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CD83 Polymorphisms and Cervical Cancer Risk

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Abstract

Objectives—Studies have suggested that polymorphisms in genes involved in immune recognition and antigen presentation are associated with cervical cancer risk. We sought to replicate a recent study which reported an association between specific SNPs on CD83 and cervical cancer and to further explore whether effects varied by age, clinical stage (in situ versus invasive), and histology (squamous carcinomas versus adenocarcinomas).

Methods—We evaluated the association between SNPs on CD83 and cervical cancer in a multicenter case-control study of cervical cancer conducted in the Eastern United States (263 cases, 307 controls), focusing on the five SNPs (RS9296925, RS853360, RS9230, RS9370729, RS750749) previously found to be associated with cervical cancer. We also pooled data from the Eastern U.S. (263 cases) with those from the original report (377 cases) to assess the effects of CD83 on the age at diagnosis, disease stage, and histology. Risk estimates (ORs) and 95% confidence intervals were estimated using logistic regression; trend tests were performed under an additive model.

Results—Consistent with the original report, carriers of the CT or CC genotypes for one of the five CD83 SNPs evaluated (rs750749) demonstrated a 30% and 50% reduction in disease risk, relative to carriers of the more common TT genotype (p-trend = 0.02). Two additional SNPs also resulted in consistent findings (rs9296925: p-trend = 0.07 and rs9370729: p-trend = 0.08), although the effects observed did not reach statistical significance at the 0.05 level. Pooled evaluation of cases from the two aforementioned studies suggested differences in the distribution of susceptibility alleles by histology; adenocarcinoma cases were more likely to be carriers of the susceptibility alleles for SNP rs9370729 (p-trend = 0.02) and SNP rs750749 (p-trend = 0.09). No differences were observed in the age or stage of diagnosis of carriers for CD83 susceptibility alleles relative to non-carriers.

Conclusions—We confirm an association between CD83 polymorphisms and cervical cancer and suggest the possibility that CD83-disease associations might be heterogenous by tumor histology.

Keywords

Human papillomaviruses; cervix; epidemiology; genetics

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Introduction

Human papillomavirus (HPV) infection has been established as a necessary but not sufficient cause of cervical cancer. Evidence suggests that host factors play a role in the natural history of HPV-associated cervical cancer. In specific, studies have suggested that polymorphisms in genes involved in immune recognition and antigen presentation are associated with disease risk [1], that immune compromised populations (HIV+, transplant) are at excess risk of HPV-associated tumors [2-4], and that specific differences in T-cell function are associated with persistence of HPV infections [5].

Multiple components of the immune response are likely to affect HPV natural history and the likelihood that an HPV infection will persist and progress to precancer and cancer. Dendritic cells (DCs) are antigen-presenting cells that induce primary immune response. Upon exposure to foreign stimuli, DCs mature and induce T-cell stimulation. One of the best known cell surface maturation markers on DCs is CD83. CD83 is a transmembrane glycoprotein of the immunoglobulin superfamily. The surface expression of CD83 was first recognized as a marker of dendritic cell maturation and has recently been shown to be expressed on various cell types [6]. CD83 expression is crucial for the maturation of CD4 positive T cells, the immunological regulation of peripheral T cell responses, and the modulation of B cell function [6,7]. In addition, the soluble form of the shed extracellular part of CD83 has immune suppressive function [8,9].

A recent study suggested a possible role for CD83 polymorphisms in cervical carcinogenesis [10]. Using a family-based approach, Zhang *et al.* [10] reported an association between five single nucleotide polymorphisms (SNP) of CD83 and cervical cancer and its in situ precursor (cervical intraepithelial neoplasia 3, CIN3). This association was reported to be strengthened in the subgroup of women with invasive cancers infected with high-risk HPV16 or 18. In vitro results supported these findings and indicated that there were several somatic mutations and novel SNPs in the promoter, exons, and introns of CD83 amongst 36 paired control and cervical tumors [10]. In addition, loss of heterozygosity was confirmed in >90% of cervical cancer specimens [10].

In this paper, we sought to replicate the findings by Zhang *et al.* [10] in an independent multicenter case-control study of in situ and invasive cervical cancer of squamous and glandular histologies. In addition, we pooled data from the multicenter study and the previous study reported by Zhang *et al.* [10] to permit assessment of CD83-disease associations within subgroups identified by histology and disease stage.

Materials and Methods

We used data and specimens from two previously described U.S. studies of cervical squamous cell carcinoma and adenocarcinoma as the basis of our evaluation [10-12].

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 (RDD) and matched to cases with glandular tumors on age, race, and telephone exchange [11-12]. Participation rates for this study were 78.8% for cases and 73.2% for controls. 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 [11-12].

The second was a family-based cervical cancer genetic epidemiology study conducted in Washington University School of Medicine (“CerGE Study”) consisting of 377 family trios.

Each trio consisted of a proband—a woman with invasive cervical cancer (ICC, 255) or CIN3 (CIN3 and/or adenocarcinoma in situ, 122)—and either her biological parents or one parent and one or more siblings. For this evaluation, only cases were included in the analyses. Three hundred and forty-one cases were Caucasian, and 36 were African-American. Among the 255 ICC, 168 tumors were squamous, 61 were adenocarcinoma, 8 were adenosquamous, and 18 were of other histologies [10]. HPV genotyping was determined by PCR-HPLC method described and conducted previously [10,13]. CD83 results from these cases were previously reported [10].

Peripheral blood or buccal samples were obtained from all the subjects. Genomic DNA was extracted from blood using QIAamp Max columns (Qiagen, Valencia, CA, USA) for the Eastern U.S. study and using overnight digestion with proteinase K and extraction with phenol/chloroform for the CerGE Study. Genomic DNA from buccal cells was extracted using Puregene DNA Purification kits (Gentra Systems, Inc.) in the CerGE study [10]. The DNAs were used for genotyping variants of CD83. The five SNPs previously identified as being significant were genotyped (i.e., rs9296925, rs863360, rs9230 rs9370729 and rs750749) by TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA) as previously described [10].

Logistic regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess the association between these CD83 polymorphisms and cervical cancer, adjusted for sex, age and study site. The five CD83 SNPs were evaluated individually (rs9296925, rs853360, rs9230, rs9370729, and rs750749). For each SNP evaluated, individuals homozygous for the common allele were considered as the baseline and compared against those who were heterozygous or homozygous for the minor allele. The haplotype structure for CD83 (rs9296925, rs853360, rs9230, rs9370729, and rs750749) was examined using Haploview version 3.11 [14]. We estimated haplotypes using the expectation-maximization algorithm [15]. Using the statistical package, HaploStats in software R (version 2.0.1) [16], overall differences in haplotype distribution between study groups were assessed using the global score test [17]. Risk estimates were evaluated from the additive model, which fitted a logistic regression model and used posterior probabilities of the haplotypes as weights to estimate the regression coefficients in an iterative manner [17], adjusting for age and race. Analyses were performed for the overall population using data from the Eastern U.S. Study. We also stratified cases by histological types and HPV positivity using pooled data from the Eastern U.S. and CerGE Studies after confirming that the allelic distribution for each of the five SNPs was comparable between studies (data not shown). For comparability with the study published by Zhang *et al.* [10], in analyses by HPV type cases positive for HPV16 and/or HPV18 were compared against all controls using the Eastern U.S. Study. Comparable results were obtained when analysis restricted to HPV16 cases was performed (data not shown). The approach of comparing HPV 16/18 positive cases against all controls was chosen since exposure to these HPV types is believed to be relatively common among sexually experienced women and therefore a large fraction of our controls were expected to have been exposed to HPV at some point after sexual debut, even if they tested negative at the time of our study. To assess whether findings were heterogeneous by histology or disease stage, direct case-case comparisons were performed to compare case groups of interest (i.e., adenocarcinomas compared to squamous cell carcinomas; invasive cases compared to in-situ cases). Analyses were performed using SAS release 9.0 (SAS Institute, Cary, NC) unless specified otherwise.

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 34.8 (SD=8.0) in the cases from the CerGE Study.

Both studies were comprised primarily of Caucasian women (85.0% in the Eastern U.S. Study and 91.5% in the CerGE Study).

In analyses restricted to the Eastern U.S. Study (Table 1), we observed a significant association between CD83 and cervical cancer for one of the five SNPs evaluated (rs750749), confirming previous findings reported by Zhang *et al.* [10]. Risk of disease was found to be 0.7 (95% CI_{CT} = 0.46-1.0) and 0.5 (95% CI_{CC} = 0.19-1.2; p-trend = 0.02; referent TT genotype). Findings consistent with those by Zhang *et al.* [10] were observed for two additional SNPs. For individuals with a genotype of CC for the SNP rs9296925, a 1.6 fold increase in risk for cervical cancer was observed (95% CI_{CC} = 0.95-2.9; referent TT genotype). For individuals with a genotype of TT for the SNP rs9370729, a 1.6 increased risk was observed (95% CI_{TT} = 0.94-2.8; referent CC genotype). The associations observed in the present study for these two additional SNPs were not significant at the 0.05 level (p-trend = 0.07 for rs9296925 and 0.08 for rs9370729). Although rs9230 showed a slight protective effect for cervical cancer (OR_{TT} = 0.6; 95%CI: 0.24-1.3, referent CC genotype), this was not significant with a p-value of 0.43. RS853360 showed no association with cervical cancer (rs853360: OR_{TT} = 1.0; 95% CI: 0.44-2.1, referent CC genotype). Similar results were observed when restricting analysis to Caucasians and in HPV-restricted analyses (Table 1). Haplotype analyses were not informative and did not suggest additional associations beyond those identified using individual SNPs (data not shown).

Data were pooled from the Eastern U.S. and CerGE studies to evaluate whether there were differences in age at diagnosis of cases by carriage status of the three alleles associated with disease risk. This evaluation was conducted separately for in situ and invasive cases since the typical age at diagnosis for these two conditions differ. We observed no difference in age by carrier status for any of the three SNPs evaluated (Table 2).

Pooled data across our two studies were also used to explore whether associations varied by tumor stage or histology. When invasive cases were compared to in situ cases, there was no evidence that these two disease states varied with respect to their distribution of any of the 3 SNPs evaluated (Table 3). In contrast, when adenocarcinoma cases were compared to SCC cases (Table 4), we did observe a significant difference between groups with respect to the distribution of SNP rs9370729; adenocarcinoma cases were 1.6-fold (95% CI: 0.92-2.7; p-trend = 0.02) more likely than SCC cases to be homozygous carriers of the susceptibility allele ("T"). There was also suggestive evidence for increased carriage of the susceptibility allele ("T") among adenocarcinomas cases compared to SCC cases for SNP rs750749 (p-trend = 0.09). No differences were observed by histology for rs9296925.

Discussion

Our results from a multicenter case-control study conducted in the Eastern U.S. suggest that CD83 polymorphisms are associated with cervical precancer/cancer risk. Evaluation of 5 specific SNPs previously suggested to be linked to cervical cancer pathogenesis revealed one SNP (rs750749) that is significantly associated with cervical precancer/cancer and two additional SNPs (rs9296925 and rs9370729) with suggestive associations consistent with those previously reported [10]. The fact that we were able to independently replicate previously reported findings suggest a true association. The underlying mechanisms whereby CD83 alterations mediate changes in disease risk (presumably through effects on dendritic cells) remain to be elucidated.

Further evaluation of pooled data from our study and the study previously reported by Zhang *et al.* indicated no differences in the associations between CD83 and disease by disease stage. This suggests that CD83 influences risk for both in-situ and invasive disease. In contrast, we

did observe evidence that associations might be stronger for tumors of glandular histology (adenocarcinomas) compared to squamous cell carcinomas of the cervix. Although this observation requires replication, if real one might speculate that alterations in immune handling of HPV preferentially affect infection of glandular cells, cells that are believed to be less permissive to HPV infection than squamous epithelial cells that lead to squamous tumors [18-19].

Previous findings have shown that carriers of rare gene alterations with high penetrance (e.g., BRCA1 and HNPCC) typically have an earlier age of tumor onset. In our pooled analysis, we did not find evidence for earlier disease onset among carriers of CD83 susceptibility alleles. This is not unexpected given the multifactorial nature of cervical cancer and the likelihood that genetic associations identified for this tumor would individually confer only a modest increase in disease risk due to low disease penetrance and as a consequence not significantly impact age at disease onset [20-22].

Limitations of this study include its modest size. We have attempted to address this limitation by first replicating previous findings in a separate study and then pooling the original and our new studies to further explore possible heterogeneity by disease stage and histology. Future confirmation of our findings in a larger study will be important.

In summary, we confirm an association between CD83 polymorphisms and cervical cancer and suggest the possibility that CD83-disease associations might be heterogenous by tumor histology.

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Table 1
Distribution and risk of cervical neoplasia associated with CD83 polymorphisms (Eastern US Study)

	Overall			Caucasian		HPV 16/18 Positive	
	Controls N (%)	Cases N (%)	Adj OR [†]	95% CI	Adj OR [‡]	Cases N (%)	Adj OR [†]
RS9296925 [*]							
TT	73 (31.3)	55 (23.5)	1.0		1.0	21 (23.3)	1.0
CT	121 (51.9)	129 (55.1)	1.4	(0.89-2.1)	1.4	51 (56.7)	1.5
CC	39 (16.7)	50 (21.4)	1.6	(0.95-2.9)	1.7	18 (20.0)	1.6
Trend			p=0.07		p=0.08		p=0.20
RS853360 [*]							
CC	121 (51.1)	124 (51.9)	1.0		1.0	47 (51.7)	1.0
CT	101 (42.6)	100 (41.8)	1.0	(0.70-1.5)	1.0	40 (44.0)	1.1
TT	15 (6.3)	15 (6.3)	1.0	(0.44-2.1)	0.8	4 (4.4)	0.5
Trend			p=0.99		p=0.61		p=0.75
RS9230 [*]							
CC	135 (56.7)	139 (58.4)	1.0		1.0	51 (56.0)	1.0
CT	87 (36.6)	89 (37.4)	1.0	(0.68-1.5)	1.0	36 (39.6)	1.1
TT	16 (6.7)	10 (4.2)	0.6	(0.24-1.3)	0.5	4 (4.4)	0.5
Trend			p=0.43		p=0.31		p=0.67
RS9370729 [*]							
CC	58 (24.5)	46 (19.4)	1.0		1.0	15 (16.7)	1.0
CT	121 (51.1)	116 (49.0)	1.2	(0.74-1.9)	1.3	49 (54.4)	1.5
TT	58 (24.5)	75 (31.7)	1.6	(0.94-2.8)	1.7	26 (28.9)	1.6
Trend			p=0.08		p=0.08		p=0.24
RS750749 [*]							
TT	129 (54.9)	151 (64.8)	1.0		1.0	54 (60.0)	1.0
CT	91 (38.7)	74 (31.8)	0.7	(0.46-1.0)	0.6	34 (37.8)	0.9
CC	15 (6.4)	8 (3.4)	0.5	(0.19-1.2)	0.4	2 (2.2)	0.3
Trend			p=0.02		p=0.009		p=0.19

^{*} dbSNP map to genome build 36.2

[†] adjusted for age and race

[‡] adjusted for age

Table 2
Mean age of carriers and non-carriers of CD83 risk alleles (Pooled Data)

SNP		N	In-Situ Mean Age	SD	p-value	N	Invasive Mean Age	SD	p-value
RS9296925	TT	35	30.5	6.9	0.293	92	39.8	10.7	0.214
	CT	114	32.0	8.3		218	38.3	9.6	
	CC	44	34.0	9.5		98	38.2	9.3	
RS9370729	CC	29	33.0	8.5	0.815	73	39.8	9.2	0.616
	CT	105	31.9	8.7		185	38.9	10.8	
	TT	61	32.1	8.0		149	38.0	8.8	
RS750749	TT	117	31.9	8.1	0.849	262	38.3	9.5	0.595
	CT	69	32.9	9.3		129	39.6	10.6	
	CC	8	31.8	6.3		12	37.8	9.8	

Table 3
Distribution and risk of cervical neoplasia associated with CD83 polymorphisms by disease stage (Pooled Data)

	In-Situ Cases N (%)	Invasive Cases N (%)	Adj OR [*]	95% CI
RS9296925	TT	36 (18.5)	1.0	
	CT	115 (59.0)	0.8	(0.49-1.2)
	CC	44 (22.6)	0.9	(0.50-1.5)
	Trend		p=0.60	
RS9370729	CC	29 (14.7)	1.0	
	CT	107 (54.3)	0.7	(0.44-1.3)
	TT	61 (31.0)	1.0	(0.59-1.8)
	Trend		p=0.55	
RS750749	TT	117 (59.7)	1.0	
	CT	71 (36.2)	0.8	(0.53-1.1)
	CC	8 (4.1)	0.7	(0.27-1.9)
	Trend		p=0.17	

^{*} Adjusted OR and 95% CI for age, race, and study site comparing invasive cases to in-situ cases

Table 4
Distribution and risk of cervical neoplasia associated with CD83 polymorphisms by histology (Pooled Data)

	SCC Cases N (%)	Adenocarcinoma Cases N (%)	Adj OR*	95% CI
RS9296925				
TT	76 (19.7)	44 (21.7)	1.0	
CT	226 (58.6)	104 (51.2)	0.8	(0.52-1.3)
CC	84 (21.8)	55 (27.1)	1.2	(0.74-2.1)
Trend			p=0.36	
RS9370729				
CC	67 (17.5)	31 (14.9)	1.0	
CT	195 (51.1)	89 (42.8)	1.6	(0.54-1.6)
TT	120 (31.4)	88 (42.3)	1.2	(0.92-2.7)
Trend			p=0.02	
RS750749				
TT	234 (61.6)	139 (67.8)	1.0	
CT	131 (34.5)	63 (30.7)	0.8	(0.57-1.2)
CC	15 (4.0)	3 (1.5)	0.3	(0.10-1.2)
Trend			p=0.09	

* Adjusted OR and 95% CI for age, race, and study site comparing adenocarcinoma cases to squamous cell carcinoma (SCC) cases