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RESEARCH ARTICLE

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Interstitial lung disease recurrence on chemotherapy rechallenge in breast cancer: a nationwide Japanese database

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ABSTRACT

Aim: The present study assessed the incidence of drug-induced interstitial lung disease (ILD) recurrence among breast cancer patients who underwent rechallenge with cancer-directed therapy.

Materials & methods: Japanese insurance claims data and the Diagnosis Procedure Combination database (2009–2022) involving 81,601 patients were analyzed to evaluate 1,042 breast cancer patients who developed ILD. Of these, 566 patients underwent cancer-directed therapy rechallenge, and 42.1% of them were re-challenged with the same therapeutic regimen that caused the initial ILD.

Results: ILD recurrence was observed in 18.9% of the patients, with a median recurrence time of 40 days. The drugs most commonly causing ILD were cytotoxic agents, and those most frequently used for rechallenge were cytotoxic agents.

Conclusion: A notable ILD recurrence rate was observed in breast cancer patients after a cancer-directed therapy rechallenge, highlighting the need for cautious treatment planning and personalised strategies to balance cancer control while mitigating ILD risk.

ARTICLE HISTORY

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KEYWORDS

Breast cancer; interstitial lung disease; rechallenge; cancer-directed therapy; claims databases

PLAIN LANGUAGE SUMMARY

This article discusses a study that researched a lung condition known as interstitial lung disease (ILD) in individuals with breast cancer who were treated again with cancer-directed therapy after recovering from ILD. ILD involves inflammation and damage to the lungs and can be a serious side effect of cancer treatment.

We analyzed data from Japanese health insurance claims and hospital records from 2009 to 2022, of 81,601 patients with breast cancer, 1,042 developed ILD that required treatment with steroids. Of the 1,042 patients, 566 underwent cancer-directed therapy again after their initial ILD episode.

The findings showed that approximately 19% of these patients experienced ILD recurrence, typically approximately 40 days after they had started cancer-directed therapy again. The most common rechallenge therapy for these patients was cytotoxic drugs, which are powerful and used to kill cancer cells.

The results of this study highlight the risk of ILD recurrence in patients with breast cancer who undergo cancer-directed therapy again. This insight is crucial for doctors and patients when deciding on cancer treatments, especially after a patient has already had ILD. This demonstrates the importance of careful planning and personalized treatment strategies to manage the risk of ILD while attempting to effectively control cancer. This study helps in understanding the trade-off between treating cancer to protect patients while not causing serious side effects such as ILD.

1. Introduction

Recent advancements in breast cancer therapeutics on advanced chemotherapeutic agents and targeted therapies have improved patient prognoses. Concurrently, these developments have escalated the risk of the potentially fatal drug-induced Interstitial Lung Disease (ILD). ILD poses significant risk to life and is characterized by inflammation and scarring of the tissue surrounding the lungs. The pathogenesis of drug-induced ILD is complex and multifactorial, involving direct pulmonary toxicity, immune-mediated mechanisms, and indirect effects related to drug metabolism and interactions [1]. An epidemiological investigation reported an incidence rate of respiratory failure due to ILD of 6.6 per 100,000 patient-years, with chemotherapeutic agents being concurrently administered in over half of these occurrences [2]. Our previous database study reported that the incidence rate of moderate-to-severe ILD in the Japanese breast cancer population was 1.41 per 100 person-years (95% CI: 1.33–1.50) [3]. This observation emphasizes the importance of careful monitoring and implementation of proactive management approaches in patients receiving these therapies. An elevated risk of ILD has been associated with the introduction of new therapeutics that act on unique molecular mechanisms, including molecular-targeted therapies and immune checkpoint inhibitors [4].

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Article highlights

- This nationwide study in Japan analyzed the recurrence of interstitial lung disease (ILD) in patients with breast cancer undergoing cancer-directed therapy rechallenge using medical claims database data (2009–2022) from 81,601 patients.
- Among 1,042 patients with breast cancer who developed ILD, 566 opted for cancer-directed therapy rechallenge, highlighting the clinical dilemma of balancing cancer treatment with ILD risk.
- ILD recurrence was observed in 18.9% of the patients who underwent cancer-directed therapy rechallenge, with a median recurrence time of 40 days.
- Cytotoxic drugs are the most frequently used treatment in cancer-directed therapy rechallenge despite their association with ILD onset.
- A substantial proportion of patients (42.1%) were re-administered the same cancer-directed therapy regimen that we believed was the cause of the initial episode of ILD.
- The study revealed a trend toward the use of endocrine therapy as an alternative in patients with a history of ILD, suggesting a shift toward treatments with a lower ILD risk profile.
- These findings indicate a clinical propensity to prioritize aggressive cancer management over the potential risks of ILD exacerbation in certain scenarios.
- This research provides essential insights for clinicians, policymakers, and patients, guiding therapeutic decision-making in oncology, with a focus on balancing effective cancer control against the risk of ILD recurrence.

Furthermore, an internationally standardized comparative analysis of drug-induced pulmonary diseases indicated a higher prevalence in Japan relative to those documented in clinical trials and observational studies from other countries [5,6]. This geographical variance is attributed to genetic predispositions, environmental factors, or differences in clinical practices and drug utilization patterns [5,7].

The impact of ILD on the quality of life and survival of patients highlights the importance of evaluating cancer treatments that balance efficacy with the potential for pulmonary toxicity. The development of ILD not only compromises lung function but often necessitates the discontinuation or modification of potentially life-saving cancer therapies, thereby impacting the overall treatment strategy and prognosis of patient. The association between ILD and anticancer agents, including novel targeted therapies, is well documented, and clinical guidelines recommend close monitoring and, in some cases, discontinuation of the offending agent upon the development of ILD [8].

A previous drug-induced manifestation of ILD has been reported as a risk factor for recurrence after drug rechallenge [5]. However, our understanding of this area of breast cancer treatment is mostly based on individual case reports, rather than extensive studies [9–12]. The use of certain anticancer therapies may be limited by the risks associated with ILD. Nevertheless, the safety and outcomes of cancer-directed therapy rechallenge in patients with a history of ILD, particularly for those with breast cancer, remain unclear. This uncertainty often leads to clinical dilemmas wherein the potential benefits of rechallenge must be weighed against the risk of exacerbating the adverse event, such as developing ILD. The research on ILD onset following cancer therapy has produced pertinent insights [1], yet the widely reported manifestation of ILD recurrence upon the rechallenge with a cancer-directed therapy regimen has not been extensively studied. This knowledge gap presents a considerable challenge to clinical decision-making, particularly in cases where alternative treatment options are limited or less effective. This lack of robust data hinders oncologists from making informed decisions regarding the reintroduction of cancer therapies in patients who have previously experienced ILD. Furthermore, the long-term outcomes of such rechallenges, including the risk-benefit ratio of continuing versus altering the anticancer regimen, remain unclear.

The aim of this retrospective, nationwide study was to illuminate the lesser-known aspects of ILD incidence and recurrence in patients with breast cancer undergoing cancer-directed therapy rechallenge. We aimed to enrich the existing knowledgebase and provide guidance for clinical decision-making for ILD management in the context of breast cancer.

2. Patients & methods

2.1. Study design and data source

This comprehensive nationwide retrospective study was designed and conducted in Japan, specifically targeting a cohort of patients with breast cancer who underwent cancer-directed therapy rechallenge and subsequently experienced ILD recurrence. The central objective of this study was to investigate the incidence and patterns of ILD recurrence in this unique patient population, thereby filling a crucial knowledge gap regarding breast cancer management in the context of previous ILD episodes. To achieve this, we utilized extensive Japanese insurance claims data. Further, from the Medical Data Vision (MDV) database, the Diagnosis Procedure Combination (DPC) data were obtained. The MDV database is a robust and expansive nationwide claims database of anonymized patient-level data of approximately 46 million patients across Japan. This data pool was sourced from 469 hospitals, representing approximately 27% of all acute care hospitals in Japan. These hospitals operate under a diagnosis procedure combination *per-diem* payment system, to provide a comprehensive and detailed dataset that captures detailed data on patient demographics, treatment modalities, clinical outcomes, and healthcare utilization patterns [13,14]. The extensive coverage of the MDV database and detailed records offer a unique opportunity to explore ILD recurrence in patients with breast cancer at the national level. This approach not only facilitates a comprehensive understanding of the prevalence and characteristics of ILD recurrence but also enables the examination of treatment patterns and their outcomes in real-world settings.

In compliance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, this observational study was exempt from requiring informed consent as it employed secondary data devoid of any identifiable patient information. The study design and execution strictly adhered to ethical standards, ensuring confidentiality and anonymity of patient data throughout the research process.

2.2. Study population

The study population was rigorously defined, and data were extracted from the MDV database of Japan to ensure

a comprehensive and reliable source of patient data. The selection process was specifically tailored to identify a distinct cohort of patients with breast cancer who were treated with anticancer therapies, to thereby determine the incidence and characteristics of ILD in this particular patient group.

2.2.1. Identification and inclusion criteria

We initially employed a two-step process to identify the patients with breast cancer.

(1) Diagnostic Record: Patients were required to have a formal diagnosis of C50 (malignant neoplasm of the breast) according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code [15].
(2) Prescription Record: Eligibility necessitated at least one prescription record of anticancer therapies (identified by the Anatomical Classification of Pharmaceutical Products code [Anatomical Therapeutic Chemical (ATC) code] [16] L01), recorded between April 2008 and June 2022. This criterion was crucial for confirming active cancer treatment, thereby focusing on patients who were undergoing or have recently completed anticancer therapy. To focus on treatments with a higher risk of ILD, we excluded patients treated solely with hormone therapy, which is generally associated with a lower risk of ILD.

2.2.2. Exclusion criteria and rationale

To further refine the study population, the following exclusion criteria were applied:

(1) Observation Period: We excluded patients with no records within 60 days of the initiation of anticancer therapy. This criterion is essential to ensure an adequate follow-up period to observe the onset and progression of ILD, thereby enhancing the reliability of the association between anticancer therapy and ILD development.
(2) Index Date: Patients whose index dates were between April 1, 2008, and March 31, 2009, were excluded to precisely analyze the incidence rate of ILD from the initiation of anticancer therapy.
(3) Other Malignancies: To maintain a focused study scope, we excluded patients diagnosed with malignant neoplasms other than breast cancer. This approach was pivotal in reducing the risk of misclassifying ILD occurrences that could be attributed to treatments for other types of cancer.

Following this selection process, we identified patients within this cohort who developed ILD, based on the criteria outlined in a later section "Definition of an Initial ILD Event." This group formed our primary analysis population, offering a detailed perspective on the occurrence of ILD in patients with breast cancer under specific therapeutic conditions. We then subdivided these patients based on whether they underwent a cancer-directed therapy rechallenge following their initial ILD episodes. For this study, cancer-directed therapy rechallenge was defined as the administration of any cancer-directed therapy after the initial ILD event, regardless of whether the same or different agents were used. This could entail the utilization of the same agent associated with the initial ILD or a different agent, contingent upon the clinical assessment of the treating physician and availability of alternative therapeutic options. Since the claims data did not indicate why or when treatment was temporarily discontinued, we classified any resumption of drug administration following the ILD episode as a "re-challenge," distinguishing it from continuous ongoing therapy. This approach was necessary given the lack of available information on the reasons for discontinuation or the timing of ILD recovery. This distinction allowed us to explore the impact of continuing cancer-directed therapy following ILD recurrence. Among the patients who underwent the rechallenge, we further assessed the proportion of ILD recurrence, employing the criteria detailed in the subsequent section "Definition of an ILD Recurrence Event."

2.3. Data collection and variables

Data collected from the MDV database included demographic information (age and sex) and clinical data (diagnosis and treatment). The primary outcome was the recurrence of ILD following a cancer-directed therapy rechallenge. Recurrence of ILD was defined as a new episode of ILD occurring after a period of resolution or stabilization of the initial ILD episode following the re-initiation of anticancer therapy. This definition was adopted to capture the true recurrence of ILD in the context of a cancer-directed therapy rechallenge.

2.4. Definition of treatment regimen

Cancer-directed therapy for breast cancer was characterized by the use of any medications listed in Supplementary Table S1. In the classification of treatment regimens, we grouped anti-HER2 antibody-drug conjugates (ADCs) together due to the limited number of patients treated with trastuzumab deruxtecan which was approved late in our study period. The initial date of anticancer therapy was designated as the index date. Any anticancer agents given within 21 days of the index date were considered part of the same regimen. The introduction of new anticancer therapies marked the end of the existing treatment regimen and the beginning of a new one. Drug combinations within each treatment regimen were categorized according to Supplementary Table S2. We carefully divided the regimens into ten groups: antibody-drug conjugates, anti-HER2 antibodies, HER2 inhibitors, anti-VEGF antibodies, PARP inhibitors, immune checkpoint inhibitors, CDK4/6 inhibitors, mTOR inhibitors, cytotoxic drugs, and others. This method of defining treatment regimens is similar to that used in our previous study [3].

2.5. Definition of an initial ILD event

The method and detailed results of the initial ILD have been previously published [3]. Drug-induced ILD events of moderate to severe intensity were identified when the following

criteria were met: 1) the presence of at least one ICD-10 code from J702, J704, J841, or J849 (indicating "interstitial pulmonary disease" or "interstitial pneumonia"), and 2) a minimum of one prescription for corticosteroids, either prednisolone exceeding 20 mg/day or methylprednisolone surpassing 80 mg/day, in line with the ILD diagnosis and treatment consensus statement [1]. An additional requirement stipulated that the prescription record for Criterion 2) must occur in the same month as the diagnosis record for Criterion 1). In cases in which multiple ILD records were observed for a single patient, only the initial occurrence was analyzed. The date of ILD onset was defined as the earliest date on which an ILD-related ICD-10 code (J702, J704, J841, or J849) co-occurred with a corticosteroid prescription of prednisolone ≥20 mg/day or methylprednisolone ≥80 mg/day, within the same calendar month. We then identified any cancer-directed therapy administered within the preceding 49 days as potentially linked to ILD development. The 49-day window reflects more than one standard treatment cycle, ensuring we captured relevant exposures in the weeks leading up to the clinically recognized ILD. This approach was necessary given that the precise subclinical start date of ILD symptoms was not directly available in claims data. This specific timeframe was selected considering typical breast cancer anticancer regimen cycles, accounting for situations in which treatment might be paused due to emerging ILD symptoms. As a result, corticosteroid treatment may be initiated in the subsequent cycle or during the following monthly visit based on symptom evaluation and progression. Although our database does not capture clinical grading tools such as the Common Terminology Criteria for Adverse Events (CTCAE), these corticosteroid thresholds generally align with CTCAE Grade ≥ 2 or ≥ 3 ILD. Consequently, by definition, only ILD events that required meaningful clinical intervention (systemic steroid therapy) were included.

2.6. Definition of an ILD recurrence event

An ILD recurrence event was defined utilizing specific criteria to ensure precision and accuracy. The criteria were as follows: 1) a minimum of one ILD-related ICD-10 code (J702, J704, J841, or J849), 2) a minimum of one prescription record of corticosteroids, with a dosage exceeding 20 mg/day of prednisolone or 80 mg/day of methylprednisolone, and 3) the event occurred subsequent to the resolution or improvement of the initial ILD event. This was determined by the reduction of the prescribed steroid dosage to below a predetermined threshold (less than 20 mg/day of prednisolone), including instances when the steroid prescription had been fully discontinued. This definition was applied specifically to patients with a history of ILD who subsequently received a new cancer-directed therapy (rechallenge). These criteria were essential for identifying ILD recurrence events as novel episodes occurring after the initial ILD had resolved or improved. The steroid dosage criteria, indicative of at least moderate severity (corresponding to CTCAE Grade 2 or higher), were applied to define recurrence events.

2.7. Statistical analysis

Demographic and clinical characteristics of the study cohort were summarized using descriptive statistical methods. ILD incidence rates were calculated based on the number of ILD occurrences per 100 person-years of observation. Treatment regimen duration was computed using the start and end dates of exposure. The exposure onset, defined as the index date for each treatment regimen, was established, while exposure cessation was defined as 21 days following the prescription date for injectable medications or the prescription date plus the duration of prescription for oral drugs. Periods during which treatment was suspended, defined as intervals from initial exposure start to the final cessation within the same regimen, were excluded from the total exposure duration calculation.

Poisson distribution was used to calculate the incidence of initial ILD and its 95% confidence interval (CI). The Clopper-Pearson method was utilized to determine the 95% CI for the proportion of ILD recurrence. For patients diagnosed with ILD during the observation period, the Kaplan-Meier method was applied to analyze the interval between the initiation of the most recent anticancer therapy and ILD occurrence. The statistical analysis approach used for this study is similar to that used in our previous work [3], specifically for analyzing the initial ILD event. All analyses were conducted using the SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Incidence and patient characteristics of initial ILD

Between 2009 and 2022, 81601 patients with breast cancer received anticancer therapy. The most commonly used regimen was cytotoxic drugs, which comprised 62.4% of all therapies. Anti-HER2 antibodies were also frequently used, accounting for 20.0% of the regimens. CDK4/6 inhibitors, anti-VEGF antibodies, antibody-drug conjugates, mTOR inhibitors, HER2 inhibitors, PARP inhibitors, immune checkpoint inhibitors and other unspecified therapies were used in 6.4%, 5.6%, 2.2%, 1.5%, 0.8%, 0.2%, 0.2% and 0.8% of the regimens, respectively. A total of 170,921 regimens were administered during the study period.

During the study period, 1,042 patients with breast cancer (1.28%) developed steroid treatment-requiring ILD (Figure 1). Table 1 summarizes the characteristics of the study population. The median age at ILD onset was 65 years (range 25–98), with the majority of patients older than 60 years (67.1%). The distribution of the number of previous anticancer treatment regimens was as follows: 40.9% received one regimen, 31.4% received two regimens, 11.9% received three regimens, and 15.8% received four or more regimens, with a median of two regimens (mean, 2.3, range 1–16). Across the entire study period, the incidence was 1.41 per 100 person-years (95% CI: 1.33–1.50) based on 1,042 ILD cases identified among 81,601 patients. The annual incidence varies over time. The detailed results of the initial ILD have been previously published [3].

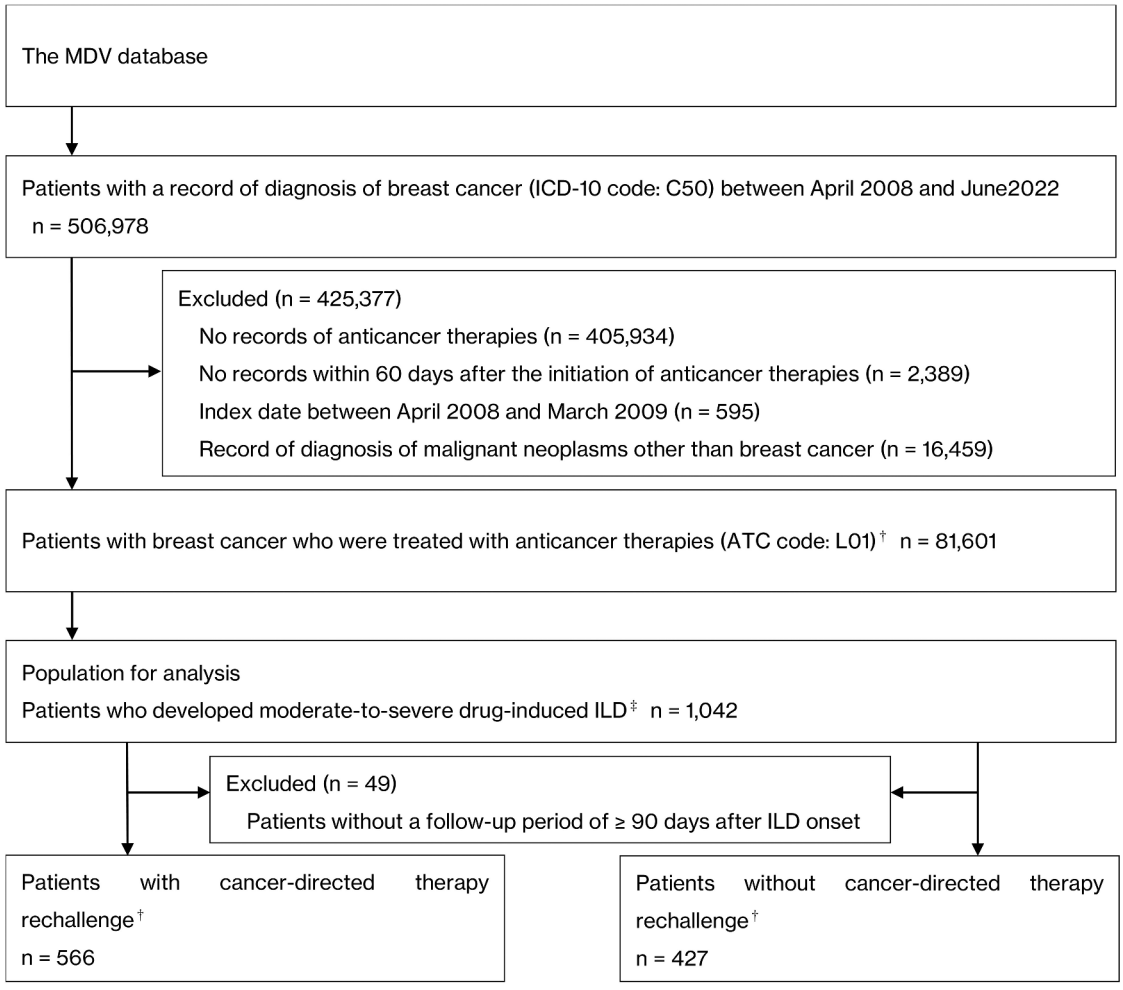

Figure 1. Flow chart of patient selection.

†These cancer-directed therapy regimens did not include the exclusive use of hormone therapy.

‡Moderate-to-severe drug-induced interstitial lung disease (ILD) was characterized as medical records that included a diagnosis of at least one ICD-10 code among J702, J704, J841, or J849, indicating the presence of "interstitial pulmonary disease" or "interstitial pneumonia," as well as at least one prescription record of high-dose corticosteroids during anticancer therapies.

3.2. Patient characteristics of cancer-directed therapy rechallenge

Table 1 shows the characteristics of the 566 breast cancer patients who underwent cancer-directed therapy rechallenge among the 1,042 patients who developed moderate-to-severe ILD. The age distribution at the time of ILD onset indicated a larger proportion of older patients, with the majority being sixty years or older (61.5%), followed by those between 40 and 60 years (35.2%), and a smaller proportion under forty years (3.4%). The median age of the patients in this group was 63 years (range, 25–92 years). Regarding their previous anticancer treatment regimens, these patients received multiple lines of therapy prior to the onset of ILD. The average number of previous treatment regimens was 2.2, with a median of 2, suggesting a varied treatment history among the patients. A notable number of patients underwent one-four or more different treatment regimens before the development of ILD. The pre-treatment regimens that these patients received before the onset of ILD encompassed a diverse range of therapeutic approaches. Many patients have been treated with cytotoxic drugs, whereas others have received treatments such as mTOR inhibitors, anti-HER2 antibodies, and CDK4/6 inhibitors. Fewer patients were administered regimens, such as antibody-drug conjugates, anti-VEGF antibodies, HER2 inhibitors, PARP inhibitors, immune checkpoint inhibitors, or other less common treatments.

3.3. Cancer-directed therapy rechallenge in patients with a history of ILD

The characteristics of cancer-directed therapy rechallenge in the 566 patients with breast cancer at post-interstitial ILD onset are presented in Table 2. The median time interval between the initial onset of ILD and the administration of cancer-directed therapy rechallenge was 48 days (range, 1–-3,089 days; average, 112.5 days).

Regarding cancer-directed therapy rechallenge treatment regimens, cytotoxic drugs were the most commonly used category, with 50.4% of patients receiving this type of treatment. Anti-HER2 antibodies were the second-most prevalent, used by 22.4% of patients. Other treatment categories included CDK4/6 inhibitors (8.7%), mTOR inhibitors

Table 1. Clinical characteristics – patients with interstitial lung disease.

	All ($n = 1,042$)	Patients with cancer-directed therapy rechallenge ($n = 566$)†	Patients without cancer-directed therapy rechallenge ($n = 427$)†
Age, n (%)			
<40	31 (3.0)	19 (3.4)	7 (1.6)
40≤ <60	312 (29.9)	199 (35.2)	106 (24.8)
60≤	699 (67.1)	348 (61.5)	314 (73.5)
Median (min, max), years	65 (25, 98)	63 (25, 92)	67 (33, 98)
Lines of previous anti-cancer treatment regimens, n (%)			
1	426 (40.9)	227 (40.1)	183 (42.9)
2	327 (31.4)	183 (32.3)	127 (29.7)
3	124 (11.9)	70 (12.4)	45 (10.5)
≥4	165 (15.8)	86 (15.2)	72 (16.9)
Median (min, max)	2 (1, 16)	2 (1, 14)	2 (1, 16)
Mean	2.3	2.2	2.3
Category of pre-treatment regimens received prior to interstitial lung disease onset, n (%)			
Antibody-drug conjugates	56 (5.4)	29 (5.1)	25 (5.9)
Anti-HER2 antibodies	175 (16.8)	108 (19.1)	63 (14.8)
HER2 inhibitors	5 (0.5)	2 (0.4)	3 (0.7)
Anti-VEGF antibodies	64 (6.1)	34 (6.0)	26 (6.1)
PARP inhibitors	1 (0.1)	1 (0.2)	0 (0.0)
Immune checkpoint inhibitors	8 (0.8)	2 (0.4)	4 (0.9)
CDK4/6 inhibitors	104 (10.0)	47 (8.3)	46 (10.8)
mTOR inhibitors	165 (15.8)	126 (22.3)	35 (8.2)
Cytotoxic drugs	456 (43.8)	213 (37.6)	222 (52.0)
Others	8 (0.8)	4 (0.7)	3 (0.7)

†Patients without a follow-up period of ≥90 days after ILD onset ($n = 49$) were excluded.

Table 2. Characteristics of cancer-directed therapy rechallenge in patients with a history of interstitial lung disease.

	$n = 566$
Time of period from initial interstitial lung disease onset to cancer-directed therapy rechallenge	
Median (min, max), days	48 (1, 3089)
Mean	112.5
Regimens	Patients, n (%)
Cancer-directed therapy rechallenge treatment regimen category	
Antibody-drug conjugates	12 (2.1)
Anti-HER2 antibodies	127 (22.4)
– Pertuzumab + Trastuzumab + Cytotoxic drugs	23 (4.1)
– Trastuzumab + Cytotoxic drugs	20 (3.5)
HER2 inhibitors	11 (1.9)
– Lapatinib + Cytotoxic drugs	10 (1.8)
Anti-VEGF antibodies	39 (6.9)
– Bevacizumab + Cytotoxic drug	37 (6.5)
PARP inhibitors	3 (0.5)
Immune checkpoint inhibitors + Cytotoxic drugs	1 (0.2)
CDK4/6 inhibitors	49 (8.7)
mTOR inhibitors	39 (6.9)
Cytotoxic drugs	285 (50.4)
Others	0 (0.0)
Patients who have identical treatment regimen with pre-treatment regimen, n(%)	238 (42.1)
Regimens of identical anticancer regimens before and after the ILD onset ($n = 238$)	
Trastuzumab deruxtecan (T-DXd)	0 (0.0)
Trastuzumab emtansine (T-DM1)	4 (1.7)
Pertuzumab + Trastuzumab + Cytotoxic drug	4 (1.7)
Lapatinib + Cytotoxic drug	1 (0.4)
Trastuzumab	4 (1.7)
Trastuzumab + Cytotoxic drug	11 (4.6)
Bevacizumab + Cytotoxic drug	8 (3.4)
Olaparib	1 (0.4)
Atezolizumab	0 (0.0)
Abemaciclib	4 (1.7)
Palbociclib	0 (0.0)
Everolimus	35 (14.7)
Cytotoxic drugs (not including any molecular targeted drug)	166 (69.7)

(6.9%), anti-VEGF antibodies (6.9%), antibody-drug conjugates (2.1%), HER2 inhibitors (1.9%), PARP inhibitors (0.5%), and immune checkpoint inhibitors (0.2%). Among the 566 patients who underwent cancer-directed therapy rechallenge, 42.1% were re-challenged with the same agent that had previously been associated with the initial ILD episode, while the rest received different agents. Among these, the most common regimens were cytotoxic drugs (not including any molecule targeted drugs), which were used by 166 patients, followed by everolimus, which was used by 35. Other regimens, such as trastuzumab with or without cytotoxic drugs, bevacizumab with cytotoxic drugs, and abemaciclib, were also noted, with various patients opting for the same treatments post-ILD as before ILD onset.

3.4. Patient characteristics without cancer-directed therapy rechallenge

Table 1 presents the characteristics of the 427 patients with breast cancer who did not undergo cancer-directed therapy rechallenge after the development of ILD. The majority of these patients (73.5%) were aged 60 years or older. A small proportion of patients were between 40 and 60 years of age (24.8%), while only 1.6% were under 40 years of age. The median age at ILD onset was 67 years (range: 33–98 years).

With respect to prior anticancer treatment regimens, the median number of regimens was 2 (range, 1–16), with an average of 2.3 regimens. A substantial proportion of patients received only one therapeutic regimen (42.9%), whereas the remaining patients received either two (29.7%), three (10.5%), or four or more regimens (16.9%).

Among the pretreatment regimens received administered before the onset of ILD, cytotoxic drugs were the most commonly used (52.0%). The other treatment categories included anti-HER2 antibodies (14.8%), CDK4/6 inhibitors (10.8%), mTOR inhibitors (8.2%), anti-VEGF antibodies (6.1%), antibody-drug conjugates (5.9%), HER2 inhibitors (0.7%), and immune checkpoint inhibitors (0.9%). A small number of patients were treated with drugs falling under the category of "Others" (0.7%).

Of these patients, 354 (82.9%) patients were followed up for a period of one year or longer, while 73 (17.1%) were followed up for less than one year. During the follow-up period, 257 (60.2%) did not receive any form of cancer-directed therapy or endocrine therapy, whereas 170 (39.8%) were treated with endocrine therapy.

Table 3. Proportion and timing of interstitial lung disease recurrence.

Cancer-directed therapy rechallenge (*n* = 566)	
Interstitial lung disease recurrence, n (%)	107 (18.9)
95% CI (%)	15.8–22.4
Time to interstitial lung disease recurrence	
Median (min, max), days	40 (1, 1597)
Patients by time to interstitial lung disease recurrence, n (%)	
≤30 days	48 (44.9)
30< ≤60 days	18 (16.8)
60< ≤90 days	7 (6.5)
90< ≤120 days	6 (5.6)
120< ≤150 days	4 (3.7)
150< ≤180 days	1 (0.9)
180< ≤210 days	6 (5.6)
210< ≤240 days	4 (3.7)
240< ≤270 days	0 (0.0)
270< ≤300 days	4 (3.7)
300< days	9 (8.4)

The time was defined as the period from the initiation date (cycle1 day1) of the most recent anti-cancer therapy and the interstitial lung disease onset date.

3.5. ILD recurrence

Among the 566 patients with breast cancer who underwent cancer-directed therapy rechallenge, 107 (18.9%) experienced ILD recurrence (95% CI: 15.8–22.4%). Table 3 provides information on the occurrence and timing of ILD recurrence. The median time to recurrence was 40 days, with the shortest interval being 1 day and the longest being 1,597 days. Nearly half of patients (44.9%) experienced a recurrence within 30 days. Subsequent intervals showed a decline in recurrence rates, with 16.8% occurring between 31 and 60 days, and smaller percentages thereafter: 6.5% between 61 and 90 days, 5.6% between 91 and 120 days, 3.7% between 121 and 150 days, 0.9% between 151 and 180 days, and similarly low percentages for subsequent 30-day intervals to up to 300 days. A small percentage (8.4%) of patients experienced recurrence after more than 300 days. A plot of the cumulative incidence of ILD recurrence is shown in Figure 2.

Table 4 shows the characteristics of the 107 patients who experienced ILD recurrence. Most of these patients were aged 60 years or older at the time of ILD onset, with a median age of 63 years (range: 25–83 years). A substantial proportion of patients had received one prior anticancer treatment regimen, with an average of 1.3 regimens across the group. In terms of pretreatment regimens before ILD recurrence, the majority of patients had received cytotoxic drugs, and a notable proportion were treated with anti-HER2 antibodies. Treatment with CDK4/6 inhibitors, mTOR inhibitors, and anti-VEGF antibodies was less common.

4. Discussion

Considering the study's primary objective of elucidating the recurrence patterns of ILD in patients with breast cancer undergoing cancer-directed therapy rechallenge, our findings contribute to the understanding of post-therapy complications. This deeper understanding is crucial, as it aids in the development of more tailored treatment strategies for this patient population. To our knowledge, this study is the first to utilize a large, nationwide claims database to

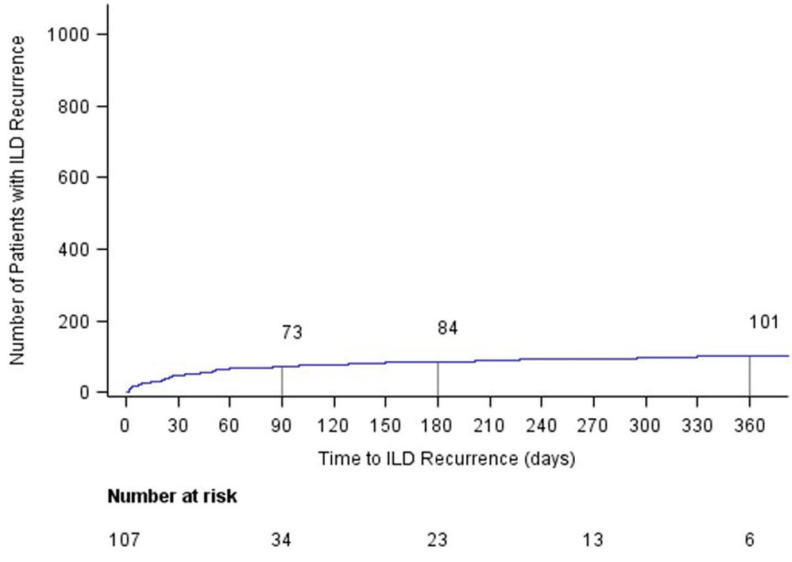

Figure 2. Cumulative incidence of ILD recurrence.

The interval between the initiation of pretreatment and the ILD recurrence was analyzed using the Kaplan-Meier method for patients.

Abbreviations: ILD, interstitial lung disease.

Table 4. Clinical characteristics – interstitial lung disease recurrence.

	n = 107
Age, n (%)	
<40	3 (2.8)
40≤ <60	37 (34.6)
60≤	67 (62.6)
Median (min, max), years	63 (25, 83)
Lines of previous anti-cancer treatment regimens, n (%)	
1	86 (80.4)
2	11 (10.3)
3	7 (6.5)
≥4	3 (2.8)
Median (min, max)	1 (1, 4)
Mean	1.3
Category of pre-treatment regimens received prior to interstitial lung disease recurrence, n (%)	
Antibody-drug conjugates	4 (3.7)
Anti-HER2 antibodies	19 (17.8)
– Pertuzumab + Trastuzumab + Cytotoxic drugs	3 (2.8)
– Trastuzumab + Cytotoxic drugs	1 (0.9)
HER2 inhibitors + Cytotoxic drugs	2 (1.9)
Anti-VEGF antibodies + Cytotoxic drugs	5 (4.7)
PARP inhibitors	0 (0.0)
Immune checkpoint inhibitors	0 (0.0)
CDK4/6 inhibitors	11 (10.3)
mTOR inhibitors	8 (7.5)
Cytotoxic drugs	58 (54.2)
Others	0 (0.0)

comprehensively characterize the epidemiology of moderate-to-severe recurrent ILD in Japanese breast cancer patients. Furthermore, the observation period, exceeding ten years, enabled an in-depth analysis of trends, providing critical insights into the long-term outcomes associated with ILD in this patient population.

Although older age was relatively common in our ILD population – consistent with previous research suggesting advanced age may increase ILD risk [1,2]—our dataset did not include comprehensive information on other known risk factors such as smoking status or specific pulmonary comorbidities. Consequently, we could not systematically analyze how these factors might influence ILD onset and recurrence.

Despite the guidelines advocating for a cautious approach toward the administration of cancer-directed therapy following an episode of ILD [8], a notable number of patients – specifically, 566 of the 1,042 who developed ILD – opted to proceed with rechallenge in Japan. This decision reflects the complex interplay between patient preferences, clinical judgment, and the evolving nature of cancer treatment protocols. This inclination underscores the broader clinical propensity toward maintaining aggressive cancer management strategies and the critical imperative of weighing the benefits of continued treatment against the potential risks of ILD exacerbation. The willingness of patients and clinicians to engage in rechallenge despite the risks underscores a notable shift in the perception of risk-benefit analysis in cancer treatment. In addition, the finding that 42.1% of patients were re-challenged with the same cancer-directed therapy previously associated with their initial ILD episode is indeed striking and warrants further discussion. When patients have advanced or refractory breast cancer and limited therapeutic alternatives, re-exposure to a known culprit agent may be considered if the initial ILD episode was moderate, resolved with treatment, and guidelines allow for individualized decisions. In such situations, the potential oncologic benefits may outweigh the risk of ILD recurrence, provided there is vigilant monitoring and prompt intervention at the earliest sign of pulmonary toxicity.

Comparatively, our study paints a more complex picture than previous research, which advised against the rechallenge of cancer-directed therapy following an ILD episode. Our findings suggest that, in real-world settings, patients and clinicians may be more willing to accept the risk of ILD recurrence in favor of continuing life-prolonging treatment. It is important to note that our definition of rechallenge included any cancer-directed therapy administered after ILD resolution, which may have captured patients who were treated with different agents less likely to cause ILD. This real-world decision-making approach in oncology highlights the need for dynamic guidelines that can be adapted to the evolving landscape of cancer treatments and patient management.

4.1. Everolimus rechallenge and rationale for permissible resumption

A notable finding in our study was the relatively frequent rechallenge with everolimus in patients who had previously experienced ILD. Unlike many other high-risk agents for which guidelines often recommend permanent discontinuation after serious pneumonitis, the product labels for everolimus permit dose interruption, reduction, and cautious resumption under specific conditions [17,18]. This permissibility reflects several key observations:

(1) Reversibility of Lower-Grade Pneumonitis: Clinical trial data have shown that mild-to-moderate everolimus-induced pneumonitis (e.g., CTCAE Grade 1–2) often resolves with temporary drug interruption and supportive care, including corticosteroids [17]. Once the patient recovers to Grade 0 or 1, the risk of recurrence at a reduced dose may be acceptable in the context of the anticipated oncologic benefit.
(2) Importance in Advanced Disease Settings: For patients with advanced or refractory malignancies, everolimus may represent a critical line of therapy when alternatives are limited. Consequently, the potential benefits of resumed tumor control can outweigh the risk of recurrent pneumonitis, provided close monitoring is in place.
(3) Dose-Adjustment: Clinical trials such as BOLERO-2 have adopted standardized approaches to manage everolimus-related pneumonitis, including structured dose modifications and treatment holidays [19]. These interventions have demonstrated feasibility in controlling or reversing pulmonary inflammation without uniformly necessitating permanent discontinuation.
(4) Individualized Risk-Benefit Assessment: Decisions to rechallenge are typically made on a case-by-case basis, taking into account the severity of the initial ILD event, the patient's clinical trajectory, prior response to therapy, and any preexisting risk factors for pulmonary toxicity.

By contrast, certain other targeted agents or ADCs are associated with higher risks of severe or fatal ILD, leading to more conservative recommendations against rechallenge once significant pulmonary toxicity develops [20]. Taken together, everolimus's relatively more flexible label guidance underscores an important principle: not all drugs implicated in ILD share the same likelihood of recurrence or severity upon rechallenge. The ability to resume everolimus at a reduced dose is therefore rooted in both the drug's risk profile and its potential clinical benefit in advanced disease settings. In our population, this translated into a discernible subset of patients who, after recovering from ILD, proceeded with everolimus-based regimens, illustrating the real-world application of these label recommendations. This flexibility in the management of everolimus dosing in the context of prior ILD severity indicates its unique role in the treatment protocols. This also suggests that the therapeutic landscape for breast cancer is evolving, with greater emphasis on individualized patient care. This reflects a measured approach in clinical practice that seeks to balance the management of adverse effects with the continuation of an effective therapeutic agent. Such a balanced approach is essential in oncology, where treatment efficacy and patient safety must be weighed against each other. This pattern of drug selection suggests that the drug's clinical profile and stipulations for redosing, as per the label, are factors of considerable influence, potentially highlighting an area that warrants further examination and thoughtful consideration in the reevaluation of existing treatment frameworks. The implications of these findings extend beyond individual patient care, suggesting a need for broader systemic changes in how we approach cancer treatment in the context of comorbidities such as ILD.

The median duration until the recurrence of ILD post-rechallenge was of 40 days (interquartile range: 10–134 days). Our previous database study reported the median time to initial onset of ILD in patients with breast cancer undergoing cancer-directed therapy was 69 days (interquartile range: 42–113 days) [3]. The shorter time to ILD recurrence compared to the initial onset might suggest a trend toward a quicker development of ILD in patients who have previously experienced it. This difference might indicate a potential increased sensitivity or vulnerability to ILD in patients with a prior history of the condition. This observation, while tentative, still holds relevance for clinical practice. It suggests that there may be a need for heightened vigilance and possibly more frequent monitoring in patients who have a history of ILD and are undergoing cancer-directed therapy rechallenge. An intriguing observation from our study is the trend among patients who did not undergo cancer-directed therapy rechallenge in favor of endocrine therapy, a decision that seems to be predicated on a calculated move toward therapeutic alternatives with a presumably lower ILD risk. This strategic pivot aligns with emerging evidence that supports the more favorable ILD risk profile of endocrine therapies [21], offering vital insight into evolving treatment paradigms in the context of ILD. The preference for endocrine therapy in this context may reflect growing recognition of the need to balance efficacy with safety, particularly in patients with a history of ILD.

Our study had several limitations that should be considered. Primarily, the reliance on claims data introduces the possibility of misclassification, as well as over- or underestimation of ILD events, since diagnoses were identified through ICD-10 codes and treatment documentation rather than direct clinical evaluation. Additionally, certain biomarkers, such as oxygen saturation (SpO_2), KL-6, and SP-D, which are recognized for their potential usefulness in diagnosing ILD, could not be utilized to define ILD events due to the absence of such data in this database. Although our study relied exclusively on claims data without laboratory or imaging results, standard ILD evaluations typically include serum biomarkers like KL-6 and SP-D, along with findings from high-resolution CT (HRCT) [1]. Elevated KL-6 or SP-D levels indicate ongoing alveolar epithelial injury and fibrotic changes, whereas HRCT imaging patterns aid in distinguishing ILD subtypes. In cases of drug-induced ILD, these diagnostic tools complement clinical assessments by confirming inflammation or fibrosis and potentially identifying alternative causes of ILD.

Another limitation is that our study only included ILD events that required steroid treatment and did not assess mild ILD manifestations, such as instances in which patients recovered after drug cessation without systemic corticosteroid intervention. The exclusion of mild ILD cases may limit the generalizability of our findings to all cases of ILD occurrence in the context of breast cancer treatment. This was because the lack of detailed grading information meant that ILDs treated with steroids were considered to be of at least moderate severity and were defined as events. Although the administration of steroids and the diagnosis of ILD were concurrent, and while the steroid dosages administered were aligned with those typically used in standard ILD treatment, it cannot be definitively confirmed that the steroids were used specifically for ILD management, which introduces a potential limitation to our findings. Therefore, corticosteroid therapy was used as a substitute indicator of ILD onset.

It should be recognized that the likelihood of developing ILD differs among various cancer treatments. In our research, we categorized diverse anticancer agents, including anti-HER2 ADCs, into the same pharmacological group despite their potentially distinct ILD risk profiles. This approach was necessary because anticancer agents are typically administered in various regimens, and treatments can be paused or interrupted during a course. Dividing the agents into excessively specific groups would lead to insufficient sample sizes within each category, making it difficult to conduct analysis and provide meaningful summaries. Additionally, our study's primary focus was not on the ILD recurrence rate for each individual drug but rather on understanding the overall post-ILD treatment patterns and ILD recurrence situations in breast cancer therapy. Therefore, we grouped the anticancer agents pharmacologically to facilitate a more generalizable analysis. While this broad classification provides a comprehensive view, it may mask agent-specific variations in ILD incidence and recurrence, as evidenced by the differing profiles of drugs such as trastuzumab deruxtecan, trastuzumab emtansine, and CDK4/6 inhibitors.

An important limitation of our study is the absence of consideration of the differences in life-threatening risks

between individual drugs in patients with ILD. The severity and outcomes associated with ILD can vary substantially between different anticancer agents. Our reliance on claims data restricted our ability to capture detailed survival outcomes, such as deaths directly attributable to ILD. Despite the inclusion of survival outcomes in the claims data utilized for this study, the presence of missing data and challenges in ascertaining mortality status rendered the information insufficient for analysis at the requisite level for this investigation. Consequently, we were unable to conduct an analysis of survival outcomes within the scope of our study. Additionally, the database did not record reasons for therapy discontinuation, nor could we confirm whether patients with no subsequent claims had transferred to another hospital, stopped therapy permanently, or died. Consequently, it limited our ability to interpret the impact of recurrence on subsequent treatment and outcomes. Moreover, due to the complexity of the data and the relatively small number of patients rechallenged with specific agents, we were unable to provide a drug-by-drug analysis of ILD severity and associated mortality risks. This limitation diminishes the clinical applicability of our results, as clinicians require detailed information on the risk profiles of specific drugs to make informed treatment decisions. This study mainly focused on anticancer treatments that possess potentially cytotoxic agents, including targeted therapy, considering the pathophysiological origins of ILD and the recognized causative agents. Hence, ILD recurrence in patients with breast cancer receiving hormonal therapy alone has not yet been evaluated. Furthermore, cytotoxic agents were broadly used in this study, the complexity of tabulating and classifying the various single agents and combination regimens limited our ability to provide a detailed analysis of specific agents

Despite these limitations, this study provides evidence of an intricate relationship between cancer treatment and ILD recurrence. It is acknowledged that considering the differences in mortality risk between drugs is crucial for clinical decision-making. The inability to analyze individual drug-related ILD severity and associated mortality limits the clinical applicability of these findings. Clinicians depend on detailed risk assessments of specific drugs to inform treatment decisions, particularly for patients with a history of ILD. Given the inherent limitations of claims-based analyses, our findings highlight the need for prospective or registry-based studies that incorporate imaging data, standardized ILD grading systems, and survival outcomes. Enhanced clinical information – including imaging, serum biomarkers, patient-reported outcomes, and detailed treatment histories – would enable a more comprehensive understanding of ILD severity, recurrence patterns, and long-term prognosis. By integrating claims data with these richer clinical datasets, future studies could more accurately identify risk factors, improve management strategies, and clarify the impact of ILD on survival among breast cancer patients. Our findings underscore the complexity of managing breast cancer in patients with a history of ILD and highlight the need for careful consideration of individual patient factors in treatment decisions. This provides an essential reference point for clinicians to navigate the challenging landscape of cancer treatment in the presence of ILD. The insights of this study are particularly valuable for informing clinical practice and guiding future research in the field. The findings of this study highlight the urgent need to develop more nuanced clinical protocols and patient-centric management strategies to ensure that effective cancer therapy, considering the risk of ILD recurrence, judiciously.

5. Conclusion

This study offers insights into the occurrence of ILD recurrence among Japanese patients with breast cancer following cancer-directed therapy rechallenge. These findings suggest that ILD recurrence may be a notable concern in this patient population. There appears to be a trend toward continuing with intensive cancer treatments, even when faced with the risk of ILD exacerbation, implying a complex relationship in clinical decision-making between the benefits of cancer therapy and the potential for adverse effects. This study contributes to a growing understanding of the need for personalized patient management and careful consideration of treatment choices, particularly in the context of ILD. This highlights the potential value of developing more nuanced treatment strategies that carefully weigh the effectiveness of cancer therapies against the risks associated with ILD recurrence.

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Author contributions

All authors have contributed to this work and approved the final manuscript. Soichiro Nishijima was responsible for study conception. Soichiro Nishijima, Keiko Sato, Tomohiro Onoue and Wataru Hashimoto designed this study and performed the data analysis. Soichiro Nishijima wrote the first draft of the manuscript, and All authors contributed to interpretation of data and critically revised the manuscript.

Disclosure statement

Soichiro Nishijima, Tomohiro Onoue and Wataru Hashimoto are employees ofDaiichi Sankyo Co., Ltd. (Tokyo, Japan). Keiko Sato is an employee of ThirdPlace LLC (Shizuoka, Japan) and received funding to consult for this study. Theauthors have no other relevant affiliations or financial involvement with anyorganisation or entity with a financial interest in or financial conflict withthe subject matter or materials discussed in the manuscript apart from thosedisclosed.

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Ethical disclosure

This study was approved by the Institutional Review Board of TokyoUniversity of Science (IRB reference number: 22024), and conducted inaccordance with legal and regulatory requirements, including data protectionlaws and the tenets of Declaration of Helsinki. Permission to use theinformation in the database for the purposes of this research was obtained fromthe dataset owner, Medical Data Vision Co., Ltd. (Tokyo, Japan). Given theutilisation of secondary, anonymized data provided by a third-party entity,Medical Data Vision Co., Ltd. (Tokyo, Japan), this research is not governed bythe Japanese Government's "Ethical Guidelines for Medical and Health ResearchInvolving Human Subjects," thus negating the necessity for informed consent.

Data sharing statement

The data sets generated and analyzed throughout this study are accessible from the corresponding author, contingent on a feasible solicitation and sanctioned permission procured from Medical Data Vision Co., Ltd.

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• **This article reviews the toxicity and adverse effects of Tamoxifen, an anti-estrogen drug used for treating hormone-dependent breast cancer.**