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# Early breast cancer in women aged 35 years or younger: A large national multicenter French population-based case control-matched analysis

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ABSTRACT

*Background:* There is a scarcity of data exploring early breast cancer (eBC) in very young patients. We assessed shared and intrinsic prognostic factors in a large cohort of patients aged ≤35, compared to a control group aged 36 to 50.

*Methods:* Patients ≤50 were retrospectively identified from a multicentric cohort of 23,134 eBC patients who underwent primary surgery between 1990 and 2014. Multivariate Cox analyses for DFS and OS were built. To assess the independent impact of age, 1 to 3 case-control analysis was performed by matching ≤35 and 36–50 years patients.

*Results:* Of 6481 patients, 556 were aged ≤35, and 5925 from 36 to 50. Age ≤35 was associated with larger tumors, higher grade, ER-negativity, macroscopic lymph node involvement (pN + macro), lymphovascular invasion (LVI), mastectomy, and chemotherapy (CT) use. In multivariate analysis, age ≤35 was associated with worse DFS [HR 1.56, 95% CI 1.32–1.84; $p < 0.001$], and OS [HR 1.29, 95% CI 1.03–1.60; $p = 0.025$], as were high grade, large tumor, LVI, pN + macro, ER-negativity, period of diagnostic, and absence of ET or CT (for DFS). Adverse prognostic impact of age ≤35 was maintained in the case control-matched analysis for DFS [HR 1.56, 95%CI 1.28–1.91, $p < 0.001$], and OS [HR 1.33, 95%CI 1.02–1.73, $p = 0.032$]. When only considering patients ≤35, ER, tumor size, nodal status, and LVI were independently associated with survival in this subgroup.

*Conclusions:* Age ≤35 is associated with less favorable presentation and more aggressive treatment strategies. Our results support the poor prognosis value of young age, which independently persisted when adjusting for other prognostic factors and treatments.

*Abbreviations:* BC, Breast Cancer; SLNB, Sentinel Lymph Node Biopsy; ALND, Axillary Lymph Node Dissection; SBR grade, Scarff-Bloom-Richardson grade; ER, endocrine receptors; HER2, Human Epidermal growth factor Receptor 2; LVI, lymphovascular invasion; luminal-A, (HER2 negative, ER positive, SBR grade 1 or 2); luminal-B, HER2-negative, (HER2 negative, ER positive, SBR grade 3); luminal-B, HER2-positive, (HER2 positive, ER positive, all grades); HER2-positive, (non-luminal, HER2 positive, ER negative); triple-negative, (basal like, HER2 negative, ER negative); ER+, positive endocrine receptor; ER-, negative endocrine receptor; HER2+, HER2 positive; HER2-, HER2 negative; pN0, no invasion; pN0i+, isolated tumor cells; pN + mi, microscopic invasion under 2 mm; pN + macro, macroscopic invasion beyond; CT, chemotherapy; RT, radiation therapy; ET, endocrine therapy; DFS, Disease Free Survival; OS, Overall Survival; HR, Hazard Ratio; 95%CI, confidence interval at 95%; ER-, Endocrine Receptor Negative; ER+, Endocrine Receptor Positive; LumA, Luminal-A subtype; LumB G3, Luminal-B HER2-negative SBR grade 3 subtype; LumB HER2+, Luminal-B HER2-positive subtype; HER2+, HER2-positive subtype; TN, Triple-Negative subtype.

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**Table 1**
Histopathological characteristics and treatments of the two populations: ≤35 and 36–50 years old.

| UNIVARIATE | | Total | ≤35 y (n = 556) | | | 36-50 y (n = 5925) | | | *p value* |
|---|---|---|---|---|---|---|---|---|---|
| Characteristics | | n | total | n | % | total | n | % | |
| Period | | 6481 | 556 | | | 5925 | | | 0.037 |
| | Before 2005 | | | 334 | 60% | | 3287 | 56% | |
| | After 2005 | | | 222 | 40% | | 2638 | 45% | |
| Tumor size | | 6392 | 542 | | | 5850 | | | <0.001 |
| | ≤5 mm | | | 38 | 7% | | 397 | 7% | |
| | 6–10 mm | | | 83 | 15% | | 1305 | 22% | |
| | 11–20 mm | | | 230 | 42% | | 2525 | 43% | |
| | >20 mm | | | 191 | 35% | | 1623 | 28% | |
| Histological type | | 6100 | 527 | | | 5573 | | | <0.001 |
| | Ductal | | | 493 | 94% | | 4775 | 86% | |
| | Lobular | | | 28 | 5% | | 665 | 12% | |
| | Mixed | | | 6 | 1% | | 133 | 2% | |
| SBR grade | | 6262 | 527 | | | 5735 | | | <0.001 |
| | Grade 1 | | | 60 | 11% | | 1733 | 30% | |
| | Grade 2 | | | 240 | 46% | | 2675 | 47% | |
| | Grade 3 | | | 227 | 43% | | 1327 | 23% | |
| ER | | 6481 | 556 | | | 5925 | | | <0.001 |
| | Negative | | | 211 | 38% | | 1141 | 19% | |
| | Positive | | | 345 | 62% | | 4784 | 81% | |
| Estrogen receptor | | 5839 | 478 | | | 5361 | | | <0.001 |
| | Negative | | | 180 | 38% | | 1003 | 19% | |
| | Positive | | | 298 | 62% | | 4358 | 81% | |
| Progesterone receptor | | 5527 | 467 | | | 5060 | | | <0.001 |
| | Negative | | | 185 | 40% | | 1217 | 24% | |
| | Positive | | | 282 | 60% | | 3843 | 76% | |
| HER2 overexpressed | | 6481 | 556 | | | 5925 | | | <0.001 |
| | No | | | 252 | 45% | | 3334 | 56% | |
| | Yes | | | 77 | 14% | | 433 | 7% | |
| | Unknown | | | 227 | 41% | | 2158 | 36% | |
| Molecular subtype | | 4425 | 329 | | | 4096 | | | <0.001 |
| | Luminal A | | | 139 | 42% | | 2724 | 67% | |
| | HER2+ | | | 31 | 9% | | 160 | 4% | |
| | Triple negative | | | 61 | 19% | | 434 | 11% | |
| | Luminal B G3 | | | 52 | 16% | | 428 | 10% | |
| | Luminal B HER2+ | | | 46 | 14% | | 350 | 9% | |
| SLNB and/or ALND | | 6470 | 554 | | | 5916 | | | <0.001 |
| | SLNB | | | 155 | 28% | | 2376 | 40% | |
| | SLNB + ALND | | | 152 | 27% | | 1768 | 30% | |
| | ALND | | | 247 | 45% | | 1772 | 30% | |
| Final lymph node status | | 6447 | 549 | | | 5898 | | | <0.001 |
| | pN0 | | | 275 | 50% | | 3489 | 59% | |
| | pN0(i+) | | | 23 | 4% | | 166 | 3% | |
| | pN + mi | | | 35 | 6% | | 474 | 8% | |
| | pN + macro | | | 216 | 39% | | 1769 | 30% | |
| LVI | | 5599 | 491 | | | 5108 | | | <0.001 |
| | No | | | 244 | 50% | | 3495 | 68% | |
| | Yes | | | 247 | 50% | | 1613 | 32% | |
| Surgery type | | 6481 | 548 | | | 5835 | | | <0.001 |
| | Lumpectomy | | | 377 | 69% | | 4516 | 77% | |
| | Mastectomy | | | 171 | 31% | | 1319 | 23% | |
| Adjuvante CT | | 6481 | 556 | | | 5925 | | | <0.001 |
| | No | | | 93 | 17% | | 2617 | 44% | |
| | Yes | | | 441 | 79% | | 3215 | 54% | |
| | Neo-adjuvant | | | 22 | 4% | | 93 | 2% | |
| Trastuzumab | | 6137 | 536 | | | 5601 | | | <0.001 |
| | No | | | 479 | 89% | | 5334 | 95% | |
| | Yes | | | 57 | 11% | | 267 | 5% | |
| RT | | 6192 | 539 | | | 5653 | | | 0.352 |
| | No | | | 40 | 7% | | 423 | 7% | |
| | Yes | | | 499 | 93% | | 5230 | 93% | |
| ET | | 6476 | 556 | | | 5920 | | | <0.001 |
| | No | | | 242 | 44% | | 1714 | 29% | |
| | Yes | | | 314 | 56% | | 4206 | 71% | |
| Relapse | | 6480 | 556 | | | 5924 | | | <0.001 |
| | No | | | 369 | 66% | | 4996 | 84% | |
| | Yes | | | 187 | 34% | | 928 | 16% | |
| Relapse type | | 1116 | 187 | | | 929 | | | 0.253 |
| | Axillary | | | 6 | 3% | | 39 | 4% | |
| | Metastatic | | | 120 | 64% | | 516 | 56% | |
| | Others | | | 38 | 20% | | 235 | 25% | |
| | Controlateral | | | 16 | 9% | | 84 | 9% | |
| | Unspecified | | | 7 | 4% | | 55 | 6% | |

## 1. Introduction

Breast cancer (BC) incidence increases with age. However, one in forty patients will be diagnosed under the age of 35, thereby making it the leading cancer in young women [1,2]. Technological and therapeutic advances have led to a significant decrease in overall mortality over time, but when examined by age groups, it appears that cancer-related death in premenopausal patients tends to remain relatively stable over time. The association between young age and prognosis has been recognized for a long time [3–5] but its independent value is still debated [6]. According to European recommendations, treatment decisions in young women should not be motivated by their age but rather by BC presentation, to avoid overtreatment [7,8]. These recommendations assume that prognostic factors that are recognized in older women are equally valid and robust in younger women. We decided to focus on women under 35 years to try to answer three questions: what is the presentation of BC in patients ≤35 years compared to older pre-menopausal patients? Is young age by itself an independent prognostic factor? And are the prognostic factors classically identified in BC also evident in this population? To this end, we compared patients ≤35 years with a group of patients aged 36 to 50 extracted from a large retrospective multi-institutional cohort.

## 2. Methods

Our data were extracted retrospectively from a multicentric database comprising 23,134 patients who underwent primary surgery for early BC, from 15 French centers between 1990 and 2014. Data concerning relapse and vital status of patients were updated annually (last update May 7, 2021). Patients were included based on histologically proven invasive BC, with sentinel lymph node biopsy (SLNB) evaluation ± axillary lymph node dissection (ALND). Patients aged ≤50 were selected and divided into two groups: patients aged ≤35 years as the population of interest and patients aged 36 to 50 as a control group of premenopausal patients. We analyzed diagnostic period, tumor size, histological type, SBR grade, endocrine receptors (ER; positivity threshold 10%), Human Epidermal growth factor Receptor 2 (HER2) status, molecular subtypes determined by immunohistochemistry, SLNB or ALND, final lymph node status, and lymphovascular invasion (LVI) [9]. Five molecular subtypes were defined: luminal-A {HER2 negative (HER2-), ER-positive (ER+), grade 1 or 2}; luminal-B HER2-negative {HER2-, ER+, grade 3}; luminal-B HER2-positive {HER2 positive (HER2+), ER+, all grade}; HER2-positive {HER2+, ER-negative (ER-)}; triple-negative {basal like, HER2-, ER-}. Final lymph node status was categorized into four groups: no invasion (pN0), isolated tumor cells (pN0i+), microscopic invasion <2 mm (pN + micro), and macroscopic invasion beyond (pN + macro) [10]. Treatments, including surgery type, chemotherapy (CT), radiation therapy (RT), and endocrine therapy (ET) were analyzed. The database did not include any mutational data, thus BRCA mutation status was not known. Disease Free Survival (DFS), defined as the time from surgery to the first event (invasive relapse, metastatic relapse, or death from any cause), and Overall Survival (OS), defined as the time from surgery to death, were analyzed. Patients with missing data on evaluated variables were removed from multivariate analysis. All procedures involving human participants were done according to the French ethical standards and the Helsinki declaration. Authorization to use the database was obtained from the strategic orientation committee of Paoli-Calmettes Institute (ClinicalTrials.gov NCT02869607).

Standard descriptive statistics were used to describe patient and tumor characteristics. Deaths with no evidence of recurrence were treated as competing events in cumulative incidence analyses. Factors associated with DFS, and OS were determined in univariate and multivariate analysis. Survivals were estimated using the Kaplan-Meier method and compared with log-rank test. Multivariate Cox analyses were built for the total cohort and specifically for the ≤35 years old cohort. The hazard ratio (HR) was determined with a 95% confidence interval [95%CI]. Significance level was set at 0.05. To further assess the independent impact of age on survivals, a 1 to 3 case-control analysis was performed by matching ≤35 to 36–50 years old patients. Coefficients of a logistic regression adjusted on histology, grade, tumor size, LVI, nodal status, ER, ET, and CT were used to compute a propensity score for each patient. Each pair (1–3) were comparable on these criteria, but distinct by age. Patients not meeting all the matching criteria were excluded. Nearest-neighbor 1:3 matching without replacement was performed with a caliper of 0.2 [11–13]. All statistical tests were two-sided. Statistical analyses were performed with SPSS-16.0 (SPSS Inc., Chicago, Illinois, USA) and R version-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

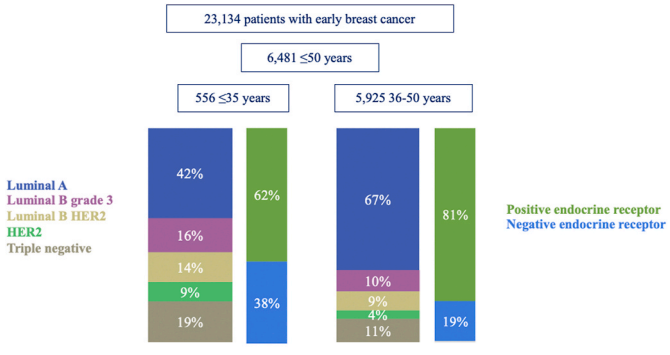


**Fig. 1.** Flow chart of the population.

## 3. Results

### 3.1. BC presentation in patients ≤35 years compared to 36–50 patients

From the 23,134 patients, a cohort of 6481 patients aged ≤50 years was extracted. Among them, 556 were aged ≤35 years and 5925 from 36 to 50 (Table 1 and Fig. 1).

Compared to the 36–50 years old group, patients ≤35 had significantly larger tumor (35% above 20 mm in ≤35 *versus* 28% in 36–50), grade 3 (43% *versus* 23%), pN + macro (39% *versus* 30%), and LVI (50% *versus* 32%). Patients ≤35 had more ER-tumors (23% *versus* 11%), and HER2+ (14% *versus* 7%). Molecular subtypes distribution was different according to age group ($p < 0.001$): luminal-A tumors were principally represented in the 36–50 patients (67% *versus* 42% of ≤35), while ≤35 patients presented more triple-negative (19% *versus* 11%), luminal-B HER2-negative (16% *versus* 10%), luminal-B HER2-positive (14% *versus* 9%), and HER2-positive (9% *versus* 4%) tumors (Fig. 1). Lobular subtype was more frequent in 36–50 years old patients (12% *versus* 5%). Age ≤35 years was significantly associated with increased rates of mastectomy (31% *versus* 23%), adjuvant CT (79% *versus* 54%), neoadjuvant CT (4% *versus* 2%), and ALND (45% *versus* 30%). No difference was observed for RT or ET use among ER + patients (Table 1).

### 3.2. Prognostic value of age ≤35 - Univariate survival analysis

With a median follow-up of 71.9 months [95%CI 70.7–73.1], DFS events occurred in 34% of ≤35 patients *versus* 16% of 36–50 ($p < 0.001$). However, no difference was observed by type of relapse (Table 1).

In univariate analysis, patients ≤35 presented lower 5- and 10-year DFS than the 36–50 cohort: 74% [95%CI 70.88–78.12] *versus* 89% [95%IC 87.89–89.51]; $p < 0.001$, and 60% [95%IC 55.52–63.68] *versus* 74% [95%IC 73.29–75.51]; $p < 0.001$, respectively (Fig. 2). HR for continuous DFS was unfavorable for ≤35 women [1.90, 95%CI 1.63–2.33, $p < 0.001$] (Table 2, Fig. 3). OS events were more frequent in the ≤35 group (19%) than in the 36–50 (9%) ($p < 0.001$). In univariate analysis, patients ≤35 presented lower 5- and 10-year OS than 36–50: 89% [95%IC 86.84–91.96] *versus* 95% [95%IC 94.76–95.84]; $p < 0.001$,

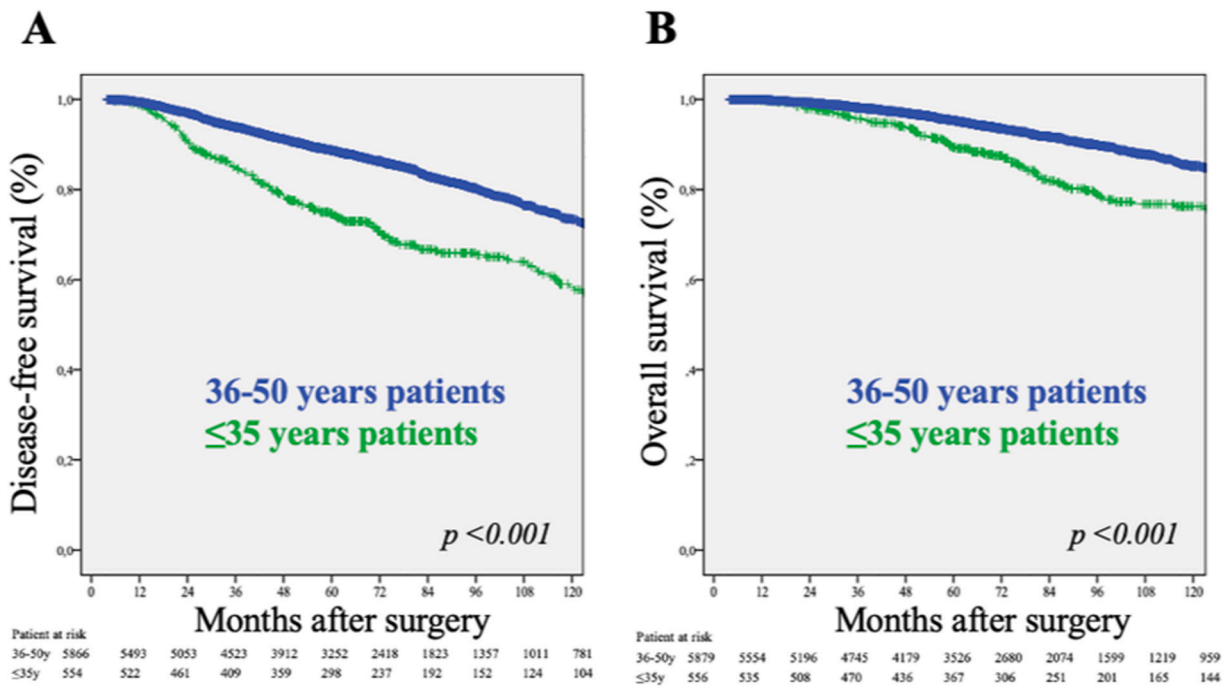


**Fig. 2.** Kaplan Meier of univariate analysis of DFS (A) and OS (B) in both cohorts.

**Table 2**
Multivariate analysis of DFS and OS in the total cohort.

| TOTAL | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| COHORT | HR | 95% CI | | *p value* | HR | 95% CI | | *p value* |
| | | min | max | | | min | max | |
| Age | 1.56 | 1.32 | 1.84 | <0.001 | 1.29 | 1.03 | 1.60 | 0.025 |
| CT | | | | | | | | |
| No | Reference category | | | | Reference category | | | |
| Adjuvant | 0.83 | 0.70 | 0.99 | 0.035 | 0.86 | 0.67 | 1.10 | 0.218 |
| Neo-adjuvant | 1.26 | 0.79 | 2.02 | 0.326 | 1.51 | 0.78 | 2.92 | 0.221 |
| ER | 0.89 | 0.73 | 1.08 | 0.239 | 0.72 | 0.56 | 0.92 | 0.010 |
| ET | 0.73 | 0.60 | 0.88 | 0.001 | 0.82 | 0.64 | 1.07 | 0.141 |
| SBR grade | | | | | | | | |
| 1 | Reference category | | | | Reference category | | | |
| 2 | 1.37 | 1.15 | 1.63 | <0.001 | 1.53 | 1.16 | 2.01 | 0.003 |
| 3 | 1.64 | 1.35 | 2.00 | <0.001 | 2.33 | 1.74 | 3.13 | <0.001 |
| Size (mm) | | | | | | | | |
| ≤5 | Reference category | | | | Reference category | | | |
| 5 to 10 | 0.77 | 0.56 | 1.06 | 0.107 | 0.56 | 0.33 | 0.94 | 0.027 |
| 10 to 20 | 0.90 | 0.66 | 1.22 | 0.484 | 0.84 | 0.52 | 1.36 | 0.477 |
| 20 to 50 | 1.12 | 0.82 | 1.52 | 0.482 | 1.26 | 0.79 | 2.03 | 0.333 |
| >50 | 2.21 | 1.54 | 3.17 | <0.001 | 2.40 | 1.41 | 4.06 | 0.001 |
| Lymph node involvement | | | | | | | | |
| pN0 | Reference category | | | | Reference category | | | |
| pN0(i+) | 1.03 | 0.67 | 1.57 | 0.902 | 0.87 | 0.41 | 1.87 | 0.722 |
| pN1mi | 0.86 | 0.63 | 1.18 | 0.347 | 1.02 | 0.62 | 1.68 | 0.941 |
| pN1macro | 1.37 | 1.17 | 1.60 | <0.001 | 1.67 | 1.34 | 2.08 | <0.001 |
| LVI | | | | | | | | |
| No | Reference category | | | | Reference category | | | |
| Yes | 1.36 | 1.18 | 1.57 | <0.001 | 1.67 | 1.37 | 2.03 | <0.001 |
| Unknown | 1.06 | 0.88 | 1.28 | 0.543 | 1.21 | 0.92 | 1.58 | 0.170 |
| Histological type | | | | | | | | |
| Ductal | Reference category | | | | Reference category | | | |
| Lobular | 0.90 | 0.72 | 1.12 | 0.336 | 0.94 | 0.68 | 1.29 | 0.688 |
| Mixed | 0.73 | 0.47 | 1.13 | 0.160 | 0.94 | 0.54 | 1.64 | 0.817 |
| Others | 0.72 | 0.51 | 1.03 | 0.073 | 0.94 | 0.58 | 1.51 | 0.786 |
| Period | | | | | | | | |
| <1995 | Reference category | | | | Reference category | | | |
| 1995–1998 | 1.08 | 0.86 | 1.36 | 0.510 | 1.00 | 0.74 | 1.34 | 0.988 |
| 1999–2004 | 0.74 | 0.62 | 0.88 | 0.001 | 0.59 | 0.47 | 0.75 | <0.001 |
| ≥2005 | 0.59 | 0.49 | 0.73 | <0.001 | 0.41 | 0.30 | 0.55 | <0.001 |

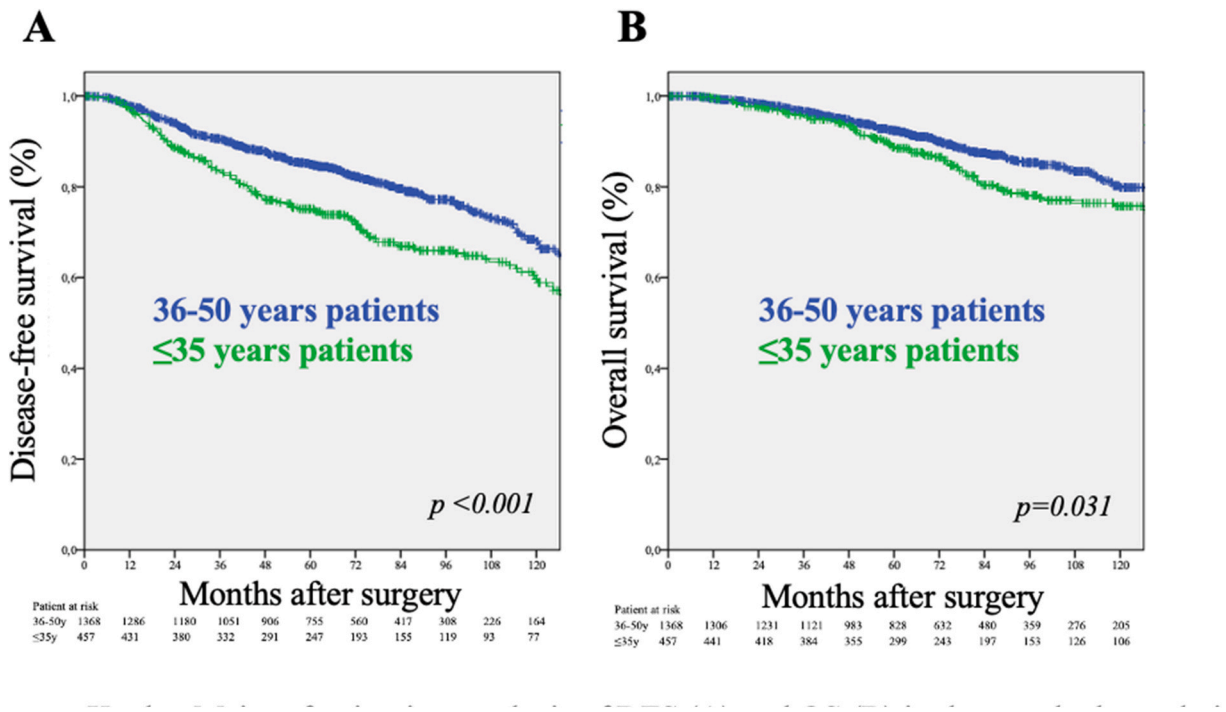


**Fig. 3.** Kaplan Meier of univariate analysis of DFS (A) and OS (B) in the matched population.

**Table 3**
Impact of young age on DFS and OS in the different analysis: univariate, multivariate and matched multivariate.

| Analysis | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95%CI | | | | 95%CI | | |
| | HR | min | max | *p value* | HR | min | max | *p value* |
| Univariate | 1.90 | 1.63 | 2.22 | <0.001 | 1.76 | 1.43 | 2.17 | <0.001 |
| Multivariate | 1.56 | 1.32 | 1.84 | <0.001 | 1.29 | 1.03 | 1.60 | 0.025 |
| Matched | 1.56 | 1.28 | 1.91 | <0.001 | 1.33 | 1.02 | 1.73 | 0.032 |

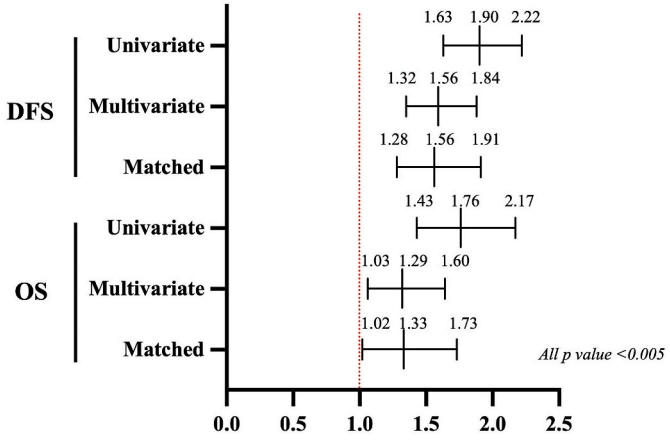


**Fig. 4.** Impact of young age on DFS and OS: summary of Hazard Ratio by Forest plot.

and 76% [95%IC 72.76–79.83] *versus* 86% [95%IC 84.81–86.59]; $p < 0.001$, respectively (Fig. 2). HR for continuous OS was unfavorable for ≤35 [1.76, 95%CI 1.43–2.17, $p < 0.001$] (Table 2, Fig. 3).

### 3.3. Prognostic value of age ≤35 - multivariate survival analysis

In a multivariate analysis including age, CT, ER, ET, grade, tumoral size, lymph node involvement, LVI, histological type, and period of diagnostic, age ≤35 was significantly associated with worse DFS [HR 1.56, 95%CI 1.32–1.84, $p < 0.001$] and OS [HR 1.29, 95%CI 1.03–1.60, $p = 0.025$] (Table 2, Fig. 3). Other independent prognostic factors were grade, tumor size, pN + macro, LVI, period after 1999, and ER-negativity (for OS only) (Table 3). In a multivariate analysis adjusted on all the previous variable and on molecular subtypes, independent negative value of age was maintained for DFS only but not OS (Supplementary Table 1).

### 3.4. Prognostic value of age ≤35 - matched population

In the 1 to 3 matched cohort (457 patients ≤35 for 1368 aged 36–50), Log-rank tests stratified on the pairs revealed a significant unfavorable impact of age ≤35 on survivals. 5- and 10-year DFS in ≤35 *versus* 36–50 were of 75% [95%IC 71.13–79.06] *versus* 85% [95%IC 83.36–86.64], and 60% [95%IC 55.20–64.20] *versus* 68% [95%IC 65.86–70.14], $p < 0.001$; 5- and 10-years OS were of 89% [95%IC 85.91–91.69] *versus* 92% [95%IC 91.18–93.62] and 76% [95%IC 71.77–79.63] *versus* 80% [95%IC 77.96–81.64], $p = 0.031$ (Fig. 4). HR for young age was 1.56 [95%CI 1.28–1.91; $p < 0.001$] for DFS and 1.33 [95%CI 1.02–1.73; $p = 0.032$] for OS (Table 2, Fig. 3).

### 3.5. Analyses focused on the ≤35 years cohort

The cohort of ≤35 years patients was analyzed according to ER status and molecular subtypes (Table 4). Among the 556 patients, 211

**Table 4**
Characteristics of ≤35 according to endocrine receptors and molecular subtype.

| ≤35 y CHARACTERISTICS | Total | ER- (n = 211) | | ER+ (n = 345) | | *p value* | Total | LumA (139) | | HER2+ [31] | | TN (61) | | LumB G3 (52) | | LumB HER2+ (46) | | *p value* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | | n | % | n | % | n | % | n | % | n | % | |
| Period | 556 | 211 | | 345 | | <0.001 | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | 0.048 |
| Before 2005 | | 156 | 74% | 178 | 52% | | | 45 | 32% | 10 | 32% | 32 | 52% | 21 | 40% | 13 | 28% | |
| After 2005 | | 55 | 26% | 167 | 48% | | | 94 | 68% | 21 | 68% | 29 | 48% | 31 | 60% | 33 | 72% | |
| Tumor size in mm | 542 | 208 | | 334 | | 0.799 | 321 | 133 | | 30 | | 61 | | 52 | | 45 | | 0.43 |
| ≤5 | | 16 | 8% | 22 | 7% | | | 9 | 7% | 4 | 13% | 6 | 10% | 4 | 8% | 2 | 4% | |
| 6 to 10 | | 29 | 14% | 54 | 16% | | | 24 | 18% | 5 | 17% | 5 | 8% | 4 | 8% | 9 | 20% | |
| 11 to 20 | | 92 | 44% | 138 | 41% | | | 60 | 45% | 13 | 43% | 26 | 43% | 22 | 42% | 15 | 33% | |
| >20 | | 71 | 34% | 120 | 36% | | | 40 | 30% | 8 | 27% | 24 | 39% | 22 | 42% | 19 | 42% | |
| Histological type | 556 | 211 | | 345 | | 0.075 | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | 0.084 |
| Ductal | | 184 | 87% | 309 | 90% | | | 119 | 86% | 31 | 100% | 53 | 87% | 49 | 94% | 45 | 98% | |
| Lobular | | 9 | 4% | 19 | 6% | | | 10 | 7% | 0 | 0% | 1 | 2% | 1 | 2% | 1 | 2% | |
| Mixed | | 1 | 0% | 5 | 1% | | | 4 | 3% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% | |
| Other | | 17 | 8% | 12 | 3% | | | 6 | 4% | 0 | 0% | 6 | 10% | 2 | 4% | 0 | 0% | |
| SBR grade | 527 | 194 | | 333 | | <0.001 | 323 | 137 | | 30 | | 58 | | 52 | | 46 | | <0.001 |
| 1 | | 18 | 9% | 42 | 13% | | | 30 | 22% | 1 | 3% | 6 | 10% | 0 | 0% | 1 | 2% | |
| 2 | | 55 | 28% | 185 | 56% | | | 107 | 78% | 12 | 40% | 7 | 12% | 0 | 0% | 20 | 43% | |
| 3 | | 121 | 62% | 106 | 32% | | | 0 | 0% | 17 | 57% | 45 | 78% | 52 | 100% | 25 | 54% | |
| Endocrine Receptor | 556 | 211 | | 345 | | | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | <0.001 |
| Negative | | 211 | 100% | 0 | 0% | | | 0 | 0% | 31 | 100% | 61 | 100% | 0 | 0% | 0 | 0% | |
| Positive | | 0 | 0% | 345 | 100% | | | 139 | 100% | 0 | 0% | 0 | 0% | 52 | 100% | 46 | 100% | |
| Estrogen receptor | 478 | 163 | | 315 | | <0.001 | 326 | 139 | | 30 | | 60 | | 51 | | 46 | | <0.001 |
| Negative | | 163 | 100% | 17 | 5% | | | 3 | 2% | 30 | 100% | 60 | 100% | 1 | 2% | 2 | 4% | |
| Positive | | 0 | 0% | 298 | 95% | | | 136 | 98% | 0 | 0% | 0 | 0% | 50 | 98% | 44 | 96% | |
| Progesterone receptor | 467 | 161 | | 306 | | <0.001 | 318 | 135 | | 30 | | 60 | | 48 | | 45 | | <0.001 |
| Negative | | 161 | 100% | 24 | 8% | | | 6 | 4% | 30 | 100% | 60 | 100% | 8 | 17% | 4 | 9% | |
| Positive | | 0 | 0% | 282 | 92% | | | 129 | 96% | 0 | 0% | 0 | 0% | 40 | 83% | 41 | 91% | |
| HER2 overexpressed | 329 | 92 | | 237 | | <0.001 | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | <0.001 |
| No | | 61 | 66% | 191 | 81% | | | 139 | 100% | 0 | 0% | 61 | 100% | 52 | 100% | 0 | 0% | |
| Yes | | 31 | 34% | 46 | 19% | | | 0 | 0% | 31 | 100% | 0 | 0% | 0 | 0% | 46 | 100% | |
| SLNB and/or ALND | 554 | 209 | | 345 | | <0.001 | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | 0.015 |
| SLNB | | 42 | 20% | 113 | 33% | | | 64 | 46% | 8 | 26% | 27 | 44% | 18 | 35% | 17 | 37% | |
| SLNB + ALND | | 35 | 17% | 117 | 34% | | | 60 | 43% | 14 | 45% | 16 | 26% | 20 | 38% | 21 | 46% | |
| ALND | | 132 | 63% | 115 | 33% | | | 15 | 11% | 9 | 29% | 18 | 30% | 14 | 27% | 8 | 17% | |
| Final lymph node status | 549 | 208 | | 341 | | 0.002 | 324 | 135 | | 31 | | 60 | | 52 | | 46 | | 0.018 |
| pN0 | | 117 | 56% | 158 | 46% | | | 69 | 51% | 13 | 42% | 35 | 58% | 19 | 37% | 23 | 50% | |
| pN0(i+) | | 4 | 2% | 19 | 6% | | | 10 | 7% | 1 | 3% | 2 | 3% | 5 | 10% | 1 | 2% | |
| pN1mi | | 5 | 2% | 30 | 9% | | | 20 | 15% | 3 | 10% | 2 | 3% | 1 | 2% | 5 | 11% | |
| pN1macro | | 82 | 39% | 134 | 39% | | | 36 | 27% | 14 | 45% | 21 | 35% | 27 | 52% | 17 | 37% | |
| LVI | 491 | 187 | | 304 | | 0.646 | 297 | 125 | | 27 | | 58 | | 47 | | 40 | | 0.268 |
| No | | 88 | 47% | 156 | 51% | | | 79 | 63% | 16 | 59% | 36 | 62% | 20 | 43% | 20 | 50% | |
| Yes | | 99 | 53% | 148 | 49% | | | 46 | 37% | 11 | 41% | 22 | 38% | 27 | 57% | 20 | 50% | |
| Surgery type | 548 | 209 | | 339 | | 0.002 | 322 | 137 | | 29 | | 61 | | 49 | | 46 | | 0.008 |
| Lumpectomy | | 162 | 78% | 215 | 63% | | | 71 | 52% | 14 | 48% | 43 | 70% | 29 | 59% | 34 | 74% | |
| Mastectomy | | 47 | 22% | 124 | 37% | | | 66 | 48% | 15 | 52% | 18 | 30% | 20 | 41% | 12 | 26% | |
| Adjuvant CT | 556 | 211 | | 345 | | 0.005 | 329 | 139 | | 31 | | 61 | | 52 | | 46 | | 0.001 |
| No | | 47 | 22% | 46 | 13% | | | 26 | 19% | 2 | 6% | 3 | 5% | 0 | 0% | 2 | 4% | |
| Yes | | 160 | 76% | 281 | 81% | | | 106 | 76% | 27 | 87% | 56 | 92% | 48 | 92% | 37 | 80% | |
| Neo-adjuvant | | 4 | 2% | 18 | 5% | | | 7 | 5% | 2 | 6% | 2 | 3% | 4 | 8% | 7 | 15% | |
| Trastuzumab | 536 | 206 | | 330 | | 0.163 | 308 | 125 | | 27 | | 60 | | 51 | | 45 | | <0.001 |
| No | | 188 | 91% | 291 | 88% | | | 125 | 100% | 10 | 37% | 60 | 100% | 51 | 100% | 9 | 20% | |
| Yes | | 18 | 9% | 39 | 12% | | | | | 17 | 63% | | | | | 36 | 80% | |
| RT | 539 | 203 | | 336 | | 0.575 | 315 | 135 | | 30 | | 55 | | 52 | | 43 | | 0.091 |

(*continued on next page*)

**Table 4** (*continued*)

| ≤35 y CHARACTERISTICS | | Total | ER- (n = 211) | | ER+ (n = 345) | | *p value* | Total | LumA (139) | | HER2+ [31] | | TN (61) | | LumB G3 (52) | | LumB HER2+ (46) | | *p value* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | | | n | % | n | % | n | % | n | % | n | % | |
| | No | | 13 | 6% | 27 | 8% | | | 18 | 13% | 5 | 17% | 5 | 9% | 5 | 10% | 1 | 2% | |
| | Yes | | 190 | 94% | 309 | 92% | | | 117 | 87% | 25 | 83% | 50 | 91% | 47 | 90% | 42 | 98% | |
| ET | | 547 | 202 | | 345 | | <0.001 | 326 | 139 | | 30 | | 59 | | 52 | | 46 | | <0.001 |
| | No | | 202 | 100% | 40 | 12% | | | 11 | 8% | 30 | 100% | 59 | 100% | 3 | 6% | 4 | 9% | |
| | Yes | | | | 305 | 88% | | | 128 | 92% | | | | | 49 | 94% | 42 | 91% | |
| Relapse type | | 187 | 88 | | 99 | | 0.08 | 81 | 24 | | 10 | | 16 | | 23 | | 8 | | 0.386 |
| | Axillary | | 1 | 1% | 5 | 5% | | | 1 | 4% | 1 | 10% | 0 | 0% | 1 | 4% | 1 | 13% | |
| | Metastatic | | 59 | 67% | 61 | 62% | | | 15 | 63% | 6 | 60% | 8 | 50% | 17 | 74% | 5 | 63% | |
| | Other | | 17 | 19% | 21 | 21% | | | 4 | 17% | 2 | 20% | 4 | 25% | 3 | 13% | 2 | 25% | |
| | Contro lateral | | 5 | 6% | 11 | 11% | | | 4 | 17% | 0 | 0% | 1 | 6% | 2 | 9% | 0 | 0% | |
| | Unknown | | 6 | 7% | 1 | 1% | | | 0 | 0% | 1 | 10% | 3 | 19% | 0 | 0% | 0 | 0% | |

presented ER- and 345 ER + tumors. Molecular subtype was available in 329 patients: 139 luminal-A; 31 HER2-positive; 61 triple-negative; 52 luminal-B HER2-negative; 46 luminal-B HER2-positive. Period of diagnostic, grade, HER2 status, lymph node treatment and status, surgery type, adjuvant CT, and ET, were significantly different according to ER status and molecular subtype.

ER-patients had more grade 3 (62% *versus* 32% in ER+), HER2+ (34% *versus* 19%), ALND (63% *versus* 33%), and pN0 (56% *versus* 46%). In the ER+, we observed more mastectomy (37% *versus* 22% in ER-) and adjuvant CT (81% *versus* 76%).

Triple-negative subgroup presented more grade 3 (78%), and CT use (92%). The luminal-B HER2-negative subgroup presents more pN + macro (52%), and LVI (57%).

In univariate analyses according to ER (Fig. 5), ER + group presented a better 5-year DFS [79%; 95%CI 75.40–82.20] and OS [94%; 95%CI 91.79–95.80] than 5-year DFS [67%; 95%CI 63.40–71.20] and OS [82%; 95%CI 78.91–85.29] in ER-group; $p = 0.002$ for DFS; $p < 0.001$ for OS.

In univariate analyses according to molecular subtype (Fig. 6), 5-year DFS were: 91% [95%CI 87.45–93.75] for luminal-A; 81% [95%CI 77.09–85.51] for luminal-B HER2-positive; 76% [95%CI 71.49–80.71] for triple-negative; 76% [95%CI 71.06–80.33] for HER2-positive; 63% [95%CI 58.09–68.51] for luminal-B HER2-negative; $p = 0.003$. The 5-year OS were: 98% [95%CI 96.62–99.57] for luminal-A; 98% [95%CI 96.08–99.32] for luminal-B HER2-positive; 89% [95%CI 85.39–92.21] for HER2-positive; 87% [95%CI 82.92–90.28] for triple-negative; 84% [95%CI 79.82–87.78] for luminal-B HER2-negative; $p < 0.001$.

In a new multivariate analysis based on the same parameters focused on ≤35 group, we observed a significative association with worse DFS and OS for pN + macro, ER-, LVI, and lobular type (for DFS only). SBR grade, ET, and adjuvant CT were not independently associated with survivals (Table 5).

## 4. Discussion

Our results support the poor prognosis value of young age, which persisted when adjusting for other prognostic factors and treatments, whether in multivariate or in matched populations.

Patients ≤35 had more severe tumor presentations and poorer survival than 36–50 patients. Young age was associated with larger tumors, higher grade, more LVI, ER-negativity, HER2-positivity, and macroscopic lymph node involvement. These unfavorable factors were associated with more aggressive treatment strategies, with higher rate of ALND, mastectomy, and systemic treatments. Tumor subtype was also affected by age category with more triple-negative (19%), luminal-B (30%) and HER2-positive (9%) tumors in the ≤35 cohort compared to the 36–50.

The literature review is challenged by the lack of homogeneity in the definition of "young woman" in previous studies dealing with the clinicopathological and molecular characteristics of BC. Some of the articles define young age as <35 years, while others focus on women <40 years. As for the control group, the challenge was to select an older group which was comparable regarding menopausal status. The upper boundary of 50 years was retained as estimated median age at menopause are 50.31 and 51.5 years in large historical retrospective and prospective cohorts [14,15]. Data on CT-induced amenorrhea or perimenopausal status were not known. Our observations are consistent with previous studies supporting the association of young age with unfavorable prognostic factors at presentation such as larger tumor size [16–19], increased macroscopic lymph node involvement [17–19], increased LVI-positivity [18,20], grade 3 [16–19], ER-negativity [17,18], as well as more aggressive treatments [17,21–23]. In our study, HER2 overexpression was more prevalent in young patients (23% *versus* 11%), consistently with previous reports. Cancello et al. reported HER2-positivity in 21% oy young patients *versus* 14% in older ($p < 0.003$) [18], Anders et al. reported 29% of HER2-positivity in women

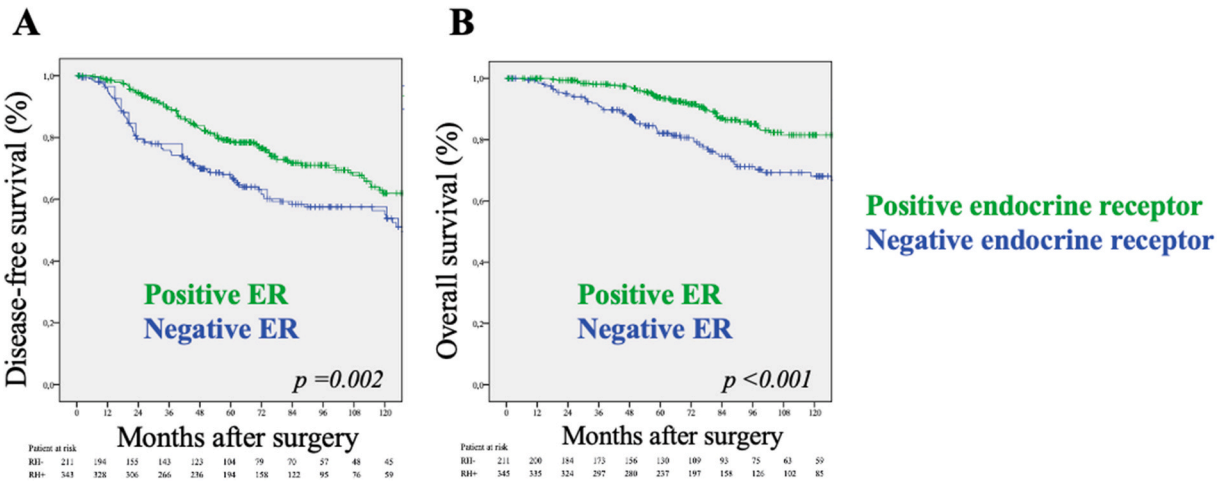


**Fig. 5.** Kaplan Meier of univariate analysis of DFS (A) and OS (B) in the <35 cohort according to endocrine receptors.

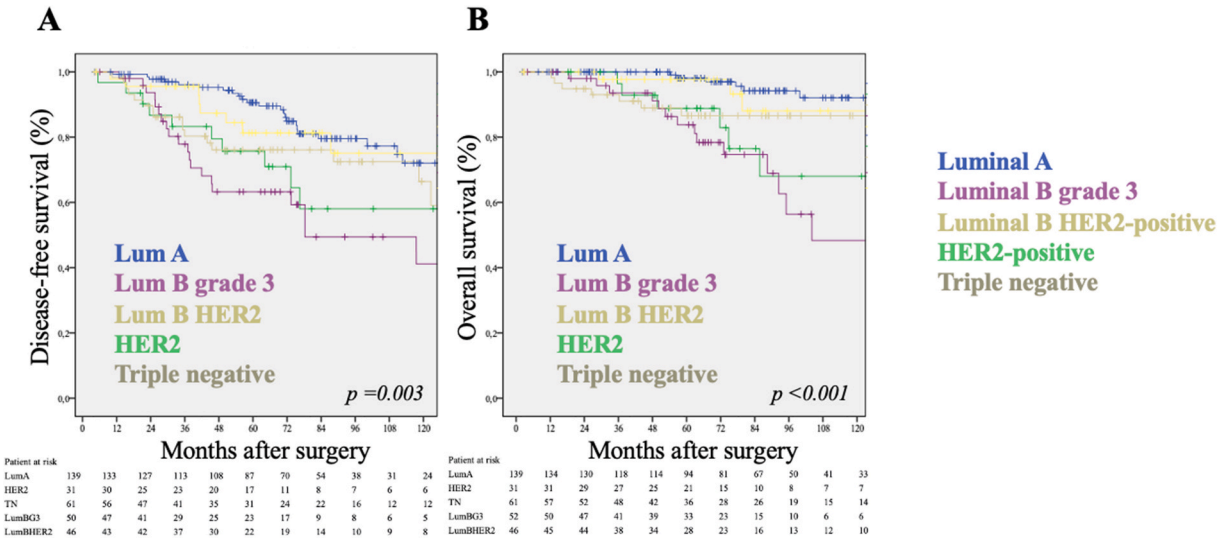


**Fig. 6.** Kaplan Meier of univariate analysis of DFS (A) and OS (B) in the <35 cohort according to molecular subtype.

<40 years *versus* 22% in patients ≤45 years and only 14% in those ≥65 years (Duke dataset) [24]. Similar findings were reported by Kim et al. with a 10% positivity rate in women ≤40 years *versus* 7% in older women *(p < 0.004)* [25]. The distribution of BC subtypes in our study is also consistent with previous reports with respectively 23% and 18% [26], and 21% and 25% [27] of triple-negative and luminal-B in young women.

DFS and OS were negatively impacted by young age. The 5-years DFS and OS in the ≤35 cohort (74% and 89%, respectively) were close to the 10-years DFS and OS in the 36–50 patients (74% and 85%, respectively). In multivariate analyses, age ≤35 was associated to worse DFS (HR1.56; *p < 0.001*) and OS (HR1.29; *p = 0.025*), as well as in the case-control matched analysis (DFS (HR1.56; *p < 0.001*) and OS (HR1.33; *p = 0.032*)). Consistently, recent periods were associated with better survival, reflecting advances in BC management. In our multivariate analysis including molecular subtypes, independent value of age was only maintained for DFS but not for OS, probably because of the loss of power. The negative impact of young age is consistent with other studies where patients <35 present worse survival, even after adjustment on tumor characteristics and treatments. The largest series to date is derived from a Japanese registry of women treated from 2004 to 2006, confirming the prognostic impact of age (<35 (n = 736) *versus* 35–50 *versus* >50 years) to the disadvantage of younger patients for both DFS (HR1.73; *p < 0.001*) and OS (HR 1.58; *p = 0.004*) [28]. Kroman et al. included 867 patients <35 years [19]. In the absence of adjuvant therapy, younger age was correlated with a higher risk of death with a relative risk of 2.18 compared to patients aged 45–49 years. To be noted that in this series the negative impact disappeared in case of adjuvant CT. Consistently, Peng et al. describes worse DFS than in older patients, even after adjustment on tumor characteristics and treatments (HR1.64, *p < 0.001*) [29]. Early stages and small tumors, where treatment can be discussed, were associated with decreased survival [16]. Age ≤35 could even be considered by some authors as the second most powerful independent risk factor after lymph node status [30,31]. As in a similar study using a propensity score on 365 women ≤40 years [32], we can consider age ≤35 as an independent factor of poor prognosis in early BC. Altogether, the negative prognostic role of young age is confirmed in multivariate analysis in most studies. These conclusions are discordant with latest ESMO's recommendations [7], and should be considered in the decision making for therapeutical strategies in young patients.

Our analyses focusing on the ≤35 years cohort identified ER-negativity, lymph node involvement, LVI and lobular type as independent prognostic factors, consistently with previous reports [33–36]. Lobular type was associated with worse DFS but had no impact on OS in the ≤35 cohort, possibly explained by the high rate of local recurrence [37]. As previously reported, lobular subtype was less frequent in young

**Table 5**
Multivariate analysis of DFS and OS in the ≤35 cohort.

| | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| ≤35 ONLY | HR | 95% CI | | *p value* | HR | 95% CI | | *p value* |
| | | min | max | | | min | max | |
| CT | | | | | | | | |
| No | Reference category | | | | Reference category | | | |
| Adjuvant | 0,71 | 0,46 | 1,11 | 0,136 | 0,59 | 0,32 | 1,08 | 0,085 |
| Neo-adjuvant | 0,35 | 0,12 | 1,05 | 0,062 | 0,41 | 0,11 | 1,56 | 0,192 |
| ER | 0,50 | 0,28 | 0,89 | 0,019 | 0,45 | 0,22 | 0,92 | 0,029 |
| ET | 0,21 | 0,69 | 2,21 | 0,476 | 0,91 | 0,44 | 1,87 | 0,796 |
| SBR grade | | | | | | | | |
| 1 | Reference category | | | | Reference category | | | |
| 2 | 1,30 | 0,72 | 2,35 | 0,383 | 1,41 | 0,59 | 3,39 | 0,445 |
| 3 | 1,27 | 0,69 | 2,34 | 0,448 | 1,77 | 0,73 | 4,28 | 0,205 |
| Size (mm) | | | | | | | | |
| ≤5 | Reference category | | | | Reference category | | | |
| 5 to 10 | 0,34 | 0,15 | 0,75 | 0,008 | 0,18 | 0,06 | 0,58 | 0,004 |
| 10 to 20 | 0,59 | 0,29 | 1,20 | 0,146 | 0,37 | 0,14 | 0,96 | 0,041 |
| 20 to 50 | 0,69 | 0,34 | 1,37 | 0,287 | 0,63 | 0,25 | 1,55 | 0,310 |
| >50 | 1,07 | 0,45 | 2,56 | 0,881 | 0,70 | 0,22 | 2,19 | 0,538 |
| Lymph node involvement | | | | | | | | |
| pN0 | Reference category | | | | Reference category | | | |
| pN0(i+) | 1,01 | 0,40 | 2,56 | 0,976 | 0,92 | 0,21 | 3,93 | 0,909 |
| pN + mi | 0,52 | 0,20 | 1,31 | 0,165 | 0,60 | 0,14 | 2,60 | 0,497 |
| pN + macro | 1,54 | 1,07 | 2,20 | 0,019 | 1,91 | 1,16 | 3,14 | 0,011 |
| LVI | | | | | | | | |
| No | Reference category | | | | Reference category | | | |
| Yes | 1,66 | 1,16 | 2,38 | 0,005 | 2,21 | 1,32 | 3,69 | 0,003 |
| Unknown | 1,77 | 1,07 | 2,94 | 0,027 | 1,75 | 0,85 | 3,59 | 0,130 |
| Histological type | | | | | | | | |
| Ductal | Reference category | | | | Reference category | | | |
| Lobular | 3,48 | 1,89 | 6,39 | <0.001 | 2,20 | 0,84 | 5,75 | 0,107 |
| Mixed | 0,00 | 0,00 | 0,00 | 0,952 | 0,00 | 0,00 | 0,00 | 0,967 |
| Others | 0,82 | 0,35 | 1,90 | 0,643 | 0,61 | 0,14 | 2,54 | 0,495 |

patients [6,18]. Multivariate analysis showed peculiarly that grade, ET, and adjuvant CT were not significantly associated with survival. This might be linked to a lack of power, limited follow up, as well as poorer compliance with ET in younger women [38]. The most unfavorable subtypes in our analysis were luminal-B HER2-negative and triple-negative BC. In this situation, grade may predominate over ER and HER2.

Our study has limitations. Among them, absence of BRCA status is a key. Approximately 12% of BC arising in women aged ≤40 years are related to germline pathogenic variants in BRCA1 or BRCA2 gene [39,40]. BRCA-related BC may have different biological characteristics, with increased triple-negative subtype in BRCA1 carriers and more luminal subtypes in BRCA2 carriers [41]. The detail about precise chemotherapy regimen for each patient was not available in our database. Patients were treated at 15 centers and adjuvant treatments may have differed. However, this multicenter cohort reflects clinical reality out of clinical trials. Despite careful methodology to minimize bias, the second major limitation of our study is its retrospective design. However, we have the advantages of limiting biases inherent in single-center studies while also reflecting real-world practice.

## 5. Conclusion

Our results support the independent poor prognosis value of young age, which persisted when adjusting for other prognostic factors and treatments. Early BC in young patients ≤35 years old is associated with less favorable presentation and more aggressive treatment strategies. Luminal-B, triple-negative and HER2-positive subtypes are over-represented compared to luminal-A.

## Ethics approval

This cohort study was approved by our institutional review board. All procedures performed in this study involving human participants were done in accordance with the French ethical standards and with the 2008 Helsinki declaration.

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## Declaration of competing interest

Alexandre de Nonneville declares Gilead (lecture fees, congress invitations), Daiichi Sankyo (lecture fees, congress invitations), Seagen (consulting fees), Lilly (lecture fees, congress invitations, consulting fees, research grants paid to institution), Novartis (consulting fees), MSD (congress invitations, lecture fees), Pfizer (research grants paid to institution). No conflict of interest declared by others authors.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.02.004.

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