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## Quality of Life in an e-Cohort of Women Treated by Endocrine Therapy for Early Breast Cancer

Louise Benoit, Carine Cambra, Roman Rouzier, Paul Cottu, Manuel Rodrigues, Fabien Reyat, Seintinelles Research Network, Claire Bonneau

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1 **Quality of life in an e-Cohort of women treated by endocrine therapy for early breast**  
2 **cancer.**

3 **Authors:**

4 Louise Benoit MD<sup>1</sup>, Carine Cambra MD<sup>1</sup>, Roman Rouzier MD, PhD<sup>1,2</sup>, Paul Cottu, MD, PhD<sup>3</sup>, Manuel  
5 Rodrigues MD, PhD<sup>3</sup>, Fabien Rey, MD, PhD<sup>4,5</sup>, Seintinelles Research Network<sup>6</sup>, Claire Bonneau MD, PhD<sup>1,2</sup>,

6 <sup>1</sup> Institut Curie – Saint Cloud, Surgical Oncology Department, 35, rue Dailly, 92210 Saint-Cloud, France

7 <sup>2</sup> Versailles St-Quentin University, Paris-Saclay University, 78180 Montigny-le-Bretonneux, France.

8 <sup>3</sup> Institut Curie – Paris, Department of Medical Oncology, Institut Curie, 26 Rue d’Ulm, 75005 Paris, France.

9 <sup>4</sup> Institut Curie – Paris, Department of Surgery, Institut Curie, 26 Rue d’Ulm, 75005 Paris, France.

10 <sup>5</sup> Residual Tumor and Response to Treatment Laboratory, RT2Lab, INSERM, U932 Immunity and Cancer,  
11 Institut Curie, Paris, France.

12 <sup>6</sup> Seintinelles, 40, rue Rémy-Dumoncel, 75014 Paris, France

13

14 **Corresponding author:**

15 Louise BENOIT, MD

16 Address: Institut Curie, Surgical Oncology Department, 35 rue de Dailly, 92210 Saint-Cloud

17 E-mail: [louise.am.benoit@gmail.com](mailto:louise.am.benoit@gmail.com)

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19

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29 **Micro abstract**

30 Quality of life (QOL) was assessed in an e-cohort of patients treated for breast cancer by  
31 endocrine therapy, by means of validated quality of life questionnaires. Endocrine therapy does  
32 not alter QOL. Individual patient characteristics (socioeconomic, education and age) were  
33 significantly associated with QOL. The use of e-cohorts must be encouraged to study patient  
34 reported outcomes without medical inference.

35 **Abstract:** (200 words)

36 *Objective:* The objective of our study was to analyse quality of life (QOL) in an e-cohort of  
37 patients treated for breast cancer (BC) by endocrine therapy (ET), by means of validated quality  
38 of life questionnaires.

39 *Study design and setting:* A retrospective, observational, e-cohort study was conducted  
40 (Seintinelles platform). Female patients treated for non-metastatic and non-recurrent BC,  
41 treated in France after 2005, filled in online questionnaires concerning: QOL (QLQ-C30 and  
42 QLQ-BR23), tolerability of treatment and demographic characteristics. A multivariate analysis  
43 including variables significant on univariate analysis ( $p < 0.05$ ) to select QOL predictors was  
44 performed.

45 *Results:* We included 1,198 patients, 1,140 of whom declared that they were taking ET (37.7%  
46 tamoxifen, 17.1% aromatase inhibitor (AI), 5.6% LHRH-agonist and 39.6% sequential  
47 tamoxifen and AI). Different tolerability profiles were observed when comparing the tamoxifen  
48 and AI groups. Treatment adherence was similar in the two groups. QOL varied slightly  
49 according to the type of ET. On multivariate analysis, ET had no impact on QOL. However,  
50 individual patient characteristics (socioeconomic, education and age) were significantly  
51 associated with QOL

52 *Conclusion:* Using a real-life study questionnaire on a large e-cohort, individual patient  
53 characteristics were strongly associated with deterioration of QOL. The use of e-cohorts must  
54 be encouraged to modulate the conclusions of randomized trials.

55

56 **Key words:** breast cancer; e-cohort; endocrine therapy; quality of life

57 **Running title:** Quality of life during endocrine therapy

58 **Word count :** 3400

## 59 **Introduction**

60 Breast cancer (BC) is the most common female cancer. In 2019, 2,088,849 new BC  
61 were diagnosed (11.6% of all cancers) (1). BC is also the leading cause of cancer mortality in  
62 women. In 2018, there were 626,679 BC deaths worldwide, representing 6.6% of all cancer  
63 deaths (1). The generic term BC includes multiple pathological and genomic entities with very  
64 variable prognosis. These subtypes are distinguished, among other things, by their level of  
65 expression of hormone receptors for oestrogen and/or progesterone. Expression of oestrogen  
66 receptors indicates the potential benefit of a long-term systemic adjuvant endocrine therapy.  
67 Endocrine therapy inhibits oestrogen receptor signalling which then prevents relapse and  
68 reduce the risk of death from BC (2). Seventy percent of breast cancers express endocrine  
69 receptors (3) and two main types of adjuvant endocrine therapy are then available: selective  
70 oestrogen receptor modulator (tamoxifen) and inhibition of oestrogen synthesis (suppression  
71 of ovarian function, aromatase inhibitors - AI). These treatments induce climacteric-type  
72 symptoms and can be responsible for adverse events that can generate limiting adverse events  
73 and significantly alter quality of life (4).

74 Over the past 20 years, screening, resulting in earlier diagnosis and improved  
75 therapeutic management, has considerably enhanced survival after BC (1). Quality of life  
76 during and after treatment of BC is therefore an essential issue in this setting of prolonged  
77 survival. Quality of life of patients treated by endocrine therapy is often assessed in selected  
78 cohorts of patients included in study protocols or presenting specific population characteristics  
79 (young patients, early-stage cancers, postmenopausal patients, etc.). Few studies, such as the  
80 CANTO (CANcer TOxicity) initiative, have reported the quality of life of patients on endocrine  
81 therapy in a real-life setting (4). E-cohorts can be useful in this setting to assess long-term  
82 quality of life after initial management of BC (5).

83 In the past years, medicine has become increasingly computerized and even  
84 multidisciplinary team meetings are through telemedicine are becoming common (6).  
85 Likewise, e-cohorts differ from traditional cohorts in terms of their mode of recruitment, as e-  
86 cohorts recruit patients via the internet (social networks, websites, etc.) and volunteers directly  
87 enter data that are subsequently studied. E-cohorts are less expensive and are associated with  
88 better participation and follow-up rates than traditional cohorts (7). However, some believe that  
89 these cohorts could be less representative of the general population, as patients who participate  
90 in e-cohorts more often belong to higher socioeconomic categories (8).

91           The objective of this study was to analyse quality of life in an e-cohort of patients  
92 treated for BC by endocrine therapy by means of validated quality of life questionnaires.

93

94

## 95 **Materials and Methods**

96 We conducted a retrospective, observational, e-cohort study by means of the  
97 Seintinelles platform.

### 98 *Platform of the Seintinelles*

99 The Seintinelles platform was created in 2013 and can be accessed at  
100 <https://www.seintinelles.com/>. The objective of this platform was to accelerate cancer research  
101 by means of closer collaboration between citizens, both patients and non-patients, and  
102 researchers via an electronic collaborative research platform dedicated to all cancers in France.  
103 "Les Seintinelles" is a non-profit organization under the French law of 1901 supported and  
104 financed by INCa (French National Cancer Institute) and the ARC foundation (Association for  
105 Research against Cancer), as well as the Chantelle® group.

### 106 *Constitution of the cohort*

107 Our e-cohort was extracted from the Seintinelles platform from 2013 to 2018. The  
108 "Seintinelles" association was responsible for informing women about launching of the study  
109 "Long-term follow-up of endocrine therapy for breast cancer" via the association's website, its  
110 Facebook page, the press or any other means of information (Twitter, for example). Women  
111 with BC were invited to register on the website in order to participate in this study. Patients  
112 themselves volunteered to participate.

113 Inclusion criteria for the present cohort were as follows: female patients, treated for  
114 non-metastatic and non-recurrent BC, diagnosed and treated in France after 2005.

### 115 *Study methods*

116 Patients responded to the survey without any medical supervision or monitoring. An  
117 initial filter questionnaire comprising 5 preliminary questions was designed to ensure the  
118 validity of the inclusion criteria for each participant. Participants who met the inclusion criteria  
119 were then given access to more questionnaires. All questionnaires had to be completed over a  
120 period of no more than two months. Participants were invited by e-mail to log in and fill in  
121 each new questionnaire.

### 122 *Data collected*

123 The following data were collected: demographic data (age, weight change after  
124 endocrine therapy, residence, socioeconomic category), treatment sequence (treatments

125 received and their chronology, type of endocrine therapy prescribed, compliance with  
126 treatment), and quality of life using the QLQ-C30 and QLQ-BR23 questionnaires.

127 The level of education variable was segmented into six categories: no schooling,  
128 primary school, middle school, high school, baccalaureate, and university, subsequently  
129 grouped into: (i) low level, patients with no schooling or up to middle school, (ii) intermediate  
130 level, patients with high school or baccalaureate level, and (iii) high level, patients with a  
131 university degree.

132 The socioeconomic category was classified into 8 groups according to the French  
133 INSEE (*Institut National de la Statistique et des Études Économiques*) (farmer, craftsperson,  
134 executive and intellectual profession, intermediate profession, employee, worker, retired,  
135 unemployed) plus a ninth category for individuals not wishing to answer this question. These  
136 9 categories were regrouped into 3 groups: (i) A, farmers, workers, retired and unemployed,  
137 (ii) B, craftspersons, intermediate professions and employees, (iii) C, executives.

138 Adherence to treatment was rated as “good” when the patient declared taking treatment  
139 every day or almost every day, “average” when the patient sometimes interrupted treatment for  
140 one week, and “bad” when the patient rarely took the treatment.

#### 141 *Quality of life questionnaires*

142 The quality-of-life questionnaires used in our study were developed by EORTC and  
143 have been validated on international and French populations. The QLQ-C30 is a general  
144 questionnaire, composed of 30 questions divided into three categories: overall health status,  
145 functional status and symptom status. The summary score, described as the mean score for all  
146 questions (excluding the financial question and global health care), was used in the following  
147 way:  $QLQ-C30 \text{ Summary Score} = (\text{Physical Functioning} + \text{Role Functioning} + \text{Social}$   
148  $\text{Functioning} + \text{Emotional Functioning} + \text{Cognitive Functioning} + 100 - \text{Fatigue} + 100 - \text{Pain} + 100 -$   
149  $\text{Nausea/Vomiting} + 100 - \text{Dyspnea} + 100 - \text{Sleeping Disturbances} + 100 - \text{Appetite Loss} + 100 -$   
150  $\text{Constipation} + 100 - \text{Diarrhoea})/13$ . The QLQ-BR23 is a specific survey for BC consisting of 23  
151 questions exploring 4 functional and 4 symptom dimensions.

152 Lower global health status and functional scale scores indicate poorer quality of life.  
153 Higher symptom scale scores indicate a higher prevalence of symptoms.

#### 154 *Ethics*

155 Processing of personal data from Seintinelles was approved by the CNIL (*Commission*  
156 *Nationale de l'Information et des Libertés*) under number 1688474.

### 157 *Statistics*

158 Patients were compared according to their treatment by endocrine therapy and the type  
159 of endocrine therapy received. Continuous variables were expressed as the mean +/- standard  
160 deviation or median and range and were compared using a Student t-test or Wilcoxon test in  
161 the case of a non-normal distribution. Categorical values were expressed as absolute number  
162 and percentage and were compared with a Chi-square test (or Fisher's exact test when  
163 necessary).

164 Multivariate analysis was performed using a logistic regression model and including  
165 variables with a p-value <0.05 on univariate analysis. For this analysis, values of the various  
166 items of the quality-of-life questionnaires were defined as high or low when they were higher  
167 or lower than the median value for the item.

168 Statistical analyses were performed using R ("R", version 3.4.3, notch, [http://cran.r-](http://cran.r-project.org/)  
169 [project.org/](http://cran.r-project.org/), The R Foundation for Statistical Computing) and R Studio ("R Studio", version  
170 1.1.383, <http://www.rstudio.com>, R Studio, Boston, USA) software.

171



172 **Results**

173 *Study population*

174 This e-cohort comprised 1,198 patients with BC with a mean age of 50.3 years.  
175 Endocrine therapy was taken by 1,140 patients (95.2%): 13 patients (1.1%) in the neoadjuvant  
176 setting, 857 patients (75.2%) as adjuvant therapy, and 281 patients (24.6%) for whom the  
177 treatment sequence was not specified. Demographic characteristics and treatments received are  
178 detailed in Table 1.

179 Among the 1,140 patients (95.2%) who received endocrine therapy, 689 patients  
180 received a single ET: 430 patients (37.7%) received tamoxifen, 195 (17.1%) received an AI  
181 and 64 received an LHRH-agonist as monotherapy (5.6%), while 451 patients (39.6%) received  
182 sequential tamoxifen and an AI (Table 2).

183 Patients receiving tamoxifen only were more likely to be younger (46.3 +/-7.8 years  
184 old), with a high level of education (77.1% of high education), a moderate to high socio-  
185 professional category (49.8% and 38.6% respectively) and were not menopausal (33.3% post-  
186 menopause) than patients receiving AI or sequential endocrine therapy (Table1).

187 Likewise, patients receiving tamoxifen alone more often underwent a conservative  
188 mastectomy (49.5%) or a breast reconstruction (<0.001) than patients with AI only. They also  
189 received more chemotherapy (76%) than patients with AI only or a sequential endocrine  
190 treatment. Details are presented Table 1.

191 *Tolerability of treatment and adherence to endocrine therapy*

192 Patients treated with AI alone compared with those treated with tamoxifen alone had  
193 significantly higher rates of myalgia (43.3% versus 60.5%, p<0.001) and lipid disorders (16.9%  
194 versus 4.7%, p<0.001) and significantly lower rates of weight changes (37.4% versus 27.7%,  
195 p=0.02, with 43.2% and 60.2% of weight gain and 56.8% and 39.8% of weight loss in the  
196 tamoxifen and AI groups, respectively). Patients treated with tamoxifen alone compared to  
197 patients treated sequentially with tamoxifen followed by AI had statistically significantly  
198 higher rates of myalgia (43.3% versus 37.3%, p=0.07) and diminished libido (35.8% versus  
199 28.8%, p=0.03). Finally, patients treated with AI alone had statistically significantly higher  
200 rates of myalgia than patients treated sequentially with tamoxifen followed by AI (60.5%  
201 versus 50.8%, p=0.02).

202 Patients treated with tamoxifen alone had significantly higher rates of hot flashes  
203 (60.2% versus 51.4%,  $p=0.01$ ), vaginal discharge (33.7% versus 24.6%,  $p=0.003$ ),  
204 metrorrhagia (9.3% versus 4.7%,  $p=0.008$ ), heavy menstrual bleeding (12.3% versus 5.8%,  
205  $p=0.009$ ), and psychological disorders (35.1% versus 28.4%,  $p=0.04$ ) than patients treated  
206 sequentially with tamoxifen followed by AI.

207 The incidence of osteoporosis, an adverse event specific to AI, was identical between  
208 patients treated with AI alone and those treated sequentially with tamoxifen and AI.

209 Adherence (Table 3) was comparable between the tamoxifen only and AI only groups.  
210 Of note, twice as many treatment discontinuations for adverse events were observed in the AI  
211 only population compared to the tamoxifen only population (9.7% versus 4.7%,  $p=0.02$ ).

#### 212 *Quality of life according to the type of endocrine therapy received (Table 3)*

213 The three dimensions of QLQ-C30 (overall health status, functional status and  
214 symptom status) were not significantly different between patients taking tamoxifen and patients  
215 not taking endocrine therapy (Table 4). Compared to patients not taking endocrine therapy,  
216 patients treated with AI alone had significantly better overall health status (65.9 versus 58.6,  
217  $p=0.01$ ) and reported less fatigue (38.7 versus 50,  $p=0.004$ ) and fewer financial difficulties (12  
218 versus 20,  $p=0.04$ ).

219 When comparing the type of endocrine therapy received, the overall health status was  
220 not different between the groups. Patients with tamoxifen alone had a higher functional  
221 capacity (84.2 versus 82.9,  $p<0.001$ ), lower work and leisure score (83.9 versus 87,  $p=0.04$ )  
222 and less constipation (19.2 versus 10.4,  $p<0.001$ ) than patients with AI only. When compared  
223 to sequential endocrine therapy, patients with tamoxifen only had a high functional capacity  
224 (84.2 versus 82.5,  $<0.01$ ). Patients with an AI only had less constipation than patients with  
225 sequential endocrine therapy (10.4 versus 17.3,  $p<0.01$ ).

226 In an exploratory analysis, the results of the QLQ-BR23 were similar for patients not  
227 taking endocrine therapy and those who did not. However, patients with AI alone only had a  
228 better sexual function and sexual pleasure scale (68 versus 77.6,  $p<0.01$  and 37 versus 38,  
229  $p=0.04$ ) than patients with tam alone. Likewise, patients with AI alone had better sexual  
230 function (77 versus 72,  $p=0.02$ ) but worse sexual pleasure (38 versus 41,  $p<0.01$ ) than patients  
231 with a sequential endocrine treatment.

#### 232 *Multivariate logistic regression analysis*

233           On multivariate analysis including all variables found to be significant on univariate  
234 analysis ( $p < 0.05$ ), only high socioeconomic category (C) was associated with a better QLQ-  
235 C30 summary score (OR=1.38, IC95%=1.07-1.77,  $p=0.01$ ) and global health score (OR=1.36,  
236 IC95%=1.04-1.77,  $p=0.02$ ). After adjustment, only patients between the ages of 35 and 50  
237 years had significantly lower global health scores (OR=0.73, IC95%=0.56-0.95,  $p=0.2$ ).  
238 Endocrine therapy did not alter quality of life according to the QLQ-C30, but AI enhanced  
239 work and leisure (OR=1.56, IC95% 1.01-2.5,  $p=0.05$ ), cognitive ability (OR=1.51, IC  
240 95%=1.08-2.13,  $p=0.02$ ) and constipation (OR=0.53, IC95% 0.36-1.78,  $p < 0.001$ ). A summary  
241 of the results is reported in Table 5 and detailed findings are presented supplementary Tables  
242 1 and 2.

243           Patients treated with endocrine therapy did not report impaired or enhanced QLQ-BR  
244 23. AI had a protective effect on the QLQ-BR 23 scale for body image and sexual function  
245 items and were associated with altered sexual pleasure. Summary results are presented Table  
246 6 and detailed results are presented in Supplementary Tables 3 and 4.

247

248 **Discussion**

249 This e-cohort study describes the quality of life of patients treated with endocrine  
250 therapy. This real-life study shows that patient-reported outcomes and quality of life differed  
251 according to the type of endocrine therapy received, while adherence was similar in the AI and  
252 tamoxifen groups. Interestingly, the patient environment (socioeconomic category, level of  
253 education and age) seems to play a crucial role in quality of life.

254 The main innovation of our study is the use of an e-cohort to evaluate the impact of  
255 endocrine therapy on quality of life, as all patients with BC were eligible to participate. The  
256 use of a self-administered questionnaire constitutes a major strength of this study. Quality of  
257 life questionnaires filled in directly by the patients allows a reduction of missing data and more  
258 reliable symptom collection (9–11). These properties are related to the good patient  
259 acceptability of this type of data collection: quick questionnaires, flexible schedules, no third  
260 party, allowing greater spontaneity without a feeling of judgement of the patient by a health  
261 professional. Quality of life assessment is often tedious because it involves long, sometimes  
262 intimate questionnaires completed in the presence of a stranger. E-cohorts constitute an  
263 appropriate alternative.

264 Patients included in our study were relatively young compared to the French general  
265 population of breast cancer. Patients participating in e-cohorts must have an internet connection  
266 and some computer literacy, which makes it more likely for younger patients to participate.  
267 Moreover, although this study was conducted on the Seintinelles website – i.e., independently  
268 of the Institut Curie - it seems likely that a large proportion of participants were treated in  
269 specialized hospital facilities, introducing possible recruitment biases. Similarly, the proportion  
270 of patients treated with chemotherapy and trastuzumab in our study appears to be very high  
271 (72.9% and 18.1%, respectively). The young age of our patients and the pejorative biological  
272 characteristics of BC in young women, may explain the high proportion of patients treated with  
273 chemotherapy. There may also be a recruitment bias in favor of the most intensively treated  
274 patients, who would be more motivated to report their experience.

275 This e-cohort comprised a majority of women from higher socioeconomic categories  
276 (47.8%), while farmers and retired and unemployed women were under-represented, a common  
277 characteristic of e-cohorts, as some populations may be over-represented due to the recruitment  
278 method (9,12,13). This phenomenon has already been reported for several e-cohorts, such as  
279 the NutriNet study, which included more than 105,000 patients (12).

280           Reported adherence was satisfactory for more than 90% of our highly selected patients,  
281 and the type of endocrine therapy did not influence the patient's adherence to treatment. These  
282 rates are higher than those reported in Murphy's meta-analysis (14), which could be explained  
283 by the fact that the patients in our study volunteered to participate in a clinical study, and were  
284 therefore probably more actively involved in their management.

285           One of the main limitations of an e-cohort study is the absence of verification of the  
286 patient's understanding of the questions. Indeed, the patient's answers could not be monitored,  
287 and most adverse events were self-reported. However, the questionnaire used in our study  
288 comprised several "filter questions" to avoid patients answering parts of the questionnaire that  
289 did not concern them, redundant questions, response aids, etc. Moreover, comparison with the  
290 QLQ-C30 reference scores reported in the EORTC manual did not reveal any significant  
291 difference with our values (15). These quality-of-life questionnaires appear to be suitable for  
292 self-administration by web-based questionnaire to an e-cohort. Specific data demanding an  
293 advanced knowledge of breast cancers cannot be assessed. Therefore, information concerning  
294 immunohistochemistry, breast cancer stage, grade or detailed nodal and metastatic status was  
295 lacking.

296           Several limitations specific to the Seintinelle cohort must be noted. First, non-validated  
297 questionnaires were used to assess treatment adherence and adverse events. Some frequent  
298 adverse events such as arthralgia and joint pain were not recorded in this cohort. Likewise,  
299 certain questions were unfortunately specific to a type of endocrine therapy (psychic disorder).

300

301           In our study, endocrine therapy or the type of endocrine therapy received did not  
302 significantly impact quality of life as assessed by the QLQ-C30 and QLQ-BR32. Our scores  
303 obtained by the QLQ-BR23 scale were similar to those obtained by Sprangers et al. on a  
304 German, Spanish and North American cohort (16). However, our results are very different from  
305 those reported by Sert *et al.* in a prospective cohort of patients treated by endocrine therapy  
306 (regardless of age and menopausal status), who found impaired quality of life in patients treated  
307 by endocrine therapy compared to those not treated by endocrine therapy (17). In their cohort,  
308 quality of life improved over time without ever reaching the level observed in patients without  
309 endocrine therapy. Van Nes found the same results in post-menopause patients (18). This  
310 difference is due to the small sample size of patients without endocrine therapy (58 patients) in  
311 our study, which make these results difficult to interpret. Length of endocrine therapy treatment

312 was not recorded in our study and certain adverse events could have waned over time.  
313 Moreover, different questionnaires were used and our study did not comprise any long-term  
314 follow-up (19). The CANTO study also used the QLQ-C30 questionnaire and found an altered  
315 summary score in patients treated by endocrine therapy (19). This difference can be explained  
316 by the fact that the symptoms were recorded 2 years after diagnosis through a regular cohort.  
317 Most studies evaluated the quality of life in a specific population (menopausal status, type of  
318 breast cancer or surgery) whereas we assessed the whole population (18,20,21). In a general  
319 study, Ganz et al also found that endocrine therapy by Tamoxifen or aromatase inhibitor did  
320 not significantly impact quality of life (22).

321

322         Assessing quality of life is of paramount importance in breast cancer patients. Indeed,  
323 patients with a better quality of life are more inclined to continue their treatment and follow-  
324 up (23). In this e-cohort study, multivariate analysis showed that individual factors  
325 (socioeconomic category, level of education, age and menopausal status) appeared to have the  
326 greatest impact on quality of life. We therefore identified a group of patients at greatest risk of  
327 deterioration of quality of life: patients aged under the age of 50 years, from a low or middle  
328 socioeconomic category (A or B), without a high level of education. These patients should be  
329 identified early, allowing the proposal of closer follow-up. Indeed, it has been showed that  
330 proposing a lifestyle modification could radically change quality of life in breast cancer patients  
331 (24). Chemotherapy was also associated with poorer scores on the QLQ-C30 scale (cognitive  
332 ability, work and leisure, dyspnoea and financial difficulties). This result should be interpreted  
333 with caution, as chemotherapy has been shown to have mainly short-term effects (19,25). In  
334 our study did not comprise any long-term follow-up of the patients.

335         There is currently a trend to de-escalate treatment in BC, notably in relation to axillary  
336 surgery and chemotherapy (26) (27) (28). However, endocrine therapy is not concerned by this  
337 movement and there is even a tendency to extend the duration and intensification of this  
338 treatment (29). The two main results emerging from this e-cohort – the absence of any major  
339 impact on quality of life and the satisfactory adherence to endocrine therapy – are in favor of  
340 the acceptability of this therapy. Patients on Tamoxifen presented lower sexual function score  
341 and more libido and weight change. However, this can be due to the pre-menopausal status and  
342 not the endocrine therapy.

343           The use of web-based questionnaires in e-cohorts must be encouraged. Post *et al.*  
344 reported improved self-esteem and quality of life, and increased physical exercise, but also a  
345 decreased stress and fatigue in patients responding to this type of questionnaire (10). Inviting  
346 patients to fill in questionnaires about their symptoms, quality of life or employment during  
347 their follow-up is perceived as support from the medical community. Moreover, the COVID-  
348 19 pandemic showed the emerging role of telemedicine (30).

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354 **Conclusion**

355           Our study describes the tolerability and adherence to endocrine therapy in an e-cohort  
356 of early breast cancer patients using validated questionnaires. We analysed adherence, adverse  
357 effects and discontinuation of treatment by patients treated with long-term endocrine therapy  
358 without medical intervention, therefore reflecting real-life clinical practice. This study did not  
359 involve any selection or any intervention on the prescribed treatment. We present a simple  
360 observation of patient-reported outcome in order to infer the use, adherence and adverse events  
361 of endocrine therapy in the participating population. In the future, this type of study could be  
362 used to confirm or modulate the conclusions of randomized trials in terms of adherence,  
363 efficacy, tolerability and safety of use in order to improve quality of care.



364 **Author contribution**

365 Louise Benoit : Conceptualization ; Data curation; Formal analysis ; Investigation; Methodology;  
366 Roles/Writing - original draft

367 Carine Cambra : Conceptualization ; Data curation; Formal analysis ; Roles/Writing - original draft

368 Roman Rouzier : Conceptualization ; Formal analysis ; Investigation; Methodology; Supervision;  
369 Validation ; Writing - review & editing.

370 Paul Cottu : Conceptualization ; Funding acquisition ; Supervision; Validation ; Writing - review &  
371 editing.

372 Manuel Rodrigues : Conceptualization ; Supervision; Validation ; Writing - review & editing.

373 Fabien Reyal : Conceptualization ; Funding acquisition ; Supervision; Validation ; Writing - review &  
374 editing.

375 Claire Bonneau : Conceptualization ; Formal analysis ; Investigation; Methodology ; Supervision;  
376 Validation ; Writing - review & editing.

377

378 **Table legends**

379 Table 1: Patient characteristics

380 Table 2 : Hormonal treatment tolerance

381 Table 3 : Hormone treatment observance

382 Table 4 : Quality of life according to the type of hormone treatment received : QLQ-C30 et QLQ-BR23

383 Table 5: Quality of life predictors: Protective and exacerbating variables on the QLQ-C30 after  
384 multivariate analysis including all variables with a  $p < 0.05$  upon univariate analysis.

385 Table 6: Quality of life predictors: Protective and exacerbating variables on the QLQ-BR23 score  
386 after multivariate analysis including all variables with a  $p < 0.05$  upon univariate analysis.

387 Supplementary Table 1: Univariate analysis QLQ-C30

388 Supplementary Table 2: Multivariate analysis QLQ-C30

389 Supplementary Table 3 : Univariate analysis – QLQ-BR23

390 Supplementary Table 4: Multivariate analysis – QLQ-BR23

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	Whole population (N=1198)	Tamoxifen only (N=430)	Aromatase inhibitor only (N=195)	Tamoxifen followed by aromatase inhibitor (N=451)	p-value	
<b>Demographic characteristics</b> Percentage or mean ± standard deviation						
Age (years)	50.3 ± 9.5	46.3 ± 7.8	56 ± 9.8	52.7 ± 9.2	<0.001 <sup>a</sup> <0.001 <sup>b</sup> 0.001 <sup>c</sup>	
Level of education*:	Low	36 (3%)	11 (2.6)	6 (3.1)	17 (3.8)	0.02 <sup>a</sup>
	Intermediate	335 (28%)	96 (22.3)	65 (33.3)	144 (31.9)	0.003 <sup>b</sup>
	High	827 (69%)	323 (77.1)	124 (63.6)	290 (64.3)	0.86 <sup>c</sup>
Socio-professional category*:	A	186 (15.7%)	45 (10.5)	47 (24.1)	79 (17.5)	<0.001 <sup>a</sup>
	B	432 (36.5%)	214 (49.8)	76 (38.9)	217 (48.1)	0.02 <sup>b</sup>
	C	567 (47.8%)	166 (38.6)	71 (36.4)	149 (33)	0.03 <sup>c</sup>
BMI (kg/m <sup>2</sup> )	24.4 ± 4.7	23.9±4.1	25.5 ± 9.8	24.3 ± 4.4	0.37 <sup>a</sup> 0.32 <sup>b</sup> 0.56 <sup>c</sup>	
Post-menopause (%)	659 (38.4%)	143 (33.3)	156 (80)	306 (67.9)	<0.001 <sup>a</sup> <0.001 <sup>b</sup> 0.004 <sup>c</sup>	
<b>Type of treatment</b> Percentage or mean ± standard deviation						
Surgery	Conservative	632 (52.8%)	213 (49.5)	114 (58.5)	244 (54.1)	0.007 <sup>a</sup>
	Mastectomy	491 (41%)	190 (44.2)	65 (33.3)	183 (40.6)	0.14 <sup>b</sup>
	NA	62 (5.2%)	27 (6.3)	16 (8.2)	24 (5.3)	0.22 <sup>c</sup>
	Lymph node dissection	1055 (88.1%)	375 (87.2)	167 (85.6)	406 (90)	0.32 <sup>a</sup> 0.51 <sup>b</sup> 0.31 <sup>c</sup>
	Breast reconstruction	268 (22.5%)	113 (26.3)	25 (12.8)	103 (22.8)	<0.001 <sup>a</sup> 0.16 <sup>b</sup> 0.006 <sup>c</sup>
Chemotherapy	874 (72.9%)	327 (76)	138 (70.8)	313 (69.4)	0.03 <sup>a</sup> 0.06 <sup>b</sup> 0.98 <sup>c</sup>	
Hormone treatment	1140 (95.2%)					
Trastuzumab	216 (18.1%)	88 (20.5)	36 (18.5)	67 (14.9)	1 <sup>a</sup> 0.17 <sup>b</sup> 0.58 <sup>c</sup>	
Radiotherapy	1046 (86.5%)	372 (86.5)	168 (86.2)	404 (89.6)	0.32 <sup>a</sup> 0.62 <sup>b</sup> 0.64 <sup>c</sup>	

501           \* : The variable level of education was regrouped into: (i) low level, patients with no schooling  
502 or with a level up to middle school, (ii) intermediate level, patients with high school or baccalaureate  
503 level, and (iii) high level, patients with university degree.

504           The socio-professional categories were regrouped into 3 groups: (i) A, farmers, workers, retired  
505 and un-employed, (ii) B, artisans, intermediate professions and employees, (iii) C, managers.

506           The p values were obtained using a Fisher test to compare:

507           <sup>a</sup> Patients who had Tamoxifen alone to those who had anti-aromatases alone

508           <sup>b</sup> Patients who had Tamoxifen alone to those who had tamoxifen sequentially

509           <sup>c</sup> Patients who had anti-aromatases alone to those who had anti-aromatases sequentially

510           *Abbreviations:* NA = not applicable

511



512 **Table 2 : Hormonal treatment tolerance**

	Tam only	AI only	Tam + AI		p-value
	n=430 (37.7%)	n=195 (17.1%)	n=451 (39.6%)		
			Period on Tam	Period on AI	
<b>Questions to patients receiving either Tam or AI</b>					
Weight change	161 (37.4%)	54 (27.7%)	147 (32.6%)	125 (27.7%)	<b>0.02<sup>a</sup></b> 0.14 <sup>b</sup> 1 <sup>c</sup>
Muscle pain	186 (43.3%)	118 (60.5%)	168 (37.3%)	229 (50.8%)	< <b>0.001<sup>a</sup></b> <b>0.07<sup>b</sup></b> <b>0.02<sup>c</sup></b>
Libido change	154 (35.8%)	60 (30.8%)	130 (28.8%)	129 (28.6%)	0.24 <sup>a</sup> <b>0.03<sup>b</sup></b> 0.57 <sup>c</sup>
Lipid disorders	20 (4.7%)	33 (16.9%)	28 (6.2%)	63 (14%)	< <b>0.001<sup>a</sup></b> 0.37 <sup>b</sup> 0.34 <sup>c</sup>
Others *	74 (17.2%)	44 (22.6%)	67 (14.9%)	92 (20.4%)	0.12 <sup>a</sup> 0.36 <sup>b</sup> 0.53 <sup>c</sup>
<b>Questions specific to patients receiving Tam</b>					
Hot flashes	259 (60.2%)	NA	232 (51.4%)	NA	<b>0.01<sup>b</sup></b>
Vaginal discharge	145 (33.7%)	NA	111 (24.6%)	NA	<b>0.003<sup>b</sup></b>
Metrorrhagia	40 (9.3%)	NA	21 (4.7%)	NA	<b>0.008<sup>b</sup></b>
Heavy periods	53 (12.3%)	NA	26 (5.8%)	NA	<b>0.009<sup>b</sup></b>
Vaginal dryness	132 (30.7%)	NA	114 (25.3%)	NA	0.08 <sup>b</sup>

Blood test disorder	21 (4.9%)	NA	24 (5.3%)	NA	0.88 <sup>b</sup>
Thromboembolic disease	3 (0.7%)	NA	5 (1.1%)	NA	0.73 <sup>b</sup>
Psychic disorder	151 (35.1%)	NA	128 (28.4%)	NA	<b>0.04<sup>b</sup></b>
Ophthalmologic disorders	56 (13%)	NA	55 (12.2%)	NA	0.76 <sup>b</sup>
Sleeping troubles	184 (42.8%)	NA	170 (37.7%)	NA	0.13 <sup>b</sup>
<b>Questions specific to patients receiving AI</b>					
Osteoporosis	NA	25 (12.8%)	NA	64 (14.2%)	0.71 <sup>c</sup>

513 The p values were obtained using a Fisher test to compare:

514 <sup>a</sup> Patients who had Tamoxifen alone to those who had anti-aromatases alone

515 <sup>b</sup> Patients who had Tamoxifen alone to those who had tamoxifen sequentially

516 <sup>c</sup> Patients who had anti-aromatases alone to those who had anti-aromatases sequentially

517 \*This question could be freely filled out by the patients.

518

519 *Abbreviations:* AI= aromatase inhibitors. Tam = Tamoxifene

520

521 **Table 3 : Hormone treatment adherence**

<b>Observance</b>	<b>Tam only (n=430)</b>	<b>AI only (n=195)</b>	<b>P value</b>
<b>Observance</b>			<b>0.08</b>
Good	286 (90.5%)	124 (96.1%)	
Average	16 (5.1%)	4 (3.1%)	
Bad	14 (4.4%)	1 (0.8%)	
NA	114	66	
<b>Premature interruption of treatment</b>			
Premature interruption of treatment	33 (7.6%)	20 (10.2%)	<b>0.02</b>
<b>Reasons</b>			
Adverse events	20 (4.7%)	19 (9.7%)	<b>0.02</b>
Pregnancy	2 (0.5%)	0	1
Personal decision	9 (2.1%)	1 (0.5%)	0.18
Switch for another endocrine treatment	1 (0.2%)	0	1
Disease progression or new cancer	1 (0.2%)	0	1

522

523 The adherence to treatment was rated as “good” if the patient declared taking the treatment  
 524 every day or almost, “average” if the patient sometimes interrupted the treatment for a week, and “bad”  
 525 if the patient rarely took the treatment.

526 *Abbreviations:* AI= aromatase inhibitors, Tam = Tamoxifene, NA= not applicable

**Table 4 : Quality of life according to the type of hormone treatment received : QLQ-C30 et QLQ-BR23**

	All patients (n=1198)	No endocrine therapy treatment (n=58)	All endocrine therapy (n=1140)	Tam only (n=430)	AI only (n=195)	Tam + AI (n=451)	Patients with versus without endocrine therapy p-value	Patients who had Tam alone to those who had AI alone p-value	Patients who had Tam alone to those who had Tam sequentially p-value	Patients who had AI alone to those who had AI sequentially p-value
<b>QLQ-C30</b>										
<b>Global Health status</b>	63 ± 19.1	58.6 ± 20.7	63.3 ± 18.9	63.1 ± 19.8	65.9 ± 18.1	63 ± 18.5	0.09	0.7	0.9	0.5
<b>Functional scale</b>										
Functional capacities	83.2 ± 15.3	86 ± 10.5	83.1 ± 15.4	84.2 ± 16.1	82.9 ± 14.8	82.5 ± 14.6	<b>0.05</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>	0.3
Work and leisure activities	84.7 ± 20.2	85.9 ± 16.8	84.6 ± 20.3	83.9 ± 21.8	87 ± 17.1	85.1 ± 19.1	0.5	<b>0.04</b>	0.2	0.3
Emotional status	67.9 ± 25.8	67.2 ± 25.2	67.9 ± 25.8	67 ± 25.5	72.4 ± 23.7	67.6 ± 26.3	0.8	0.4	0.6	0.5
Cognitive function	72.2 ± 25.7	74.7 ± 28.3	72.1 ± 25.5	70.3 ± 27.2	76.9 ± 23.1	72.7 ± 24.1	0.5	0.06	0.1	0.1
Social relations	77.3 ± 27.7	75 ± 28.3	77.4 ± 27.6	76.3 ± 28.8	82.5 ± 24.9	78 ± 26	0.5	0.4	0.2	0.2
<b>Symptom scale</b>										
Fatigue	43.2 ± 27	50 ± 26	43.8 ± 27	43.9 ± 28	38.7 ± 26.5	42 ± 25.8	<b>0.04</b>	0.4	0.4	0.2
Nausea and vomiting	5.6 ± 13.5	6.9 ± 15.6	5.6 ± 13.4	5.4 ± 13.6	5.6 ± 13.9	5.2 ± 12.7	0.5	0.5	0.3	0.2
Pain	39 ± 28	36.2 ± 27.6	39.1 ± 28	39.2 ± 28.8	36.2 ± 26.5	39.2 ± 28.1	0.4	0.2	0.9	0.1
Dyspnea	19.5 ± 24.6	15.5 ± 26.6	19.7 ± 24.4	19.9 ± 23.9	20.7 ± 25.8	18.6 ± 23.9	0.3	0.3	0.4	0.2
Insomnia	44.4 ± 36.1	39.1 ± 35.4	44.7 ± 36.1	45.6 ± 36.8	40.9 ± 36	44.2 ± 35.4	0.2	0.4	0.5	0.5
Lack of appetite	7.8 ± 18.3	6.9 ± 18.5	7.9 ± 18.3	8.8 ± 19.5	7 ± 18.3	6.9 ± 16.7	0.7	0.6	0.4	0.6
Constipation	17 ± 27.2	17.2 ± 24.4	17 ± 27.3	19.2 ± 28.9	10.4 ± 22.2	17.3 ± 27.3	0.9	<b>&lt;0.01</b>	0.3	<b>&lt;0.01</b>
Diarrhea	8.6 ± 19	7.5 ± 16.6	8.6 ± 19.1	7.3 ± 17.1	9.2 ± 21.3	8.9 ± 18.9	0.6	0.5	0.6	0.3
Financial difficulties	15.9 ± 28.7	20.1 ± 31.2	15.6 ± 28.6	18.8 ± 31.8	12 ± 25	13.7 ± 26.3	0.3	0.2	0.08	0.6
<b>QLQ-BR23</b>										
<b>Functional dimension</b>										
Body image	64.1 ± 32.2	64.5 ± 28.5	64.1 ± 32.4	62.3 ± 32.7	69.6 ± 31.5	64.4 ± 32.1	0.9	0.05	0.6	0.2
Sexual function	71.7 ± 25.8	70.7 ± 24.4	71.7 ± 25.8	68.1 ± 26.1	77.6 ± 26	72.6 ± 25.1	0.8	<b>&lt;0.001</b>	0.3	<b>0.02</b>
Sexual pleasure	40.2 ± 29.7	41.9 ± 28.4	41.1 ± 29.7	37.9 ± 30.2	38.4 ± 30	41.3 ± 28	0.7	<b>0.04</b>	0.8	<b>&lt;0.01</b>
Future perspectives	49.4 ± 33.8	48.9 ± 30.7	49.5 ± 33.9	48.7 ± 34.7	54.7 ± 32.5	48.7 ± 33.8	0.9	0.06	0.3	0.2
<b>Symptom dimension</b>										
Adverse events of treatment	19.9 ± 15.1	18.1 ± 17.9	19.9 ± 14.9	20.2 ± 15.4	18.5 ± 14.3	19.8 ± 14.5	0.4	0.1	0.3	0.5
Breast symptoms	24.4 ± 20.5	25.0 ± 19.8	24.4 ± 20.6	21.5 ± 25.5	19.7 ± 21.7	19.8 ± 23.9	0.8	0.5	0.4	0.4
Arm and axillary symptoms	24.5 ± 21.6	20.3 ± 20.7	24.8 ± 21.6	25.5 ± 22.1	22.6 ± 21.4	24.3 ± 20.9	0.1	0.2	0.5	0.1
Hair loss	46.5 ± 37.4	45.5 ± 42.9	46.5 ± 37.2	41.3 ± 36.3	40.7 ± 37.5	51.4 ± 38.1	0.9	0.8	<b>0.02</b>	0.3

The p values are obtained using a Student's t-test. comparing each category to the values of the "No hormone treatment" category.

The scores for "global health status" and functional scales are lower as the quality of life deteriorates. The symptom scale scores are higher the more important the symptoms are.

*Abbreviations* : Tam = Tamoxifene, AI= aromatase inhibitor, Tam + AI= sequential treatment Tamxifene and aromatase inhibitor

**Table 5: Quality of life predictors: Protective and exacerbating variables on the QLQ-C30 after multivariate analysis including all variables with a p<0.05 upon univariate analysis.**

Scale		Protective variables	Exacerbating variables
<b>Summary score</b>		High socio-professional category (C)	
<b>Global health score</b>		High socio-professional category (C)	Age 35-50 years
<b>Functional score</b>	Functional capacity	High socio-professional category (C) High level of education Trastuzumab therapy only	Menopause
	Work and leisure	Aromatase inhibitor only High level of education Mastectomy	Chemotherapy
	Emotional state	High socio-professional category (C) Low socio-professional category (A) Trastuzumab therapy only	
	Cognitive ability	Low socio-professional category (A) Aromatase inhibitor only High level of education	Breast reconstruction Chemotherapy
	Social relations		Breast reconstruction
<b>Symptom scale</b>	Fatigue		Age 35-50 years Intermediate socio-professional category (B)
	Nausea and vomiting		Age < 35 years
	Pain	High level of education	
	Dyspnea		Chemotherapy
	Insomnia		Menopause
	Lack of appetite	Radiotherapy	Age 35-50 years
	Constipation	Aromatase inhibitor only	Age < 35 years Axillary surgery
	Diarrhea		Age 35-50 years
	Financial difficulties	High socio-professional category (C) Mastectomy	Age < 35 years Chemotherapy

**Table 6: Quality of life predictors: Protective and exacerbating variables on the QLQ-BR23 score after multivariate analysis including all variables with a p<0.05 upon univariate analysis.**

Scale		Protective variables	Exacerbating variables
<b>Functional score</b>	Body image	Aromatase inhibitor only	Mastectomy Chemotherapy
	Sexual function	Aromatase inhibitor only Menopause	Age < 35 years
	Sexual pleasure		Aromatase inhibitor only
	Future perspectives		
<b>Symptom scale</b>	Adverse events	High level of education	
	Breast symptoms	Menopause Mastectomy	Axillary surgery Radiotherapy
	Axillary symptoms	Low socio-professional category (A)	Axillary surgery Mastectomy Radiotherapy
	Hair loss		Menopause Low socio-professional category (A)