Explaining the Relationships Between Age, Endocrine Therapy Persistence, and Risk of Recurrence in Hormone Receptor–Positive Early Breast Cancer: A Nationwide Cohort Study

Elise Dumas, PhD[1,2]; Floriane Jochum, MD, PhD[2,3]; Florence Coussy, MD, PhD[2,4]; Anne-Sophie Hamy, MD, PhD[2,4]; Alena Majdling, MD[5]; Sophie Houzard, MD[6]; Christine Le Bihan-Benjamin, MD[6]; Fabien Reyal, MD, PhD[2,7,8]; Paul Gougis, MD, PhD[2]; and Mats Julius Stensrud, MD, PhD[1]

DOI https://doi.org/10.1200/JCO.24.01131

ABSTRACT

PURPOSE Young age is associated with increased risk of recurrence in hormone receptor (HR)–positive early-stage breast cancer (eBC). Lack of adherence to endocrine therapy (ET) is a potential reason for the lower survival proportions observed in younger patients, but the survival benefits of improving adherence to ET in young patients remain unknown.

MATERIALS AND METHODS Using data from the French National Health Data System and target trial emulation methods, we considered three sustained ET persistence strategies (allowing treatment gaps of no more than 30, 90, or 180 continuous days) and estimated the 5-year disease-free survival (DFS) benefit of sustained ET persistence compared with observed ET persistence.

RESULTS A total of 121,601 patients with HR-positive eBC were included in the analyses, of whom 29.8% was younger than 50 years at diagnosis. Younger patients had lower DFS and were more likely to discontinue ET than older patients. In patients 34 years and younger, strict ET persistence (≤30-day gaps) improved 5-year DFS proportions from 74.5% to 78.8% (4.3 percentage points [95% CI, 2.6 to 7.2]) compared with observed persistence. ET persistence strategies allowing for ≤90-day and ≤180-day gaps reduced the 5-year DFS benefit in patients 34 years and younger to 1.3 (95% CI, 0.2 to 3.7) and 1.0 (95% CI, −0.2 to 3.4) percentage points, respectively. By contrast, DFS benefits of improved ET persistence in patients after 50 years old did not exceed 1.9 percentage points, compared with observed persistence, regardless of the persistence definition.

CONCLUSION The survival benefit that could be achieved with strict ET persistence in women 34 years and younger with HR-positive eBC highlights the need for tailored strategies to improve ET persistence in this population.

ACCOMPANYING CONTENT

Data Supplement

Accepted January 28, 2025
Published March 5, 2025

J Clin Oncol 00:1-12

View Online Article

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases in 2020.[1] BC is a heterogeneous disease that is conventionally classified into subtypes on the basis of the expression of hormone receptors (HR, estrogen and progesterone) and human epidermal growth factor receptor 2 (*HER2*).[2] These subtypes exhibit varying levels of risk for disease recurrence, metastatic spread, response to treatment, and overall survival and guide the selection of appropriate BC therapy, particularly with endocrine therapy (ET) for HR-positive tumors.[3] Despite its importance in preventing recurrence in patients with HR-positive early-stage (nonmetastatic) BC,[4] the efficacy of ET could be compromised by treatment discontinuation, or nonpersistence, which is often defined as a 3- to 6-month interruption in ET treatment continuity.[5-7]

Approximately 6%-7% of patients with BC are young women diagnosed before age 40 years.[8] Young age at BC diagnosis is associated with disease recurrence and specific mortality, despite the use of more aggressive treatment in younger patients.[9] More recently, young age at diagnosis was found to be associated with poorer BC prognosis for patients with HR-positive tumors, but not with HR-negative tumors.[10-15] Young age is associated with ET discontinuation, with nonpersistence risks reported to be up to 22% at 5 years, considering a 6-month gap.[16] Thus, low ET persistence has

CONTEXT

Key Objective

What is the potential benefit of improving persistence to adjuvant endocrine therapy (ET) on disease-free survival (DFS) in patients with early-stage breast cancer for each specific age group?

Knowledge Generated

Strict persistence to adjuvant ET, without treatment gaps of 30 continuous days or more, improved 5-year DFS proportions by 4.3 percentage points in patients younger than 34 years and 2.6 percentage points in patients age 35-39 years. In older patients, the 5-year DFS benefit did not exceed 1.9 percentage points.

Relevance *(S.B. Wheeler)*

This study using real-world data projected meaningful survival benefits with perfect adherence to adjuvant ET among younger women with BC, with relatively little benefit of perfect adherence in older women. Such data can point to opportunities to develop tailored intervention strategies that target younger women, in particular, who are at greater risk for nonadherence.*

*Relevance section written by JCO Associate Editor Stephanie B. Wheeler, PhD, MPH.

been hypothesized as a reason for the lower survival proportions in young patients.[17] However, to date, no study has formally evaluated the potential survival benefits of improving adherence to ET in young patients.

Randomized experiments that study different persistence strategies have not been conducted and would likely be ethically infeasible. In the absence of such trial data, we used large, real-world data from France to evaluate the effect of persistence strategies. Specifically, the health insurance system database (SNDS) aggregates all the medical and administrative information related to the reimbursement of health care expenses in France.[18] However, causal analysis of these nonexperimental data requires care. Target trial emulation has been recently proposed as a framework for designing observational studies mimicking key features of randomized controlled trials, thereby reducing the risk of fundamental design flaws and highlighting potential sources of bias that could result in spurious causal conclusions.[19-21]

We used a comprehensive cohort of patients with HR-positive early-stage BC in France derived from SNDS data to emulate three sustained ET persistence strategies (allowing treatment gaps of no more than 30, 90, or 180 days) and estimate the 5-year disease-free survival (DFS) benefit of ET persistence compared with observed ET persistence.

MATERIALS AND METHODS

Ethics and Data Protection

The study was authorized by the French data protection agency (*Commission nationale de l'informatique et des libertés*—CNIL) under registration number 920092. No informed consent was required because the data used in the study were deidentified and reused for research purposes, in accordance with French regulations applicable to the SNDS data.

Data Source and Cohort Inclusion/Exclusion Criteria

We used nationwide retrospective data from the previously published French Early Breast Cancer Cohort (FRESH),[22] which were released from the SNDS database within the Oncology Data Platform available at the French National Cancer Institute.[18,23] The FRESH cohort includes women with early-stage BC newly diagnosed between January 1, 2011, and December 31, 2017, identified by a diagnosis code for BC within the period considered. We further excluded individuals not covered by the main health insurance scheme (*Régime Général*), not undergoing breast surgery, not receiving chemotherapy, targeted therapy, or ET as part of the initial treatments, with evidence of concomitant cancer of another localization, previous cancer, or metastatic disease at diagnosis, diagnosed before age 18 years or after age 70 years, with inconsistent or missing data, or with evidence of disease recurrence before adjuvant ET onset.

Age at Diagnosis

We calculated age at BC diagnosis as the interval from birth to the BC diagnosis date rounded to the nearest year. Age was categorized into detailed ranges (18-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69 years) and further grouped into <50 and ≥50 years. We dichotomized age at a cutoff of 50 years as age 50 years marks the commencement of the systematic screening program in France and aligns with the median age of menopause.

HR Status

Tumors from patients who initiated ET within 365 days of initial BC surgery were classified as HR-positive; otherwise, tumors were classified as HR-negative. ET consisted of tamoxifen or an aromatase inhibitor (AI), either with or without a gonadotropin-releasing hormone agonist (GnRHa). Our main cohort consisted of patients with HR-positive tumors, but we maintained a complementary cohort of HR-negative tumors for comparative analysis.

ET Persistence

ET persistence was computed on the basis of outpatient dispensing of tamoxifen and AIs. We evaluated three definitions of ET persistence, denoted by ≤30-day, ≤90-day, and ≤180-day gaps and characterized by no previous ET discontinuation for more than 30, 90, or 180 consecutive days, respectively. We considered a patient to have discontinued ET for 30 consecutive days if the patient had not been dispensed ET in the previous 30 consecutive days and could not be covered by an excess of pills from a previous dispensing. Similar definitions were given for 90 and 180 days. We evaluated ET discontinuation until BC recurrence or death. We did not consider molecule switch a form of discontinuation. We provide further details in the Data Supplement (Table S1 and Fig S1).

Outcome

The primary end point was DFS, defined as the absence of BC recurrence (including locoregional recurrence, contralateral recurrence, or distant recurrence) and death. The identification of BC recurrence was based on procedures, molecules, or diagnoses indicative of cancer recurrence or metastasis, as detailed in the Data Supplement (Table S2). We set time zero at the date of adjuvant ET onset for patients with HR-positive tumors and at the date of initial BC surgery for patients with HR-negative tumors.

Statistical Analysis

We first estimated DFS and ET persistence by age group using Kaplan-Meier survival curves and reported the proportions of DFS and ET persistence at 5 years. We performed subgroup analyses by HR and *HER2* status when estimating DFS. This initial descriptive analysis is noncausal and is not intended to emulate a target trial.

Next, we emulated a target trial to quantify the DFS benefit that could be achieved under sustained ET persistence compared with observed ET persistence. We use the term sustained ET persistence to denote a hypothetical regimen in which patients are prevented from discontinuing ET, for one of the three definitions of ET discontinuation that were considered.[24] We used a cloning, censoring, and weighting approach.[21] This involved (1) cloning each patient and assigning one clone to each of the ET persistence regimens (natural, ≤30-day, ≤90-day, and ≤180-day gaps), (2) censoring the clones at the first ET discontinuation according to the definition used, and (3) weighting the clones to account for bias because of time-fixed and time-varying confounding. The time-fixed covariates were *HER2* status, nodal status (node-positive/node-negative), type of breast surgery (lumpectomy/mastectomy), use of radiotherapy, use of chemotherapy, chemotherapy setting (adjuvant only, neoadjuvant with or without adjuvant), and deprivation index. The time-varying covariates were comorbid conditions (cardiovascular, psychiatric, endocrine or metabolic, or any other), use of GnRHa, and history of ET noncoverage.

We estimated DFS under sustained ET persistence from nonparametric Kaplan-Meier survival curves on the weighted population. We used the nonparametric bootstrap with 1,000 iterations to estimate 95% CIs. Further details, especially regarding the identification of covariates, are provided in the Data Supplement (Table S3).

We performed 11 sensitivity analyses to assess the stability of the results. These sensitivity analyses included a negative control outcome (otolaryngologist visit) analysis and analyses with different target populations, different definitions of ET persistence, different calculations of inverse probability weights, and different covariates encoding. See the Data Supplement for details.

RESULTS

Patients' Baseline Characteristics

Among 448,090 women with a diagnosis code of BC between 2011 and 2017, we included 143,580 patients: 121,601 in the HR-positive cohort and 21,979 in the HR-negative cohort (Fig 1). In the HR-positive cohort, 29.8% of patients were younger than 50 years at BC diagnosis (Fig 2). Women younger than 50 years, compared with older women, were more likely to be diagnosed with lymph node involvement (26.2% *v* 20.2%), undergo mastectomy (34.5% *v* 21.2%), and receive chemotherapy (63.1% *v* 40.3%), but less likely to present with comorbid conditions at the time of BC diagnosis (Table 1). The distribution of ET regimens in women younger than 50 years was as follows: 91.5% of patients received tamoxifen only, 1.7% received tamoxifen combined with GnRHa, 4.9% received AIs only, and 1.9% received AIs combined with GnRHa. Among women younger than 50 years, those exposed to GnRHa were more likely to be diagnosed with node-positive disease (36.1% *v* 25.8%), to undergo mastectomy (50.0% *v* 33.9%), and to receive chemotherapy (74.0% *v* 62.7%; Data Supplement, Table S4). The median follow-up was 46.4 months (IQR, 26.1-67.3), and 9.2% of patients (n = 11,161) experienced recurrence or died during follow-up.

Relationship Between Age and DFS per HR Status

In patients with HR-positive tumors, younger age was associated with decreased DFS compared with older age, with

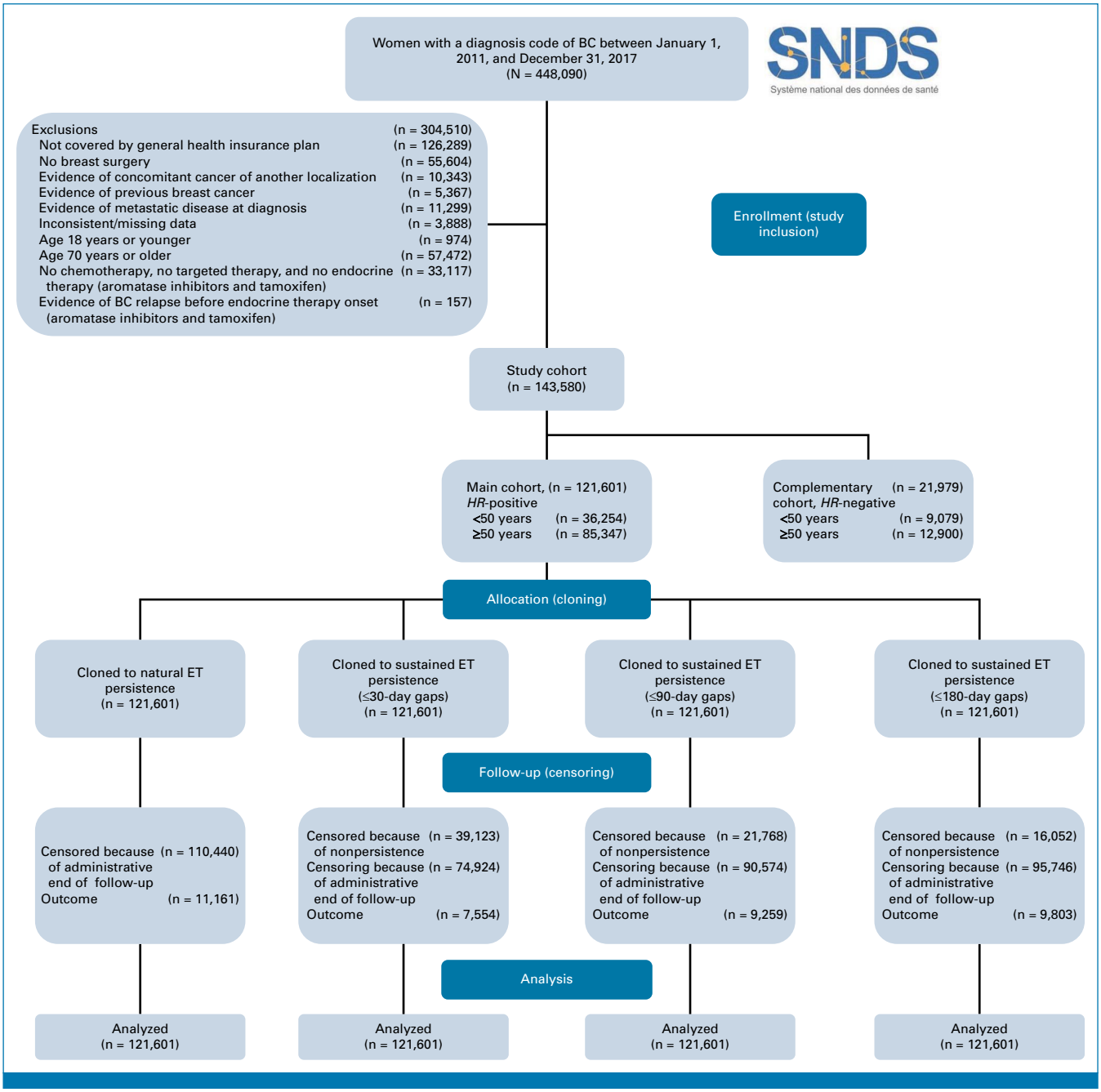

FIG 1. Study CONSORT diagram. BC, breast cancer; ET, endocrine therapy; HR, hormone receptor; SNDS, Système National des Données de Santé.

5-year DFS proportions of 86.0% (95% CI, 85.6 to 86.5) for patients diagnosed before age 50 years compared with 88.9% (95% CI, 88.6 to 89.2) for patients diagnosed after age 50 years (Table 2). More precisely, 5-year DFS proportions increased with age until 50 years, ranging from 74.5% (95% CI, 72.3 to 76.9) in patients 34 years and younger to 88.4% (95% CI, 87.8 to 89.0) for those age 45-49 years (Fig 3A). After 50 years old, DFS proportions were less variable across age groups, with estimated values ranging from 88.2% (95% CI, 87.7 to 88.8) for patients age 55-59 years to 89.8% (95% CI, 89.3 to 90.4) for patients age 50-54 years (Fig 3B). We observed similar variations in DFS across age groups when further subcategorizing HR-positive tumors by *HER2* status although for patients 35 years and older, the differences in 5-year DFS were less for *HER2*-positive than for *HER2*-negative disease (Data Supplement, Fig S2). In patients with HR-negative tumors, DFS proportions were less variable across all age groups both before and after age 50 years, with 5-year DFS proportions ranging from 75.5% (95% CI, 72.9 to 78.2) for patients 34 years and younger to 78.1% (95%

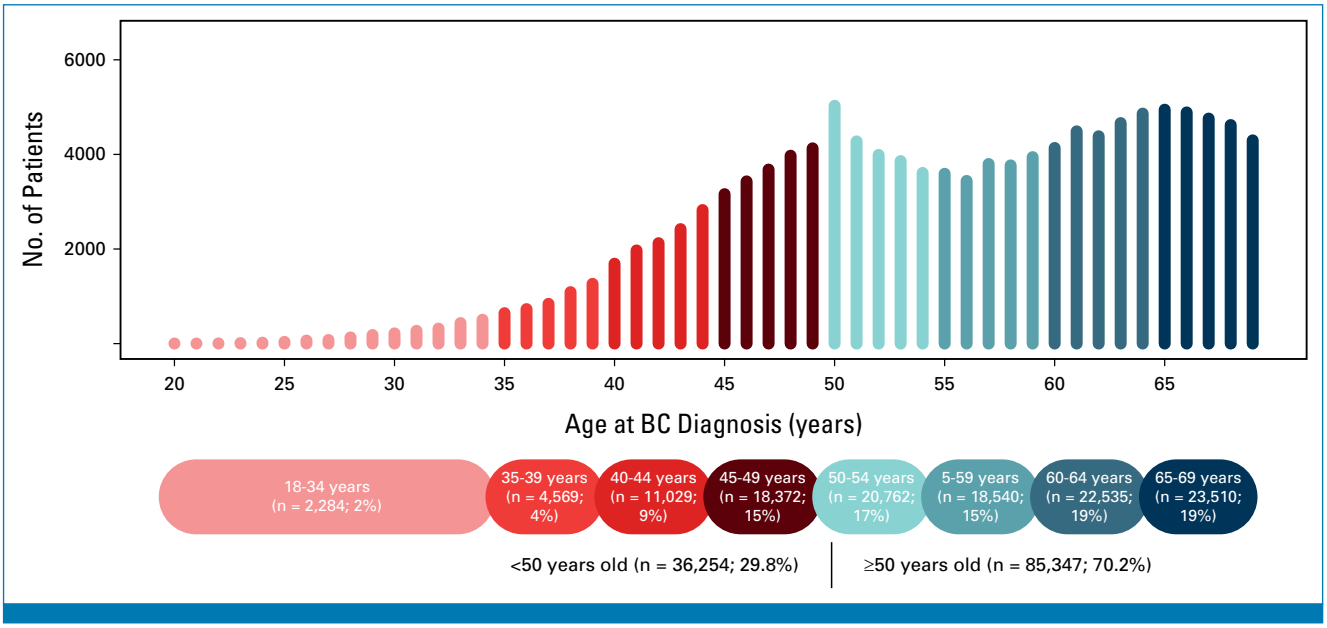

FIG. 2. Distribution of age in the cohort of patients with HR-positive tumors. BC, breast cancer; HR, hormone receptor.

CI, 76.5 to 79.7) for patients age 50-54 years (Figs 3C and 3D, Data Supplement, Table S5). We observed similar results when further subcategorizing the cohort of HR-negative tumors into *HER2*-negative/HR-negative and *HER2*-positive/HR-negative (Data Supplement, Fig S3).

Relationship Between Age and ET Persistence

In the cohort of patients with HR-positive tumors, younger age was associated with higher risks of ET discontinuation (Data Supplement, Table S6). More specifically, we observed an increase in 5-year ET persistence proportions with age, peaking in the 55-59 years age group (Data Supplement, Fig S4). These trends were consistent across the three definitions of ET discontinuation (≤30-day, ≤90-day, or ≤180-day gaps).

DFS by Age Under Sustained ET Persistence

Sustained ET persistence resulted in higher 5-year DFS proportions compared with observed persistence in all age groups (Table 2). DFS benefits were generally increasing with the stringency of the definition used for ET discontinuation, with ≤30-day gaps leading to the highest DFS benefit, followed by ≤90-day and ≤180-day gaps, respectively. Under strategies that ensure sustained ET persistence with ≤30-day gaps, the 5-year DFS proportions in patients younger than 50 years did not align with the DFS proportions achieved for older patients (Data Supplement, Fig S5).

The benefit in DFS achieved by sustained ET persistence varied in magnitude depending on age (Figs 4 and 5). In patients 34 years and younger, stricter persistence (≤30-day gaps) increased 5-year DFS by 4.3 percentage points (95% CI, 2.6 to 7.2) compared with observed persistence, from 74.5% to 78.8%. Compared with allowing gaps of up to 30 days, allowing gaps of up to 90 days reduced the DFS benefit from 4.3 to 1.3 percentage points (95% CI, 0.2 to 3.7) and allowing gaps of up to 180 days further reduced the DFS benefit to 1.0 percentage points (95% CI, −0.2 to 3.4). In patients age 35-39 years, DFS benefit under ≤30-day gaps was 2.6 percentage points (95% CI, 1.5 to 4.1). After 50 years old, DFS benefit never exceeded 1.9 percentage points (95% CI, 1.6 to 2.4), as achieved in patients age 55-59 years under ≤30-day gaps.

We found similar results for patients exposed to GnRHa at ET onset (Data Supplement, Table S7). For patients with HR-positive/*HER2*-positive disease, the DFS benefit of sustained ET persistence was similar to the main analysis for patients younger than 40 years. In the negative control outcome analysis, the differences in otolaryngologist visit frequency under sustained versus observed ET persistence never exceeded −0.8 percentage points. Other sensitivity analyses assessing the robustness of the results with respect to changes in the weights, in ET persistence strategies, or in the definition of covariates yielded results analogous to those of the primary analysis.

DISCUSSION

We found that younger age was associated with decreased DFS compared with older age in the cohort of patients with HR-positive tumors, but not in the cohort of patients with HR-negative tumors. Younger age was also associated with more frequent ET discontinuation. DFS proportions under sustained ET persistence in patients younger than 50 years did not equal those of older patients. However,

TABLE 1. Patient's Characteristics in the Cohort of Women With *HR*-Positive Early-Stage BC by Age Group (<50 years old, ≥50 years old)

Characteristic	Overall, No. (%)	<50 Years Old, No. (%)	≥50 Years Old, No. (%)
Patients	121,601	36,254 (29.8)	85,347 (70.2)
BC biology			
BC subtype			
HER2−/HR+ (luminal)	110,782 (91.1)	31,665 (87.3)	79,117 (92.7)
HER2+/HR+	10,819 (8.9)	4,589 (12.7)	6,230 (7.3)
Nodal status			
Node-negative	94,895 (78.0)	26,759 (73.8)	68,136 (79.8)
Node-positive	26,706 (22.0)	9,495 (26.2)	17,211 (20.2)
BC treatments			
Type of BC surgery			
Lumpectomy	91,011 (74.8)	23,745 (65.5)	67,266 (78.8)
Mastectomy	30,590 (25.2)	12,509 (34.5)	18,081 (21.2)
Radiotherapy			
No	9,246 (7.6)	2,907 (8.0)	6,339 (7.4)
Yes	112,355 (92.4)	33,347 (92.0)	79,008 (92.6)
Chemotherapy			
No	64,348 (52.9)	13,380 (36.9)	50,968 (59.7)
Yes	57,253 (47.1)	22,874 (63.1)	34,379 (40.3)
Chemotherapy setting[a]			
Adjuvant only	47,706 (83.3)	17,883 (78.2)	29,823 (86.7)
Neoadjuvant with or without adjuvant	9,547 (16.7)	4,991 (21.8)	4,556 (13.3)
Endocrine therapy regimen[b]			
AIs	72,183 (59.4)	1,774 (4.9)	70,409 (82.5)
Tamoxifen	47,834 (39.3)	33,159 (91.5)	14,675 (17.2)
Tamoxifen combined with GnRH agonists	672 (0.6)	619 (1.7)	53 (0.1)
AIs combined with GnRH agonists	912 (0.7)	702 (1.9)	210 (0.2)
Socioeconomic factors			
Deprivation index			
First quintile (least deprived)	23,274 (19.1)	7,482 (20.6)	15,792 (18.5)
Second quintile	24,272 (20.0)	7,296 (20.1)	16,976 (19.9)
Third quintile	23,790 (19.6)	7,029 (19.4)	16,761 (19.6)
Fourth quintile	23,968 (19.7)	6,855 (18.9)	17,113 (20.1)
Fifth quintile (most deprived)	24,126 (19.8)	6,737 (18.6)	17,389 (20.4)
Overseas departments	2,171 (1.8)	855 (2.4)	1,316 (1.5)
No. of comorbid conditions at BC diagnosis			
0	56,865 (46.8)	23,831 (65.7)	33,034 (38.7)
1	30,501 (25.1)	8,179 (22.6)	22,322 (26.2)
2-4	29,531 (24.3)	3,915 (10.8)	25,616 (30.0)
5+	4,704 (3.9)	329 (0.9)	4,375 (5.1)
Category of comorbid conditions[c]			
Psychiatric	26,179 (21.5)	6,326 (17.4)	19,853 (23.3)
Endocrine and metabolism	30,619 (25.2)	3,579 (9.9)	27,040 (31.7)
Cardiovascular	34,384 (28.3)	3,336 (9.2)	31,048 (36.4)
Any other	15,747 (12.9)	3,449 (9.5)	12,298 (14.4)

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; GnRH, gonadotropin-releasing hormone; HR, hormone receptor.
[a]The Chemotherapy setting category is presented only for the subset of patients who received chemotherapy.
[b]Molecule dispensed on the date of adjuvant endocrine therapy onset.
[c]Categories are not mutually exclusive.

ensuring strict ET persistence (≤30-day gaps) resulted in DFS benefits of 4.3 percentage points (95% CI, 2.6 to 7.2) and 2.6 percentage points (95% CI, 1.5 to 4.1) in 5-year DFS proportions in patients 34 years and younger and age 35-39 years, respectively. While the survival benefit of strict ET persistence was larger in these patients compared with their older counterparts, there was also a prominent reduction in DFS in settings allowing gaps up to 90 and 180 days in the youngest age groups.

Earlier studies indicated that, among patients with HR-positive disease, younger individuals have a higher risk of recurrence,[13] BC-specific mortality[14] and overall mortality[14] compared to older patients. This trend was not observed in patients with HR-negative disease. Our findings are consistent with these earlier studies. The decreased DFS proportions remained in *HER2*-positive/HR-positive disease for the youngest patients, 34 years and younger.

We observed 5-year ET discontinuation risks of 21.5% when allowing ≤90-day gaps, in patients younger than 50 years. Similarly, earlier studies showed high risks of nonadherence and discontinuation of ET in younger patients.[7,25] Reasons for discontinuation specific to young age might include side effects like hot flashes and vaginal symptom burden, sexual toxicity, feelings of being inadequately informed, negative emotions regarding the therapy, and desire for or experience of pregnancy.[26,27]

Because ET nonpersistence is associated with decreased DFS in women with HR-positive tumors,[16] authors hypothesized that low persistence could explain the low survival observed in young patients.[12] Our results partly support this hypothesis. Specifically, for patients diagnosed before age 34 years, we showed that persistence to ET with ≤30-day gaps could increase the 5-year DFS by 4.3 percentage points compared with what is observed with unmanaged persistence. We also found that the effect of ET persistence varied with age, with strict persistence being more beneficial to young patients compared with older patients. It is possible that the effect of ET persistence in the youngest patients is related to accelerated tumor growth kinetics, driven by elevated circulating levels of endogenous estrogen after ET discontinuation,[28] but further research is required to validate this hypothesis. The differences in DFS proportions under observed persistence, used here as reference for DFS benefit, may also partly explain these results.

In our study, DFS proportions under emulated ET persistence in patients younger than 50 years did not equal those of older patients, suggesting that ET discontinuation alone does not fully explain the observed survival differences between age groups within HR-positive tumors. Other contributing factors may include diagnostic delays,[29] more aggressive tumors,[9] and challenges in achieving chemotherapy-induced amenorrhea in younger patients.[30] In this context, we observed that patients younger than 50 years with HR-positive tumors were more likely to present with node-positive tumors at diagnosis and to be treated with more aggressive treatments including total mastectomy and neoadjuvant chemotherapy. Similarly, our findings that age is not associated with DFS in HR-negative BC may be explained by younger patients receiving more aggressive treatments that may compensate for age-related differences in disease severity.

TABLE 2. Number of Patients, Number of Events, and 5-Year DFS Proportions Along With Their 95% CIs for the Cohort of Patients With *HR*-Positive Tumors

			5-Year DFS, % (95% CI)			
				Emulated ET Persistence		
Age Group, Years	Patients, No.	Events, No.[a]	Observed ET Persistence (natural)	≤30-Day Gaps	≤90-Day Gaps	≤180-Day Gaps
<50 years old	36,254	3,834	86 (85.6 to 86.5)	87.9 (87.4 to 88.5)	86.8 (86.3 to 87.3)	86.7 (86.2 to 87.1)
18-34	2,284	434	74.5 (72.3 to 76.9)	78.8 (76 to 81.6)	75.8 (73.1 to 78.4)	75.5 (72.6 to 78.3)
35-39	4,569	639	80.8 (79.4 to 82.3)	83.4 (81.5 to 85.3)	81.6 (79.8 to 83.3)	81.7 (80 to 83.3)
40-44	11,029	1,116	86.5 (85.7 to 87.3)	88.2 (87.3 to 89.2)	87.2 (86.4 to 88.2)	87 (86.1 to 87.9)
45-49	18,372	1,645	88.4 (87.8 to 89)	89.7 (89 to 90.3)	88.9 (88.3 to 89.5)	88.8 (88.2 to 89.4)
≥50 years old	85,347	7,327	88.9 (88.6 to 89.2)	90.6 (90.3 to 90.9)	89.7 (89.5 to 90)	89.5 (89.2 to 89.8)
50-54	20,762	1,616	89.8 (89.3 to 90.4)	91.2 (90.6 to 91.8)	90.6 (90.1 to 91.2)	90.3 (89.8 to 90.9)
55-59	18,540	1,738	88.2 (87.7 to 88.8)	90.2 (89.6 to 90.7)	89.1 (88.5 to 89.7)	88.8 (88.3 to 89.4)
60-64	22,535	1,988	88.7 (88.2 to 89.3)	90.4 (89.8 to 90.9)	89.4 (88.9 to 90)	89.3 (88.7 to 89.8)
65-69	23,510	1,985	88.7 (88.2 to 89.3)	90.5 (90 to 91.1)	89.8 (89.2 to 90.3)	89.5 (89 to 90)

NOTE. Results are presented for all age groups under observed (natural) ET persistence and under emulated ET persistence defined as ≤30-day gaps, ≤90-day gaps, and ≤180-day gaps. 95% CIs for observed ET persistence were derived on the basis of the standard procedure for Kaplan-Meier survival curve estimates (Greenwood formula for cumulative hazard). CIs for emulated ET persistence were obtained using bootstrapping for 1,000 iterations.

Abbreviations: DFS, disease-free survival; HR, hormone receptor; ET, endocrine therapy.

[a]The number of events is the number of patients experiencing BC recurrence or death under observed ET persistence.

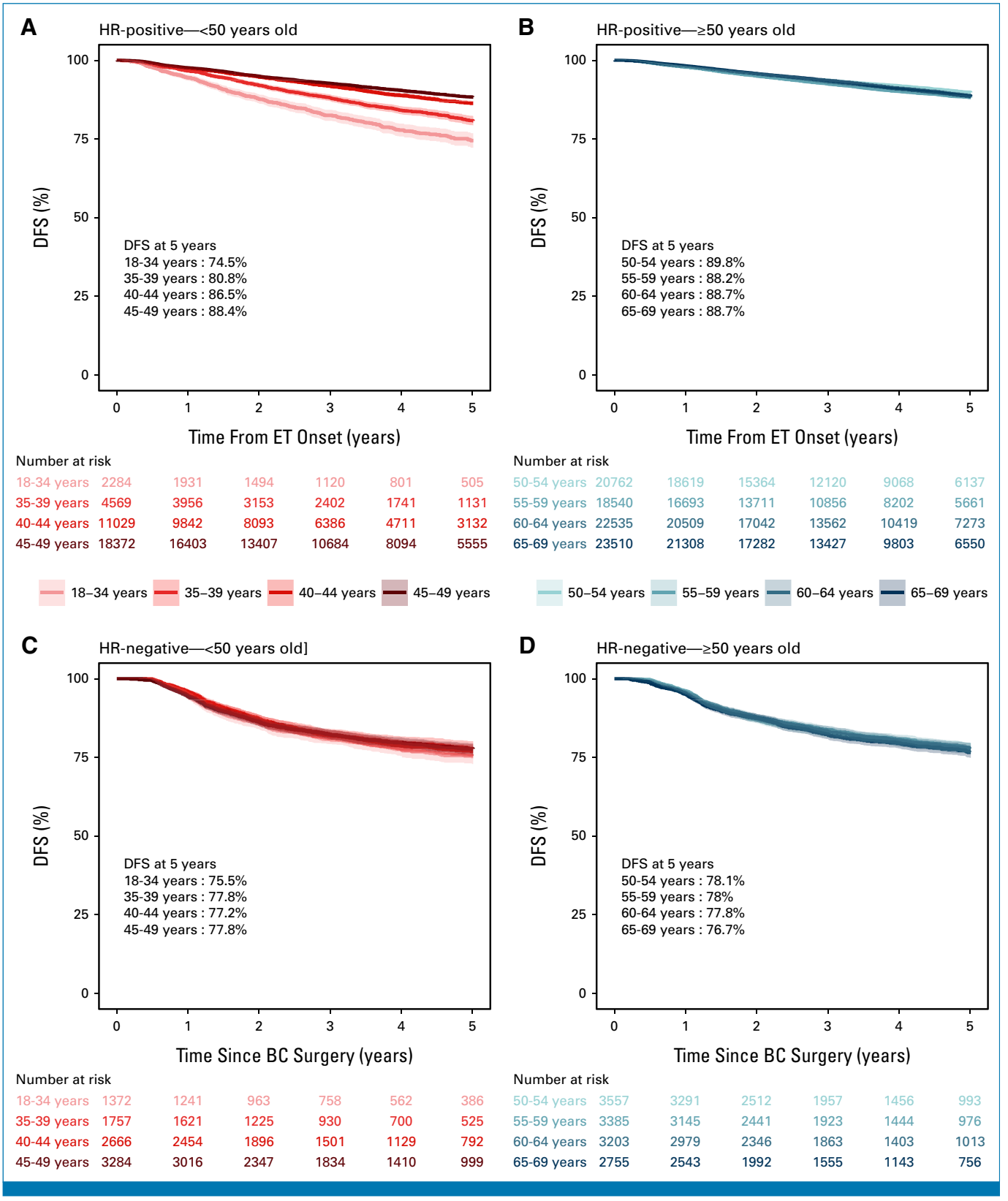

FIG 3. DFS and 95% CIs by age subgroups in the cohort of HR-positive tumors for patients diagnosed (A) before age 50 years and (B) after age 50 years and in the cohort of HR-negative tumors for patients diagnosed (C) before age 50 years and (D) after age 50 years. CIs for the DFS curves were derived on the basis of the standard procedure for Kaplan-Meier survival curve estimates (Greenwood formula for cumulative hazard). BC, breast cancer; ET, endocrine therapy; DFS, disease-free survival; HR, hormone receptor.

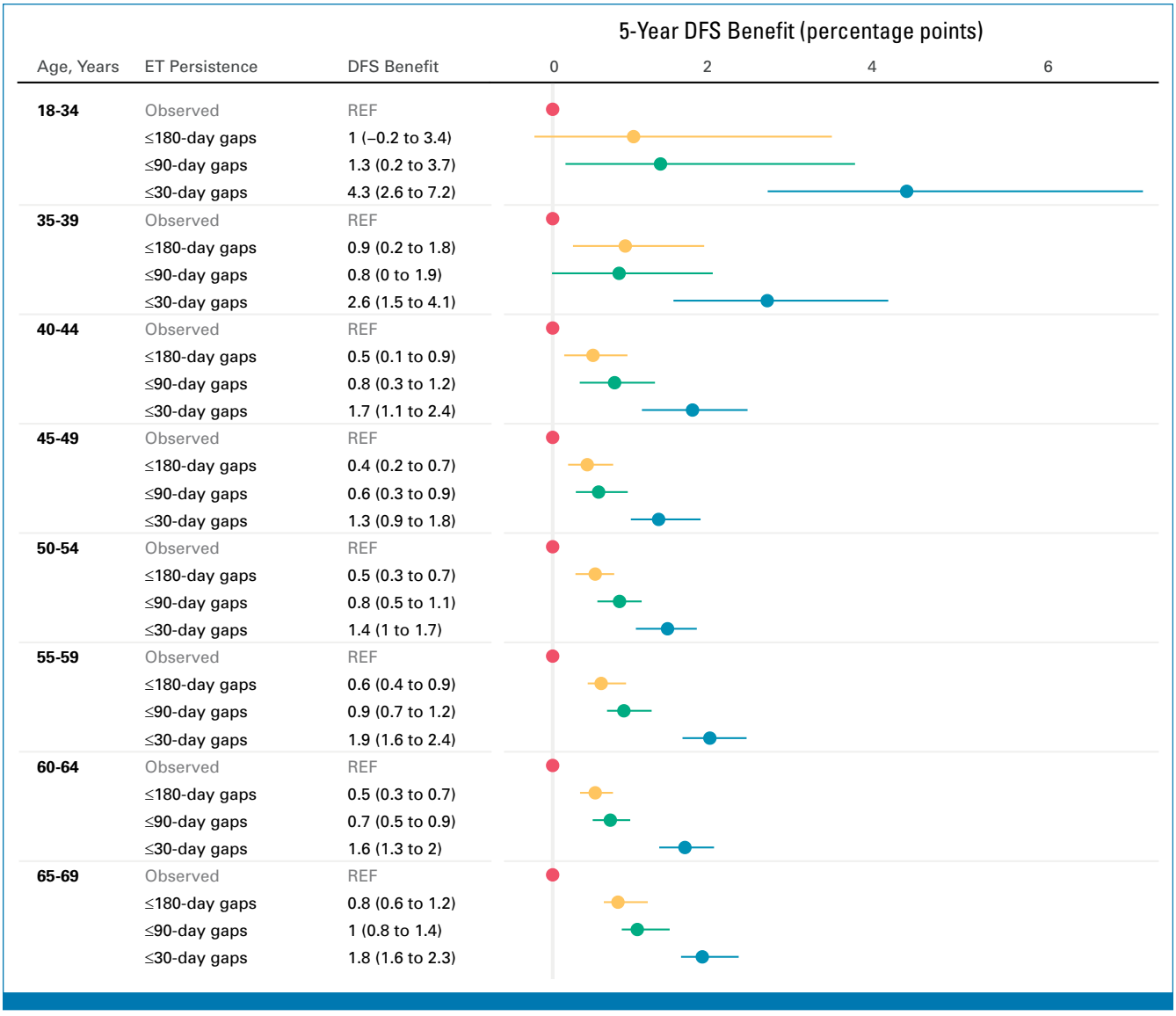

FIG 4. Five-year DFS benefit (in percentage points) and 95% CIs for emulated versus observed ET persistence, for the three definitions allowing gaps of no more than 30, 90, or 180 days and by age group. CIs were obtained by bootstrapping for 1,000 iterations. BC, breast cancer; DFS, disease-free survival; ET, endocrine therapy.

By including extensive patient data across France, collected over nearly a decade, our study comprises 121,601 patients with HR-positive early-stage BC. We used causal inference methodology that, under explicit assumptions, allows for a causal interpretation of results and avoids biases inherent to observational studies. Yet, our study has limitations. First, we rely on observational data sourced from the SNDS, which may be sensitive to misclassification bias. Previous studies validated the use of SNDS data to identify cancer cases[31] and drug adherence.[32-34] Second, we assumed that patients would take all the drugs they received. If some patients do not take the drugs they receive, then our analysis will underestimate the risk of discontinuation. We would also expect this to lead to an underestimation of the true DFS benefit of sustained ET use: the true benefit of ET persistence might be even greater than our results suggest. We could not access ET dispensed during hospital stays, but our sensitivity analysis did not suggest a considerable bias because of this missing information. Third, it was not possible in our study to distinguish luminal A from luminal B tumors. Fourth, we cannot exclude the presence of unmeasured confounding, potentially varying by age group, which may weaken the causal interpretation of the results. However, such biases were not detected in any of the sensitivity analyses. Finally, our results are limited to patients who initiated ET and may not be generalizable to populations with different distributions of ET persistence or with different characteristics. An interesting group consists of patients exposed to GnRHa. Previous studies have shown that GnRHa use does not affect ET adherence.[35-37] In a sensitivity analysis, we

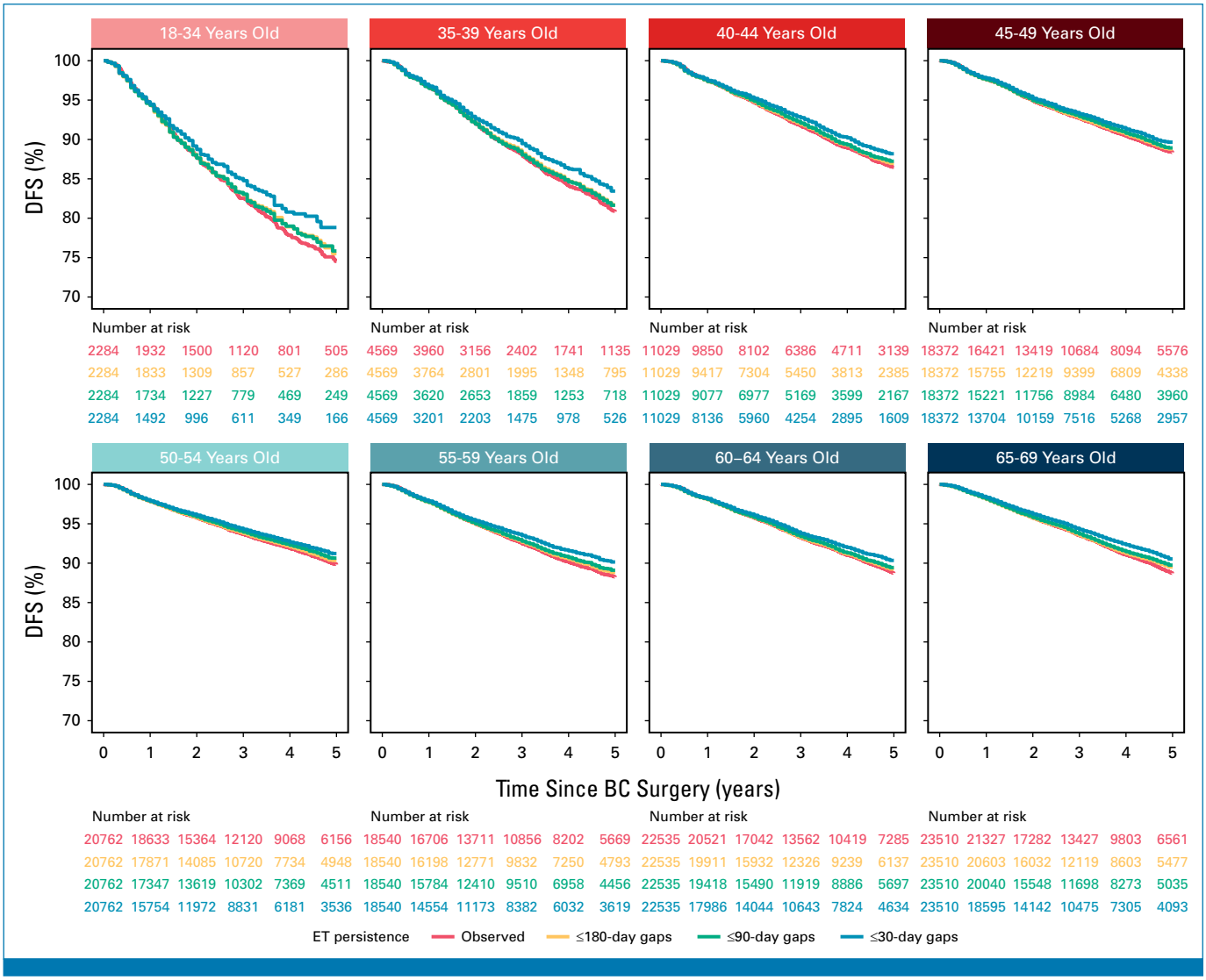

FIG 5. DFS for the cohort of patients with HR-positive tumor under observed (uncontrolled) ET persistence and under controlled ET persistence, with the three definitions allowing gaps of no more than 30, 90, or 180 days, respectively, for each age subgroup. BC, breast cancer; DFS, disease-free survival; ET, endocrine therapy; HR, hormone receptor.

found that the DFS benefit of ET persistence in patients exposed to GnRHa was similar to that in the whole population. Therefore, it is unlikely that low GnRHa uptake affects the generalizability of our result, but further research is needed to confirm this. Similarly, our results may not be generalizable to individuals not enrolled in the main health insurance scheme.

Our findings that not only younger patients are at higher risk for ET discontinuation but also their prognosis is more adversely affected by ET discontinuation suggest that further efforts should be made to improve ET persistence in this population. Strategies to achieve this could include close monitoring, comprehensive information about the importance of adherence, and prompt identification and management of side effects.[26] Additional investigations to uncover the distinctions in BC biology and treatment effectiveness in younger women with HR-positive tumors could motivate new strategies to improve prognosis for this high-risk group.

AFFILIATIONS

[1]Institute of Mathematics, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
[2]Residual Tumor & Response to Treatment Laboratory, RT2Lab, Translational Research Department, INSERM, U932 Immunity and Cancer, Université Paris Cité, Paris, France
[3]Department of Gynecology, Strasbourg University Hospital, Strasbourg, France

[4]Department of Medical Oncology, Université Paris Cité, Institut Curie, Paris, France
[5]Centre René Hughenin, Medical Oncology Department, Saint Cloud, France
[6]Health Data and Assessment, Health Survey Data Science and Assessment Division, French National Cancer Institute (Institut National du Cancer INCa), Boulogne-Billancourt, France
[7]Department of Surgical Oncology, Université Paris Cité, Institut Curie, Paris, France
[8]Department of Surgery, Institut Jean Godinot, Reims, France

CORRESPONDING AUTHOR

Elise Dumas, PhD; e-mail: elise.dumas@epfl.ch.

DISCLAIMER

The funder was not involved in study design; the collection, analysis, and interpretation of data; the writing of this article; or the decision to submit it for publication.

PRIOR PRESENTATION

Presented in part at the ESMO Congress 2024, Barcelona, Spain, September 13-17, 2024.

SUPPORT

Supported by Monoprix, INCa grant number 18-127 (COMBIMMUNO: Comedications and comorbidities in breast cancer: Deciphering Interactions Between Immune Infiltration, Response to Treatment, and Prognosis project), and the Swiss National Science Foundation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.01131.

AUTHOR CONTRIBUTIONS

Conception and design: Elise Dumas, Florence Coussy, Anne-Sophie Hamy, Fabien Reyal, Mats Julius Stensrud
Financial support: Mats Julius Stensrud
Administrative support: Mats Julius Stensrud
Provision of study materials or patients: Sophie Houzard, Christine Le Bihan-Benjamin, Fabien Reyal
Collection and assembly of data: Elise Dumas, Anne-Sophie Hamy, Sophie Houzard, Christine Le Bihan-Benjamin, Fabien Reyal
Data analysis and interpretation: Elise Dumas, Floriane Jochum, Florence Coussy, Anne-Sophie Hamy, Alena Majdling, Fabien Reyal, Paul Gougis, Mats Julius Stensrud
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the Department of Health Data and Assessment, Health Survey Data Science and Assessment Division, and French National Cancer Institute (Institut National du Cancer INCa) for providing us with access to the cancer cohort.

REFERENCES

1. Arnold M, Morgan E, Rumgay H, et al: Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast 66:15-23, 2022
2. Dai X, Li T, Bai Z, et al: Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res 5:2929-2943, 2015
3. Loibl S, Poortmans P, Morrow M, et al: Breast cancer. Lancet 397:1750-1769, 2021
4. Burstein HJ, Somerfield MR, Barton DL, et al: Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. J Clin Oncol 39:3959-3977, 2021
5. He W, Fang F, Varnum C, et al: Predictors of discontinuation of adjuvant hormone therapy in patients with breast cancer. J Clin Oncol 33:2262-2269, 2015
6. Hershman DL, Shao T, Kushi LH, et al: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 126:529-537, 2011
7. Hershman DL, Kushi LH, Shao T, et al: Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28:4120-4128, 2010
8. Anders CK, Johnson R, Litton J, et al: Breast cancer before age 40 years. Semin Oncol 36:237-249, 2009
9. Narod SA: Breast cancer in young women. Nat Rev Clin Oncol 9:460-470, 2012
10. Ryu JM, Yu J, Kim SI, et al: Different prognosis of young breast cancer patients in their 20s and 30s depending on subtype: A nationwide study from the Korean Breast Cancer Society. Breast Cancer Res Treat 166:833-842, 2017
11. Liu Y-R, Jiang Y-Z, Yu K-D, et al: Different patterns in the prognostic value of age for breast cancer-specific mortality depending on hormone receptor status: A SEER population-based analysis. Ann Surg Oncol 22:1102-1110, 2015
12. Partridge AH, Hughes ME, Warner ET, et al: Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol 34:3308-3314, 2016
13. Lian W, Fu F, Lin Y, et al: The impact of young age for prognosis by subtype in women with early breast cancer. Sci Rep 7:11625, 2017
14. Zheng H, Ge C, Lin H, et al: The impact of age on outcomes of breast cancer in different hormone receptor and HER2 groups. PLoS One 18:e0280474, 2023
15. Azim HA, Michiels S, Bedard PL, et al: Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 18:1341-1351, 2012
16. Collin LJ, Cronin-Fenton DP, Ahern TP, et al: Early discontinuation of endocrine therapy and recurrence of breast cancer among premenopausal women. Clin Cancer Res 27:1421-1428, 2021
17. Partridge AH, Wang PS, Winer EP, et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 21:602-606, 2003
18. Tuppin P, Rudant J, Constantinou P, et al: Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique 65:S149-S167, 2017 (suppl 4)
19. Hernán MA, Sauer BC, Hernández-Díaz S, et al: Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 79:70-75, 2016
20. Hernán MA, Robins JM: Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 183:758-764, 2016
21. Hernán MA: How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ 360:k182, 2018
22. Dumas E, Laot L, Coussy F, et al: The French Early Breast Cancer Cohort (FRESH): A resource for breast cancer research and evaluations of oncology practices based on the French National Healthcare System Database (SNDS). Cancers 14:2671, 2022
23. Bousquet PJ, Lefeuvre D, Tuppin P, et al: Cancer care and public health policy evaluations in France: Usefulness of the national cancer cohort. PLoS One 13:e0206448, 2018
24. Wanis KN, Sarvet AL, Wen L, et al: Grace periods in comparative effectiveness studies of sustained treatments. J R Stat Soc Ser A Stat Soc: 187:796-810, 2024
25. Murphy CC, Bartholomew LK, Carpentier MY, et al: Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. Breast Cancer Res Treat 134: 459-478, 2012
26. Franzoi MA, Agostinetto E, Perachino M, et al: Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol 22: e303-e313, 2021
27. Ruddy KJ, Gelber SI, Tamimi RM, et al: Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol 32:1151-1156, 2014
28. Yager JD, Davidson NE: Estrogen carcinogenesis in breast cancer. N Engl J Med 354:270-282, 2006
29. Partridge AH, Hughes ME, Ottesen RA, et al: The effect of age on delay in diagnosis and stage of breast cancer. Oncologist 17:775-782, 2012

30. Wang Y, Li Y, Liang J, et al: Chemotherapy-induced amenorrhea and its prognostic significance in premenopausal women with breast cancer: An updated meta-analysis. Front Oncol 12:859974, 2022
31. Ajrouche A, Estellat C, De Rycke Y, et al: Evaluation of algorithms to identify incident cancer cases by using French health administrative databases. Pharmacoepidemiol Drug Saf 26:935-944, 2017
32. Noize P, Bazin F, Pariente A, et al: Validity of chronic drug exposure presumed from repeated patient interviews varied according to drug class. J Clin Epidemiol 65:1061-1068, 2012
33. Palmaro A, Moulis G, Despas F, et al: Overview of drug data within French health insurance databases and implications for pharmacoepidemiological studies. Fundam Clin Pharmacol 30:616-624, 2016
34. Bezin J, Duong M, Lassalle R, et al: The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 26: 954-962, 2017
35. Reeder-Hayes KE, Mayer SE, Lund JL: Adherence to endocrine therapy including ovarian suppression: A large observational cohort study of US women with early breast cancer. Cancer 127: 1220-1227, 2021
36. Francis PA, Regan MM, Fleming GF, et al: Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 372:436-446, 2015
37. Saha P, Regan MM, Pagani O, et al: Treatment efficacy, adherence, and quality of life among women younger than 35 years in the International Breast Cancer Study Group TEXT and SOFT adjuvant endocrine therapy trials. J Clin Oncol 35:3113-3122, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Explaining the Relationships Between Age, Endocrine Therapy Persistence, and Risk of Recurrence in Hormone Receptor–Positive Early Breast Cancer: A Nationwide Cohort Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Fabien Reyal
Stock and Other Ownership Interests: Avatar Medical
Honoraria: Avatar Medical

Paul Gougis
Consulting or Advisory Role: BMS
Research Funding: Sanofi
Travel, Accommodations, Expenses: Eisai

Mats Julius Stensrud
Stock and Other Ownership Interests: Novartis
Honoraria: Novartis
Consulting or Advisory Role: Novartis

No other potential conflicts of interest were reported.