Stromal cell-derived factor-1 G801A polymorphism and the risk factors for cervical cancer

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Abstract. Although certain studies have demonstrated no association between the stromal cell-derived factor-1 (*SDF1-3'*) G801A single nucleotide polymorphism (SNP) and cervical carcinoma, the interactions between the *SDF1-3'* G801A SNP and contraceptive use, menopausal status, parity and tobacco smoking remain to be fully elucidated. Using polymerase chain reaction-restriction fragment length polymorphism, the distribution of *SDF1-3'* G801A genotypes in patients with cervical cancer (n=462) against control groups (n=497) was investigated. Logistic regression analysis, adjusting for age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status, did not identify the *SDF1-3'* G801A polymorphism as a genetic risk factor for cervical cancer. The adjusted odds ratio (OR) for patients with the A/G, vs. G/G genotype was 1.203, with a 95% confidence interval (CI) of 0.909-1.591 (P=0.196). The adjusted OR for the A/A, vs. G/G genotype was 1.296 (95% CI=0.930-1.807; P=0.125) and for the A/A or A/G, vs. G/G genotype was 1.262 (95% CI=0.964-1.653; P=0.090)]. The P-value of the χ^2 test of the trend observed for the *SDF1-3'* G801A polymorphism was at the borderline of being statistically significant (p_{trend}=0.0484). Stratified analyses between the distribution of the *SDF1-3'* G801A genotypes and cervical cancer risks demonstrated that this polymorphism may be a risk factor for patients with a positive history of tobacco smoking (1.778; 95% CI=1.078-2.934; P=0.0235). These findings suggested that the *SDF1-3'* G801A polymorphism may be a genetic risk factor for cervical cancer in patients with a positive history of tobacco smoking.

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Introduction

Cervical tumors are the most common type of gynecological malignancy worldwide and constitute the tenth most frequent type of cancer occurring in females in developed countries (1,2). The number of young females affected by cervical cancer has been increasing (1-3). Cervical carcinogenesis encompasses the transformation of normal cervical epithelium to cervical intraepithelial neoplasia (CIN), which may develop into an invasive cervical tumor (4,5). There are several risk factors for cervical cancer, including human papillomavirus, impairment of the immune system, expression of tumor suppressor genes and gain of function mutations in proto-oncogenes (4,5). In addition, contraceptive use, tobacco consumption, age and environmental exposures are also considered possible causative factors in cervical cancerogenesis (6). C-X-C motif chemokine 12 is a chemokine, also termed stromal cell-derived factor-1 (SDF1), which binds to the CXCR4/CXCR7 receptors (7).

The human *SDF1* gene is expressed as α and β alternative splice variants (8). SDF1 is involved in lymphopoiesis and myelopoiesis and attracts lymphocytes, megakaryocytes, endothelial cells and stem cells (9-11). In addition, the interaction of SDF1 with CXCR4 controls the embryonic growth of vascular, cardiac, neuronal and craniofacial systems (12). However, the binding of SDF1 to CXCR4 contributes to the progression of cancer of the colon, pancreas, ovaries, prostate, lung, stomach, mouth, breast and skin, in addition to cervical cancer (13-21).

SDF1 is present in common genetic variants due to a G801A transition in the 3'-untranslated region (rs 1801157) (22). The possible role of the *SDF1-3'* A variant in the increased levels of transcription and protein has been reported (22). Certain studies have demonstrated no association between the *SDF1-3'* G801A single nucleotide polymorphism (SNP) and cervical carcinoma (23,24), however, the interaction between the *SDF1-3'* G801A SNP with other known risk factors of cervical cancer remain to be fully elucidated. In the present study, the *SDF1-3' G801A* genotype and allele frequencies were investigated in patients with cervical cancer (n=462) and healthy controls (n=497) in the Polish population, stratified based on contraceptive use, menopausal status, parity and history of tobacco smoking.

Table I. Clinical and demographic characteristics of patients and controls.

Characteristic	Patient (n=462) n (%)	Control (n=497) n (%)
Mean age (years) ± SD[a]	52.4±9.4	51.9±11.2
Tumor stage		
IA	63 (13.6)	
IB	62 (13.4)	
IIA	56 (12.1)	
IIB	57 (12.3)	
IIIA	146 (31.6)	
IIIB	55 (11.9)	
IVA	11 (2.4)	
IVB	12 (2.6)	
Histological grade		
G1	89 (19.3)	
G2	147 (31.8)	
G3	101 (21.9)	
Gx	125 (27.0)	
Histological type		
Squamous cell carcinoma	383 (82.9)	
Adenocarcinoma	62 (13.4)	
Other	17 (3.7)	
Pregnancy		
Never	55 (11.9)	59 (11.9)
Ever	407 (88.1)	438 (88.1)
Oral contraceptive pill use		
Never	250 (54.1)	281 (56.5)
Ever	212 (45.9)	216 (43.5)
Tobacco smoking		
Never	298 (64.5)	328 (66.0)
Ever	164 (35.5)	169 (34.0)
Menopausal status		
Premenopausal	165 (35.7)	195 (39.2)
Postmenopausal	297 (64.3)	302 (60.8)
HPV genotype		
16 and 18	315 (68.2)	
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68	362 (78.3)	

[a]Age at first diagnosis. HPV, human papillomavirus; SD, standard deviation.

Patients and methods

Patients and controls. The patients consisted of 462 females with histologically-determined cervical carcinoma, according to the International Federation of Gynecology and Obstetrics. All the females were enrolled between April 2007 and January 2014 at the Department of Radiotherapy, Greater Poland Cancer Center (Poznań, Poland; Table I). The controls included 497 unrelated healthy female volunteers, who were matched by age to the patients (Table I). Data regarding pregnancy, oral contraceptive use, tobacco smoking and menopausal status were obtained during clinical interviews. All individuals were Caucasian and were enrolled from the Wielkopolska (Greater Poland) area of Poland. The patients and controls provided written informed consent and the study was approved by the Local Ethical Committee of Poznań University of Medical Sciences (Poznań, Poland).

Genotyping. DNA was isolated from peripheral blood leucocytes using a salting-out procedure, in which 10 ml peripheral blood were obtained using BD Vacutainer® (Becton Dickinson, Franklin Lakes, NJ USA). The presence of the *SDF1-3'*G801A (rs 1801157) transition was determined by polymerase chain reaction (PCR) using Dream Taq DNA Polymerase (Thermo Scientific,

Table II. Association between the stromal cell-derived factor-1-*3*' 'G801A (rs 1801157) polymorphism and cervical cancer.

Genotype	Patient (frequency)	Control (frequency)	Odds ratio (95% CI)	P-value[a]	Adjusted odds ratio (95% CI)[b]	P-value[a]	P_{trend}
G/G	289 (0.63)	337 (0.68)	Referent	-	Referent		
A/G	149 (0.32)	144 (0.29)	1.207 (0.914-1.593)	0.1849	1.203 (0.909-1.591)	0.196	**0.0484**
A/A	24 (0.05)	16 (0.03)	1.749 (0.911-3.57)	0.0892	1.296 (0.930-1.807)	0.125	
A/G+A/A	173 (0.37)	160 (0.32)	1.261 (0.966-1.646)	0.0878	1.262 (0.964-1.653)	0.090	
Minor allele frequency	0.21	0.18					

[a]χ^2 analysis. [b]Odds ratios were adjusted by age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status. Significant results are highlighted in bold font. CI, confidence interval.

Vilnius, Lithuania) and a PTC-200 DNA Engine Thermocycler (MJ Research Inc, St. Bruno, QC, Canada). The primer sequence was as follows, 5'-TTATTGTACTTGCCTTATTAGAG-3' and 5'-GTAGTTCACCCCAAAGGACC-3'. The PCR was followed by digestion with *Msp*I (C/CGG; Thermo Scientific) according to manufacturer's instructions. The *SDF1-3' A* allele remained uncut at 732 bp, whereas the *SDF1-3' G* allele was cleaved into 456 bp and 276 bp fragments. The DNA fragments were separated by electrophoresis on a 3% agarose gel and visualized with ethidium bromide staining (Sigma-Aldrich, Poznań, Poland). The presence of the *SDF1-3'* G801A transition was also confirmed by Sanger sequencing of 15% of the samples, which were randomly selected.

Statistical analysis. The distinction in genotypic and allelic prevalence between patients and controls, and their genotypic deviation from the Hardy-Weinberg (HW) equilibrium was evaluated using a χ^2 test. The polymorphism was assessed for association with cervical cancer incidence using a χ^2 test for trend (p_{trend}), odds ratio (OR) and 95% confidence intervals (CI). Unconditional logistic regression analysis was used to adjust for the effect of confounders, including age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Distribution of the SDF1-3' *G801A polymorphism in females with cervical cancer*. The prevalence of the *SDF1-3'* G801A genotypes did not exhibit a significant divergence from the HW equilibrium between the cases and controls. The distribution and adjusted analysis of the *SDF1-3'* G801A genotypes in females with cervical cancer are presented in Table II.

The frequency of the *SDF1-3' A/A* genotype was ~1.7-fold higher in patients compared with controls. The *SDF1-3'* A/G heterozygous genotype frequency was higher in patients with cervical cancer compared with controls, at 0.32 and 0.29, respectively. The *SDF1-3'* minor allele frequency was also higher in patients compared with controls, and was 0.21 and 0.18, respectively. The P-value of the χ^2 test of the trend observed for the *SDF1-3'* G801A polymorphism was at the borderline of being statistically significant ($p_{trend}=0.0484$). Logistic regression analysis did not demonstrate that the SDF1-3' G801A polymorphism was a risk factor for cervical cancer. The adjusted OR for patients with the A/G, vs. G/G genotype was 1.203 (95% CI=0.909-1.591; P=0.196), the adjusted OR for A/A, vs. G/G was 1.296 (95% CI=0.930-1.807;P=0.125) and for A/A or A/G, vs. G/G was 1.262 (95% CI=0.964-1.653; P=0.090).

Stratified analysis between the SDF1-3' *G801A genotypes and cervical cancer risks*. The age adjusted analysis of the *SDF1-3'* G801A genotypes and cervical cancer risk, stratified by pregnancy, oral contraceptive use, tobacco smoking, and menopausal status is presented in Table III. An increase in cervical cancer risk was observed only among patients with a positive history of tobacco smoking for the adjusted OR with the A/A, vs. G/G genotype at 1.778 (95% CI=1.078-2.934; P=0.0.0235). However, no significant association was observed between *SDF1-3'* G801A and smoking for the A/G, vs. GG (1.180; 95% CI=0.731-1.905; P=0.4975) or A/A or A/G, vs. A/A genotype (1.352; 95% CI=0.862-2.122; P=0.1877]. Furthermore, no significant association was observed between *SDF1-3'* G801A and pregnancy, oral contraceptive use or menopausal status (Table III). No association was observed between the *SDF1-3'* G801A polymorphism and tumor stage, histological grade or type of tumor (data not shown) on stratification of the patients based on clinical characteristics.

Discussion

The *SDF1-3' A* gene variant has been suggested as a factor that upregulates SDF1α levels, and the SDF1/CXCR4/CXCR7 axis is considered to contribute significantly to the biology and metastasis of several types of cancer (22,25). In addition, the SDF1-CXCR4 interaction has been demonstrated to be important in the progression of cervical cancer (26-30). Wei *et al* (26) suggested that the progression of cervical tumors is accompanied with an increased production of SDF1α. In addition to these findings, Huang *et al* (27) demonstrated an increase in the co-expression levels of SDF1/CXCR4 in CIN and cervical carcinoma as a durative process in cervical cancerogenesis. The SDF1-CXCR4 axis initiates invasiveness via changes to the adhesion and secretion of matrix metalloproteinase-2. (OMIM *120360) and promotes the metastasis of tumor cells

Table III. Stratified analyses between the distribution of stromal cell-derived factor-1-*3'* *G801A* genotypes and cervical cancer risks: Pregnancy, oral contraceptive use, tobacco smoking and menopausal status.

	Patient (n)			Control (n)				
Risk factor	G/G	G/A	A/A	G/G	G/A	A/A	Adjusted odds ratio (95% CI)[b]	P-value[d]
Pregnancy								
Ever	255	132	20	297	127	14	1.200 (0.892-1.615)[a]	0.228
							1.255 (0.879-1.790)[b]	0.210
							1.245 (0.936-1.656)[c]	0.132
Never	34	17	4	40	17	2	1.635 (0.662-4.038)[a]	0.281
							1.801 (0.694-4.677)[b]	0.220
							1.898 (0.798-4.510)[c]	0.143
Oral contraceptive use								
Ever	131	69	12	146	63	7	1.210 (0.797-1.839)[a]	0.370
							1.492 (0.907-2.453)[b]	0.113
							1.293 (0.865-1.932)[c]	0.208
Never	158	80	12	191	81	9	1.083 (0.737-1.594)[a]	0.682
							1.127 (0.713-1.783)[b]	0.608
							1.117 (0.771-1.621)[c]	0.557
Smoking								
Ever	99	51	14	113	49	7	1.180 (0.731-1.905)[a]	0.498
							1.778 (1.078-2.934)[b]	**0.025**
							1.352 (0.862-2.122)[c]	0.189
Never	190	98	10	224	95	9	1.165 (0.822-1.653)[a]	0.390
							1.139 (0.715-1.814)[b]	0.582
							1.195 (0.853-1.674)[c]	0.300
Menopausal status								
Premenopausal	105	55	5	132	56	7	1.331 (0.839-2.111)[a]	0.223
							1.003 (0.475 -2.119)[b]	0.994
							1.322 (0.844-2.070)[c]	0.221
Postmenopausal	184	94	19	205	88	9	1.159 (0.812 -1.653)[a]	0.415
							1.490 (0.986 -2.252)[b]	0.058
							1.261 (0.898-1.770)[c]	0.181

[a](G/A vs. G/G); [b](A/A vs. G/G); [c](A/A and A/G vs. G/G), [d]χ^2 analysis. All P-values were adjusted by age. Significant results are highlighted in bold.

toward lymph nodes and the pelvic cavity in patients with cervical cancer (29,30). SDF1α also provokes significant signal transduction events, including chemotaxis and rescue from apoptosis in cervical cancer cells (21,30). In addition to these findings Majka *et al* (21) demonstrated that SDF1α augments cervical cancer cell scattering and supported the nuclear localization of the β-catenin gene and also increased its target gene expression, cyclin D1. In addition, it was observed that SDF1α interacts with CXCR4 and leads to the activation of numerous downstream cytoplasmic signaling pathways, which support the invasiveness of cervical cancer (21).

Genetic variants of *SDF1* may have an impact on cervical cancer development and its clinicopathological variables. In the present study, the *SDF1-3'* G801A SNP was not identified as a risk factor for cervical cancer. The present observations are in agreement with those by Maley *et al* (23) and Tee *et al* (24), which also observed no association between the *SDF1-3'* G801A polymorphism and risk of cervical cancer. However, in the present study, the P-value assessment of the trend observed for the *SDF1-3'* G801A polymorphism was on the borderline of statistical significance. In addition, the present study revealed that the *SDF1-3'* A/A genotype may be a risk for cervical cancer in females with a positive history of tobacco smoking. This is consistent with previous reports suggesting the possible causative role of tobacco consumption in cervical carcinogenesis (6,31,32). However, no other confounding variables, including contraceptive use, menopausal status or parity affected the *SDF1-3'* G801A polymorphism as a risk factor for cervical cancer.

The *SDF1-3'* G801A polymorphism has been reported as a risk factor in the development of breast, laryngeal, oral, lung, prostate and hepatocellular carcinoma, as well as lymphoma (33-39). The effect of the *SDF1-3'* G801A SNP on SDF1α biosynthesis has been based mainly on the analysis of subjects infected with human immunodeficiency (HIV) (22). The *SDF1-3'* A variant has been suggested as a genetic variant,

which increases the production of SDF1α (22). These findings were consistent with a study by Chang *et al* (40) who observed that fibroblasts from patients with colon cancer and the *SDF1-3'* GA or AA genotypes biosynthesized three times more SDF1α transcript compared with fibroblasts with the GG genotype. In addition, Garcia-Moruja *et al* (41) demonstrated that the *SDF1-3'* A transcript variant exhibited a two-fold longer half-life than the *SDF1-3'* G transcript variant. By contrast, a study by Kimura *et al* (42), using Epstein-Barr virus-transformed lymphoblastoid cell lines, did not observe any effects of the *SDF1-3'* G801A SNP on the SDF1α mRNA levels. In addition to these findings, Watanabe *et al* (43), using the syncytium model, also observed no correlation between the *SDF1-3'* G801A SNP gene variant and syncytium-inducing HIV (43).

In conclusion, the present genetic study is the first, to the best of our knowledge, to demonstrate that the *SDF1-3'* A gene variant may be a risk factor for cervical carcinoma in patients with a positive history of tobacco smoking; therefore this evaluation should be replicated in other independent ethnicities.

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