

# Peroxiredoxin-1 as a prognostic factor in patients with ovarian cancer

Jacek Sieńko<sup>1,A-F</sup>, Justyna Teliga-Czajkowska<sup>2,B</sup>, Ewa Przytula<sup>3,B</sup>, Krzysztof Czajkowski<sup>1,E-F</sup>, Roman Smolarczyk<sup>4,E-F</sup>, Dominika Nowis<sup>5,6,A-B,D-F</sup>

<sup>1</sup> 2nd Department of Obstetrics and Gynecology, Medical University, Warsaw, Poland

<sup>2</sup> Department of Obstetrics and Gynecology Didactics, Medical University, Warsaw, Poland

<sup>3</sup> Department of Pathology, The Medical Center of Postgraduate Education, Warsaw, Poland

<sup>4</sup> Department of Gynecological Endocrinology, Medical University, Warsaw, Poland

<sup>5</sup> Department of Immunology, Centre for Biostructure Research, Medical University, Warsaw, Poland

<sup>6</sup> Laboratory of Experimental Medicine, Centre of New Technologies, Warsaw University, Poland

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## Abstract

**Introduction and objective.** Peroxiredoxin-1 (PRDX-1) belongs to a family of antioxidant enzymes and has proved to be a versatile molecule regulating cell growth, differentiation and apoptosis. PRDX1-regulated signaling pathways play an important role in the progression and metastasis of human tumours, especially in breast, esophageal and lung cancers. The aim of the study was to evaluate the expression of PRDX-1 in ovarian cancer tissues, and to test the clinical value of PRDX-1 as a prognostic factor in this malignancy.

**Materials and method.** PRDX-1 expression was assessed by automated immunohistochemistry in tumours taken from 55 patients with ovarian cancer during primary surgery. Specimen were formalin-fixed and preserved in paraffin-embedded blocks. The results were correlated with clinicopathological data.

**Results.** A high expression of PRDX-1 was observed in 20% of cases, and was associated with worse compliance to chemotherapy protocol ( $P < 0.002$ ), worse response to chemotherapy ( $P < 0.04$ ), and higher levels of CA 125 after the 1<sup>st</sup> line treatment ( $P < 0.004$ ). PRDX-1 positive subjects had a significantly lower 5-year disease-free survival (9.1% vs. 42.6%,  $P < 0.01$ ) and a lower 5-year overall survival (9.1% vs. 56.7%;  $P < 0.002$ ). Multivariate analysis showed that a high expression of PRDX-1 is an independent prognostic factor of poor, overall survival ( $P < 0.002$ ) and a disease-free survival ( $P < 0.01$ ).

**Conclusion.** Results of the study show that PRDX-1 expression in tumour tissues can be another biomarker of prognosis in patients with ovarian cancer.

## Key words

Peroxiredoxin-1, PRDX-1, ovarian cancer, overall survival, disease free survival

## INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer-related death in females in developed countries [1]. Lack of clear early symptoms or sufficiently sensitive screening tests is the reason that 80% of patients are diagnosed with ovarian cancer when it is already widespread within the peritoneal cavity [2]. Despite some improvement in treatment, the 5-year survival rate in stages III and IV does not exceed 41% and 20%, respectively [2]. The standard therapeutic approach for ovarian cancer is upfront surgery followed by a combination of platinum and taxane-based chemotherapy. Outcome is strictly related to the degree of treatment protocol completed [3]. The risk of severe complications often limits optimal surgery [4, 5], and drug resistance and toxicity are the most important obstacles for effective chemotherapy [6, 7]. Those problems could probably be at least partly overcome by the selection of appropriate treatment regimens dependent on prognostic / predictive factors. Very few biomarkers, e.g. BRCA mutation, influence specific treatment selection in

ovarian cancer [8]. Thus, the search for novel tumour markers that would play a role as prognostic factors seems to be one of important goals to help customize ovarian cancer treatment which, in turn, could result in better prognosis.

Peroxiredoxin-1 (PRDX-1) is a member of a family of thiol-specific antioxidant proteins that influence hydrogen peroxide levels and mediate signal transduction pathways [9]. PRDX-1 was first reported as an antioxidant enzyme, but its physiological role in oxidation–reduction balance remains unclear because of its high susceptibility to oxidative stress [10]. It has a regulatory function in cell proliferation, differentiation and apoptosis [11]. PRDX-1 oligomers, which function as chaperones under oxidative stress conditions, can interact with the c-Myc oncogene and suppress its transcriptional activity, in turn inhibiting tumorigenesis and promoting tumour cell apoptosis [12, 13, 14]. On the other hand, in certain circumstances, PRDX-1 may act as an oncogene and suppress tumour cell death by directly associating with transcription factors, such as nuclear factor kappa B (NF- $\kappa$ B) and androgen receptor (AR) [15, 16]. PRDX-1 is over-expressed in many human malignant tumours, including lung, breast, urinary, esophageal, hepatocellular and endometrial carcinomas [17, 18, 19, 20, 21, 22]. However, specific role of PRDX-1 in mammary carcinomas is

Address for correspondence: Jacek Sieńko, 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Karowa 2, 00-315, Warsaw, Poland  
E-mail: jacek.sienko@wum.edu.pl

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controversial. PRDX-1 functions as a chaperone to enhance the transactivation potential of NF- $\kappa$ B in ER-breast cancer cells, and then suppresses tumour cell death [18]. High expression of PRDX-1 in human breast cancer is associated with higher tumour grade and a higher risk of local recurrence after radiotherapy [25, 26]. Nevertheless, biomarker studies have demonstrated that PRDX-1 protects estrogen receptors (ER $\alpha$ ) from oxidative stress-induced suppression, and is a protein marker of favourable prognosis in mammary tumours [27]. As in breast cancer, the role of PRDX-1 in esophageal cancer remains ambiguous. It promotes tumourigenesis by functioning as an 'accomplice' of certain oncoproteins or by the activation of its antioxidant enzyme, but it may also play a role as a tumour suppressor through the stimulating of a cyclin-dependent kinase inhibitor – p21 – over-expression [10, 27]. Riddell et al. have shown that the interaction of PRDX-1 with the Toll-like receptor 4 (TLR4) stimulates tumour angiogenesis via up-regulation of vascular endothelial growth factor (VEGF) expression in prostatic carcinoma, suggesting that it plays a certain role in malignancy growth, invasion and metastasis [19]. In a previous study, the authors compared the PRDX family over-expression in ovarian cancer; however, the study was performed at the mRNA level [A1]. The aim of the current study is to investigate peroxiredoxin-1 at the protein level as a potential biomarker for prognosis in patients with ovarian cancer.

## MATERIALS AND METHOD

The study was conducted under the approval of the local Ethics Committee and performed in accordance with the World Medical Association Declaration of Helsinki. All subjects provided written informed consent.

The study included 55 patients with ovarian cancer, primary treated in the Princess Anna Mazowiecka Hospital (Medical University of Warsaw) between 2003–2010. Tissue samples were collected for immunohistochemistry from tumour tissues taken during surgical resection, formalin-fixed and preserved in paraffin-embedded blocks. Clinicopathological data were obtained from medical records. The patients were observed 71–4,848 day from the initial treatment (mean 1807 $\pm$ 1,576 days). After excluding the patients who died during the observation, the mean follow-up time was 2,936 $\pm$ 1,544 days (213–4848 days).

**Immunohistochemical staining for PRDX-1.** Sections (4- $\mu$ m thick) obtained from cancerous tissues were deparaffinized in xylene and rehydrated in descending gradient alcohols. For antigen retrieval, EnVision™ FLEX Target Retrieval Solution, High pH was used according to the manufacturer's instruction. Immunohistochemical (IHC) reaction was performed in a Dako Autostainer (Agilent Technologies) using an EnVision FLEX Mini Kit. High pH (Agilent Technologies) PRDX1 was detected with rabbit polyclonal antibody (Cat No HPA007730, Sigma-Aldrich). IHC staining was assessed by an experienced pathologist. The samples were categorized as negative if PRDX-1 expression was either imperceptible or very weak. A positive result was only assigned to a strong expression of PRDX-1.

**Statistical analysis.** The results were presented as mean  $\pm$  standard deviation (SD). Significant statistical differences

between groups were assessed applying the chi-square test, exact Fisher test or Student's *t* test. The Kaplan–Meier method was employed to plot survival curves, and differences in survival were compared using the log-rank test. The Cox regression model was used to ascertain the value of independent prognosis for postoperative patients with ovarian cancer.  $P < 0.05$  was considered statistically significant.

## RESULTS

A strong expression of PRDX-1 was found in 11 (20%) cases of ovarian cancer which enabled them to be classified in the PRDX-1 positive group. In the PRDX-1 negative group (N=44), 31 cases presented a very weak/minimal expression of PRDX-1. PRDX-1 expression was present in the cytoplasm of cancerous cells, but not in the stroma. The clinicopathological characteristic of the groups according to PRDX-1 expression is presented in Table 1.

**Table 1.** Clinicopathological characteristic of the PRDX-1 negative and positive groups

Age [years]	54.4 $\pm$ 9.78	59.7 $\pm$ 10.9	0.12
• Histological type n (%)			
• Serous	20 (45.5%)	7 (63.6%)	0.68
• Endometrioid	14 (31.8%)	2 (18.2%)	
• Clear cell Mucinous	7 (15.9%)	1 (9.1%)	
	3 (6.8%)	1 (9.1%)	
Stage n (%)			
I	21 (50%)	2 (18.2%)	0.07
II	3 (6.8%)	0 (0%)	
III	19 (43.2%)	9 (81.8%)	
IV	0 (0%)	0 (0%)	
Grade n (%)			
1	6 (15.8%)	2 (25%)	0.52
2	20 (52.6%)	5 (62.5%)	
3	12 (31.6%)	1 (12.5%)	
CA 125 before initial treatment [U/L]	851.9 $\pm$ 1192.4	1048.64 $\pm$ 1375.3	0.64
Largest tumour size [cm]	15.5 $\pm$ 6.5	13.1 $\pm$ 13.8	0.40

Values are mean $\pm$ SD or present a number (%) of cases in groups. Student's *t* test or exact Fisher test were applied, respectively

The groups did not differ in terms of well-known prognostic factors, such as age, tumour stage and grade, CA 125 concentration before treatment or the largest tumour size. The patients received standard treatment that included surgery and adjuvant platinum-based chemotherapy. The results of the first-line treatment are presented in Table 2.

Optimal results of surgery defined as no visible residual volume was achieved in 47.7% of PRDX-1 negative and 18.2% of PRDX-1 positive patients (NS). 44 (100%) PRDX-1 negative but only 8 PRDX-1 positive patients (72.7%) received at least 6 courses of platinum derivatives (Cisplatin or Carboplatin) ( $P < 0.002$ ). The differences in response to the first line treatment were significant if stratified as any response vs. progression ( $P < 0.04$ ). CA 125 level assessed after the end of the first line chemotherapy treatment was significantly lower in the PRDX-1 negative group (5.73 $\pm$ 3.77 vs. 78.25 $\pm$ 124.62 U/L,  $P < 0.004$ ).

**Survival analyses.** Kaplan-Meier curves (Fig. 1) analysis was used to compare the overall survival (OS) and disease-

**Table 2.** Correlation between PRDX-1 expression and the clinical results achieved during treatment

	PRDX-1 negative N=44	PRDX-1 positive N=11	P
Optimal surgery (no residual volume)	21 (47.7%)	3 (18.2%)	0.081
At least 6 cycles of chemotherapy completed	44 (100%)	8 (72.7%)	0.002
Response to treatment			0.052
• Complete remission	33 (75%)	4 (36.4%)	0.04
• Partial remission	6 (13.6%)	3 (27.2%)	
• Stabilization	1 (2.3%)	0 (0%)	
• Progression	4 (9.1%)	4 (36.4%)	
Any response vs. progression	40 (90.9%)	7 (63.6%)	
	4 (9.1%)	4 (33.4%)	
CA 125 after first-line treatment [U/L]	5.73+/-3,77	78.25+/-124.62	0.004

Values are mean+/-SD or present a number (%) of cases in groups. Student's t test or exact Fisher test were applied, respectively

free survival (DFS) between PRDX-1 positive and negative patients. PRDX-1 positive subjects had a significantly higher risk of recurrence (DFS 9.1% vs. 42.6% within 5 years;  $P<0.01$ ) and a lower probability of a 5-year survival (9.1% vs. 56.7%;  $P<0.002$ ), compared to PRDX-1 negative patients. Univariate analysis showed that PRDX-1 expression, tumour stage (early vs. advanced ovarian cancer), histological type (serous vs. non-serous) and CA 125 before treatment (twice elevated above reference value) have prognostic value on OS and DFS (Tab. 3).

Multivariate analysis revealed that PRDX-1 is an independent marker of poor prognosis, both for DFS and OS (Tab. 4). Tumour stage was also an independent predictor of OS and DFS and CA 125 elevated at least twice above reference value was the third independent prognostic factor for DFS, but not for OS.

## DISCUSSION

PRDX-1 was found to be over-expressed in many different cancers [18, 19, 29]. A high expression of PRDX-1 was usually associated with poor outcomes [10, 24, 24, 26]. In this study, 1 in 5 cancers presented a high expression of PRDX-1. In the study by Cai et al., 74.4% of cancerous tissues of pancreatic cancer tested positive for PRDX-1 [28]. This would be comparable with the presented results (76.4%) if the groups

**Table 3.** Univariate analysis of factors associated with OS and DFS. The Cox regression model

Variable	OS			DFS		
	RR	95% CI	P	RR	95% CI	P
PRDX-1 negative vs. positive	0.25	0.11–0.55	0.0006	0.31	0.15–0.67	0.002
Age <60 years vs. >60 years	0.86	0.40–1.86	0.71	0.22	0.38–1.55	0.46
Tumour size <20 cm vs. >20cm	0.60	0.27–1.29	0.19	0.65	0.32–1.31	0.23
FIGO I-II vs. III-IV	0.15	0.06–0.37	0.00003	0.16	0.07–0.34	0.000002
Grade 2–3 vs. 1	1.19	0.40–3.51	0.75	0.84	0.32–2.2	0.73
Non-serous vs. serous tumour	0.40	0.18–0.85	0.02	0.33	0.17–0.67	0.002
CA 125 before treatment <70U/L vs. >70U/L	0.18	0.04–0.77	0.02	0.13	0.03–0.55	0.005

RR – relative risk of death or relapse/progression, respectively

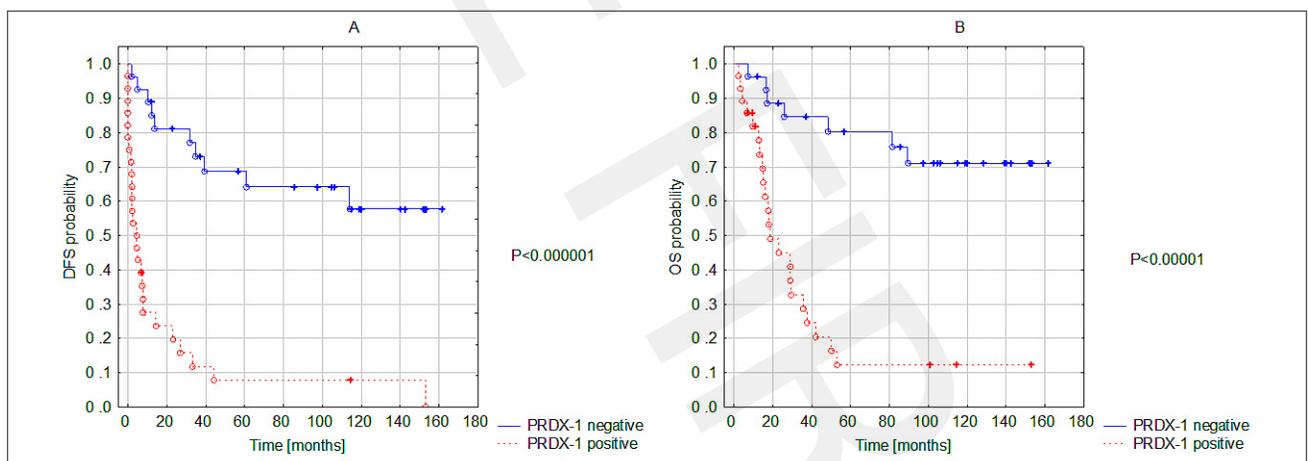
**Table 4.** Multivariate Cox regression analysis of factors associated with OS and DFS

Variable	OS			DFS		
	RR	95% CI	P	RR	95% CI	P
PRDX-1 negative vs. positive	0.28	0.11–0.71	0.007	0.38	0.16–0.90	0.03
FIGO 1–2 vs. 3–4	0.24	0.08–0.74	0.001	0.29	0.11–0.75	0.01
Non-serous vs. serous tumour	0.81	0.36–1.83	0.61	0.55	0.25–1.21	0.14
CA 125 before treatment <70U/L vs. >70U/L	0.34	0.07–1.62	0.17	0.21	0.05–0.97	0.04

RR – relative risk of death or relapse/progression, respectively

were to be stratified in an analogous format, e.g. no vs. any expression of PRDX-1. Statistical analysis of the data obtained in the current study revealed that division of the group into high vs. no/minimal expression of PRDX-1 subgroup, better correlated with outcomes, rather than the inclusion of cases with minimal expression of PRDX-1 to the PRDX-1 positive group. This may be because a strong expression of PRDX-1 reflects a biologically-meaningful over-expression of this protein in the samples.

In this study, a high expression of PRDX-1 was found to be accompanied with worse results in the first line treatment. Although the differences in the percentage of optimal surgery

**Figure 1.** Kaplan-Meier analysis of A. – disease-free survival (DFS) and B. – overall survival (OS). Log rank test.

were not statistically significant, both its compliance with chemotherapy protocol and response to chemotherapy were poorer. As the main reason for premature chemotherapy termination was progression, it is suspected that high expression of PRDX-1 could be one of the factors involved in the development of resistance to platin. This hypothesis may be supported by the *in vitro* study by Kalinina et al, which found that cisplatin resistance formation is accompanied by a significant increase in the expression of PRDX1, PRDX2, PRDX3, and PRDX6 genes in human ovarian carcinoma SKOV-3 cells [29]. Kubota et al. identified another member of the PRDX family – peroxiredoxin 2, as a predictive biomarker of response to induction chemotherapy in osteosarcoma [30].

Very little is known about the biological meaning of peroxiredoxins, especially that of PRDX-1, as a prognostic factor in ovarian cancer. Li et al. studied the prognostic values of the peroxiredoxins family in ovarian cancer [31]. The study investigated protein expression profiles in normal ovarian tissues and cancerous ovarian tissues using the Human Protein Atlas database, and made a compilation of several available databases (Gene Expression Omnibus, the Cancer Biomedical Informatics Grid, and The Cancer Genome Atlas) to compare PRDX's expression at the mRNA level. The study found that the elevated expression of PRDX-3, PRDX-5, and PRDX-6 mRNAs showed poorer OS, and the expression PRDX-5 and PRDX-6 also were able to predict poor progression-free survival (PFS). The prognostic value of PRDX-1 in that study was unclear, as the results were either insignificant for all patients or inconsistent for subjects with clinical stage 1 and 2 (better OS and poorer PFS, excluding histological grade 1 for PFS).

This study has demonstrated that high expression of PRDX-1 in cancerous tissue is strongly associated with a shorter DFS and OS. These observations are consistent with the results of other studies, excluding those of ovarian cancer tumours [21, 28]. Sun et al. found that PRDX-1 expression in hepatocellular carcinoma (HCC) cells was significantly associated with numerous parameters of aggressive disease, including an increased tumour size, multiple tumour nodules, microvascular invasion, an advanced Edmondson grade, an incomplete tumour capsule, a higher serum AFP, and advanced stages of the TNM staging system which, in turn, resulted in shorter OS and DFS [21].

In the study by Cai et al., PRDX-1 expression in pancreatic cancer correlated with histological grade, perineural invasion, lymph node metastases, CA 19-9 level and the TNM stage. Moreover, PRDX-1 was a negative and independent predictor of survival and recurrence [28].

There is growing evidence that PRDX-1 is a multi-directionally acting protein involved in tumorigenesis. Not only is it closely related to tumour angiogenesis in pancreatic cancer [29], but it also suppresses proteasome inhibitor-mediated cell death affecting signal-regulating kinase 1 (ASK1) activation in human thyroid cancer [32]. PRDX-1 equally promotes tumorigenesis by regulating the activity of the mTOR/p70S6K pathway in oesophageal squamous cell carcinoma [34].

As demonstrated, PRDX-1 is an independent prognostic factor in patients with ovarian cancer who have undergone surgery. It makes PRDX-1 a candidate for more comprehensive studies in order to determine its significance as a biomarker useful in planning the strategy of treatment. No study was found that allowed comparison of the presented results of

PRDX-1 staining with another group of ovarian cancer patients. However, the existence of a study suggesting that positive PRDX-1 expression can be an independent predictor of favourable prognosis in breast cancer positive for estrogen receptors, is significant [25].

Total peroxiredoxin expression, including PRDX-1, was also associated with prolonged survival in patients with follicular lymphoma [34]. Ding et al. suggested that both redox and chaperone activity determine the role of PRDX1 in the promotion or suppression of oncogenesis in certain types of cancer [10]. These findings seem to demonstrate the complexity of PRDX-1 functions in different tissues and cancers and force the authors of the current study to limit their predictions on the possible role of this biomarker in other malignancies or experimental models. The main limitation of this study is its relatively small sample size. Therefore, final conclusions should be made with caution until further larger studies are conducted.

## CONCLUSIONS

The study shows that a high expression of PRDX-1 is associated with shorter overall and disease-free survival, and serves as an independent prognostic factor for poor OS and DFS in patients with ovarian cancer.

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