original reports abstract

Serum Detection of Nonadherence to Adjuvant Tamoxifen and Breast Cancer Recurrence Risk

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PURPOSE Nonadherence to long-term treatments is often under-recognized by physicians and there is no gold standard for its assessment. In breast cancer, nonadherence to tamoxifen therapy after surgery constitutes a major obstacle to optimal outcomes. We sought to evaluate the rate of biochemical nonadherence to adjuvant tamoxifen using serum assessment and to examine its effects on short-term, distant disease-free survival (DDFS).

PATIENTS AND METHODS We studied 1,177 premenopausal women enrolled in a large prospective study (CANTO/NCT01993498). Definition of biochemical nonadherence was based on a tamoxifen serum level < 60 ng/mL, assessed 1 year after prescription. Self-reported nonadherence to tamoxifen therapy was collected at the same time through semistructured interviews. Survival analyses were conducted using an inverse probability weighted Cox proportional hazards model, using a propensity score based on age, staging, surgery, chemotherapy, and center size.

RESULTS Serum assessment of tamoxifen identified 16.0% of patients (n = 188) below the set adherence threshold. Patient-reported rate of nonadherence was lower (12.3%). Of 188 patients who did not adhere to the tamoxifen prescription, 55% self-reported adherence to tamoxifen. After a median follow-up of 24.2 months since tamoxifen serum assessment, patients who were biochemically nonadherent had significantly shorter DDFS (for distant recurrence or death, adjusted hazard ratio, 2.31; 95% CI, 1.05 to 5.06; $P = .036$), with 89.5% of patients alive without distant recurrence at 3 years in the nonadherent cohort versus 95.4% in the adherent cohort.

CONCLUSION Therapeutic drug monitoring may be a useful method to promptly identify patients who do not take adjuvant tamoxifen as prescribed and are at risk for poorer outcomes. Targeted interventions facilitating patient adherence are needed and have the potential to improve short-term breast cancer outcomes.

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INTRODUCTION

Previous studies suggested that 30% to 50% of patients with chronic conditions in developed countries are nonadherent to prescribed medications.[1,2] Annually in the United States, nonadherence to chronic medications is responsible for increased mortality rate, hospitalizations and health care costs.[1,3] Nonadherence also affects patient-physician relationships, possibly leading to breakdown in trust and communication.[2,4] In addition, because health care systems are evolving into models where health care providers' payments are tied to outcomes, nonadherence can also affect health care providers' reimbursement.[5] Therefore, optimizing adherence may lead to dramatic improvements in health outcomes, patient satisfaction, and costs.

To design effective programs supporting adherence, it is first essential to better recognize when actual medication use differs from the prescribed regimen. There is no gold standard to identify nonadherence, with the prevalent use of indirect methods, commonly based on pharmacy prescription refills and patient-administered questionnaires, which, although informative, do not capture the actual medication intake. Particularly, it has been shown that patient self-report tends to overestimate adherence rates from two- to four-fold and pharmacy claims do not perfectly reflect medication intake, especially if out-of-pocket costs are low.[6] Direct methods, such as measurement of the level of the drug or its metabolites in the blood or urine are less well studied and are not currently used in clinical practice.[3,4,7,8] Furthermore, nonadherence is a complex phenomenon with a multitude of associated factors, including patient, health care provider, and disease-specific features, making it hard to identify and intervene on causes of nonadherence.[1,3]

Most (80%) breast cancer patients have hormone receptor–positive (HR+) disease and > 90% of these

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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patients present with stage I to III disease, rendering them eligible for curative treatment.[9] For patients with HR+ breast cancer receiving adjuvant endocrine therapy, previous studies suggested that nonadherence is a prevalent issue.[10-12] Because 5 years of adjuvant endocrine therapy reduces disease recurrence rate by 50% throughout the first 10 years and mortality rate by a third throughout the first 15 years,[9] and extending the duration of endocrine therapy beyond 5 years can also affect risk of recurrence by up to 40%, nonadherence constitutes a major obstacle to optimal disease and survival outcomes.[9,13] In premenopausal patients with HR+ breast cancer, especially those younger than 40 years, nonadherence to adjuvant endocrine therapy seems to be a major issue, and evidence suggests poorer survival outcomes in this population compared with older ones, partly due to higher nonadherence rates.[14]

The Cancer Toxicities (CANTO) study (ClinicalTrials.gov identifier: NCT01993498) has prospectively collected detailed tumor, treatment, toxicities, health-related patient reported outcomes (HRPROs), and biologicical data on a cohort of 12,012 women with newly diagnosed early breast cancer.[15] In this study, we evaluated the hypothesis that therapeutic drug monitoring may promptly identify patients who are nonadherent to breast cancer adjuvant endocrine therapy and at risk for a worse outcome. To do this, we examined nonadherence by serum assessment of tamoxifen among premenopausal patients of the CANTO cohort in the first year after the start of adjuvant endocrine treatment, and we studied its impact on short-term breast cancer survival outcomes.

PATIENTS AND METHODS

Study Design and Patient Selection

Data source. The CANTO cohort enrolled patients across France from 2012 to 2018. Eligibility criteria included patients ≥ 18 years, with a primary diagnosis of invasive stage cT0-cT3, cN0-3 breast cancer and no previous treatments for current breast cancer. Patients were assessed at diagnosis and shortly after primary treatment (ie, primary surgery, chemotherapy, or radiotherapy, whichever came last), at the time of endocrine therapy prescription, if indicated, and then at years 1, 3, and 5 after the initial post-primary treatment evaluation. Data collection at each time point included clinical, treatment (including medication adherence assessed by a trained clinical research nurse [CRN]), toxicity data, HRPROs, and serum samples.[15] The protocol is available in the Data Supplement.

Study oversight. CANTO is coordinated by UNICANCER, the National Cooperative Group of French Cancer Centers. The study was approved by the national regulatory authorities and ethics committee (ID-RCB: 2011-A01095-36, 11-039). All patients enrolled in the study provided written informed consent, including consent for the biological data collection.

Variables Assessment

Assessment of nonadherence. Nonadherence at year 1 after tamoxifen prescription was defined as nonpersistence (early discontinuation) and/or suboptimal medication implementation (eg, interruptions, skipped doses), in accordance with ESPACOMP Medication Adherence Reporting Guidelines at least 1 year after tamoxifen prescription.[16] We focused on women who potentially initiated tamoxifen therapy and excluded those who were prescribed tamoxifen but did not agree to initiate the treatment.

Nonadherence at year 1 was determined using an objective and direct method, tamoxifen serum assessment (biochemical nonadherence; the primary outcome); and a subjective and indirect method, patient's self-declaration (the secondary outcome).

Definition of primary outcome (biochemical nonadherence). Blood samples were immediately stored at −80°C after collection (ET EXTRA Biological Resource Center, Gustave Roussy, NF 96-900 certified). Tamoxifen serum level was determined by liquid chromatography-tandem mass spectrometry on 200 to 400 μL of serum in the multiple reaction monitoring mode of a 6460 triple quadrupole mass spectrometer (Agilent Technologies, Waldbronn, Germany).[17]

We used a predefined threshold of 60 ng/mL for defining biochemical nonadherence to tamoxifen on the basis of previous pharmacological studies.[17-20] Of note, tamoxifen serum concentration does not vary by CYP2D6 polymorphisms, unlike its main metabolite, endoxifen.[21] Drug-drug interactions with CYP2D6 inhibitors (eg, paroxetine or fluoxetine) do not influence tamoxifen levels.[22] There are a few drugs, such as rifampicin, aminogluthetimide, curcumin, and piperine, which may decrease tamoxifen serum levels.[23-25]

Tamoxifen metabolism and pharmacokinetic and cutoff definition of biochemical nonadherence are detailed in the Data Supplement.

Definition of secondary outcome. Patients' self-declarations (defined in the Data Supplement) on adherence to tamoxifen were collected by trained CRNs through semi-structured interviews at the same time as the blood collection for tamoxifen serum assessment. Patients were considered as having declared nonadherence if they mentioned one of the following conditions: no ongoing hormone therapy, treatment interruption, or treatment discontinuation during the year before assessment.

Assessment of survival outcomes. For survival analyses, we focused primarily on distant disease-free survival (DDFS), given that locoregional recurrences are frequently amenable to definitive treatment, thus limiting results interpretation in a cohort with a relatively short follow-up and

limited number of recurrences. DDFS was defined as time from serum assessment of tamoxifen to date of distant recurrence or death by any cause.[26] Secondarily, we examined breast cancer–free interval (BCFI), which was defined as time from tamoxifen serum assessment to date of contralateral breast cancer; local, regional, or distant recurrence; or death resulting from breast cancer.[26]

Because our focus was to assess the impact of nonadherence at year 1 after tamoxifen prescription, a landmark analysis was performed and, per the CONSORT diagram (Fig 1), all patients with a distant disease event before this time were excluded upfront from this study.

Study covariates. All study covariates were categorized as reported in Table 1, including baseline sociodemographic, clinical, and behavioral factors, treatment toxicities, and HRPROs shortly after treatment prescription.

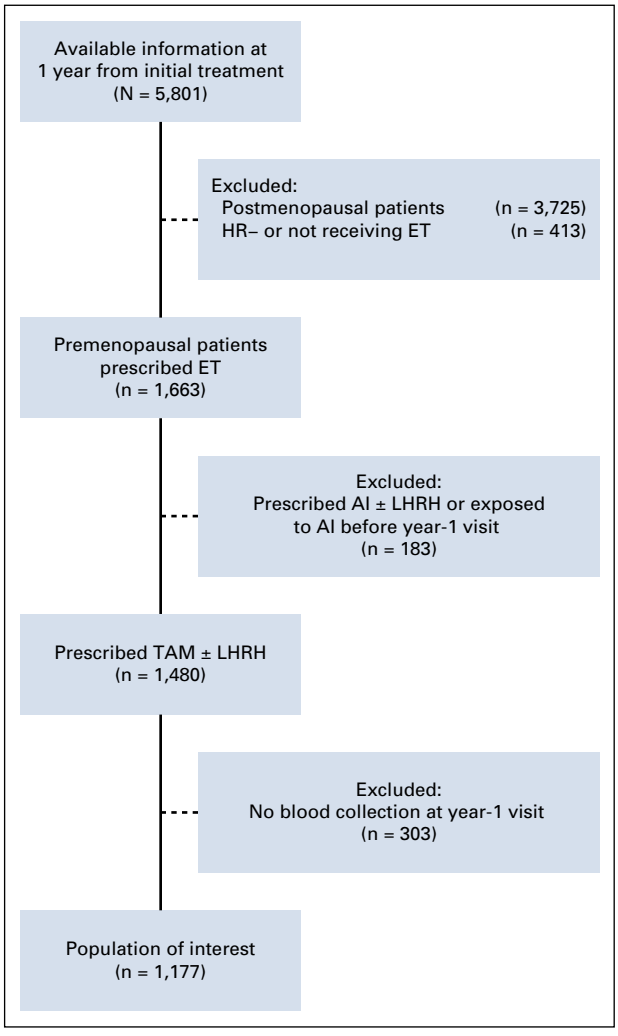

FIG 1. CONSORT diagram of study participants. AI, aromatase inhibitor; ET, endocrine therapy; HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; TAM, tamoxifen.

Statistical Analysis

Concordance between serum assessment and patient's self-report was determined by χ^2 test, and estimated using the Cramer V coefficient. Multivariate logistic regression modeled the association of relevant covariates with nonadherence at year 1 after tamoxifen prescription. Several methods were used to examine the independent impact of biochemical nonadherence and patient-reported nonadherence on DDFS. Time-to-event outcomes were estimated and plotted using the Kaplan-Meier method. To deal with confounding, as a primary analysis, we used propensity score (PS) inverse probability treatment weighting (IPTW)[27] in a Cox model. To assess robustness of results, a multivariable Cox proportional hazards model was also performed as a sensitivity analysis. Variables included in both the PS IPTW and Cox proportional hazards models were known breast cancer prognostic factors and included age at diagnosis, TNM staging, type of surgery, receipt of (neo)adjuvant chemotherapy, and center size. In secondary sensitivity analyses, PS IPTW was first weighted by Charlson Comorbidity Index score and then by marital status, education, body mass index, smoking habits, anxiety, depression, and symptoms at treatment initiation.

PS diagnostics were performed using a user-written package *pstest* (by E. Leuven and B. Sianesi, Boston College) for Stata (StataCorp, College Station, TX). Variance estimation was optimized by using a bootstrapped PS[27] and, to deal with instability that can ensue from large weights, a stabilized IPTW was implemented.[28] Because the year-1 visit did not occur exactly at the same time from diagnosis for all patients, description of time between scheduled visits in adherent and nonadherent patients was also performed. All time-to-event analyses met proportional hazards assumption as assessed by the Schoenfeld residuals. Given the low DDFS event rate, median follow-up was the median of the observed follow-up times using data from all patients.

There were low rates of missing variables, which were considered missing at random among adherent and nonadherent patients (Table 1), given balanced distribution between groups. Therefore, no multiple imputation was performed. Secondary analyses focused on BCFI were performed. All tests were two-sided and $P \leq .05$ was considered statistically significant. No formal adjustment for multiplicity was performed, given the observational nature of the study. The analyses were performed using Stata, version 15.1 (StataCorp).

RESULTS

Study Cohort

From the 5,801 women enrolled in CANTO with available data, we first excluded those who were postmenopausal at cancer diagnosis (n = 3,725), those with HR− breast cancer or not receiving endocrine therapy (n = 413), and

TABLE 1. Demographic, Social, Clinical and Pathologic Characteristics at Baseline and Treatment Details

	Overall Cohort		Serum-Defined Adherence			
			Adherent		Nonadherent	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total No. of participants	1,177	100	989	84.0	188	16.0
Tamoxifen serum concentration, ng/mL						
Median (IQR)	110 (80-144)		119 (96-152)		6 (6-38)	
Range, min-max	6-298		60-298		6-60	
Age, years						
Median	45.0		45.0		46.0	
IQR	41.0-49.0		41.0-49.0		42.0-50.0	
Age, years						
≤ 35	91	7.7	73	7.4	18	9.6
> 35 to ≤ 40	164	13.9	143	14.5	21	11.2
> 40 to ≤ 50	762	64.7	641	64.8	121	64.4
> 50	160	13.6	132	13.3	28	14.9
Charlson Comorbidity Index score						
0	975	88.2	830	89.4	145	81.9
≥ 1	130	11.8	98	10.6	32	18.1
Missing	72	6.1	61	6.2	11	5.9
Body mass index						
Underweight	47	4.0	39	3.9	8	4.3
Normal	728	62.0	615	62.2	113	60.4
Overweight	252	21.4	213	21.6	39	20.9
Obese	148	12.6	121	12.2	27	14.4
Missing	2	0.2	1	0.1	1	0.5
Smoking status						
No or previous smoker	905	78.0	774	79.1	131	71.6
Smoker	256	22.0	204	20.9	52	28.4
Missing	16	1.4	11	1.1	5	2.7
Education						
Primary school	50	4.5	39	4.1	11	6.3
High school	498	44.5	409	43.4	89	50.6
College or higher	570	51.0	494	52.4	76	43.2
Missing	59	5.0	47	4.8	12	6.4
Household income, €						
< 1,500	112	10.2	85	9.2	27	15.8
≥ 1,500 to < 3,000	415	37.9	339	36.7	76	44.4
≥ 3,000	568	51.9	500	54.1	68	39.8
Missing	82	7.0	65	6.6	17	9
Marital status						
Living as couple	951	84.8	813	86.2	138	77.5
Living alone	170	15.2	130	13.8	40	22.5
Missing	56	4.8	46	4.7	10	5.3

(continued on following page)

TABLE 1. Demographic, Social, Clinical and Pathologic Characteristics at Baseline and Treatment Details (continued)

	Overall Cohort		Serum-Defined Adherence			
			Adherent		Nonadherent	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Histology						
Invasive carcinoma, NST	944	80.3	791	80.1	153	81.4
Invasive lobular carcinoma	132	11.2	112	11.3	20	10.6
Mixed NST/lobular	35	3	32	3.2	3	1.6
Other	65	5.5	53	5.4	12	6.4
Missing	1	0.1	1	0.1	0	0
Histologic grade						
1	203	17.3	167	16.9	36	19.1
2	635	54.1	535	54.3	100	53.2
3	336	28.6	284	28.8	52	27.7
Missing	3	0.3	3	0.3	0	0
AJCC TNM stage						
I	519	44.1	432	43.7	87	46.3
II	508	43.2	426	43.1	82	43.6
III	149	12.7	130	13.2	19	10.1
Missing	1	0.1	1	0.1	0	0
IHC-defined subtype						
HR+/HER2−	995	84.5	834	84.3	161	85.6
HR+/HER2+	182	15.5	155	15.7	27	14.4
Surgery type						
BCS	788	66.9	659	66.6	129	68.6
Mastectomy	389	33.1	330	33.4	59	31.4
Axillary management						
Axillary dissection	570	48.4	478	48.3	92	48.9
Sentinel node/none	607	51.6	511	51.7	96	51.1
Radiotherapy						
Yes	1,068	90.7	897	90.7	171	91
No	109	9.3	92	9.3	17	9
(Neo)adjuvant CT type						
Anthracyclines, taxanes	691	58.7	590	59.7	101	53.7
Anthracycline based	24	2	18	1.8	6	3.2
Taxane based	44	3.7	40	4	4	2.1
Missing regimen	1	0.1	1	0.1	0	0
No	417	35.4	340	34.4	77	41
HER2-directed therapy						
Yes	146	12.4	129	13	17	9
No	1,031	87.6	860	87	171	91

(continued on following page)

TABLE 1. Demographic, Social, Clinical and Pathologic Characteristics at Baseline and Treatment Details (continued)

	Overall Cohort		Serum-Defined Adherence			
			Adherent		Nonadherent	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
EORTC QLQ-C30 severe fatigue (score > 40) after tamoxifen prescription[38]						
Yes	440	40	350	37.6	90	53.3
No	660	60	581	62.4	79	46.7
Missing	77	6.5	58	5.9	19	10.1
EORTC QLQ-C30 severe insomnia (score > 40) after tamoxifen prescription						
Yes	454	41.5	369	39.8	85	50.9
No	641	58.5	559	60.2	82	49.1
Missing	82	7.0	61	6.2	21	11.2
HADS anxiety after tamoxifen prescription[39]						
Normal	561	51	486	52.2	75	44.6
Borderline	291	26.5	241	25.9	50	29.8
Anxiety	247	22.5	204	21.9	43	25.6
Missing	78	6.6	58	5.9	20	10.6
HADS depression after tamoxifen prescription[39]						
Normal	902	82.1	775	83.2	127	75.6
Borderline	136	12.4	107	11.5	29	17.3
Depression	61	5.6	49	5.3	12	7.1
Missing	78	6.6	58	5.9	20	10.6
CTCAE, version 4, toxicities after tamoxifen prescription (any grade)						
Any gynecologic adverse effects	584	50.8	483	49.8	101	55.8
Hot flashes	863	75	727	75	136	75.1
Musculoskeletal symptoms	571	49.9	462	47.7	109	61.9
Concentration impairment	499	43.7	411	42.6	88	49.4
Any neuropathy	316	27.7	26.5	27.2	54	30.3
High-recruitment center (> 100 patients)						
Yes	1,152	97.9	968	97.9	184	97.9
No	25	2.1	21	2.1	4	2.1

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast conservative surgery; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; HR, hormone receptor; IHC, immunohistochemistry; IQR, interquartile range; IQR, interquartile range; max, maximum; min, minimum; NST, no special type; QLQ, Quality-of-Life Questionnaire.

those prescribed aromatase inhibitors before the year-1 visit (n = 183). We then selected all women who were premenopausal at diagnosis and were prescribed and agreed to take adjuvant tamoxifen (n = 1,480). Finally, we selected women among whom tamoxifen serum assessment was performed at year 1 after tamoxifen prescription (n = 1,177; Fig 1). Characteristics of nonparticipant patients who were excluded due to absence of blood assessment (n = 303 of 1,480 [20.5%]) are reported in the Data Supplement. Nonparticipant patients had lower likelihood of belonging to a high-volume recruitment center; no other major differences emerged between groups.

Among the analytic cohort, median time from tamoxifen prescription to measurement of nonadherence was 16.2 months (interquartile range [IQR], 15.1-17.8 months). Median age was 45 years (IQR, 41-49 years). Patients' characteristics at baseline and treatment details are reported in Table 1.

Nonadherence at Year 1 After Tamoxifen Prescription

Tamoxifen serum concentrations at year 1 after prescription ranged between < 6 and 298 ng/mL, with

TABLE 2. Concordance Between Serum and Self-Declaration Methods to Assess Adherence

Self-Declaration	Serum Assessment, No. (%)		
	Adherent	Nonadherent	Total
Adherent	928 (93.8)	104 (55.3)	1,032 (87.7)
Nonadherent[a]	61 (6.2)[b]	84 (44.6)	145[c] (12.3)
Total	989 (84.0)	188 (16.0)	1,177

NOTE. Concordance: 86% (95% CI, 84% to 88%); χ^2 $P < .0001$; Cramer V = 0.4293.

[a]A patient was considered self-declared nonadherent if she cited one of the following conditions: no ongoing hormone therapy, treatment interruption, or treatment discontinuation preceding the year-1 assessment.

[b]A total of 61 patients were adherent by serum assessment, but declared to be nonadherent: 50 were due to treatment interruptions, and 11 were due to treatment discontinuation.

[c]Of the 145 patients who self-reported nonadherence, 57 declared interruptions, 52 discontinued treatment, and 37 had switched to an aromatase inhibitor due to toxicity.

a median of 110 ng/mL (Table 1; Data Supplement). Overall, 188 patients (16%) were below the set biochemical adherence threshold of tamoxifen at year 1; 145 patients (12.3%) self-declared to be nonadherent: 89 (7.6%) reported tamoxifen discontinuation and 56 (4.7%) reported temporary interruptions. Among the 145 patients declaring to be nonadherent, less than half (n = 67) provided a personal or medical reason for nonadherence. Among these, toxicity was mentioned by 57 patients. Of 188 patients who were biochemically nonadherent, 104 (55.3%) stated that they had been regularly taking tamoxifen over the past year. None of those with tamoxifen serum levels < 60 ng/mL was exposed to any of the drugs that may interfere with tamoxifen serum levels. Although biochemical and self-declared nonadherence were significantly associated ($P < .0001$), only moderate concordance between the two methods was found (concordance: 86%; 95% CI, 84% to 88%; Cramer V = 0.429; Table 2).

Biochemical nonadherence was associated with multiple factors. Patients not living with a partner as a couple (*v* with a partner; adjusted odds ratio [aOR], 1.72; 95% CI, 1.02 to 2.89), those with more comorbidities (Charlson comorbidity score ≥ 1 *v* 0; aOR, 1.85 95% CI, 1.09 to 3.15), and patients who did not receive treatment with (neo)adjuvant chemotherapy (*v* those who received chemotherapy; aOR, 1.74; 95% CI, 1.04 to 2.91) had higher odds of biochemical nonadherence. In addition, symptoms after tamoxifen prescription (median time from prescription to assessment, 3.9 months [95% CI, 3.0 to 5.1 months]) including musculoskeletal symptoms (aOR, 1.58; 95% CI, 1.06 to 2.37) and severe fatigue (aOR, 1.65; 95% CI, 1.07 to 2.5) increased the risk of biochemical nonadherence (Fig 2). Factors associated with patient-reported nonadherence are described in the Data Supplement.

Impact of Nonadherence at Year 1 After Tamoxifen Prescription on Survival Outcomes

After a median follow-up of 24.2 months from tamoxifen prescription (IQR, 22.8-27.0), 38 events were registered (Data Supplement) among 1,057 patients eligible for survival analysis. The median DDFS follow-up was balanced between adherent and nonadherent groups defined by serum assessment (median, 24.3 [IQR, 22.8-27.5] *v* 24.1 [IQR, 21.3-25.8] for nonadherence). In the PS IPTW, the proportion of patients alive and without distant recurrence at 3 years was 95.4% in the adherent cohort and 89.5% in the nonadherent cohort (Fig 3A). In the multivariate IPTW model, nonadherent patients had a 131% increase in the risk of death or disease recurrence (hazard ratio [HR], 2.31; 95% CI, 1.05 to 5.06).

Diagnoses of the models' performance are fully presented in the Data Supplement. Sensitivity and secondary analyses including BCFI demonstrated consistent results (Fig 3B; Data Supplement). Full univariable and multivariable models are presented in the Data Supplement. No difference in DDFS or BCFI outcomes was found between self-reported adherence and nonadherence (Data Supplement).

DISCUSSION

Nonadherence to adjuvant endocrine therapy for early breast cancer is often under-recognized partly because of the unavailability of a gold standard method for its detection and challenges in incorporating assessments of adherence into routine clinical practice. Our study emphasizes that the real-life prevalence of nonadherence to medications is still not well quantified: health care providers tend to overestimate to what extent patients take their prescribed, long-term, oral treatments, whereas patients tend to underreport treatment discontinuations or interruptions.[29] Studies that tried to quantify the prevalence of nonadherence have yielded heterogeneous results, mostly reporting on indirect estimations obtained using patient self-report and prescription refill data.[1,2,7] In breast cancer, previous studies based on indirect methods suggested that nonadherence to adjuvant endocrine therapy over 5 years ranges from 25% to 50%, with this proportion increasing over time.[10-12,30] Only one study measured adherence to endocrine therapy by using an objective method based on drug serum assessment, although it did not provide correlations with breast cancer outcomes.[8] In our study, serum assessment was able to identify a worryingly high proportion of patients, one in six, who were nonadherent to therapy at only 1 year after treatment prescription. Patient self-reports underestimated rates of nonadherence. Notably, 55% of patients who were nonadherent by serum assessment might not overtly acknowledge nonadherence.

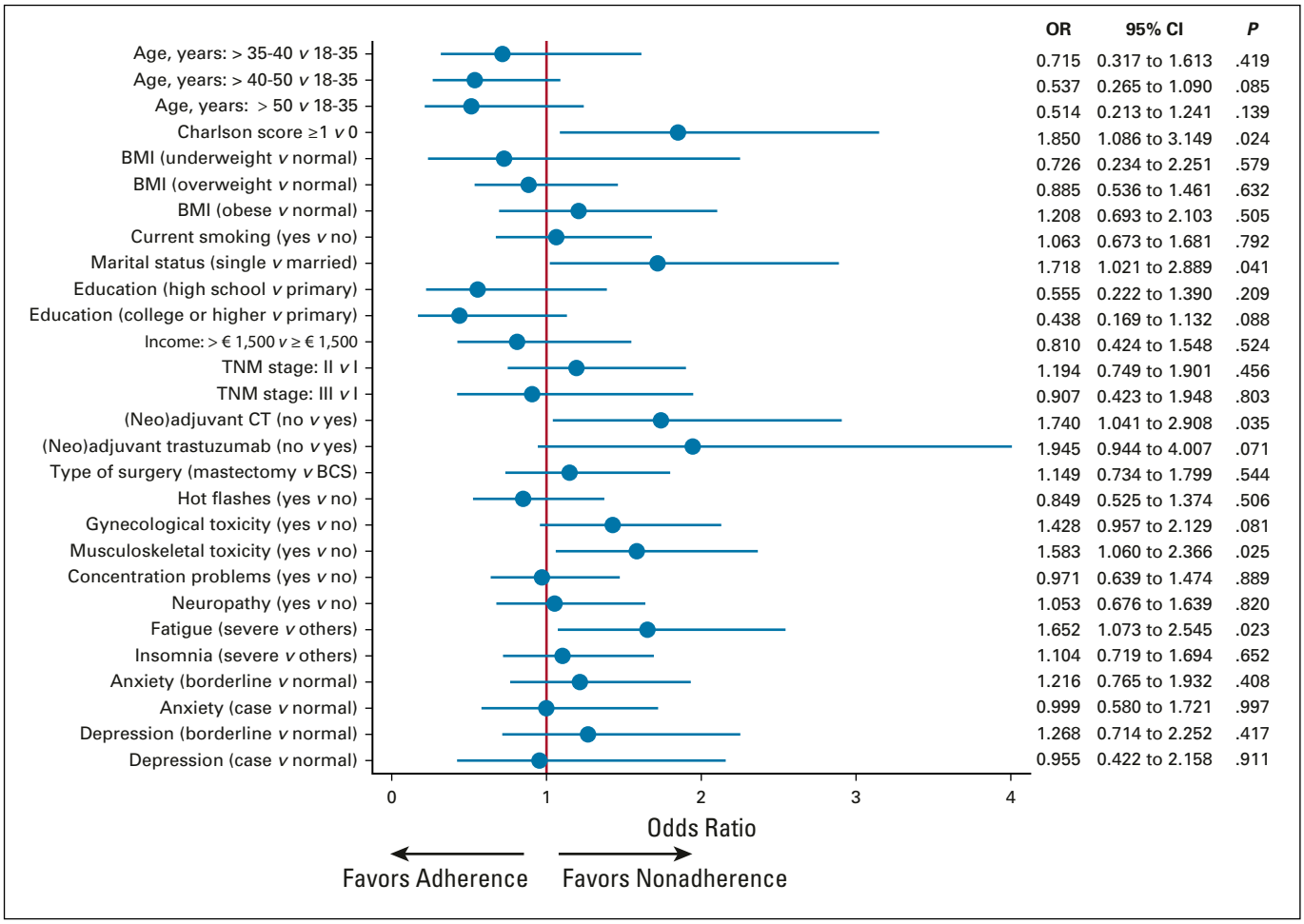

FIG 2. Multivariate estimates of variables associated with serum-defined adherence. Severe fatigue and insomnia were defined as the respective subscale European Organization for Research and Treatment of Cancer–C30 score > 40.[38] Anxiety and depression were defined using the Hospital Anxiety and Depression Scale.[39] BMI, body mass index; CT, chemotherapy; OR odds ratio.

Furthermore, nonadherence by serum assessment measured as early as year 1 after treatment prescription emerged as marker of poorer outcomes regardless of other main prognostic factors, suggesting that risk of recurrence increases as soon as the patients start to be nonadherent. Although it is unusual to see a significant impact on outcomes with such short-term follow-up among patients with HR+ breast cancer, results of prior research are consistent with our findings. Conflicting results were reported across different studies, suggesting the possibility that inadequate exposure to tamoxifen due to nonadherence may lead to a suboptimal concentration of its active metabolites.[20,31] Prior retrospective analyses based on pharmacy claims data also suggested a negative impact of nonadherence on breast cancer outcomes but used an arbitrary cutoff of 80% medication possession ratio to define adequate adherence.[32-34] However, pharmacy claims typically cannot be obtained in real time on an individual patient level and thus cannot be used to tailor treatment in the clinic.[1,10,11]

This study provides important insights on the complexity of nonadherence. We found that sicker, nonpartnered patients and those with higher symptom burden, including more severe fatigue and musculoskeletal symptoms, had a higher likelihood of being nonadherent to therapy. Most of these associations have also been observed in other chronic diseases, such as HIV, cardiac diseases, and diabetes, and are explained by several differences in social and clinical characteristics across patients. In addition to these previously known barriers, patients who did not receive adjuvant chemotherapy were also more likely not to be adherent to tamoxifen in our analysis. We hypothesize that these patients are less aware of the health risks related to their disease and misconceive the beneficial impact of adjuvant endocrine therapy on breast cancer outcomes.

CANTO offered an unparalleled opportunity to test the performance of therapeutic drug monitoring in adjuvant treatment of breast cancer. Nevertheless, we acknowledge some limitations. First, we used tamoxifen concentration thresholds that have not been previously validated to define biochemical nonadherence. However, we used a conservative approach based on previous

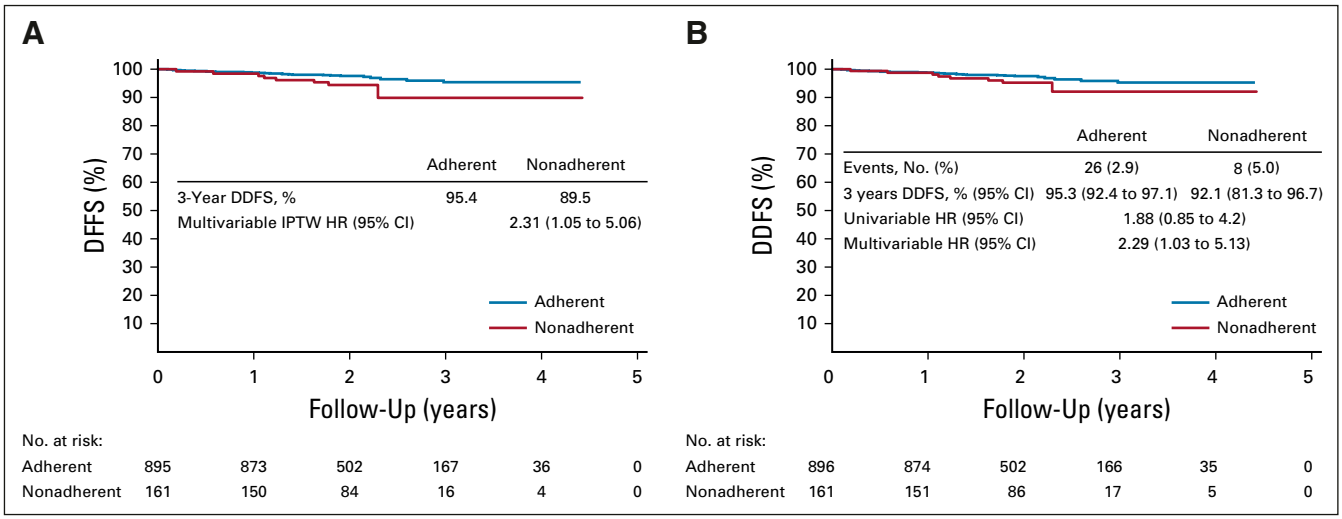

FIG 3. Distant disease-free survival (DDFS; distant recurrences and death) according to serum-defined adherence status in (A) the IPTW cohort and in the (B) non-IPTW cohort. Time 0 defines the time of the post-tamoxifen prescription visit and date of serum assessment of tamoxifen. HR, hazard ratio; IPTW, inverse probability treatment weighting.

pharmacological studies[18-20] that focused on the 3-month steady-state tamoxifen concentration, which all our patients should have achieved. In addition, we did not assess active tamoxifen metabolites or CYP2D6 genotypes, although both might be associated with breast cancer outcomes and adverse effects from tamoxifen that ultimately influence treatment adherence.[20,35] Second, the self-reported assessment of adherence and respective reasons were not based on validated scales, but they still reflect what is currently done in clinical practice. Although CRNs systematically asked for and collected the reasons for treatment interruption or discontinuation, only a small number of patients disclosed this information, limiting our ability to capture the complexity of factors affecting medication-taking behavior. Third, because of the low number of events and the lack of validation cohort, we cannot draw definitive conclusions on the generalizability of the negative impact of nonadherence on breast cancer outcomes. Nevertheless, our results are clinically plausible and the broad range of inclusion and exclusion criteria in CANTO suggest external validity of our results. Fourth, we are aware that it is hard to isolate the true impact of nonadherence to tamoxifen on outcomes because it is part of a multitude of health-related behaviors influencing prognosis.[36] Indeed, because of the observational design, we cannot exclude unmeasured confounding affecting our survival analyses. Nevertheless, we used a PS weighting including relevant, known prognostic factors, aiming for a comprehensive adjustment in our analyses.[27,28] Fifth, we cannot exclude the impact of awareness of being observed on adherence (the Hawthorne effect). Nevertheless, in our study, the long-term observation, assessment of multiple clinical and biologic data, and evaluation of adherence using indirect and direct methods may minimize this effect.[37] Finally, our results may not be generalizable to other populations, because we restricted our analysis to the French premenopausal population with breast cancer.

This study adds to the understanding of the multifaceted and complex issue of nonadherence' to chronic medications, suggesting that therapeutic drug monitoring may be an important tool to identify nonadherent patients who are at risk for a distant relapse event early in their adjuvant treatment trajectory. The impact of interventions to optimize adherence on a population level could thus be large. Targeted interventions managing adherence to adjuvant endocrine therapy are needed and have the potential to improve breast cancer outcomes.

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