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# **Original Research Article**

# Risk factors for recurrence of invasive breast cancer after primary surgery in patients followed at the medical oncology and palliative care department of Soavinandriana Hospital Center

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# **ABSTRACT**

**Background:** Breast cancer mortality is often linked to recurrence or progression. This study aims to identify and describe the risk factors for recurrence in invasive breast cancers after primary surgery.

**Methods:** A case-control study was conducted from January 1, 2017, to December 31, 2023.

**Results:** The study included 55 cases and 55 controls. Identified risk factors for recurrence include age under 50 (OR 3.21; p=0.005), partial mastectomy (OR 7.7; p=0.001), vascular emboli or perineural invasion (OR 2.85; p=0.019), poor resection margin (R+) (OR 16.36; p=0.00),  $\geq$ 25% lymph node invasion (OR 5.33; p=0.002), capsular rupture (OR 8.78; p=0.000), CA 15-3  $\geq$ 30 U/ml (OR 6.66; p=0.01), and lack of radiotherapy (OR 3.39; p=0.002) or chemotherapy (OR 4.07; p=0.001) as adjuvant treatments.

Conclusions: The identified risk factors align with those in existing literature and should be considered to enhance breast cancer treatment.

Keywords: Breast, Cancer, Invasive, Recurrence, Surgery

# INTRODUCTION

Breast cancer is a disease where normal mammary cells become malignant, growing uncontrollably into tumors. If untreated, these tumors can spread to other tissues, forming metastases.<sup>1</sup> It is the most common cancer in women, surpassing colorectal and lung cancers, and poses a significant public health challenge.<sup>2-4</sup>

Breast cancer affects women worldwide, with its incidence increasing with age.<sup>5</sup> In Madagascar, 259 breast cancer

cases were recorded at the J. Ravoahangy Andrianavalona hospital between 1996 and 1998, and 189 cases from 2007 to 2010.<sup>6,7</sup> At the Soavinandriana hospital, 75 cases were recorded from 2012 to 2014, while 62 cases were treated at the Tanamabao Fianarantsoa University Hospital from 2011 to 2018.<sup>7,8</sup>

Breast cancer mortality is often linked to recurrence or progression, especially when the disease is not fully eradicated by treatment.<sup>9</sup> Several risk factors for recurrence have been identified, with varying results

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depending on the study population and methods. These include tumor multifocality, histological type, vascular emboli, young age, tumor size, lymph node involvement, absence of hormone receptors, Scarf Bloom Richardson grade, elevated CA 15-3 levels, and the use of radiotherapy or adjuvant chemotherapy. Literature reports recurrence rates between 3% and 20%, regardless of the type of surgery performed, highlighting the need for regular, long-term follow-up after treatment. 10-12

This study aims to identify risk factors for recurrence in women who did or did not receive adjuvant treatment after primary surgery.

# **METHODS**

This was a monocentric, analytical case-control study conducted at the Medical Oncology and Palliative Care Department of the Soavinandriana Hospital Center. The study period spanned from 1<sup>st</sup> January 2017, to 31<sup>st</sup> December 2023, with data collection conducted from 1<sup>st</sup> June to 31<sup>th</sup> March 2023.

The study included women with surgically treated breast cancer, specifically invasive carcinomas classified as T0 to T3, with or without regional lymph node involvement (pN0 or pN+), but without distant metastasis (M0), according to the TNM classification. Only patients who had undergone initial surgery and completed a maximum of five years of follow-up at the Oncology and Palliative Care Department were included.

Patients with T1 to T3 invasive breast cancer who had unknown or no follow-up were excluded, as well as those with T4 invasive breast cancer or metastatic disease. Patients who received neoadjuvant treatment were also

excluded, regardless of tumor size or the presence of metastasis.

Cases were defined as patients who had undergone primary surgery, received or not received adjuvant hormone treatments (radiotherapy, chemotherapy, anti-HER2 therapy, therapy) based or immunohistochemical and experienced analysis, recurrence within five years. All patients meeting these criteria were included in the case group. Controls were women who had undergone primary surgery, received or not received adjuvant treatments, but did not experience recurrence within five years. Controls were randomly selected and not matched to cases.

The parameters studied included

Patient characteristics. Clinical and radiological characteristics of the tumor.

Surgical details

Date and type of surgery performed, including partial mastectomy (lumpectomy, quadrantectomy, pyramidectomy), total mastectomy (modified Patey procedure), and associated axillary dissection. Histopathological analysis of the surgical specimen. axillary dissection, adjuvant treatments.

#### **RESULTS**

During the study, 1,275 cancer cases were recorded, including 297 breast cancer cases (23.29%). Among these, 55 cases experienced recurrence, while 55 did not where included, with a maximum 5-year follow-up.

Table 1: Characteristics of the study population.

Characteristics	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Age at diagnoses				
<35 years	2 (3.6)	0 (0.0)	3.21 [1.4 -7.37]	0.005
35 to 49 years	24 (43.6)	12 (21.8)		
≥50 years	29 (52.7)	43 (78.2)		
Menarche				
Late menarche (≥15 years)	16 (29.1)	14 (25.5)	1.04 [0.45-2.39]	2.39
Early menarche (≤11 years)	7 (12.7)	4 (7.3)	0.53 [0.14-1.95]	0.34
Normal menarche (11-15 years)	32 (58.2)	37 (67.3)	1.47 [0.67-3.21]	0.3

Age under 50 was a significant risk factor for recurrence (OR: 3.21; CI: 1.4-7.37; p=0.005) (Table 1). cT1 tumors showed a protective effect against recurrence (OR: 0.29; CI: 0.10-0.83; p=0.017) (Table 2), with no other clinical characteristics showing a significant difference.

Partial mastectomy without axillary dissection increased recurrence risk (OR: 7.7; CI: 2.12-28.35; p=0.001), while total mastectomy with axillary dissection reduced it (OR: 0.28; CI: 0.12-0.66; p=0.003). The absence of axillary

dissection was a major risk factor (OR: 6.66; CI: 2.29-19.35; p=0.000) (Table 2).

Vascular embolus, perineural invasion, poor resection margins (R+), and higher SBR grade were significant risk factors for recurrence. Vascular/perineural invasion (OR:

2.85; CI: 1.17-6.95; p=0.019) and R+ margins (OR: 16.36; CI: 4.44-60.28; p=0.00) increased recurrence, while grade I tumors were protective (OR: 0.27; CI: 0.09-0.78; p=0.013) (Table 4).

Table 2: Clinical characteristics of breast cancer.

Characteristics	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Discovery mode				
Self-palpation	31 (56.4)	26 (47.3)	0.68 [0.32-1.47]	0.33
Clinical manifestation	23 (41.8)	28 (50.9)		
Unknown/other	1 (1.8)	1 (1.8)		
Clinical cTNM classification				
cT1	6 (10.9)	16 (29.1)	0.29 [0.10-0.83]	0.017
cT2	36 (65.5)	27 (49.1)	0.5 [0.23-1.08]	0.079
cT3	12 (21.8)	11 (20.0)	0.89 [0.35-2.25]	0.84
Unknown	1 (1.8)	1 (1.8)		
cN0	28 (50.9)	37 (67.3)	0.53 [0.24-1.18]	0.12
cN+	24 (43.6)	17 (30.9)		
Unknown	3 (5.5)	1 (1.8)		

**Table 3: Type of primary surgery.** 

Type of surgery	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Partial mastectomy without axillary dissection	17 (30.9)	3 (5.5)	7.7 [2.12-28.35]	0.001
Total mastectomy without axillary dissection	5 (9.1)	2 (3.6)	2.15 [0.39-5.32]	0.36
Partial mastectomy with axillary dissection	5 (9.1)	7 (12.7)	0.68 [0.20-2.30]	0.54
Total mastectomy with axillary dissection	28 (50.8)	43 (78.2)	0.28 [0.12-0.66]	0.003

Table 4: Pathological characteristics of surgical specimens.

Characteristics	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Histological type				
Invasive carcinoma (non-specific type)	39 (70.9)	39 (70.9)	1.40 [0.55-3.53]	0.47
Invasive carcinoma (specific type)	14 (25.5)	10 (21.8)		
Unknown	2 (3.6)	6 (10.9)		

No significant differences were observed for immunohistochemical characteristics or tumor phenotype, but pT1 tumors (OR: 0.36; CI: 0.13-0.99; p=0.043) and pN0 (OR: 0.33; CI: 0.14-0.76; p=0.009) were protective against recurrence (Table 5).

The absence of lymph node invasion (OR: 0.27; CI: 0.09-0.75; p=0.01) and the invasion of more than 25% of nodes

(OR: 5.33; CI: 1.75-16.24; p=0.002) were significant factors for recurrence. Capsular rupture was also a major risk factor (OR: 8.78; CI: 2.51-30.7; p=0.000) (Table 6).

Stage IA showed a protective effect against recurrence (OR: 0.16; CI: 0.03-0.77; p=0.012) (Table 7), while an initial CA 15-3 level >30 U/mL was a strong risk factor (OR: 6.66; CI: 1.33-33.28; p=0.01) (Table 8).

The absence of radiotherapy (OR: 3.39; CI: 1.53-7.48; p=0.002) and hormone therapy (OR: 4.07; CI: 1.81-9.15; p=0.001) were significant risk factors for recurrence.

Chemotherapy and anti-HER2 therapy showed no significant effect on recurrence (Table 9).

Table 5: Pathological TNM classification of surgical specimens.

pTNM classification	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
pT				
pT1	7 (12.7)	15 (27.3)	0.36 [0.13-0.99]	0.043
pT2	33 (60.0)	28 (50.9)	0.73 [0.33-1.61]	0.44
pT3	13 (23.6)	8 (14.5)	0.57 [0.21-1.52]	0.26
Unknown	2 (3.6)	4 (7.3)		
pN				
pN0	14 (25.5)	27 (49.1)	0.33 [0.14-0.76]	0.009
pN+	26 (47.3)	20 (36.4)	1.61 [0.73-3.53]	0.23
pNx	11 (20.0)	4 (7.4)	3.23 [0.95-10.94]	0.050
Unknown	4 (7.4)	4 (7.3)		

Table 6: Lymph node involvement characteristics.

Lymph node involvement	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
0%	8 (14.5)	21 (38.2)	0.27 [0.09-0.75]	0.010
≤ 25%	8 (14.5)	11 (20.0)	0.81 [0.28-2.37]	0.71
> 25%	16 (29.1)	6 (10.9)	5.33 [1.75-16.24]	0.002
Unknown	23 (41.8)	17 (30.9)		
Capsular rupture				
Yes	17 (30.9)	4 (7.3)	8.78 [2.51-30.70]	0.000
No	15 (27.3)	31 (56.4)		
Unknown	23 (41.8)	20 (36.4)		

Table 7: Tumor staging of breast cancer.

Tumor stage	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
IA	2 (3.6)	10 (18.2)	0.16 [0.03-0.77]	0.012
IIA	25 (45.5)	22 (40.0)	0.73 [0.33-1.62]	0.44
ПВ	16 (29.1)	12 (21.8)	1.40 [0.58-3.36]	0.44
IIIA	10 (18.2)	7 (12.7)	1.28 [0.44-3.75]	0.64
IIIB	0 (0.0)	0 (0.0)		
IIIC	0 (0.0)	0 (0.0)		
Unknown	2 (3.6)	4 (7.3)		

Table 8: CA 15-3 levels during initial management.

CA 15-3 level	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
>30 U/ml	9 (16.4)	2 (3.6)	6.66 [1.33-33.28]	0.01
≤30 U/ml	27 (49.1)	40 (72.7)		
Unknown	19 (34.5)	13 (23.6)		

Table 9: Adjuvant treatments after primary surgery.

Adjuvant treatment	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Radiotherapy				
No	39 (70.9)	23 (41.8)	3.39 [1.53-7.48]	0.002

Continued.

Adjuvant treatment	Cases (n=55) N (%)	Controls (n=55) N (%)	OR [95% CI]	P value
Yes	16 (28.1)	32 (58.2)		
Chemotherapy				
No	8 (14.5)	7 (12.7)	1.16 [0.39-3.47]	0.78
Yes	47 (85.5)	48 (87.3)		
Hormone therapy				
No	32 (58.2)	14 (25.5)	4.07 [1.81-9.15]	0.001
Yes	23 (41.8)	41 (74.5)		

# **DISCUSSION**

The mean age of patients was 54.45±11.19 years, ranging from 30 to 79. In the case group, the mean was 52.87±11.82 years (30-72), and in the control group, it was 56.02±10.38 years (35-79). These findings align with the literature: Abena et al reported a mean of 50 years (21-87), and Chauleur C et al found 57 years (27.8-87.4). 13,14 Most participants were aged 50 or older, reflecting the high prevalence of breast cancer in women over 50, as seen in other studies where the incidence in women under 35 ranges from 2% to 24%. 13-15 Age at diagnosis was a significant risk factor for recurrence, with patients aged 35-49 having a threefold higher risk (OR: 3.21; CI: 1.4-7.37; p=0.005). This is consistent with other research linking younger age to higher recurrence rates and poorer prognosis. 14-17 Differences may be due to population characteristics and selection methods, complicating the cT2 tumors were the most common in both groups: 36 (65.5%) in the case group and 7 (49.1%) in the control group. cT1 tumors were more frequent in the control group (16; 29.1%) than in the case group (6; 10.9%). cT1 classification was a protective factor, with a significant difference (OR: 0.29; CI: 0.10-0.83; p=0.017). Tumor size is a well-known prognostic factor for recurrence and should be considered alongside other factors like surgical margins to assess complete tumor resection. 18,19 Chauleur C et al found a significant link between tumor size and recurrence (p=0.0038), with larger tumors having a higher recurrence risk.<sup>20</sup> Lymph node involvement (clinically palpable adenopathy) was more common in the case group (24; 43.6%) than in the control group (17; 30.9%), but it was not statistically linked to recurrence in this study (OR: 0.53; CI: 0.24-1.18; p=0.12). Lymph node involvement is widely recognized as a key prognostic factor for breast cancer, with Chauleur C et al reporting a significant association with recurrence (p=0.0034).20 Palpable adenopathy requires thorough clinical examination, though subclinical lymph node involvement can only be detected by ultrasound or histopathological testing.

In both groups, many patients lacked a BIRADS radiological classification. ACR4 and ACR5 classifications were most common, while ACR2 and ACR3 were less frequent. The difference between groups was not statistically significant, suggesting that BIRADS classification does not influence recurrence in this study.

BIRADS is commonly used to assess tumor malignancy and guide clinical decisions, with categories 4 and 5 associated with higher recurrence risk, as noted by Kim SY et al and Gweon HM et al.<sup>21,22</sup> However, BIRADS mainly offers a diagnostic approach, while histopathological examination is the key test for determining malignancy. Discrepancies between radiological and histopathological findings may explain the lack of association between BIRADS classification and recurrence in our study.

Total mastectomy with axillary lymph node dissection was the most common surgery in both groups: 28 (50.8%) in the case group and 43 (78.2%) in the control group. Partial mastectomy without axillary dissection was more frequent in the case group (17; 30.9%) than in the control group (3; 5.5%). Partial mastectomy without axillary dissection was a significant risk factor for recurrence (OR: 7.7; CI: 2.12-28.35; p=0.001), while total mastectomy with axillary dissection was protective (OR: 0.28; CI: 0.12-0.66; p=0.003). The type of surgery is a well-established factor in recurrence risk, with the importance of proper surgical choice emphasized in the literature.<sup>17</sup> While total mastectomy was once the standard for all tumor sizes, conservative surgery is now preferred for early-stage cancers, offering similar long-term outcomes. 23,24 However, some patients treated conservatively may still experience recurrence.<sup>14</sup> The choice of surgery should be considered alongside other factors, such as resection margins and lymph node dissection quality, with tumor size playing a central role in decision-making.

his study focused solely on invasive breast carcinoma. Invasive ductal carcinoma of no special type was the most common subtype in both groups: 39 (70.9%) in the case group and 39 (70.9%) in the control group. However, histological type did not significantly affect recurrence (OR: 1.40; CI: 0.55-3.53; p=0.47). Literature on histological type and recurrence varies. Bollet et al found no significant difference between specific and non-specific invasive carcinomas (p=0.9), as did Brewster et al (p=0.55).<sup>25</sup> In contrast, Chauleur C et al found a significant association (p=0.0033).<sup>20</sup>

Stage IA breast cancers were more common in the control group (10; 18.2%) than in the case group (2; 3.6%), with stage IA identified as a protective factor (OR: 0.16; CI: 0.03-0.77; p=0.012). Stages IIA and IIB were most

frequent in both groups, with stage II representing 41 (74.1%) of cases and 34 (61.8%) of controls. This predominance of stage I and II cancers aligns with studies by Bertheau et al (73%) and Escoute et al (76.4%).<sup>26,27</sup> Tumor stage is a well-established risk factor for recurrence, with higher stages linked to increased risk. Recurrence risk based on stage should also consider factors like tumor size, lymph node involvement, and metastases.

More than half of the patients in both groups had CA 15-3 levels  $\leq$ 30 U/ml, more so in the control group (40; 72.7%) than in the case group (27; 49.1%). A CA 15-3 level >30 U/ml was a risk factor for recurrence, increasing the risk by seven times (OR: 6.66; CI: 1.33-33.28; p=0.01). CA 15-3 levels are recognized as a prognostic factor and are used for patient follow-up. Chauleur et al found that elevated levels at surgery predicted an increased risk of metastatic recurrence (p=0.03).

More than half of the control group (32; 58.2%) received radiotherapy, compared to 28.1% in the case group. 16 A higher proportion of the control group also received hormone therapy (41; 74.5%) vs. the case group (23; 41.8%). The absence of radiotherapy and hormone therapy were identified as risk factors for recurrence, increasing the risk by three times (OR: 3.39; CI: 1.53-7.48; p=0.002) and four times (OR: 4.07; CI: 1.81-9.15; p=0.001), respectively. Most patients in both groups received chemotherapy (87.3% in controls, 85.5% in cases), but neither chemotherapy nor targeted anti-HER2 therapy affected recurrence. Literature shows mixed results: Brewster et al. found chemotherapy and radiotherapy had no significant impact on recurrence risk, while hormone therapy reduced recurrence risk (OR: 84.7; CI: 80.3-88.2; p=0.001).25 Sparano et al reported the absence of chemotherapy as a recurrence risk factor, and Kurtz et al found radiotherapy reduced local recurrences when combined with surgery. 30,31 Targeted anti-HER2 therapy was too rare in this study for comparison. Although hormone therapy reduced recurrence risk here, it may have prescribed empirically due to limited immunohistochemical testing.

# Limitations of the study

This study, being retrospective in nature, was subject to inherent limitations, particularly the risk of information bias, as data were extracted exclusively from patient medical records. Additionally, the sample size, drawn from a single hospital center, may not be representative of the broader population.

Despite these limitations, the study offers valuable insight into breast cancer management in Madagascar, especially by highlighting key factors associated with recurrence after initial surgery. While it does not aim to identify all recurrence-related factors, it contributes meaningfully to understanding real-world clinical outcomes.

#### **CONCLUSION**

This study confirms that age at diagnosis, conservative surgery, the presence of vascular emboli or perineural invasion, as well as insufficient resection margins, are major risk factors for invasive breast cancer recurrence. Additionally, the extent of lymph node involvement and the absence of adjuvant treatments, such as radiotherapy and chemotherapy, have been identified as key determinants in the occurrence of recurrences. These findings highlight the need for a personalized and rigorous management approach, particularly for younger patients with high-risk tumor characteristics. Further studies are required to refine therapeutic strategies and optimize postoperative follow-up to reduce recurrences and improve the prognosis of patients with invasive breast cancer.

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Institutional Ethics Committee

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