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TITLE: Factors associated with enrolment in clinical trials among women with early-stage breast cancer

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HIGHLIGHTS OF THE STUDY

- Only a small percentage of patients with cancer have access to innovation
- Rate of enrolment in clinical trials among women with early breast cancer exceeded what previously found in other settings
- Clinical and geographical factors seem to be associated to access to innovation in clinical trials
- Enrolment in clinical trials is associated with better quality of life and clinical outcomes

ABSTRACT:

Background

Clinical trials allow to develop innovative treatments and ameliorate the quality of clinical care in oncology. Data show that only a minority of patients is enrolled in clinical trials. We assessed enrolment in clinical trials and its correlates among women with early breast cancer.

Methods

We included 9516 patients with stage I-III breast cancer from the multicenter, prospective CANTO study (NCT01993498), followed-up until year-4 (Y4) post-diagnosis (dx). We assessed factors associated with enrolment using multivariable logistic regression. In exploratory, propensity score matched analyses, we used multiple linear regression to evaluate the relationship of enrolment in clinical trials with Quality of Life (EORTC QLQ-C30 summary score) and described clinical outcomes (distant disease event [dDE], invasive disease event [iDE], and death by any cause) according to enrolment.

Results

Overall, 1716 patients (18%) were enrolled in a clinical trial until Y4 post-dx of breast cancer. Socio-economic factors were not associated with enrolment. Centers of intermediate volume were most likely to enroll patients in clinical trials (vs low volume, Odds Ratio [OR] 1.45 [95% Confidence Intervals, CI 1.08 to 1.95], $p=0.0124$). Among 2118 propensity-score matched patients, enrolment was associated with better QOL at Y4 (adjusted mean difference vs not enrolled +1.37, 95% CI +0.03 to +2.71, $p=0.0458$), and clinical outcomes (enrolled vs not enrolled, dDE 7.3% vs 10.1% $p=0.0206$; iDE 8.2% vs 10.5% $p=0.0732$; death by any cause 2.8% vs 3.7% $p=0.2707$).

Conclusions

In this large study, one-in-five patients enrolled on a clinical trial until Y4 after dx of early breast cancer. Geographical and center-related factors were significantly associated with enrolment in clinical trials. Inclusion in clinical trials seemed associated with improved QOL and clinical outcomes. Access to innovation

for early-stage breast cancer patients should be encouraged and facilitated by overcoming organizational and geographical barriers to recruitment.

KEYWORDS: Breast Neoplasms, Clinical Trial, Survivorship, Quality of Life

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AUTHORS CONTRIBUTION

Daniele Presti: Conceptualization, Methodology, Software, Investigation, Formal analysis, Data Curation, Writing-Original draft preparation **Antonio Di Meglio:** Conceptualization, Methodology, Supervision, Data Curation, Writing-Original draft preparation **Julie Havas:** Software, Validation **Davide Soldato, Pietro Lapidari, Elise Martin, Barbara Pistilli, Christelle Jouannaud, George Emile, Olivier Rigal, Marion Fournier, Patrick Soulie, Marie-Ange Mouret-Reynier, Carole Tarpin, Mario Campone, Sophie Guillermet, Anne-Laure Martin, Sibille Everhard:** Data curation, Writing- Reviewing and Editing

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript.

MANUSCRIPT

1. Introduction

Clinical trials are the backbone and foundation of modern evidence-based oncology, as they represent a fundamental instrument to develop innovative treatments and test strategies that can optimize the quality of clinical care. Literature suggests how being enrolled in clinical trials may improve survival and reduce morbidity in patients with cancer of all types, thanks to early access to the latest and most promising investigational interventions, and close clinical monitoring¹⁻⁴. Participation in clinical trials and equal access to innovation represent therefore key aspects in modern oncology care. According to the National Comprehensive Cancer Network (NCCN), “the best management for any patient with cancer is in a clinical trial”⁵. Nevertheless, it has been estimated that only 3% to 5% of eligible adult cancer patients in the United States⁶ and 2 to 11% in Australia⁷ are enrolled in clinical trials, mostly at the time of cancer recurrence. Trends regarding clinical trial enrollment seem not to have changed substantially over time, suggesting that barriers to trial participation are still numerous and sometimes difficult to overcome, and that access to innovation may be still suboptimal^{6,8}. Several studies tried to elucidate the reasons for low recruitment in clinical trials, usually giving emphasis to patient-related barriers, and evaluating patients’ attitude and motivations about enrolment^{9,10}. Fear of delay of initiation of antineoplastic drugs, or fear of being enrolled in the placebo arm due to randomization procedures were identified as major drivers of non-participation¹¹. In addition, about 85% of patients receive treatment in community or in small-volume facilities of care, whereas only about 15% are treated in larger, urban academic centers, where the number of available protocols is generally higher¹². Socioeconomic and demographic issues can also influence patients’ decision-making regarding clinical trial participation. For example, participation in a clinical trial usually requires an increased frequency of follow-up visits, more testing and more procedures, possibly leading to concerns about travel costs, particularly among patients that have longer travel times to their facility of care or lower income¹³. On the contrary, some factors were found to be associated with higher rates of enrolment in clinical trials, including younger age, male sex, Caucasian race, and having later-stage cancer¹⁴. However, although some factors that may act as barriers or facilitators to clinical trial enrolment were identified, limitations of prior studies include the lack of an extensive characterization of clinical, socio-economic, tumor and treatment-related information that may represent relevant determinants of enrolment. Furthermore, previous studies were often single-institution experiences^{2,4,15,16}. In addition, evidence regarding determinants of enrolment in clinical trials among patients with early-stage breast cancer is still limited.

In the present analysis, we specifically aimed to examine factors associated with enrolment in clinical trials among women with early breast cancer, using data from the CANcer TOxicity cohort (CANTO). In addition, we assessed the relationship of enrolment in clinical trials with long-term (a) patient-reported functional health and symptom burden, and (b) survival outcomes.

2. Patients and Methods

2.1. Data source

CANTO (ClinicalTrials.gov/NCT01993498) is a prospective observational cohort-study that includes patients with stage I-III breast cancer across 26 participating French cancer centers since 2012. CANTO recruiting centers include 20 comprehensive cancer centers, two university hospitals in Paris, two public non-teaching hospitals and two private hospitals (Supplementary Figure 1). UNICANCER, the National Cooperative Group of French Cancer Centers, coordinates CANTO. The CANTO study was approved by the national regulatory authorities on September 14th 2011 (ref 2011-A011095-36) and central ethical committee for human subjects (CPP - Ile de France 7, on October 14th 2011 - ref 11-039). All patients were age ≥ 18 years and provided written informed consent at inclusion. Patients were assessed at diagnosis of breast cancer, and follow-up data were available through year-4 (Y4) after diagnosis at the time of the present analysis. Patients could choose to enroll in concomitant observational or interventional studies at any time during the follow-up period. CANTO study procedures were previously published¹⁷. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies¹⁸ to assess the quality of our report.

2.2. Study Cohort

For this analysis, we had access to information from 9597 patients with early breast cancer from the CANTO cohort. We excluded 81 patients with unknown participation status in concomitant research studies and those that were enrolled in concomitant studies but study information was unavailable or inaccessible. Overall, 9516 patients were included in the final analytic cohort (Figure 1). The aim of this study was to find associations between baseline cohort characteristics (collected at diagnosis of breast cancer) and likelihood of subsequent enrolment in clinical trials. Particularly, we assessed whether patients were enrolled in a clinical trial at any time over the course of their participation to the CANTO cohort study.

2.3. Variables of interest

2.3.1. Clinical trials enrolment variables

Clinical trials enrolment variables were: a) clinical trials enrolment rate (e.g., whether patients enrolled or not in a clinical trial over the course of their participation in the CANTO study [from breast cancer diagnosis through Y4 after diagnosis]); b) the number and c) the type of clinical trial in which patients enrolled. Enrolment in a clinical trial was defined as participation in a concomitant interventional study comparing a new therapeutic approach to the standard of care, or testing a new clinical strategy through a direct intervention on the patient¹⁹. Being included only in observational studies did not account as enrolment in clinical trials.

2.3.2. Other variables

Clinical variables. Clinical, socio-demographic and economic (educational level, income and occupation), tumor and treatment-related characteristics, and data regarding cancer center of care (including geographical region and patient volume [expressed as the number of patients included in the CANTO cohort by center]) were available at breast cancer diagnosis and categorized as in Table 1. Anxiety and depression were assessed through the Hospital Anxiety and Depression (HADS) Scale²⁰.

Patient-reported outcomes (PRO). PRO were collected using the the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life (QOL) questionnaires QLQ-C30²¹, BR23²², and FA12²³. A higher-order QOL metric, the C30 Summary Score (C30 SumScore), was used to assess overall QOL. The C30 SumScore incorporates 13 (functional: physical, emotional, social, cognitive, and role; symptoms: fatigue, pain, nausea/vomiting, sleep disturbance, dyspnea, appetite loss, constipation, diarrhea) of the 15 domains from EORTC QLQ-C30 (global health status and financial difficulties excluded)^{24,25}. PRO were available in CANTO at diagnosis, and at year-1 (Y1), -2 (Y2), and -4 (Y4) after diagnosis.

Survival outcomes. A distant disease event (dDE) was defined a distant breast cancer recurrence or death by any cause; 2) Invasive disease event (iDE) was defined as any invasive breast cancer recurrence (ipsilateral, regional, contralateral, or distant), second primary invasive cancer, or death by any cause; 3) death by any cause (following standard DATECAN definitions)²⁶.

2.4. Statistical Analysis

Primary analyses. First, we used descriptive statistics to summarize clinical trials enrolment variables. Then, cohort characteristics at diagnosis were tabulated, overall and by enrolment in clinical trials. Chi-square tests and Wilcoxon rank sum tests were used to compare characteristics according to enrolment for categorical and continuous variables, as appropriate. A multivariable logistic regression model was used to assess factors associated with clinical trials enrolment at any time over the course of the participation to the CANTO

cohort study. All patients that had information about enrollment status at any point over post-diagnosis follow-up were included.

Exploratory analyses. We assessed the relationship of enrolment in clinical trials with PRO and clinical outcomes. A propensity score matched analysis was performed to reduce the potential influence of confounding factors and balance characteristics between patients enrolled and not enrolled in clinical trials. This propensity score analysis was performed following standard guidelines previously reported in Literature²⁷. In order to calculate the propensity scores, we included in a logistic regression model all the variables assessed at baseline, including year of breast cancer diagnosis (as in Table 1), and we obtained the predicted probability of enrolment in clinical trials based on each patient characteristic. Once the propensity scores were calculated, subjects were matched by single score. Among patients selected and matched by propensity scores, the longitudinal evolution of PRO (EORTC QLQ-C30, BR23, and FA12) from diagnosis to Y4 was described according to clinical trials enrolment. A multiple linear regression model evaluated the association between clinical trials enrolment and C30 SumScore at Y4 after diagnosis, adjusting by C30 SumScore and covariates at baseline. the rates of dDE, iDE, and death by any cause were compared by enrolment in clinical trials using chi-square tests.

Sensitivity Analyses. To confirm the robustness of our findings, we performed the analyses of factors associated with enrolment among a subset of patients diagnosed with breast cancer from 2012-2015, who had complete follow-up available 4 years after diagnosis at the time of the most recent database update (n=7810).

All tests were two-sided with a 95% Confidence Interval (CI) and a p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SAS statistical software Version 9.4.

3. Results

3.1. Cohort Characteristics

Patients' characteristics are reported in Table 1. Overall, median age at diagnosis was 57.0 years (interquartile range [Q1-Q3] 17.0 years). The majority of patients included in the cohort were post-menopausal women (62.8%), with Charlson comorbidity score of 0 (80.8%), and reported at least doubtful symptoms of anxiety (60.5%). More than half of patients were diagnosed with stage II (41.6%) or III (9.7%) breast cancer, 76.0% of them had a hormone receptor positive HER2 negative breast cancer, 81.0% received hormonal therapy and 91.2% radiotherapy.

3.2. Enrolment in clinical trials and associated factors

The rate of enrolment in clinical trials was 18.0 % in the overall cohort (1716/9516 patients); 89% of patients were recruited in only one clinical trial, 10% concomitantly in two clinical trials, while approximately 1% in three or four clinical trials. The majority of patients were enrolled in phase III drug-evaluation studies (n=641), phase III not-drug evaluation studies (n=549) and phase II drug-evaluation studies (n=398), while only a few patients (n=59) were recruited in early-phase clinical trials (Table 2).

After multivariable adjustment, factors independently associated with enrolment in clinical trials were: age at diagnosis (40-50 vs >65 years, Odds Ratio [OR] 0.79 [95% Confidence Intervals, CI 0.64 to 0.98], p=0.0300; 50-65 vs >65 years, OR 0.75 [95% CI, 0.63 to 0.90], p=0.0021), not reporting anxiety symptoms at diagnosis (Normal vs Doubtful case/case OR 1.17 [95% CI 1.01 to 1.35], p=0.0363), Region of residency (Center/North vs Ile de France OR 1.26 [95% CI, 1.05 to 1.51] p=0.0145; South vs Ile de France OR 1.51 [95% CI 1.20 to 1.89] p=0.0004), being followed-up in an intermediate volume center of care (intermediate vs low volume center OR 1.43 [95% CI 1.07 to 1.92], p=0.0161) tumor stage (stage II versus stage I OR 1.56 [95% CI 1.33 to 1.84], p<.0001; stage III versus stage I OR 1.32 [95% CI 1.01 to 1.73], p=0.0451), and adjuvant treatments such as hormonal therapy (yes vs no OR 1.34 [95% CI 1.11 to 1.62], p=0.0021) and radiotherapy (yes vs no OR 1.98 [95% CI 1.43 to 2.76], p<.0001). Full results are displayed in Table 3 and Supplementary Figure 2; details regarding rates of enrolment in clinical trials by different Regions are displayed in Supplementary Figure 3.

3.3. Exploratory analyses: PRO and survival outcomes by enrolment in clinical trials

The propensity scores matching analysis brought to the selection of 2118 patients with similar propensity scores. Baseline cohort characteristics of the propensity-score selected population are displayed in the Supplementary table 1. C30 SumScore behaved similarly in patients enrolled and not enrolled in a clinical trial (Figure 2). Scores for all QLQ-C30, BR23, and FA12 domains at diagnosis, Y1, Y2, and Y4 are displayed in Supplementary tables 2 and 3. There was a significant association between the C30 SumScore at Y4 and the enrolment in clinical trials (Mean difference vs not enrolled +1.37, 95% CI 0.03 to +2.71, p=0.0458) (Supplementary Table 4). Among the propensity-score selected patients, 7.3% of those enrolled in clinical trials had a dDE compared to 10.1% among those not enrolled (p=0.0206). In addition, the rate of iDE was 8.2% among patients enrolled in clinical trials and 10.5% in those not enrolled (p=0.0732). Lastly, death by any cause was 2.8% among patients enrolled in clinical trials and 3.7% among those not enrolled (p=0.2707). The overall number of events by enrolment in clinical trials in the cohort of 2118 patients selected after the propensity score matched analysis is displayed in the Supplementary Table 5.

3.4. Sensitivity analyses

We performed a sensitivity analysis on a subset of patients diagnosed with breast cancer from 2012-2015, who had complete follow-up available 4 years after diagnosis (n=7810). Factors associated with enrolment in clinical trials were consistent with the main analysis. Results are displayed in Supplementary Table 6.

4. Discussion

Our analysis showed that among patients with early breast cancer, one-in-five enrolled in a clinical trial over a period of time extending from diagnosis to four years after, with the majority of them participating to phase III clinical trials and few patients participating to more than one study. We found some differences in clinical (age, stage of disease, anxiety) and geographical (region of residency, facilities of care) characteristics between patients enrolled in clinical trials and not. Trial participation did not seem to pose additional burden on patient-reported QOL four years after diagnosis, and seemed associated with improved clinical outcomes, as showed by similar PROs and lower rates of invasive disease events among patients who were enrolled on a clinical trial.

We believe that this study offers valuable insights into factors associated with clinical trial enrolment and expands upon the existing literature on the topic. First, we found that elderly women had the highest likelihood of enrolment in clinical trials in this cohort. Contrary to our findings, older adults are generally underrepresented in clinical trials. This was usually attributed to medical comorbidities, stringent trial eligibility criteria, and patient or physician misconceptions about the risks of enrolment among elderly individuals^{28,29}. A possible explanation of a relatively good representation of the over 65 years of age category in this study is that many patients in our cohort could access trials focused on supportive care, symptom management, and amelioration of QOL such as for example the ART-THERAPIE trial³⁰ or the BEAUTY trial³¹. On the other hand, factors contributing to the lower enrolment rates among younger patients, including those age 40 to 65 in our cohort, are less well understood, including in previous Literature. Among these, physician's failure to propose access to innovation was described as a strong barrier to enrolment in younger patients in previous studies^{15,32,33}.

Second, some patient-related clinical factors were associated with enrolment. Particularly, an anxiety trait was associated with lower enrolment in clinical trials. As also suggested by previous studies, uncertainties, fear of potential adverse events, fear of delay of initiation of antineoplastic drugs or fear of being enrolled in the placebo arm due to randomization procedures, possible painful procedures, may possibly reduce

willingness to participate in clinical studies³⁴. For instance, a survey by Mancini J et al on 115 women enrolled in clinical trials from 21 centers in France, pointed out how 43.0% of participants expressed mild regret to have chosen to participate, and 25.8% expressed moderate to strong regret after agreeing to participate in a randomized controlled clinical trial³⁵. On the contrary, a strong clinical barrier to the participation in clinical trials previously reported in the literature such as comorbidities³⁶ was not associated with enrolment in our cohort.

Third, we did not find major differences in enrolment rates across socio-economic strata in our cohort, as income and education level did not seem to be associated with enrolment. However, we acknowledge that these social determinants may represent important drivers of enrolment in healthcare systems other than the French system. Financial issues were identified as an important barrier to clinical trial participation, especially in the United States³⁷, where insurances may not cover non-routine services³⁸. While in France many health services are often accessible with no extra cost to the whole population, due to universal health coverage, in some countries, such as the United States, patients may have to deal with additional costs when participating in clinical trials, especially when this requires them to travel to their follow-up centres for additional tests or procedures that are only available locally, or cannot be obtained elsewhere³⁹.

Fourth, center-related features seemed to be one of the most relevant determinants of enrolment in clinical trials. This finding may relate to availability of research infrastructures that can facilitate enrolment, both for patients and for physicians. Facilitators of enrolment may indeed come from the optimization of local research infrastructures, providing facilities to physicians that can optimize the process of recruitment and trial managing.

In addition, we performed exploratory analyses that also yielded interesting findings. We showed that enrolment in clinical trials seems to be associated with better PRO four years after diagnosis and lower recurrence rates. Whether the enrolment in clinical trials improves survival beside the clinical setting or trial outcomes still remains debated. Previously, one study designed by Chow et al proved that enrollment into cancer trials could independently predict lower overall and cancer specific mortality in patients with common cancers³. Although exploratory, results of our study are consistent with these findings and provide further insight into the relationship between enrolment in trials and relapse among a specific population such as patients with early breast cancer.

We recognize that our study has some limitations. Our cohort is selected from patients that participated in CANTO, which is *per se* a multicenter cohort-study. Indeed, the high proportion of comprehensive cancer centers in the recruiting institutions might have led to an overestimation of the results. CANTO focuses on

women diagnosed with breast cancer and followed-up in France, therefore this analysis may not be generalizable to all women and healthcare systems of other countries. Some attrition was present with increasing missing data, particularly in PROs at later time-points. CANTO did not include information about the date and duration of enrolment clinical trials, as participation could happen anytime over four years after diagnosis. However, to accommodate for potential of premature study termination due to breast cancer recurrence or death, all models included breast cancer prognostic factors. . CANTO includes only patients with stage I-II-III breast cancer without evidence of active disease or relapse, therefore we acknowledge potential bias from study termination for patients who develop disease progression. Analyses of clinical outcomes may be underpowered due to the limited number of events in this early-stage cohort of women with breast cancer and limited follow-up time for survival events. For these reasons survival outcomes were summarized descriptively, as opposed to be assessed in a formal time-to-event analysis by enrollment group, and our results should be interpreted with caution as they were considered exploratory. Strengths include that this is the first multicentre prospective study to focus exclusively on the enrolment in clinical trials among women diagnosed with early breast cancer, with availability of a large amount of longitudinal PRO up to four years after diagnosis.

5. Conclusions

This study focused on the enrolment rate and factors related to enrolment in clinical trials among women diagnosed with early breast cancer. One in five women were enrolled in a clinical trial after diagnosis of early-stage breast cancer. In this population, the rate of enrolment exceeded what was previously found in different settings. While patients seem adequately represented irrespective of clinical and treatment related features, mostly clinical (age, anxiety traits) and geographical (region of residency, facilities of care) factors seem to be those associated to access to innovation in clinical trials. Enrolment did not negatively impact QOL and there were suggestions of improved clinical outcomes among women who participated in clinical trials. Access to innovation should be facilitated and encouraged by overcoming factors associated with impaired recruitment.

CONFLICT OF INTEREST DISCLOSURES

BP reports personal fees from Astra Zeneca, Myriad, Pfizer, Pierre Fabre, Daiichi-Sankyo, and non-financial support from Daiichi-Sankyo, Merus, Puma, Pfizer, Astra Zeneca. The other authors declare no conflicts of interest for this study.

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Table 1. Baseline cohort characteristics, overall and according to clinical trials enrolment.

N (%)	Whole cohort	According to clinical trial enrolment		
		Yes	No	P*
Total	9516	1716 (18.0)	7800 (82.0)	
Age at diagnosis, years				
Median (Q1-Q3)	57.0 (48.5-65.5)	57.7 (48.1-66.3)	56.8 (48.6-65.4)	0.1080
Missing	-	-	-	
Age at diagnosis, years				
<40	672 (7.1)	136 (20.2)	536 (79.8)	0.0021
40-50	2145 (22.5)	384 (17.9)	1761 (82.1)	

50-65	4154 (43.7)	688 (16.6)	3466 (83.4)	
≥65	2545 (26.7)	508 (20.0)	2037 (80.0)	
Missing	-	-	-	
BMI at diagnosis				
Median (Q1-Q3)	24.8 (22.0-28.7)	25.3 (22.3–29.1)	24.7 (21.9-28.7)	0.0012
Missing	55	4	51	
BMI at diagnosis				
<25	4832 (51.1)	815 (16.9)	4017 (83.1)	0.0015
≥25	4629 (48.9)	897 (19.4)	3732 (80.6)	
Missing	55	4	51	
Menopausal status				
Premenopausal	3514 (37.2)	617 (17.6)	2897 (82.4)	0.3161
Postmenopausal	5925 (62.8)	1089 (18.4)	4836 (81.6)	
Missing	77	10	67	
Charlson Comorbidity Index				
0	7049 (80.8)	1202 (17.0)	5849 (83.0)	0.0210
1+	1672 (19.2)	325 (19.4)	1347 (80.6)	
Missing	795	189	606	
Depression, categorical				
Normal	7087 (81.6)	1301 (18.4)	5786 (81.6)	0.3774
Doubtful case-Case	1602 (18.4)	279 (17.4)	1323 (82.6)	
Missing	827	136	691	
HADS Depression^a, score				
Mean (SD)	4.2 (3.7)	4.1 (3.6)	4.3 (3.7)	0.0647
Missing	827	136	691	
Anxiety, categorical				
Normal	3434 (39.5)	661 (19.2)	2773 (80.8)	0.0394
Doubtful case-Case	5250 (60.5)	919 (17.5)	4331 (82.5)	
Missing	832	136	696	
HADS Anxiety^a, score				
Mean (SD)	9.0 (4.2)	8.7 (4.2)	9.0 (4.2)	0.0205
Missing	832	136	696	
Marital status				

In a relationship	6786 (77.9)	1236 (18.2)	5550 (81.8)	0.8015
Not in a relationship	1928 (22.1)	356 (18.5)	1572 (81.5)	
Missing	802	124	678	
Having a child				
Yes	8313 (96.5)	1524 (18.3)	6789 (81.7)	0.8324
No	303 (3.5)	57 (18.8)	246 (81.2)	
Missing	900	135	765	
Familiar history of breast cancer				
Positive	2122 (22.7)	379 (17.9)	1743 (82.1)	0.8419
Negative	7230 (77.3)	1305 (18.0)	5925 (82.0)	
Missing	164	32	132	
Personal history of previous cancer				
Yes	735 (7.9)	118 (16.0)	617 (84.0)	0.1607
No	8613 (92.1)	1561 (18.1)	7052 (81.9)	
Missing	168	37	131	
Previous breast surgery				
Yes	694 (7.3)	94 (13.5)	600 (86.5)	0.0014
No	8776 (92.7)	1615 (18.4)	7161 (81.6)	
Missing	46	7	39	
Highest education level				
Primary or lower	1285 (14.8)	255 (19.8)	1030 (80.2)	0.0605
High school	4029 (46.6)	751 (18.6)	3278 (81.4)	
College graduate or higher	3341 (38.6)	571 (17.1)	2770 (82.9)	
Missing	861	139	722	
Monthly Household Income (Euros/month)				
< 2000/month	2288 (28.6)	430 (18.8)	1858 (81.2)	0.0763
2000 - 4000/month	3730 (46.6)	710 (19.0)	3020 (81.0)	
≥ 4000/month	1990 (24.8)	332 (16.7)	1658 (83.3)	
Missing	1508	244	1264	
Occupational class				

Chief executives, managers and intellectual professions	3925 (45.1)	668 (17.0)	3257 (83.0)	0.0020
Middle-class workers ^b	3249 (37.4)	612 (18.8)	2637 (81.2)	
Self employed and manual workers ^c	1365 (15.7)	270 (19.8)	1095 (80.2)	
Unemployed, retired	160 (1.8)	43 (26.9)	117 (73.1)	
Missing	817	123	694	
Region of residency				
Île-de-France	2632 (27.7)	391 (14.9)	2241 (85.1)	<.0001
Center/North of France ^d	4989 (52.4)	940 (18.8)	4049 (81.2)	
South of France ^e	1895 (19.9)	385 (20.3)	1510 (79.7)	
Missing	-	-	-	
Anonymized COC				
High volume	2320 (24.4)	373 (16.1)	1947 (83.9)	0.0004
Intermediate volume	6454 (67.8)	1232 (19.1)	5222 (80.9)	
Low volume	742 (7.8)	111 (15.0)	631 (85.0)	
Missing	-	-	-	
COC and patients region of residence				
COC in the same region	8591 (90.3)	1550 (18.0)	7041 (82.0)	0.9424
COC in a different region/foreign patients	925 (9.7)	166 (17.9)	759 (82.1)	
Missing	-	-	-	
Tumor stage				
I	4582 (48.7)	644 (14.0)	3938 (86.0)	<.0001
II	3911 (41.6)	864 (22.1)	3047 (77.9)	
III	912 (9.7)	188 (20.6)	724 (79.4)	
Missing	111	20	91	
Tumor subtype				
HR+/HER-	7186 (76.0)	1318 (18.3)	5868 (81.7)	0.0951
HR±/HER2+	1317 (13.9)	248 (18.8)	1069 (81.2)	
HR-/HER2-	954 (10.1)	149 (15.6)	805 (84.4)	

Missing	59	1	58	
Chemotherapy				
Yes	5041 (53.0)	997 (19.8)	4044 (80.2)	<.0001
No	4475 (47.0)	719 (16.1)	3756 (83.9)	
Missing	-	-	-	
Surgery				
Mastectomy	2539 (26.7)	456 (18.0)	2083 (82.0)	0.9100
Conservative surgery	6971 (73.3)	1259 (18.1)	5712 (81.9)	
Missing	6	1	5	
Hormone therapy				
Yes	7679 ^f (81.0)	1442 (18.8)	6237 (81.2)	0.0003
No	1797 ^g (19.0)	272 (15.1)	1525 (84.9)	
Missing	40	2	38	
Radiotherapy				
Yes	8661 (91.2)	1630 (18.8)	7031 (81.2)	<.0001
No	831 (8.8)	82 (9.9)	749 (90.1)	
Missing	24	4	20	
Anti-HER2 therapy				
Yes	1158 (12.2)	230 (19.9)	928 (80.1)	0.0879
No	8341 (87.8)	1485 (17.8)	6856 (82.2)	
Missing	17	1	16	
Abbreviations: BMI, body mass index; COC, center of care; HADS, Hospital Anxiety and Depression Scale; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Q1-Q3, interquartile range; SD, standard deviation				
*Chi square for categorical variables, Wilcoxon rank sum test for continuous variables				
^a Anxiety and Depression were assessed using the Hospital Anxiety and Depression Scale (HADS) ²⁰ .				
^b Includes clerks, service and sales workers, technicians and associates				
^c Includes farmers, workers, freelancers, artisans and merchant				
^d Center/North of France includes Brittany, Normandy, Hauts de France, Pays de la Loire, Grand Est, Bourgogne-Franche-Comtè, Centre-Val de Loire, and Other regions or foreign countries				
^e South of France includes Provence-Alpes-Cote d'Azur, Occitane, Corsica, Nouvelle Aquitaine, and Auvergne-Rhône-Alpes				

^f 87.3% had a HR+HER2- early breast cancer and 12.7% a HR+ HER2+ early breast cancer.
^g 6.6% had a HR+HER2- early breast cancer, 29.2% a HR+HER2+ early breast cancer, 95.2% a triple negative breast cancer

Table 2. Type of clinical trials among patients that enrolled on a clinical trial.

TYPE OF STUDY	N°patients enrolled N=1716* (%)
Phase III drug assessing	641 (37.3)
Phase III not drug assessing	549 (32.0)
Phase III supportive care	136 (7.9)
Phase II-III	3 (0.2)
Phase II-III-supportive care	19 (1.1)
Phase II drug assessing	398 (23.2)
Phase II-not drug assessing	20 (1.2)
Phase II supportive care	21 (1.2)
Phase I-II	57 (3.3)
Phase I	2 (0.1)

* Numbers do not add up to 1716 as patients could be enrolled in more than 1 type of CT at the same time. Note, among patients enrolled in clinical trials, there were 90 patients that also participated in concomitant observational studies.

Table 3. Multivariable logistic regression of factors associated with enrolment in clinical trials (N=9516)

Effect	Adjusted* OR	95% Confidence Intervals		p-Value
AGE <40 vs >65	0.96	0.70	1.31	0.7902
AGE 40-50 vs >65	0.79	0.64	0.98	0.0300
AGE 50-65 vs >65	0.75	0.63	0.90	0.0021

BMI ≥ 25 vs <25	1.05	0.91	1.21	0.5268
Charlson ≥1 vs 0	1.09	0.91	1.29	0.3527
Depression normal vs doubtful case/case	1.00	0.83	1.21	0.9994
Anxiety normal vs doubtful case/case	1.17	1.01	1.35	0.0363
Relationship No vs Yes	0.98	0.80	1.19	0.8295
Children no vs yes	1.13	0.79	1.60	0.5068
BC familiar history negative vs positive	0.99	0.84	1.17	0.9134
Previous cancer No vs Yes	1.09	0.82	1.44	0.5395
Previous breast surgery no vs yes	1.18	0.89	1.56	0.2421
High school vs Primary school	1.13	0.90	1.42	0.3031
College or higher vs Primary school	1.09	0.82	1.44	0.5580
Income <2000 vs 2000-4000	0.91	0.75	1.09	0.3045
Income >4000 vs 2000-4000	0.92	0.77	1.10	0.3761
Middle-class workers vs Executive, managers	1.04	0.86	1.24	0.6899
Unemployed, retired, vs Executive, managers	1.49	0.89	2.49	0.1281
Manual workers and s vs Executive, managers	1.04	0.82	1.32	0.7409
Residency center-north vs Ile de France	1.26	1.05	1.51	0.0145
Residency south vs Ile de France	1.51	1.20	1.89	0.0004
Center volume intermediate (200-1000) vs low (<200)	1.45	1.08	1.95	0.0124
Center volume high (>1000)	1.17	0.84	1.63	0.3597

vs low (<200)				
Different Region vs Same Region between residence and center of care	0.98	0.77	1.23	0.8365
STAGE II vs STAGE I	1.56	1.33	1.84	<.0001
STAGE III vs STAGE I	1.32	1.01	1.73	0.0451
Chemotherapy Yes vs No	1.12	0.94	1.33	0.2167
Conservative surgery vs Mastectomy	1.07	0.89	1.28	0.4740
Hormone-therapy Yes vs No	1.34	1.11	1.62	0.0021
Radiotherapy Yes vs No	1.98	1.43	2.76	<.0001
Anti-HER2 therapy Yes vs No	1.14	0.92	1.40	0.2286
* Adjusted for all factors in the table, including year of breast cancer diagnosis				
Abbreviations: BC, breast cancer; BMI, body mass index; HER2, human epidermal growth factor receptor 2; OR, odds ratio				

FIGURE LEGENDS

Figure 1. CONSORT diagram of patient population

Figure 2. Line graphs with mean Summary Score values (EORTC Quality of Life Questionnaire [QLQ]

C30) over time by enrolment in clinical trials. C30 Summary Score is calculated using the mean scores for 13 of the 15 QLQ-C30 domains (the Global Health and the Financial Impact scales are not included).

Higher C30 Summary Scores indicate a better quality of life. Abbreviations: dx, diagnosis; Y1, one year after diagnosis; Y2, two years after diagnosis; Y4, four years after diagnosis.

Supplementary Figure 1: CANTO participating centers

Supplementary Figure 2. Forest plot of factors associated with enrolment in clinical trials.

Abbreviations: AUC, area under the curve; BC, breast cancer; BMI, body mass index, CoC, center of care; HER2, human epidermal growth factor receptor 2

Supplementary Figure 3: patients accrual by Region of residency (% of patients enrolled)

Patients with Stage I-III breast cancer diagnosed or presenting for care at one of 26 participating CANTO institutions between March 2012 and February 2017 (N= 9597)

Exclusion criteria:

- Participation status in concomitant research studies unavailable
- Patients enrolled in concomitant studies but study information unavailable or inaccessible

n=36

n=45

Final cohort

(N= 9516)

