 value
Ismail Al-Khalil W (2022)[188]	Syria	* CYP2D6 genotype
Tsai CJ (2022)[211]	Taiwan	* Regimen of breast-conserving surgery (BCS) alone
Wu CE (2016)[212]	Taiwan	* Age < 40 or > 65 years * Advanced nodal stage
Hsieh KP (2014)[140]	Taiwan	* Discontinuation of ET * Non-adherence to ET * Older age (≥ 50) * Treatment with chemotherapy or radiotherapy * Charlson Comorbidity Index (CCI) score ≥ 2 * Low income
Aphinives P (2014)[213]	Thailand	* Treatment with ANA alone vs ANA followed by LET
Unal C (2023)[214]	Turkey	* Younger age ≤ 45 * Menopausal status * Higher Oncotype DX recurrence score

Abbreviations: CYP2D6 (cytochrome P450 2D6), TAM (tamoxifen), ET (endocrine therapy), HR- (hormone receptor-negative), ANA (anastrozole), LET (letrozole)

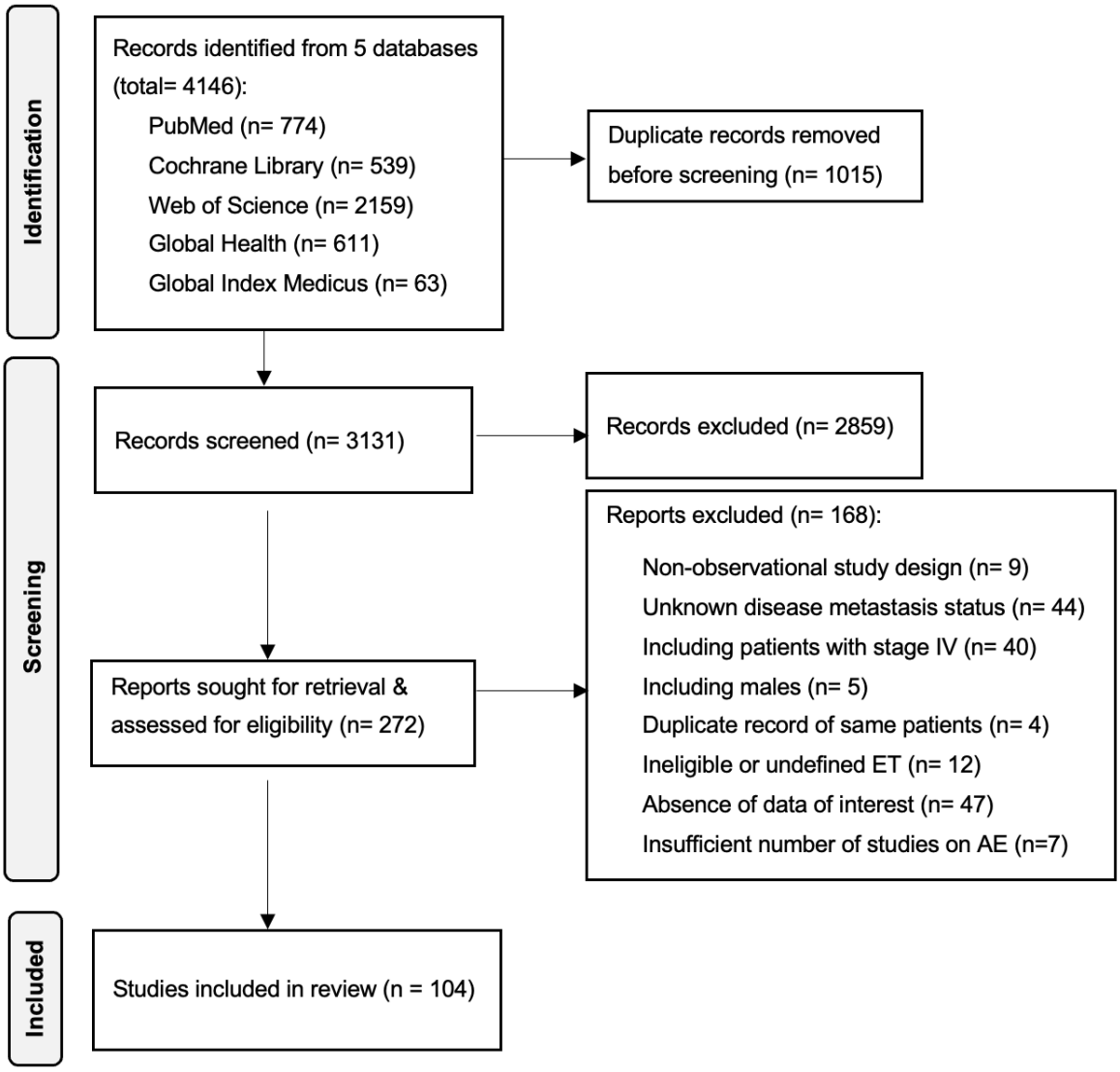


Figure 1.1: PRISMA Flow Diagram of the Literature Search

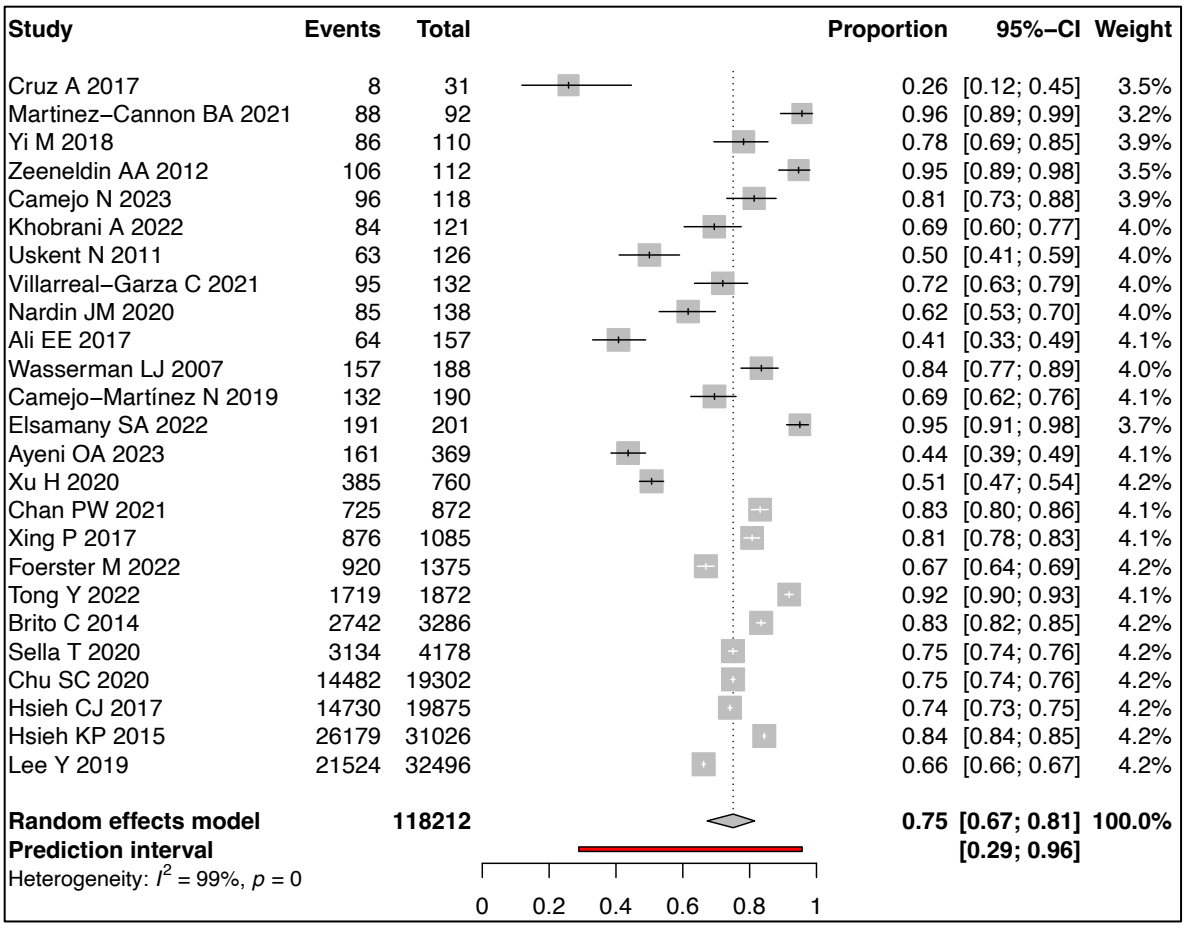


Figure 1.2: Meta-Analysis of Adherence Rates to Endocrine Therapies Among Women in Developing Countries

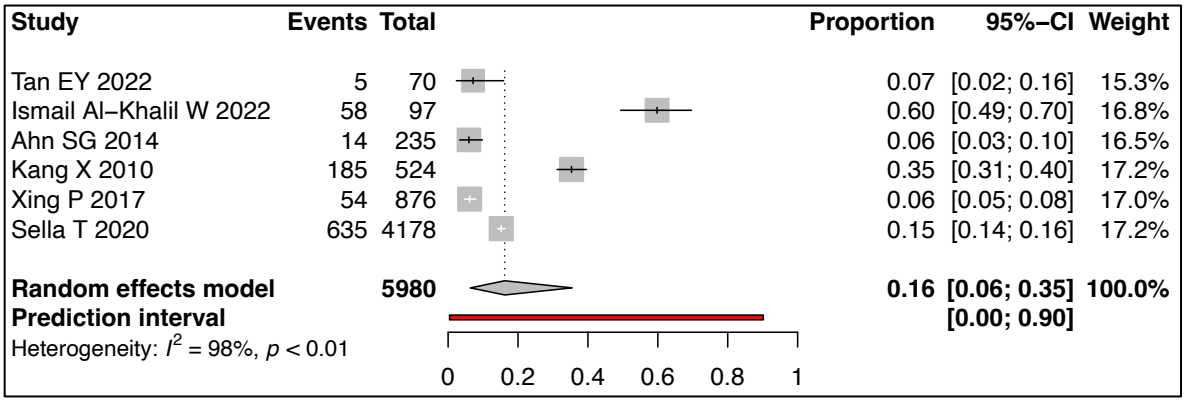


Figure 1.3-a: Meta-Analysis of 5-Year Recurrence Rates Among Endocrine Therapy Users

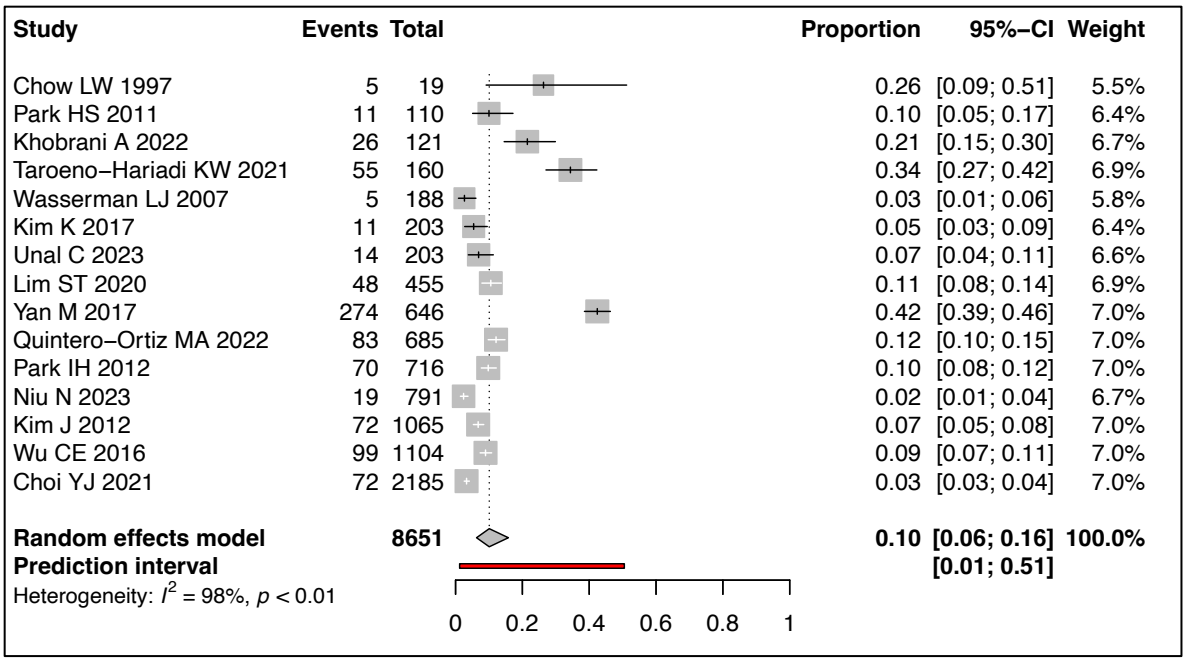


Figure 1.3-b: Meta-Analysis of Recurrence Rates After 5 Years Among Endocrine Therapy Users

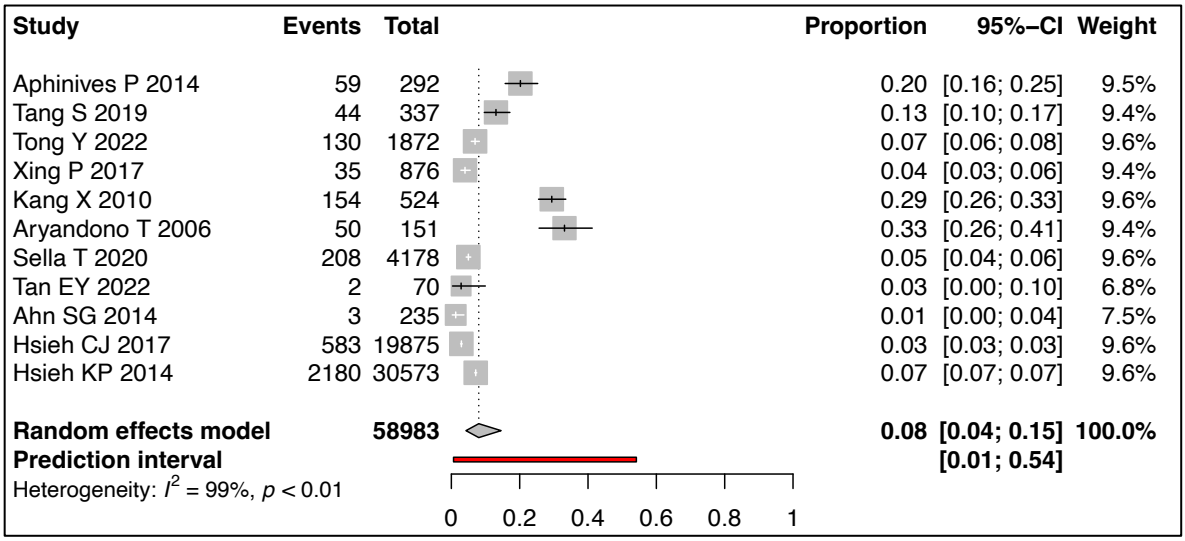


Figure 1.4-a: Meta-Analysis of 5-Year All-Cause Mortality Rates Among Endocrine Therapy Users

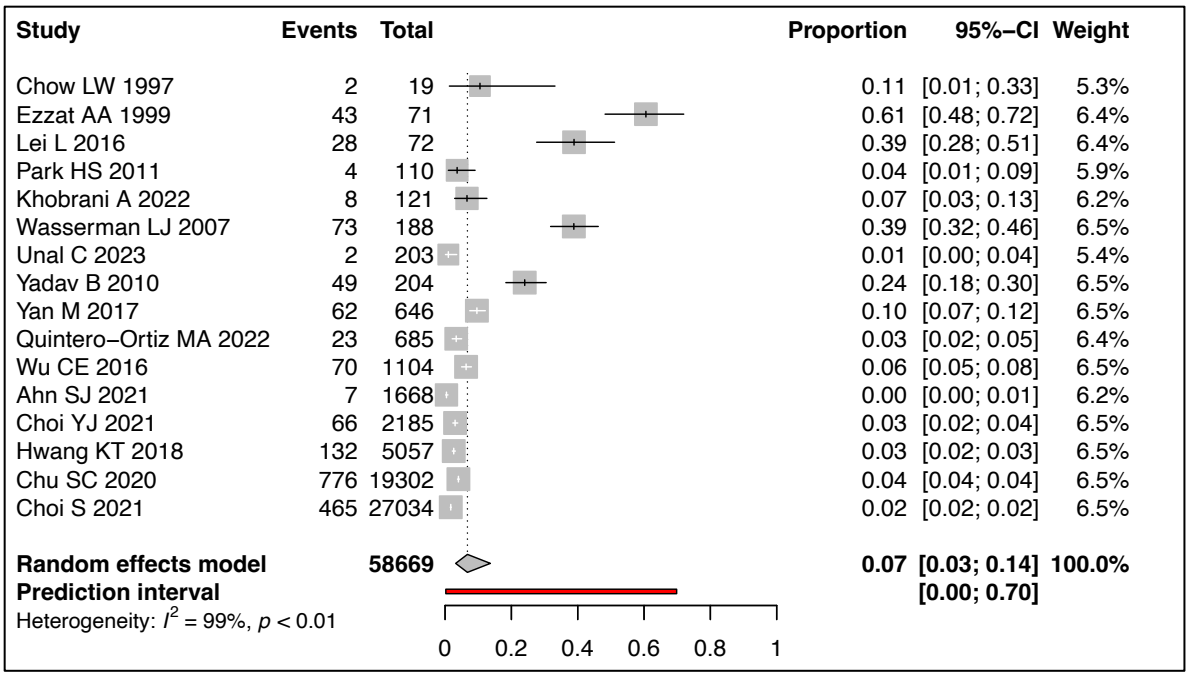


Figure 1.4-b: Meta-Analysis of All-Cause Mortality Rates After 5 Years Among Endocrine Therapy Users

CHAPTER 4

CARDIOVASCULAR AND METABOLIC ADVERSE EVENTS OF ENDOCRINE THERAPIES IN WOMEN WITH BREAST CANCER: A DISPROPORTIONALITY ANALYSIS OF REPORTS IN THE FDA ADVERSE EVENT REPORTING SYSTEM [2]

[2] Elshafie S, Villa-Zapata L, Tackett RL, Zaghloul IY, Young HN. Cancer Med. 2025 Jan;14(1): e70548. doi: 10.1002/cam4.70548. Reprinted here with permission of the publisher.

Abstract

Introduction: Emerging evidence suggests potential cardiovascular toxicities from oral endocrine therapies (ETs); however, results are conflicting. This study comprehensively examined adverse reactions of ETs and investigated cardiovascular and metabolic safety signals within the FDA Adverse Event Reporting System (FAERS).

Methods: Reports in the FAERS through December 2023 were analyzed for documented reactions to tamoxifen, letrozole, anastrozole and exemestane in female breast cancer patients. Standardized queries were used to identify cases of cardiovascular (myocardial infarction, heart failure, arrhythmia, stroke) and metabolic (hypertension, dyslipidemia, hyperglycemia) disorders. Descriptive and disproportionality analyses were performed to assess reports and detect safety signals.

Results: Among 14,327 unique ET-related reports, arthralgia (n=1,873 events) was the most prevalent reaction. We identified 2,170 cardiovascular and 2,252 metabolic events associated with ETs. Letrozole had the highest reporting rate of cardiac arrhythmia (7.7%) and showed positive signals for both arrhythmia (reporting odds ratio [ROR]: 2.2; 95% confidence interval [CI]: 1.8-2.5) and myocardial infarction (ROR: 1.9; 95% CI: 1.4-2.6). We also observed a significantly increased risk of heart failure with letrozole (ROR=1.3; 95%CI: 1.1 – 1.6) and stroke with tamoxifen (ROR=1.7; 95%CI 1.5-2.1). Only anastrozole was significantly associated with metabolic dysfunctions with a notable hyperglycemia reporting rate of 12.2%.

Conclusion: Our findings provide valuable evidence on common reactions as well as controversial cardiovascular and metabolic abnormalities associated with the real-world use of ETs for breast cancer. Ongoing benefit-risk assessment and close monitoring of

cardiac function during treatment, particularly in high-risk women, are warranted to optimize cancer outcomes while minimizing cardiovascular injury.

Introduction

Adverse drug reactions (ADRs) are concomitant hazards of therapeutic use that may lead to treatment discontinuation, morbidity, mortality, and substantial economic costs.[26,231] Historical iatrogenic disasters have triggered careful consideration and surveillance of pharmaceutical products' adverse reactions;[232] however, this response has not been as rigorous in cancer treatment. Proof of maximum survival efficacy often takes precedence over potential toxicities of anticancer therapies, even though these toxicities can be serious and life-threatening posing a critical concern to patients.[34] Additionally, insights into the ADRs of oncology medications emerge primarily from clinical trials which are usually limited by the small number of participants, variability of regimens, exclusion of certain patient populations, and short follow-up durations.[233,234]

The limited information on ADRs along with the increasing life expectancy of cancer patients have prompted national health authorities to expand their focus to integrate safety data from real-world clinical practices.[235] This approach aims to address latent and long-term issues of anticancer medications, optimize treatment outcomes, and improve patients' quality of life during their illness and forward into survivorship.

Currently, the number of overall cancer survivors in the United States (US) exceeds 18 million with female breast cancer ranking at the top accounting for over 4 million survivors.[236] Oral endocrine therapies (ETs) have been a fundamental component of breast cancer treatment in both the curative and palliative care settings.[237] Tamoxifen (TAM) marked the first ET approved by the US Food and Drug Administration (FDA) in the late 1970s and was followed later by aromatase inhibitors (AIs), including anastrozole (ANA), letrozole (LET), and exemestane (EXE).[13]

Many adverse reactions to ETs are still underreported, rarely examined, or completely unrevealed. Recent controversial and inconclusive evidence has linked some ET regimens to serious cardiovascular complications.[238,239] These potential risks are particularly concerning given the observed high rate of heart-related deaths among breast cancer survivors.[62] The prevalence of cardiovascular problems in these women is explained by the interplay of risk factors (e.g., age, obesity) between cancer and cardiovascular diseases, and the cardiotoxic effects of typical breast cancer treatments (e.g., radiotherapy, anthracycline chemotherapeutics).[240] In addition to patient vulnerability, recent expert recommendations to extend ET courses up to 10 years for more favorable clinical outcomes may subsequently increase the occurrence of adverse events.[241]

The long-term administration of systemic ETs emphasizes the importance of a detailed assessment of overall adverse reactions and the evaluation of emerging cardiovascular issues. Utilizing data from pharmacovigilance platforms can complement the current evidence and bridge the knowledge gap in the cardiovascular safety profile of ETs. The purpose of this study was to identify the commonly reported adverse events of each ET and investigate safety signals of specific cardiovascular events among female breast cancer cases within the FDA database.

Methods

This study adheres to the latest Reporting of A Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV) guidelines to ensure transparency and comprehensiveness in our reporting.[242]

Data source

This retrospective pharmacovigilance study was designed to evaluate adverse reactions attributable to the real-world use of oral ETs (TAM, LET, ANA, and EXE) within the FDA Adverse Event Reporting System (FAERS). The FAERS is a publicly available database that supports the FDA's surveillance of the safety of pharmaceutical products in the post-marketing phase. This tool provides information on reports submitted to the FDA by manufacturers, healthcare professionals, and consumers.

Data collection

The FAERS database was searched using both brand and generic names of each medication under study. All retrieved reports of ET reactions that occurred exclusively in females through the end of 2023 were downloaded from the FAERS dashboard.[243] Data files were imported into Microsoft Excel spreadsheets for initial data management. The reason for medication use was limited to malignant breast tumors (of any subtype or stage), and cases with other clinical indications were excluded. Reports that involved irrelevant reactions (such as administration errors, quality complaints, treatment ineffectiveness) or contained a non-ET regimen as a co-suspected product were also removed to eliminate the confounding effect of concomitant medications. Duplicate entries were identified through identical patient age and weight, reported events, as well as the date and country of event occurrence, and were subsequently removed. The final list of cases was cross-checked and verified by a second researcher to ensure data integrity and reliability.

Outcome definitions

We reported the most frequent ADRs (5% or above) for each therapy based on the Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA)

version 27.0. The PTs are used to define terminologies for reactions in the database. Cardiovascular-related adverse events were extracted and grouped according to the Standardized MedDRA Queries (SMQs) which are validated composites of multiple terms related to a specific medical condition. Primary complications of interest included myocardial infarction, heart failure, arrhythmia, and stroke (cerebrovascular disorders). We also investigated metabolic dysfunctions that increase the risk of adverse cardiovascular outcomes, including hypertension, dyslipidemia, and hyperglycemia (weight changes and blood glucose abnormalities). A detailed definition of the SMQs used in our study is available in the Supplementary Appendix D.

Statistical analysis

Descriptive statistics (counts and percentages) were calculated for cases and reported reactions by treatment regimen over the study period. Reports were characterized by the mean age of patients, reporter type, seriousness, event outcomes, and the region where the event occurred. The frequency for each category of common reactions was estimated and tabulated. Disproportionality metrics (reporting odds ratio [ROR], proportional reporting ratio [PRR], and information component [IC]) and their corresponding 95% confidence intervals (CIs) were computed for each regimen alone in comparison to all other ETs (reference group) across the abovementioned outcomes using R software version 4.3.2. A signal means a possible causal relationship between a medication and an adverse event that suggests the need for further action to prevent harm.[244] Safety signals were deemed positive or significant when the following criteria were met altogether: a) the number of co-occurrences was ≥ 3 and the lower limit of the

95% CI of the ROR exceeded 1, b) the PRR was ≥ 2 with an associated chi-square (X^2) of ≥ 4, and c) the lower limit of the 95% CI of the IC (IC_{025}) exceeded 0.[245–247]

Applying simultaneous concordance of these three algorithms which conform to different methodologies (frequentist and Bayesian statistics) allowed for the reduction of false-positive associations and led to accurate and reliable signal detection. These conservative considerations originated from the variability in disproportionality findings based on the type of measure used and the lack of a single well-accepted standard index for signal identification.[248] Similar approaches were used in other previous studies.[249,250]

Results

Reports characteristics

Out of more than 83,000 reports in the FDA database, we identified and analyzed 14,327 unique safety reports pertaining to ETs in women with breast cancer (Figure 2.1). The ANA regimen had the highest number of reports which accounted for more than one-third of the total (n=5,182; 36%) and was followed by LET (n=3,491; 24%). Approximately half (49%) of all reports were documented by healthcare professionals, whereas 39% were documented by consumers. Contributions to the submissions from the US were comparable to those from other countries.

Patients who received TAM were the youngest (61 years on average; standard deviation=13) while the mean ages of those on AI therapies were slightly older (from 65 to 67 years; standard deviation=11). Few cases were defined as metastatic or advanced stage. Most reactions were identified as serious by the submitters. Hospitalization represented 36%, 29%, 25% and 18% of ADR outcomes of TAM, LET, EXE and ANA respectively. Table 2.1 summarizes the main characteristics of the analyzed reports.

Common events

Data that was collected from the FAERS contained 7,417 safety issues related to ETs. Among all events, the number of commonly reported reactions ranged from as low as 7 for TAM to up to 31 for ANA with an overall 35 unique common adverse outcomes for all therapies combined. Higher-grade complications included depression, dyspnea, pulmonary embolism, and uterine polyps. Depression was specifically reported for ANA at a rate of 11%, while pulmonary embolism and uterine polyps were exclusive to TAM with a frequency of 6% each. Dyspnea occurred with all therapies and ranged from 5% to 7%.

Arthralgia or joint discomfort was the most prevalent symptom (n=1,873; 25%) across all ETs; however, the rate differed by regimen: 7% for TAM and 19%, 22% and 50% for LET, EXE and ANA respectively. Other consistently reported adverse reactions across the four therapies included hot flushes, fatigue, and dyspnea. The highest frequencies were generally observed in ANA users. Table 2.2 displays the common events for each therapy.

Cardiovascular and metabolic events

Among all reports of ETs, we identified a total of 2,170 cardiovascular events (15 cases per 100 reports). Heart failure was the most frequent cardiovascular event (n=695; 5%), while myocardial infarction was the least (n=171; 1%). LET had the highest number of adverse cardiovascular effects with cardiac arrhythmia being reported the most at a rate of 8%. In addition, a total of 2,252 metabolic events related to ETs were reported. Hyperglycemia was common with the highest rate observed for ANA (12%). Hypertension was rarely mentioned in TAM reports (n=28; 1%). Results of the descriptive analyses of cardiovascular and metabolic reactions are listed in Table 2.3.

The disproportionality analysis showed safety signals for arrhythmia [ROR=2.2 (95%CI: 1.8 – 2.5), PRR=2.1 (X^2 =93.3) and IC_{025} =0.5] and myocardial infarction [ROR=1.9 (95%CI: 1.4 – 2.6), PRR=2.0 (X^2=17.5) and IC_{025}=0.3] from LET therapy. A significantly higher likelihood of stroke development was observed with TAM (ROR=1.7; 95%CI: 1.5 – 2.1) and heart failure with LET (ROR=1.3; 95%CI: 1.1 – 1.6). These associations showed statistically significant RORs but did not meet the PRR condition for signal detection. ANA was the only regimen associated with a significantly higher risk of reporting any metabolic disorder, including hypertension, dyslipidemia, and hyperglycemia. Table 2.4 presents the results of the pharmacovigilance analysis for each ET compared to all other therapies (reference group).

Discussion

Our evaluation of adverse event reports of oral ETs that have been widely used to treat non-metastatic and advanced breast cancer (TAM, LET, ANA and EXE) identified multiple safety concerns. Musculoskeletal disorders, specifically joint pain were the most common problems across treatment regimens. We also found evidence of significant toxicities on the heart and blood vessels associated with ETs. LET ranked the highest for cardiac arrhythmia, myocardial infarction, and cardiac failure, while TAM exhibited a significantly high risk of stroke. ANA was the only therapy linked to a significant increase in reporting metabolic dysfunctions.

The observation of arthralgia as the most frequent reaction among women with breast cancer aligns with findings from our recent meta-analysis of patients from developing countries and a review that mapped adverse effects of ETs.[251,252] In addition to joint discomfort which can be disabling and limit daily activities, other common but more

medically significant complications included depression, pulmonary embolism, uterine polyps, and dyspnea. Treatment-induced depression is an emerging challenge in breast cancer survivorship because of its high prevalence and detrimental effects on cancer prognosis.[253] The risk of lung embolism and gynecological disorders (polyps) caused by TAM should also be carefully considered, especially given the evident treatment implication in thromboembolic events and uterine cancer development.[254,255] Close vigilance of symptom distress and provision of supportive care strategies are essential to ensure patient safety and improve their quality of life.

Cardiovascular toxicities of breast cancer treatments have gained significant interest due to the observed increase in cardiac-specific morbidities and mortalities among cancer survivors.[62,256] Although some research has revealed previously unrecognized adverse cardiovascular effects of ETs, conflicting and mixed results are often reported.[238,239,257–259] For instance, participants in an international randomized clinical trial who were assigned to LET were more likely to develop myocardial ischemia than those who received TAM, and both groups showed a similar risk for cardiac failure outcomes.[257] In contrast, a large UK-based cohort demonstrated an 86% increase in the incidence of heart failure and no differences in the risk of myocardial infarction or stroke in women receiving any AI compared to TAM users.[239] Similar findings were presented in another study of Italian women.[258]

With regard to metabolic disorders, findings from published studies were inconsistent. A recent study suggested a positive correlation between the administration of AIs (unspecified by type) and the occurrence of hypertension, dyslipidemia, and diabetes.[259] However, none of these associations were detected in a meta-analysis of

clinical trials.[238] Additionally, Thomas et al. documented adverse metabolic effects linked to ETs, particularly noting negative impacts on lipid profiles and glucose tolerance.[260] Another comprehensive review evaluated the conflicting evidence surrounding metabolic outcomes of ET regimens.[261]

A thorough update of the safety information in therapy package inserts is warranted to inform patients and alert healthcare providers to take appropriate precautions against the critical and potentially fatal (though unlabeled) problems detected in our study. These warnings should specifically involve routine monitoring of heart rate and myocardial injury during LET therapy, and the implementation of follow-up measures for ANA users to detect changes in blood pressure, lipids, and glucose levels. This proactive approach will help to prevent, mitigate, and manage reactions before permanent damage occurs.

The selection of ET or decision on a regimen switch for better cancer care should be supported by knowledge of the patient's cardiac health status and an ongoing individualized benefit-risk assessment of treatment. Despite the identified adverse reactions, the life-saving benefits of ETs must be reinforced. The administration of oral ET regimens in both early and advanced stages of breast cancer has significantly enhanced disease control, prevented cancer progression, and improved patient survival.[237,262]

Our study comprehensively examined the reactions of individual ET regimens and provided valuable insights into their adverse cardiovascular and metabolic effects in a real-world setting using standard definitions of outcomes to ensure accuracy and avoid bias. However, this study has several limitations. Although the FAERS database has been a primary and useful platform for pharmacovigilance activities and has enabled the detection of several medication safety signals, underreporting of ADRs remains a major

challenge.[263,264] Therefore, the true risk of adverse events might be much higher than estimated. Conversely, overestimation is also possible, particularly when more severe events are disproportionately reported. Since submission to the pharmacovigilance database is voluntary, the reporting process is biased, and the data is exclusive to submitted cases not the entire population of ET users. It is also difficult to verify the accuracy of information, including the determined causal drug responsible for a specific event. Additionally, the same case may be reported multiple times resulting in duplicate entries. The number of reports is influenced by prescribing practices, usage patterns, as well as the time a medication has been on the market. Reporting rates may also vary based on the regulations in place at the time of approval. Finally, some critical variables, such as lifestyle behaviors, pre-existing comorbidities, and co-prescribed medications could impact patient responses and introduce confounding effects on outcomes.

In conclusion, the global and cardiovascular safety of ETs was effectively evaluated using the FAERS database. Numerous broad-spectrum adverse events were commonly reported among female breast cancer patients with the real-world use of ETs. Our analysis identified signals of major cardiac reactions as well as significant increases in certain cardiovascular and metabolic abnormalities associated with specific regimens. These findings highlight the importance of close monitoring of cardiovascular function during therapy and ongoing assessment of the treatment benefit-risk ratio, particularly in women who are already at high risk of developing toxicities. The integration of cardiac surveillance strategies into routine oncology practice will help to achieve comprehensive patient care that optimizes cancer outcomes while minimizing cardiovascular injury.

Table 2.1: Characteristics of reports of ET reactions in the FAERS (up to 2023)

Attribute	Regimen			
	TAM N=2,866	LET N=3,491	ANA N=5,182	EXE N=2,788
Patient				
Age, mean years (SD)	61 (13)	65 (11)	66 (11)	67 (11)
Age unspecified	395 (14)	830 (24)	869 (17)	315 (11)
Reporter				
Healthcare professional	1,552 (54)	2,287 (65)	1,888 (37)	1,285 (46)
Consumer	613 (21)	1,034 (30)	2,551 (49)	1,387 (50)
Unspecified	701 (25)	170 (5)	743 (14)	116 (4)
Indication				
Metastatic cancer	47 (2)	343 (10)	159 (3)	328 (12)
Reaction severity				
Serious	2,649 (92)	3,153 (90)	3,160 (61)	1,974 (71)
Nonserious	217 (8)	338 (10)	2,022 (39)	814 (29)
Reaction outcomes*				
Death	168 (6)	278 (8)	125 (2)	130 (5)
Life-threatening	207 (7)	138 (4)	126 (2)	69 (3)
Hospitalization	1,040 (36)	995 (29)	928 (18)	687 (25)
Disability	305 (11)	217 (6)	363 (7)	112 (4)
Required intervention	549 (19)	19 (0.5)	270 (5)	12 (0.4)
Congenital anomaly	8	0	2	1
Other outcomes	1,145 (40)	2,181 (62)	1,939 (37)	1,363 (49)
Country of event occurrence				
US	403 (14)	749 (21)	2,946 (57)	1,406 (50)
Other	979 (34)	2,358 (68)	1,454 (28)	943 (34)
Unspecified	1,484 (52)	384 (11)	782 (15)	439 (16)

Abbreviations: ANA: anastrozole; ET: endocrine therapy; EXE: exemestane; FAERS: FDA Adverse Event Reporting System; LET: letrozole; SD: standard deviation; TAM: tamoxifen; US: United States

All values are expressed as n (%) unless otherwise noted

* A report could indicate more than one outcome

Table 2.2: Commonly reported reactions for each ET regimen

Events	Anastrozole		Exemestane		Letrozole		Tamoxifen	
	N	%	N	%	N	%	N	%
Total	2,025	100	1,483	100	2,208	100	1,701	100
Arthralgia	1,005	49.6	329	22.2	421	19.1	118	6.9
Hot flush	564	27.9	137	9.2	158	7.2	87	5.1
Fatigue	385	19.0	175	11.8	218	9.9	90	5.3
Pain in extremity	327	16.1	105	7.1	143	6.5	-	-
Weight increased	305	15.1	75	5.1	-	-	93	5.5
Alopecia	293	14.5	106	7.1	-	-	-	-
Insomnia	285	14.1	117	7.9	-	-	-	-
Nausea	280	13.8	105	7.1	152	6.9	-	-
Headache	278	13.7	109	7.3	129	5.8	-	-
Bone Pain	268	13.2	94	6.3	151	6.8	-	-
Pain	242	12.0	109	7.3	167	7.6	-	-
Asthenia	239	11.8	95	6.4	118	5.3	-	-
Myalgia	230	11.4	101	6.8	149	6.7	-	-
Dizziness	181	8.9	101	6.8	127	5.8	-	-
Dyspnea	140	6.9	79	5.3	155	7.0	86	5.1
Fall	128	6.3	-	-	116	5.3	-	-
Diarrhea	124	6.1	79	5.3	-	-	-	-
Depression	222	11.0	-	-	-	-	-	-
Arthritis	215	10.6	-	-	-	-	-	-
Back Pain	194	9.6	-	-	-	-	-	-
Gait disturbance	162	8.0	-	-	-	-	-	-
Oedema peripheral	155	7.7	-	-	-	-	-	-
Hypoesthesia	148	7.3	-	-	-	-	-	-
Paresthesia	144	7.1	-	-	-	-	-	-
Osteoporosis	141	7.0	-	-	-	-	-	-
Hypertension	125	6.2	-	-	-	-	-	-
Carpal tunnel syndrome	120	5.9	-	-	-	-	-	-
Musculoskeletal stiffness	116	5.7	-	-	-	-	-	-
Trigger finger	114	5.6	-	-	-	-	-	-
Cough	111	5.5	-	-	-	-	-	-
Muscle spasms	110	5.4	-	-	-	-	-	-
Malaise	-	-	125	8.4	-	-	-	-
Pruritus	-	-	75	5.1	-	-	-	-
Pulmonary embolism	-	-	-	-	-	-	96	5.6
Uterine polyp	-	-	-	-	-	-	93	5.5

Table 2.3: Frequency of cardiovascular and metabolic disorders associated with ETs

Event*	ET regimen				Total N=14,327
	TAM N=2,866	LET N=3,491	ANA N=5,182	EXE N=2,788	
Myocardial infarction	37 (1.3)	65 (1.9)	38 (0.7)	31 (1.1)	171 (1.2)
Cardiac failure	97 (3.4)	206 (5.9)	252 (4.9)	140 (5.0)	695 (4.9)
Arrhythmia	93 (3.2)	269 (7.7)	212 (4.1)	99 (3.6)	673 (4.7)
Stroke	188 (6.6)	162 (4.6)	145 (2.8)	136 (4.9)	631 (4.4)
Hypertension	28 (1.0)	141 (4.0)	242 (4.7)	101 (3.6)	512 (3.6)
Dyslipidemia	43 (1.5)	67 (1.9)	151 (2.9)	42 (1.5)	303 (2.1)
Hyperglycemia	220 (7.7)	307 (8.8)	632 (12.2)	278 (10.0)	1,437 (10.0)

*Grouped by Standardized MedDRA Queries (SMQs)

Abbreviations: ANA: anastrozole; ET: endocrine therapy; EXE: exemestane; LET: letrozole; TAM: tamoxifen

All values are expressed as number of cases (%)

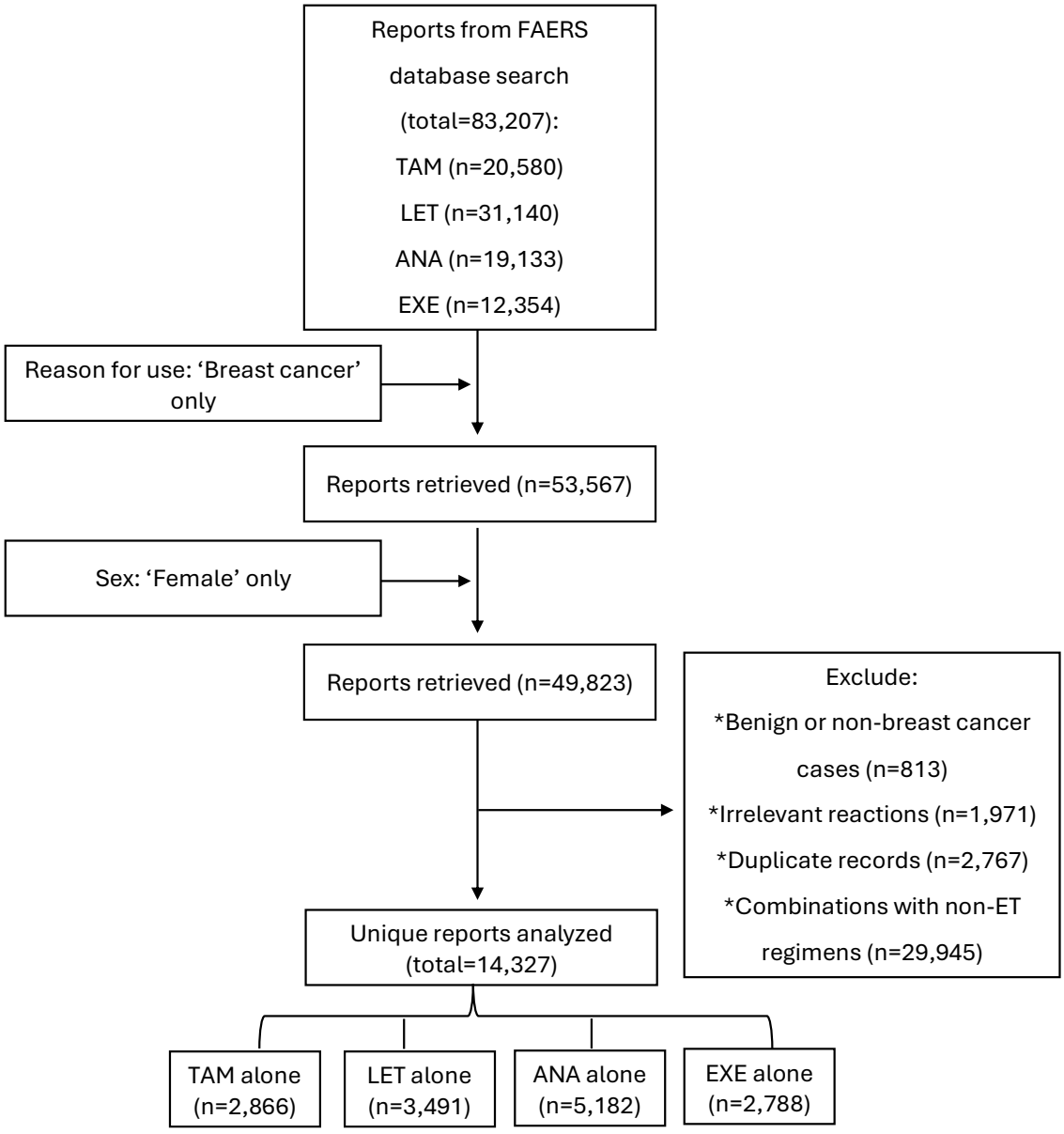
Table 2.4: Disproportionality analysis results for cardiovascular and metabolic disorders associated with endocrine therapies

Event*	ET regimen											
	TAM			LET			ANA			EXE		
	ROR (95% CI)	PRR	IC_{025}	ROR (95% CI)	PRR	IC_{025}	ROR (95% CI)	PRR	IC_{025}	ROR (95% CI)	PRR	IC_{025}
Myocardial infarction	1.1 (0.8-1.6)	1.1	-0.4	**1.9 (1.4-2.6)**	**2.0**	**0.3**	0.5 (0.3-0.7)	0.5	-1.2	0.9 (0.6-1.4)	0.9	-0.7
Cardiac failure	0.6 (0.5-0.8)	0.6	-0.8	**1.3 (1.1-1.6)**	1.3	**0.1**	1.0 (0.9-1.2)	1.0	-0.2	1.0 (0.9-1.3)	1.0	-0.2
Arrhythmia	0.6 (0.5-0.8)	0.6	-0.8	**2.2 (1.8-2.5)**	**2.1**	**0.5**	0.8 (0.7-0.9)	0.8	-0.4	0.7 (0.6-0.9)	0.7	-0.7
Stroke	**1.7 (1.5-2.1)**	1.7	**0.4**	1.1 (0.9-1.3)	1.1	-0.2	0.5 (0.4-0.6)	0.5	-0.9	1.1 (0.9-1.4)	1.1	-0.1
Hypertension	0.2 (0.2-0.3)	0.2	-2.4	1.2 (1.0-1.4)	1.2	-0.1	**1.6 (1.3-1.9)**	1.6	**0.2**	1.0 (0.8-1.3)	1.0	-0.3
Dyslipidemia	0.7 (0.5-0.9)	0.7	-1.0	0.9 (0.7-1.2)	0.9	-0.5	**1.8 (1.4-2.2)**	1.8	**0.2**	0.7 (0.5-0.9)	0.7	-1.0
Hyperglycemia	0.7 (0.6-0.8)	0.7	-0.6	0.8 (0.7-0.9)	0.8	-0.4	**1.4 (1.3-1.6)**	1.4	**0.2**	1.0 (0.9-1.1)	1.0	-0.2

*Grouped by Standardized MedDRA Queries (SMQs)

Abbreviations: ANA: anastrozole; CI: confidence interval; ET: endocrine therapy; EXE: exemestane; IC_{025}: lower limit of the 95% confidence interval of the information component; LET: letrozole; PRR: proportional reporting ratio; ROR: reporting odds ratio; TAM: tamoxifen

Bold font indicates meeting significance condition



Abbreviations: ANA: anastrozole; EXE: exemestane; FAERS: FDA Adverse Event Reporting System; LET: letrozole; TAM: tamoxifen

Figure 2.1 Study Flowchart

CHAPTER 5

REAL-WORLD TELEHEALTH UTILIZATION AND ITS IMPACT ON MEDICATION ADHERENCE, CLINICAL OUTCOMES, AND HEALTHCARE COSTS IN BREAST CANCER: A CLAIMS-BASED COHORT STUDY [3]

[3] Elshafie S and Villa Zapata L. To be submitted to a peer-reviewed journal.

Abstract

Background: The rapid expansion of digital health, especially since the COVID-19 pandemic offers a promising avenue to improve care delivery and optimize treatment outcomes. This study evaluated telehealth utilization and its impact on long-term endocrine therapy adherence, clinical outcomes, and healthcare costs among nonelderly women with nonmetastatic breast cancer.

Methods: This retrospective cohort study used 2017–2023 claims data from the Commercial Encounters Merative MarketScan database. Eligible patients were women under 65 years old who were diagnosed with nonmetastatic breast cancer in 2018, initiated oral endocrine therapy (tamoxifen or aromatase inhibitors) and maintained continuous insurance for one year before diagnosis and five years after treatment initiation. Telehealth utilization was assessed as a binary (user vs. nonuser) and continuous (number of visits) measure. Primary outcomes were endocrine therapy adherence, metastasis incidence, and patient-incurred direct healthcare costs. Statistical associations between telehealth and outcomes were tested using generalized linear models.

Results: Among 1,141 eligible patients (mean age: 51 years), 874 (77%) used telehealth services resulting in 8,350 visits over five years. Telehealth utilization was consistent across age groups and insurance plan types but varied significantly by geographic region, urban-rural status, comorbidity burden, and endocrine therapy regimen. By the fifth year, only 50% of the cohort were adherent, and 5% developed metastasis. Telehealth use was significantly associated with better adherence (adjusted odds ratio = 1.58; 95% CI: 1.31–1.91; p <0.0001) but not with reduced metastasis rates. Notably,

telehealth users incurred 15% higher out-of-pocket medical costs compared to nonusers ($p < 0.0001$), though prescription costs did not differ significantly.

Conclusions: These findings demonstrate significant variability in telehealth utilization and underscore its potential to support long-term adherence to endocrine therapy among commercially insured nonelderly women with breast cancer. However, the associated financial burden highlights the need for policy initiatives to optimize the affordability and accessibility of telehealth services within oncology care.

Introduction

Breast cancer is the most prevalent cancer among women worldwide,[1] accounting for approximately one-third of new cancer diagnoses in the United States (US) annually.[2] While early stages of the disease are often curable with appropriate therapeutic interventions, long-term management is critical for reducing the risk of cancer recurrence. Endocrine therapy (ET) has been a cornerstone treatment for hormone receptor-positive (HR+) breast cancer which comprises the majority of cases.[237] Adherence to ET over extended periods (5–10 years) is essential for optimizing disease-free survival outcomes.[265] However, adherence rates remain suboptimal, particularly among young women, due to multiple factors such as treatment-related side effects, financial burden, and healthcare access limitations.[103,220,222,251]

Addressing barriers to adherence requires effective strategies that carefully consider cost implications, given the financial toxicity of cancer care. Breast cancer management has the highest national medical expenditures among all cancer types at annual costs exceeding $29 billion.[39] Patients with cancer endure significant costs for medical services, diagnostic procedures, pharmaceutical medications, supportive care and indirect expenses (e.g., lost productivity, transportation, extra childcare during treatment).[38] Financial distress is more paramount among nonelderly patients who are ineligible for public insurance coverage and therefore bear high out-of-pocket (OOP) expenses.[40,266] Additional challenges, such as cancer-related work absenteeism and competing obligations further strain their ability to afford care.[266,267]

The rapid expansion of digital health, especially since the COVID-19 pandemic presents a promising platform to improve care delivery, overcome treatment barriers, and

potentially minimize costs.[268] Telehealth, defined broadly as the remote delivery of healthcare services through telecommunication technologies,[269] facilitates timely access to providers, enhances patient engagement, and mitigates logistical and structural barriers to care.[270] Although previous research has examined the role of telehealth in chronic disease management, limited evidence exists on its impact on ET adherence and associated clinical and economic outcomes in breast cancer patients.

This study evaluates the real-world utilization of telehealth services among commercially insured nonelderly women with nonmetastatic breast cancer and examines its association with ET adherence, metastasis incidence, and overall patient-incurred healthcare costs. We hypothesize that telehealth use is associated with improved medication adherence and reduced long-term healthcare costs through enhanced disease management. Leveraging large-scale administrative claims data from the Merative MarketScan database which captures healthcare utilization patterns among millions of working-age individuals, this study provides valuable insights into the potential benefits and limitations of telehealth in oncology care, particularly for vulnerable patient populations.

Methods

Data Source

This retrospective cohort study includes data from the Merative MarketScan database, an administrative claims database of privately insured patients representing a significant portion of the US working population with employer-sponsored or individually purchased commercial health insurance. The database provides comprehensive real-world information on clinical services, procedures, prescribed treatments along with their

associated financial elements and has been widely used for research on health behaviors, longitudinal healthcare utilization, pharmaceutical costs, and clinical outcomes. Although the claims data are fully de-identified, the study protocol was submitted to the Institutional Review Board of the University of Georgia which deemed the research activity exempt from review requirements (PROJECT00010237).

Study Design

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure transparent and high-quality reporting.[271] In this retrospective cohort study, we examined the association between telehealth utilization and three key outcomes: adherence to ET, metastasis development, and direct OOP healthcare costs within a commercially insured population in the US. To minimize inherent biases in nonrandomized observational studies, we applied a new-user design,[272] a rigorous approach that excludes prevalent treatment users and focuses on individuals initiating therapy for the first time.

Eligible females who initiated ET (tamoxifen, letrozole, anastrozole, or exemestane) following a breast cancer diagnosis in 2018 were identified and followed for five years. The index date (time zero) was defined as the date of the first prescription fill for any of these medications. Patients were observed from the index date until the end of the follow-up period, during which the study outcomes were assessed. To account for temporal trends, changes in outcome estimates were evaluated annually. All covariates were measured at or before the index date to adjust for their potential influence on the outcomes. A schematic diagram illustrating the study design is provided in Figure 3.1.

Study Population

Medical and pharmacy claims data were used to identify women under the age of 65 with commercial insurance who were newly treated with oral ET (branded or generic) following a primary breast cancer diagnosis in 2018. Breast cancer diagnoses were identified using the International Classification of Diseases Clinical Modification- tenth revision (ICD-10-CM) codes (C50.x). Incident ET users were defined as patients with no previous prescription claims for tamoxifen or aromatase inhibitors (letrozole, anastrozole, or exemestane) in the period preceding their first prescription. The study cohort included women who were prescribed a single endocrine agent as well as those who switched agents during the study period. Treatment exposure was determined using National Drug Codes (NDCs) for tamoxifen and aromatase inhibitors in dispensed prescription claims. A comprehensive list of treatment codes that were used for cohort creation is provided in Supplementary Table 1 (Appendix E).

Patients' eligibility criteria required continuous insurance enrollment: (a) for at least one year prior to diagnosis to establish treatment history and baseline health status, and (b) for a minimum of five years from the date of the first filled ET prescription to enable longitudinal follow-up. Women with advanced disease, defined as progression to distant organ(s) at the time of cancer diagnosis or prior to ET initiation, were excluded. Additionally, patients who developed metastases within three months of treatment initiation were excluded to account for potential delays in clinical data reporting and the administrative nature of the dataset. The presence of ICD-10-CM diagnostic codes for secondary malignancies (C77.x, C78.x, C79.x and C80.0) was used as evidence of possible metastasis.

Variables Definition

Telehealth was defined as healthcare services delivered remotely via telecommunication technologies regardless of the setting and was identified in the administrative claims data using corresponding billing procedure codes, modifiers, or place of service codes. To assess **telehealth utilization**, we created a dichotomous variable to classify patients as either telehealth users or nonusers as well as a continuous variable to measure the total number of telehealth visits per patient.

The implications of telehealth utilization were assessed and compared across key outcomes. We evaluated adherence to ET, the incidence of metastasis, and the total direct healthcare payments incurred by patients over the five-year follow-up period. **Adherence** was measured by the Proportion of Days Covered (PDC): the percentage of days on which a patient had access to the prescribed medication during a specified time frame. The PDC ranges from 0% to 100%, with higher values indicating consistent prescription refills and better adherence. In alignment with established thresholds in prior research, women were classified as adherent if their PDC was ≥80%. **Metastasis** outcomes were defined as an incident diagnosis of secondary malignancy during the follow-up period.

Cost indicators included patient-level expenses for deductibles, copayments, and coinsurance associated with outpatient services, hospitalizations, and prescription medications. To enable meaningful comparisons across different years, all costs were adjusted for inflation and standardized to 2023 US dollars (USD) using the medical care component of the Consumer Price Index (CPI). The CPI data were obtained from the official website of the US Bureau of Labor Statistics (available at: https://www.bls.gov/cpi/).

Covariates were included in the analyses to account for their potential confounding effects: patient's age at cancer diagnosis (categorized into four groups), geographic region, rurality status (classified as rural if the Metropolitan Statistical Area [MSA] value was zero), insurance plan coverage (categorized as Preferred Provider Organization [PPO], Health Maintenance Organization [HMO], Consumer-Driven Health Plan [CDHP], High-Deductible Health Plan [HDHP], or other), and the type of endocrine agent received. To adjust for baseline health status, the Charlson Comorbidity Index (CCI) was calculated for each patient. The CCI assigns weighted scores to preexisting comorbid conditions based on their associated mortality risk, with higher scores indicating a greater comorbidity burden and worse prognosis.[273,274] A detailed description of all variables, including their definitions and categorization is provided in Supplementary Table 2 (Appendix F).

Statistical Analyses

Descriptive statistics (means, medians and percentages) were calculated to summarize the demographic and baseline clinical characteristics of the study cohort and their healthcare claims. Differences between telehealth users and nonusers were assessed using bivariate analyses, including chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables, and the nonparametric Wilcoxon rank-sum test for nonnormally distributed continuous variables.

Telehealth utilization, total direct costs for outpatient and inpatient services, and prescription costs were aggregated for each patient (a) over the entire study period and (b) annually from the ET index date through each subsequent year of the five-year follow-up period. Adherence to ET was measured by calculating the total number of days of drug supply divided by the number of days in the observation period, then multiplied by 100 for

interpretability. The number of patients with incident metastasis during the treatment period was determined.

To assess overall trends, key measures were visually plotted for the entire cohort over time and year-wise changes were statistically compared between telehealth users and nonusers (reference group). For binary outcomes such as adherence status and metastasis incidence, generalized linear mixed-effects models (GLMMs) with a logistic link function were used to estimate odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). Parameter estimation was performed using maximum likelihood approximation with fixed effects for the predefined set of covariates. For continuous outcomes such as OOP costs, generalized linear models (GLMs) with a Gamma distribution and log link function were applied to test mean differences.

Model selection was guided by the nature and distribution of each outcome variable, with random effects included to account for within-subject correlations across repeated measures. The null hypotheses tested whether the risks of nonadherence, metastasis incidence, and average OOP costs were equivalent between groups over time. All data management and statistical analyses were performed using SAS software (version 9.4 TS1M6, SAS Institute, Cary, NC). Statistical significance was determined at a p-value of ≤ 0.05.

Results

Patient Selection

A search of the administrative commercial claims database identified more than 44,000 women under the age of 65 with recorded breast cancer diagnosis codes in 2018. After excluding patients who did not meet the continuous insurance enrollment criteria or

lacked dispensed prescriptions for ETs, 9,483 patients remained. Of these, 8,044 were identified as new users of treatment (i.e., no history of prior prescriptions). We further excluded patients who were not continuously enrolled for five years post-treatment initiation (n=6,626) and those with metastatic disease before, at, or within three months of treatment initiation (n=277). The final study cohort consisted of 1,141 patients who met all inclusion criteria. Figure 3.2 presents a flowchart outlining the cohort selection process and the number of patients at each step.

Cohort Characteristics

Table 3.1 summarizes the demographic and clinical characteristics of the 1,141 women included in the study cohort. The mean age was 51 years (standard deviation [SD]: 6 years) with more than half of the patients aged 45 to 54 years. Geographically, most patients were from southern states (n=497; 44%), and a small proportion resided in rural areas (n=113; 10%). The most common type of commercial insurance plan was PPO (n=512; 46%). Patients exhibited a moderate burden of comorbidities with 92% having a CCI score of 2 or 3.

All included women initiated ET in the same year as their breast cancer diagnosis. The majority of tumors (92%) were estrogen receptor positive. One-third of the patients (n=385; 34%) received tamoxifen alone, another third (n=374; 33%) were prescribed a single aromatase inhibitor (primarily anastrozole), and the remaining 33% switched between agents during the study period.

Telehealth Utilization and Five-Year Outcomes

Over the five-year study period, 77% of the cohort (874 of 1,141 patients) utilized telehealth services at least once, accounting for a total of 8,350 visits. Patient characteristics

such as age and insurance plan type were generally comparable between telehealth users and nonusers. However, significant differences were observed across specific factors. Telehealth use varied by geographic region ($p = 0.0064$) with the highest prevalence in the West (86%) and the lowest in the North Central region (71%). Urban residents had higher telehealth utilization rates than rural residents (78% vs. 70%, $p = 0.0480$). Additionally, patients with higher comorbidity scores were more likely to use telehealth services ($p = 0.0073$), and a significantly greater proportion of patients who switched ETs utilized telehealth compared to those on monotherapy ($p = 0.0013$).

By the fifth year of ET, only half of the cohort remained adherent to their medication with a five-year average PDC of 76% indicating that patients had access to their medication on approximately 3 out of every 4 days. Among the 1,141 patients, 57 (5%) developed metastasis within five years with an average time to metastasis of 2.3 years (SD: 1.3 years). All-cause hospitalizations occurred in 153 patients (13%) with an average hospital stay of four days.

Total medical care expenditures over the five-year period exceeded $8.5 million averaging $7,510 per patient (SD: $5,782). Adjusted prescription costs amounted to over $2.1 million with an average of $1,854 per patient. Notably, ET prescriptions accounted for only 9% of total prescription spending. A summary of cohort measures over the follow-up period is listed in Table 3.2.

Assessment of Temporal Trends

Figure 3.3 (a–d) visualizes the evolving patterns of telehealth utilization, medication adherence, metastasis incidence, and healthcare costs over the study period. Telehealth utilization increased sharply, rising nearly sevenfold during the second year of

endocrine treatment. This surge coincided with the onset of the COVID-19 pandemic in 2020 (see Supplementary Table 3 Appendix G). Utilization peaked in the third year with over 48% of patients using telehealth services, followed by a slight decline in subsequent years. The number of telehealth visits mirrored the utilization trend and reached a maximum of 2,178 visits in the third year.

Adherence rates steadily declined over the treatment duration. The proportion of adherent patients was 75% in the first year but progressively decreased to 36% by the fifth year. In contrast, metastasis incidence rates remained relatively low and fluctuated slightly throughout the five-year period. Average total medical care expenditures per patient steadily declined over the first two years, decreasing from $1,794 in year one to $1,320 in year two. This reduction was followed by a modest increase and subsequent stabilization through the remainder of the observation period. In contrast, average prescription costs per patient increased consistently, fluctuating between $252 and $515 annually.

Statistical testing of individual temporal trends showed a strong and significant relationship for adherence proportions ($p = 0.0092$) with time since ET initiation explaining 92% of the variance in adherence. On average, adherence proportions decreased by approximately 9% as time progresses. The trend for prescription costs revealed marginal significance ($p = 0.0502$), suggesting a positive relationship between costs and time with OOP prescription expenses expected to increase by approximately $62 annually. None of the remaining measures showed significant changes over time.

Assessment of Relationships

Telehealth utilization was significantly associated with increased adherence to ET in both the baseline model and after adjusting for temporal tends and relevant patient-level

factors (OR = 1.58; 95% CI: 1.31–1.91; p <0.0001). These findings remained robust even after excluding influential observations from the analysis. The odds of adherence were the highest in the first year but declined significantly over time. In the adjusted model, other significant predictors of adherence included geographic region, insurance plan type, and the specific ET agent received with the lowest adherence odds observed among tamoxifen users. In contrast, factors such as age group, rurality and baseline comorbidity level were not significantly associated with adherence.

No significant relationship was observed between telehealth utilization and metastasis incidence over five years (OR = 1.54; 95% CI: 0.69–3.47; p = 0.2961). However, telehealth use was significantly associated with increased OOP medical care costs with telehealth users spending 15% more than nonusers (95% CI: 9%–22%; p <0.0001). The model also showed significant yearly trends in costs with the highest expenditures occurring in year one, the lowest in year two, and relative stability from years three through five. Geographic region and insurance plan type were significant contributors to cost differences. Notably, telehealth utilization was not associated with changes in prescription costs.

Discussion

Our findings demonstrate that telehealth utilization among nonelderly women with breast cancer increased during the COVID-19 pandemic and remained an integral part of their care. However, notable variations were observed based on geographic location, urban-rural status, comorbidity burden, and ET regimen. Telehealth use was significantly associated with improved adherence to ET but was also linked to higher long-term costs.

The increased telehealth usage among patients with higher comorbidities and those who switched treatments reflects the convenience of remote care for managing complex health conditions and facilitating additional follow-up or monitoring. However, several challenges may hinder broader telehealth adoption within the US healthcare system, including patient and provider preferences, reimbursement policies, limited clinician training in telehealth practices, and inconsistent access to digital technology.

Despite the general decline in ET adherence over time, telehealth users had higher odds of maintaining adherence throughout the five-year follow-up period. These results highlight the potential of telehealth to promote medication persistence and are consistent with previous studies demonstrating improved chronic disease management and enhanced medication adherence through digital and telecommunication platforms. A systematic review of 13 studies showed evidence on the effectiveness of telehealth in increasing medication adherence across various chronic conditions.[275] Similarly, recent meta-analyses revealed the effectiveness of telehealth in enhancing medication adherence among patients with diabetes and stroke.[276,277]

We did not find a significant relationship between telehealth utilization and reduced metastasis incidence. The sustainable overall low rates of metastasis and hospitalizations suggest effective disease management within the studied cohort. This finding implies that while telehealth supports adherence, it may not directly influence disease progression within the observed timeframe. Additional factors such as cancer biology, treatment response, and broader healthcare access disparities may have a more substantial role in determining clinical outcomes.[278]

Despite its positive impact on adherence, telehealth users incurred higher OOP costs compared to nonusers, primarily due to increased expenses for medical services. However, Patel et al. reported an average cost savings of $186 per telehealth visit among 11,688 cancer patients with mainly private insurance in Florida over a 15-month period.[279] These contrasting findings underscore the complexity of telehealth's financial implications which may vary based on healthcare policies, insurance coverage, and service utilization patterns.

Other studies have highlighted telehealth's potential for cost savings through various mechanisms, including reduced travel expenses, increased care efficiency, fewer unnecessary specialist referrals, and lower rates of hospitalizations and emergency department visits.[280] These benefits suggest that while telehealth may lead to higher direct medical costs in some cases, its broader economic impact could result in overall healthcare savings, particularly when indirect costs and system-wide efficiencies are considered. Future policy efforts should focus on optimizing telehealth accessibility and cost-effectiveness while minimizing the financial burden of care delivery for patients.

This study is the first to use large-scale real-world data to evaluate telehealth utilization and its long-term clinical and economic implications in this vulnerable population. It offers important insights for clinicians, policymakers, and insurers emphasizing the benefits of telehealth integration in enhancing treatment adherence while also highlighting the need for cost-saving strategies to ensure equitable access. The combined year-by-year and overall study period analysis approach captured both temporal and longitudinal trends in telehealth utilization, adherence patterns, clinical outcomes, and financial impacts. This methodology also minimized confounding effects from external

factors, such as healthcare policy changes during the COVID-19 pandemic and variations in telehealth reimbursement policies, while aligning adherence measurements more precisely with individual treatment timelines rather than calendar years.

Further research is warranted to explore patient-reported experiences, satisfaction, quality of life outcomes and the overall cost-effectiveness of telehealth in oncology care. Future studies should examine the impact of telehealth expansion in rural and underserved populations where structural barriers to traditional care are more pronounced.

This study has several limitations. It was restricted to nonelderly patients with commercial insurance, so results may not be generalizable to individuals over 64 years old or those with public insurance. Additionally, the requirement for continuous longitudinal insurance coverage for at least six years limits applicability to populations with shorter coverage durations who may differ in their health status and socioeconomic level. Furthermore, the adherence measurement method by prescription refills may not accurately reflect actual medication consumption. Our cost estimations were limited to direct healthcare expenditures and did not include indirect costs or potential savings. Finally, cancer–specific variables such as surgical procedures and receipt of adjuvant therapies were not examined.

In conclusion, telehealth utilization among nonelderly breast cancer patients demonstrated variation across geographic, clinical, and treatment-related factors over the five-year follow-up period. While telehealth proved to be a valuable tool for supporting long-term adherence to endocrine treatment within a commercially insured population, it did not significantly impact metastasis rates. As digital health technologies continue to advance, future research should focus on optimizing telehealth implementation strategies

to enhance patient outcomes, address affordability concerns, and promote equitable access to care across diverse populations.

Table 3.1: Demographic and Baseline Clinical Characteristics of the Study Cohort

Socio Demographics	Total (N=1,141)
Age at diagnosis	
Mean years ± SD	51 ± 6
Median years (IQR)	52 (47-56)
Age group	
< 35	11 (1)
35-44	133 (12)
45-54	609 (53)
55-64	388 (34)
Region	
Northeast	197 (17)
North Central	284 (25)
South	497 (44)
West	161 (14)
Rurality	
Urban	885 (78)
Rural	113 (10)
Unknown	143 (12)
Plan type	
PPO	512 (46)
HMO	189 (17)
CDHP	169 (15)
HDHP	141 (13)
Others	113 (9)

Clinical Factors	
Comorbidity (CCI score)	
Mean score ± SD	2 ± 1
0-1	0 (0)
2-3	1,055 (92)
> 3	86 (8)
Estrogen receptor status	
Positive	1049 (92)
Negative	20 (2)
Unknown	72 (6)
Endocrine treatment	
TAM	385 (34)
AIs [LET, ANA, EXE]	374 [89, 274, 11] (33)
Switchers	382 (33)

All values are expressed as numbers (percentages) unless otherwise noted.

Abbreviations: AI: aromatase inhibitor; ANA: anastrozole; CCI: Charlson Comorbidity Index; CDHP: Consumer-Driven Health Plan; EXE: exemestane; HDHP: High-Deductible Health Plan; HMO: Health Maintenance Organization; IQR: interquartile range; LET: letrozole; PPO: Preferred Provider Organization; SD: standard deviation; TAM: tamoxifen

Table 3.2: Summary of Study Cohort Measures Over the Five-Year Follow-Up

Measure	Mean ± SD	Total (n)	Percentage (%) [a]
Telehealth Utilization			
User (≥ 1 visit)	-	874	77%
Nonuser	-	267	23%
Total visits (count)	7 ± 18	8,350	-
Adherence Status			
Adherent	-	571	50%
Nonadherent	-	570	50%
Adherence rate (PDC)	76% ± 39% [b]		-
Clinical Outcomes			
Did not develop metastasis	-	1,076	95%
Developed metastasis	-	57	5%
Time to metastasis (years)	2.3 ± 1.3	-	-
Hospitalized for any reason (≥ 1)	-	153	13%
Length of Stay (days)	4 ± 4	853	-
Cost Summary (USD)			
Outpatient medical costs	$7,312 ± $5,600	$8,342,545	-
Inpatient medical costs	$830 ± $1,914	$226,622	-
Total medical costs	$7,510 ± $5,782	$8,569,166	-
Total prescription costs	$1,854 ± $3,738	$2,115,132	-
Endocrine prescription costs	$171 ± $317	$195,570	-

PDC: Proportion of Days Covered; SD: standard deviation; USD: United States dollar

[a] Percentages are calculated based on the total cohort size (N=1,141).

[b] Percentages may exceed 100% when the total days of drug supply (numerator) surpass the number of days in the observation period (denominator), such as when patients refill prescriptions early.

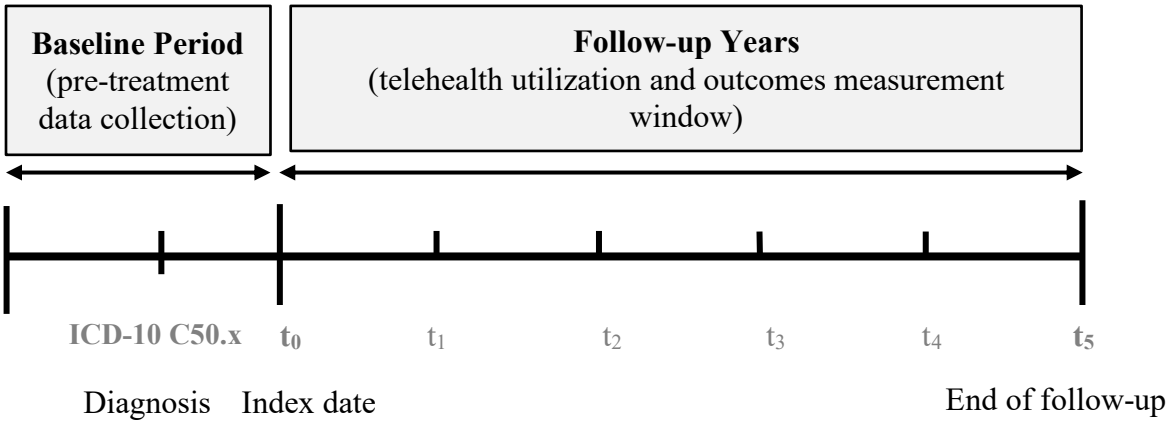
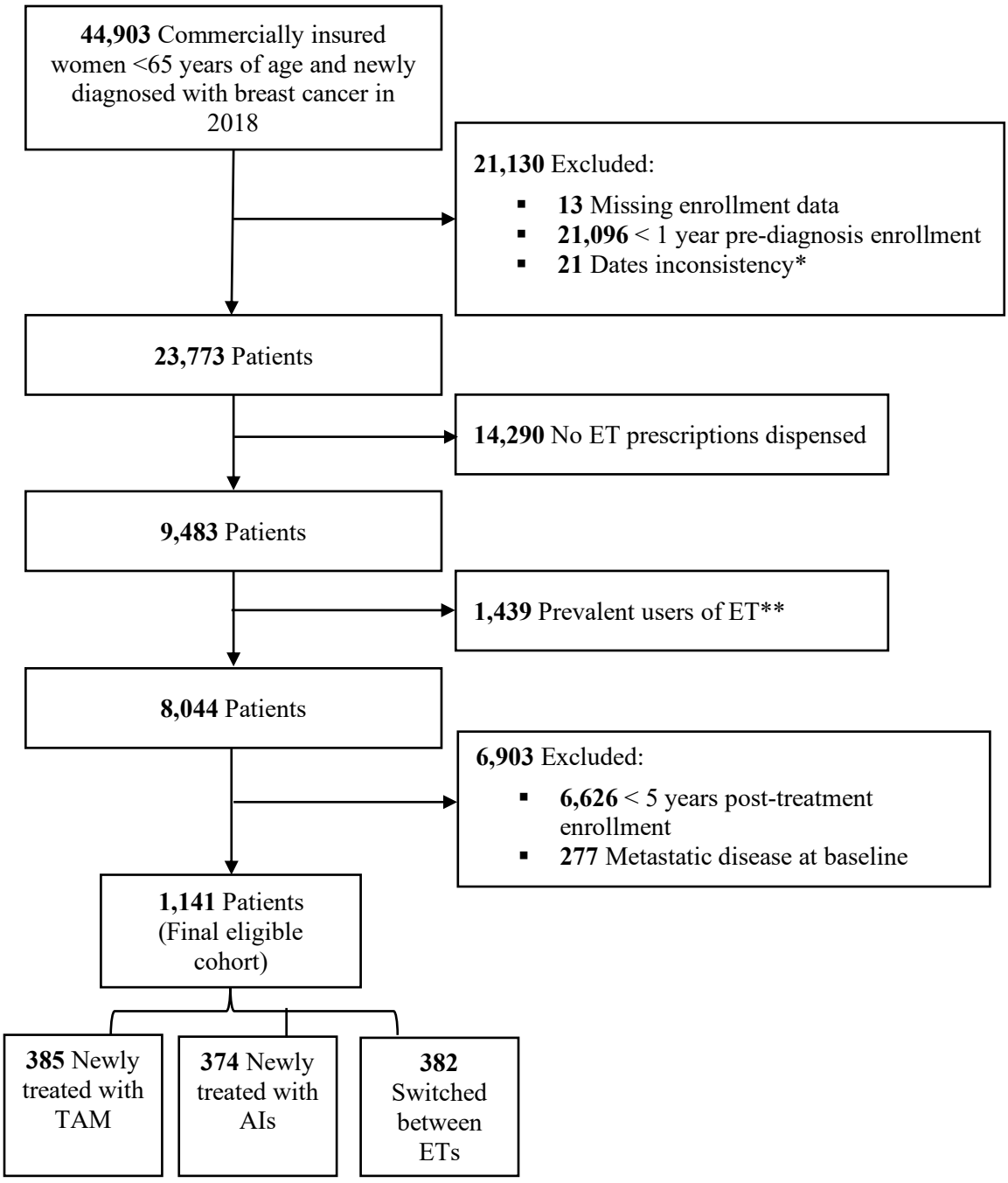


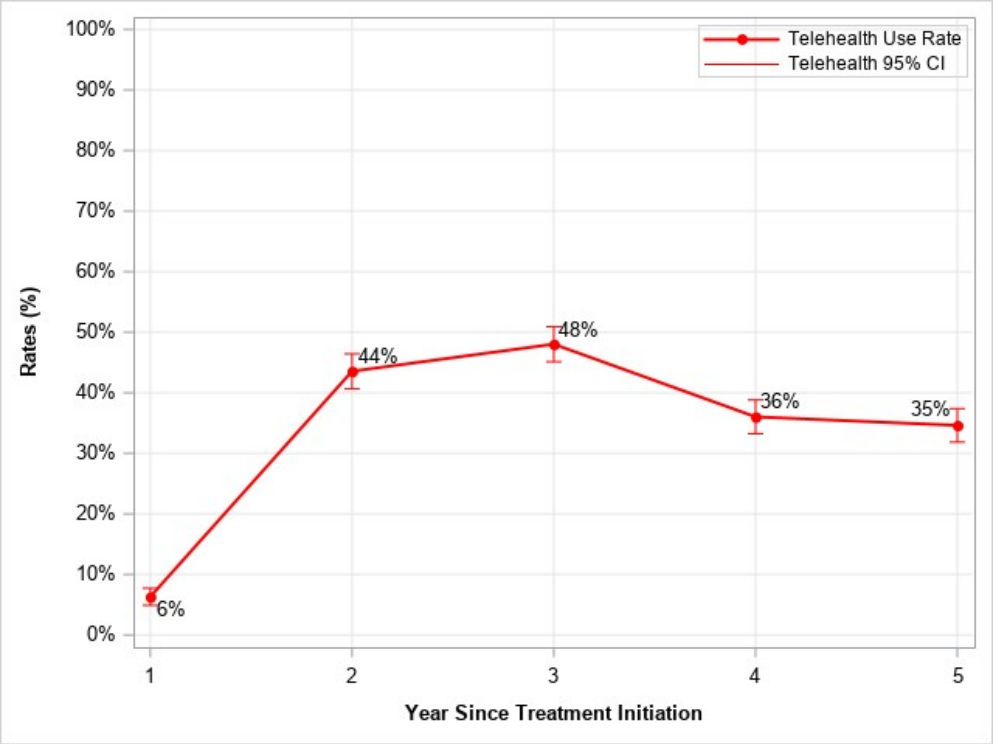
Figure 3.1: Schematic Diagram of the Study Design and Timeline, 2017-2023



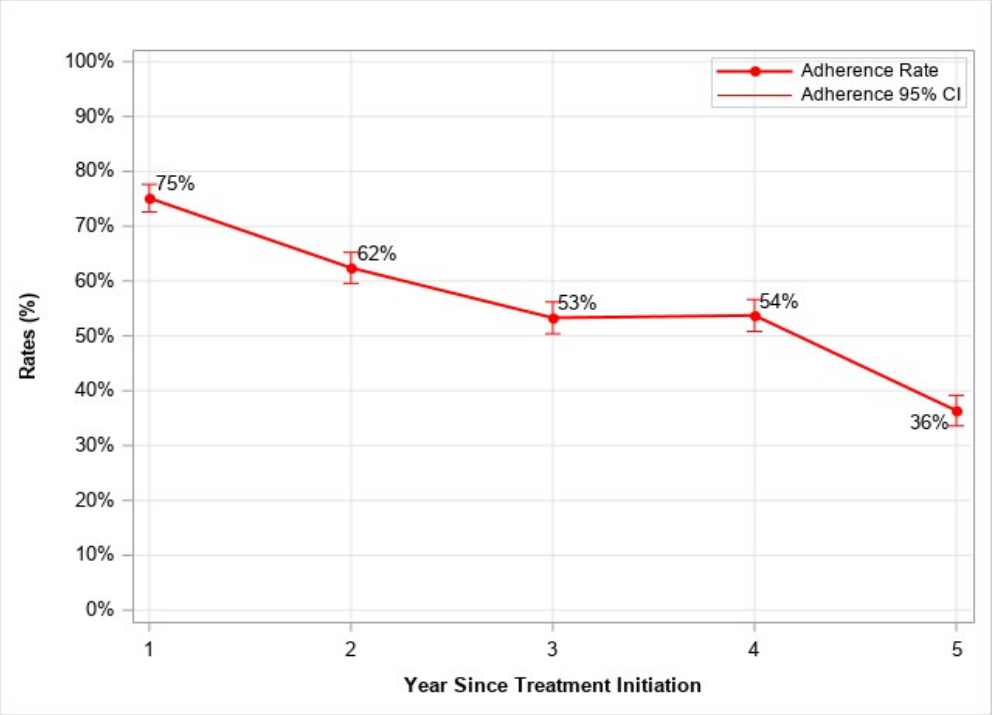
*Diagnosis date is not within the enrollment period; **Previous use of ET before cancer diagnosis
ET: endocrine therapy; TAM: tamoxifen; AI: aromatase inhibitor including letrozole, anastrozole, or exemestane

Figure 3.2: Flowchart of Patients Included in the Study Cohort

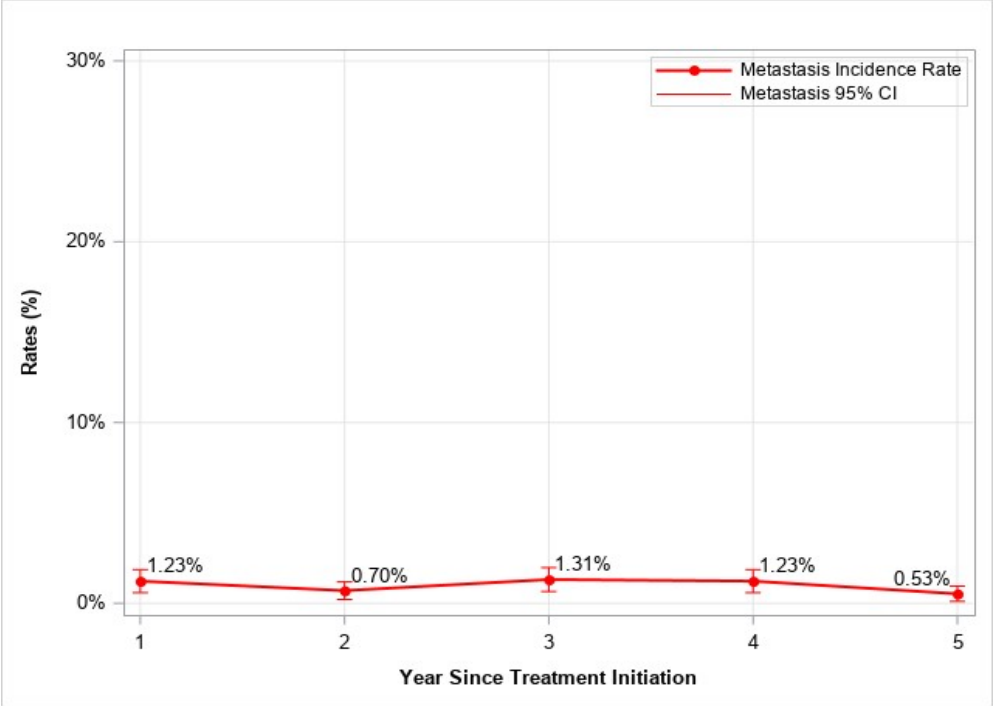
a. Telehealth utilization in each year



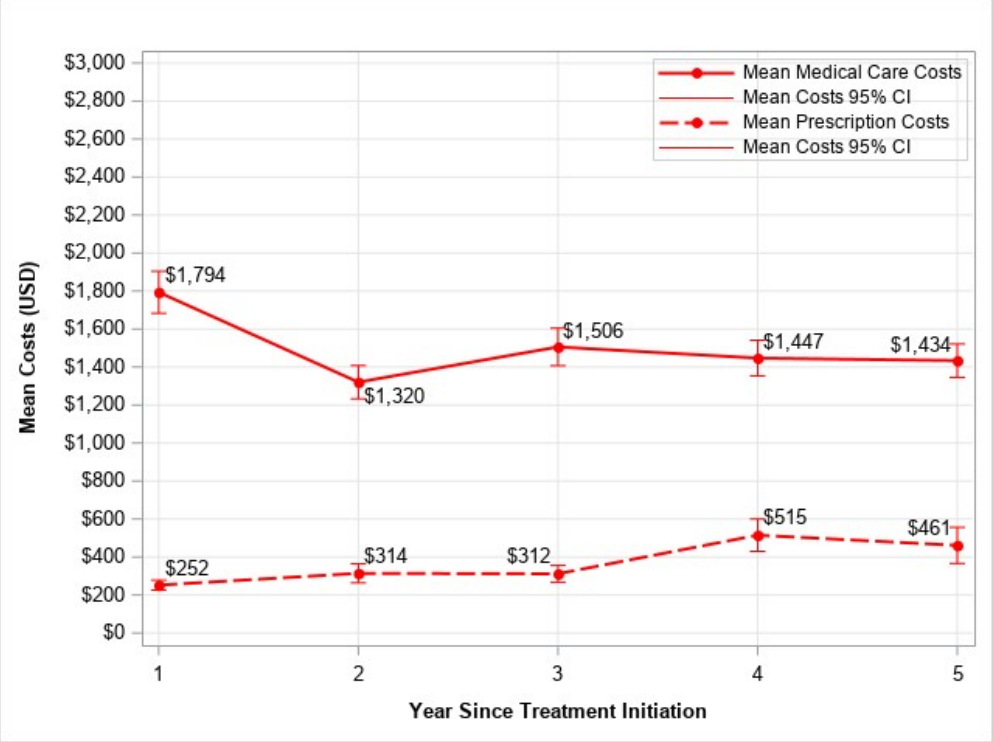
b. Endocrine therapy adherence in each year



c. Annual incidence rates of cancer metastasis over five years



d. Average medical care and prescription costs per patient in each year



CI: confidence interval

Figure 3.3: Trends in Telehealth Utilization, Endocrine Therapy Adherence, Cancer Metastasis, and Healthcare Costs Over Time

CHAPTER 6

CONCLUSIONS

This dissertation systematically examined key dimensions of endocrine therapy in breast cancer, with a focus on adherence patterns, safety profiles, and the potential of telehealth to enhance treatment outcomes. Through rigorous meta-analyses, in-depth safety evaluations, and real-world data analyses, this research provides significant insights into the challenges faced by both patients and healthcare providers in optimizing the use of endocrine therapy. The findings underscore the importance of a comprehensive, multifaceted approach that incorporates adherence support, proactive management of adverse effects, personalized treatment strategies, improved financial accessibility, and the integration of digital health innovations to advance patient-centered cancer care.

The research revealed that adherence to endocrine therapy remains suboptimal, with approximately one in four women failing to maintain the recommended treatment regimen. Younger age and treatment-related side effects emerged as significant contributors to nonadherence. The meta-analysis emphasized the variability in adherence rates, particularly in developing countries where healthcare infrastructure and patient support systems are less robust. These findings highlight the need for targeted patient-centered interventions that address specific barriers to adherence. For example, younger patients often face distinct challenges—such as fertility concerns and financial instability—that may be mitigated through policy reforms, effective counseling, and community-based programs aimed at improving adherence and treatment outcomes.

Endocrine therapies were associated with a wide range of adverse effects, with certain regimens exhibiting significant cardiovascular toxicities, including cardiac arrhythmia, myocardial infarction, heart failure, stroke, and metabolic dysfunctions. Providing effective cancer care in this context necessitates a multidisciplinary approach that engages both oncologists and cardiologists, emphasizes proactive symptom management, ensures close cardiovascular monitoring, and incorporates individualized patient counseling. Furthermore, patient education programs that clearly communicate potential side effects and offer coping strategies can improve treatment tolerability, enhance quality of life, and support long-term adherence—ultimately leading to better clinical outcomes.

The analysis of telehealth utilization demonstrated its potential to enhance medication adherence, but with a simultaneous increase in healthcare costs. By enabling remote monitoring and facilitating timely clinical interventions, telehealth emerged as a valuable tool for promoting sustained adherence, particularly among commercially insured nonelderly women with breast cancer. Telehealth platforms offer virtual consultations, medication reminders, and symptom tracking features that foster patient engagement and support self-management. However, the financial implications of telehealth highlight the need for policies to optimize its affordability and facilitates broader integration into oncology care. To fully achieve telehealth's potential, healthcare systems must adopt innovative delivery models that expand access, ensure equity, and provide continuous high-quality care, ultimately improving survivorship outcomes and quality across diverse patient populations.

Future research should further explore socioeconomic and racial disparities in endocrine therapy adherence across diverse healthcare systems to inform the development of targeted interventions aimed at reducing inequities in cancer care. Longitudinal studies investigating the long-term side effects of endocrine therapies and their genetic predictors are also warranted to enhance understanding of treatment risks and facilitate personalized therapeutic strategies. Additionally, research should assess the sustainability, optimal frequency, and duration of telehealth visits, as well as identify the most effective telehealth-derived services for improving adherence and clinical outcomes. Integrating telehealth with other digital health technologies, such as mobile applications and wearable devices, may further advance personalized care delivery, increasing accessibility and effectiveness for cancer patients.

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APPENDICES

Appendix A: Search String and Results

PubMed (all years - August 31, 2023): 774 # Records

(aromatase inhibitor[tiab] OR estradiol receptor antagonist[tiab] OR estrogen receptor antagonist[tiab] OR Anastrozole[tiab] OR Anastrazole[tiab] OR Arimidex[MH] OR Letrozole[tiab] OR Femara[MH] OR Fémara[MH] OR Exemestane[tiab] OR Aromasil[MH] OR Aromasin[MH] OR Aromasine[MH] OR Examestane[MH] OR Tamoxifen[tiab] OR Nolvadex[MH] OR Novaldex[MH] OR Soltamox [MH] OR Tamoxifen Citrate[MH] OR Tomaxithen[MH] OR Zitazonium[MH])

AND

('breast cancer'[tiab] OR 'breast neoplasm'[tiab] OR breast carcinoma[tiab] OR breast tumor[MH] OR cancer of breast[MH] OR cancer of the breast[MH] OR human mammary carcinoma[MH] OR malignant neoplasm of breast[MH] OR malignant tumor of breast[MH] OR mammary cancer[MH] OR mammary carcinoma, human[MH] OR mammary neoplasm, human[MH] OR mammary neoplasms, human[MH] OR neoplasms, breast [MH] OR tumors, breast[MH])

AND

(developing countr*[tiab] OR less developed [tiab] OR least developed [tiab] OR low-income[tiab] OR middle-income[tiab] OR 'low and middle income countr*'[tiab] OR LMIC[tiab] OR constrain* resource[tiab] OR limit* resource[tiab] OR Africa*[tiab] OR Asia*[tiab] OR South America*[tiab] OR Latin America*[tiab] OR Central America*[tiab]

OR Caribbean[tiab] OR Arab*[tiab] OR Middle East*[tiab] OR Afghanistan*[tiab] OR Albania*[tiab] OR Algeria*[tiab] OR Angola*[tiab] OR Argentina*[tiab] OR Armenia*[tiab] OR Azerbaijan*[tiab] OR Bangladesh*[tiab] OR Belarus*[tiab] OR Belize*[tiab] OR Benin*[tiab] OR Bhutan*[tiab] OR Bolivia*[tiab] OR Bosnia*[tiab] OR Botswana*[tiab] OR Brazil*[tiab] OR Burkin*[tiab] OR Burundi*[tiab] OR Cabo Verd*[tiab] OR Cambodia*[tiab] OR Cameroon*[tiab] OR Central African Republic[tiab] OR Chad*[tiab] OR China[tiab] OR Chinese[tiab] OR Colombia*[tiab] OR Comoros*[tiab] OR Comorian*[tiab] OR Congo*[tiab] OR Costa Rica*[tiab] OR Cote divoire*[tiab] OR Ivoirian*[tiab] OR Cuba*[tiab] OR Djibouti*[tiab] OR Dominica*[tiab] OR Ecuador*[tiab] OR Egypt*[tiab] OR El Salvador*[tiab] OR Salvadoran*[tiab] OR Eritrea*[tiab] OR Eswatini*[tiab] OR Ethiopia*[tiab] OR Fiji*[tiab] OR Gabon*[tiab] OR Gambia*[tiab] OR Gaza[tiab] OR Georgia*[tiab] OR Ghana*[tiab] OR Grenada*[tiab] OR Grenadines*[tiab] OR Guatemala*[tiab] OR Guinea*[tiab] OR Guyana*[tiab] OR Haiti*[tiab] OR Herzegovina*[tiab] OR Hondura*[tiab] OR India*[tiab] OR Indonesia*[tiab] OR Iran*[tiab] OR Iraq*[tiab] OR Jamaica*[tiab] OR Jordan*[tiab] OR Kazakh*[tiab] OR Kenya*[tiab] OR Kiribati*[tiab] OR Korea*[tiab] OR Kosovo*[tiab] OR Kyrgyz*[tiab] OR Lao[tiab] OR Laotian*[tiab] OR Lebanon[tiab] OR Lebanese[tiab] OR Lesotho*[tiab] OR Liberia*[tiab] OR Libya*[tiab] OR Macedonia*[tiab] OR Madagascar*[tiab] OR Malawi*[tiab] OR Malaysia*[tiab] OR Maldiv*[tiab] OR Mali[tiab] OR Malian*[tiab] OR Marshall Island*[tiab] OR Mauritania*[tiab] OR Mauriti*[tiab] OR Mexic*[tiab] OR Micronesia*[tiab] OR Moldova*[tiab] OR Mongolia*[tiab] OR Montenegr*[tiab] OR Morocc*[tiab] OR Mozambi*[tiab] OR Myanmar*[tiab] OR Namibia*[tiab] OR Nepal*[tiab] OR Nicaragua*[tiab] OR Niger*[tiab] OR Pakistan*[tiab]

OR Palau*[tiab] OR Palestin*[tiab] OR Papua*[tiab] OR Paraguay*[tiab] OR Peru*[tiab] OR Philippin*[tiab] OR Russia*[tiab] OR Rwanda*[tiab] OR Samoa*[tiab] OR Sao Tome*[tiab] OR Senegal*[tiab] OR Serbia*[tiab] OR Sierra Leone*[tiab] OR Solomon Island*[tiab] OR Somali*[tiab] OR South Africa*[tiab] OR Sri Lanka*[tiab] OR St Lucia*[tiab] OR Saint Lucia[tiab] OR St Vincent*[tiab] OR Saint Vincent[tiab] OR Sudan*[tiab] OR Surinam*[tiab] OR Syria*[tiab] OR Tajik*[tiab] OR Tanzania*[tiab] OR Thai*[tiab] OR Timor*[tiab] OR Togo*[tiab] OR Tonga*[tiab] OR Tunisia*[tiab] OR Turk*[tiab] OR Tuvalu*[tiab] OR Uganda*[tiab] OR Ukraine*[tiab] OR Uzbek*[tiab] OR Vanuatu*[tiab] OR Venezuela*[tiab] OR Vietnam*[tiab] OR West Bank*[tiab] OR Yemen*[tiab] OR Zambia*[tiab] OR Zimbabw*[tiab] OR Brunei*[tiab] OR Hong Kong*[tiab] OR Hongkong*[tiab] OR Singapore*[tiab] OR Taiwan*[tiab] OR Bahrain*[tiab] OR Israel*[tiab] OR Kuwait*[tiab] OR Oman*[tiab] OR Qatar*[tiab] OR Saudi[tiab] OR Emirat*[tiab] OR UAE[tiab] OR Baham*[tiab] OR Barbados[tiab] OR Barbadian[tiab] OR Trinidad*[tiab] OR Tobago*[tiab] OR Trinbagonian*[tiab] OR Trini[tiab] OR Panama*[tiab] OR Chile*[tiab] OR Uruguay*[tiab])

Appendix B: Pooled Rates of Discontinuation, Safety Outcomes, Recurrence, and Mortality at Specific Time Points

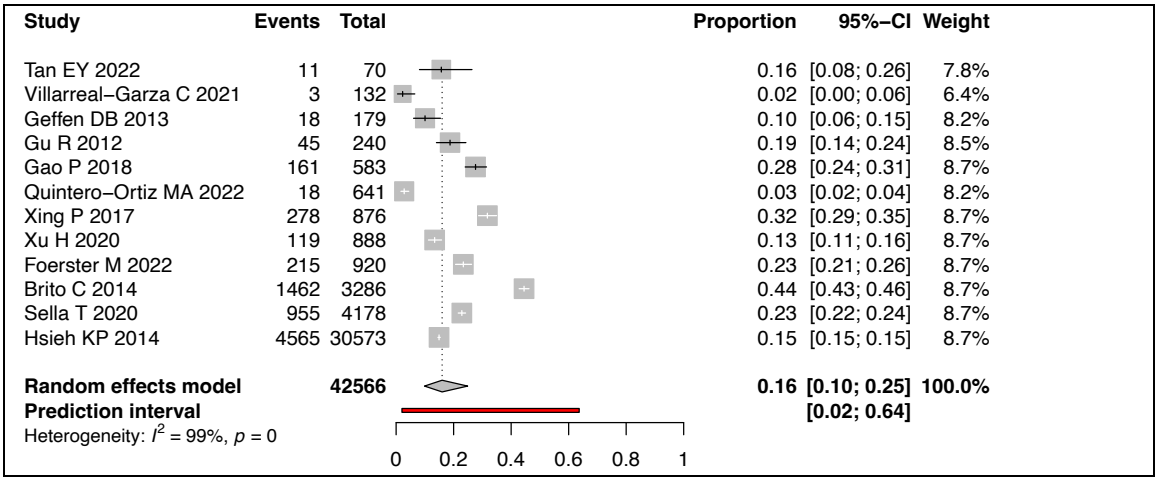

Figure A: Forest plot of discontinuation rate

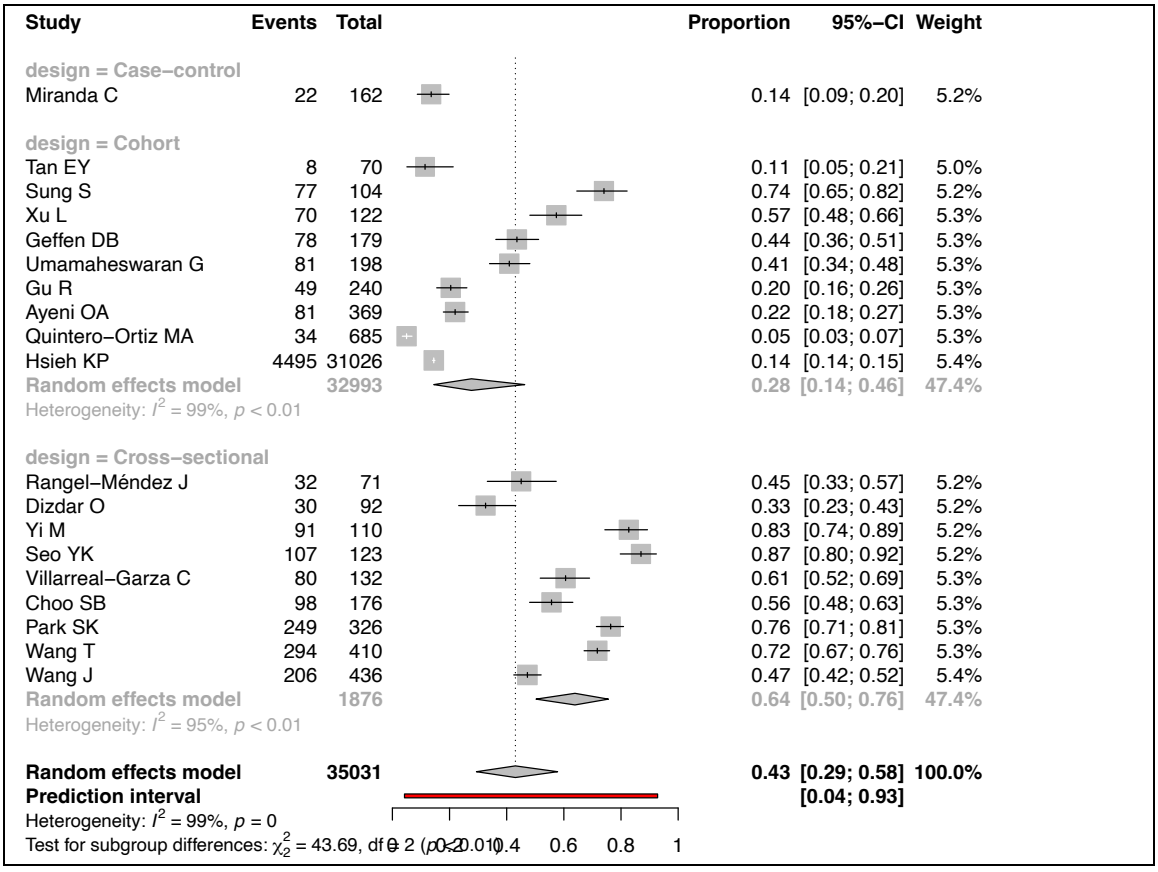

Figure B-1: Forest plot of musculoskeletal pain by study design

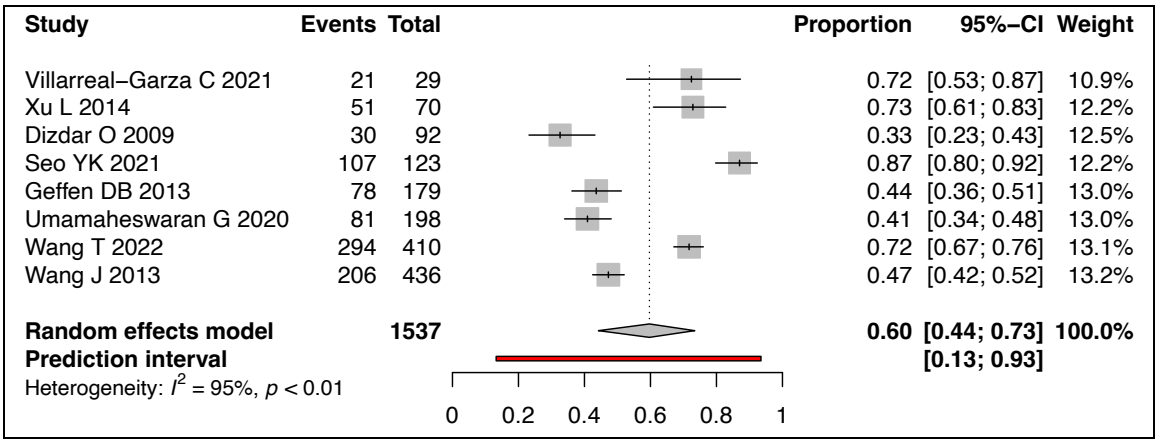

Figure B-2: Forest plot of musculoskeletal pain in AI users

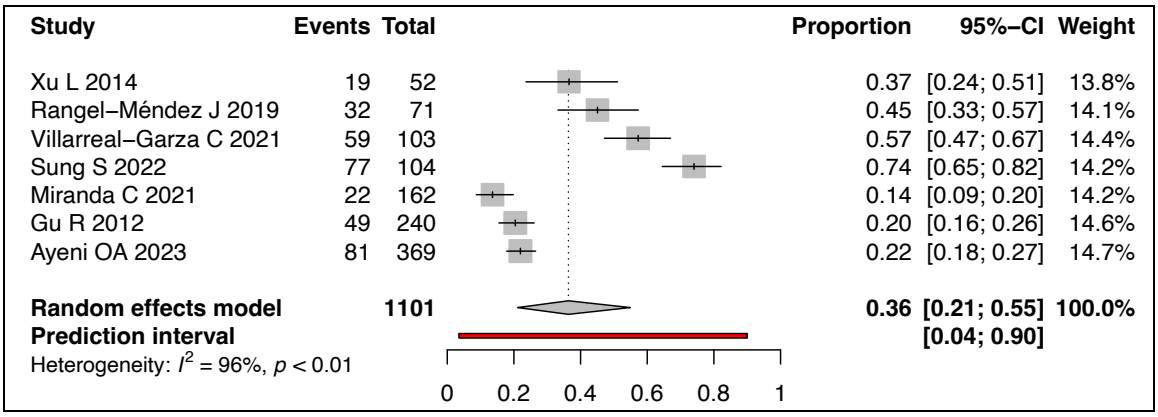

Figure B-3: Forest plot of musculoskeletal pain in TAM users

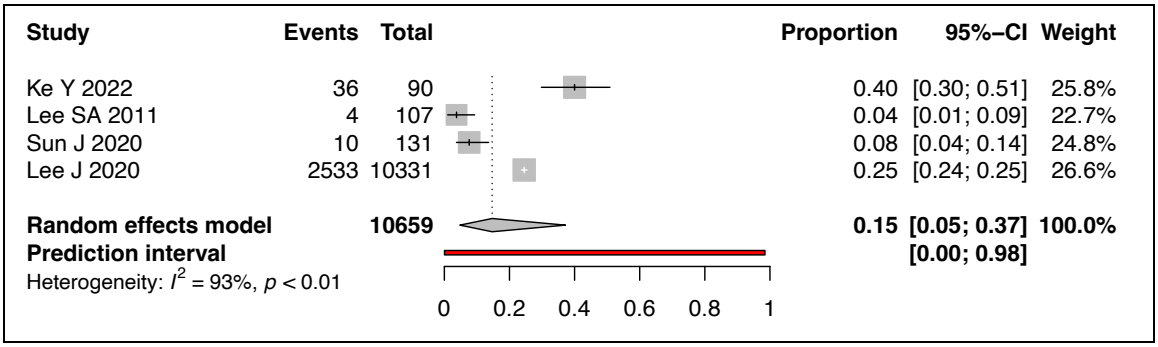

Figure B-4: Forest plot of osteoporosis in AI users

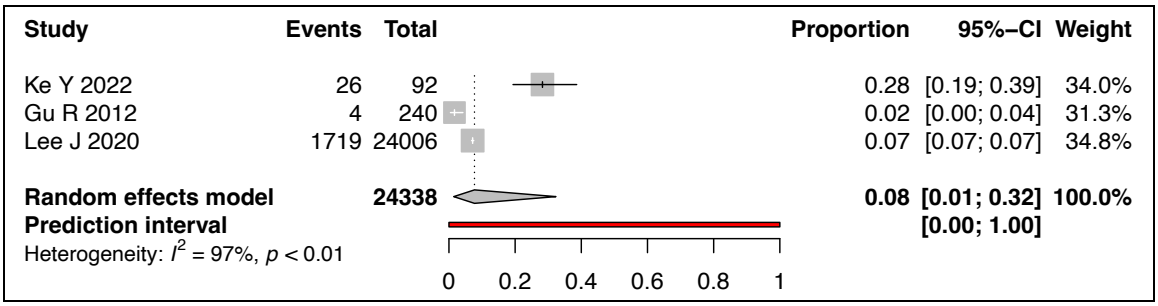

Figure B-5: Forest plot of osteoporosis in TAM users

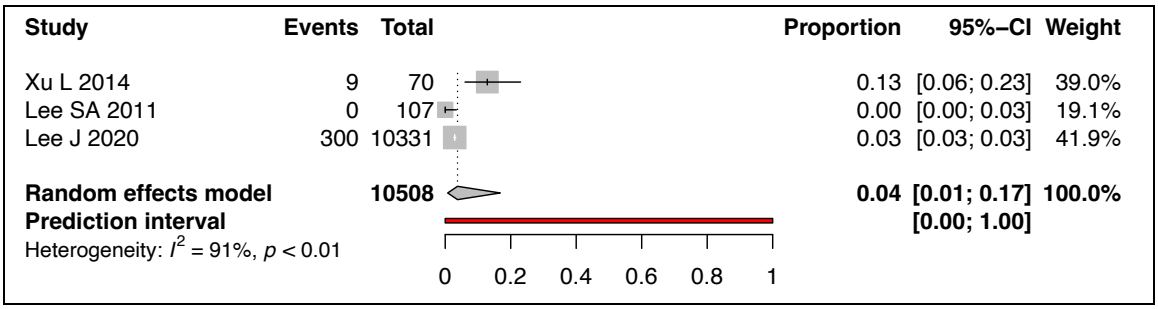

Figure B-6: Forest plot of fractures in AI users

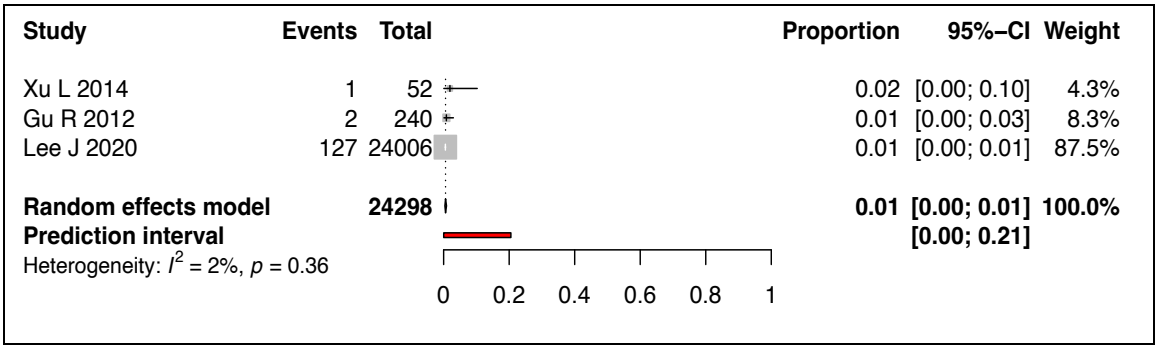

Figure B-7: Forest plot of fractures in TAM users

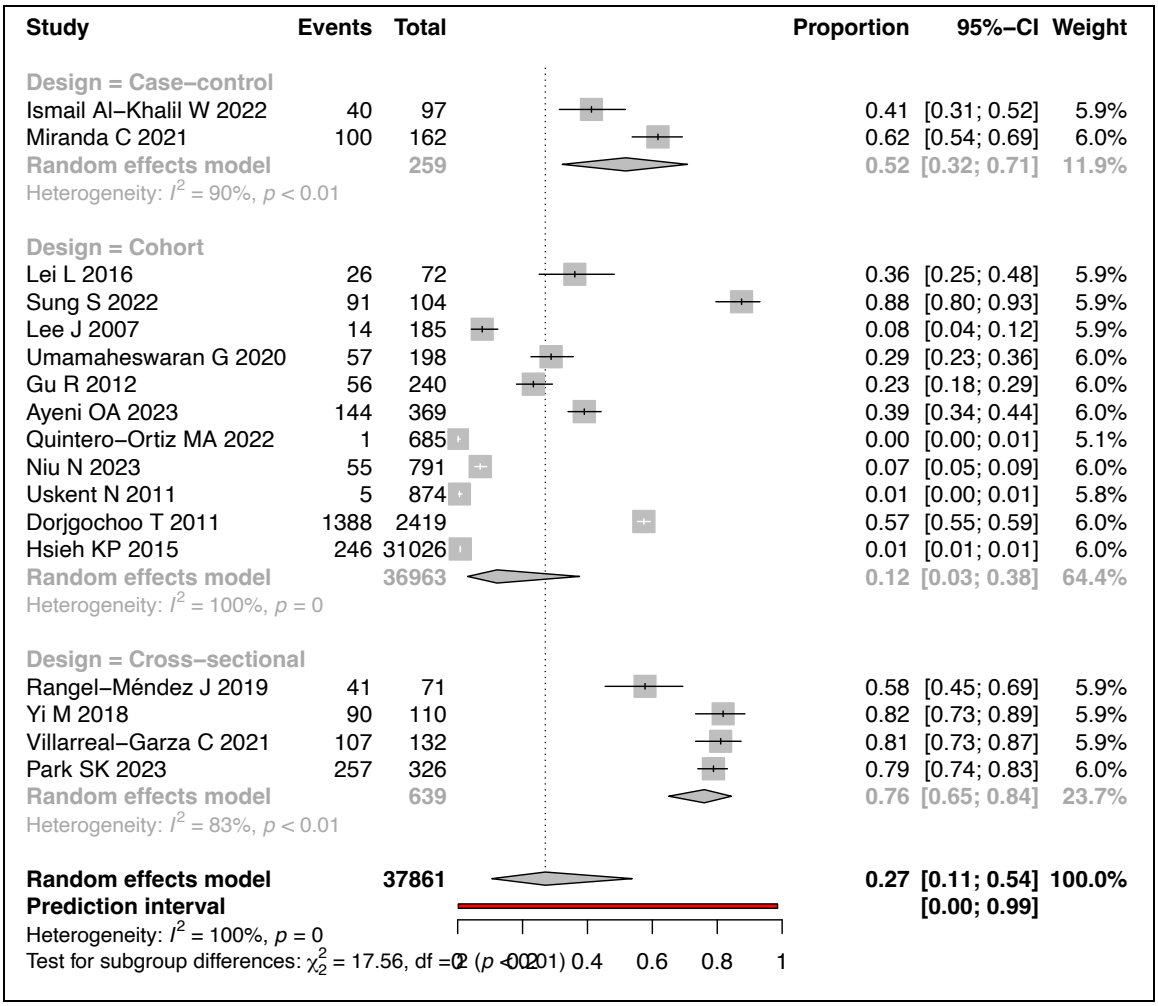

Figure B-8: Forest plot of hot flashes by study design

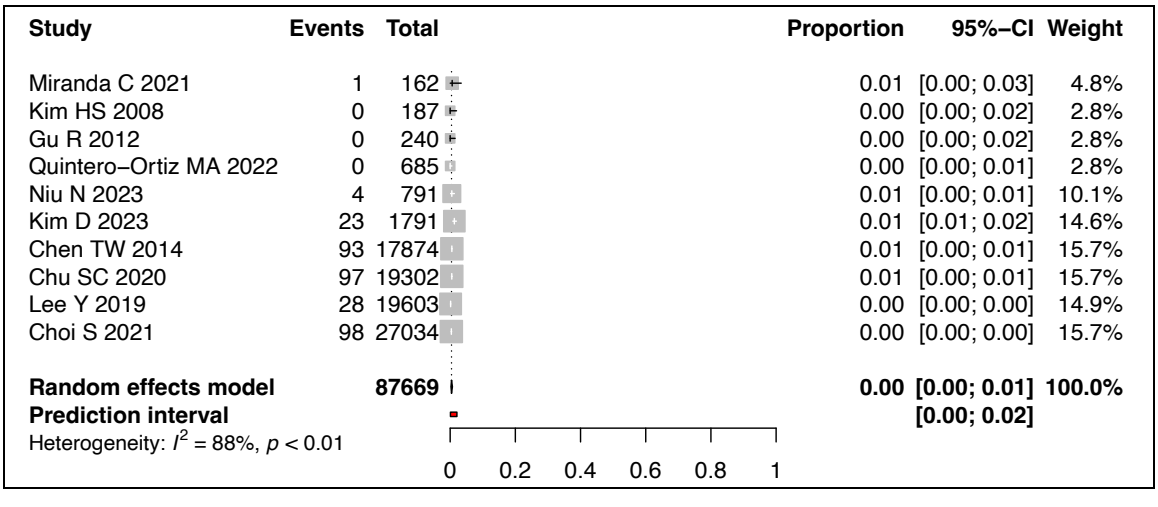

Figure B-9: Forest plot of endometrial cancer

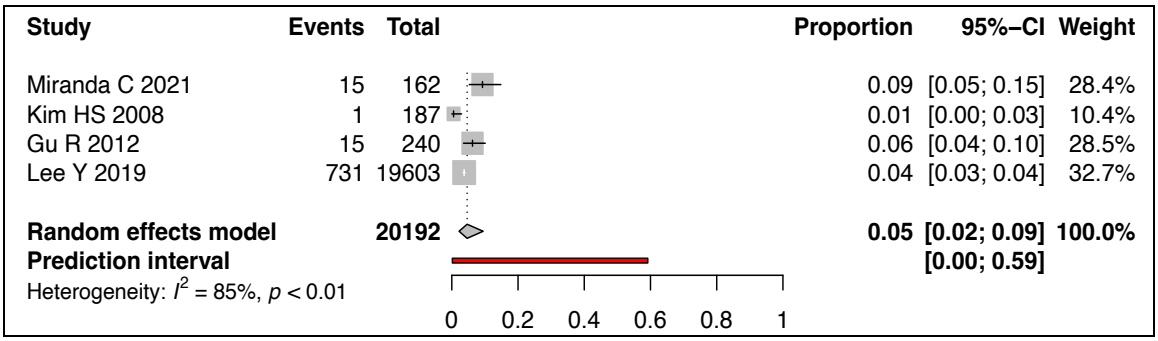

Figure B-10: Forest plot of endometrial hyperplasia (TAM only)

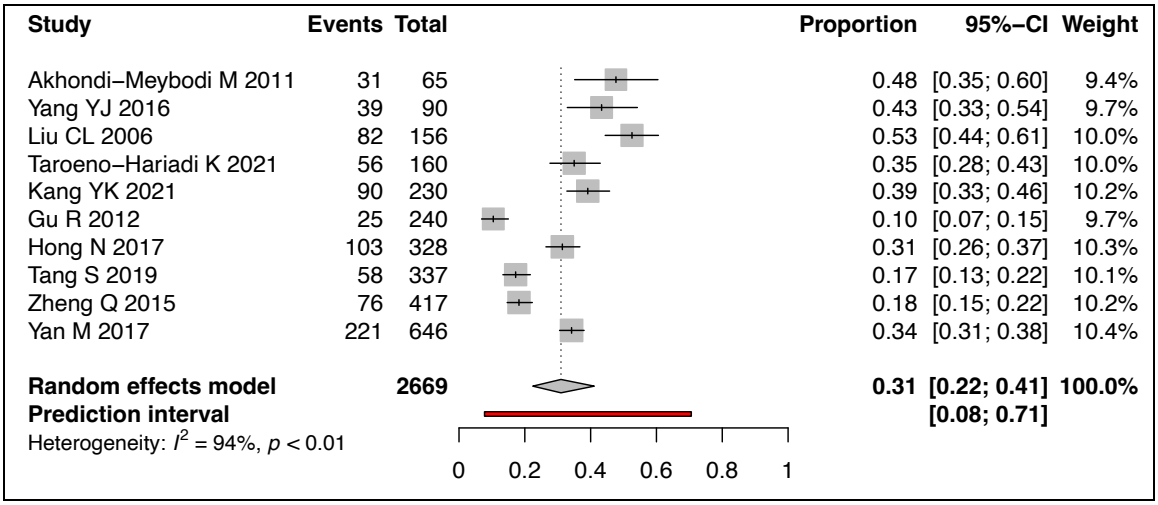

Figure B-11: Forest plot of fatty liver disease

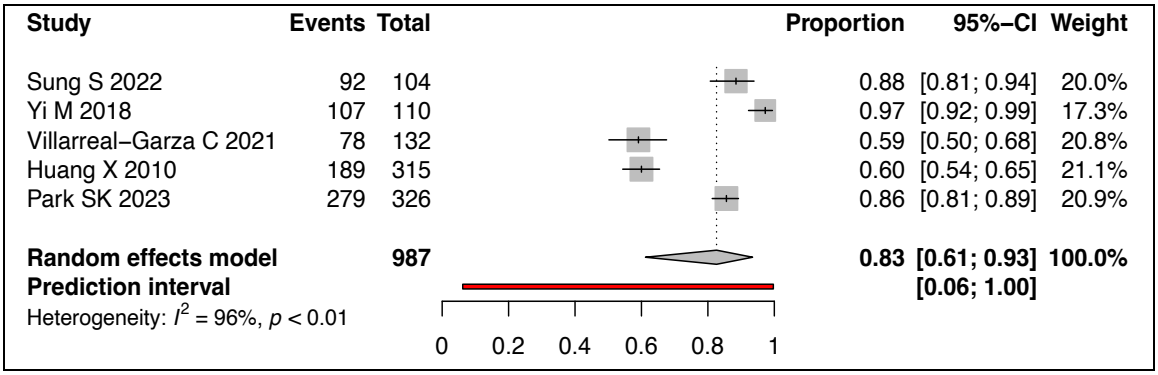

Figure B-12: Forest plot of fatigue

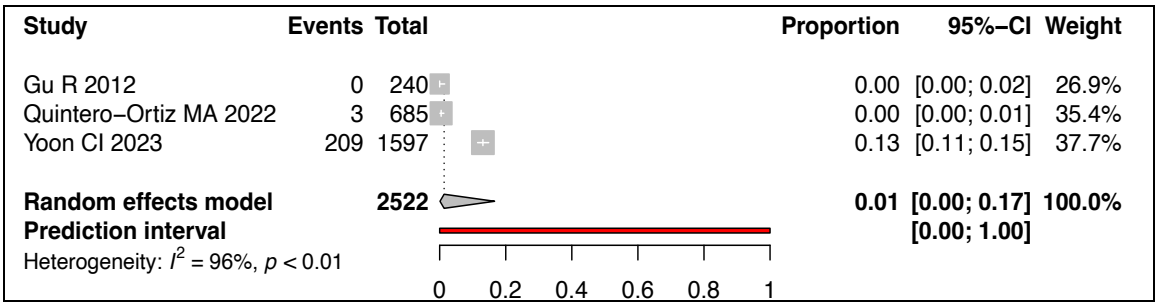

Figure B-13: Forest plot of cataract

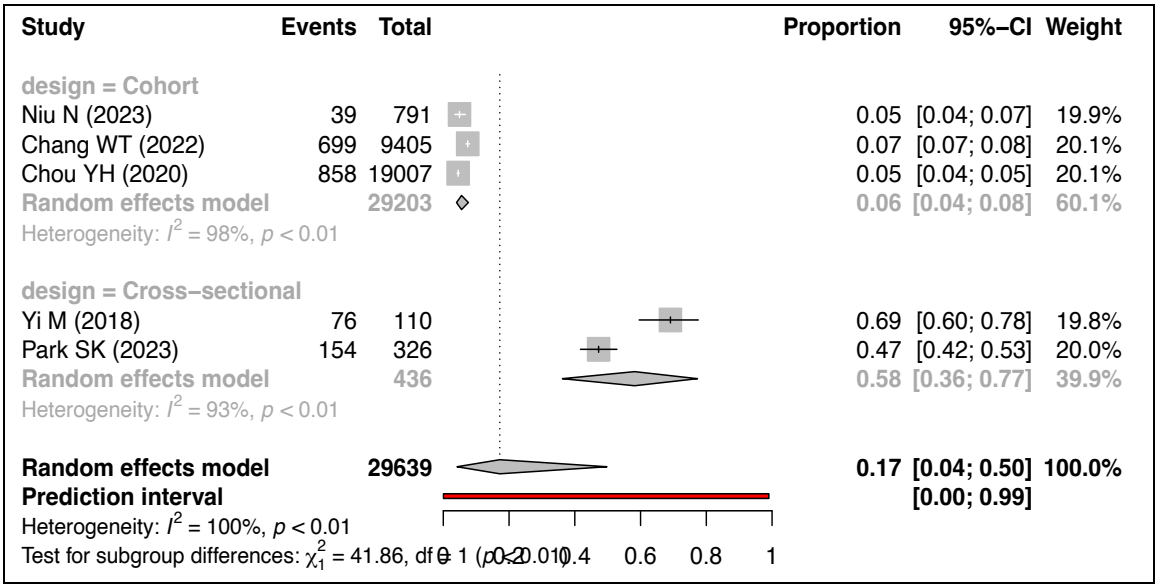

Figure B-14: Forest plot of cardiovascular events by study design

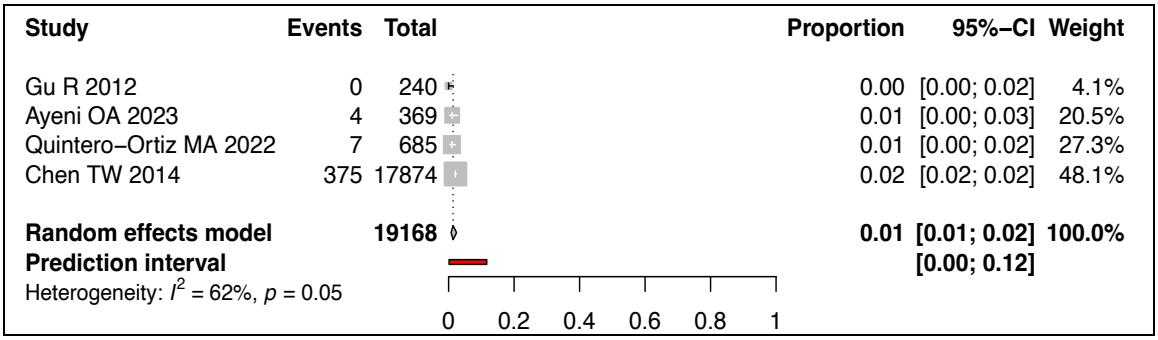

Figure B-15: Forest plot of thromboses

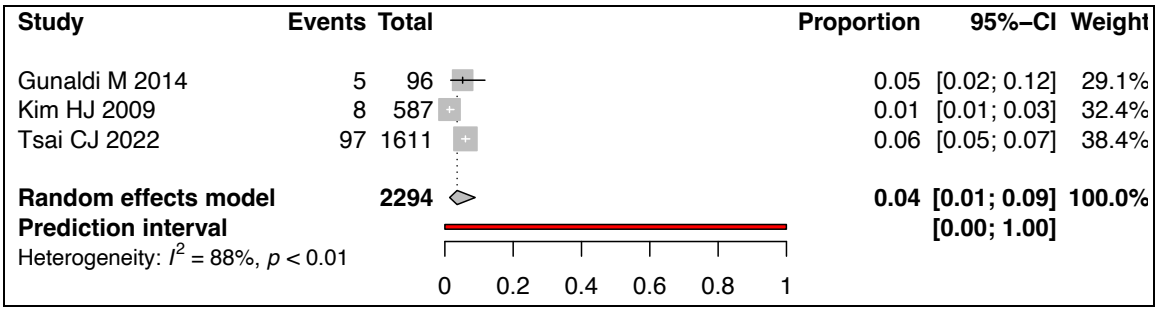

Figure C-1: Forest plot of recurrences at 3 years

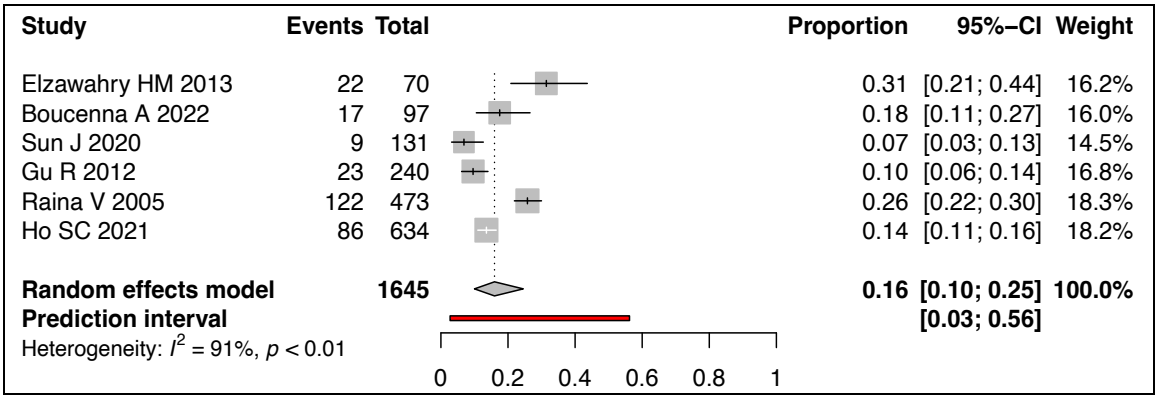

Figure C-2: Forest plot of recurrences at 4 years

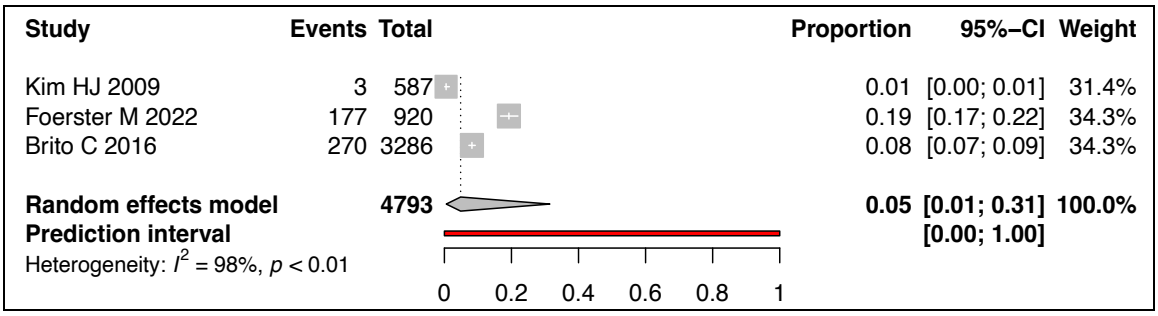

Figure D-1: Forest plot of death at 3 years

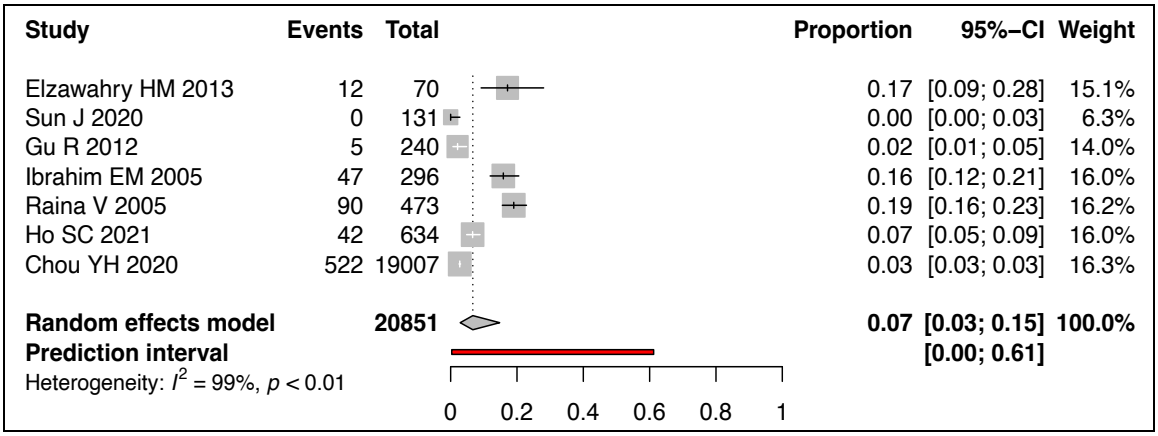

Figure D-2: Forest plot of death at 4 years

Appendix C: Risk of Bias Assessment

Case-control studies (JBI)									
First author name (year)	**Identification criteria**	**Groups comparability**	**Meaningful exposure period**	**Exposure ascertainment**	**Outcome assessement**	**Confounding factors identification**	**Strategies for confounding factors**	**Appropriate statistical analysis**	**Overall quality**
Ismail Al-Khalil W (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Miranda C (2021)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Cross-sectional studies (JBI)									
First author name (year)	**Inclusion criteria**	**Subjects & setting description**	**Condition measurement**	**Exposure ascertainment**	**Outcome assessement**	**Confounding factors identification**	**Strategies for confounding factors**	**Appropriate statistical analysis**	**Overall quality**
Ali EE (2017)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Camejo N (2023)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Choo SB (2019)	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	**Good**
Cruz A (2017)	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	**Fair**
Dizdar O (2009)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Elsamany SA (2022)	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢	**Fair**
Huang X (2010)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Liem GS (2015)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Lima MTM (2017)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Martinez-Cannon BA (2021)	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	**Good**
Park SK (2023)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Rangel-Méndez J (2019)	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	**Good**
Seo YK (2021)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Villarreal-Garza C (2021)	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	**Good**
Wang J (2013)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Wang T (2022)	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	**Good**
Xu H (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Yi M (2018)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**
Zeeneldin AA (2012)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	**Good**

Figure E-1: Risk of bias assessment for case-control and cross-sectional studies

Cohort Studies (JBI)									
First author name (year)	Exposure ascertainment	Outcome assessement	Free of outcome at baseline	Reported follow-up time	Complete follow-up	Confounding factors identification	Strategies for confounding factors	Appropriate statistical analysis	Overall quality
Ahn SG (2014)	+	?	+	+	+	+	+	+	Good
Ahn SJ (2021)	?	+	+	+	+	+	+	+	Good
Akhondi-Meybodi M (2011)	?	+	+	?	+	+	+	+	Fair
Aphinives P (2014)	+	+	+	+	+	+	+	+	Good
Aryandono T (2006)	+	+	+	+	?	+	+	+	Good
Ayeni OA (2023)	+	+	+	+	+	+	+	+	Good
Boucenna A (2022)	+	+	+	+	+	+	+	+	Good
Brito C (2014)	+	+	+	+	+	+	+	+	Good
Brito C (2014)	+	+	+	+	+	+	+	+	Good
Brito C (2016)	+	+	+	+	+	+	+	+	Good
Camejo-Martínez N (2019)	+	+	+	+	+	+	+	+	Good
Chan PW (2021)	+	+	+	+	+	+	+	+	Good
Chang WT (2022)	+	+	+	+	+	+	+	+	Good
Chen TW (2014)	+	+	+	+	+	+	+	+	Good
Choi S (2021)	+	+	+	+	+	+	+	+	Good
Choi YJ (2021)	+	+	+	+	+	+	+	+	Good
Chou YH (2020)	+	+	+	+	+	+	+	+	Good
Chow LW (1997)	+	+	+	+	+	+	+	+	Good
Chu SC (2020)	+	+	+	+	+	+	+	+	Good
Dorjgochoo T (2011)	+	+	?	+	?	+	+	+	Fair
Elzawahry HM (2013)	+	?	+	+	+	+	+	+	Good
Ezzat AA (1999)	+	+	+	+	+	+	+	+	Good
Foerster M (2022)	+	+	+	+	+	+	+	+	Good
Gao P (2018)	+	?	+	+	-	+	+	+	Fair
Geffen DB (2013)	+	?	?	+	+	+	+	+	Fair
Gu R (2012)	+	+	+	+	+	+	+	+	Good
Gunaldi M (2014)	+	?	+	+	?	+	+	+	Fair
Hathila TN (2015)	+	?	+	-	+	+	+	+	Fair
Ho SC (2021)	+	+	+	+	+	+	+	+	Good
Hong N (2017)	+	+	+	+	?	+	+	+	Good

Figure E-2: Risk of bias assessment for cohort studies

Cohort Studies (JBI)									
First author name (year)	Exposure ascertainment	Outcome assessement	Free of outcome at baseline	Reported follow-up time	Complete follow-up	Confounding factors identification	Strategies for confounding factors	Appropriate statistical analysis	Overall quality
Hsieh CJ (2017)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Hsieh KP (2014)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Hsieh KP (2015)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Hwang KT (2018)	🟡	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Fair
Ibrahim EM (2005)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Jung M (2010)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Kang YK (2021)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Kang X (2010)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Ke Y (2022)	🟢	🟢	🔴	🟢	🟢	🟢	🟢	🟢	Good
Khobrani A (2022)	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🟢	Fair
Kim D (2023)	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Kim HJ (2009)	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	Good
Kim HS (2008)	🟢	🟢	🟡	🟢	🟢	🔴	🔴	🟢	Fair
Kim J (2012)	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Good
Kim K (2017)	🟡	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Fair
Koo H (2016)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Lee J (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Lee J (2007)	🟡	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Fair
Lee SA (2011)	🟢	🟡	🔴	🟢	🟢	🟢	🟢	🟢	Fair
Lee Y (2019)	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Fair
Lei L (2016)	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Good
Lim ST (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Liu CL (2006)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Nardin JM (2020)	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	Good
Niu N (2023)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Oh J (2022)	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Park HS (2011)	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Park IH (2012)	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Good
Quintero-Ortiz MA (2022)	🟡	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Fair
Raina V (2005)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good

Figure E-2: Risk of bias assessment for cohort studies (Continued)

Cohort Studies (JBI)									
First author name (year)	Exposure ascertainment	Outcome assessement	Free of outcome at baseline	Reported follow-up time	Complete follow-up	Confounding factors identification	Strategies for confounding factors	Appropriate statistical analysis	Overall quality
Sella T (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Shin JJ (2019)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Sun J (2020)	🟡	🟢	🟢	🟢	🟢	🟢	🔴	🟢	Fair
Sung S (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Tan EY (2022)	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Good
Tang S (2019)	🟢	🟡	🟡	🔴	🟡	🟢	🟢	🟢	Poor
Taroeno-Hariadi K (2021)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Tiong V (2014)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Tong Y (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Tsai CJ (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Umamaheswaran G (2020)	🟢	🟢	🟢	🔴	🟡	🟢	🟢	🟢	Fair
Unal C (2023)	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	Good
Uskent N (2011)	🟢	🟡	🟡	🟢	🔴	🔴	🔴	🟢	Poor
Wang J (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Wasserman LJ (2007)	🟢	🟡	🟢	🟢	🟢	🔴	🔴	🟢	Fair
Wu CE (2016)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Xing P (2017)	🟢	🟢	🟢	🟢	🔴	🟢	🟢	🟢	Good
Xu L (2014)	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟢	Fair
Yadav B (2010)	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🟢	Fair
Yan M (2017)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Yang YJ (2016)	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟢	Fair
Yoon CI (2023)	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good
Zheng Q (2015)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Good

Figure E-2: Risk of bias assessment for cohort studies (Continued)

Answer key	Risk of bias	Rating
🟢 Yes	low	Good
🔴 No	moderate	Fair
🟡 Unclear	high	Poor

Appendix D: Definition of SMQs for Studied Outcomes

Myocardial infarction	
'Acute cardiac event'	'Blood creatine phosphokinase abnormal'
'Acute coronary syndrome'	'Blood creatine phosphokinase increased'
'Acute myocardial infarction'	'Cardiac ventricular scarring'
'Angina unstable'	'Coronary artery restenosis'
'Blood creatine phosphokinase MB abnormal'	'ECG electrically inactive area'
'Blood creatine phosphokinase MB increased'	'ECG signs of myocardial infarction'
'Coronary artery embolism'	'Electrocardiogram Q wave abnormal'
'Coronary artery occlusion'	'Electrocardiogram ST segment abnormal'
'Coronary artery reocclusion'	'Electrocardiogram ST segment elevation'
'Coronary artery thrombosis'	'Electrocardiogram ST-T segment elevation'
'Coronary bypass thrombosis'	'Electrocardiogram U wave inversion'
'Coronary vascular graft occlusion'	'Infarction'
'Heart-type fatty acid-binding protein increased'	'Myocardial necrosis marker increased'
'Kounis syndrome'	'Scan myocardial perfusion abnormal'
'Myocardial infarction'	'Vascular graft occlusion'
'Myocardial necrosis'	'Vascular stent occlusion'
'Myocardial reperfusion injury'	'Vascular stent thrombosis'
'Myocardial stunning'	
'Papillary muscle infarction'	
'Periprocedural myocardial infarction'	
'Post procedural myocardial infarction'	
'Postinfarction angina'	
'Silent myocardial infarction'	
'Troponin I increased'	
'Troponin increased'	
'Troponin T increased'	

Cardiac failure		
'Acute left ventricular failure'	'Artificial heart implant'	'Left ventricular dysfunction'
'Acute pulmonary oedema'	'Atrial natriuretic peptide abnormal'	'Left ventricular enlargement'
'Acute right ventricular failure'	'Atrial natriuretic peptide increased'	'Lower respiratory tract congestion'
'Cardiac asthma'	'Bendopnoea'	'Myocardial depression'
'Cardiac failure'	'Brain natriuretic peptide abnormal'	'Myocardial strain imaging abnormal'
'Cardiac failure acute'	'Brain natriuretic peptide increased'	'N-terminal prohormone brain natriuretic peptide abnormal'
'Cardiac failure chronic'	'Cardiac cirrhosis'	'N-terminal prohormone brain natriuretic peptide increased'
'Cardiac failure congestive'	'Cardiac contractility decreased'	'Neonatal dyspnoea'
'Cardiac failure high output'	'Cardiac contractility modulation therapy'	'Nocturnal dyspnoea'
'Cardiogenic shock'	'Cardiac device implantation'	'Oedema'
'Cardiohepatic syndrome'	'Cardiac device reprogramming'	'Oedema blister'
'Cardiopulmonary failure'	'Cardiac dysfunction'	'Oedema due to cardiac disease'
'Cardiorenal syndrome'	'Cardiac index decreased'	'Oedema neonatal'
'Chronic left ventricular failure'	'Cardiac output decreased'	'Oedema peripheral'
'Chronic right ventricular failure'	'Cardiac resynchronisation therapy'	'Orthopnoea'
'Congestive hepatopathy'	'Cardiac ventriculogram abnormal'	'Peripheral oedema neonatal'
'Cor pulmonale'	'Cardiac ventriculogram left abnormal'	'Peripheral swelling'
'Cor pulmonale acute'	'Cardiac ventriculogram right abnormal'	'Post cardiac arrest syndrome'
'Cor pulmonale chronic'	'Cardio-respiratory distress'	'Prohormone brain natriuretic peptide abnormal'
'Ejection fraction decreased'	'Cardiomegaly'	'Prohormone brain natriuretic peptide increased'
'Heart failure with midrange ejection fraction'	'Cardiothoracic ratio increased'	'Pulmonary congestion'
'Heart failure with preserved ejection fraction'	'Central venous pressure increased'	'Right ventricular diastolic collapse'
'Heart failure with reduced ejection fraction'	'Cerebrocardiac syndrome'	'Right ventricular dilatation'
'Hepatojugular reflux'	'Chronic myocarditis'	'Right ventricular dysfunction'

Cardiac failure (continued)		
'Left ventricular failure'	'Coronary sinus dilatation'	'Right ventricular enlargement'
'Low cardiac output syndrome'	'Diastolic dysfunction'	'Scan myocardial perfusion abnormal'
'Neonatal cardiac failure'	'Dilatation ventricular'	'Stroke volume decreased'
'Obstructive shock'	'Dynamic cardiomyoplasty'	'Surgical ventricular restoration'
'Pulmonary oedema'	'Dyspnoea paroxysmal nocturnal'	'Systolic dysfunction'
'Pulmonary oedema neonatal'	'Global longitudinal strain abnormal'	'Temporary mechanical circulatory support'
'Radiation associated cardiac failure'	'Heart and lung transplant'	'Venous pressure increased'
'Right ventricular ejection fraction decreased'	'Heart transplant'	'Venous pressure jugular abnormal'
'Right ventricular failure'	'Heart transplant failure'	'Venous pressure jugular increased'
'Ventricular failure'	'Heart-lung transplant failure'	'Ventricular assist device insertion'
	'Hepatic vein dilatation'	'Ventricular compliance decreased'
	'Implantable cardiac monitor replacement'	'Ventricular dysfunction'
	'Intracardiac pressure increased'	'Ventricular dyssynchrony'
	'Jugular vein distension'	'Ventricular outflow tract dredging'
	'Left ventricular diastolic collapse'	'Wall motion score index abnormal'
	'Left ventricular dilatation'	

Arrhythmia		
'Accelerated idioventricular rhythm'	'Bradyarrhythmia'	'Electrocardiogram ambulatory abnormal'
'Accessory cardiac pathway'	'Bradycardia'	'Electrocardiogram change'
'Adams-Stokes syndrome'	'BRASH syndrome'	'Electrocardiogram delta waves abnormal'
'Agonal rhythm'	'Brugada syndrome'	'Electrocardiogram P wave abnormal'
'Anomalous atrioventricular excitation'	'Bundle branch block bilateral'	'Electrocardiogram PR prolongation'
'Arrhythmia supraventricular'	'Bundle branch block left'	'Electrocardiogram PR shortened'
'Arrhythmia'	'Bundle branch block right'	'Electrocardiogram QRS complex prolonged'
'Arrhythmic storm'	'Bundle branch block'	'Electrocardiogram QT prolonged'
'Atrial conduction time prolongation'	'Cardiac arrest'	'Electrocardiogram repolarisation abnormality'
'Atrial escape rhythm'	'Cardiac death'	'Electrocardiogram RR interval abnormal'
'Atrial fibrillation'	'Cardiac fibrillation'	'Electrocardiogram RR interval prolonged'
'Atrial flutter'	'Cardiac flutter'	'Electrocardiogram RR interval shortened'
'Atrial parasystole'	'Cardiac telemetry abnormal'	'Electrocardiogram U wave inversion'
'Atrial standstill'	'Cardio-respiratory arrest'	'Electrocardiogram U wave present'
'Atrial tachycardia'	'Central bradycardia'	'Electrocardiogram U-wave abnormality'
'Atrioventricular block complete'	'Cerebrocardiac syndrome'	'Extrasystoles'
'Atrioventricular block first degree'	'Chronotropic incompetence'	'Familial atrial fibrillation'
'Atrioventricular block second degree'	'Conduction disorder'	'Fascicular block'
'Atrioventricular block'	'Congenital supraventricular tachycardia'	'Frederick's syndrome'
'Atrioventricular conduction time shortened'	'Defect conduction intraventricular'	'Heart alternation'
'Atrioventricular dissociation'	'Early repolarisation syndrome'	'Heart rate abnormal'
'Atrioventricular node dysfunction'	'ECG P wave inverted'	'Heart rate decreased'
'Bezold-Jarisch reflex'	'Ectopic atrial rhythm'	'Heart rate increased'
'Bifascicular block'	'Electrocardiogram abnormal'	'Heart rate irregular'

Arrhythmia (continued)		
'Holiday heart syndrome'	'Respiratory sinus arrhythmia magnitude abnormal'	'Tachyarrhythmia'
'Ictal bradycardia syndrome'	'Respiratory sinus arrhythmia magnitude decreased'	'Tachycardia paroxysmal'
'Inappropriate sinus tachycardia'	'Respiratory sinus arrhythmia magnitude increased'	'Tachycardia'
'Junctional ectopic tachycardia'	'Retrograde p-waves'	'Torsade de pointes'
'Lenegre's disease'	'Rhythm idioventricular'	'Trifascicular block'
'Long QT syndrome'	'Sinoatrial block'	'Ventricular arrhythmia'
'Loss of consciousness'	'Sinus arrest'	'Ventricular asystole'
'Nodal arrhythmia'	'Sinus arrhythmia'	'Ventricular dyssynchrony'
'Nodal rhythm'	'Sinus bradycardia'	'Ventricular extrasystoles'
'Pacemaker generated arrhythmia'	'Sinus node dysfunction'	'Ventricular fibrillation'
'Pacemaker syndrome'	'Sinus tachycardia'	'Ventricular flutter'
'Palpitations'	'Sudden cardiac death'	'Ventricular parasystole'
'Parasystole'	'Sudden death'	'Ventricular pre-excitation'
'Paroxysmal arrhythmia'	'Supraventricular bradycardia'	'Ventricular tachyarrhythmia'
'Paroxysmal atrioventricular block'	'Supraventricular extrasystoles'	'Ventricular tachycardia'
'Pulseless electrical activity'	'Supraventricular tachyarrhythmia'	'Wandering pacemaker'
'Rebound tachycardia'	'Supraventricular tachycardia'	'Withdrawal arrhythmia'
'Reperfusion arrhythmia'	'Syncope'	'Wolff-Parkinson-White syndrome'

Stroke		
'Agnosia'	'Capsular warning syndrome'	'Cerebellar ischaemia'
'Amaurosis fugax'	'CARASIL syndrome'	'Cerebellar microhaemorrhage'
'Angiogram cerebral abnormal'	'Carotid aneurysm rupture'	'Cerebellar stroke'
'Aphasia'	'Carotid angioplasty'	'Cerebral aneurysm perforation'
'Balint's syndrome'	'Carotid arterial embolus'	'Cerebral aneurysm ruptured syphilitic'
'Basal ganglia haematoma'	'Carotid arteriosclerosis'	'Cerebral angioplasty'
'Basal ganglia haemorrhage'	'Carotid artery aneurysm'	'Cerebral arteriosclerosis'
'Basal ganglia infarction'	'Carotid artery bypass'	'Cerebral arteriovenous malformation haemorrhagic'
'Basal ganglia stroke'	'Carotid artery disease'	'Cerebral artery embolism'
'Basilar artery aneurysm'	'Carotid artery dissection'	'Cerebral artery occlusion'
'Basilar artery occlusion'	'Carotid artery insufficiency'	'Cerebral artery perforation'
'Basilar artery perforation'	'Carotid artery occlusion'	'Cerebral artery restenosis'
'Basilar artery stenosis'	'Carotid artery perforation'	'Cerebral artery stenosis'
'Basilar artery thrombosis'	'Carotid artery restenosis'	'Cerebral artery stent insertion'
'Benedikt's syndrome'	'Carotid artery stenosis'	'Cerebral artery thrombosis'
'Brachiocephalic arteriosclerosis'	'Carotid artery stent insertion'	'Cerebral bypass surgery'
'Brachiocephalic artery occlusion'	'Carotid artery stent removal'	'Cerebral cavernous malformation'
'Brachiocephalic artery stenosis'	'Carotid artery thrombosis'	'Cerebral cyst haemorrhage'
'Brain hypoxia'	'Carotid blowout syndrome'	'Cerebral endovascular aneurysm repair'
'Brain injury'	'Carotid endarterectomy'	'Cerebral gas embolism'
'Brain stem embolism'	'Carotid revascularisation'	'Cerebral haematoma'
'Brain stem haematoma'	'Central nervous system haemorrhage'	'Cerebral haemorrhage foetal'
'Brain stem haemorrhage'	'Central pain syndrome'	'Cerebral haemorrhage neonatal'
'Brain stem infarction'	'Cerebellar artery occlusion'	'Cerebral haemorrhage'
'Brain stem ischaemia'	'Cerebellar artery thrombosis'	'Cerebral haemosiderin deposition'
'Brain stem microhaemorrhage'	'Cerebellar atherosclerosis'	'Cerebral infarction foetal'
'Brain stem stroke'	'Cerebellar embolism'	'Cerebral infarction'
'Brain stem thrombosis'	'Cerebellar haematoma'	'Cerebral ischaemia'
'Brain stent insertion'	'Cerebellar haemorrhage'	'Cerebral microembolism'
'CADASIL'	'Cerebellar infarction'	'Cerebral microhaemorrhage'

Stroke (continued)		
'Cerebral microinfarction'	'Embolic cerebral infarction'	'Inner ear infarction'
'Cerebral reperfusion injury'	'Embolic stroke'	'Internal capsule infarction'
'Cerebral revascularisation'	'Epidural haemorrhage'	'Internal carotid artery deformity'
'Cerebral septic infarct'	'Extra-axial haemorrhage'	'Intra-cerebral aneurysm operation'
'Cerebral small vessel ischaemic disease'	'Extradural haematoma evacuation'	'Intracerebral haematoma evacuation'
'Cerebral thrombosis'	'Extradural haematoma'	'Intracranial aneurysm'
'Cerebral vascular occlusion'	'Extraischaemic cerebral haematoma'	'Intracranial artery dissection'
'Cerebral vasoconstriction'	'Foetal cerebrovascular disorder'	'Intracranial haematoma'
'Cerebral venous thrombosis'	'Foville syndrome'	'Intracranial haemorrhage neonatal'
'Cerebral ventricular rupture'	'Haemorrhage intracranial'	'Intracranial tumour haemorrhage'
'Cerebrovascular accident prophylaxis'	'Haemorrhagic cerebellar infarction'	'Intraventricular haemorrhage neonatal'
'Cerebrovascular accident'	'Haemorrhagic cerebral infarction'	'Intraventricular haemorrhage'
'Cerebrovascular disorder'	'Haemorrhagic stroke'	'Ischaemic cerebral infarction'
'Cerebrovascular insufficiency'	'Haemorrhagic transformation stroke'	'Ischaemic stroke'
'Cerebrovascular pseudoaneurysm'	'Heidelberg classification'	'Jugular vein embolism'
'Cerebrovascular stenosis'	'Hemianaesthesia'	'Lacunar infarction'
'Charcot-Bouchard microaneurysms'	'Hemiasomatognosia'	'Lacunar stroke'
'Claude's syndrome'	'Hemiataxia'	'Lateral medullary syndrome'
'Congenital hemiparesis'	'Hemidysaesthesia'	'Lateropulsion'
'Cortical hand stroke'	'Hemihyperaesthesia'	'Malignant middle cerebral artery syndrome'
'CSF bilirubin positive'	'Hemihypoaesthesia'	'Meningorrhagia'
'CSF red blood cell count positive'	'Hemiparaesthesia'	'Metabolic stroke'
'Delayed ischaemic neurological deficit'	'Hemiparesis'	'Middle cerebral artery stroke'
'Diplegia'	'Hemiplegia'	'Migrainous infarction'
'Dysarthria'	'Hunt and Hess scale'	'Millard-Gubler syndrome'
'Embolic cerebellar infarction'	'Hypoxic-ischaemic encephalopathy'	'Modified Rankin score decreased'

Stroke (continued)		
'Modified Rankin score increased'	'Putamen haemorrhage'	'Subdural haematoma'
'Monoparesis'	'Quadriparesis'	'Subdural haemorrhage neonatal'
'Monoplegia'	'Quadriplegia'	'Subdural haemorrhage'
'Moyamoya disease'	'Retinal artery occlusion'	'Superficial siderosis of central nervous system'
'NIH stroke scale abnormal'	'Reversible cerebral vasoconstriction syndrome'	'Temporal artery stenosis'
'NIH stroke scale score decreased'	'Reversible ischaemic neurological deficit'	'Thalamic infarction'
'NIH stroke scale score increased'	'Right hemisphere deficit syndrome'	'Thalamic stroke'
'Occipital lobe stroke'	'Ruptured cerebral aneurysm'	'Thalamus haemorrhage'
'Paralysis'	'Septic cerebral embolism'	'Thrombotic cerebral infarction'
'Paraparesis'	'Spinal artery embolism'	'Thrombotic stroke'
'Paraplegia'	'Spinal artery thrombosis'	'Transient ischaemic attack'
'Paresis'	'Spinal cord haematoma'	'Vascular encephalopathy'
'Parietal lobe stroke'	'Spinal cord haemorrhage'	'Vascular stent occlusion'
'Perinatal stroke'	'Spinal cord infarction'	'Vascular stent stenosis'
'Periventricular haemorrhage neonatal'	'Spinal cord ischaemia'	'Vein of Galen aneurysmal malformation'
'Pituitary apoplexy'	'Spinal epidural haematoma'	'Vertebral artery aneurysm'
'Pituitary haemorrhage'	'Spinal epidural haemorrhage'	'Vertebral artery arteriosclerosis'
'Post cardiac arrest syndrome'	'Spinal stroke'	'Vertebral artery occlusion'
'Post procedural stroke'	'Spinal subarachnoid haemorrhage'	'Vertebral artery perforation'
'Post stroke depression'	'Spinal subdural haematoma'	'Vertebral artery stenosis'
'Posthaemorrhagic hydrocephalus'	'Spinal subdural haemorrhage'	'Vertebral artery thrombosis'
'Precerebral arteriosclerosis'	'Stroke in evolution'	'Vertebrobasilar artery dissection'
'Precerebral artery aneurysm'	'Subarachnoid haematoma'	'Vertebrobasilar infarction'
'Precerebral artery dissection'	'Subarachnoid haemorrhage neonatal'	'Vertebrobasilar insufficiency'
'Precerebral artery embolism'	'Subarachnoid haemorrhage'	'Vertebrobasilar stroke'
'Precerebral artery occlusion'	'Subclavian steal syndrome'	'Visual agnosia'
'Precerebral artery thrombosis'	'Subcortical stroke'	'Visual midline shift syndrome'
'Pseudo-occlusion of internal carotid artery'	'Subdural haematoma evacuation'	'Weber's syndrome'

Hypertension		
'Accelerated hypertension'	'Blood pressure orthostatic increased'	'Hypertensive cerebrovascular disease'
'Aldosterone urine abnormal'	'Blood pressure systolic abnormal'	'Hypertensive crisis'
'Aldosterone urine increased'	'Blood pressure systolic increased'	'Hypertensive emergency'
'Angiotensin converting enzyme abnormal'	'Catecholamine crisis'	'Hypertensive encephalopathy'
'Angiotensin converting enzyme increased'	'Catecholamines urine abnormal'	'Hypertensive end-organ damage'
'Angiotensin I abnormal'	'Catecholamines urine increased'	'Hypertensive heart disease'
'Angiotensin I increased'	'Dialysis induced hypertension'	'Hypertensive nephropathy'
'Angiotensin II abnormal'	'Diastolic hypertension'	'Hypertensive urgency'
'Angiotensin II increased'	'Diuretic therapy'	'Labile blood pressure'
'Angiotensin II receptor type 1 antibody positive'	'Eclampsia'	'Labile hypertension'
'Blood aldosterone abnormal'	'Ectopic aldosterone secretion'	'Malignant hypertension'
'Blood aldosterone increased'	'Ectopic renin secretion'	'Malignant hypertensive heart disease'
'Blood catecholamines abnormal'	'Endocrine hypertension'	'Malignant renal hypertension'
'Blood catecholamines increased'	'Epinephrine abnormal'	'Maternal hypertension affecting foetus'
'Blood pressure abnormal'	'Epinephrine increased'	'Mean arterial pressure increased'
'Blood pressure ambulatory abnormal'	'Essential hypertension'	'Metabolic syndrome'
'Blood pressure ambulatory increased'	'Gestational hypertension'	'Metanephrine urine abnormal'
'Blood pressure diastolic abnormal'	'HELLP syndrome'	'Metanephrine urine increased'
'Blood pressure diastolic increased'	'Hyperaldosteronism'	'Neurogenic hypertension'
'Blood pressure fluctuation'	'Hypertension neonatal'	'Nocturnal hypertension'
'Blood pressure inadequately controlled'	'Hypertension'	'Norepinephrine abnormal'
'Blood pressure increased'	'Hypertensive angiopathy'	'Norepinephrine increased'
'Blood pressure management'	'Hypertensive cardiomegaly'	'Normetanephrine urine increased'
'Blood pressure orthostatic abnormal'	'Hypertensive cardiomyopathy'	'Orthostatic hypertension'

Hypertension (continued)		
'Page kidney'	'Renal sympathetic nerve ablation'	'Superimposed pre-eclampsia'
'Postoperative hypertension'	'Renal vascular resistance increased'	'Supine hypertension'
'Pre-eclampsia'	'Renin abnormal'	'Syndrome Z'
'Prehypertension'	'Renin increased'	'Systolic hypertension'
'Primary hyperaldosteronism'	'Renin-angiotensin system inhibition'	'Tyramine reaction'
'Procedural hypertension'	'Renovascular hypertension'	'White coat hypertension'
'Pseudoaldosteronism'	'Retinopathy hypertensive'	'Withdrawal hypertension'
'Renal artery revascularisation'	'Secondary aldosteronism'	
'Renal hypertension'	'Secondary hypertension'	

Dyslipidemia	
'Acquired mixed hyperlipidaemia'	'Lipid metabolism disorder'
'Apolipoprotein B/Apolipoprotein A-1 ratio increased'	'Lipids abnormal'
'Atherogenic index of plasma abnormal'	'Lipids decreased'
'Atherogenic index of plasma decreased'	'Lipids increased'
'Atherogenic index of plasma increased'	'Lipoprotein (a) abnormal'
'Autoimmune hyperlipidaemia'	'Lipoprotein (a) decreased'
'Blood cholesterol abnormal'	'Lipoprotein (a) increased'
'Blood cholesterol decreased'	'Lipoprotein abnormal'
'Blood cholesterol esterase increased'	'Lipoprotein increased'
'Blood cholesterol increased'	'Lipoprotein metabolism disorder'
'Blood triglycerides abnormal'	'Low density lipoprotein abnormal'
'Blood triglycerides decreased'	'Low density lipoprotein decreased'
'Blood triglycerides increased'	'Low density lipoprotein increased'
'Diabetic dyslipidaemia'	'Metabolic syndrome'
'Dyslipidaemia'	'Non-high-density lipoprotein cholesterol decreased'
'Familial high density lipoprotein deficiency'	'Non-high-density lipoprotein cholesterol increased'
'Familial hypertriglyceridaemia'	'Primary hypercholesterolaemia'
'Fat overload syndrome'	'Remnant hyperlipidaemia'
'High density lipoprotein abnormal'	'Remnant-like lipoprotein particles increased'
'High density lipoprotein decreased'	'Total cholesterol/HDL ratio abnormal'
'High density lipoprotein increased'	'Total cholesterol/HDL ratio decreased'
'Hypercholesterolaemia'	'Total cholesterol/HDL ratio increased'
'Hyperlipidaemia'	'Type I hyperlipidaemia'
'Hypertriglyceridaemia'	'Type II hyperlipidaemia'
'Hypertriglyceridaemic waist phenotype'	'Type IIa hyperlipidaemia'
'Hypo HDL cholesterolaemia'	'Type IIb hyperlipidaemia'
'Hypotriglyceridaemia'	'Type III hyperlipidaemia'
'Intermediate density lipoprotein decreased'	'Type IV hyperlipidaemia'
'Intermediate density lipoprotein increased'	'Type V hyperlipidaemia'
'LDL/HDL ratio decreased'	'Very low density lipoprotein abnormal'
'LDL/HDL ratio increased'	'Very low density lipoprotein decreased'
'Lecithin-cholesterol acyltransferase deficiency'	'Very low density lipoprotein increased'

Hyperglycemia		
'Abnormal loss of weight'	'Blood triglycerides increased'	'Diabetic wound'
'Abnormal weight gain'	'Body mass index decreased'	'Diabulimia'
'Acidosis'	'Body mass index increased'	'Euglycaemic diabetic ketoacidosis'
'Acquired generalised lipodystrophy'	'Carbon dioxide combining power abnormal'	'Fructosamine increased'
'Adiponectin decreased'	'Carbon dioxide combining power decreased'	'Fulminant type 1 diabetes mellitus'
'Alpha hydroxybutyric acid increased'	'Central obesity'	'Gestational diabetes'
'Altered state of consciousness'	'Coma'	'Glucose tolerance decreased'
'Anti-GAD antibody positive'	'Continuous glucose monitoring'	'Glucose tolerance impaired in pregnancy'
'Anti-IA2 antibody positive'	'Dehydration'	'Glucose tolerance impaired'
'Anti-insulin antibody increased'	'Depressed level of consciousness'	'Glucose tolerance test abnormal'
'Anti-insulin antibody positive'	'Diabetes complicating pregnancy'	'Glucose urine present'
'Anti-insulin receptor antibody increased'	'Diabetes mellitus inadequate control'	'Glycated albumin increased'
'Anti-insulin receptor antibody positive'	'Diabetes mellitus'	'Glycated serum protein increased'
'Anti-islet cell antibody positive'	'Diabetes with hyperosmolarity'	'Glycosuria during pregnancy'
'Anti-zinc transporter 8 antibody positive'	'Diabetic arteritis'	'Glycosuria'
'Blood 1,5-anhydroglucitol decreased'	'Diabetic coma'	'Glycosylated haemoglobin abnormal'
'Blood cholesterol increased'	'Diabetic coronary microangiopathy'	'Glycosylated haemoglobin increased'
'Blood glucose abnormal'	'Diabetic hepatopathy'	'Hepatogenous diabetes'
'Blood glucose fluctuation'	'Diabetic hyperglycaemic coma'	'Hunger'
'Blood glucose increased'	'Diabetic hyperosmolar coma'	'Hypercholesterolaemia'
'Blood insulin abnormal'	'Diabetic ketoacidosis'	'Hyperglycaemia'
'Blood insulin decreased'	'Diabetic ketoacidotic hyperglycaemic coma'	'Hyperglycaemic crisis'
'Blood lactic acid increased'	'Diabetic ketosis'	'Hyperglycaemic hyperosmolar nonketotic syndrome'
'Blood osmolarity increased'	'Diabetic metabolic decompensation'	'Hyperglycaemic seizure'

Hyperglycemia (continued)		
'Hyperglycaemic unconsciousness'	'Ketoacidosis'	'Postprandial hypoglycaemia'
'Hyperlactacidaemia'	'Ketonuria'	'Pseudodiabetes'
'Hyperlipidaemia'	'Ketosis-prone diabetes mellitus'	'Slow response to stimuli'
'Hyperosmolar state'	'Ketosis'	'Steroid diabetes'
'Hyperphagia'	'Lactic acidosis'	'Syndrome Z'
'Hypertriglyceridaemia'	'Latent autoimmune diabetes in adults'	'Thirst'
'Hypoglycaemia'	'Lipids increased'	'Type 1 diabetes mellitus'
'Hypoinsulinaemia'	'Loss of consciousness'	'Type 2 diabetes mellitus'
'Hypoinsulinism'	'Maternally inherited diabetes and deafness'	'Type 3 diabetes mellitus'
'Impaired fasting glucose'	'Metabolic acidosis'	'Underweight'
'Impaired insulin secretion'	'Metabolic syndrome'	'Unresponsive to stimuli'
'Increased appetite'	'Monogenic diabetes'	'Urine glucose/creatinine ratio abnormal'
'Increased insulin requirement'	'Neonatal diabetes mellitus'	'Urine glucose/creatinine ratio decreased'
'Indeterminate glucose tolerance'	'Neonatal hyperglycaemia'	'Urine glucose/creatinine ratio increased'
'Insulin autoimmune syndrome'	'New onset diabetes after transplantation'	'Urine ketone body present'
'Insulin resistance'	'Obesity'	'Weight decreased'
'Insulin resistant diabetes'	'Overweight'	'Weight increased'
'Insulin therapy'	'Pancreatogenous diabetes'	'Wolfram syndrome'
'Insulin tolerance test abnormal'	'Polydipsia'	
'Insulin-requiring type 2 diabetes mellitus'	'Polyuria'	

Appendix E: National Drug Codes for Endocrine Therapies

Endocrine Therapy	National Drug Code
Tamoxifen	54483121, 54483126, 54483413, 54483422, 54883125, 54883425, 93078201, 93078205, 93078210, 93078256, 93078405, 93078406, 93078410, 93078486, 172565649, 172565658, 172565670, 172565680, 172565746, 172565760, 172565770, 172565780, 310060018, 310060025, 310060060, 310060075, 310060412, 310060430, 310060490, 310073060, 310073130, 378014405, 378014491, 378027401, 378027493, 403150571, 555044603, 555044605, 555044609, 555044663, 555090401, 555090405, 555090414, 591223218, 591223260, 591223319, 591223330, 591247218, 591247260, 591247319, 591247330, 13632012301, 38779034101, 38779034103, 38779034104, 38779034105, 38779034108, 38779034110, 38779034130, 38779034140, 38779034150, 38779034180, 42254034390, 49452757101, 49452757102, 49452757103, 49452757104, 49452757105, 49452757106, 49452775301, 49452775302, 49452775303, 49452775304, 49452775305, 50090094200, 50090253301, 51552083802, 51862044601, 51862044605, 51862044610, 51862044630, 51862044705, 51862044710, 51862044718, 51862044760, 51862044918, 51862044960, 51862045030, 51862045090, 51927297600, 51927507600, 52372075601, 52372075602, 54569038200, 54569038202, 54569376500, 54569376501, 54569571600, 54569585700, 54569853100, 54569860200, 54868300400, 54868300401, 54868300402, 54868300403, 54868300404, 54868300405, 54868428700, 54868428701, 54868428702, 54868428703, 54868428704, 55175550006, 55289058530, 57866661501, 57866661801, 58016065760, 60346004832, 60346090060, 60429090960, 60429091030, 62991115101, 62991115102, 62991115103, 62991115104, 63275986502, 63275986504, 63275986505, 63275986509, 63307047001, 63307047005, 63370025110, 63370025115, 63370025125, 63370025135, 63739026901, 63739026910, 63739026915, 63739026942, 66105083201, 66105083203, 66105083206, 66105083209, 66105083210, 68084092411, 68084092421, 68084093511, 68084093521, 68258596006, 68382082614, 68382082701, 68382082706, 75840011001, 89141012301
Letrozole	54026913, 78024915, 78088150, 93762056, 378207105, 378207193, 603418016, 16729003410, 16729003415, 35356040930, 42254024330, 42291037490, 50268047611, 50268047615, 51991075910, 51991075933, 53217010830, 54569571400, 54868415100, 54868625200, 55111064630, 59651018030, 59651018090, 60505325503, 60505325508, 62756051183, 63323077230, 68084080311, 68084080321, 68258595503
Anastrozole	54016413, 93753656, 310020130, 310020137, 378603405, 378603477, 378603493, 395815735, 395815737, 781535631, 904619546, 904622961, 12280034630, 16571042103, 16729003510, 16729003515, 16729003516, 21695099030, 33261095700, 33261095730, 33261095760, 33261095790, 35356027030, 38779227403, 38779227404, 38779227406, 38779255503, 38779255504, 38779255506, 42043018003, 42254016130, 42291008530, 42291008590, 42291010530, 43063038306, 43063038315, 46144020001, 46144020005, 50090245300, 50268007511, 50268007515, 51079032301, 51079032306, 51655063853, 51927443500, 51991062010, 51991062033, 54569573100, 54569619800, 54868500000, 54868613000, 54868613001,

	55111064730, 55175550503, 58597808001, 58597808002, 58597808004, 59651023630, 59651023690, 60258086603, 60429028630, 60429028690, 60505298503, 60687011211, 60687011221, 62033037606, 62559067030, 62756025013, 62756025083, 63275993001, 63275993002, 63275993003, 63275993004, 63275993005, 63323012930, 66336053330, 66336053390, 66435041530, 67877017110, 67877017130, 68001015504, 68001015508, 68084044821, 68382020906, 68382020910, 72789000815, 72789000890, 76418001301, 76519122403
Exemestane	9766304, 54008013, 378500193, 832059530, 47781010830, 49999098630, 51991000533, 54569573200, 54868526100, 59762285801, 60687013211, 60687013221, 63629126201, 68382038306, 69097031602

Appendix F: Description of Variables Used in the Study

Variable Name	Definition
Telehealth utilization	Dummy variable: indicates telehealth use.
	Continuous measure: number of telehealth visits.
Adherence status (Outcome of interest)	Dummy variable: indicates adherent patients with Proportion of Days Covered (PDC) ≥80%.
Metastasis (Outcome of interest)	Number of patients with an incident diagnosis of metastatic cancer during the follow-up period.
Direct costs (Outcome of interest)	Continuous measure: total direct medical and pharmaceutical costs paid by patients for deductibles, copayments, and coinsurance.
Patient Age	Average age of the patient at first cancer diagnosis.
	Ordinal variable: categorized into four groups: < 35, 35-44, 45-54, and 55-64.
Geographic region	Nominal variable: indicates whether patients were in the Northeast, North Central, South, or West.
Rurality status	Dummy variable: indicates patients not living in a Metropolitan Statistical Area.
Insurance plan type	Nominal variable: indicates insurance type (Preferred Provider Organization, Health Maintenance Organization, Consumer-Driven Health Plan, High-Deductible Health Plan, or other).
Type of endocrine agent	Nominal variable: indicates receipt of tamoxifen, a single aromatase inhibitor, or a switch from one agent to another.
CCI	Index of baseline health status: weighted scores assigned to each patient based on the number and severity of preexisting comorbid conditions.

CCI: Charlson Comorbidity Index

Appendix G: Annual Summary of Telehealth Users and Visits

Calendar Year	Telehealth Users (n)	Telehealth Visits (n)
2018	37	210
2019	61	463
2020	627	2276
2021	465	2086
2022	414	2003
2023	296	1312