IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2016; 7(9): 1088-1094. doi: 10.7150/jca.15258

Research Paper

Overexpression of the PSAT1 Gene in Nasopharyngeal Carcinoma Is an Indicator of Poor Prognosis

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Received: 2016.02.12; Accepted: 2016.04.26; Published: 2016.05.25

Abstract

Purpose: Nasopharyngeal carcinoma (NPC) is a common cancer in southern China and Southeast Asia, but risk stratification and treatment outcome in NPC patients remain suboptimal. Our study identified and validated metabolic drivers that are relevant to the pathogenesis of NPC using a published transcriptome. Phosphoserine aminotransferase 1 (*PSAT1*) is an enzyme that is involved in serine biosynthesis, and its overexpression is associated with colon cancer, non-small cell lung cancer and breast cancer. However, its expression has not been systemically evaluated in patients with NPC.

Materials and Methods: We evaluated two public transcriptomes of NPC tissues and benign nasopharyngeal mucosal epithelial tissues that deposited in the NIH Gene Expression Omnibus database under accession number GSE34574 and GSE12452. We also performed immunohistochemical staining and assessment of *PSAT1* in a total of 124 NPC patients received radiotherapy and were regularly followed-up until death or loss. The endpoints analyzed were local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS).

Results: We retrospectively evaluated 124 patients with NPC and found that high *PSAT1* expression was associated with poor prognosis of NPC and indicator of advanced tumor stage. High *PSAT1* expression also correlated with an aggressive clinical course, with significantly shorter DSS (HR= 2.856, 95% CI 1.599 to 5.101), DMFS (HR= 3.305, 95% CI 1.720 to 6.347), LRFS (HR= 2.834, 95% CI 1.376 to 5.835), and OS HR= 2.935, 95% CI 1.646-5.234) in multivariate analyses.

Conclusions: Our study showed that *PSAT1* is a potential prognostic biomarker and higher expression of *PSAT1* is associated with a poor prognosis in NPC.

Key words: *PSAT1*, Nasopharyngeal carcinoma, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignancy that originates in the nasopharynx, and it exhibits a complex biology that is not fully understood. The incidence of NPC is rare in most populations, such as Europe and the United States, but it is a common cancer in southern China and

Southeast Asia[1] and other populations, including the Middle East/North Africa and the Arctic. Genetics interact with the environment and contribute to the development of NPC because of the racial and ethnic geographical distribution of NPC worldwide[2].

A previous study used published data in endemic areas and demonstrated that concurrent chemoradiotherapy was an effective treatment for locally advanced NPC and improved overall survival[3]. A study also showed neoadjuvant chemotherapy and concurrent chemoradiotherapy can reduce distant failure as compared with concurrent chemoradiotherapy alone[4]. However, the percentage of patients with distant metastases is high in NPC, and patients with distant metastases exhibit poor prognosis[5-10]. Accordingly, NPC management should consider individual patient differences using recognized prognostic factors. It is important to identify biomarkers that are independently associated with rapidly progressive tumors to designate an appropriate treatment.

It is getting clear that cancer cells acquire alterations in the metabolism of carbohydrates, proteins, lipids and nucleic acids to meet the requirements for rapid proliferation[11]. Cancer cells need high amounts of nonessential and essential amino acids to fuel essential anabolic processes. Growing evidence suggests that amino acid metabolic pathways are also chemotherapeutic targets[12]. We used the published transcriptome of NPC to find genes involved in tumorigenesis[13] and demonstrated that phosphoserine aminotransferase 1 (*PSAT1*) was a prominently upregulated gene in the regulation of amino acid metabolism.

PSAT1 was observed in the brains and livers of sheep[14]. *PSAT1* is involved in the second step of serine biosynthesis, and it converts 3-phosphohydroxypyruvate to L-phosphoserine[15]. *PSAT1* plays an important role in metabolic functions. *PSAT1* deficiency leads to seizures and acquired microcephaly[16], and overexpression of *PSAT1* correlates with cancer development[17]. However, information on the functions of *PSAT1* in the regulation of cell proliferation and tumorigenesis and the association between *PSAT1* overexpression and clinical implications in patients with NPC are not clear. Our study evaluated the influence of *PAST1* expression on the clinical outcome of NPC patients.

Materials and methods

Analysis of published transcriptomic datasets

We evaluated one public transcriptome containing expression profiling data of (GSE34574) which contains expression profiling data deposited in the NIH Gene Expression Omnibus database. The raw CEL files of Affymetrix HUMAN Genome U133 Plus 2.0 microarray platform were imported into Nexus Expression 3 software (BioDiscovery) to analyze all probe sets without pre-selection or filtering. Supervised comparative analyses and functional profiling were performed to identify significant differentially expressed genes, and special attention was paid to pathways involved in amino acid biosynthesis in Gene Ontology (GO:0008652). Genes with $P \leqq 0.01$ and a $\log_2$-transformed expression fold change >1 were selected for further analysis. To crossly validate the findings, we also analyze another transcriptome dataset (GSE12452) for the selection of candidate gene as already been described in our previous publication[18].

Patients and tumor specimens

The institutional review board approved the procurement of formalin-fixed NPC tissue for this study (IRB10501-006). In brief, a total of 124 formalin-fixed paraffin-embedded tissue samples from NPC patients were used for *PSAT1* immunohistochemical evaluations. These patients were regularly followed up by physicians after biopsy in the Chi-Mei Medical Center. Patients who were initially diagnosed with NPC without distant metastasis underwent tissue biopsy between January 1998 and December 2002. Two pathologists (C.F. Li and T.J Chen) classified tumors by histological type based on WHO classifications[19]. Tumor stage was adjusted according to the American Joint Committee on Cancer Tumor-Nodes-Metastasis (TNM) classification of malignant tumors[20].

Immunohistochemical staining and assessment of PSAT1

Formalin-fixed, paraffin-embedded tissue samples were cut into 4-μm-thick sections. Paraffin-embedded tissues were deparaffinized using xylene, rehydrated in ethanol, and heated in a microwave using methods described in our previous study[21]. Tissue samples were washed in Tris-buffered saline for 15 min, and slides were incubated with a primary monoclonal antibody against *PSAT1* (1:100; Abcam).

Treatment and follow-up

All 124 NPC patients received a complete course of 3-dimensional radiotherapy (3DRT) in a constant protocol and were regularly followed-up until death or loss. The mean follow-up duration was 3 years. Patients with stage II-IV disease received concurrent cisplatin-based chemotherapy in addition to radiotherapy.

Statistical analysis

The SPSS 14 software package was used to perform statistical data analyses. Chi-square or Fisher's exact test analyzed the relationship between *PSAT1* immunohistochemical expression and various clinicopathological parameters. The endpoints analyzed were local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) which were calculated from the starting date of radiotherapy to the date of an event. Patients lost to follow-up were censored on the latest follow-up date. Multivariate analysis was performed using the Cox proportional hazards model. We also performed Kaplan-Meier analysis to compare the survival curves in NPC patients with different groups. The log-rank test was used to investigate differences in survival times between two groups. A *P*-value <0.05 was considered statistically significant.

Results

PSAT1 was the most significantly upregulated gene associated with amino acid biosynthetic pathway in NPC.

Table 1 provides a summary of 8 significant differentially expressed genes associated with amino acid biosynthesis in the transcriptome of nasopharyngeal carcinomas (GSE34574). Of these, *ASNS*, *PSPH*, and *PSAT1* exhibited upregulated mRNA expression and *PSAT1* demonstrated the most significant upregulation (Logs ratio=4.2088, *P*<0.0001, Fig. 1). Interestingly, we also confirmed *PSAT1* as the most significantly upregulated gene in an independent GEO dataset (GSE12452) which discloses *PSAT1* upregulaiton is most associated with the development of NPC (tumor versus non-tumor, log2 ratio=2.0392, *P*<0.0001) in those associated with amino acid biosynthesis. Accordingly, we further evaluated the clinicopathological significance of *PSAT1* expression by immunohistochemistry.

Table 1. Summary of differentially expressed genes associated with amino acid biosynthesis in the transcriptome of nasopharyngeal carcinomas (GSE34574)

Probe	Comparison 1 Log ratio (NPC vs. Non-tumor tissue)	p-value	Gene Symbol	Gene Name	Biological Process	Molecular Function
223062_s_at	4.2088	<0.0001	***PSAT1***	phosphoserine aminotransferase 1	L-serine biosynthetic process, amino acid biosynthetic process, metabolic process, pyridoxine biosynthetic process	catalytic activity, phosphoserine transaminase activity, pyridoxal phosphate binding, transaminase activity, transferase activity
205047_s_at	3.4002	<0.0001	*ASNS*	asparagine synthetase	amino acid biosynthetic process, asparagine biosynthetic process, glutamine metabolic process, metabolic process	asparagine synthase (glutamine-hydrolyzing) activity, ligase activity
217956_s_at	2.3727	0.0031	*ENOPH1*	enolase-phosphatase 1	amino acid biosynthetic process, metabolic process, methionine biosynthetic process	catalytic activity, hydrolase activity, magnesium ion binding, metal ion binding, phosphoglycolate phosphatase activity
203774_at	2.0694	0.0004	*MTR*	5-methyltetrahydrofolate-homocysteine methyltransferase	amino acid biosynthetic process, central nervous system development, folic acid and derivative biosynthetic process, methionine biosynthetic process, nervous system development	cobalamin binding, cobalt ion binding, dihydropteroate synthase activity, homocysteine S-methyltransferase activity, metal ion binding, methionine synthase activity, methyltransferase activity, protein binding, transferase activity, zinc ion binding
205048_s_at	1.543	0.0047	*PSPH*	phosphoserine phosphatase	L-serine biosynthetic process, L-serine metabolic process, amino acid biosynthetic process, cell proliferation, metabolic process	catalytic activity, hydrolase activity, magnesium ion binding, phosphoric monoester hydrolase activity, phosphoserine phosphatase activity, protein binding
203576_at	-1.3603	0.0002	*BCAT2*	branched chain aminotransferase 2; mitochondrial	amino acid biosynthetic process, branched chain family amino acid biosynthetic process, branched chain family amino acid catabolic process, branched chain family amino acid metabolic process, metabolic process	branched-chain-amino-acid transaminase activity, catalytic activity, transaminase activity, transferase activity
204608_at	-1.3908	0.0008	*ASL*	argininosuccinate lyase	amino acid biosynthetic process, arginine biosynthetic process, arginine biosynthetic process via ornithine, arginine catabolic process, urea cycle	argininosuccinate lyase activity, catalytic activity, lyase activity
207076_s_at	-3.6325	0.0001	*ASS1*	argininosuccinate synthetase 1	amino acid biosynthetic process, arginine biosynthetic process, urea cycle	ATP binding, argininosuccinate synthase activity, ligase activity, nucleotide binding, protein binding

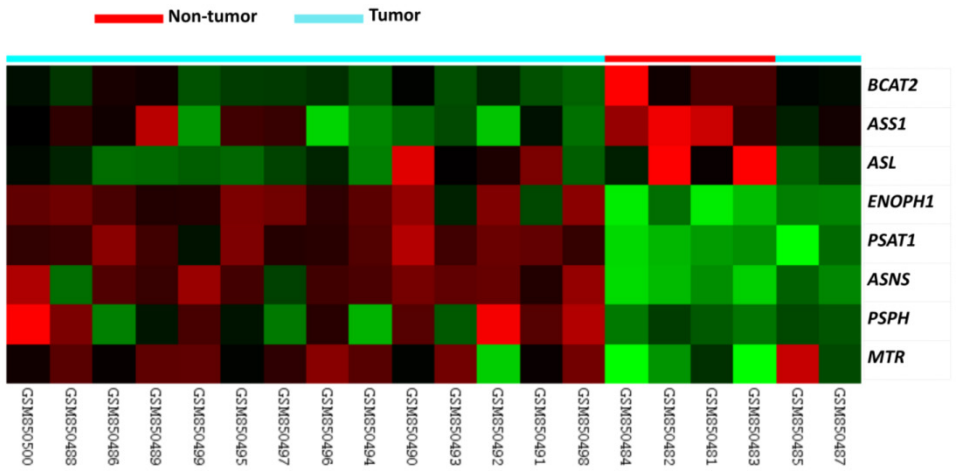

Figure 1. Published transcriptomic datasets of NPC versus benign nasopharyngeal tissues samples were evaluated. *PSAT1* was an upregulated gene in the regulation of amino acid biosynthesis in the clustering analysis. Nasopharyngeal carcinoma (blue lines) and benign tissue (red lines) specimens are indicated at the top of the heatmap, and expression levels of upregulated and downregulated genes are expressed as a series of brightness of red and green colors, respectively. Unaltered mRNA expression is coded black.

Clinicopathological features of our NPC cohort

Table 2 shows the associations between *PAST1* expression and important clinicopathological variables. The 124 cases of NPC consisted of 5 keratinizing squamous cell carcinomas, 54 non-keratinizing differentiated carcinomas, and 65 undifferentiated carcinomas. There were 95 males and 29 females, and 26 cases were older than 60 years of age. Thirty-eight cases were classified as stages I and II, and 85 cases were classified as stages III and IV. The mean follow-up period was 3 years, and the median duration to tumor-associated mortality was 2 years. The median durations to distal metastasis and local recurrence were 10 and 16 months, respectively.

Immunohistochemical expression of *PSAT1* and associations with clinicopathological features and treatment outcomes

Low *PAST1* expression was significantly associated with T1–T2 classification (*P*=0.024) and stages I-II classification (*P*=0.019), but it was not related to histological grade. Of all important clinicopathological paraneters, T3–4 status, N2–3 status and AJCC III–IV stages, and high *PAST1* expression were all significantly predictive of worse outcomes for the three survival endpoints analyzed in univariate analyses (Table 3, Fig. 3). AJCC III–IV stages remained prognostically independent for DSS (*P*=0.041, hazard ratio [HR]= 2.072), LRFS (*P*=0.028, HR= 2.935), and OS (*P*= 0.036, HR= 2.108) in multivariate comparisons, but it lost statistical significance for DMeFS (Table 4). Moreover, high *PAST1* expression also predictive a more aggressive clinical course, with significantly shorter DSS (HR= 2.856, 95% CI 1.599 to 5.101), DMeFS (HR= 3.305, 95% CI 1.720 to 6.347), LRFS (HR= 2.834, 95% CI 1.376 to 5.835), and OS (HR= 2.935, 95% CI 1.646-5.234) in multivariate analyses.

Table 2. Associations between *PSAT1* expression with other important clinicopathological variables.

Parameters	Category	*PSAT1* Exp.		p-value
		Low Exp.	High Exp.	
Gender	Male	47	48	0.832
	Female	15	14	
Age (years)	<60 years	47	51	0.378
	>=60 years	15	11	
Primary tumor (T)	T1-T2	46	34	**0.024***
	T3-T4	16	28	
Nodal status (N)	N0-N1	31	25	0.279
	N2-N3	31	37	
Stage	I-II	25	13	**0.019***
	III-IV	37	49	
Histological grade	Keratinizing	3	2	0.445
	Non-keratinizing	30	24	
	Undifferentiated	29	36	

Discussion

PSAT1 is an aminotransferase that plays an important role in linking catabolic pathways (glycolysis) and amino acid (serine) biosynthesis. *PSAT1* is responsible for the second step in serine synthesis, and it converts 3-phosphohydroxypyruvate to phosphoserine. Serine is an important carbon source for purine nucleotides, phosphatidylcholine, phosphatidylserine, and other cellular metabolites. Cancer cells use glucose and glutamine to support energy and anabolic metabolism[22,23], and *PSAT1* is overexpressed in some cancer cells. Cancer cells use non-amino acid precursors to synthesize glycine and serine, which was first noted in lymphomas[24].

A previous study demonstrated that serine biosynthesis played an important role in bone metastatic breast cancer. Three enzymes, *PSAT1*, phosphoserine phosphatase (*PSPH*) and phosphoglycerate dehydrogenase (*PHGDH*), were responsible for the phosphorylated pathway of L-serine biosynthesis[25]. Jason et al. found that much of the glycolytic carbon in melanoma was redirected to serine and glycine metabolism via *PHGDH*. *PSAT1* expression was also observed in melanoma[26]. *PSAT*1 is weakly expressed in normal colon tissue but is overexpressed in colon cancer, and its expression is associated with disease progression[27-28]. Yoon et al. followed 78 patients with recurrent colon cancer during a median follow-up duration of 55.5 months and found that *PHGDH*, pyruvate dehydrogenase kinase 1, and *PSAT* expression was significantly higher in tumor cells than normal tissue. Univariate analysis for recurrence-free survival in colon tumor cells demonstrated that pyruvate dehydrogenase kinase 2 positivity was the only positive prognostic factor, but there was no significant difference in multivariate analysis[29].

Table 3. Univariate log-rank analyses.

Parameters	Category	No. of case	DSS		DMeFS		LRFS		OS	
			No. of event	p-value	No. of event	p-value	No. of event	p-value	No. of event	*P*-value
Gender	Male	95	45	0.7870	38	0.6128	30	0.3240	46	0.7220
	Female	29	14		11		7		14	
Age (years)	<60 years	98	48	0.8600	42	0.3091	29	0.8206	49	0.8049
	>=60 years	26	11		7		8		11	
Primary tumor (T)	T1-T2	80	32	**0.0289***	25	**0.0085***	19	**0.0180***	32	**0.0204***
	T3-T4	44	27		24		18		28	
Nodal status (N)	N0-N1	56	18	**0.0008***	17	**0.0132***	12	**0.0160***	19	**0.0011***
	N2-N3	68	41		32		25		41	
Stage	I-II	38	10	**0.0020***	9	**0.0072***	5	**0.0026***	10	**0.0020***
	III-IV	86	49		40		32		49	
Histological grade	Keratinizing/Non-keratinizing	47	20	0.1980	17	0.2753	15	0.9521	20	0.1522
	Undifferentiated	77	39		32		22		40	
PAST1 Exp.	Low Exp.	60	17	**<0.0001***	13	**<0.0001***	11	**0.0002***	17	**<0.0001***
	High Exp.	64	42		36		26		42	

*, Statistically significant; DSS, disease-specific survival; DMeFS, distal metastasis-free Survival; LRFS, local recurrence-free survival; OS, overall survival.

Table 4. Multivariate survival analyses

Parameter	Category	DSS			DMeFS			LRFS			OS		
		H.R	95% CI	p-value	H.R	95% CI	p-value	H.R	95% CI	p-value	H.R	95% CI	p-value
Stage	I-II	**1**	-	**0.041***	1	-	0.093	**1**	-	**0.028***	**1**	-	**0.036***
	III-IV	**2.072**	**1.030-4.168**		1.890	0.900-3.969		**2.935**	**1.122-7.677**		**2.108**	**1.048-4.238**	
PAST1 Exp.	Low Exp.	**1**	-	**<0.001***	**1**		**<0.001***	**1**	**-**	**0.005***	**1**	-	**<0.001**
	High Exp.	**2.856**	**1.599-5.101**		**3.305**	**1.720-6.347**		**2.834**	**1.376-5.835**		**2.935**	**1.646-5.234**	

*, Statistically significant; DSS, disease-specific survival; DMeFS, distal metastasis-free Survival; LRFS, local recurrence-free survival; OS, overall survival

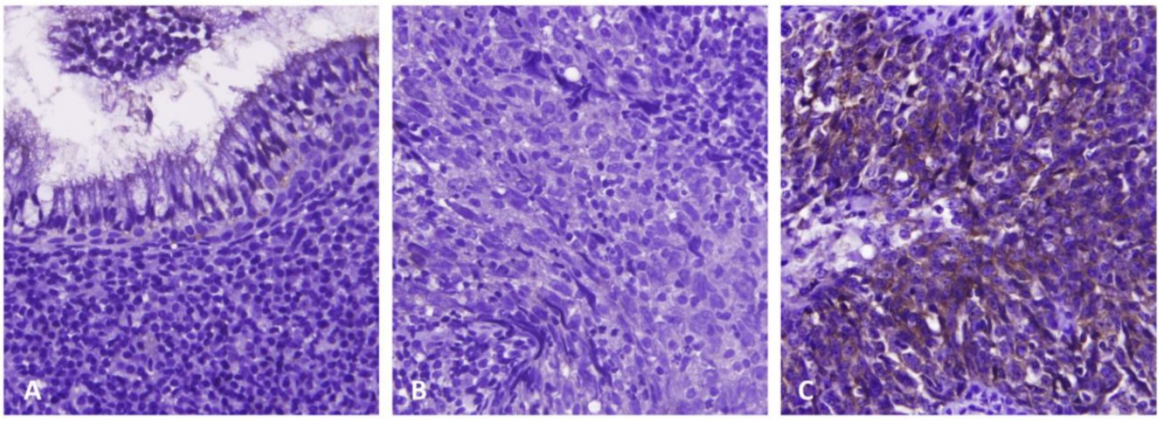

Figure 2. Immunoexpression of *PSAT1* in benign nasopharyngeal epithelial tissue (A), low-stage (B), and high-stage (C) nasopharyngeal carcinomas, respectively. Immunohistochemically, *PSAT1* expression was barely detected in benign nasopharyngeal epithelial tissue and low-stage nasopharyngeal carcinoma, but it significantly upregulated in high-stage nasopharyngeal carcinoma

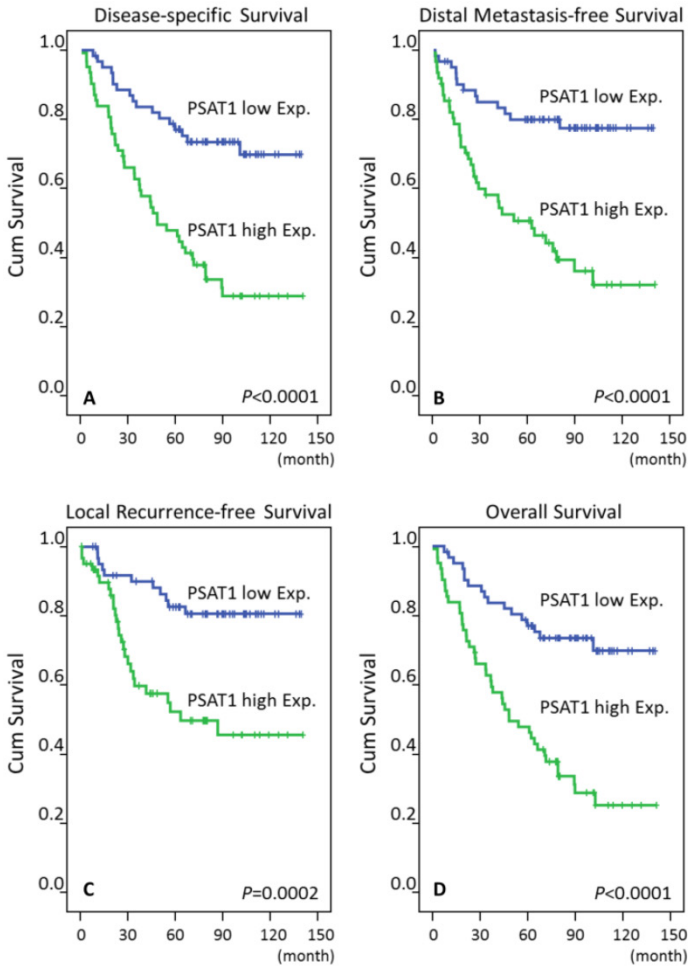

Figure 3. Log-rank test revealed that *PSAT1* overexpression was predictive of poor prognosis, including disease-specific survival, distant metastasis-free survival, local recurrence-free survival, and overall survival.

The regulatory mechanism of *PSAT1* expression remains largely unknown. But it has been reported that MicroRNA (MiR)-340, playing a role in tumor suppression in esophageal squamous cell carcinoma, inhibits tumor proliferation via targeting of *PSAT1*, and *PSAT1*. In this manner, MiR-340 is involved in cancer cell proliferation and invasion in esophageal squamous cell carcinoma, suggesting a possible regulatory mechanism of *PSAT1* expression[30]. Few if any previous reports have disclosed the role of *PSAT1* in regulating cell proliferation. It is interesting that *PSAT1* is overexpressed in non-small cell lung cancer, and it is involved in tumor cell proliferation and cell cycle progression. *PSAT1* enhances G1 activity via modulation of cyclin D1 degradation and Rb-E2F pathway activity, suggesting its unique intracellular signaling axis[31].

Our study found that high *PSAT1* expression was a potent prognostic factor for DSS, DMeFS, LRFS and OS in NPC patients. The identification of biomarkers that independently correlate with tumor aggressiveness is important for the individualized management of high risk NPC. We confirmed increased hazard ratios of DSS, DMeFS, LRFS and OS in NPC patients with advanced stages (III-IV). A significant association between *PSAT1* expression, primary tumor size, nodal status and AJCC stage of NPC was observed. Therefore, we hypothesized that high *PSAT1* expression may represent NPC progression via an amino acid biosynthetic process.

PSAT1 overexpression in colon and breast cancers correlates with advanced tumor stage, chemoresistance and poor prognosis to endocrine therapy[28]. A high expression level of *PSAT1* was associated with an advanced stage of NPC and poor prognosis compared to the NPC patients with low *PSAT1* expression in our study. The role of *PSAT1* in tumorigenesis and NPC development and progression and the use of *PSAT1* as a treatment target require further investigation.

In conclusion, *PSAT1* was overexpressed in the transcriptome of NPC, and NPC protein was identified in NPC tissue using immunohistochemistry. *PSAT1* was associated with

advanced tumor stage, and it independently predicted a poor prognosis of NPC.

Competing Interests

The authors have declared that no competing interest exists.

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