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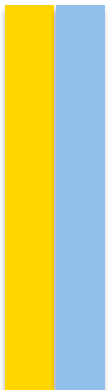
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Breast cancer in young women: what are the differences in diagnosis, treatment and outcome?

Joana Vanessa Pinto da Silva

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Porto, Junho de 2025

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Mestrado Integrado em Medicina

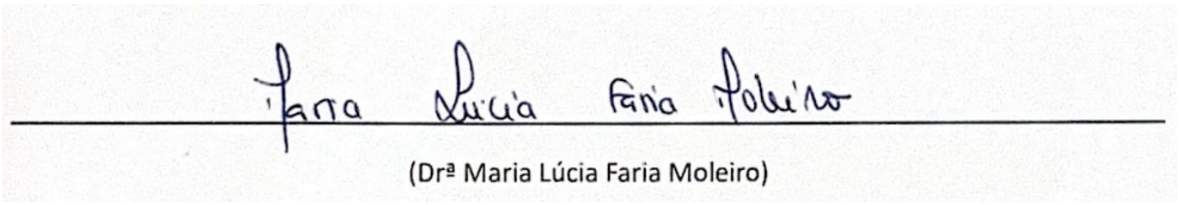
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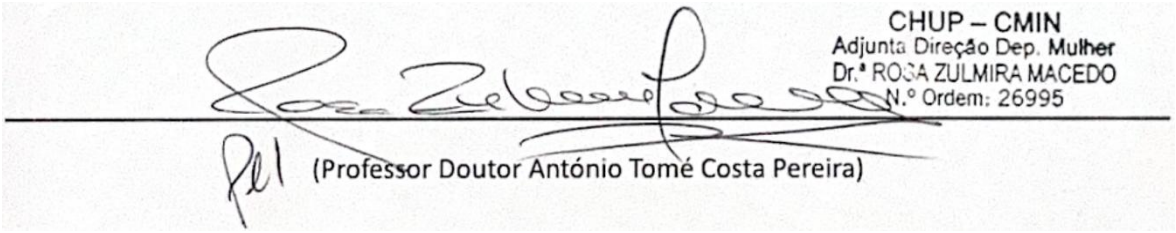
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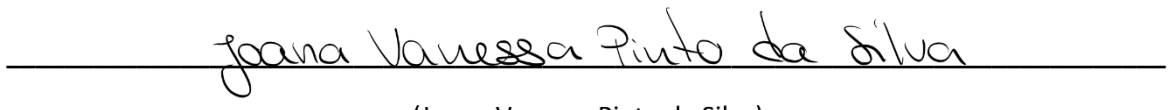
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Declaration of Scientific Integrity

I, Joana Vanessa Pinto da Silva, a student in the Integrated Master's Program in Medicine at the Faculty of Medicine and Biomedical Sciences, University of Porto, hereby affirm that the present dissertation represents the result of my individual academic work and reflects my original research efforts, critical analysis, and interpretation.

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"Nothing is so painful to the human mind

as a great and sudden change."

Mary Shelley, *Frankenstein*

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Resumo

Introdução: O cancro da mama em mulheres jovens representa um desafio clínico único. Por um lado, apresenta características biológicas distintas e um diagnóstico frequentemente tardio; por outro, tem um forte impacto nas esferas reprodutiva e psicossocial. Este estudo teve como objetivo avaliar e comparar as características clínicas, patológicas e terapêuticas do cancro da mama em mulheres com menos de 50 anos, com foco nas diferenças entre os grupos etários ≤40 e 41–49 anos.

Métodos: Realizou-se um estudo retrospetivo envolvendo 327 doentes do sexo feminino diagnosticadas com cancro da mama antes dos 50 anos, e tratadas, entre janeiro de 2014 e dezembro de 2023, num centro hospitalar terciário português (Unidade Local de Saúde de Santo António). Foram recolhidos e analisados dados clínicos, demográficos, patológicos e terapêuticos, dividindo-se as pacientes em dois grupos etários (≤40 vs. 41–49 anos). A análise descritiva e comparativa foi realizada através do SPSS, com recurso ao teste *t de Student*, ao teste de *Mann-Whitney U* e ao teste do qui-quadrado, considerando-se significativo um valor de $p < 0,05$.

Resultados: Do total da amostra, 28,1% (n=92) das doentes tinham ≤40 anos. Os fatores de risco que mostraram diferenças estatisticamente significativas foram os IMC, o número de gestações / partos e consumo de álcool (todos superiores no grupo 41–49 anos). As mulheres mais jovens apresentaram uma taxa significativamente superior de tumores clinicamente detetáveis (78,3% vs. 57,0%), menor taxa de estadio tumoral clínico inicial ao diagnóstico (cT1: 31,2% vs. 41,3%) e indicação para tratamento sistémico neoadjuvante (52,2% vs. 29,8%). Verificaram-se também características tumorais mais agressivas, incluindo maior grau histológico (Grau III: 47,3% vs. 38,3%), índice de proliferação Ki-67 >30% (54,3% vs. 37,4%) e sobre-expressão de HER2 (31,6% vs. 14,9%). A expressão de recetores hormonais foi significativamente inferior no grupo mais jovem, tanto para o recetor de estrogénio, como para o recetor de progesterona. A realização de testes genéticos revelou uma prevalência superior de mutações patogénicas no grupo ≤40 anos (24,0% vs. 12,8%), sendo a BRCA2 a mais frequente. A referenciação para consulta de preservação da fertilidade nas mulheres jovens foi relativamente baixa (38%). No contexto da mastectomia, a reconstrução mamária primária foi realizada na maioria dos casos em ambos os grupos; no entanto, o uso de implantes foi mais frequente nas mulheres mais velhas (58,1% vs. 38,1%), enquanto as mais jovens recorreram mais frequentemente a expansores (33,3% vs. 14,5%), uma diferença estatisticamente significativa. A taxa de recidiva foi ligeiramente superior no grupo ≤40 (10,0% vs. 8,3%), embora essa diferença não tenha sido estatisticamente significativa.

Conclusão: As mulheres jovens com cancro da mama apresentam tumores com características mais agressivas, enfrentam desafios reprodutivos específicos e requerem estratégias terapêuticas e de acompanhamento adaptadas à sua faixa etária. Estes resultados reforçam a importância de abordagens diferenciadas, diagnóstico precoce, aconselhamento genético abrangente, preservação da fertilidade e planeamento do seguimento em sobreviventes.

Palavras-chave: Cancro da mama; Tumores mamários; Rastreio oncológico; Mulheres jovens; Mulheres pré-menopáusicas; Preservação da fertilidade

Abstract

Introduction: Breast cancer (BC) in young women represents a unique clinical challenge due to its distinct biological features, delayed diagnosis, and impact on reproductive and psychosocial health. This study aimed to evaluate and compare the clinical, pathological, and treatment characteristics of BC in women under 50 years old, focusing on differences between those aged ≤40 and 41–49.

Methods: We conducted a retrospective study of 327 female patients diagnosed with BC under the age of 50, and treated, at a Portuguese tertiary care center (Santo António University Hospital), between January 2014 and December 2023. Clinical, demographic, pathological, and treatment-related data were collected and analyzed, with patients divided into two age groups (≤40 vs. 41–49 years). Descriptive and comparative analysis was performed in SPSS, using Student's t-test, Mann-Whitney U test and Chi-square test, with $p < 0.05$ considered statistically significant.

Results: Among the total sample, 28.1% (n=92) of the patients were aged ≤40. BC risk factors that had statistically significant differences were BMI, number of gestations / parity and alcohol consumption (all superior in the 41–49 years old group). Younger women had a significantly higher rate of clinically detected tumors (78.3% vs. 57.0%), lower rate of small clinical tumor staging (cT1: 31.2% vs. 41.3%), and more indication for neoadjuvant systemic therapy (52.2% vs. 29.8%). They also showed significantly more aggressive tumor characteristics, including higher histologic grade (Grade III: 47.3% vs. 38.3%), elevated Ki-67 index >30% (54.3% vs. 37.4%), and increased HER2 overexpression (31.6% vs. 14.9%). Hormone receptor positivity was significantly lower in the younger group for both estrogen receptor (ER) and progesterone receptor (PR) expression. Genetic testing revealed a higher prevalence of pathogenic mutations in women ≤40 (24.0% vs. 12.8%), with BRCA2 being the most frequent. Counseling for fertility preservation was comparatively low among the younger group (38.0%). In the mastectomy setting, both groups underwent primary reconstruction in most cases; however, implant-based reconstruction was more frequent in the older group (58.1% vs. 38.1%), while younger patients received tissue expanders more often (33.3% vs. 14.5%), a statistically significant difference. Recurrence rates were slightly higher in the ≤40 group (10.0% vs. 8.3%), but it was not statistically significant.

Conclusion: Young women with breast cancer display more aggressive tumor characteristics, face unique reproductive challenges, and require distinct treatment and support strategies. These findings highlight the need for age-specific care approaches and reinforce the importance of early diagnosis, comprehensive genetic counseling, fertility preservation, and survivorship planning in this population.

Keywords: Breast cancer; Breast tumors; Cancer screening; Young women; Premenopausal women; Fertility preservation; Age-related oncology

Abbreviations

BC – Breast cancer

BMI – Body mass index

ER – Estrogen receptor

ESMO – European Society of Medical Oncology

HER2 – Human Epidermal Growth Factor Receptor-type 2

IARC – Agency for Research on Cancer

PR – Progesterone receptor

ULSSA – Santo António University Hospital

WHO – World Health Organization

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INTRODUCTION

As reported by the World Health Organization (WHO), in 2022, breast cancer (BC) ranked as the second most prevalent cancer type after lung cancer. However, it continues to be the most frequently diagnosed cancer in women and remains the leading cause of cancer-related deaths, as well as the fourth most common cause of death overall.[1] A recent analysis by the International Agency for Research on Cancer (IARC) suggests that one in every 20 women will face a BC diagnosis during their lifetime. Furthermore, should existing trends continue, it is estimated that by the year 2050, there will be 3.2 million new cases of BC and 1.1 million associated fatalities annually.[1]

While the majority of BC cases and deaths worldwide occur in individuals aged 50 and older, a noteworthy portion involves younger women, and this trend appears to be rising in recent years. In Europe, about 19% of new BC cases are diagnosed in women under 50. Although the death rate from BC among younger women is lower than the incidence rate, it remains around 8%.[1]

Depending on different studies, consensus guidelines and review articles, there are various ways to divide age groups: a number of them consider early onset BC as before age 40, others as before age 35, while some others further subdivide pre-menopausal women into those with very-early onset disease (before age 40) and relatively early onset disease (40 to 49 years of age). [2–7] In this study, we will use the European Society of Medical Oncology (ESMO) consensus definition of "young women" as women under the age of 40 years at BC diagnosis. This definition is important because many BC characteristics seem to be different in this young group.[3,7]

Approximately 70 to 80% of early-stage, non-metastatic breast cancers can be cured.[8] This highlights the significance of BC screening. However, healthy young women at average risk for BC are generally not considered candidates for routine screening using imaging techniques. Consequently, many young women are often diagnosed only after experiencing breast issues or other symptoms that necessitate mammography.[9] Mammography is the standard test, but its sensitivity is lower in young women due to their higher breast density.[10–12] In contrast, breast ultrasounds can serve as a more sensitive diagnostic tool, with the additional advantage of distinguishing solid masses from both simple and complex cysts.[13]

Numerous modifiable risk factors have been extensively documented, encompassing lifestyle risk factors (i.e., physical activity, body mass index (BMI), smoking and alcohol consumption), reproductive and hormonal risk factors (i.e., number and age at pregnancies, breastfeeding and hormonal therapy) and even iatrogenic risk factors (i.e. radiation exposure).[14,15] While most cases of BC are sporadic, 5 to 10% of all BC cases are associated with family history and genetic predisposition.[16] Moreover, among women younger than 30, this proportion can escalate to 25%, with the BRCA1 and BRCA2 genes identified as the most significant ones contributing to heightened susceptibility.[16]

Some studies have indicated that distinct differences exist among various age groups concerning certain modifiable risk factors. While delayed childbirth (after the age of 30 years) is known to be a risk factor for BC in women above 35 years old, it seems that early childbirth constitutes a risk factor for BC in women younger than 35 years. A similar assertion applies to multiparity, which is known to serve as a protective factor in postmenopausal women; however, it puts women of childbearing age at risk due to the transient increase in risk in the following months post-partum.[17–20] Additionally, obesity is a well-established risk factor for BC. Nonetheless, several studies have

identified an inverse relationship between BMI and the development of BC in premenopausal women, with lean young women exhibiting a higher incidence of BC. Despite this, a high BMI remains significantly associated with an increased risk of inflammatory breast cancer, the most lethal type of BC, irrespective of age group.[21–23]

Concerning tumor characteristics, discernible differences are also evident. Young women more frequently exhibit BC with aggressive clinicopathological features, including higher grade tumors, larger tumor size, poor tumor differentiation, an increased proportion of triple negative phenotypes, Human Epidermal growth factor Receptor-type 2 (HER2) positive tumors, augmented Ki-67 expression and more extensive lymph node involvement contrasted to older women.[12,24–26]

Regarding treatment options and outcomes, there exists a deficit of age-specific clinical characteristics or data pertaining to younger women, as most of the standard treatments have been tested predominantly in older patients. The options for local therapy include mastectomy or breast-conserving surgery, which may subsequently be followed by radiation therapy. As observed in older women, factors influencing surgical decisions encompass tumor size, tumor location, the potential to achieve a favorable cosmetic outcome, previous radiation exposure, or any contraindication to radiation, as well as patient preference. Nonetheless, younger women generally exhibit higher local recurrence rates in comparison to older counterparts when subjected to breast-conserving surgery.[27,28] In light of this, in addition to appropriate radiotherapy, adjuvant therapy with chemotherapy and/or hormonal therapy should be strongly considered in young women.[29,30]

Evidence indicates that young age constitutes an independent prognostic factor for survival in BC.[31] Moreover, various large-scale studies demonstrate that young age at diagnosis is strongly correlated with a significantly increased risk of recurrence and mortality.[32,33] Collectively, these factors result in young women with BC experiencing poorer prognosis and outcomes.[30,33]

Additionally, breast cancer in young women demands focused attention because of its distinct morphologic and prognostic features, as well as other unique considerations such as fertility. While a BC diagnosis can be profoundly distressing for women across all age demographics, it is particularly challenging for younger women, as it introduces a variety of unique psychological and emotional challenges. These challenges encompass, but are not limited to, everyday interactions with spouses and children, disturbances in body image and sexuality, premature menopause, and loss of fertility.[34,35] For this reason, treatment planning for young women should also incorporate personalized psychological support and genetic counseling.[12,36,37]

Considering this, the objective of this study was to analyze the population of BC patients under the age of 50 years at our hospital to determine whether differences exist between women aged 41-50 and those younger.

METHODS

Study Population

The study population of this retrospective study consists of BC cancer patients under 50 years old who were diagnosed and/or treated in Santo António University Hospital's (ULSSA) Breast Unit, in a 10-year interval, corresponding to the period between January 2014 and December 2023. The study population comprised 376 female patients diagnosed with BC. Out of these, 22 patients were excluded, as they were lost to follow-up or chose to be treated in a different Center after being diagnosed at our hospital, while 11 were also excluded because they had a diagnosis and initial treatment conducted at another Hospital. Additionally, 11 patients were excluded due to bilateral carcinomas, 3 due to breast metastasis from a primary tumor of another location, and 2 were excluded due to a final diagnosis of borderline phyllodes tumor. Therefore, a total of 49 patients were excluded, and the final study population consisted of 327 BC patients (Figure 1).

Data Collection

Clinical and demographic data were obtained through review of ULSSA's electronic medical records. A structured database was created to record all collected variables, bearing in mind patient anonymization.

We have collected demographic characteristics, such as age at diagnosis and BMI; and gynecological and obstetric history such as age at menarche, number of gestations, number of births, and age at first childbirth, breastfeeding history (if applicable), use of hormonal contraception (type and duration); as well as lifestyle characteristics such as alcohol consumption and smoking history.

Concerning clinical information, we have collected data such as personal history of breast pathology; family history of breast cancer (including age of onset in family members), and ovarian cancer; reasons for initial consultation (symptoms, altered imaging exam, family history or known mutation); time from symptoms/signs onset to consultation/exams, and type of breast lesion (infraclinical or clinical).

Regarding tumor characteristics, anatomopathological reports of the biopsy performed at the time of diagnosis, as well as the radiological reports were evaluated in order to collect the type of neoplasm, histological subtype, tumor grade, and tumor size; clinical tumor stage (according to the AJCC Cancer Staging Manual, Eighth Edition[38]); and estrogen receptor (ER) status, progesterone receptor (PR) status, and HER-2 status, as well as Ki-67 expression.

Additionally, we have reviewed data about the management after diagnosis (evaluation for fertility preservation, for women under 40 years; and genetic consultation), and chosen treatment modality (surgery, neoadjuvant systemic treatment, or palliative care). When surgery was performed, the type of primary surgical treatment (conservative surgery or mastectomy), breast reconstruction, axillary surgery, and adjuvant treatment type were noted.

Information about follow-up and outcomes was also gathered, including the existence of recurrence and time to recurrence, pregnancy after diagnosis, delivery of live birth, and breastfeeding after diagnosis.

Statistical Methods

Data analysis was performed using IBM SPSS Statistics 29 software for Windows (IBM SPSS, Armonk, NY, USA). Descriptive statistics were employed to summarize the data, including means, medians, minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables.

Patients were divided into two age groups (older than 40 years old and younger than 50 *versus* 40 years old or younger), and these groups were compared. The Kolmogorov-Smirnov test was used to evaluate normal distribution. Comparison between groups was performed according to the type of variable. For continuous variables, the Independent Samples T-test and Mann-Whitney tests were used according to whether normal distribution was verified; for categorical variables, the Chi-square test for independence was used. It was assumed to have a 95% confidence interval and a significant difference if the p-value was less than 0.05.

The primary goals of this study were to understand, first, if there were significant differences in how the diagnosis was achieved, and second, to notice significant differences in cancer type and stage at diagnosis. Other data was also compared and are also presented, trying to help the current understanding of breast cancer in young women.

Ethical Considerations

This study was approved by the local Ethics Committee. Furthermore, a full waiver of consent was requested and promptly accepted, considering that data was to be collected without the patients' knowledge. To ensure anonymity, in the database, patients were identified by a randomly selected number ranging from 1 to 376, without any correlation to personal data or sensitive information. Any registry of identification numbers used to access the clinical records of the selected patients or any other sensitive information that could potentially identify patients was permanently eliminated upon data entry completion.

RESULTS

General Patient Characteristics

During the 10-year interval studied, from the 1610 breast cancers diagnosed and treated in the ULSSA's Breast Unit, 327 female patients met the inclusion criteria: 235 women aged 41–49 years (included in Group 1; n=235) and 92 women aged ≤40 years (included in Group 2; n=92). For simplicity reasons, throughout this study, the 41–49 years group will sometimes be mentioned as Group 1 (G1) or older patients' group, while the ≤40 years group will be mentioned as Group 2 (G2) or younger patients' group.

All patients were female and, at the time of the data retrieval, 21 of them had passed away during follow-up, accounting to 6.4% of the total study population. Of those deaths, 14 were in G1 and 7 belonged to G2 (7.6% of this group vs. 5.9% of G1).

Global patient characteristics in both groups are presented in Table I, as well as p-values obtained from the group's comparison.

The number of diagnosed BC in women younger than 50 was not homogeneous during the studied period, 2020 being the year with the most cases in general (n=44), as well as the biggest number of cases in young women (n=23) (Figure 2).

The mean age at diagnosis was 45.5 years for the older group and 35.9 years for the younger group, while the median age at diagnosis was 46 years and 37 years, respectively. The younger patient in the ≤40 years group was 24 at the diagnosis.

BMI showed a mean of 25.72 Kg/m^2 [17.1-40.57Kg/m^2] in the 41–49 age group, while the ≤40 age group presented a mean of 24.43 Kg/m^2 [17.18-46.28 Kg/m^2]. The comparison between groups found that this difference was significant (p-value = 0,015).

A minority of women in the two study groups were outlined as being smokers (25.00% in G1 and 18.70% in G2). When it comes to alcohol consumption, 13.80% of the older patients were reported as consumers, while 3.30% of the younger patients met the same criteria, a difference found to be significant (p-value = 0,005).

Gynecological and Obstetric History

Data from gynecological and obstetric history can be found in Table I. The mean number of gestations was 1.8 in the 41–49 age group, with a maximum number of 10 gestations in this group, while in the ≤40 age group the mean corresponded to 1.3 and the maximum to 5. Concerning the number of births, the average in G1 is 1.4 with a maximum of 5 births, and in G2 the mean and maximum are 1.1 and 3, respectively. Nulliparity was present in 31% of the G2 patients compared to 15.3% of the G1 group. Differences in these variables were all considered significant.

In the women older than 40 years, the mean age at first childbirth was 27.9 years and 27.1 years for the women aged 40 or younger. When it comes to breastfeeding, 87.8% of the women in the first group who had children reported having breastfed, compared to compared to 84.1% in the second group.

While 69.7% of patients of older age group had used hormonal contraception, 78.3% of the younger cohort reported the same. Among those who used hormonal contraception, the combined pill was

the most common type, used by 90.10% of women in G1 and 80.80% in G2. In both groups, it was reported that most patients used hormonal contraception for a period of five years or longer (83.90% in G1 and 78.10% in G2).

Previous Personal and Familial History

The personal history of breast pathology was found to be significant between the two groups. While in G1 cysts (14.50%) were predominant, in G2 the fibroadenoma (16.30%) was the most prevalent. However, 69.80% of patients in the first group and 73.90% of the second denied personal history of benign breast disease.

A family history of BC was reported in 30.6% of the 41–49 age group, with 30,6% of patients in this group having one direct relative diagnosed with BC, 10.4% having two direct relatives, and 3.0% having 3 or more direct relatives with this neoplasm. Additionally, 16,3% of the patients had a positive family history for BC before age 50, and 5.2% presented a positive family history for ovarian cancer. In the ≤40 group, a family history of BC was reported in 39.6% of the patients, with 26.4% having one case of BC in a direct relative, 9.9% having two diagnosed direct relatives, and 3.3% having at least 3 relatives. Furthermore, 19.1% of patients reported family history of BC before age 50, and 6,5% had cases of ovarian cancer in the family.

These results about familial history did not reach a statistically significant difference and are presented in Table II.

Tumor Presentation

The presenting symptoms/signs reported at diagnosis were statistically significative different between groups (Table III). The leading reason for initial consultation was a combination of symptoms and abnormal imaging, reported by 45.1% in G1 and 68.5% in G2. Only one patient, belonging to the ≤40 group, was directed to a consultation in the Breast Unit due to a known mutation. The most common breast complaint at the initial consultation, across both groups, was a palpable breast mass (38.50% in G1 and 54.30% in G2). However, most patients of G1 (43.6%) did not present with any complaints or symptoms as of the first consultation. The mean time from symptoms to initial consultation or realization of the first exam was 14.3 weeks in the 41–49 group and 18.2 weeks in the ≤40 group, which was not statistically significant.

Most of the time, BC manifested as a clinical lesion in both groups. However, whilst in G1 the difference between the proportion of clinical (57.0%) and infraclinical lesions (43.0%) was of 10.0%, but, when it comes to G2, this difference was substantially more statistically significant (78.3% versus 21.7%), corresponding to 56.6%.

Tumor Characteristics

Invasive carcinoma was the predominant type of neoplasm in both groups (87.20% G1 and 87.00% in G2) and ductal carcinoma was the most common histological subtype (84.60% in G1 and 89.00% in G2). While grade 2 tumors were the most common in G1 (45.40%), grade three took first place in G2 (47.30%). In situ carcinomas represented 12,8 and 13% of the cases in G1 and G2, respectively.

The global mean tumor size was 28.8 mm and 31.4 mm for the 41–49 and ≤40 age groups, respectively. It was verified that, across both groups, tumors *in situ* presented on average with a

larger size (35.5mm in G1 and 33.2mm in G2) than invasive carcinoma (27.7mm in G1 and 31.1mm in G2).

When considering clinical staging of invasive tumors, the most frequently diagnosed tumors were cT2 in both groups (41.70% in G1 and 48.80% in G2), followed by cT1c (31.90% in G1 and 30.00% in G2) (Figure 3). The least identified tumors in the older group were cT1a (0.50%), while in the younger group, no cT1b tumors were identified. Additionally, 31 tumors *in situ* were diagnosed in the first group, while 12 were detected in the second group. These data comparisons were statistically significant.

Molecular tumor characteristics also presented significant differences between groups. Estrogen receptor positivity was high in both groups, with G1 exhibiting 86.6% ER-positive BC for invasive carcinomas and 93.5% for tumors *in situ*, and G2 showing 76.2% for invasive BC and 91.7% for *in situ* tumors. A similar pattern was observed regarding PR positivity, although these results did not achieve a significant difference (78.2% of invasive BC and 58.1% of tumors in situ in G1, along with 67.5% and 63.6% of invasive and in situ carcinomas, respectively, in G2 expressed PR). Concerning HER-2 status, even though both age groups presented with a majority of HER-2 negativity, a greater percentage of patients in the 41–49 group (85.1%) expressed this characteristic when compared to the ≤40 group (68.4%). A noteworthy statistical difference between G1 and G2 was equally verified in terms of Ki-67 expression. In the older group, 43.6% expressed this protein marker in an index between 10-30%, while the younger one exhibited an overexpression of Ki-67, with 54.3% of cases with an index of >30%.

When comparing clinical tumor stage, according to the AJCC Cancer Staging Manual, Eighth Edition [38], in both groups, a preponderance of BC cases were diagnosed at an early stage. In the older age group, 35.3% of patients presented with stage IA and 22.1% with stage IB, and in the younger age group, 27.5% and 18.8% of women presented with stage IA and IB, respectively. Stage IV was observed in 15 older patients and in 9 younger patients (representing 7.4% and 11.3% of each group).

All of the aforementioned data is presented in Tables IV, V and VI.

Treatment, Follow-up and Outcomes

The prevalent chosen primary treatment modality in the older age group was surgery (67.7%), while in the younger women, neoadjuvant systemic therapy (52.2%) took precedence. Palliative care was a frontline option in 15 and 6 patients in G1 and G2, respectively (4 and 2 patients, in each group, had already died during this follow-up). Regarding operated patients in primary treatment, in G1, the greater portion of them underwent breast-conserving surgery (61.00%), while in G2, the preferred option was mastectomy (53.80%). In the mastectomy setting, most patients had primary reconstruction in both groups, but, while in G1, breast implant was the preferred option over breast expander (5.1% vs. 14.5%), in G2 both options had similar frequence (38.1% for breast implant and 33.3% for breast expander), which was considered significative.

Surgery of the axilla did not show significant differences between the groups, with most patients undergoing only axillary lymph node biopsy (82.3% in G1 and 76.9% in G2).

Nearly the entirety of women of both groups were candidates for at least one adjuvant treatment (97.70% of G1 and 93.00% of G2), with hormone therapy being the principal option (85.8% of G1

and 81.0% of G2). Nevertheless, radiotherapy was also frequent, since 77.90% and 77.50% of patients of the 41–49 group and the ≤40 group, respectively, received this treatment. Chemotherapy was indicated in 41% of G1 patients, vs. 29% of G2 patients, but this difference did not reach statistical significance.

During the follow-up provided in the study, recurrence happened in 28 patients (19 in the older group and 9 in the younger one). This means a recurrence rate of 8.30% in G1, occurring on average 2.1 years after the final radiotherapy session or after surgery (accounting for the individual who did not receive radiotherapy). While among the younger patients, these numbers corresponded to a 10% recurrence rate, on average, 2 years after treatment. The prevailing type of recurrence was the appearance of distant metastasis in both groups.

The results related to these variables are demonstrated on Table VII.

Genetic testing

As shown in Table VIII, genetic testing was performed in most patients, namely in G2 (92.4%). Of the patients who completed it, 23.8% of the older age group and 53.3% of the younger one did so directly after being diagnosed, while 46% and 38% of the first and second groups, respectively, had a genetic consultation in a later phase of the follow-up. These results were found to be statistically significant.

A sole individual, of the ≤40 group, had an already known genetic mutation linked to a higher BC predisposition.

In the 41–49 group, mutations were found in 12.8% of women, and in the younger age group, 24% of women presented pathological genetic variants, and this difference was also statistically significant. In both cases, the mutated BRAC2 gene was the most common finding.

Fertility Preservation and Pregnancy

Four cases of BC were diagnosed during pregnancy (or in the year after giving birth), all in women younger than 40.

Considering that in Portugal, until recent years, only women younger than 40 years were potential candidates for fertility preservation treatments, of the patients included in G2, only 38% were evaluated in a fertility consultation, or received some kind of advice related to fertility preservation. Of these women, 37.1% proceeded with oocyte cryopreservation.

After BC diagnosis and treatment, 7 of the women under 40 years were able to develop a pregnancy, on average, 2.5 years after the end of adjuvant treatment. Of these pregnancies, 4 resulted from previously preserved oocytes, using medically assisted reproduction techniques. The other 3 were spontaneous pregnancies. Despite such, of these 7 pregnancies, only 5 resulted in live births. Notwithstanding, 3 of these women were able to breastfeed their babies.

DISCUSSION

This retrospective study aimed to investigate and provide a detailed analysis of the clinicopathological characteristics of BC in women under 50 years of age, as well as the treatment orientation. This limit of age was chosen because until 2024, 50 years old was the age defined to begin breast cancer screening in Portugal, so younger women were not routinely evaluated. This group of women was less understood, but it already represents around one-fifth of breast cancer diagnoses in our Breast Cancer Unit.

Additionally, we established two comparison groups: women aged 41 to 49 years and those 40 years old and younger. The ESMO fifth international consensus recognizes the age of 40 as the threshold for defining breast cancer in young women.[3] This younger demographic is often diagnosed with more aggressive tumors, and even those with luminal-A cancers generally have a less favorable prognosis compared to older counterparts.[39] Beyond breast cancer characteristics, we also aimed to examine differences in diagnostic pathways, treatment choices, and the outcomes achieved.

Epidemiological and Demographic Context

The younger cohort in our study (≤40 years) corresponds to 5.7% of the breast cases treated in our Unit during the 10-year interval studied. The total number of cases below 50 years old (n= 327) represents 20.3% of the cases. This age distribution is consistent with European data estimating that around 19% of BC cases occur in women under 50, and that incidence rates among women under 40 have been increasing in several European countries.[22] Our incidence data in the 10 year period studied did not follow a homogenous trend, but globally, breast cancer in women younger than 50 were more frequent in the period between 2019-2023 than in the previous years (Figure 2).

The youngest patient in our series was diagnosed at age 24, further supporting the observation that BC can develop even in very early reproductive years, underscoring the need for heightened awareness and clinical suspicion in this group. This mirrors findings in international cohorts where breast cancer has been diagnosed as early as the second decade of life.[40,41]

Tumor Presentation and Diagnostic Pathways

A striking finding in this study was the predominance of clinical evident lesions over infraclinical ones in both groups, but with a higher frequency among younger women (78.3% *versus* 57.0%). Moreover, clinical tumor size was also significantly different between groups in our study with higher cT classification in younger patients (Figure 3). Missing data from nodal status made its analysis impossible, but literature also presents evidence of more nodal disease at presentation in younger patients.[42]

A previous cohort study of 585 women under 40 years with BC, showed that reported that the first evidence of their cancer was a self-detected breast abnormality.[43] Our results support previous literature indicating that younger patients are more likely to present symptomatically, particularly with palpable masses, rather than through screening.[10,11,43] This is explained primarily because these patients are not included in routine breast cancer screening. Moreover, there are considerable limitations of mammography in younger women, where high breast density reduces sensitivity, as previously emphasized.[10,11] This emphasizes the need for more individualized diagnostic protocols

in these patients, such as supplemental imaging modalities like ultrasound or MRI in high-risk or symptomatic younger women.

All these data support the importance of physical exams and awareness of early symptoms.

Pathological and Molecular Characteristics

In line with prior studies, our data reveal a more aggressive tumor profile among younger women.[5,44] Compared to the 41–49 age group, the ≤40 group showed a higher prevalence of grade III tumors (47.3% vs. 38.3%), increased Ki-67 proliferation index >30% (54.3% vs. 37.4%), and greater proportion of HER2-positive tumors (31.6% vs. 14.9%).

These findings are consistent with the literature showing that younger age correlates with aggressive phenotypes, including triple-negative and HER2-enriched subtypes, high proliferation rates, and lymph node involvement.[24–26] The POSH study (UK) and others have shown that these aggressive subtypes are more common in women under 40 and are associated with worse survival outcomes.[24,45–47]

Additionally, while hormone receptor positivity was still relatively high across both groups, younger women had lower ER and PR expression. This might contribute to differences in responsiveness to endocrine therapy, which has been shown to be more effective in older, hormone receptor-positive populations.[48–50]

Risk Factors and Genetic Background

Familial history did not presented substantial differences in the groups of our work, but younger patients had a higher rate of positive results in the genetic testing for pathogenic mutations, particularly BRCA2, aligning with global data suggesting a relatively high percentage of BC in women under 30 may be hereditary.[51–54] To exemplify, in a study made in Germany, in a cohort of 802 women with triple-negative breast cancer without family history, the prevalence of BRCA mutations was 32.9% in the 20–29 age group and 26.3% in women under 40.[51] In our study, 24% of younger women had a detectable mutation, compared to 12.8% in the older group. This is higher than the 5 to 10% estimated genetic breast cancer in general population.[16] These findings support the routine use of genetic counseling and testing in younger patients and it may influence surgical and systemic treatment decisions.

Regarding reproductive factors, younger women had fewer gestations and births. While parity is generally protective against BC in postmenopausal women, it may increase short-term risk in premenopausal women due to hormonal surges during pregnancy.[18–21] Actually, 4 women in the younger group were diagnosed with BC during pregnancy or in the following year.

In terms of BMI, the differences between groups were significant, as the younger group had a lower average BMI compared to the 41–49 age group. While obesity is a well-established risk factor for BC in postmenopausal women, its role in premenopausal patients is more nuanced. Some studies suggest that higher BMI may be inversely associated with the risk of developing premenopausal breast cancer.[55] However, obesity in younger patients has been associated with worse outcomes and more aggressive disease features once cancer develops.[56] This dual role of BMI suggests a complex interaction between adiposity, hormonal environment, and tumor biology in younger women, which warrants further investigation in larger, prospective cohorts.

Alcohol consumption was also found to be significantly different between groups, with older age group presenting a higher proportion of alcohol consumption. This underlines the importance of a healthy lifestyle for BC prevention as previously studied.[57]

Treatment Modalities and Outcomes

Our study revealed distinct patterns in treatment strategies between groups. These differences reflect not only age-based clinical decision-making but also underlying tumor biology and patient-specific prognostic profiles.

In our cohort, 53.8% of younger women underwent mastectomy, significantly more than the 39% in the 41–49 years group. This aligns with global trends showing that younger women are more likely to choose or be recommended for mastectomy, often due to more aggressive disease at presentation, higher rates of BRCA mutations, and family history, and a desire to reduce recurrence risk and avoid radiation.[12,58] This pattern is consistent with findings from the POSH study, which reported a 10-year local recurrence rate of 11.68% in women who had breast-conserving surgery, compared to 4.93% in those who underwent mastectomy, in a cohort of women aged ≤40.[24] Furthermore, these findings align with literature indicating that younger patients often receive more aggressive treatments, yet paradoxically experience higher local recurrence rates, particularly after breast-conserving surgery.[28,29]

A notable difference was also observed in the type of primary breast reconstruction post-mastectomy. In the older group (G1), implants were used more frequently than expanders (58.1% vs. 14.5%), while in younger women (G2), both methods were used at similar rates (38.1% vs. 33.3%), a statistically significant variation. This may reflect preferences in the context of younger patients, who may prioritize longer-term aesthetic outcomes and therefore accept more staged reconstruction processes. Younger women might also be more frequently offered expander-based reconstruction due to higher rates of neoadjuvant chemotherapy or postmastectomy radiotherapy, where delayed or staged reconstruction is often recommended to optimize outcomes and minimize complications.[59,60]

In our study, a significant 52.2% of women aged 40 years or younger received neoadjuvant systemic therapy, in contrast to 29.8% in the older demographic. This disparity likely reflects both the more advanced stage of disease at presentation and the higher prevalence of aggressive biological subtypes.

Adjuvant therapies were widely administered in both groups, with hormone therapy and radiotherapy being the most common. However, fewer younger patients received endocrine therapy, likely due to lower hormone receptor positivity. An important aspect to evaluate in a future study is the young patients' adherence to endocrine therapy, stated as being an important issue contributing to reduced overall survival.[61]

Although not statistically significant, a higher recurrence rate was observed in the younger group (10.0% vs. 8.3%), with a shorter time to recurrence (mean 2.0 vs. 2.1 years). While this difference is small numerically, it is clinically significant, particularly when considered alongside more aggressive tumor features such as higher rates of HER2 positivity (31.6% vs. 14.9%), higher Ki-67 >30% (54.3% vs. 37.4%), and higher prevalence of grade III tumors.

These biological features likely explain the faster and more frequent recurrence seen in younger women, even when they receive aggressive therapy. This pattern has been echoed in other studies, showing that younger age at diagnosis is an independent risk factor for poorer outcomes and earlier recurrence.[32–34]

Fertility and Psychosocial Aspects

Notably, only 38% of women under 40 were referred for fertility consultation, but just 37% of these preserved oocytes before treatment initiation. This may be explained because most patients in the younger group had children before the BC diagnosis and only 31.5% were nulliparous. Still, these low numbers may also reflect persistent barriers, including time constraints before starting treatment, limited access, and psychosocial stress. These challenges, along with concerns about body image, early menopause, and parenting, significantly affect quality of life and treatment satisfaction.[35,36]

Despite these values, it is important to note that most young patients treated with chemotherapy were offered GnRh analogues, but these data were not retrieved in our initial database and objective data are not available. Although it seems important, GnRH analogues do not substitute adequate fertility preservation methods as stated in the ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5).[7]

Our findings highlight the urgent need for systematic fertility counseling and psychological support as part of multidisciplinary care for young BC patients.[7]

On a positive note, 7 women (7.6% of the younger group) became pregnant post-treatment, 4 of them through assisted reproduction with preserved oocytes, and 5 live births occurred. In 3 cases, breastfeeding was possible, which is in line with current recommendations stating that breastfeeding may be possible and safe even after BC.[62]

Limitations and Future Directions

This study presents valuable insights into the clinicopathological and therapeutic distinctions in breast cancer among women under 50; however, several limitations must be acknowledged.

First, the retrospective design inherently introduces limitations such as incomplete or missing data, especially in areas such as adherence to endocrine therapy, use of GnRH analogues, and psychosocial support received. Medical records may vary in completeness and detail, particularly for older cases or follow-up information, which may have impacted on the accuracy and granularity of our findings.

Second, although the sample size (n=327) is robust for a single-center study, the number of younger patients (n=92) remains limited, potentially limiting the generalizability of the findings to broader populations. Referral bias, or demographic particularities may have influenced the sample characteristics, particularly regarding access to genetic testing or fertility preservation counseling. The number of patients included in this study may also have limited the power to detect statistically significant differences in some clinical outcomes, such as recurrence or survival, especially in subgroup analyses.

Third, certain variables, such as adherence to treatment, socioeconomic status, psychological support, and patient preferences, were not assessed but may play a crucial role in treatment

decisions and outcomes. These unmeasured confounders may introduce selection bias and limit the depth of interpretation.

Additionally, the follow-up period was not standardized across patients, and our analysis focused primarily on recurrence rather than long-term survival or quality of life. As a result, the study is unable to assess disease-specific or overall survival differences between groups, which would be essential to fully understand prognostic implications.

The BMI values included in the study are also subject to potential bias. Since weight was generally recorded during the first oncology or Breast Unit consultation, rather than at the precise moment of diagnosis (i.e. immediately after biopsy results became available), this may not accurately represent the pre-diagnostic weight of patients. Emotional stress, dietary changes, or early clinical interventions may have already influenced body weight between the moment of diagnosis and when they were formally weighted, thereby limiting the interpretability of BMI in relation to disease risk or tumor biology.

Future research should aim to overcome these limitations through prospective, multicenter studies with larger and more diverse cohorts. Incorporating standardized follow-up protocols, quality-of-life assessments, treatment adherence tracking, and socioeconomic data would enhance the robustness of future analyses. Furthermore, greater emphasis should be placed on understanding barriers to fertility preservation, genetic counseling access, and psychosocial care, especially among younger women.

Lastly, integration of genomic and molecular profiling could offer more personalized insights into the unique tumor biology of young patients, guiding age-adapted screening strategies and therapeutic decision-making.

CONCLUSION

In our study, statistically significant differences were seen on some risk factors for BC (BMI, obstetric history, alcohol consumption, personal history of breast disease and first symptoms/signs), but also in tumor characteristics such as type of breast lesion (clinical/infraclinical), cT, ER status, HER-2 status and Ki-67 expression. Moreover, genetic test results, primary treatment option and breast reconstruction during primary surgery were also found to have significant differences between both groups.

Our findings are mostly consistent with existing literature, indicating that breast cancer in younger women typically presents with distinct and more aggressive biological behavior, and is more frequently associated with genetic mutations. These features, combined with the increased likelihood of an incomplete reproductive plan, pose significant clinical challenges and demand nuanced, age-adapted management strategies.

The greater tumor aggressiveness, lower hormone receptor expression, and higher rates of HER2 positivity in younger patients support the need for more intensive therapeutic approaches, as well as timely genetic testing and counseling. Moreover, the underutilization of fertility preservation services may suggest gaps in holistic care for this population.

This study contributes to the growing evidence that young women with breast cancer constitute a unique clinical subgroup, for whom early detection strategies, individualized treatment planning, and long-term survivorship care are essential. By enhancing awareness and improving multidisciplinary interventions, we may be able to mitigate disparities in outcomes and support both survival and quality of life in this vulnerable group.

Ultimately, we hope that this study will encourage more robust, prospective, and multicenter research efforts that deepen our understanding of breast cancer in young women and lead to more personalized, equitable care models in the future.

APPENDIX

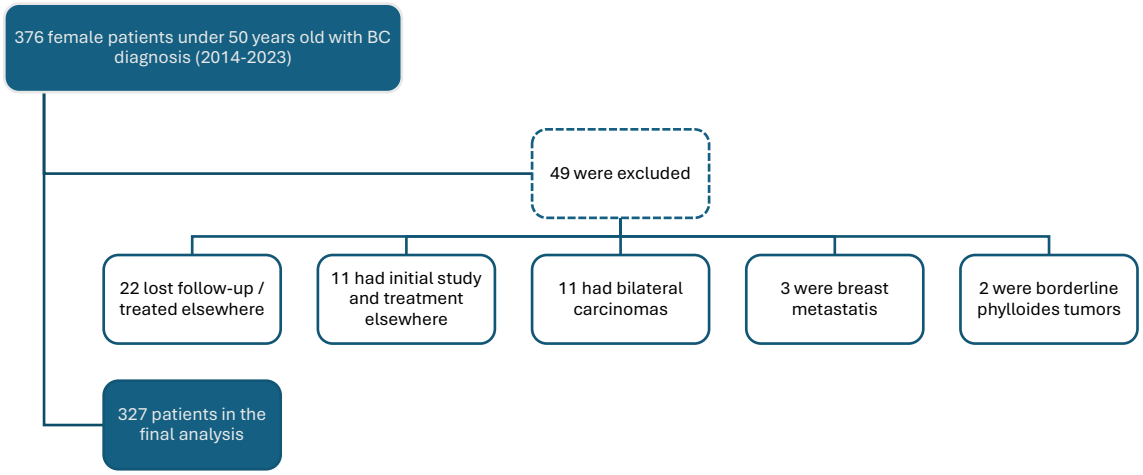
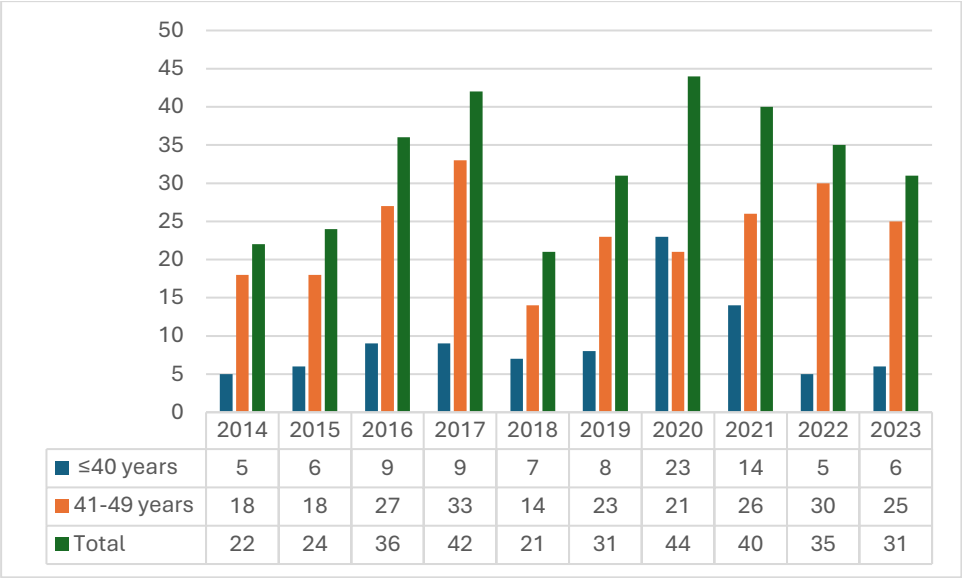


Figure 1 – Patient selection and final study population.



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
≤40 years	5	6	9	9	7	8	23	14	5	6
41-49 years	18	18	27	33	14	23	21	26	30	25
Total	22	24	36	42	21	31	44	40	35	31

Figure 2 – Number of breast cancer cases, in women younger than 50 years old, between January 2014 and December 2023.

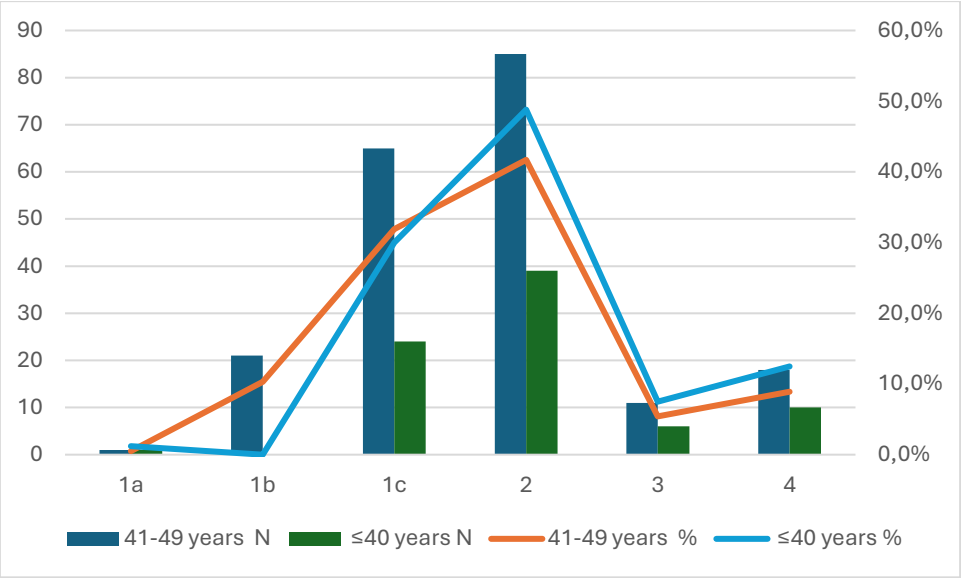


Figure 3 – Clinical tumor size staging in both groups (absolute numbers – N – and percentage inside the group - %).

Table I – General groups' characteristics and p-values for means / distribution comparison.

		41–49 age group	≤40 age group	p-value
Age at diagnosis (years)	*Mean*	45.5	35.9	
	Median	46	37	
BMI (Kg/m^2)	*Mean*	25,72	24,43	**0.015**
	Median	24,95	23,43	
	Minimum	17,1	17,18	
	Maximum	40,57	46,28	
Smoking	*Yes*	58 (25%)	17 (18.7%)	0.245
	No	174 (75%)	74 (81.3%)	
Alcohol	*Yes*	32 (13.8%)	3 (3.3%)	**0.005**
	No	200 (86.2%)	88 (96.7%	
Age at Menarche (years)	*Mean*	12.3	12.5	0.730
	Minimum	9	7	
	Maximum	17	18	
Number of gestations	*Mean*	1.8	1.3	**0.007**
	Minimum	0 (N=34; 14.5%)	0 (N = 27; 29.3%)	
	Maximum	10	5	
Number of deliveries	*Mean*	1.4	1.1	**0,000**
	Minimum	0 (N=36; 15.3%)	0 (N=29; 31.5%)	
	Maximum	5	3	
Age at first child delivery	*Mean*	27.8	27.1	0.558
	Minimum	16	17	
	Maximum	42	40	
Breastfeeding	*Yes*	172 (87.8%)	53 (84.1%)	0.598
	No	24 (12.2%)	10 (15.9%)	
Hormonal contraception use	*Yes*	161 (69.7%)	72 (78.3%)	0.158
	No	70 (30.3%)	20 (21.7%)	
Type of hormonal contraception (when applicable)	*Combined pill*	145 (90.1%)	59 (80.8%)	0.145
	Isolated progestative method	14 (8.7%)	12 (16.4%)	
	Pill and other method	2 (1.2%	2 (2.7%)	
Duration of hormonal contraception use (when applicable)	*Less than 5 years*	26 (16.1%)	16 (21.9%)	0.358
	5 or more years	135 (83.9%)	57 (78.1%)	

Table II – Personal and familial history of breast disease and p-values for distribution comparison.

		41–49 age group	≤40 age group	p-value
Personal history of breast disease	*No*	164 (69.8%)	68 (73.9%)	**0,012**
	Fibroadenoma	22 (9.4%)	15 (16.3%)	
	Cyst	34 (14.5%)	3 (3.3%)	
	Mastitis / abscess	5 (2.1%)	5 (5.4%)	
	Breast discharge / excision of galactophores	1 (0.4%)	0 (0%)	
	Other	9 (3.8%)	1 (1.1%)	
Familial history of breast cancer (in first degree)	*No*	130 (56%)	55 (60.4%)	0,885
	1 family member	71 (30.6%)	24 (26.4%)	
	2 family members	24 (10.4%)	9 (9.9%)	
	3 family members	7 (3%)	3 (3.3%)	
Familial history of breast cancer below 50 years old	*No*	195 (83.7%)	72 (80.9%)	0,620
	Yes	38 (16.3%)	17 (19.1%)	
Familial history of ovarian cancer	*No*	220 (94.8%)	86 (93.5%)	0,600
	Yes	12 (5.2%)	6 (6.5%)	

Table III – Clinical tumor characteristics at presentation and p-values for means / distribution comparison.

		41–49 age group	**≤40 age group**	**p-value**
First symptoms / signs	*None*	102 (43.6%	23 (25%)	**0,002**
	Breast pain	8 (3.4%)	3 (3.3%)	
	Palpable lesion	90 (38.5%)	50 (54.3%)	
	Nipple discharge	8 (3.4%)	3 (3.3%)	
	Skin change	4 (1.7%)	2 (2.2%)	
	Nipple change	3 (1.3%)	2 (2.2%)	
	More than one sign / symptom	19 (8.1%)	9 (9.8%)	
Time from first symptoms until medical evaluation (weeks)	*Mean*	14.3	18.2	0,070
	Median	8	12	
	Minimum	1	2	
	Maximum	100	150	
Type of breast lesion	*Infraclinical*	101 (43%)	20 (21.7%)	**0, 000**
	Clinical	134 (57%)	72 (78.3%)	

Table IV – Breast cancer type, histological subtype, tumor grade, and clinical tumor stage (cT) according to each group, and p-values for distribution comparison.

		41–49 age group		**≤40 age group**		**p-value**
Type of breast cancer	*Invasive*	205 (87.2%)		80 (87%)		0,972
	In situ	30 (12.8%)		12 (13%)		
Histological subtype	*Ductal*	198 (84.6%)		81 (89%)		0,241
	Lobular	22 (9.4%)		3 (3.3%)		
	Mixed	1 (0.4%)		0 (0%)		
	Others	14 (5.6%)		8 (7.7%)		
Tumor grade	I	45 (19.7%)		11 (12.1%)		0,081
	II	104 (45.4%)		37 (40.7%)		
	III	80 (34.9%)		43 (47.3%)		
Clinical tumor stage (cT)	is	30		12		**0,010**
	1a	1 (0.5%)	87 (41,3%)	1 (1.2%)	25 (31,2%)	
	1b	21 (10.3%)		0 (0%)		
	1c	65 (31.9%)		24 (30%)		
	2	85 (41.7%)		39 (48.8%)		
	3	11 (5.4%)		6 (7.5%)		
	4	18 (8.9%)		10 (12.5%)		

Table V – Tumor size according to tumor type and age cohort, and p-values for mean comparison.

		41–49 age group			≤40 age group			p-value
		General	Invasive	In situ	General	Invasive	In situ	
Tumor size (mm)	*Mean*	28,8	27,7	35,5	31,4	31,1	33,2	0,127
	Median	22	22	32	25,5	26	19	
	Minimum	4	4	5	4	4	7	
	Maximum	150	150	100	110	110	70	

Table VI – Molecular tumor characteristics and TNM classification, according to tumor subtype and age cohorts, p-values for distribution comparison.

		41–49 age group		**≤40 age group**		**p-value**
		Invasive	In situ	Invasive	In situ	
Estrogen receptors	*Positive*	175 (86,6%)	29 (93,5%)	61 (76,2%)	11 (91,7%)	**0,040**
	Negative	27 (13,4%)	2 (6,5%)	19 (23,8%)	1 (8,3%)	
Progesterone receptors	*Positive*	158 (78,2%)	18 (58,1%)	54 (67,5%)	7 (63,6%)	0,127
	Negative	44 (21,8%)	13 (41,9%)	26 (32,5%)	4 (36,4%)	
HER-2	*Positive*	30 (14,9%)		25 (31,6%)		**0,002**
	Negative	171 (85,1%)		54 (68,4%)		
Ki-67	< 10%	39 (20,0%)		12 (14,8%)		**0,023**
	10-30%	85 (43,6%)		25 (30,9%)		
	> 30%	71 (36,4%)		44 (54,3%)		
Clinical staging (TNM)	IA	72 (35,3%)		22 (27,5%)		0,485
	IB	45 (22,1%)		15 (18,8%)		
	IIA	27 (13,2%)		11 (13,8%)		
	IIB	15 (7,4%)		8 (10,0%)		
	IIIA	2 (1,0%)		4 (5,0%)		
	IIIB	14 (6,9%)		6 (7,5%)		
	IIIC	7 (3,4%)		2 (2,5%)		
	IV	15 (7,4%)		9 (11,3%)		

Table VII - Treatment modalities and outcomes for invasive cancer in each group and p-values for distribution comparison.

			41–49 age group	≤40 age group	p-value
Primary treatment	*Surgery*		159 (67.7%)	38 (41.3%)	**0,000**
	Systemic neoadjuvant treatment		61 (26%)	48 (52.2%)	
	Systemic palliative treatment		15 (15%)	6 (6.5%)	
Breast primary surgery	*Tumorectomy*		97 (61%)	18 (46.2%)	0,105
	Mastectomy		62 (39%)	21 (53.8%)	
Breast reconstruction during primary surgery	*No*		17 (24.4%)	6 (28.6%)	**0,043**
	Tissue expander		9 (14.5%)	7 (33.3%)	
	Breast implant		36 (58.1%)	8 (38.1%)	
Axillary primary surgery	*Sentinel lymph node biopsy*		130 (82.3%)	30 (76.9%)	0,493
	Axillary dissection		28 (17.7%)	9 (23.1%)	
Breast surgery after NAST	*Tumorectomy*		42 (51.9%)	22 (42.3%)	0,101
	Mastectomy		39 (48.1%)	30 (57.3%)	
Breast reconstruction during surgery (after NAST)	*No*		33 (84.6%)	22 (73.3%)	0,401
	Tissue expander		2 (5.1%)	2 (6.7%)	
	Breast implant		4 (10.3%)	6 (20%)	
Axillary surgery (after NAST)	*Sentinel lymph node biopsy*		30 (41.7%)	28 (53.8%)	0,205
	Axillary dissection		42 (58.3%)	24 (46.2%)	
Adjuvant therapy	*No*		5 (2.3%)	6 (7%)	0,081
	Yes		212 (97.7%)	80 (93%)	
Type of adjuvant therapy	*Hormone therapy*		182 (85.8%)	64 (81%)	0,352
	Chemotherapy		87 (41%)	23 (29%)	0,077
	Radiotherapy		166 (77.9%)	62 (77.5%)	1,000
Recurrence			19 (8.3%)	9 (10%)	0,662
	Time until recurrence (years)	Mean	2,1	2	0,982
	Recurrence site	Breast	3	1	0,824
		Axilla	1	1	
		At distance	15	7	

Table VIII – Genetic testing application in both cohorts and obtained results.

Variable			**41–49 age group**	**≤40 age group**	
Genetic test	No		71 (30.2%)	7 (7.6%)	**0,000**
	Yes	*At diagnosis*	56 (23.8%)	49 (53.3%)	**0,000**
		During follow-up	108 (46%)	35 (38%)	
		Known familial mutation	0 (0%)	1 (1.1%)	
Positive tests		ATM	4	3	0,379
		BRCA1	2	2	
		BRCA2	8	7	
		CHEK2	3	3	
		PALB2	4	3	
		MSH	3	2	
		TOTAL	30 (12.8%)	22 (24%)	**0,019**

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