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Breast Cancer Risk and Prognostic Factors in Two Argentine Settings

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ABSTRACT

Objectives: The purpose of this study was to compare risk and prognostic factors of invasive breast cancer in two Argentine populations. Patients and Methods: a total of 625 women with invasive breast cancer at different stages were studied: 270 patients from the city of La Plata, and 355 patients from the city of Neuquén. Demographic features and reproductive history were considered as risk factors, while prognostic factors included histopathological features. Statistical analysis was performed. Results: The age at diagnosis was significantly lower in Neuquén than in La Plata; stage III was observed in La Plata at a mean age of 49 years versus 54 years in Neuquén; cutaneous and/or thoracic wall invasion was found at diagnosis in Neuquén, while it was absent in all La Plata patients. Tumor size versus age showed a negative statistical significant relationship; the percentage of HER2/neu-positives in Neuquén was significantly higher than in La Plata, while estrogen/progesterone receptor status showed the contrary. Histological and nuclear grades in Neuquén compared to La Plata were significantly higher, while vascular invasion showed the converse. Considering the number of children, significant differences between groups were found, and also, patients who had breastfed presented a lower number of metastatic lymph nodes than those who had not. Conclusions: La Plata and Neuquén constitute two different populations. The factors that contribute to dividing the groups could be related to the malignant histological characteristics of the tumors, but also the length of breastfeeding and number of children could play a role. (J CANCEROL. 2015;2:??-??)

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Key words: Breast cancer. Risk factor. Prognostic factor. Socioeconomic status. Argentine setting.

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INTRODUCTION

In Argentina, breast cancer is a remarkable and serious health problem; it has been estimated that there are 17,000 new cases of breast cancer diagnosed each year (total Argentine population: 42,154,000 inhabitants). This tumor location is the commonest cause of cancer death in women, reaching 5,400 deaths per year[1], and constitutes the second highest mortality rate in Latin America (National Ministry of Health 2009). In Argentina, there are no studies evaluating breast cancer risk and prognostic factors in different geographical areas.

Breast cancer risk factors include age at menarche and menopause, age at first full-term pregnancy, number of live births, and breastfeeding[2,3] since they impact on lifetime number of ovulatory cycles modifying the exposure to endogenous ovarian hormones[2,4].

The discovery of highly penetrant breast cancer susceptibility genes, such as the BRCA genes in the mid 1990s[5], emphasized the importance of genetic factors; also, a family history of breast cancer is related to genetic influences.

In addition to genetic and reproductive factors, the combination of social, economic, and environmental characteristics is considered to be breast cancer risk factor[6,7]. Furthermore, influences on incidence rates have also been attributed to differences in the use of mammography, diet, physical activity, body size, and alcohol consumption[8].

On the other hand, a variety of clinical and pathological factors are used to categorize patients in order to assess prognosis. These include, among others, age, axillary lymph node status, tumor size, disease stage, histological and nuclear grade, lymphovascular invasion, hormone receptor status, and HER2/neu status. Many prognostic factors are related to early diagnosis, which emphasizes socioeconomic status.

Also, other factors may play an important role in the etiology of breast cancer. Incidence rates for breast cancer vary throughout the world and it is currently believed that environmental factors and migrations are important issues[9-11].

The purpose of this research is to study and compare risk and prognostic factors in two groups of Argentine patients with primary invasive breast cancer belonging to two different settings.

MATERIALS AND METHODS

Study participants and data collection

A total of 625 women who had a histologically confirmed diagnosis of invasive primary breast cancer were included; 270 patients were from a private clinic in the city of La Plata (province of Buenos Aires) and 355 patients from a Public Hospital in the city of Neuquén (province of Neuquén). All women meeting residential and first diagnosed with invasive primary breast carcinoma in 2002 to 2007 were eligible as cases. There were no racial or ethnic differences between the two groups of women; all of them were born in Argentina.

The Argentine Healthcare System includes public health care, which is owned by the Government, Medical Insurance, and the private sector.

The city of La Plata is the capital of the province of Buenos Aires with 650,000 inhabitants, while Neuquén is the capital of the province of Neuquén with 550,000 inhabitants and is located in Patagonia, 1,160 km to the southwest of La Plata.

Risk and prognostic factors are summarized in table 1. Staging was performed following the American Joint Committee on Cancer (AJCC) guideline 2002. Estrogen receptor (ER) and progesterone receptor (PR) cutoff values were ≥ 5% of the total, while HER2/neu status was determined by immunochemistry as HER2/neu 3-positive[12].

Table 1. Risk and prognostic factors in La Plata and Neuquén patients

Risk factors		LPP	NP
Age at diagnosis (2)			
– ns < 0.05	± sd	56 ± 14	53 ± 13
– Range		25-92	25-89
• ≤ 35		%	%
• 36-45		4.0	7.0
• 46-55		19.1	20.2
• 56-65		20.7	29.8
• 66-75		24.9	21.3
• > 75		17.3	21.2
		13.4	7.0
Menarche (2)			
– ns < 0.05	± sd	12.9 ± 1.5	13.0 ± 1.4
– Range		10-16	8-17
Menopause (1)		47.2 ± 5.6	47.0 ± 5.9
– ns < 0.0	± sd		
– ns	Premenopausal	43%	44%
	Postmenopausal	57%	56%
Breastfeeding (3)		6.9 ± 9.4	9.6 ± 9.8
– s, p < 0.05,	± sd		
– Range (months)		0-48	0-72
– s, p < 0.0001	yes	51.7%	77.7%
– OR 6.923	no	48.3%	22.3%
Parity (3)			
– ns	± s.d	1.9 ± 1.2	2.7 ± 2.0
– s, p < 0.001		0-4	0-16
– Range			
– s, p < 0.03	yes	74.3%	87.3%
– OR 3.766	no	25.7%	12.7%
– Prognostic factors		LPP	NP
Metastatic lymph nodes (1, s and 3, s)			
– s, p < 0.02	± sd	1.6 ± 14.3	2.9 ± 4.9
– s, p < 0.0001	Negative (1)	76,0%	50,5%
– OR 3.105	Positive		
– s, p < 0.02	≤ 3 (2)	9.0%	25.0%
– OR 1.994	> 3 (3)	14.0%	23.2%
– Not assessed		1.0%	1.3%
Tumor size (1, s and 3, s)			
– s, p < 0.008	± sd cm	1.55 ± 0.65	1.80 ± 0.88
– ns	T1	53.0%	42.0%
– ns	T2	40.0%	42.0%
– s, p < 0.03, OR 9.24	T3	7.0%	16.0%
Differentiation degree (1, s and 3, s)			
– s, p < 0.0001		2.08 ± 0.66	2.50 ± 0.63
– s, p < 0.0001, OR 1.93	well	17.2%	7.9%
– s, p < 0.0001, OR 1.446	moderate	55.2%	35.8%
– s, p < 0.0001, OR 2.66	poor	27.6%	59.2%

(Continued)

Table 1. Risk and prognostic factors in La Plata and Neuquén patients *(continuation)*

Risk factors		LPP	NP
Differentiation degree (1, s and 3, s)			
– s, p < 0.0001		2.08 ± 0.66	2.50 ± 0.63
– s, p < 0.0001, OR 1.93	well	17.2%	7.9%
– s, p < 0.0001, OR 1.446	moderate	55.2%	35.8%
– s, p < 0.0001 OR 2.66	poor	27.6%	59.2%
Nuclear grade (1, s and 3, s)			
– s, p < 0.001	± sd	1.9 ± 0.8	2.2 ± 0.7
– s, p < 0.0001, OR 0.347	1	34.3%	15.1%
– s, p < 0.0001, OR 2.884	2	39.4%	50.3%
– s, p < 0.0001, OR 2.967	3	26.3%	34.6%
Vascular invasion (3, s)			
– s, p < 0.02	Positive	28.0%	17.4%
– OR 0.561	Negative	72.0%	82.6%
Estrogen/progesterone receptors (3, s)			
– s, p < 0.02	Positive	82.1%	72.8%
– OR 0.522	Negative	17.9%	27.2%
HER2/neu (3, s)			
– s, p < 0.004	Positive	15.9%	32.4%
– OR 2.864	Negative	85.9 %	68.5%

LPP: La Plata patients; NP: Neuquén patients; sd: standard deviation; ns: non-significant; s: significant; OR: overall risk.

The populations included in this study comprised women who were treated at institutions related to the Faculty of Medical Sciences of the National University of La Plata. Procedures followed the World Medical Association Declaration of Helsinki (Finland, 1964) and further modifications. Each participant gave written consent and data were made anonymous and coded into a database. All data were obtained from clinical records. This research was approved by the local Ethical Investigation Committees.

Variables description

Variables included in the analysis as risk factors were: age at diagnosis, which was treated as continuous and grouped in five classes as follows ≤ 25, 26-35, 36-45, 46-55, 56-65, 66-75, ≥ 75 years;

age at menarche, which was treated as continuous only; menopause, which was treated as continuous or grouped as binomial premenopausal and postmenopausal; breastfeeding, which was recorded as continuous in months, with discrete groups 0, 1-3, 4-6, 7-12, 12-24, 24-60, ≥ 60 years and binomial as yes or no; finally, parity was treated as discrete (number of children) and binomial as yes or no.

Variables considered in the analysis as prognostic factors included metastatic lymph nodes, which were discrete, and data were grouped as negative, ≤ 3, and > 3, while cases excluded from some analysis were those "not assessed". Tumor size was treated as continuous, expressed in centimeters, and with three discrete groups (T1, T2, T3; AJCC, 2002); differentiation degree was discrete from well (1), moderate (2), and poor (3) (AJCC, 2002), while nuclear degree was discrete; finally, vascular invasion, estrogen and progesterone receptors, and HER2/neu expression were binomial as positive and negative.

Data analysis

Patients were grouped, taking into account risk and prognostic factors, and positive responses were evaluated by means of frequency analysis (Chi-Square test $p < 0.05$)[1]. Normality of continuous variables was tested by Kolmogorov-Sminorv test and data were normalized when necessary; some of them were grouped to be included in frequency analysis, and differences of continuous and discrete variables between groups were analyzed employing analysis of variance (ANOVA; $p < 0.05$). Logistic regression analysis was applied to binomial and multinomial variables[13,14].

RESULTS

Risk factors under analysis are summarized in table 1. A demographic characteristic considered here was age at diagnosis. The average age of both populations did not show any significant differences. However, when frequency analysis was performed at the grouped ages, a significant difference was found ($p < 0.05$) since 63% of Neuquén patients were less than 55 years old versus 44% of La Plata patients.

In La Plata, approximately one in two women have never breastfed and as many as 74.3% had at least one child, while in Neuquén one in four have never breastfed and 87.3% had at least one child. Breastfeeding showed significant differences between groups ($p < 0.05$) (Fig. 1). Taking into account the number of children, significant differences between groups were found (Table 1, Fig. 2). In contrast, age at menarche and menopause status did not present significant differences between groups.

In La Plata patients, disease stages were: stage I, 36%; stage II, 38%; stage III, 24%; and stage IV, 2%; while in Neuquén patients, disease stages were: stage I, 14.5%; stage II, 47.4%; stage III, 28.4%; and stage IV, 9.7%. While stage III was observed at a mean age of 49 years in La Plata patients, in Neuquén patients it was observed at 54 years (significant difference); considering this parameter, a remarkable difference between the two populations was found since cutaneous and/or thoracic wall invasion was found at diagnosis in 14.5% of Neuquén patients, while it was absent in all La Plata patients.

Prognostic factors corresponding to La Plata and Neuquén patients are also summarized in table 1. With respect to axillary nodal status, ANOVA showed significant differences between La Plata and Neuquén patients. Both groups showed advanced stages in younger patients.

In order to compare lymph node group frequencies in both populations, a frequency analysis was performed and significant differences between the patterns of distribution were found ($p < 0.005$).

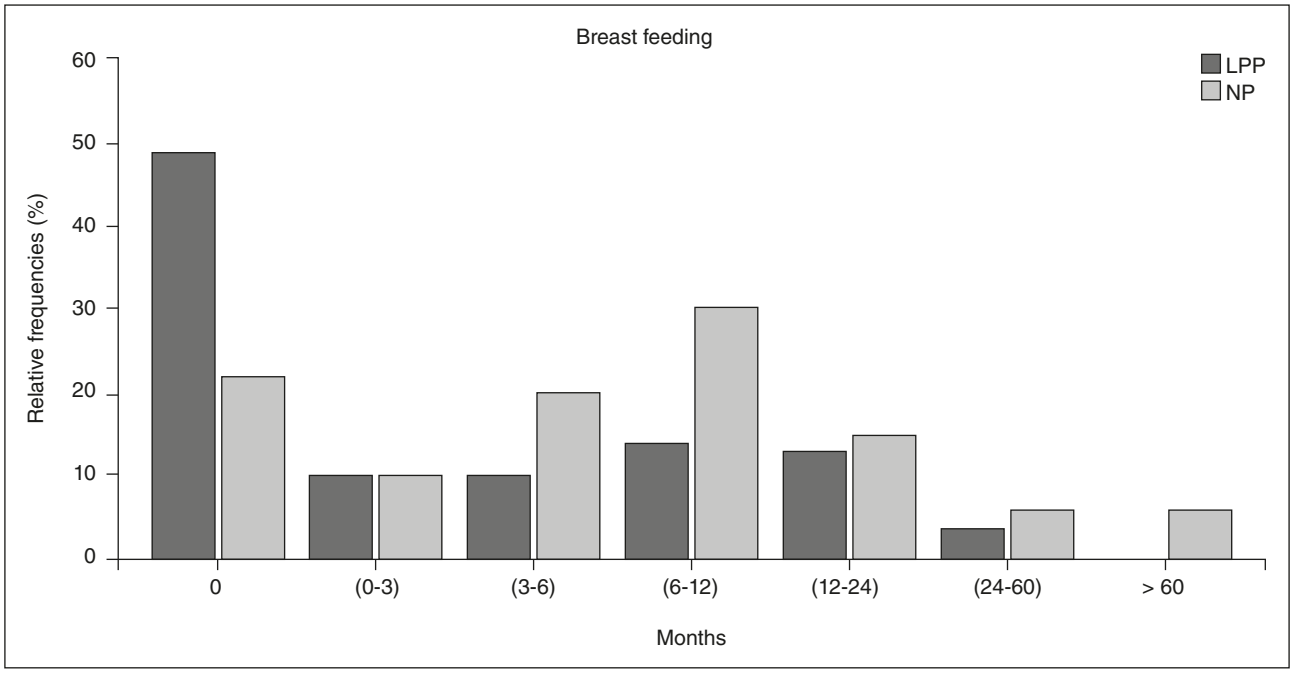

Figure 1. Distribution of breastfeeding in Neuquén and La Plata patients (significant differences by ANOVA p < 0.0001 and OR 6.923). Results are expressed as percentages. LPP: La Plata patients; NP: Neuquén patients.

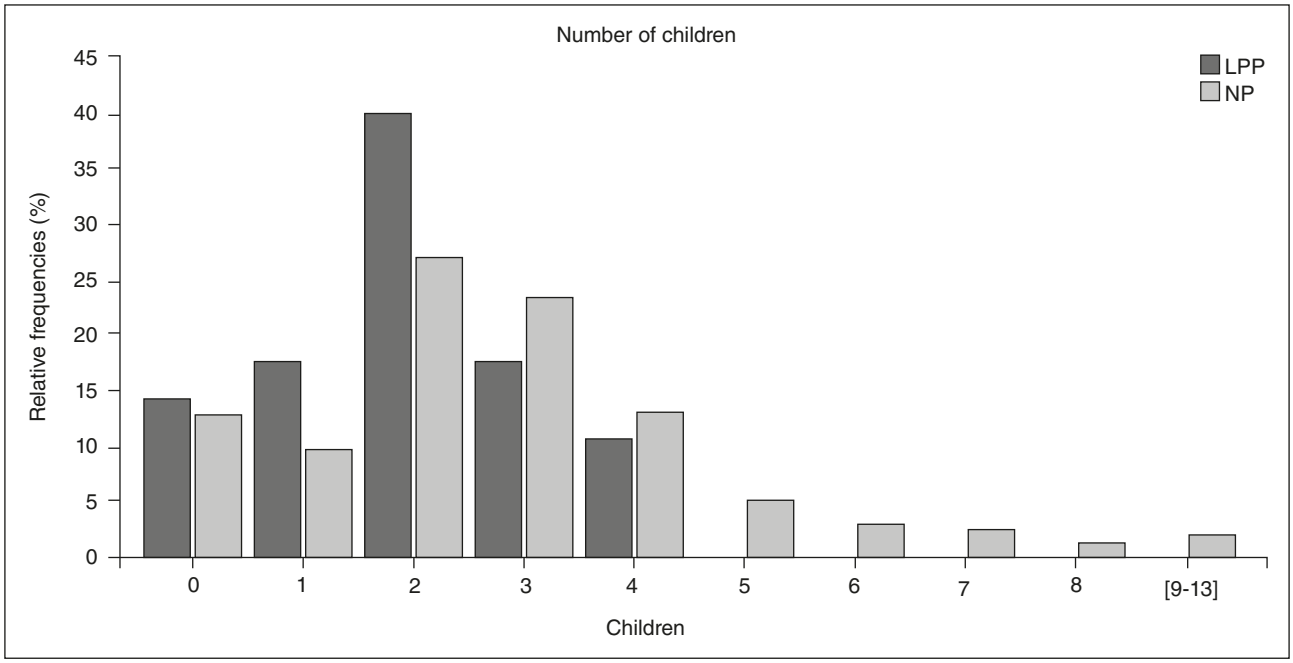

Figure 1. Distribution of breastfeeding in Neuquén and La Plata patients (significant differences by ANOVA p < 0.0001 and OR 6.923). Results are expressed as percentages. LPP: La Plata patients; NP: Neuquén patients.

Table 2. Percentage distribution of La Plata and Neuquén patients grouped according to their estrogen receptor, progesterone receptor, and HER2/neu statuses

Tumor subtypes (ER/PR/HER2/neu)	LPP	NP
Luminal A-like +/+/–	73.1%	58.0%
Luminal B-like +/+/+	9.0%	22.8%
HER2 overexpression –/–/+	6.9%	9.6%
Basal-like –/–/–	11.5%	9.6%

ER: estrogen receptor; PR: progesterone receptor; LPP: La Plata patients; NP: Neuquén patients.

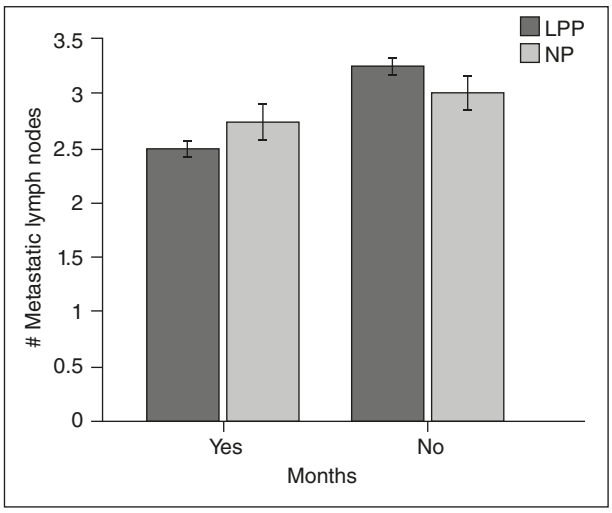

Figure 3. Number of metastatic lymph nodes in patients with children and who breastfed versus patients without children and did not breastfeed in Neuquén and La Plata patients ($p < 0.005$). LPP: La Plata patients; NP: Neuquén patients.

Tumor sizes (T) at diagnosis were: 53% of La Plata patients presented T1; 40%, T2; and 7%, T3; while 42% of Neuquén patients presented T1; 42%, T2; and 16%, T3. ANOVA showed statistical differences between populations ($p < 0.008$); frequency analysis supported the ANOVA results ($p < 0.005$). Two-way ANOVA showed that for a determined tumor size, Neuquén patients had a higher number of metastatic lymph nodes than La Plata patients ($p < 0.0001$). In general, tumor size versus age showed a negative relationship; this observation was only significant for La Plata patients ($p < 0.02$).

Histological differentiation and nuclear grade in Neuquén patients compared to La Plata patients were significantly higher: $p < 0.00001$ and $p < 0.0006$, respectively. However, tumors of La Plata patients showed more vascular and lymphatic invasion compared to Neuquén patients ($p < 0.01$).

The HER2/neu status presented differences between the two populations. The percentage of positive Neuquén patients was significantly higher than positive La Plata patients ($p < 0.05$). With respect to ER/PR status, the contrary was found (Table 1), and HER2/neu-positive Neuquén patients were more frequently < 55 years old. Furthermore, patients were grouped according to ER, PR, and HER2/neu expression; the results are summarized in table 2. Significant differences were found in the group $ER^+/PR^+/HER2/neu^-$ and $ER^+/PR^+/HER2/neu^+$; in triple positive groups, La Plata patients were younger than Neuquén patients (mean age 45.3 vs. 51.6 years), while the contrary was found in triple-negative Neuquén patients (Neuquén patients: 48.5 years old vs. La Plata patients: 54 years old).

In both populations, it was observed that patients who had breastfed presented a lower number of metastatic lymph nodes than those who had not; employing ANOVA, significant differences were found ($p < 0.005$) (Fig. 3).

DISCUSSION

In order to clarify the influence of risk and prognostic factors in breast cancer, we performed a comparison of these factors in two Argentine patient populations with different geographical locations and different health systems.

Although there were no ethnic differences between La Plata and Neuquén patients, analyzing risk and prognostic factors we concluded that these two groups constituted two different populations. The

factors that contributed to divide the groups were in part related to the malignant histological characteristics of the tumors, such as histological differentiation and nuclear grade, which were higher in Neuquén patients than in La Plata patients, while vascular invasion was more frequently found in La Plata patients. Added to this, the expression of ER, PR, and HER2/neu was different in both populations; employing these parameters, we subdivided the patients in different groups (Table 3).

Table 3. Percentage of tumors that showed vascular and lymphatic invasion in relation to disease stage

Stage/Group	LPP %	NP %
I	16.6	11.9
II	28.2	18.2
III	41.6	23.2
IV	100.0	15.0

LPP: La Plata patients; NP: Neuquén patients.

In our study, we found that Neuquén patients were diagnosed at a younger age than La Plata ones, and Neuquén patients presented more disseminated disease at first diagnosis (stage I was present in 36% of La Plata patients in contrast to 14.5% in Neuquén patients); also, tumor size was significantly higher in Neuquén than in La Plata patients. Factors considered to reduce breast cancer risk are also related to lifestyle and cultural customs, such as number of births and breastfeeding. In our study, these factors were higher in Neuquén than in La Plata patients and, in both populations, we found an inverse relationship between these factors and the number of metastatic lymph nodes. This inverse relationship is interesting because, as it is known, breastfeeding diminishes the risk of breast cancer[3]. A large study performed in the UK in 2002 compared breastfeeding history in women who had breast cancer with women who had not. It involved the histories of 50,000 women with breast cancer and nearly 100,000 women without. The longer the women had breastfed during their lifetime, the less likely they were to get breast cancer. According to this study, breastfeeding lowered breast cancer risk by 4.3% for every year of breastfeeding; there is also a 7% reduction in risk of breast cancer for each child born. It is possible that these differences may be explained, at least partially, by the fact that breast tissue of normally cycling women contains different identifiable types of lobules and, during pregnancy and lactation, progression from ductules to secretory acini fully differentiated occurs[15]. More differentiated lobular structures have been found to originate in tumors whose malignancy is inversely related to the degree of differentiation of the parent structure[16]; it could also be possible that cancer cells present in parous women could have a lesser capability of metastasis. On the other hand, a mutagenic event may take place early in life in the primitive ductal structures or during puberty and could multiply during puberty and develop cancer[15].

Finally, in comparison with women from developed countries, in both Argentine populations, breast cancer was diagnosed at a younger age and presented more advanced stages at diagnosis. In this sense, in USA women, invasive breast cancer stages in 2010 were: stage I, 52%; stage II, 31%; stage III, 11%; and stage IV, 5% and mean age at diagnosis was 61 years; the highest number of women were diagnosed between 55 and 64 years old[17]. These figures are different from the Argentine ones, and the differences have been related to many risk factors[18-20].

Our findings provide important information for designing detailed studies that aim to improve our understanding of the epidemiology and the biology of breast cancer in the Argentine population, and to design targeted campaigns for prevention and early diagnosis.

DECLARATION OF INTERESTS

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