Short Communication

Evaluation of the Association with Cervical Cancer of Polymorphisms in Syndecan-1, a Heparan Sulfate Proteoglycan Involved with Viral Cell Entry

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Abstract

Infection with 1 of ~15 oncogenic human papillomaviruses is known to be linked to the development of all histologic forms of cervical cancer. We evaluated whether polymorphisms in syndecan-1 (*SDC-1*), a gene whose protein product is believed to be involved in human papillomavirus entry into epithelial cells, were associated with histologic subtypes of cervical cancer. A total of 293 *in situ*/invasive adenocarcinoma cases, 260 *in situ*/invasive squamous cell carcinoma cases, and 478 controls from two studies conducted in the Eastern United States and Seattle area were evaluated. DNA from peripheral blood was used for testing. We sequenced 5 exons and 60 nucleotides upstream of the start codon for SDC-1 in a random subset of 50 cases and 50 controls from the Eastern U.S. Study and identified two polymorphisms (E84E, rs2230924 and Pro-27 C → T, rs11544860). PCR-based testing was done to evaluate risk associated with these two polymorphisms. Polymorphisms of SDC-1 were not associated with risk of squamous cell carcinomas of the cervix. Similarly, there was no evidence for an association between SDC-1 exon 3 polymorphisms and risk of cervical adenocarcinomas. A marginally significant increase in risk of cervical adenocarcinoma was associated with the presence of the Pro-27 polymorphism (pooled odds ratios, 1.6; 95% confidence intervals, 0.99-2.6), an effect that was restricted to the Eastern U.S. Study. Our results indicate a lack of association between SDC-1 polymorphisms and risk of squamous cell carcinomas of the cervix. An association between SDC-1 Pro-27 polymorphism and cervical adenocarcinoma cannot be ruled out. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2504–8)

Introduction

Human papillomaviruses (HPV) have been established as the causative agent for cervical cancer. The mechanisms by which the virus enters and infects cervical epithelial cells are not completely understood. Furthering our understanding of viral entry patterns might provide important insight into the natural history of HPV and HPV-associated diseases, which could in turn, lead to new strategies for the prevention of HPV infection and disease.

Previous *in vitro* work has identified heparan sulfate proteoglycan as a likely primary attachment receptor for HPV (1). Syndecans (SDC) are one of two heparan sulfate families of membrane-bound proteoglycans; the most predominant of the SDCs is SDC-1 (2, 3). Absence of SDC-1 reduces HPV virus particle binding and renders K562 cells (cells that lack heparan sulfate proteoglycans except for minor amounts of endogenous betaglycan) resistant to low-virus inoculum (2). Thus, SDC-1 is a strong candidate HPV receptor on human epithelial cells.

Polymorphisms in genes that encode membrane proteins used by a virus to gain entry into cells have been shown to correlate with infectivity and subsequent disease risk for viruses other than HPV (e.g., *CCR5Δ32* and HIV infection; refs. 4-6). We hypothesized that a similar mechanism might exist for HPV and cervical cancer, and evaluated the association between variants of *SDC-1* and the risk of cervical cancer.

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Materials and Methods

We used data and specimens from two previously described United States case-control studies of cervical squamous cell carcinoma and adenocarcinoma as the basis of our evaluation. The first was a multicenter study conducted in the Eastern United States (''Eastern U.S. Study'') consisting of 124 *in situ*/invasive cervical adenocarcinomas or adenosquamous carcinomas, 139 *in situ*/invasive squamous cell carcinomas of the cervix, and 307 controls identified through random-digit telephone dialing and matched to cases with glandular tumors on age, race, and telephone exchange (7). The second was a population-based study conducted in the three metropolitan counties of western Washington state (''Seattle Area Study'') consisting of 169 *in situ*/invasive cervical adenocarcinomas or adenosquamous carcinomas, 121 invasive squamous cell carcinomas of the cervix, and 171 controls identified through random-digit telephone dialing. Cases were diagnosed between January 2000 and March 2003 and controls were frequency-matched to cases on age in 5-year groups and assigned reference dates to correspond with case diagnosis dates (8). Participation rates for the two studies were 78.8% for cases and 73.2% for controls in the Eastern U.S. Study, and 62.4% for cases and 66.3% for controls in the Seattle Area Study. As previously described, the Eastern U.S. Study used a PCR-based reverse line blot detection method to determine HPV DNA genotypes in exfoliated cervical cells, whereas the Seattle Area Study used ELISA assays to test for HPV-16 L1 capsid antibodies in serum (7, 8). Additional details of these two studies have been previously published (7-9).

To identify and genotype *SDC-1* polymorphisms, we used PCR to amplify and then sequence the 5 exons and 60 nucleotides upstream of the start codon in a random set of 50 cases and 50 controls from the Eastern U.S. Study. This sequencing effort resulted in the identification of two variations in our study population: rs2230924 (E84E) and rs11544860 (Pro-27 C → T). No other variations were observed. Fragments containing these two single nucleotide polymorphisms (SNP) were amplified using the following pairs of primers: (*a*) syn-5 (5′-ctctgcttctggtcctgcag-3′) and syn-6 (5′-gaggccagatgagtggtcg-3′) for E84E, and (*b*) syn-1 (5′-caagagagcatcgagcagcg-3′) and syn-14 (5′-acgtgcacccgccggcat-3′) for Pro-27. The PCR amplification was done at 60°C annealing temperature, and for Pro-27, DMSO was added to the reaction (10% final concentration). The two SNPs were genotyped either by sequencing or by using TaqMan Assays (Applied Biosystems) in the 472 participants (83%) in the Eastern U.S. Study for whom DNA was available for testing. As a point of reference, Pro-27 was genotyped by direct sequencing in both cohorts. Exon 3, sequenced in the Eastern U.S. Study only, was evaluated using both direct sequencing and TaqMan Assays (73 by direct sequencing only, 317 by TaqMan only, and 89 using both methods; concordance rate = 100%). To determine whether the association observed between C → T Pro-27 polymorphism and risk of cervical adenocarcinoma in the Eastern U.S. Study could be reproduced in a second, similar population, Pro-27 SNP testing using the same procedure was done among the 371 participants (80.5%) in the Seattle Area Study for whom DNA was available for testing. Pro-27 was found to be in Hardy-Weinberg equilibrium among controls in both studies (Eastern U.S. Study, $P = 0.99$; and Seattle Area Study, $P = 0.99$). Similarly, the exon 3 polymorphism tested for in our Eastern U.S. Study was found to be in Hardy-Weinberg equilibrium ($P = 0.87$). All assays were conducted blind to case-control status of the study subjects.

We evaluated the effect of the Pro-27 polymorphism on *SDC-1* mRNA expression using total RNA extracted from B cell lines from 24 healthy blood donors (equal numbers with the CC and CT genotypes) using Trizol (Invitrogen). The RNA samples were transcribed into cDNA using Superscript II (Invitrogen). The transcription level of *SDC-1* was examined using TaqMan Gene Expression Assays (Applied Biosystems) and normalized to 18S rRNA transcription according to the manufacturer's recommendations.

Logistic regression analyses were done to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess the association between *SDC-1* polymorphisms and cervical cancer. Homogeneity of the ORs between the two studies was assessed using the Breslow-Day test. Because we hypothesized that polymorphisms in *SDC-1* might influence viral infectivity of epithelial cells by HPV, we evaluated whether there was evidence of increased HPV infection rates among controls who were carriers of the *SDC-1* Pro-27's less common allele (i.e., allele T) relative to those who were homozygous for the wild-type allele. This was done separately for the two studies because HPV testing of controls in the Eastern U.S. Study was done by PCR-based DNA testing of cervical exfoliated cells, whereas in the Seattle Area Study, assessment of HPV exposure among controls was done by testing serum for the presence of antibodies against the HPV-16 capsid protein. Comparison of proportional differences in HPV DNA positivity and mean differences in mRNA expression level of the Pro-27 polymorphism in B cells was tested using Fisher exact test and Wilcoxon rank sum test, respectively. Analyses were done using SAS release 9.0 (SAS Institute).

Results

The mean age for the cases and controls was 38.1 (SD, 10.7) and 39.3 (SD, 11.2) years, respectively, in the Eastern U.S. Study and 39.0 (SD, 10.8) and 42.8 (SD, 13.2) in the Seattle Area Study, respectively. Both studies were comprised primarily of Caucasian women (85.0% in the Eastern U.S. Study and 86.4% in the Seattle Area Study).

We did not find an association between the exon 3 polymorphism and risk of cervical cancer in the Eastern U.S. Study (Table 1). The C → T change at position −27 of the SDC-1 promoter was associated with a marginally significant 80% elevation in risk of cervical adenocarcinoma (adjusted OR, 1.8; 95% CI, 0.95-3.4; prevalence of CC genotype, 89.5% in controls and 82.3% in adenocarcinoma) but not squamous cell carcinoma (adjusted OR, 1.2; 95% CI, 0.56-2.4; prevalence of CC genotype, 87.5% in squamous cell carcinoma; Table 1). Given these findings, subsequent testing of specimens from the Seattle Area Study focused on the Pro-27 polymorphism. In this second study, we did not observe a significant increase in risk of cervical adenocarcinoma or squamous cell carcinoma associated with this promoter region

Table 1. Risk of cervical cancer associated with *SDC-1* polymorphisms, by histologic type and study

Genotype	Control	Squamous cell carcinoma			Adenocarcinoma		
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)*	*n* (%)	OR (95% CI)	OR (95% CI)*
Exon 3 (rs2230924) polymorphism							
Eastern U.S. Study							
GG	123 (53.0)	60 (49.6)	1.0	1.0	62 (49.6)	1.0	1.0
AG/AA	109 (47.0)	61 (50.4)	1.1 (0.74-1.8)	1.2 (0.77-1.9)	63 (50.4)	1.1 (0.74-1.8)	1.1 (0.74-1.8)
AG	95 (41.0)	54 (44.6)	1.2 (0.74-1.8)	1.2 (0.77-1.9)	53 (42.4)	1.1 (0.70-1.7)	1.1 (0.70-1.7)
AA	14 (6.0)	7 (5.8)	1.0 (0.39-2.7)	1.2 (0.44-3.1)	10 (8.0)	1.4 (0.60-3.4)	1.4 (0.60-3.4)
Pro-27 (rs11544860) polymorphism							
Eastern U.S. Study							
CC	204 (89.5)	105 (87.5)	1.0	1.0	102 (82.3)	1.0	1.0
CT/TT	24 (10.5)	15 (12.5)	1.2 (0.61-2.4)	1.2 (0.56-2.4)	22 (17.7)	1.8 (1.0-3.4)	1.8 (0.95-3.4)
CT	23 (10.1)	15 (12.5)	1.3 (0.63-2.5)	1.2 (0.58-2.5)	22 (17.7)	1.9 (1.0-3.6)	1.9 (1.0-3.5)
TT	1 (0.4)	0 (0.0)	—	—	0 (0.0)	—	—
Seattle Area Study							
CC	98 (86.0)	75 (85.2)	1.0	1.0	110 (82.7)	1.0	1.0
CT/TT	16 (14.0)	13 (14.8)	1.1 (0.48-2.3)	1.3 (0.58-2.9)	23 (17.3)	1.3 (0.64-2.6)	1.2 (0.60-2.5)
CT	15 (13.2)	13 (14.8)	1.1 (0.51-2.5)	1.4 (0.61-3.1)	22 (16.5)	1.3 (0.64-2.7)	1.3 (0.61-2.7)
TT	1 (0.9)	0 (0.0)	—	—	1 (0.8)	0.9 (0.06-14)	0.6 (0.03-9.3)
Pooled analyses							
CC	302 (88.3)	180 (86.5)	1.0	1.0	212 (82.5)	1.0	1.0
CT/TT	40 (11.7)	28 (13.5)	1.2 (0.70-2.0)	1.2 (0.70-2.1)	45 (17.5)	1.6 (1.0-2.5)	1.6 (0.99-2.6)
CT	38 (11.1)	28 (13.5)	1.2 (0.73-2.1)	1.3 (0.74-2.2)	44 (17.1)	1.6 (1.0-2.6)	1.7 (1.0-2.7)
TT	2 (0.6)	0 (0.0)	—	—	1 (0.4)	0.7 (0.06-7.9)	0.5 (0.04-5.6)

*Adjusted for age, race, and study site where appropriate.

polymorphism (adjusted OR, 1.2; 95% CI, 0.60-2.5 for adenocarcinoma; and adjusted OR, 1.3; 95% CI, 0.58-2.9 for squamous cell carcinoma; prevalence of CC genotype, 86.0% in controls, 82.7% in adenocarcinoma, and 85.2% in squamous cell carcinoma; Table 1). When we pooled the data from the two studies, a marginally significant 60% elevation in risk of cervical adenocarcinoma was observed among carriers of the *SDC-1* Pro-27's less common allele (adjusted OR, 1.6; 95% CI, 0.99-2.6; heterogeneity between studies, $P = 0.45$; Table 1). There was no increased risk of squamous cell carcinomas associated with this polymorphisms in our pooled analysis (adjusted OR, 1.2; 95% CI, 0.70-2.1; heterogeneity between studies, $P = 0.80$).

The *SDC-1* Pro-27 less common allele was observed in 12.2% of Caucasian controls in the Eastern U.S. Study, 15.5% of Caucasian controls in the Seattle Area Study, and in none of the limited number of non-Caucasian controls from either of the two studies. The analyses described above were largely unchanged when we restricted the analysis to Caucasian participants. Age and study site adjusted OR estimates from pooled analyses of Caucasian women were 1.5 for adenocarcinoma (95% CI, 0.93-2.4; heterogeneity between studies, $P = 0.65$) and 1.2 for squamous cell carcinoma (95% CI, 0.71-2.1; heterogeneity between studies, $P = 0.92$).

Among Caucasian controls in the Eastern U.S. Study, HPV DNA positivity was observed in 21.7% of carriers of the *SDC-1* Pro-27 less common allele compared with 14.8% of those who did not carry at least one less common allele ($P = 0.37$ by Fisher exact test). Comparable results were observed in the Caucasian controls of the Seattle Area Study with HPV antibody positivity in 43.8% of the Pro-27 less common allele compared with 37.7% in those with the more common allele ($P = 0.78$ by Fisher exact test).

Although numbers were limited, we also evaluated the associations with *SDC-1* polymorphisms stratified by cigarette smoking, lifetime sexual partners, number of live births, and HPV status—but none altered our interpretation. There was no statistically significant difference between homozygous (Pro-27 CC; $n = 12$) and heterozygous (Pro-27 CT; $n = 12$) individuals in the level of transcription of SDC-1 in B cell lines by median [median (SD) for homozygous, 0.87 (0.90) and heterozygous, 0.70 (0.62); $P = 0.24$] or by percentage using the overall median value as cutoff for positivity (50% for both homozygous and heterozygous).

Discussion

Our results suggest that the two polymorphisms of *SDC-1* that we evaluated were not associated with risk of squamous cell carcinomas of the cervix, and that the *SDC-1* exon 3 polymorphism is not associated with risk of cervical adenocarcinomas. In contrast, we did observe some evidence for an association between a C → T change at position −27 of the *SDC-1* promoter and risk of cervical adenocarcinomas in a pooled analysis of two studies. This association was observed overall and in analyses restricted to Caucasian women, and was consistent with the modest elevation in the prevalence of HPV infections that we observed among controls who were carriers of the Pro-27 variant of *SDC-1*. Our finding was of borderline statistical significance, however, and the effect was restricted to one of our two studies. In addition, attempts to evaluate functional differences in *SDC-1* expression in cells from carriers and noncarriers of the Pro-27 polymorphism indicated no evidence of such differences. Given these conflicting findings, additional studies of the association between *SDC-1* Pro-27 polymorphisms and cervical adenocarcinoma would be required before any definitive conclusions can be made. Laboratory studies to determine the functional relevance of the *SDC-1* Pro-27 polymorphism might be warranted

prior to any attempt to confirm the association observed herein in future epidemiologic investigations.

An association between *SDC-1* Pro-27 polymorphism and adenocarcinomas, but not squamous cell carcinomas, of the cervix might be explained by at least two mechanisms. First, it is possible that *SDC-1* polymorphisms preferentially affect the infectivity of glandular epithelial cells from which cervical adenocarcinomas are thought to arise. Although little is currently known about the expression of *SDC-1* in different histologic compartments of the cervix, there is some evidence which indicates that different heparan sulfates may be found on different cell surfaces (e.g., SDC in basolateral compartments; refs. 10-12). Despite the lack of direct data on differential expression of *SDC-1* in different types of cervical cells, it is possible that there might be specific localization that ties to disease risk. Alternatively, mechanisms of viral cell attachment and entry might vary between different HPV types (13-17). If so, and if HPV-18 infectivity is preferentially affected by the *SDC-1* Pro-27 polymorphism, one might expect to observe an association between *SDC-1* Pro-27 polymorphisms that are specific to cervical adenocarcinomas because HPV-18 accounts for a larger fraction of cervical adenocarcinomas compared with squamous cell carcinomas (18-25). In our study, we were not able to assess this possibility directly due to the limited number of cases with specific HPV types.

The limitations of this study include its modest size, which is largely unavoidable given that cervical adenocarcinomas are rare and account for only 10% to 20% of all cervical cancers diagnosed in most countries (18). We attempted to minimize this problem by pooling data across the two largest United States–based epidemiologic studies of cervical adenocarcinoma with DNA samples. Such pooling was justifiable given that both studies were conducted among largely Caucasian women within the United States using comparably well-defined epidemiologic designs. Second, we were limited in our ability to evaluate the possibility that *SDC-1* polymorphisms directly affect HPV infectivity among our controls because cervical exfoliated specimens required for HPV DNA testing were only available from one of our two studies. As a consequence, findings from our evaluation did not reach statistical significance, although it did trend in the direction that supported an association between *SDC-1* Pro-27 C → T change and HPV infectivity. HPV antibody data available from the second study was consistent with this observation, although the magnitude of the effect observed was small and not statistically significant. Third, *in vitro* assessment of SDC-1 expression in cells obtained from carriers and noncarriers of the *SDC-1* Pro-27 T allele was limited by the absence of cells from TT homozygotes. It is also unclear whether results obtained from lymphocytes could be extrapolated to epithelial cells, and further, to different histologic types of cells from the cervical epithelium. Finally, it should be noted that our study focused on only 2 SNPs within *SDC-1*, whereas an additional 21 SNPs (including 8 TagSNPs) identified by HapMap were not evaluated. These additional SNPs were not included in our study because direct sequencing of women indicated that they were either absent or present at a very low frequency, which would preclude our ability to evaluate them in the present study.

In summary, pooled data from the two largest studies of cervical adenocarcinoma in the United States suggest a modest increase in risk of cervical adenocarcinoma associated with a polymorphism in the promoter region (Pro-27) of *SDC-1*, whereas no such evidence was observed for squamous cell carcinomas of the cervix.

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