

# Psoriasin (S100A7) Expression Is Associated with Poor Outcome in Estrogen Receptor-negative Invasive Breast Cancer<sup>1</sup>

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## ABSTRACT

**Purpose:** Psoriasin (S100A7) is highly expressed in pre-invasive ductal carcinoma *in situ* of the breast and persistent expression occurs in some invasive carcinomas. This study explores the clinical significance of psoriasin in relation to patient survival in invasive breast cancer.

**Experimental Design:** We examined psoriasin expression by immunohistochemistry in a cohort of 122 estrogen receptor-negative invasive ductal carcinomas.

**Results:** Psoriasin expression was observed in 64 of 122 cases (52%) but was not correlated with other prognostic factors (including progesterone receptor, stage, size, grade, and nodal status) within this cohort. However, in univariate analysis, psoriasin expression (nuclear and cytoplasmic) was associated with a shorter time to progression ( $P < 0.04$ ) and poor survival ( $P < 0.03$ ). In multivariate analysis, cytoplasmic psoriasin also emerged as independent indicator of time to progression (hazard ratio, 1.86; 95% confidence interval, 1.02–3.39;  $P = 0.044$ ) and survival (hazard ratio, 2.12; 95% confidence interval, 1.06–4.23;  $P = 0.033$ ).

**Conclusions:** These results suggest that psoriasin expression may be associated with a worse prognosis in estrogen receptor-negative invasive ductal carcinomas and raise the possibility that psoriasin expression may also be an indicator of risk of progression in ductal carcinoma *in situ*.

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## INTRODUCTION

The management of breast carcinoma depends on the estimation of the biological potential for progression. However, as diagnosis increasingly occurs at earlier stages in the natural history of the disease, established indicators such as nodal status are lacking as discriminators of low and high risk of progression (1, 2). Treatment decisions must increasingly rest on tissue-based morphological markers (2) of behavior such as tumor grade and steroid receptor status (3) and the identification of additional biological markers is needed (1). The development of invasiveness is perhaps the most critical biological event and factor in early breast cancer progression (4, 5). It is likely that genes associated with invasiveness may offer improved prognostic markers in early preinvasive and invasive disease and that such genes may show altered expression in between preinvasive and invasive disease.

The S100 proteins comprise a family of calcium-binding proteins. Altered expression of several members of the S100 gene family has been reported in association with breast cancer progression, including S100A2 and S100A4 (6, 7). We have previously identified psoriasin (S100A7) as a differentially expressed gene between DCIS<sup>3</sup> and invasive carcinoma (8). We and others (9) have also shown that psoriasin is low in normal breast and benign pathologies and among the most highly expressed genes in high-grade DCIS (8, 9). Although expression is often reduced in invasive carcinoma (8), persistent expression is seen in a subset of invasive tumors where it is associated with markers of poor prognosis, including a strong association with ER-negative status (10). To explore further the role of psoriasin in progression, we have examined the relationship between psoriasin expression and outcome in ER-negative primary invasive breast carcinomas.

## MATERIALS AND METHODS

**Study Cohort.** All breast tumor cases used for this study were selected from the Manitoba Breast Tumor Bank (Winnipeg, Manitoba, Canada), which operates with the approval from the Faculty of Medicine, University of Manitoba, Research Ethics Board. As has been previously described (11, 12), tissues are accrued at the bank from cases at multiple centers within Manitoba, rapidly collected and processed to create matched formalin-fixed, paraffin-embedded and frozen tissue blocks with the mirror image surfaces oriented by colored inks. The histology and cellular composition of every sample in the bank is interpreted in H&E-stained sections from the face of the former tissue block. A study set of 122 consecutive invasive breast carcinomas was selected on the basis of (a) ER-negative status (defined as  $<10$  fmol/mg protein), (b) minimum follow-up duration of 6 months, and (c) predominantly invasive ductal tumor type, either alone or mixed with

<sup>3</sup> The abbreviations used are: DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor; NS, not significant; CI, confidence interval.

Table 1 Clinical and pathological features of the study cohort

Parameter		Tumors		Psoriasis expression			
		#	%	Cytoplasmic		Nuclear	
				#	%	#	%
ER <sup>a</sup>	-ve	122	(100)	64	(52)	37	(30)
	+ve	0	(0)				
PR <sup>b</sup>	-ve	100	(82)	59	(59)	34	(34)
	+ve	22	(18)	5	(23)	3	(14)
Nodal status	-ve	56	(46)	29	(52)	13	(23)
	+ve	65	(53)	34	(52)	23	(35)
Grade <sup>c</sup>	Unknown	1	(1)	1	(100)	1	(100)
	Low	10	(8)	2	(20)	1	(10)
	Intermediate	52	(43)	30	(58)	18	(35)
	High	60	(49)	32	(53)	18	(30)
Size	≤2 cm	30	(25)	15	(50)	6	(20)
	>2 cm	88	(72)	47	(53)	29	(33)
INFL <sup>d</sup>	Unknown	4	(3)	2	(50)	2	(50)
	Low	77	(63)	41	(53)	23	(30)
	High	45	(37)	23	(51)	14	(31)
Type	Ductal	117	(96)	62	(53)	36	(31)
	Lobular mixed	5	(4)	2	(40)	1	(20)
Age	≤50	54	(44)	26	(48)	16	(30)
	>50	68	(56)	38	(56)	21	(31)

<sup>a</sup> ER -ve, <10 fmol/mg protein.

<sup>b</sup> PR -ve, <15 fmol/mg protein.

<sup>c</sup> Nottingham system.

<sup>d</sup> Tumor inflammation/immune response was assessed in the H&E-stained tumor tissue section as either low (absent or sparse lymphocytic infiltrates) or high (lymphoid aggregates and/or prominent diffuse lymphocytic infiltrates).

lobular type, and blocks containing predominantly invasive carcinoma were used for the study. The clinicopathological characteristics of the study case series are shown in Table 1.

**Immunohistochemistry.** A psoriasis-specific rabbit polyclonal antibody was used that specifically recognizes a 14 amino acid peptide corresponding to the COOH terminus of psoriasis (KQSHGAAPCSGGSQ). Immunohistochemical staining for psoriasis was performed essentially as previously described (10), using an automated tissue immunostainer (Ventana Medical Systems, Phoenix, AZ) and 3,3'-diaminobenzidine immunohistochemistry kit and bulk reagents supplied by manufacturer. Briefly, the staining protocol was set to "Extended Cell Conditioning" procedure, followed by 12-h incubation with primary antibody (concentration 1: 3000) and 32-min incubation with secondary antibody. Positive staining was assessed by light microscopy, and levels of expression were determined by estimation of the proportion of positive epithelial cells within each cross section as described previously (10). Psoriasis cytoplasmic and nuclear expression were assessed separately, and the psoriasis nuclear/cytoplasmic intensity ratio was calculated from the separate intensity scores.

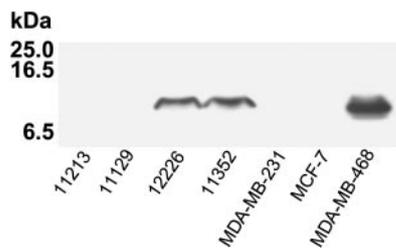
**Statistics and Analysis.** Associations with clinicopathological variables were determined by Fisher's exact test, and correlations were assessed by the Spearman test. Time to progression was defined as the time from initial surgery to the date of any clinically documented local or distant disease recurrence or death attributed to breast cancer. Survival was defined as the time from initial surgery to the date of death attributed to breast cancer. All other deaths were censored. In addition to these two endpoints, overall survival was also assessed and was defined as the time from initial surgery to deaths from any cause, whether known to be breast cancer specific or not. The association with

progression and survival was assessed by both univariate (Log-rank test and Kaplan-Meier method) and multivariate (Cox regression model) analysis. All tests were performed using SAS statistical analysis software.

## RESULTS

The specificity of the antibody was confirmed by blockade of the signal by preincubation with the peptide and by comparison with other antipsoriasis antibodies, including a chicken IgY antipsoriasis antibody that had previously been generated against the same peptide, as described previously (10). Experiments were also performed to compare immunoblotting signals with immunohistochemical profiles in cell lines and invasive breast ductal carcinomas (Fig. 1). Expression of a single 11.7 kDa psoriasis band was present by Western blot only in the MDA-MB-468 cell line [known to express psoriasis (9)] but not in MDA-MB-231 or MCF7 cells [known not to express psoriasis (9)], which express several other S100 proteins (9, 13, 14). In tumors, psoriasis was also seen by Western blot assay in cases that exhibited strong psoriasis immunohistochemistry staining but was absent in tumors that were negative by immunohistochemistry.

The clinicopathological features of the cohort of 122 women with invasive ductal breast carcinoma are described in detail in Table 1. Among these patients, the median age was 52 years, the median tumor size was 2.7 cm, and the median ER and PR levels were 2 and 7.5 fmol/mg, respectively. The median duration of follow-up for the entire cohort was 45 months (range, 6–106 months). At the time of analysis, 58 women were alive and well (48%), 47 women (38%) had died of breast cancer, and 8 women were alive with recurrent disease. Nine (9) women had died of



**Fig. 1** Expression of psoriasin protein detected in selected breast tumors and cell lines. Psoriasin expression is detected as a single specific band ( $M_r$  11.7 kDa) by Western blot in tumors 12226 and 11352 and in the MDA-MB-468 cell line.

unknown or other causes. Expression of psoriasin was detected in 64 of 122 cases (52%). Psoriasin expression was focal ( $\leq 10\%$  of tumor cells) in 23 of 64 cases, heterogeneous ( $>10$  to  $<75\%$  of tumor cells) in 29 of 64 cases, and marked ( $>75\%$  of tumor cells) in 12 of 64 cases. All positive tumors showed cytoplasmic expression, and among these, nuclear expression of psoriasin was also observed in 37 (30%) tumors (Table 1 and Fig. 2, A–C). Positive staining was also frequently observed within stromal inflammatory and fibroblast-like cells in the stroma immediately adjacent to regions of positivity within the tumor cell compartment but not in stroma in distant regions or normal tissues. Occasional weak staining was observed in normal ducts and benign and hyperplastic epithelial elements, and expression was observed within associated DCIS components. For the purpose of subsequent statistical analysis, all cases with positive cells were considered as positive cases, and this fraction corresponded to the proportion of ER-negative tumors found to be positive by Western blot in our previous study (10).

In univariate analysis, psoriasin expression measured as cytoplasmic or nuclear expression was not correlated with other prognostic factors (including PR, size, grade, stage, and nodal status). In addition, no association was seen with inflammatory cell infiltration in this cohort. However, both cytoplasmic and nuclear psoriasin expression were associated with short time to progression ( $P = 0.0374$  and  $P = 0.0166$  respectively) and breast cancer-specific survival ( $P = 0.0235$  and  $P = 0.0273$ ; Fig. 2, D and E). Among other prognostic factors, a significant association was also found between stage and outcome (time to progression,  $P < 0.0001$ ; survival,  $P < 0.0001$ ), nodal status and outcome (time to progression,  $P = 0.0074$ ; survival,  $P = 0.0055$ ), but not with grade, size, or PR. A high nuclear/cytoplasmic psoriasin ratio was also associated with both early recurrence and survival ( $P = 0.0009$  and  $P = 0.02$ ). Additional analysis of psoriasin relative to overall survival (rather than breast cancer-specific survival) showed similar and significant associations with poor overall survival for cytoplasmic and nuclear psoriasin expression ( $P = 0.0082$  and  $P = 0.0077$ ) and also higher psoriasin nuclear/cytoplasmic ratio ( $P = 0.0026$ ).

Multivariate analysis was performed using the Cox proportional hazard model and included stage, nodal status, tumor size, PR status, age, and grade together with the nuclear psoriasin and cytoplasmic psoriasin status. Only tumor stage and cytoplasmic psoriasin expression emerged as significant independent poor prognostic predictors of time to progression (stage, hazard ratio, 2.92,

95% CI, 1.83–4.67,  $P < 0.0001$ ; cytoplasmic psoriasin hazard ratio, 1.86, 95% CI, 1.02–3.39,  $P = 0.044$ ) and survival (stage, hazard ratio, 2.91, 95% CI, 1.69–5.02,  $P = 0.0001$ ; cytoplasmic psoriasin hazard ratio, 2.12, 95% CI, 1.06–4.23,  $P = 0.033$ ).

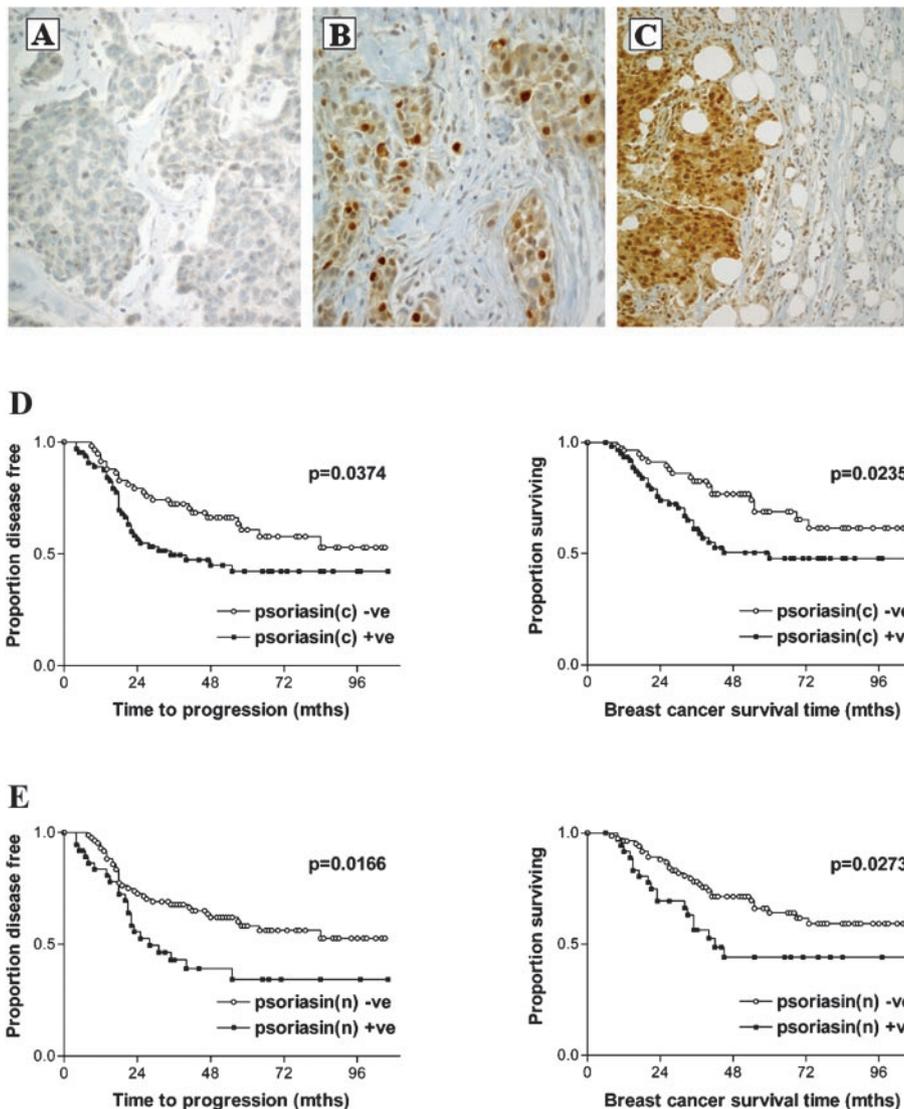
## DISCUSSION

Psoriasin (S100A7) was initially identified as a protein highly expressed in abnormally differentiating keratinocytes derived from psoriatic skin lesions (15). It was later found as a cDNA expressed in primary invasive breast tumors (16). We and others (8, 9) have subsequently shown that psoriasin is most highly expressed in preinvasive DCIS and that although it can often be down-regulated in adjacent invasive components (8), persistent expression in invasive carcinomas is associated with indicators of poor prognosis (8–10).

Altered expression of several S100 proteins has been associated with breast tumor progression (9, 13). Most interest has focused on S100A4 (6), which was initially identified to be differentially expressed between nonmetastatic and metastatic rodent mammary tumor cell lines (17). In breast cell lines, S100A4 expression can also directly influence the metastatic phenotype (18, 19) and in tumors has recently been associated with poor prognostic factors and outcome (20).

In contrast to S100A4, which is expressed in stroma and tumor cells (21, 22), psoriasin expression in the breast is restricted to the epithelial cell component (10). Several factors govern its regulation in cell lines, including stress-related factors such as growth factor deprivation, confluency, and loss of adhesion (9), as well as regulation by the activator protein 1 transcription factor and steroid hormones, including retinoic acid and estrogen (8, 16, 23, 24). The highest levels of expression are also seen in ER-negative cell lines (9), although psoriasin can be induced by estrogen in the ER-positive MCF7 cell line (16). In breast tumors, high levels of psoriasin expression in DCIS may reflect the presence of these stress-related factors existing within the restricted confines of the ductal space and as indicated by the frequent occurrence of intraductal necrosis in high-grade lesions (25–28). In both DCIS and invasive tumors, psoriasin is also associated with ER-negative status (10). In our previous study of 57 invasive tumors, psoriasin protein expression was seen in 10 of 23 ER-negative tumors ( $<10$  fmol/mg protein) but in 0 of 34 ER-positive tumors. Although this association was highly significant when ER status was determined by ligand binding assay (9, 10), it was not as marked when ER and psoriasin expression were directly compared by immunohistochemistry (9). This may be attributable to the different sensitivity of the two ER assays. We therefore chose to examine the relationship with survival in a cohort restricted to ER-negative tumors and nevertheless observed a significant relationship between cytoplasmic psoriasin and worse outcome within this poor prognosis group (29), which was independent of tumor grade, stage, size, and nodal status. There was a trend toward increased nuclear psoriasin expression and node-positive status (Table 1), however, the indication here that in this subgroup psoriasin may be a poor prognostic factor that is not closely linked to stage or nodal status suggests that it may reflect a biological property that is separate from the ability to metastasize or a property that is necessary but not sufficient such as invasion.

The biological role of psoriasin in breast tumors is unclear.



*Fig. 2* Psoriasin expression determined by immunohistochemistry and outcome in invasive breast cancer. A–C demonstrate negative, positive (predominantly nuclear), and positive (predominantly cytoplasmic) psoriasin expression. D and E show Kaplan Meier curves to demonstrate a relationship between cytoplasmic (D) and nuclear (E) psoriasin expression and time to progression, and breast cancer survival within the entire cohort. Psoriasin negative cases (○) and positive cases (■).

One potential role may lie in facilitating the host inflammatory cell response, and previous studies have implicated psoriasin as a chemotactic factor for lymphocytes and neutrophils in skin disease (30). We have also previously observed that it can be associated with increased inflammatory cell infiltrates across all types of invasive breast tumors (10). However, this relationship has not persisted when analysis is restricted to the two more common subsets of invasive ductal and lobular type tumors in two different studies (9, 10). Another potential role may lie in a direct influence on the breast cancer cell. Psoriasin protein is not only secreted but has also been localized to both nuclear and cytoplasmic compartments [in common with other S100 proteins (31)], and it has been suggested on the basis of its pattern of regulation and expression that psoriasin expression may play a role in the development of resistance to apoptosis (9). Interaction with fatty acid-binding proteins and transglutaminases (32, 33) has been reported, and we have also recently identified an interaction with the ran-associated protein RanBPM (34). RanBPM (35) has several putative functions

but has also recently been shown to be capable of promoting migration of renal carcinoma cells (36), suggesting an unproven but potential mechanism for psoriasin to influence invasiveness.

In summary, these results show that psoriasin expression may be an independent prognostic factor for outcome in invasive breast cancer. It remains to be determined if and how psoriasin might play a causal role in invasion and breast tumor progression. Nevertheless, it will be important to explore the prognostic significance of psoriasin in preinvasive DCIS and as an indicator of risk of progression to invasive disease.

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# Clinical Cancer Research

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