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Trends in endocrine therapy prescription and survival in patients with non-metastatic hormone receptor positive breast cancer treated with endocrine therapy: A population based-study

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ABSTRACT

Purpose: To identify prognostic factors of invasive–disease free survival (iDFS) in women with non-metastatic hormone receptor positive (HR+) breast cancer (BC) in daily routine practice.
Methods: We performed a retrospective study using data from the Côte d'Or breast and gynecological cancer registry in France. All women diagnosed with primary invasive non-metastatic HR + BC from 1998 to 2015 and treated by endocrine therapy (ET) were included. Women with bilateral tumors or who received ET for either metastasis or relapse were excluded. We performed adjusted survival analysis and Cox regression to identify prognostic factors of iDFS.
Results: A total of 3976 women were included. Age at diagnosis, ET class, SBR grade, treatment, stage and comorbidity were independently associated with iDFS. Women who had neither surgery nor radio-therapy had the highest risk of recurrence (HR = 3.75, 95%CI [2.65–5.32], p < 0.0001). Receiving aromatase inhibitors (AI) was associated with a lower risk of recurrence (HR = 0.70, 95%CI [0.54–0.90], p = 0.055) compared to tamoxifen. Compared to women with no comorbidities, women with 1 or 2 comorbidities were more likely to receive AI (OR = 1.63, 95%CI [1.22–2.17], p = 0.0009).
Conclusions: Comorbidities, age at diagnosis and previous treatment were associated with iDFS in non-metastatic HR + BC patients. This study also showed that women who received tamoxifen for their cancer experienced worse iDFS compared to women treated with AI.

1. Introduction

In patients with hormone receptor positive (HR+) early breast cancer (BC), endocrine therapy (ET) is currently the standard of treatment, and reduces both recurrence and mortality rates [1]. Tamoxifen and aromatase inhibitors (AI) are the two main categories of ET, and are typically prescribed for a period of at least 5 years [2]. Treatment for 5 years with tamoxifen reduces recurrence rates in ER-positive early BC by about half during years 0 through 4, and by about one third in the subsequent 5 years. It also reduces the annual rate of death by 31% among women with ER + BC, regardless of age (1). AI have shown benefit in terms of both efficacy and safety [3], particularly among post-menopausal BC patients [4,5]. AI have

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also shown efficacy in reducing 10-year BC mortality rates [6]. Many randomized clinical trials have demonstrated the efficacy of ET in reducing recurrence, but few, if any data exist on the efficacy of ET in daily routine practice and the trends in prescription of ET over time.

To assess the real-life efficacy of drugs, population-based cancer registries and medical databases are important tools. In France, cancer registries collect information about cancer cases occurring in a given local, regional or national area in a systematic manner. They provide exhaustive information regarding the actual care pathways of cancer patients, as well as epidemiological data. We performed a population-based study using data from the Côte d'Or Breast and Gynecological cancer registry to identify prognostic factors of invasive–disease free survival (iDFS) in women with non-

metastatic HR + BC in real life. We also describe trends in ET use over time.

2. Materials and methods

2.1. Study design

This retrospective study was performed on data from the Côte d'Or breast and gynecological cancer registry. This registry is the only one in France to focus on breast and gynecological cancers. It has been collecting comprehensive data on all cases of breast and gynecological cancers occurring in residents of the Côte d'Or Department since 1982. The registry is licensed by the French national data protection authority.
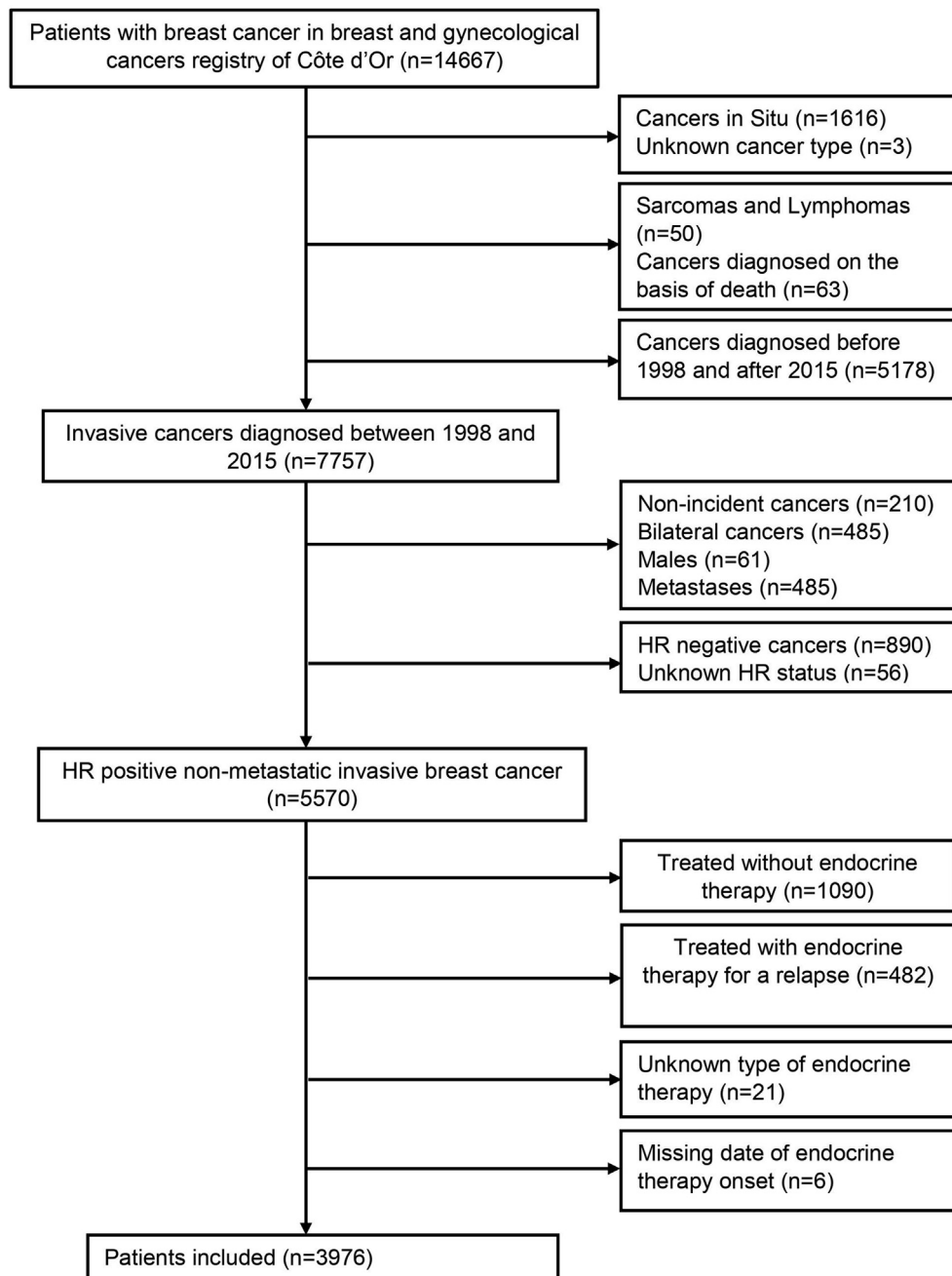

Fig. 1. Flow chart.

2.2. Study population

All women with primary invasive non-metastatic HR + BC diagnosed from 1998 to 2015 and treated by ET were included. Patients with either unknown HR status or unknown type of ET were excluded. Patients who received ET for either metastasis or relapse were not included. Women with bilateral tumors were also excluded. The cut-off date for analyses was set at November 1, 2018. This study was performed in accordance with the ethical standards of the national research committee and the 1964 Helsinki declaration and its later amendments.

2.3. Invasive-disease free survival (iDFS)

iDFS was defined as the time from diagnosis to first recurrence (loco-regional or distant recurrence), including second invasive primary BC or death, whichever came first [7].

2.4. Variables

Age at diagnosis, stage at diagnosis, histological type, surgery, treatments (including type of ET and date of initiation), Scarff-Bloom-Richardson (SBR) grade, comorbidities, HER2 status, and menopausal status were extracted from the registry of breast and gynecological cancers of the Côte d'Or. Tumor stage was based on pathological stage information, supplemented by clinical stage information if pathological stage was unavailable or unknown. In case of neoadjuvant chemotherapy, tumor stage was based on clinical stage information only. Patients who did not experience a recurrence or who were alive at the cut-off date were censored. Tumor stage was categorized according to American Joint Committee on Cancer (AJCC). The time between diagnosis and introduction of ET was calculated. Surgery was defined in three categories: None, conservative and mastectomy. Receiving chemotherapy (yes versus no) was defined as the administration of any kind of chemotherapy. We classed treatment in five categories: Breast-conserving Surgery (BCS) followed by radiotherapy, BCS alone, mastectomy alone, mastectomy followed by radiotherapy, and neither surgery nor radiotherapy. Comorbidities was assessed using the Charlson Comorbidity Index (CCI).

2.5. Statistical analyses

Clinical and sociodemographic data are described as mean ± standard deviation or median (range) for quantitative variables, and as number and percentage for categorical variables. Percentages for subcategories were calculated from the available data; missing values were not taken into account. Charlson Comorbidity Index was categorized in three classes: 0, 1–2 and ≥3. Menopause status was classified as premenopausal and postmenopausal. SBR grade was categorized as low, intermediate or high. Two periods of diagnosis were defined, namely diagnosis before or after 2004. Age at diagnosis respected the log-linearity hypothesis and was therefore included in the analyses as a quantitative variable. Adjusted survival curves were generated by applying the "DIRADJ" option in the PROC PHREG statement of SAS. Multivariable logistic regression was performed to identify factors associated with the choice of ET. The frequency of ET prescriptions was estimated according to ET class or type. Cox proportional hazards regression was used to identify the prognostic factors of iDFS. The Cox model was adjusted for the period of diagnosis, and the time between diagnosis and ET initiation. Variables with a p-value <0.20 by univariate analyses were included in the multivariable model, and backward selection was applied. Correlations and

Table 1
Demographic, clinical and treatment characteristics of the study population.

Variable	Whole population N = 3976
Age (years)	
Mean (SD)	61.9 (13.6)
Median (IQR)	61.5 (51.2–72)
Time between diagnosis and ET initiation (days)	
Mean (SD)	150 (103.4)
Median (IQR)	127 (81–230)
Year of diagnosis	
1998	103 (2.6)
1999	108 (2.7)
2000	146 (3.7)
2001	185 (4.6)
2002	203 (5.1)
2003	246 (6.2)
2004	228 (5.7)
2005	236 (5.9)
2006	246 (6.2)
2007	207 (5.2)
2008	206 (5.2)
2009	190 (4.8)
2010	266 (6.7)
2011	245 (6.2)
2012	297 (7.5)
2013	308 (7.7)
2014	280 (7.0)
2015	276 (6.9)
Stage	
I	1938 (48.8)
II	1866 (47.0)
III	169 (4.2)
Unknown	3
AJCC Stage	
Low	1938 (48.8)
High	2035 (51.2)
Unknown	3
Scarff-Bloom Richardson Grade	
Low	1149 (29.5)
Intermediate	2117 (54.3)
High	632 (16.2)
Unknown	78
HER2 Status	
Positive	503 (14.1)
Negative	3077 (85.9)
Unknown	396
Histologic Type	
Ductal	3160 (79.6)
Lobular	628 (15.8)
Others	181 (4.6)
Unknown	7
Hormonal status	
Postmenopausal	2634 (72.7)
Premenopausal	988 (27.3)
Unknown	354
Charlson comorbidity Index	
0	2713 (79.6)
1 - 2	642 (18.9)
≥ 3	52 (1.5)
Unknown	569
Type of ET	
Anastrozole	1235 (31.1)
Exemestane	160 (4)
Letrozole	1021 (25.7)
Tamoxifen	1560 (39.2)
Class of ET	
Aromatase Inhibitors	2416 (60.8)
Tamoxifen	1560 (39.2)
Neoadjuvant Chemotherapy	
Yes	268 (6.7)
No	3708 (93.3)
Radiotherapy	
Yes	3438 (86.5)
No	538 (13.5)
Surgery	
Breast Conserving Surgery	2944 (74.0)

Table 1 (continued)

Variable	Whole population N = 3976
Mastectomy	894 (22.5)
None	138 (3.5)
Progression	
Yes	929 (23.4)
No	3045 (76.6)
Progression Type	
Loco-regional recurrence	30
Metastases	82
Second contralateral breast cancer	116
Death	701

ET: Endocrine Therapy; AJCC: American Join Cancer Committee; SD: standard deviation; IQR: Interquartile Range.

interactions were tested between variables. A p-value <0.05 was considered statistically significant. We performed a sensitivity analysis using propensity score method in other to assess the real effect of ET class on iDFS. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Clinical and pathological features

A total of 3976 women treated by ET for HR + non-metastatic BC were identified (Fig. 1). Average age was 61.9 ± 13.6 years old. Most women were post-menopausal (73%), with high grade tumors

Table 2
Demographic, clinical and treatments characteristics according to ET type.

Variables	Aromatase Inhibitors N = 2416 (%)	Tamoxifen N = 1560 (%)	P-value
Age (years)			<.0001
Mean (SD)	66.9 (11.4)	54.2 (12.9)	
Median (IQR)	65.8 (58.5–74.8)	52.6 (45–62.5)	
Time between diagnosis and initiation of ET (days)			<.0001
Mean (SD)	153.6 (99)	144.3 (109.7)	
Median (IQR)	126 (91–231)	128 (55–228)	
Stage			.1810
I	1167 (48.4)	771 (49.4)	
II	1133 (46.9)	733 (47)	
III	114 (4.7)	55 (3.6)	
Unknown	2	1	
Stage AJCC			.4936
Low	1167 (48.4)	771 (49.4)	
High	1247 (51.6)	788 (50.6)	
Unknown	2	1	
Scarff-Bloom Richardson Grade			.0022
Low	719 (30)	430 (28.6)	
Intermediate	1326 (55.4)	791 (52.6)	
High	349 (14.6)	283 (18.8)	
Unknown	22	56	
HER2 Status			.0121
Positive	298 (13)	205 (16)	
Negative	2001 (87)	1076 (84)	
Unknown	117	279	
Histologic Type			.0002
Ductal	1871 (77.6)	1289 (82.8)	
Lobular	427 (17.7)	201 (12.9)	
Others	114 (4.7)	67 (4.3)	
Unknown	4	3	
Hormonal status			<.0001
Postmenopausal	2050 (93.2)	584 (41.1)	
Premenopausal	150 (6.8)	838 (58.9)	
Unknown	216	138	
Charlson comorbidity Index			<.0001
0	1613 (73.3)	1100 (91.1)	
1 - 2	536 (24.4)	106 (8.7)	
≥ 3	50 (2.3)	2 (0.2)	
Unknown	217	352	
Neoadjuvant Chemotherapy			<.0001
Yes	123 (5.1)	143 (9.2)	
No	2293 (94.9)	1417 (90.8)	
Radiotherapy			<.0001
Yes	2026 (83.9)	1410 (90.4)	
No	390 (16.1)	150 (9.6)	
Surgery			.0748
Breast conserving surgery	1736 (71.8)	1208 (77.4)	
Mastectomy	557 (23.0)	337 (21.6)	
None	123 (5.1)	15 (1.0)	
Progression			.0582
Yes	550 (22.8)	396 (25.4)	
No	1866 (77.2)	1164 (74.6)	
Progression type			
Recurrence	13	30	
Metastases	79	56	
Second contralateral breast cancer	59	57	
Death	399	253	

ET: Endocrine Therapy; AJCC: American Joint Committee on Cancer; SD: standard deviation; IQR: Interquartile Range.

(54%), without comorbidities (78%), and 76% had conservative surgery. Three thousand four hundred and thirty-eight women (86.5%) had radiotherapy. Overall, 39.2% and 60.8% of women received tamoxifen and AI respectively. Twenty-three percent had either local or regional recurrence, distant metastasis or death. The clinical and pathological features of women are shown in Table 1.

3.2. Patient characteristics according to endocrine therapy

Among the 3976 patients included, 1560 (39.2%) received tamoxifen, 1235 (31.1%) received anastrozole, 1021 (25.7%) had letrozole and only 160 (4%) women had exemestane (Table 2). Compared to women who received tamoxifen, women who received AI were older (66.9 ± 11.4 vs. 54.2 ± 12.9, P < 0.0001), had a longer mean time between diagnosis and initiation of ET (153.6 vs 144.3 days, p < 0.0001), were more frequently postmenopausal and had more comorbidities (p < 0.0001) (Table 2).

3.3. Invasive-disease free survival

After a median follow-up of 8.27 years (IQR: 4.92–13.07), 929 (23.4%) patients had an event. In total, 701 patients died, 116 had contralateral breast cancer, 30 had loco-regional relapse and 82 had distant metastasis. Fig. 2 shows iDFS adjusted for age according to ET class and type. AI administration was associated with a lower risk of recurrence than tamoxifen use (HR = 0.85, 95%CI [0.74–0.98], p = 0.03).

3.4. Prognostic factors of iDFS

Table 3 shows the independent prognostic factors for iDFS identified by multivariable Cox regression analysis. Age, ET class, SBR grade, stage, treatment, and comorbidity were all found to be independent predictors of iDFS. Women who had neither surgery nor radiotherapy had the highest risk of recurrence (HR = 3.75, 95% CI [2.65–5.32], p < 0.0001). Treatment with AI was associated with

Table 3
Factors associated with invasive-disease-free survival by multivariable Cox proportional hazards regression.

Variables	Hazard Ratio [95% CI]	P-value
ET		.0055
Tamoxifen	Reference	
AI	0.70 [0.54–0.90]	
Age (per additional year)	1.06 [1.05–1.07]	<.0001
Treatment		<.0001
BCS + radiotherapy	Reference	
BCS	1.39 [0.86–2.25]	
Mastectomy	1.60 [1.19–2.14]	
Mastectomy + radiotherapy	1.73 [1.40–2.15]	
No Surgery	3.75 [2.65–5.32]	
Stage		.038
Low	Reference	
High	1.22 [1.01–1.48]	
Grade		.0038
Low	Reference	
Intermediate	1.21 [0.99–1.47]	
High	1.54 [1.20–1.99]	
CCI		<.0001
0	Reference	
1–2	1.21 [0.99–1.48]	
≥3	2.94 [1.91–4.53]	

CI: Confidence Interval; ET: Endocrine Therapy; AI: Aromatase Inhibitors; BCS: Breast Conserving Surgery; CCI: Charlson Comorbidity Index.

a reduced risk of recurrence (HR = 0.70, 95%CI [0.54–0.90], p = 0.0055). When looking at each type of ET separately, letrozole and anastrozole were associated with a reduced risk recurrence compared to tamoxifen (supplementary file S1).

3.5. Frequency of endocrine therapy over time

Fig. 3 shows the trend in ET prescriptions over time according to class and type of ET. Before 2003, almost all women were treated with tamoxifen; thereafter, the percentage of women treated with
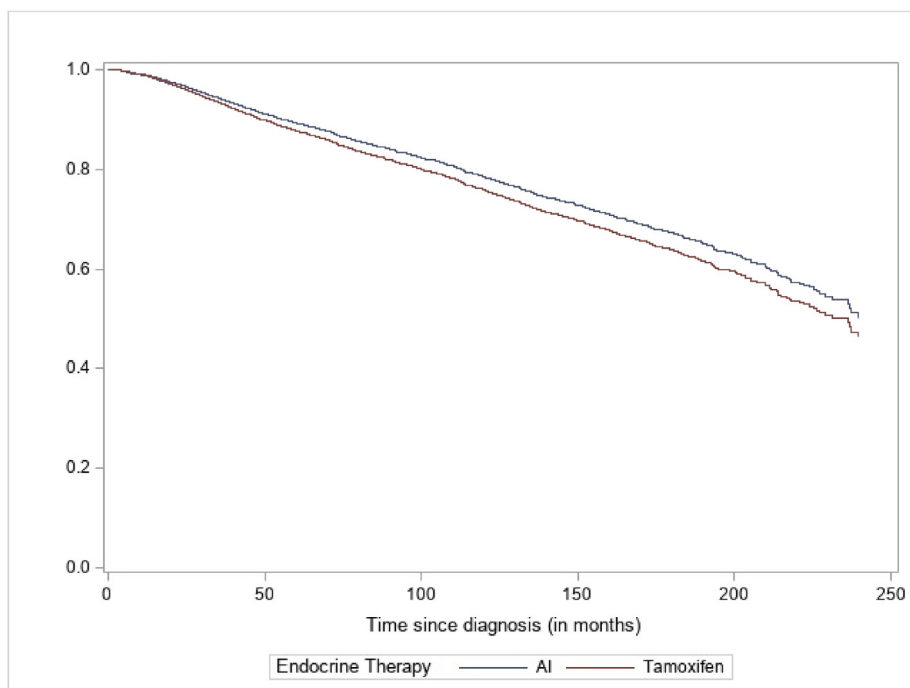

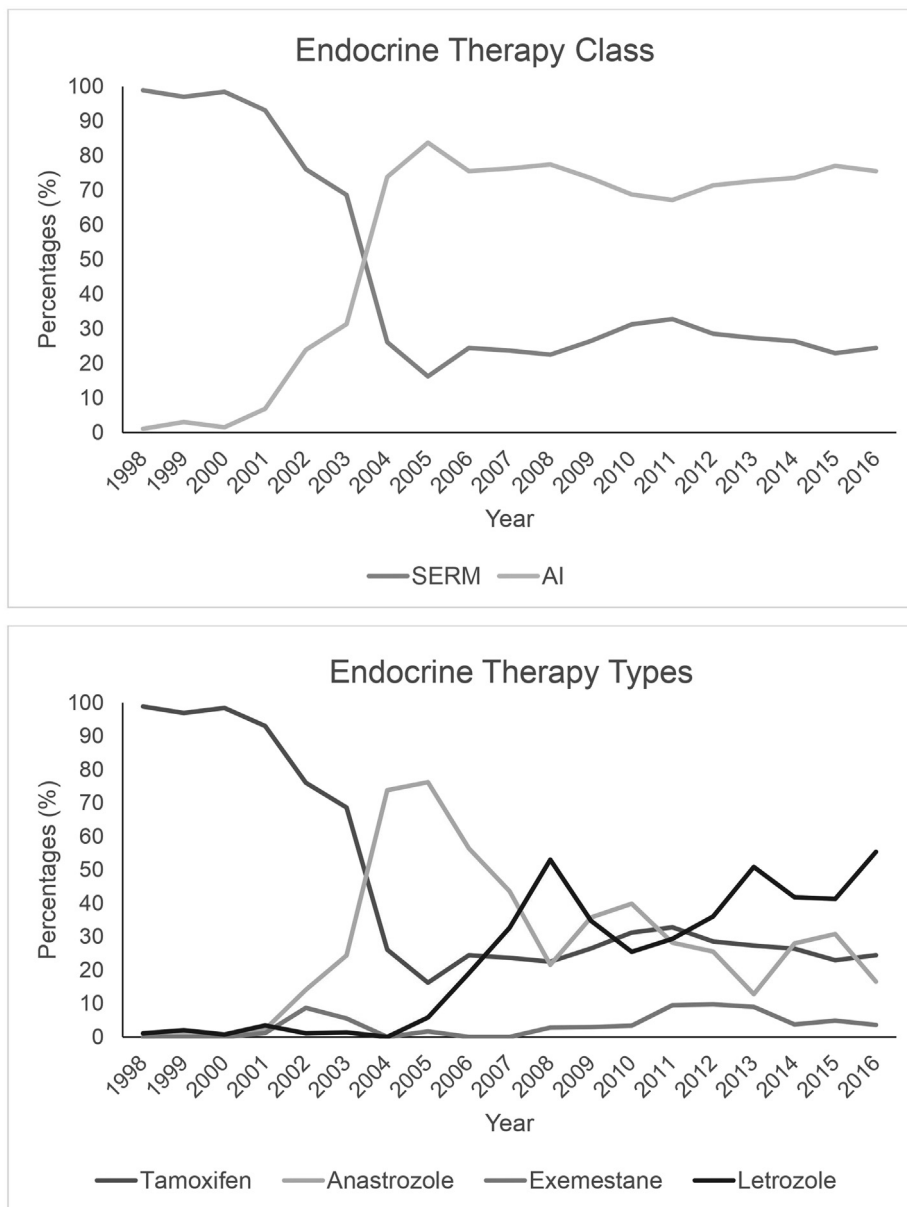**Fig. 2.** Age-adjusted survival curves according to ET class.

Fig. 3. Trends in ET prescription according to class and type over time.

tamoxifen decreased from almost 99% in 1998 to 68% in 2003. By 2004, women received mainly anastrozole, and this trend continued until 2008 and the release of letrozole. Around 2010, we noted an increase in the use of tamoxifen and anastrozole, and the introduction of exemestane. In 2015, all molecules were in use, with letrozole being the most frequently prescribed.

3.6. Factors associated with the choice of ET

Age and comorbidities were found to be significant predictors of the choice of ET. Compared to women with a CCI = 0, women with a CCI of 1 or 2 were more likely to receive AI (OR = 1.63, 95%CI [1.22—2.17], p = 0.0009). Histological type and surgery were also predictors of the choice of ET class. Indeed, women with lobular cancer (OR = 1.36, 95%CI [1.04—1.77], p = 0.02) were more likely to receive AI compared to those with ductal cancer. Both mastectomy (OR = 3.73, 95%CI [1.36—10.25], p = 0.0107) and BCS (OR = 5.14, 95% IC [1.85—14.26], p = 0.0017) were associated with an increased

likelihood of receiving AI (supplementary File S2).

4. Discussion

The aim of this population-based study was to identify the prognostic factors of iDFS among women treated by ET for invasive non metastatic HR + BC. We also investigated trends in prescription of ET over the whole study period.

We found that women who received tamoxifen experienced worse iDFS compared to women treated with AI. In our study, after adjustment, there was an independent relation between ET class and iDFS, whereby AI were associated with a lower risk of recurrence. This result is concordant with the results of clinical trials [6,8,9]. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) study [6], the authors performed a meta-analysis of individual data from 31,920 post-menopausal women with estrogen-receptor positive early breast cancer in randomized trials comparing 5 years of AI versus 5 years of tamoxifen; 5 years of AI

versus 2–3 years of tamoxifen then AI to year 5; and 2–3 years of tamoxifen then AI to year 5 versus 5 years of tamoxifen. The authors found that AI reduced recurrence rates by about 30% compared with tamoxifen. Two other trials [8,9] among premenopausal women with HR + early BC reported that adjuvant treatment with exemestane plus ovarian suppression significantly reduced recurrence, as compared with tamoxifen plus ovarian suppression.

We found that comorbidity status was an independent predictor of iDFS in women with BC treated with ET. Aside from the fact that comorbidities are an important prognostic factor in early BC [10], they are generally also associated with the presence of polypharmacy, defined i.e. the use of several medications per day [11]. Indeed, women who had comorbidities mostly had chronic diseases requiring use of more than one drug, and over time, this can hamper medication compliance. ET medication is no exception to this phenomenon [12]. Poor compliance with ET has been shown to be associated with decreased survival [13,14], increased risk of recurrence [13], as well as poor prognosis [15] in BC patients. Polypharmacy is known to be a key factor in adherence to adjuvant ET [16], while comorbidity has also been shown to influence ET adherence [17].

In our study, women who underwent mastectomy were more likely to experience recurrence than women who received BCS in combination with radiotherapy. The European Society of Medical Oncology (ESMO) guidelines strongly recommend postoperative radiotherapy after BCS [18]. Many studies have shown the importance of BCS with postoperative radiotherapy in reducing in-breast tumor recurrence and in improving overall survival in early stage BC [19–22]. In a meta-analysis, the EBCTCG group showed that radiotherapy reduced the 10-year risk of first recurrence from 35.0% to 19.3%, and reduced the 15-year risk of BC death from 25.2% to 21.4% among women who underwent BCS [19]. Furthermore, in a Swedish multicenter cohort study, de Boniface et al. reported that BCS followed by whole-breast irradiation was superior to mastectomy without irradiation in terms of both overall survival (79.5 versus 64.3% respectively at 13 years) and breast cancer-specific survival (90.5 versus 84.0% at 13 years) [20]. Killander et al. were unable to identify any subgroup that could be spared postoperative radiotherapy after BCS [22]. On the contrary, the PRIME II study, published by Kunkler et al. showed that omission of radiotherapy could be considered in older patients with lower risk tumors after BCS [23].

Concerning the frequency of ET over time, tamoxifen was the only type of ET prescribed before 2003, while AI became the most frequently prescribed type of ET after 2008. This is likely because tamoxifen was the only ET available for three decades. With the reports of the American Society of Clinical Oncology (ASCO) in 2004 [24] and the St Gallen Conference in 2005 [25], the ET landscape in BC changed dramatically, particularly with the introduction of third-generation AI for the treatment of early BC. With the use of AI recommended in postmenopausal women, and BC occurring around 60 years of age, this may explain why AIs were the most frequently prescribed form of ET after 2008.

Age and comorbidity were found to be strong predictors of the choice of ET by multivariable logistic regression analysis. These findings are congruent with clinical guidelines [18,26]. Indeed, the ASCO recommends taking account of age and baseline comorbidities when choosing ET [26], while ESMO guidelines also recommend that preexisting comorbidities should help determine the choice of ET. Moreover, Kemp et al. found that comorbidities, particularly osteoporosis and arthritis, were predictors of the choice of therapy after adjustment for other covariates [27].

Patients with lobular BC were more likely to receive AI in our study. Like other BCs with either estrogen or progesterone receptors, HR + lobular BC responds well to ET. In the Breast International Group (BIG) 1-98 study, comparing the relative effectiveness of letrozole and tamoxifen in patients with invasive ductal or lobular carcinoma, the authors found that patients with lobular BC benefitted more from AI compared to tamoxifen [28].

Our study highlights the utility of cancer registries for purposes other than cancer surveillance, namely providing epidemiological data, with estimates of incidence and mortality. The strengths of this study include the large sample size and the use of adjusted survival curves to compare iDFS according to ET class. However, this study also has some limitations. We did not assess compliance with ET, which may play an important role in BC. Thus, we are unable to determine whether the better survival observed in the AI group was due to the efficacy of AI compared to tamoxifen, or to the fact that women on AI may be more compliant than women taking tamoxifen.

In summary, this study identified prognostic factors of iDFS in women with non-metastatic HR + BC in daily routine practice using data from the Côte d'Or breast cancer registry. We also described trends in ET prescription over time. ET class, age at diagnosis, comorbidities, and stage were independently associated with iDFS. In patients treated with ET, clinicians must assess the individual risk for each patient in order to provide optimal care. Further studies that investigate patient compliance and side effects are necessary to confirm these findings.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.06.003.

Ethical approval

The Côte d'Or breast and gynecological cancer registry is licensed by the French national data protection authority for the treatment of data on women who have had breast cancer.

Informed consent

"Not applicable".

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