Predictive Factors to Lymph Node Involvement on Breast Cancer

Fatores Preditivos para o Envolvimento de Linfonodos no Câncer de Mama

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ABSTRACT

Axillary lymph nodes metastases (ALM) are considered to be the most important prognostic factor for breast cancer. Data from 306 infiltrating ductal carcinomas consecutively diagnosed and treated over a period of 20 months were analised through a case-control study to assess predictive factors for the ocurrence of ALM. Bivariate analysis showed that some of variables were statistically associated ($p \leq 0.05$) with ALM: age at menarche, surgical treatment, tumor size, skin involvement, nuclear pleomorphism (NP), and vascular invasion (VI). Unconditional logistic regression reveled some independent predictive factors for ALM ($p < 0.05$): patient's age, tumor size, NP, VI, and the interaction term tumor size and patient's age, where tumor size was only predictive for ALM in patients $\geq$ 60 years. Age at diagnosis, tumor size, NP, and VI were independents predictors for ALM. C-erbB-2, cathepsin D, MIB-1, PCNA and p53, and hormonal receptors were not useful ALM predictors in bivariate and multivariate analysis.

Key words: *breast neoplasms; infiltrating duct carcinoma; biological tumor markers; neoplasms metastasis; lymph nodes.*

RESUMO

A detecção precoce do câncer de mama (CM) é um fator de reconhecida importância no tratamento e prognóstico das pacientes, e as metástases para os linfonodos axilares (MLA) são os preditores mais importantes do seu prognóstico. A partir de um estudo caso-controle com 306 carcinomas ductais infiltrantes (CDI), foi construido um modelo preditivo da ocorrência de MLA em pacientes com CM (casos: CDI com MLA; controles: CDI sem MLA). Foram estudadas variáveis relacionadas às pacientes e ao tumor (características macro e microscópicas e marcadores tumorais). Na análise bivariada, algumas variáveis se associaram estatisticamente com o desfecho em questão, porém, na regressão logística não condicional, somente as seguintes variáveis foram fatores preditivos independentes: idade da paciente, tamanho do tumor, pleomorfismo nuclear, invasão vascular e/ou linfática (IV/IL) e o termo de interação tamanho do tumor e idade da paciente, onde o tamanho do tumor só foi fator preditivo em pacientes com 60 anos ou mais. De acordo com os resultados deste estudo somente as variáveis idade da paciente, tamanho do tumor, pleomorfismo nuclear e IV/IL foram fatores preditivos para a ocorrência de MLA. Tanto os receptores hormonais quanto os marcadores tumorais estudados (c-*erb*B-2, catepsina D, MIB-1, PCNA e p53) não se mostraram importantes para predizer o desfecho em estudo, tanto na análise bivariada quanto na análise multivariada.

Palavras-chave: neoplasias mamárias; carcinoma de ductos infiltrante; marcadores biológicos de tumor; metástase neoplásica; gânglios linfáticos.

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INTRODUCTION

Breast cancer is the most important cancer among women in Brazil and a major public health issue. In 1999, 31.200 new cases and 7.300 deaths are expected in the country, accounting for 23.2% of all cancer sites among women. Differently than what happened in other industrialized countries, mammography is scarcely performed among the poorest population strata, and diagnosis is often established when the disease is already in an advanced stage.

Lymph node involvement at diagnosis is currently accepted as the most important prognostic factor to breast cancer evolution. Nevertheless, 20% to 30% of patients showing negative lymph nodes may further present disease recurrence and high mortality, thus deserving an intensive therapeutic approach usually not used in such conditions. Indeed, the ascertainment of predictive factors that allows identification of breast cancer cases of poor evolvement has become a challenge to reduce breast cancer mortality.

Other prognostic factors such tumor size, histology, nuclear pleomorphism, vascular invasion and hormonal receptors have been used to predict tumor behavior either according to overall survival or local recurrence of breast cancer.[13] On the other hand, debate still remains on the use of tumor markers as reliable predictors for breast cancer prognosis.[14-16]

Taking into account that lymph node involvement is accepted as one of the best predictors to breast cancer evolvement, and that infiltrating ductal carcinoma (IDC) is its most prevalent histological type and displays worst prognosis,[6,10,17] this study was carried out to ascertain if selected breast cancer prognostic factors are also predictors for axillary lymph nodes metastasis.

METHODS

All malignant breast tumors (incident cases) submitted to surgery with axillary lymph nodes dissection by the Mastology Service of the Cancer Hospital/Brazilian National Cancer Institute, in Rio de Janeiro, Brazil, from January 1, 1995, through August 31, 1996, ware assessed. Respective slides review was carried out twice at the Surgical Pathology Service by two pathologists (authors ALAE and LMMCR) regardless consultation to any other patient data.

Thus, 398 malignant tumors were ascertained and 306 of them classified as IDC. The later were further stratified upon the presence/absence of lymph nodes metastasis, thus yielding two groups: 162 IDC tumor patients with lymph nodes metastasis, henceforth named cases, and 144 IDC patients without lymph nodes metastasis (controls).

Macroscopic and microscopic study characteristics were the following: type of surgical specimen (quadrantectomy; segmentectomy; simple mastectomy; Patey mastectomy; radical mastectomy; other); tumor size (largest diameter in centimeters); formation of tubules ($\geq$ 75%; 10 to 74%; < 10%); nuclear pleomorphism (low; moderate; high); number of mitoses per ten high-power fields - hpf (< 10/hpf; 11 to 20/hpf; $\geq$ 20/hpf); histological grade as proposed by Bloom and Richardson[18] and later modified by Elston and Ellis[4] (well-differentiated or grade I; moderately differentiated or grade II; poorly differentiated or grade III); vascular and or lymphatic invasion; multicentricity; skin involvement; total number of lymph nodes examined; total number of lymph nodes involved by neoplasm; presence of perinodal fat infiltration, and surgical limits.

Recovery of antigen in the immunohistochemical preparations was performed by moist heat (pressure cooker), and the method of detection was the peroxidase-antiperoxidase reaction (PAP). The preparations were also analyzed at the same time by the two pathologists aforementioned. Assessment of stained neoplastic cells distribution was performed, and only those moderately or intensely stained were considered as positive; weakly stained cells were considered negative. The cut-off point used to separate positive and negative stains was 10% of stained cells (this criterion is used by various authors in the specialized literature.[7,15,19] Other cut-off points were used to quantify cells staining were: (+) 10% to 25%; (++) 25% to 75%; (+++) > 75%. For estrogen receptors, progesterone receptors, MIB-1, PCNA, and p53, nuclear positivity was considered. For c-*erb*B-2, positivity was searched in the cytoplasmatic membrane, and for cathepsin D it was the presence of stained granules in the cytoplasm of tumor cells.

Data obtained from patient files were the following: age at diagnosis; time between initial symptoms and first consultation at the HC/INCA; age at menarche; age at menopause for patients having reached menopause naturally or by surgery; number of pregnancies, births and spontaneous or induced abortions; age at first at-term delivery for patients having given childbirth; family history of breast cancer; parenthood degree according to family history of breast cancer (mother; daughter; sister; grandmother; aunt; cousin; other); family history of other types of cancer; anatomical location of family cancer (ovary; endometrium; colon; other).

Databank organization was performed using the EPI-INFO software version 6.04 (U.S. Department of Health and Human Services and Public Health Service and Centers for Disease Control, USA). Bivariate analysis was carried out and included crude odds ratios (OR) ascertainment with 95% confidence intervals (CI), in order to estimate the degree of association between the study variables and hormonal receptors status; chi-square test (χ^2) of linear trend for ordinal variables; chi square test of independence (χ^2) to evaluate null hypothesis of the observed associations; Mantel-Haenszel OR (OR_{MH}) and 95% confidence intervals, following stratification of selected variables. Further, unconditional logistic regression was developed for the construction of parsimonious models in the determination of lymph nodes metastasis as outcome in patients with breast IDC using EGRET software (*Epidemiological Graphics, Estimation, and Testing*, version 0.26.6, 1985-1991, *SERC & CYTEL*).

Independent variables tested in the multivariate analysis (logistic regression) were chosen following the previous stages (bivariate and stratified analyses) as well as biological criteria evaluated by the authors. Potential confounders and variables showing significant p-values (at 5%) for presence of interaction were selected for logistic regression, as well as variables of biological interest.

Finally, kappa coefficients were ascertained to evaluate reliability of nuclear and histological grade estimated in this study.

RESULTS

Histological grade reability among pathologists was ascertained, yielding to a kappa value of 0.83, standard error of 0.04. Similar procedure was carried out with nuclear pleomorphism identification, with kappa value of 0.90 and standard error of 0.05.

Mean and median age among cases and controls was 57 yr. old (1st quartile Q_1: 47 yr., 3rd quartile Q_3: 68 yr). The mean tumor size was 4.5 cm among cases and 3.8 among controls (χ^2 = 7,11, p=0.008). The total number of analyzed lymph nodes did not differ among cases and controls, ranging from 4 to 65 (mean 21, s=9.2, median 20, 1st quartile: 15 and 3rd quartile: 25).

Cases and controls showed similar patterns according to histological grade and mitosis number (Table 1). On the other hand,

Table 1 – Microscopic characteristics among cases and controls, Rio de Janeiro, 1995-96

	Cases	%	Controls	%	OR	95% C.I.
Histological grade						
I Well differentiated	37	22,8%	34	23,6%	1,00	[reference]
II Moderately differentiated	85	52,5%	75	52,1%	1,04	0,60-1,82
III Poorly differentiated	40	24,7%	35	24,3%	1,05	0,55-2,01
Total	162	100 %	144	100 %		
		χ^2=0,03	(p=0,99)		χ^2 trend =0,02 (p=0,88)	
Tubular structures						
≥ 75%	8	4,9%	11	7,6%	1,00	[reference]
10-74%	60	37,0%	34	23,6%	2,43	0,89-6,62
<10%	94	58,0%	99	68,8%	1,31	0,50-3,39
Total	162	100 %	144	100 %		
		χ^2=6,76	(p=0,03)		χ^2 trend =1,32 (p=0,25)	
Nuclear pleomorphism						
Low	3	1,9%	9	6,2%	1,00	[reference]
Moderate	107	66,0%	98	68,1%	3,28	0,86-12,45
High	52	32,1%	37	25,7%	4,22	1,07-16,64
Total	162	100 %	144	100 %		
		χ^2=4,88	(p=0,09)		χ^2 trend =3,32 (p=0,07)	
Mitoses						
≤ 10/hpf	83	51,2%	78	54,2%	1,00	[reference]
11 to 20/hpf	55	34,0%	44	30,5%	1,17	0,71-1,94
> 20/hpf	24	14,8%	22	15,3%	1,03	0,53-1,98
Total	162	100 %	144	100 %		
		χ^2=0,41	(p=0,8)		χ^2 trend =0,09 (p=0,77)	
Vascular invasion						
Present	68	42,0%	31	21,5%	2,64	1,54-4,54
Absent	94	58,0%	113	78,5%		
Total	162	100 %	144	100 %		
		χ^2=14,56	(p=0,0001)			

χ^2 trend: linear trend chi square statistic

Table 2 - Association between lymph node metastasis and selected variables, Rio de Janeiro, 1995-96

Variable	Comparison groups	OR crude	95% C.I.	χ^2 (p-value)
Surgery	Mastectomy *vs.* minor surgeries	4,90	2,03–12,22	16,77 (0,0001)
Vascular invasion	Present *vs.* absent	2,64	1,54-4,54	14,56 (0,0001)
Menarche	≤ 11 yr. *vs.* > 11 yr.	2,16	1,08-4,34	5,70 (0,02)
Skin involvement	Present *vs.* absent	1,85	1,04-3,33	5,04 (0,03)
Tumor size	≥ 4 cm *vs.* < 4 cm	1,65	1,00-2,71	4,46 (0,04)
Surgical limits	Affected *vs.* unaffected	1,64	0,79-3,45	2,08 (0,15)
Side	Right *vs.* left	1,37	0,85-2,22	1,89 (0,17)
Menopause	Pre-menopause *vs.* post-menopause	1,36	0,79-2,35	1,41 (0,24)
Symptoms onset	< 6 months *vs.* ≥ 6 months	1,29	0,79-2,12	1,16 (0,28)
Multicentricity	Present *vs.* absent	1,26	0,69-2,30	0,64 (0,42)
Parity	≤3 pregnancies *vs.* >3 pregnancies	1,22	0,70-2,10	0,57 (0,45)
Estrogen receptors	Negative *vs.* positive	1,20	0,74-1,95	0,64 (0,42)
Patient's age	< 60 yr. *vs.* ≥ 60 yr.	1,18	0,72-1,92	0,48 (0.49)
PCNA	Positive *vs.* negative	0,77	0,45-1,32	1,05 (0,31)
p53	Positive *vs.* negative	0,66	0,35-1,25	1,90 (0,17)
Age first pregnancy	≥ 30 yr. *vs.* < 30 yr.	0,59	0,24-1,46	1,58 (0,21)

Table 3 - Association between lymph node metastasis and tumor size by selected variables, Rio de Janeiro, 1995-96

Variables	OR crude	Comparison groups	OR (95% C.I.)	OR_{MH} (95% C.I.)	Interaction p-value
Surgery	1,65	Mastectomy	1,14 (0,67-1,95)	1,24 (0,76-2,01)	0,09
		Minor surgeries	10,80 (0,57-385,58)		
Vascular invasion	1,65	Present	1,96 (0,75-5,16)	1,44 (0,89-2,33)	0,41
		Absent	1,26 (0,68-2,35)		
Menarche	1,55	≥ 11 yr.	1,29 (0,33-5,08)	1,59 (0,99-2,58)	0,70
		> 11 yr.	1,66 (0,94-2,93)		
Skin involvement	1,65	Present	1,31 (0,39-4,33)	1,48 (0,92-2,38)	0,80
		Absent	1,52 (0,86-2,72)		
Surgical limits	1,63	Affected	1,65 (0,37-7,48)	1,59 (1,00-2,54)	0,95
		Unaffected	1,58 (0,92-2,71)		
Size	1,65	Right	1,51 (0,73-3,13)	1,62 (1,02-2,59)	0,78
		Left	1,73 (0,85-3,55)		
Menopause	1,57	Pre-menopause	0,74 (0,27-2,02)		0,06
		Post-menopause	2,09 (1,12-3,88)		
Symptoms onset	1,61	< 6 months	1,90 (0,95-3,80)	1,64 (1,02-2,65)	0,49
		≥ 6 months	1,35 (0,61-3,02)		
Multicentricity	1,54	Present	1,30 (0,39-4,30)	1,54 (0,95-2,47)	0,72
		Absent	1,60 (0,90-2,85)		
Parity	1,54	≤ 3 pregnancies	1,88 (1,03-3,45)	1,57 (0,98-2,52)	0,23
		> 3 pregnancies	0,98 (0,36-2,69)		
Estrogen receptors	1,65	Negative	1,38 (0,63-3,04)	1,62 (1,01-2,61)	0,56
		Positive	1,84 (0,92-3,66)		
Patient's age	1,59	< 60 yr.	0,99 (0,49-1,97)		0,04
		≥ 60 yr.	2,77 (1,26-6,17)		
PCNA	1,65	Positive	1,65 (0,92-2,95)	1,67 (1,05-2,67)	0,93
		Negative	1,73 (0,61-4,96)		
P53	1,65	Positive	0,75 (0,21-2,66)	1,72 (1,08-2,75)	0,10
		Negative	2,07 (1,18-3,64)		
Age first pregnancy	1,46	≥ 30 yr.	2,72 (0,35-22,95)	1,47 (0,79-2,75)	Not calculated
		< 30 yr.	1,34 (0,64-2,80)		
Nuclear	1,65	Low	0,00 (0,00-57,86)	1,54 (0,96-2,49)	Not calculated
		Moderate	1,94 (1,04-3,62)		
		High	0,96 (0,35-2,62)		
Tubular structures	1,65	≥ 75%	1,40 (0,13-15,75)	1,69 (1,05-2,70)	0,55
		10-74%	1,16 (0,45-3,02)		
		< 10%	2,05 (1,08-3,90)		

cases showed higher proportions of tumors displaying less tubular structures (p=0.03), higher nuclear pleomorphism (p =0.09) and vascular invasion (p=0.0001). Bivariate analysis carried out with several variables and lymph nodes metastasis as outcome (Table 2) revealed statistically significant odds ratios (OR) for the following: surgery (mastectomy *vs.* minor interventions), OR 4.90 (95% C.I. 2.03-12.22); vascular invasion, OR 2.64 (95% C.I. 1.54-4.54); age at menarche, OR 2.16 (95% C.I. 1.08-4.34); skin involvement OR 1.85 (95% C.I. 1.04-3.33); and tumor size, OR 1.65 (95% C.I. 1.00-2.71).

Stratified analysis with several variables was performed on the association between tumor size and lymph nodes metastasis aiming to control potential confounding (Table 3). Mantel Hanszel odds ratios (OR_{M-H}) were obtained for the following variables: tumor p53, OR_{M-H} 1.72 (95% C.I. 1.08-2.75); PCNA, OR_{M-H} 1.67 (95% C.I. 1.05-2.67), nuclear pleomorphism OR_{M-H} 1.54 (95% C.I. 0.96-2.49); tubular formation, OR_{M-H} 1.69 (95% C.I. 1.05-2.70); estrogen receptor, OR_{M-H} 1.62 (95% C.I. 1.01-2.61); parity, OR_{M-H} 1.57 (95% C.I. 0.98-2.52); age at menarche, OR_{M-H} 1.59 (95% C.I. 0.99-2.58); breast side (right *vs.* left), OR_{M-H} 1.62 (95% C.I. 1.02-2.59). Effect modification (interaction) in the aforementioned association was observed with the variables patient's age (p=0.04) and menopause (pre *vs.* post), p=0.06 (Table 3).

Finally, unconditional logistic regression was carried out and a parsimonious model including the variables nuclear pleomorphism, lymphatic invasion, patient's age, tumor size and an interaction term between patient's age and tumor size (likelihood ratio test = 24.66, 5 d.f., p<0.001) was chosen (Table 4).

DISCUSSION

Selection and information bias are usually a main flaw in case-control studies. Aiming to ascertain their influence in this investigation, we evaluated some potential key variables which could influence our results. The first one was the time interval between initial symptoms and first consultation among cases and controls (p=0.51), which indicates absence of statistically significant differences among both groups according to this variable.

Differential probability of lymph nodes metastasis identification among cases and controls was searched towards the distributions of reviewed lymph nodes (p=0.42). Thus, both groups did not differ according to total number of reviewed lymph nodes, suggesting they had had similar probabilities to have identified lymph nodes metastasis if present.

In some series, the majority of breast cancer cases was diagnosed among women 45-50 yr. old,[9] but ours was older (median age at diagnosis 57 yr. old). As previously reported by Recht and Houihan,[20] we also observed a weak and statistically non significant association between age at diagnosis and lymph nodes involvement. A statistically significant association between age at menarche (11 yr. as a cut-off point) and lymph nodes involvement was also observed in our data (Table 2).

Tumor size, the most important predictor of lymph nodes involvement in breast cancer, showed a statistically significant association with that outcome (p<0.05), and revealed the dramatic reality still observed in Brazil according to breast cancer medical care: median tumor size in our data was 4.0 cm.

Despite some debate,[20] histological grade is also acknowledged as an important predictor for lymph nodes involvement in the literature, and high grade tumors have been related to an increased frequency of lymph nodes metastasis and to a poor evolution.[2,4,17]

In our study, histological grade was ascertained towards a blind evaluation carried out by two pathologists following Bloom and Richardson[18] procedures, further modified by Elston and Ellis.[4] Reliability analysis revealed an inter-observer agreement of 83% (p<0.0001), being 90% for nuclear pleomorphism (p<0.0001). Any association between histological grade and metastasis presence was observed, but a borderline association between nuclear pleomorphism and metastatic lymph nodes involvement (p=0.07) was observed (Table 1).

Vascular invasion has been reported in the literature ranging between 5% to 49%,[5,22] and we observed this condition in 32.4% of patients, being twice more frequent among cases than controls (vascular invasion was considered as positive whenever reported by both pathologists, and negative otherwise). This condition has also been associated as an independent predictor for breast cancer evolution in terms of general survival, metastasis-free survival and disease-free survival.[5,22-25] Accordingly with the literature[10,20,2] our data revealed an association between vascular invasion and axillary lymph nodes metastasis (p<0.0001).

Table 4 – Model parameters (unconditional logistic regression), cases and controls, Rio de Janeiro, 1995-96

Terms	p-value	OR	95% C.I.
β_0	0,011	0,62E-01	0,74E-02-0,53
Moderate vs. low pleomorphism	0,046	8,607	1,043-70,99
High vs. low pleomorphism	0,032	10,44	1,228-88,80
Vascular invasion	< 0,001	2,543	1,483-4,359
Patient's age	0,041	2,075	1,031-4,177
Tumor size (women ≤ 60 yr.)	0,025	2,367	1,113-5,033
Tumor size (women < 60 yr.)	0,027	0,7669	0,3917-1,502

Likelihood ratio test = 24.658, 5 d.f., p < 0.001

Despite several reports on the association of hormonal receptors with a better evolution in breast cancer,[2,3,13] some divergent observations have also been published.[2,2] In accordance to the latter, our data does not support an association between hormonal receptors and absence of metastasis to axillary lymph nodes among breast cancer patients.

Usually, breast cancer patients without axillary lymph nodes involvement do not present metastasis and local recurrence; therefore, they do not require adjuvant therapy. Nevertheless, some present a different evolution, remaining a challenge their identification. The use of acknowledged prognostic factors for patients without lymph nodes involvement further presenting poor survival has offered a weak contribution, and the search of new ones has been stimulated. Among them, *c-erb*B-2,[24,2] Cathepsin D,[15] MIB-1,[13,17] PCNA[11,14] and p53[8] have been suggested.

High *c-erb*B-2 expression has been reported in breast cancer, ranging between 15 to 64%.[30,31] In our data, 34.6% of tumors revealed membrane positivity to c-*erb*B-2, and only 7.5% showed diffuse positivity. Accordingly to other authors, [19,32,33]our study also did not find association between c-*erb*B-2 and axillary lymph nodes metastasis, which remains a controversial result not observed by some researchers.[34,35]

Increased cathepsin D expression was ascertained in this study by citoplasmatic immuno-reactivity of tumor cells as reported elsewhere.[15,36] Similarly than reported by others,[37,38] an association between cathepsin D expression and lymph nodes involvement was not observed in our data.

The rate of tumor cell proliferation is an important and sensitive prognostic marker of different cancer sites including breast cancer. Different methods, such as microscopic morphometry, flux citometry and immunohistochemistry, among others,[39] and antigens such as PCNA, MIB-1 and Ki-67[40] have been developed to evaluate this cellular activity.

The IDC analyzed in this study revealed 59.5% of positivity to MIB-1 and 72.2% for PCNA, being both markers strongly associated in this study ($p<0.0001$). A similar observation was reported by Haerslev et al.[11] In accordance to some reports[14,41] and disaccord to others,[11,42] statistically significant association between MIB-1 or PCNA with axillary metastasis was not observed in our study.

Mutated p53 gene is quite a common phenomena in several human tumors, particularly breast cancer, which accumulate anomalous p53 protein in tumor cell nucleus. The p53 nuclear immunoreactivity has been considered an indirect indicator of p53 gene mutation, and has been detected in breast cancer ranging from 9% to 52%.[8,]

In our study, 17.6% IDC displayed p53 positivity, and, differently than reported in the literature, a statistically non-significant inverse association between p53 and lymph nodes involvement was observed (OR 0.66, 95% C.I. 0.35-1.25, $p=0.17$). In a review carried out by Barbareschi,[8] the association between p53 and lymph nodes involvement was just observed in one among eight studies. Sirvente et al.,[16] Wakasugi[44] also did not find such association, while Chen et al.,[35] Hanzal et al.[45] found it. As a whole, such divergent results reinforce Barbareschi[8] point-of-view on the need for further research to confirm whether p53 could be indeed considered as an independent predictor to breast cancer evolution.

Following multivariate analysis, the predictive variables included in our model were age at diagnosis, tumor size, nuclear pleomorphism, vascular invasion and the interaction term between tumor size and age. Highest odds ratio (Table 3) were observed for nuclear pleomorphism (moderate *vs.* low grade, OR 8.61, 95% C.I. 1.04-70.99, $p<0.05$, and high *vs.* low grade, OR 10.44, 95% C.I. 1.23-88.8, $p<0.05$).

Analyzing the inclusion of an interaction term between tumor size and age, we observe the latter modifies the effect on the association between tumor size and axillary lymph nodes metastasis. Therefore, that association among women 60 yr. or older diagnosed with breast cancer provides a moderate risk estimate (OR 2.37, 95% C.I. 1.11-5.03), meanwhile no association is observed among younger women (OR 0.77, 95% C.I. 0.39-1.50). This model is in accordance with others previously reported in the literature.[2,6,10,17]

CONCLUSIONS

In this study, the best predictive variables to axillary lymph nodes involvement in breast cancer were patient´s age, tumor size, nuclear pleomorphism and vascular invasion. Neither hormonal receptors nor selected tumor markers (c-*erb*B-2, cathepsin D, MIB-1, PCNA and p53) were good predictors for that outcome in the studied sample.

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