Young Women With Breast Cancer in Brazil: A Population-Based Study Epidemiology of Breast Cancer in Young Women

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Abstract

Background: Worldwide, breast cancer is the most frequent cancer in woman. The incidence in young women has been increasing in the last decade, mainly in developing countries. The aim of this study was to report the incidence of breast cancer in young patients (≤ 40 y) from 2007 to 2014 in a poor region of Brazil.

Results: There were a total of 660 cases within a period of 8 years, with an average of 82 cases per year, and with median age of 36 years, ranging from 16 to 40 years. The most frequent cases were invasive carcinoma of no special type (87%), stage II (34.2%), positive for the progesterone receptor (PR, 51.6%), and for estrogen receptor (ER, 59.1%) and positive familial history of cancer (44.5%). These patients are mainly from the urban area (90%) and poorly educated (66.6% completed elementary school). Significant differences were observed for overall survival for the independent variables: age group ($p = 0.012$), clinical staging ($p< 0.001$), PR ($p= 0.003$), ER ($p= 0.029$) and pregnancy ($p= 0.021$). No significant difference was found between the survival curves of patients HER2+ or HER2-. The standardized rates for age (ASR) per 100,000 was 3.0-5.3%, which is low when compared to the Global Cancer Observatory (ASR 8.3%) or Brazil (ASR 10.8%).

Conclusion: although the incidence of young women has increased in the country, especially in the study region, it has remained stable in the population studied in the last 8 years.

Highlights

→ The incidence of breast cancer in young women (< 40 years) did not increase significantly for the last 10 years and the ASR in this region is lower than in Brazil.

→ The median age of the patients was 36 years, the majority were Caucasian (61,4%), had low education (only elementary school) (66%) and lived in urban areas (90.3%).

→ Most of the patients were nulliparous and diagnosed < 30 years, with tumors ER/PR- and stage IV.

→ Breast cancer was more aggressive in woman aged < 30 years with 10y-OS 56.5% and 30–40 years, 73.9% ($P = 0.023$).

Background

Breast cancer is the most common cancer among women worldwide and has the highest mortality rate [1, 2]. Less than 7% of all breast cancer cases are diagnosed in women under 40 years old (defined as “young women” for this article), however, the incidence of breast cancer in young women has increased worldwide. This can be attributed to the lack of efficacy for breast cancer screening in public policy in this age group, since in many countries regular mammograms are not recommended for women under 40 years, but also to the changes in the behavior such as obesity [1, 3–5]. It has been suggested that breast

cancer in women under 40 year represents a distinct entity with different clinical outcomes and tumor biology. Most tumors are luminal B, positive Her2, and triple-negative [6, 7]. Younger patients are diagnosed at a higher tumor stage and therefore with larger tumor size and nodal involvement, resulting in a more aggressive disease and a worse prognosis [4, 8].

Germline mutation in tumor suppressor genes as BRCA1 and BRCA2 confers an autosomal dominant inheritance named hereditary breast and ovarian cancer syndrome (HBOC) that accounts for 5 to 10% of breast cancer diagnosis in young woman [9]. Lakhani and colleagues determined that a woman between the ages of 30 and 34 with an ER-negative, grade 3 tumor has 26.5% chance of harboring a BRCA1 mutation compared to 5% chance in women with the same age range with any tumor type [10, 11].

The incidence of breast cancer in young women can differ among ethnicity. In African-American, 16.7% of women under 35 harbor a BRCA mutation [12], and in a selected Brazilian population it has been shown that 21.5% of patients harbor BRCA mutation [13]. Brazilian ethnicity is an admixture from many ethnicities, but mainly Caucasian and African [13].

The increasing incidence of breast cancer in the young is greatest in developing countries, since they prioritize health actions focused on infectious diseases, maternal-infant health and external causes. Prevention and screening of young women, diagnosis and adequate treatment needs investment from the public sector, which is directly proportional to the economic situation of the population. [14, 15]

In summary, less developed regions with variations in access to health services show higher rates of young women with breast cancer and breast cancer mortality. There is thus a need to understand the characteristics of young woman diagnosed with breast cancer in Brazil, especially in the Northeastern state, due to its economically disadvantaged characteristics. [3]

The aim of this study was to characterize breast cancer in young women seen a reference oncologic hospital of the Northeast Brazil.

Methods

In this retrospective study, data was collected from medical records of patients diagnosed with breast cancer ≤ 40 years between 2007 and 2014 at the Hospital Liga Norte Riograndense Contra o Câncer, Natal, Rio Grande do Norte. We selected the final year as 2014 to ensure a minimum of 10-year follow-up. The study was approved by the institutional review board and informed consent was obtained from all subjects (CAAE: 24342519.8.0000.5293).

The data collected were race, age group, residence in rural or urban areas, parity, family history of cancer, alcoholism, smoking, use of hormone therapy, the practice of sedentary lifestyle, staging at diagnosis, hormone receptor status, HER2 status, treatment performed, outcome and outpatient follow-up. The TNM classification of the American Joint Committee on Cancer Staging System for 2010 Breast cancer was used.

Data analysis was divided into three parts. First, the age-standardized incidence rate (ASR) was estimated using the world standard population suggested by Segi (1960) and modified by Doll et al. (1966) [14]. Then, exploratory data analysis was carried out to discover possible trends, relationships, and patterns associated with the studied variables.

Finally, analysis of overall survival were performed using the Kaplan-Meier non-parametric estimator. To verify the existence of significant differences in the estimated curves, the Log- Rank test was used, and to identify the independent effect of the explanatory variables of survival, the Cox proportional hazards model (Hazard Hatio - HR) was used. In all tests, a significance level of 5% was assumed. The software R (version 3.4) was used in the statistical analysis.

Results

We identified 660 women aged ≤ 40 years diagnosed with breast cancer from 2007 to 2014, resulting in an average of 82 cases per year (Table 1). This implies a standardized incidence rate of 33.8 cases per 100,000 women over an 8-year period, and an average of 4.2 cases per 100,00 women per year. The Age-standardized incidence rate (ASR) varied from 3.0 to 5.3, registering its peak in 2009 and decreasing between 2012 and 2014 (Fig. 1A).

Table 1
Distribution of breast cancer cases in young women during 2007–2014 in a cancer care center in Brazil

Year	Cases in all ages	Cases in young women	%
2007	509	58	11,4%
2008	618	82	13,3%
2009	630	104	16,5%
2010	541	68	12,6%
2011	589	74	12,6%
2012	639	96	15,0%
2013	686	94	13,7%
2014	694	84	12,1%
Total	**4.906**	**660**	**13,5%**

The average age at diagnosis was calculated using two age groups: <30 years old, 10.1% and 30–40 years old, 89.9%. The median age of the patients was 36 years (range 16 to 40 years). The patients were mainly Caucasian (61,4%), following by *Pardo* (32,4%), and African-Brazilian (6,2%). The level of education was low, only 66% completed elementary school; and 90.3% of the patients lived in an urban area. The most observed histological type was invasive carcinoma of no special type (87.3%), followed by other histologic types such as non-infiltrating intraductal carcinoma 5.7% and other types 7%. The

distribution by tumor stage was 34.2% stage II, 30.8% stage III, 18.9% in stage IV, 12.2% stage I and 3.9% *in situ* carcinoma. More than half of the tumors were positive for hormone receptors, where 51.6% were positive for the progesterone receptor (PR) and 59.1% for the estrogen receptor (ER). A total of 596 patients (91,0%) underwent surgery, mainly mastectomy (77%) and quadrantectomy (22,7%). Most of the patients had positive family history of cancer (44.5%), but this data was not well described in the medical record, the same for smoking and alcohol, since only 8,9% of patients were smokers and 2,6% consume alcohol.

Significant differences were observed for 10-year overall survival (10y-OS) among the categories of independent variables: age group ($p = 0.012$), clinical staging ($p < 0.001$), PR ($p = 0.003$), ER ($p = 0.029$) and parity (0.021). No significant difference in 10y-OS was observed according to HER-2 status. In Fig. 1B, a significant difference in 10y-OS was observed between the group < 30 years (56.5%) and 30–40 years (73.9%). In Fig. 2A, we observed that clinical staging is indirectly proportional to the OS, where 35.2% of the patients were in stage IV, this feature is evidenced when we group early versus late stage (I/II vs III/IV, Fig. 2A). The patients with ER and PR negative tumors showed worse 10y-OS then positives (68% and 67,7%, respectively), with PR presenting the worse prognosis ($p = 0.0031$) (Fig. 3A and 3B). And finally, we wonder if the parity could interfere in the 10y-OS among young breast cancer patients, and we observed that patients with at least 1 child had 74.2% survival and nulliparous, 60.4% ($p = 0.0015$), thus, there is a 14.2% survival superiority among parous women (Fig. 2B). In conclusion, the worse prognosis was found in patients with < 30 years, have tumors negative for ER and PR, tumor stage IV and nulliparous.

Cox model was used adjusting the overall survival data and the factors analyzed, such as: the variables age group, tumor staging, PR and ER status. According to Table 2, it is possible to observe that patients under 30 years diagnosed with breast cancer had a 2-fold higher risk of death than those between 30 and 40 years; patients diagnosed with clinical stage III/IV have 8 times more risk of death than those with stage I/II; the risk of death was 78% higher in women with PR -; and, 60% higher in women with ER -.

Table 2
– Adjusted Cox Regression Model for survival analysis of young women with breast cancer (2007 to 2014).

Variable	HR	CI 95% (HR)	p-valor
Age group			
< 30	2,01	[1,24 – 3,26]	0,004
30–40	1	-	-
Staging			
I / II	1	-	-
III / IV	8,24	[4,94 – 13,70]	< 0,001
PR			
PR+	1	-	-
PR-	1,78	[1,23 – 2,59]	0,002
ER			
ER+	1	-	-
ER-	1,60	[1,10 – 2,40]	0,009
HR = Hazard Ratio; CI = confidente interval			

Discussion

Breast cancer incidence rates have been increasing in many countries in Asia, Africa, and South America. According to the recent Population Cancer Registry Golestan (GPCR) report, a rapid increase in age-specific incidence rates of breast cancer has been reported. About 7% of all breast cancers diagnosed in the United States are in young woman with less than 40 years. Although the incidence of breast cancer in younger women is lower than in elderly women, it is known that their related risk factors are distinct [7, 17].

The Age standardized rate (ASR) in our study ranged from 3.0 to 5.3, which is less than the data released by GLOBALCAN, where the ASR in the World was 8.3% and in Brazil 10.8%. Therefore, the incidence in Rio Grande do Norte was stable, unlike the situation in other cities in Brazil, such as Porto Alegre and Goiânia, which had a variation in the incidence rate from one year to the next of 4.6 and 4.4%, respectively [18].

For the last decade, breast cancer incidence and mortality among young women from Middle Income Countries (such as Brazil and Bolivia) is increasing. In one Brazilian study, the Average Annual Percentage Change (AAPC) was 5.22%, 5.53% and 4.54% for the age groups up to 39, 40 to 59 and 60 years and over, respectively [19]. Of the five Brazilian regions, the Northeast, which is less economically favored, stands out with the highest increase in breast cancer mortality among women aged 20 to 49 years old in the period 1996 to 2013. This is related to late diagnosis and less modern treatments available in the public sector, since women in the public sector present with a higher initial stage at the time of diagnosis, when compared to the private sector. [3, 14]

In Colombia, Cardona e Agudelo [20] observed an upward trend in breast cancer mortality rates in women 20–44 years from 1994 to 2003, although the mortality rates from this cancer in women 45–64 years remained constant during the same period. An increase in breast cancer mortality rates was also observed in Iran from 1995 to 2004 and was greater in women 15–49 years compared to 50 years. The same trend can be observed in China, with an Average Annual Percentage Change (AAPC) of 2.9 (95%CI: 2.5–3.4) in breast cancer incidence in women 15–49 years from 1973 to 2005 [21]. In a developed country, such as the United States, an increase in breast cancer incidence in women with 25–35 years with metastasis was observed from 1976 to 2009 (AAPC 2.07; 95%CI: 1.57–2.58), the same in France (1991–2003) in women up to 49 years [22] and in Spain (1980–2004) in women 25–44 years [23].

South America has a cancer incidence rate of 56.8 per 100,000 women, high when compared to Australia / New Zealand, Europe and North America [4, 24]. This is probably due to differences in the prevalence of risk factors, such as family history, reproductive factors and lifestyle, in addition to access to early detection, including screening [3, 7]. In our study, the result of women < 40 years of age with breast cancer is approximately 13% in relation to the total number of cases and, despite stabilizing over the years analyzed, differing from the data of the countries mentioned, it shows that the number of young women in our service is compatible with the global one (Table 1).

Consistent with other studies, we observed the incidence rates significantly higher among women living in urban areas than among women in rural areas [25, 26]. The reasons for these differences are: diagnostic bias, as women in urban areas have easier access to health services [27, 28], as well as the distinction related to lifestyle, reproduction, overweight, and obesity [29–31].

As for the level of education, 66.6% of the patients had only high school. This data points to an impairment due to a low level of education and limited access to information about how to avoid the disease, perform self-examination, and the importance of early diagnosis [7]. Additionally, there may be an association with rural residence, less access to hormonal contraceptives, greater parity and longer breastfeeding periods, which provide greater protection against breast cancer [4].

Although there is a predominance of patients aged 30–40 years, we observed a shorter survival in younger patients (< 30 years). Studies have shown that women with breast cancer diagnosed at younger ages more often have a genetic predisposition to the disease and tend to have more aggressive tumors [32–35].

Our patients were mainly diagnosed with invasive carcinoma of no special type (87%), stage II (34.2%), positive for the progesterone receptor (PR, 51.6%), and for estrogen receptor (ER, 59.1%), positive family history of cancer (44.5%). The worst 10y-OS was observed in patients with < 30 years, negatives for ER and PR, tumor stage IV and nulliparous. Younger women have more aggressive disease, including higher stages, negative hormone receptors, increased basal-like subtypes, lymph node positivity, and larger tumors. The factors of pre- and postmenopausal women differ because, in that same study, it was shown that the higher waist to hip ratio was associated with a reduced risk of breast cancer among young women, but with a high risk among older women [18, 24, 36].

There is a better therapeutic response for woman with ER/PR + tumors due to hormone therapy [6], and conversely, triple negative molecular subtype has a worse prognosis, since it is significantly more aggressive, recurrent and without effective therapy [5, 24, 36, 37].

Analyzing the parity status, a lower survival is observed in those who never had children. This factor is predictable, because according to the American Cancer Society (2019) [32], parity before the age of 30 and breastfeeding are protective factors for women [37, 38]. Parity was associated with an increased risk among young women and a reduced risk among older women, while breastfeeding was protective for young women. In comparison, when stratified by age, menopausal status was not associated with distinct risk factors or characteristic tumor profiles [35].

A total of 91% of patients underwent mastectomy, much more than conservative surgery, which can be related to the fact 49,7% of the patients were diagnosed at stage III/IV (N = 302). Mastectomy at early stages no longer corresponds to longer survival, because quadrantectomy associated with other therapies can provide the same effect with a significant reduction in the psychosocial impact on the woman's quality of life [38, 39].

Based on these results, it is necessary to rethink the screening policies to be more accessible and include young women, such as to offer annual clinical breast examination and imaging exams.

Finally, the incidence of young woman diagnosed with breast cancer in our cohort was low and did not increase for the last 10 years. This observation could be explained due to the subdivision of hospitals that provide cancer care in the state of Rio Grande do Norte. The State is divided into eight Health Regions, or four macro-regions. The hospital where this study was conducted is a philanthropic institution responsible for oncologic care in the metropolitan macro-region corresponding to regions I, III, V and VII, or 64.1% of the state's population. There are three hospitals that attend in more rural regions, collaborating for a greater coverage of the oncologic population.

Conclusion

We could observe a stability in the incidence of breast cancer in young women in the studied population, with the rate of 13.5% during the past 10 years, and good performance in the management of these patients in the reference hospital.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board and informed consent was obtained from all subjects (#CAAE: 24342519.8.0000.5293) according to the Ethics Committee from Liga Norte Riograndense contra o Cancer, Natal, Brazil. The study was conducted in accordance with Brazilian relevant guidelines and regulations according to Declaration of Helsinki.

Consent for publication

In the Ethics approval we have the consentient of the Liga Norteriograndense contra o Cancer to use anonymous clinical data from the institution.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due lack of ethical approval for sharing the raw data, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Rebecca and Thais collected data and wrote the manuscript. Ythalo is the statistician who did analysis and graphs. Diana and Teresa are oncologist for breast cancer and helped with analysis and writing the manuscript. Tirzah supervised all the study.

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Figures

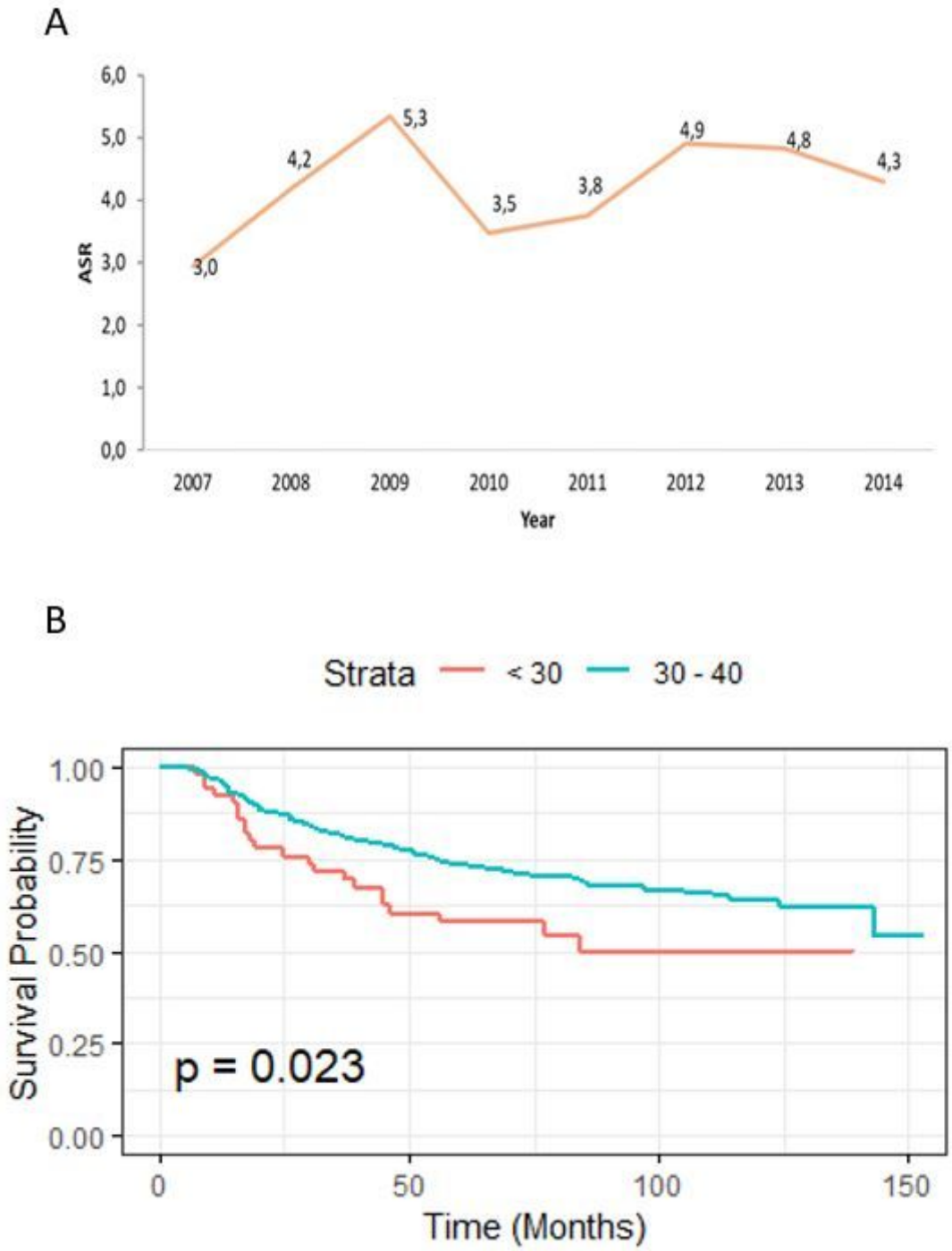

Figure 1

Evidence of breast cancer in young women during the period from 2007 to 2014. A. The incidence rate declined during the years 2009 to 2010 (1.8%) and subsequently remained unchanged between 4.3 and 4.9%. Age-standardized incidence rate (ASR). B: 10y-OS according to age where 56.5% in <30 years and 73.9% in 30-40 years. Therefore, we can infer greater aggressiveness in younger women.

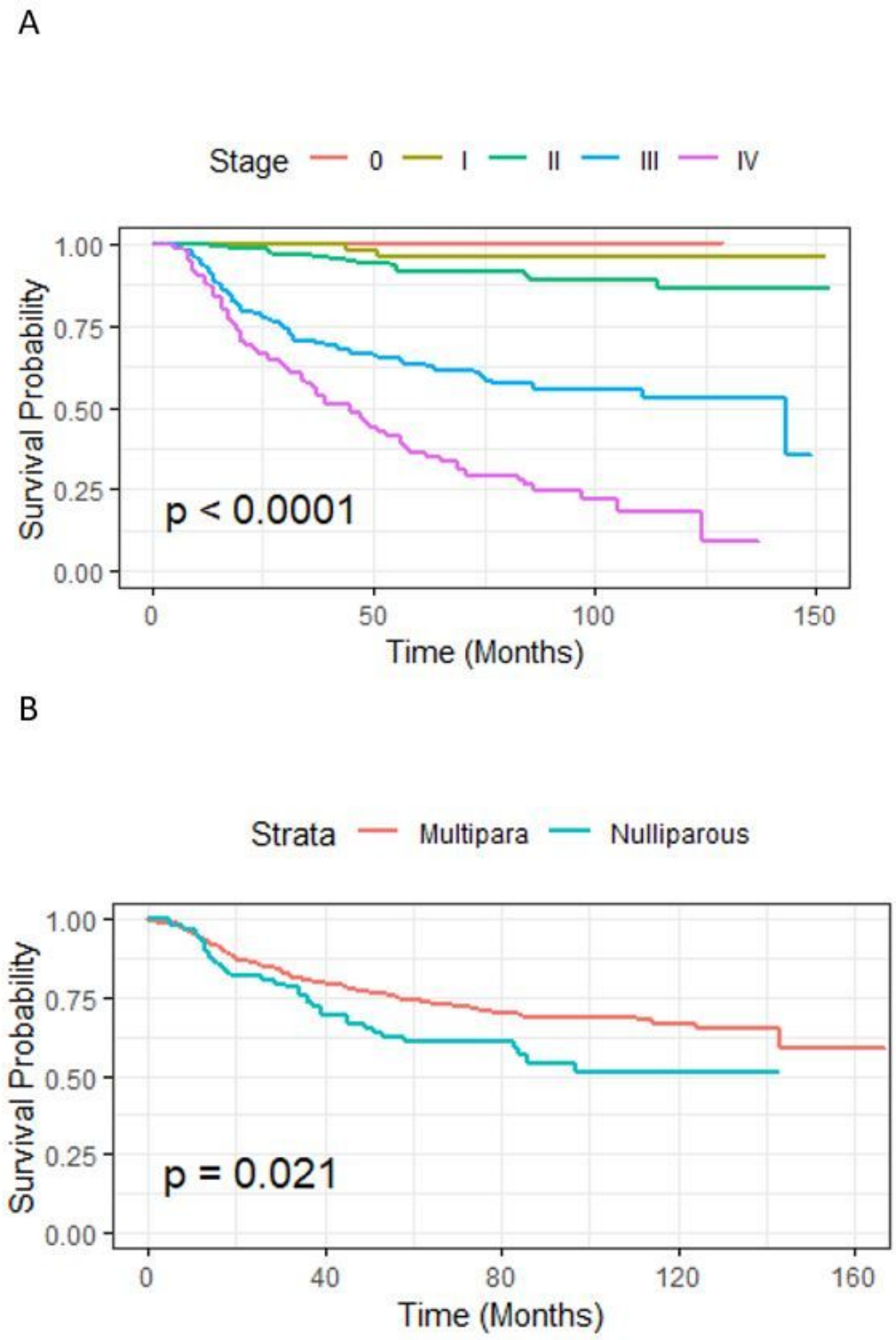

Figure 2

A. 10y-OS according to tumor staging where patients with carcinoma in situ had 100%, stage I 96.6%, stage II 89.6%, stage III 62.3% and stage IV 35.2%. B: 10y-OS according to parity (nulliparous versus multipara). There is a 14.2% survival superiority among parous women.

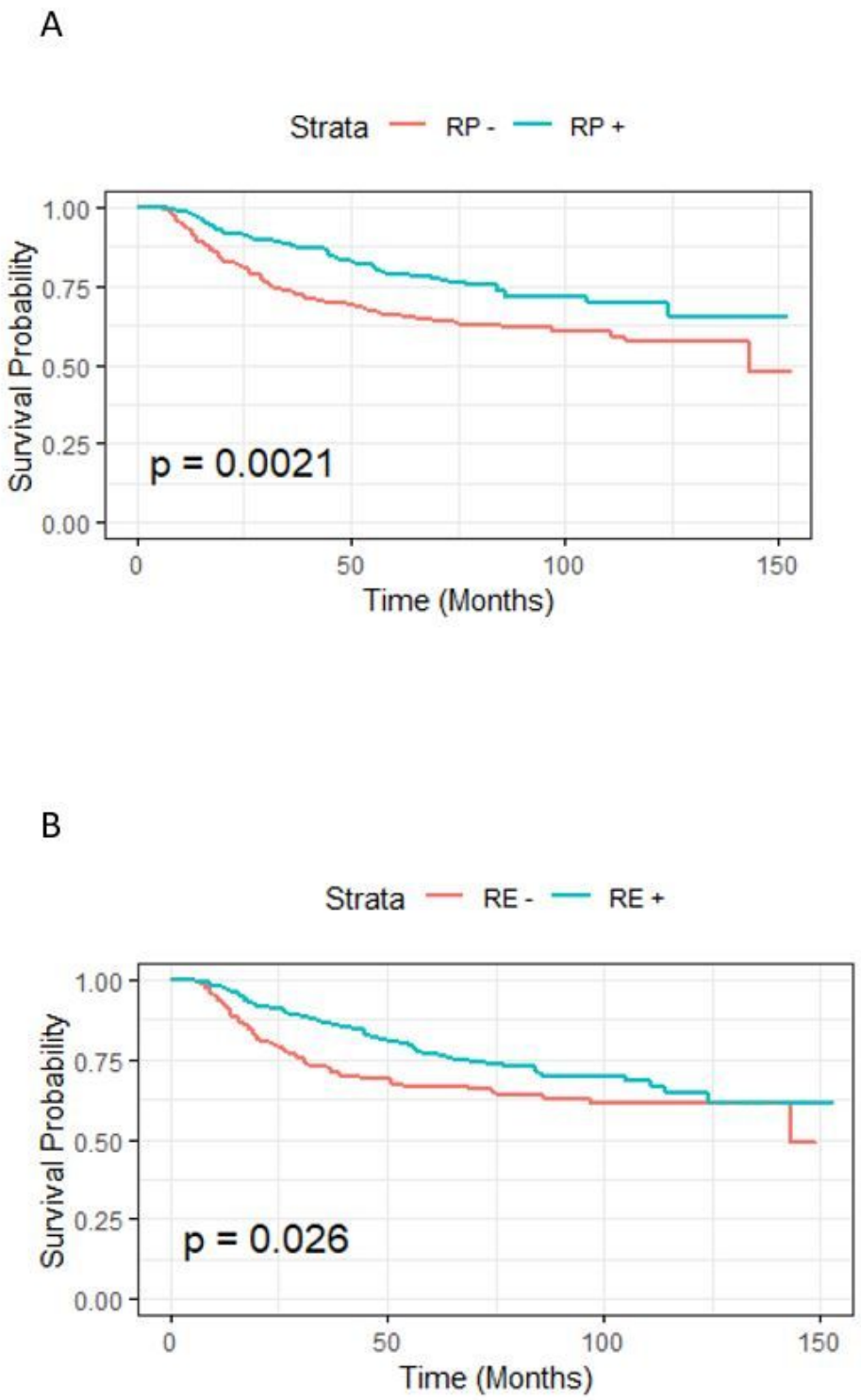

Figure 3

A. 10y-OS according to the expression of progesterone receptors, 79.4% with PR statistical significance (p = 0.0031). B. 10y-OS according to the estrogen receptor expression was 77.4% (p = 0.029).