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Genetic variation in CD83 and risks of cervical and vulvar cancers: A population-based case–control study

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Abstract

Objectives—The CD83 glycoprotein is a marker of dendritic cell maturation that may contribute to the T cell response to oncogenic human papillomavirus (HPV) infection. Whether single nucleotide polymorphisms (SNPs) in CD83 influence the risk of HPV-related genital cancers has not been adequately studied. We investigated whether the common genetic variation of the CD83 region was associated with the risks of cervical and vulvar cancers in a population-based case–control study conducted in the Seattle-Puget Sound Region.

Methods—A total of 17 tagSNPs were genotyped in the CD83 region of 886 cervical cases, 517 vulvar cases and 1100 controls. Odds ratio (OR) and 95% confidence intervals (CI) were computed to assess the risk of cervical and vulvar cancers. The interaction between the tagSNPs and cigarette smoking was also explored.

Results—TagSNPs in the CD83 chromosomal region were not associated with risk of either cervical or vulvar cancer. TagSNP rs853360 was associated with a decreased risk of cervical squamous cell carcinoma (SCC) (OR = 0.80; 95% CI: 0.66–0.98).

Conclusions—Our results do not suggest that the common genetic variation of CD83 is related to cervical or vulvar cancers. The association between tagSNP rs853360 and risk of cervical SCC is likely to be due to chance. If larger or pooled studies confirm our results, CD83 has little or no influence in the risk of HPV-related cancers.

Keywords

Keywords: Human papillomavirus; Cervix; Vulva; Epidemiology; Genetics

Introduction

All cervical carcinomas, and a majority of vulvar carcinomas, are caused by oncogenic human papillomavirus (HPV) infection [1–3]. The immune system plays a critical role in HPV-induced carcinogenesis, primarily evidenced by the increased incidence of HPV-related cancers among immunosuppressed subjects [4,5] and the efficacy of prophylactic

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vaccines in preventing pre-invasive HPV-related lesions [6]. In addition, common genetic variation in several immune response genes has been related to cervical cancer [7–9].

In recent years, the glycoprotein CD83 of the immunoglobulin superfamily has received attention for its immune function and its potential immunotherapy role [10,11]. CD83 is expressed on the surface of mature dendritic cells and it is consider a maker of maturation [12]. In the presence of the HPV, immature dendritic cells undergo a number of physiological and functional changes to later induce the activation and differentiation of naïve T cells [13]. Some of those changes are the up-regulation of expression of membrane proteins, such as CD83 or the major histocompatibility complex (MHC) classes I and II molecules, where the antigen is bound and presented to the naïve T-cells [11,14].

CD83 polymorphisms have been studied in relation to the risk of cervical cancer [15,16]. Zhang et al. found that five single nucleotide polymorphisms (SNPs) of the CD83 gene were significantly associated with invasive cervical cancer [15]. However, the study only provided p-values and, thus, it was unclear how strongly, and in which direction (increased or decreased), the minor alleles of these SNPs were associated with these malignancies. A subsequent study evaluated the SNPs previously reported by Zhang et al. but found that only one was significantly associated (inversely) with cervical cancer risk [16]. However, neither of the previous studies looked at the interaction of these SNPs with other characteristics, such as smoking, that are risk factors for squamous cell cervical cancer. In addition, no prior studies have examined CD83 genetic variants in relation to vulvar cancer.

Using data from a population-based case–control study, we assessed common genetic variation in the CD83 genetic region in relation to cervical and vulvar carcinomas. We further examined these associations stratifying for different stages of these diseases, *in situ* or invasive, and different histologies of cervical cancer, squamous cell carcinoma (SCC) or adenocarcinoma. Lastly, we explored whether cigarette smoking and genetic variation in CD83 interact, modifying the risks of cervical SCC or vulvar cancers.

Methods

Study design and population

The study population and collection of specimens have been described previously [17,18]. Briefly, a case–control study was conducted among residents of a 13-county area in Western Washington State covered by the Cancer Surveillance System (CSS), a population-based tumor registry that is part of the Surveillance, Epidemiology and End Results program of the National Cancer Institute [19]. Eligible cases were women 1) newly diagnosed invasive SCC or adenocarcinoma of the cervix, or invasive or *in situ* SCC of the vulva between January 1986 and June 1998 or between January 2000 and December 2004, and residents of King, Pierce, or Snohomish counties at the time of diagnosis; and 2) with newly diagnosed *in situ* adenocarcinoma of the cervix between January 1990 and June 1998 or between January 2000 and December 2004, and residents of King, Pierce, Snohomish, or 10 additional counties covered by the CSS. Controls were women without a history of cervical or vulvar cancers, residents of the same counties as the cases, and selected using random digit telephone dialing [17]. They were frequency matched to cases on 5-year age groups and county of residence. A randomly selected date, the reference date, similar to the diagnosis date of the cases was assigned to controls. All women in the study were aged 18–74 years at the time of diagnosis or reference date.

Data and specimen collection

In-person interviews were conducted to obtain information on events prior to each woman's diagnosis date (cases) or reference date (controls). Questions covered demographic

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characteristics, reproductive and smoking history, family history of cancers, and other factors known or suspected of being related to the risk of anogenital cancers. Beginning in 1991, 5 years after the beginning of the study, blood samples from which DNA could be isolated were collected at the time of the in-person interview. Participants who had been recruited prior to 1991 were re-contacted to provide blood samples. Buccal cell samples were collected using a standardized oral rinse procedure from participants who chose not to provide blood samples (3% of subjects).

Response proportions

A total of 1384 cervical cancer cases, 791 vulvar cancer cases (response proportions 65.6% and 64.7%, respectively), and 2177 controls (63.5% response proportion, which is the RDD screening response, 92.4%, multiplied by the interview response, 68.7%) were interviewed. Of those, 91.5%, 92.0%, and 83.9%, respectively, had peripheral blood or oral rinse from which we could extract DNA in our study. Seventy-two percent of cervical cancer cases and 83% of vulvar cancer cases had archival tumor tissue available that was tested for HPV DNA [17,18].

SNP selection and genotyping

CD83 covers about 19 kb at 6p23 and contains 5 exons. We used the CEU-HapMap population of unrelated individuals to identify 36 SNPs with minor allele frequency (MAF) greater than 5% within CD83 as well as 4 kb both upstream and downstream. Two SNPs in the CD83 region previously reported to be associated with cervical cancer (rs104498684 and rs9230) [15] were not included because they were not present in the HapMap database at the time of SNP selection. The SNAGGER algorithm was used to efficiently select a subset of the 36 SNPs with coverage of the CD83 chromosomal region of $r^2 \geq 0.80$ as tagSNPs [20]. Of the 36 SNPs, one SNP (rs853361) was excluded because it was not suitable for genotyping using the Illumina Goldengate technology (Illumina Inc., San Diego, CA). A total of 19 tagSNPs were selected to provide information on the remaining 35 SNPs and were chosen for genotyping. Of the 19 SNPs, two (rs2235369 and rs11758033) failed genotyping.

Data analysis

Women with zero lifetime sex partners (0.2% of cervical cases, 0.2% of vulvar cases and 1.3% of controls) were excluded so that the analysis (and inference) was restricted to women who could have been exposed to oncogenic HPV. Analyses were carried out using the R software environment (version 2.12.1 for Macintosh). Hardy–Weinberg equilibrium was calculated among controls using an exact test [21]. Linkage disequilibrium (LD) was estimated using the r^2 measure among the successfully genotyped tagSNPs, and the corresponding heatmap was computed using a modified version of the R statistical package LDheatmap [22]. TagSNPs rs853366 and rs750749 showed strong LD ($r^2 = 0.98$) and only results for rs750749 are reported. Odds ratios (OR) and 95% confidence intervals (CI) for a given SNP were estimated using unconditional logistic regression assuming an additive model of inheritance, with the predictor being the number of minor alleles for that SNP (values: 0 (reference), 1, 2). Associations were adjusted for age as a continuous variable. Interaction between tagSNP genotypes and smoking (current vs. not current) were assessed using a likelihood ratio test (LRT) comparing a 4-predictor model (age, tagSNP genotype, smoking and the product of the genotype and smoking) to a 3-predictor model (age, tagSNP genotype and smoking). Analyses were restricted to Caucasian subjects (88.8% of cervical cases, 95.0% of vulvar cases and 92.1% of controls) to reduce potential bias from population stratification [23].

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Results

A total of 886 cervical cases, 517 vulvar cases and 1100 controls were included in the analysis. Characteristics of the study participants are shown in Table 1. Compared with controls, cervical cases were younger, more likely to be current smokers and had more lifetime sex partners. Vulvar cases were slightly older, more likely to be current smokers, had less education, and more lifetime sex partners than controls.

None of the CD83 tagSNP genotypes deviated from Hardy–Weinberg Equilibrium (Supplemental Table 1). The tagSNPs exhibited little evidence of LD (all $r^2<0.80$) (Supplemental Fig. 1).

We did not observe associations between any of the CD83 SNP genotypes and risks of cervical or vulvar cancers (Table 2). We found only one marginally significant association between CD83 SNP genotypes and risks of cervical SCC and adenocarcinoma (Table 3). Specifically, the A allele of rs853360 was associated with a decreased risk of cervical SCC (OR = 0.80, 95% CI: 0.66–0.98). When cervical adenocarcinoma was stratified between *in situ* and invasive, carriers of the G allele in rs750749 were at a significant increased risk of *in situ* cervical adenocarcinoma compared with non-carriers (Supplemental Table 2). No associations were observed between CD83 SNPs and risks of *in situ* or invasive vulvar cancer (data not shown).

The association between tagSNP rs853360 genotype and risk of cervical SCC was similar when the analysis was restricted to tumors with positive HPV16 DNA, excluding tumors that were HPV18 positive, (OR = 0.77, 95% CI: 0.58–1.02, based on 169 cases) as well as tumors positive for HPV18 DNA, excluding tumors that were HPV16 positive, (OR = 0.85, 95% CI: 0.46–1.56, based on 32 cases). An analogous analysis for cervical adenocarcinoma provided comparable results to cervical SCC (HPV16 DNA only tumors: OR = 0.89, 95% CI: 0.67–1.18, based on 157 cases; HPV18 DNA only tumors: OR = 0.86, 95% CI: 0.56–1.32, based on 65 cases). Lastly, there was no evidence of a multiplicative interaction between tagSNP rs853360 genotype and smoking on the risk of cervical SCC (relative to non-current smokers homozygous for the G allele, the OR = 0.84, 95% CI: 0.66– 1.06 for non-current smokers with the A allele; the OR = 2.25, 95% CI: 1.62–3.16 for current smokers homozygous for the G allele; the OR = 1.58, 95% CI: 1.11–2.25 for current smokers with the A allele; LRT P-value for the multiplicative effect: 0.41).

Discussion

Little evidence was found of the contribution of common genetic variability in the CD83 gene to the risk of cervical cancer and no association was observed between the genetic variation in CD83 and the risk of vulvar cancer in our study.

To our knowledge, the genetic variation in CD83 has previously been examined in relation to cervical cancer but not other infection related cancers (including other HPV-related cancers). Four SNPs analyzed in our study (rs9296925, rs853360, rs9370729, and rs750749) were previously reported to be significantly associated with the risk of invasive cervical cancer when the analysis was restricted to the HPV16/18 subtypes [15]. In a subsequent study, only SNP rs750749 was found to be significantly associated with a decreased risk of cervical cancer, but the association was only observed when all HPV types were combined [16]. In contrast, we found this SNP to be associated with a significantly increased risk but only for *in situ* cervical adenocarcinoma. If a true association between rs750749 and the risk of cervical cancer were to exist, one would expect consistent results across studies.

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It has been suggested that the association between CD83 genetic variants and cervical cancer risk might differ between SCC and adenocarcinomas [16], but we observed only marginal differences between these two histologies. Despite some variability in the strength of the association between different HPV genotypes and cervical SCC or adenocarcinoma, with HPV18 being more strongly associated with cervical adenocarcinoma [24,25], we did not observe that the association between tagSNP rs853360 and the risk of either cervical SCC or adenocarcinoma differed depending on whether HPV16 or HPV18 was present in the tumor.

Unlike Zhang et al., but as suggested in Yu et al., we did not find evidence that the association between CD83 variants and disease risk was different in *in situ* vs. invasive stages [15,16].

Our findings might have been influenced by the study size, which could have prevented us from observing a weak influence of common CD83 SNPs on the risks of cervical and/or vulvar cancers, especially in the stratified and interaction analyses. Nevertheless, our sample size is larger than either of the two earlier studies of cervical cancer and CD83 (377 family trios [15] or 263 cases and 307 controls [16]). Another limitation is that controls were not tested for HPV and their history of cervical disease was only obtained by means of the interview. However, this limitation was also present in previous studies of the association between CD83 and cervical cancer. Our study cannot distinguish in which steps of cervical/vulvar carcinogenesis, if any, allelic variation of CD83 might be most relevant (infection of HPV vs. development of cancer after infection). Instead, our results need to be looked at as a global measure of the risk of development of these HPV-related cancers. It is also worth noting that the few associations observed in our study could have been due to chance, since there were a large number of hypotheses tested in the study. Finally, there were several differences of the participants across the different studies. Subjects in our study were unrelated and self-identified as Caucasians. Subjects in Zhang et al. were family trios, thus accounting for the genetic background and other risk factor history of the families, but 10% of the families self-identified themselves as African-American [15]. Subjects in Yu et al.'s analyses were unrelated but included different races for most analyses [16].

In summary, our results suggest that common genetic variation in CD83 is not related to the risks of cervical and vulvar cancer. To provide more definitive evidence, a pooled analysis of all available studies or a much larger study would be needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of anogenital cancer cases and control subjects, Seattle–Puget Sound Region, 1986–2004.

Characteristics	Controls (N = 1100) n (%)	Cervical cancer cases (N = 886) n (%)	Vulvar cancer cases (N = 517) n (%)
Age[a] (years)			
18–34	266 (24.2)	318 (35.9)	80 (15.5)
35–44	304 (27.6)	287 (32.4)	161 (31.1)
45–64	388 (35.3)	243 (27.4)	203 (39.3)
65–74	142 (12.9)	38 (4.3)	73 (14.1)
Highest level of education[a]			
High school graduate or less	323 (29.4)	279 (31.5)	207 (40.0)
Some college or more	777 (70.6)	607 (68.5)	310 (60.0)
Cigarette smoking[a]			
Never smoked	574 (52.2)	406 (45.8)	104 (20.1)
Former smoker	300 (27.3)	239 (27.0)	115 (22.2)
Current smoker	226 (20.5)	241 (27.2)	298 (57.6)
Lifetime sex partners[a]			
1	293 (26.6)	93 (10.5)	40 (7.7)
2–4	338 (30.7)	251 (28.3)	109 (21.1)
5–14	343 (31.2)	383 (43.2)	230 (44.5)
15+	124 (11.3)	159 (17.9)	137 (26.5)
Unknown/missing	2 (0.2)	–	1 (0.2)
Tumor HPV DNA			
Negative	–	103 (11.6)	79 (15.3)
Positive	–	535 (60.4)	350 (67.7)
Missing	–	248 (28.0)	88 (17.0)
Type of HPV DNA[b]			
HPV16 or HPV18	–	495 (92.5)	319 (91.1)
Other HPV types	–	40 (7.5)	31 (9.7)

[a] At diagnosis/reference date.

[b] Among subjects with positive tumor HPV DNA.

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Table 2

Association between CD83 tagSNPs and cervical and vulvar cancer risks, Seattle–Puget Sound Region, 1986–2004.

		Cervical cancer			Vulvar cancer		
SNP	**MAF (controls) %**	**MAF (cases) %**	**OR[a]**	**(95% CI)**	**MAF (cases) %**	**OR[a]**	**(95% CI)**
rs12205252	20.4	21.2	1.09	(0.93–1.28)	21.6	1.06	(0.88–1.28)
rs6929821	26.4	26.2	1.01	(0.87–1.17)	27.3	1.04	(0.88–1.23)
rs3799925	45.2	43.9	0.95	(0.83–1.08)	45.1	1.00	(0.86–1.16)
rs3799924	18.8	17.7	0.90	(0.76–1.07)	17.7	0.94	(0.77–1.14)
rs4715877	29.4	29.5	1.03	(0.89–1.19)	28.6	0.95	(0.81–1.13)
rs853358	21.2	21.9	1.07	(0.91–1.26)	21.8	1.03	(0.86–1.24)
rs7743206	14.9	14.9	0.97	(0.81–1.16)	14.9	1.01	(0.82–1.25)
rs9296925	47.9	48.1	1.00	(0.88–1.14)	47.7	0.99	(0.85–1.15)
rs853360	25.8	24.8	0.94	(0.81–1.08)	25.0	0.96	(0.81–1.14)
rs1050648	6.6	6.8	1.02	(0.79–1.32)	6.8	1.06	(0.79–1.43)
rs3734665	20.3	20.6	1.03	(0.87–1.21)	21.1	1.05	(0.87–1.26)
rs10949227	36.7	37.5	1.05	(0.91–1.20)	37.2	1.02	(0.87–1.19)
rs9370729	39.4	39.8	1.01	(0.88–1.15)	38.3	0.96	(0.82–1.11)
rs17354216	5.9	5.5	0.99	(0.75–1.31)	6.7	1.15	(0.85–1.56)
rs750749	18.6	19.5	1.06	(0.90–1.25)	17.0	0.90	(0.74–1.09)
rs853369	40.9	39.0	0.90	(0.78–1.03)	42.7	1.09	(0.93–1.27)

Number of controls: 1100; number of cervical cancer cases: 886; number of vulvar cancer cases: 517.

MAF: minor allele frequency.

[a]Age-adjusted OR assuming an additive model.

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Table 3

Association between CD83 tagSNPs and cervical cancer risk by histology of the disease, Seattle–Puget Sound Region, 1986–2004.

		SCC (invasive)			Adenocarcinoma (in situ and invasive)		
SNP	**MAF (controls) %**	**MAF (cases) %**	**OR[a]**	**(95% CI)**	**MAF (cases) %**	**OR[a]**	**(95% CI)**
rs12205252	20.4	22.5	1.16	(0.95–1.42)	20.3	1.05	(0.86–1.28)
rs6929821	26.4	28.0	1.10	(0.91–1.32)	25.2	0.96	(0.80–1.15)
rs3799925	45.2	44.5	0.98	(0.83–1.15)	43.9	0.94	(0.80–1.11)
rs3799924	18.8	16.6	0.85	(0.68–1.06)	18.7	0.95	(0.78–1.17)
rs4715877	29.4	31.2	1.11	(0.92–1.33)	28.2	0.98	(0.82–1.17)
rs853358	21.2	21.4	1.02	(0.83–1.26)	21.7	1.06	(0.87–1.29)
rs7743206	14.9	15.1	1.00	(0.79–1.26)	15.0	0.97	(0.77–1.21)
rs9296925	47.9	44.4	0.87	(0.73–1.03)	50.4	1.10	(0.94–1.30)
rs853360	25.7	21.9	**0.80**	**(0.66–0.98)**	27.1	1.05	(0.88–1.25)
rs1050648	6.6	5.6	0.83	(0.58–1.18)	7.3	1.08	(0.79–1.47)
rs3734665	20.3	19.6	0.96	(0.78–1.19)	20.8	1.03	(0.84–1.26)
rs10949227	36.7	39.4	1.13	(0.95–1.35)	36.4	1.02	(0.86–1.20)
rs9370729	39.4	38.6	0.96	(0.81–1.15)	39.9	0.99	(0.84–1.17)
rs17354216	5.9	4.2	0.73	(0.49–1.09)	6.4	1.20	(0.86–1.67)
rs750749	18.6	17.7	0.94	(0.76–1.17)	20.9	1.15	(0.94–1.41)
rs853369	40.9	39.5	0.93	(0.78–1.10)	38.5	0.86	(0.73–1.02)

Number of controls: 1100; number of cervical SCC cases: 390; number of cervical adenocarcinoma cases: 469.

MAF: minor allele frequency.

Bold indicates significance at the 5% level.

[a]Age-adjusted OR assuming an additive model.