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ORIGINAL PAPER

Circulating IL-1β levels, polymorphisms of *IL-1B*, and risk of cervical cancer in Chinese women

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Abstract

Purpose Long-term human papillomavirus (HPV) infection is a prerequisite for cervical cancer. IL-1β and IL-1Ra expression levels play an important role in cervical carcinogenesis. Several functional genetic variants in *IL1B* and *IL-RN* have been reported to be associated with IL-1β expression and cancer susceptibility. In the current study, we hypothesized that plasma IL-1β levels, *IL-1B* and *IL-RN* polymorphisms were candidate biomarkers for cervical cancer.

Methods We measured plasma IL-1β levels and genotyped *IL-1B* and *IL-RN* polymorphisms in a case–control study of 404 cervical cancer cases and 404 controls in Chinese women.

Results The mean plasma IL-1β levels in cervical cancer cases (42.19 $\pm$ 31.55 pg/ml) was significantly higher than those in controls (34.86 $\pm$ 22.68 pg/ml, $P = 0.0002$), and plasma IL-1β levels above the 75% quartiles in controls (IL-1$\beta \geq$ 46.94 pg/ml) were associated with a 1.74-fold significantly increased risk of cervical cancer [95% confidence interval (CI), 1.28–2.36], compared with those of lowest quartile. Multivariate logistic regression analyses revealed that the variant genotypes, *IL-1B* T-31C TC/CC and C-511T CT/TT, were associated with a significantly increased risk of cervical cancer [adjusted odds ratio (OR), 1.60; 95% CI, 1.16–2.21 for −31TC/CC, and adjusted OR, 1.52; 95% CI, 1.10–2.09 for −511CT/TT, respectively), especially among subjects having higher levels of IL-1β. However, *IL-RN* VNTR polymorphism was not associated with cervical cancer risk in the current study. Furthermore, the significant differences of IL-1β concentration between cervical cancer cases and controls were observed only among subjects carrying T-31C or C-511T variant genotypes.

Conclusion Functional *IL-1B* genotypes may modify plasma IL-1β concentrations to contribute to the etiology of cervical cancer in Chinese women; however, further perspective studies are warranted to test the causal effects of IL-1β concentration in cervical carcinogenesis.

Keywords IL-1β · *IL-1B* · Polymorphism · Cervical cancer · Molecular epidemiology

Abbreviations

CI	Confidence interval
HPV	Human papillomavirus
IL-1β	Interleukin-1β
LD	Linkage disequilibrium
OR	Odds ratio
RFLP	Restriction fragment length polymorphism
SNPs	Single nucleotide polymorphisms
VNTR	Number of tandem repeats

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Introduction

Cervical cancer is the second most common cancer among women worldwide after breast cancer (Parkin and Bray 2006). It is well known that the major risk factor for cervical cancer is the infection of high-risk types of human papillomavirus (HPV), but most of the infections regress without intervention, suggesting that an effective host immune response might be an important determinant of susceptibility to HPV-related cervical cancer.

Cytokines, as the products of host response to inflammation, play an important role in the defense against viral infection. The IL-1 family, including IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra), is an important part of the innate immune system (Arend 2002; Dinarello 1991). IL-1α and IL-1β are agonists of cell membrane IL1 type 1 receptors, whereas IL-1Ra is a competitive antagonist. Both IL-1α and IL-1β are involved in inflammation, and they induce the expression of other pro-inflammatory genes, and inducible nitric oxide syntheses. Pro-inflammatory cytokines may play a role in the early stages of carcinogenesis, as they can induce growth factors and cause the production of reactive oxygen intermediates. IL-1Ra is an anti-inflammatory cytokine that competitively binds to IL-1 receptor with nearly equal avidity as IL-1β but does not initiate signal transduction (Arend et al. 1998). Many association studies have also suggested a genetic influence of the *IL1* loci in a variety of diseases that have an inflammatory component (Chang et al. 2005; El-Omar et al. 2000; Francis et al. 1999). With respect to cervical cancer, studies have shown that IL-1β (Behbakht et al. 2002; Belokrinitskaia et al. 2003; Tjiong et al. 2001) and IL-1Ra (Fujiwaki et al. 2003) expression levels play an important role in carcinogenesis.

The *IL-1B* and *IL-1RN* genes (encoding for IL-1β and IL-1Ra, respectively) are located on chromosome 2q14, within a 360-kb region (Bidwell et al. 1999). Two common functional single nucleotide polymorphisms (SNPs) were found in *IL-1B* promoter, one T-to-C transition at position −31 (rs16944) and the other C-to-T substitution at position −511 (rs1143627) (El-Omar et al. 2000). The T-31C substitution is located in a TATA-box motif of *IL-1B* that markedly affect the binding of several transcription factors (Chen et al. 2006; El-Omar et al. 2000; Lind et al. 2007), and both of the SNPs have been reported to influence the transcription activity of *IL-1B* (Chen et al. 2006). In the second intron of the *IL-1RN* gene, there is a variable number of tandem repeats (VNTR) with 86-bp in length (Tarlow et al. 1993), and the *IL1RN* *2 allele (2 repeats) is reported to be associated with increased IL-1β production in vitro (Santtila et al. 1998). El-Omar et al. (2000) first reported that *IL-1B* −31 and −511 loci contributed to *Helicobacter pylori* related gastric cancer risk in Scottish and Polish populations, which was subsequently confirmed in other ethnic groups from USA (El-Omar et al. 2003) and Portugal (Machado et al. 2003). For *IL-1RN*, studies from Caucasians showed that the homozygous carriage of the *IL1RN*2* allele was associated with an increased risk of gastric cancer (El-Omar et al. 2000; Machado et al. 2003), however, this association was not replicated in Asian populations (Zeng et al. 2003). Few studies evaluated the *IL-RN* VNTR polymorphism and risk of cancers other than gastric. In a small case–control study of 68 cases with squamous cell vulvar cancer and 228 healthy controls in Caucasians, Grimm et al. reported that the *IL1RN*2* allele was protective against vulvar cancer (OR 0.5; 95% CI 0.3–0.9) (Grimm et al. 2004). Mustea et al. (2003) suggested that the *IL1RN*2* allele played a role in cervical cancer risk using 113 women with cervical cancer and 107 controls with benign diseases.

Although several studies suggested that IL-1β production was related to the immune response against HPV-associated cervical cancer (Behbakht et al. 2002; Belokrinitskaia et al. 2003; Tjiong et al. 2001), no study examined the association between circulating IL-1β levels as well as genetic variants in *IL-1* family and cervical cancer risk. In the presented study, we hypothesized that both circulating IL-1β levels and functional polymorphisms in *IL-1* family genes were associated with altered risk of cervical cancer. To test this hypothesis, we simultaneously detected plasma IL-1β levels and genotyped *IL-1B* T-31C, C-511T and *IL-1RN* VNTR polymorphisms in a case–control study of 404 cervical cancer patients and 404 cancer-free controls in Chinese women.

Materials and methods

Study population

This case–control study consisted of 404 incident cervical cancer patients and 404 cancer-free controls and was approved by the institutional review board of Nanjing Medical University. The cases were consecutively recruited between March 2006 and April 2007 from the First Affiliated Hospital of Nanjing Medical University and the Tumor Hospital of Nantong City, Jiangsu, China. All the cases were Han Chinese women and were histopathologically confirmed cervical cancer. The patients donated 5-ml venous blood as soon as they were admitted to the hospital and the exclusion criteria included previous cancer, other metastasized cancer, and previous radiotherapy or chemotherapy. The controls were randomly selected from a pool of individuals who participated in a community-based screening program for non-infectious diseases conducted in Jiangsu Province during the same period as the cases were

recruited. These control subjects had no self-reported cancer history and were frequency-matched to the cases on age (±5 years) and residential areas (rural and urban). After informed consent was obtained, each subject was personally interviewed to obtain information on demographic data, menstrual and reproductive history, and family history of cancer (any reported cancer in first-degree relatives).

IL-1β quantitative measurement

The plasma IL-1β level was measured by using a sandwich enzyme immunoassay assay (Quantikine IL-1β immunoassay kit, AD Biotech Co. Ltd, USA). Each 96-well plate contained the same number of the samples from cases and controls. The concentration of IL-1β (pg/ml) was calculated by reference to a standard curve according to the manufacturer's instructions.

Genotyping

Genomic DNA was extracted from the leukocyte pellet obtained from the buffy coat of each blood sample. We used a modified PCR-restriction fragment length polymorphism (RFLP) assay to type the two polymorphisms in *IL-1B* promoter as we described previously (Liu et al. 2006). Because the *IL-1RN* has variable numbers of an identical tandem repeat of 86 bp, we used the direct PCR assay to detect it (Hu et al. 2006). The 240-bp product contained two 86 bp repeats (allele II), the 326 bp product three 86 bp repeats (allele IV), the 412 bp product four 86 bp repeats (allele I), and the 498 bp product five 86 bp repeats (allele III). Genotyping was performed without knowing the subjects' case/control status, and the approximately equal number of samples from cases and controls were assayed in each 96-well PCR plate with a positive control of a DNA sample with known heterozygous genotype. Ten percent of the samples (48 cases and 48 controls) were randomly selected to perform the repeated assays, and the results were 100% concordant.

Statistical analysis

Differences in demographic characteristics, selected variables, plasma IL-1β levels and frequencies of the genotypes of *IL-1B* T-31C, C-511T and *IL-1RN* between the cases and controls were evaluated by using the χ^2 test (for categorical variables) and student t test (for continuous variables). General linear model was used to compare the differences in IL-1β levels between IL polymorphisms with adjustment as indicated. The associations between *IL-1* genotypes and cervical cancer risk were estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs) from both univariate and multivariate logistic regression analyses. Dummy variables of the quartile of plasma IL-1β levels were created to calculate the ORs and 95% CIs (with the highest quartile on the distribution in controls as the reference category) as an estimate of the relative risk in the logistic regression analyses. All the statistical analyses were performed with Statistical Analysis System software (v.8.0e; SAS Institute, Cary, NC).

Results

The selected characteristics of the cases and controls enrolled in this study were summarized in Table 1. There were no significant differences between the cases and controls for the mean age ($P = 0.751$), age at menarche (0.082), age at menopausal ($P = 0.081$), smoking status (0.129) and menopausal status ($P = 0.098$). However, compared with the control subjects, the cervical cancer cases had a significantly lower age at having first live birth ($P < 0.001$), more parities ($P = 0.01$) and higher frequency of family history of any self-reported cancers ($P = 0.003$). Of the 404 cervical cancer cases, 363 (89.8%) were squamous cell carcinoma, 32 (8.0%) adenocarcinoma, 4 (1.0%) adenosquamous carcinoma, and 5 (1.2%) were undifferentiated carcinomas or others.

The mean plasma IL-1β levels in cervical cancer cases were 42.19 ± 31.55 pg/ml, which was significantly higher than those in controls (34.86 ± 22.68 pg/ml, $P = 0.0002$). As shown in Table 2, when the highest quartile of IL-1β level in controls (46.94 pg/ml) was used as the cut-off value for calculating the OR (95% CI) as a dichotomized variable, 37.1% (150 of 404) of the cervical cancer cases were above this level, which accounted for a 1.74-fold (95% CI, 1.28–2.36) significantly increased risk of cervical cancer after adjustment for age, smoking status, menopausal status, family history of cancer and parity.

The genotype distributions of *IL-1B* T-31C, C-511T and *IL-1RN* in the cases and controls were shown in Table 3. The observed genotype frequencies for the two polymorphisms of *IL-1B* were in Hardy–Weinberg equilibrium in the controls ($P = 0.513$ and 0.792, respectively). Logistic regression analyses showed that the −31TC heterozygote was associated with a 65% significantly increased risk of cervical cancer (adjusted OR, 1.65; 95% CI, 1.17–2.31), while −31CC with a 50% elevated risk with borderline significance (adjusted OR, 1.50; 95% CI, 0.99–2.26), compared with the −31TT wild-type homozygote. Overall, the variant genotypes (−31TC/CC) were associated with a significantly increased risk of cervical cancer in the dominant genetic model (adjusted OR, 1.60; 95% CI, 1.16–2.21). Likewise, compared with −511CC wild-type homozygote, −511CT heterozygote was associated with a

Table 1 Demographic and selected variables in cervical cancer cases and controls

Variable	Cervical cancer (n = 404) N (%)	Controls (n = 404) N (%)	P value
Age, year (mean ± SD)	54.89 ± 12.89	54.62 ± 11.22	0.751
Age at menarche, year (mean ± SD)[a]	16.09 ± 1.99	16.33 ± 1.96	0.082
Age at menopausal, year (mean ± SD)[b]	48.96 ± 3.95	49.56 ± 3.56	0.081
Age at first live birth, year (mean ± SD)[c]	22.59 ± 3.16	24.60 ± 3.19	<0.001
Smoking status			0.129
Smoker	28 (6.9)	18 (4.5)	
Non-smoker	376 (93.1)	386 (95.5)	
Menopausal status			0.098
Premenopausal	171 (42.3)	148 (36.6)	
Postmenopausal	233 (57.7)	256 (63.4)	
Parity			0.010
0–1	153 (38.0)	190 (47.0)	
2	108 (26.8)	108 (26.7)	
>2	142 (35.2)	106 (26.2)	
Family history of any cancer			0.003
No	294 (72.8)	330 (81.7)	
Yes	110 (27.2)	74 (18.3)	
Histological types			
Squamous cell carcinoma	363 (89.8)		
Adenocarcinomas	32 (8.0)		
Adenosquamous carcinoma	4 (1.0)		
Others	5 (1.2)		
Stage			
CIN3	2 (0.5)		
I	114 (28.2)		
II	208 (51.5)		
III	52 (12.9)		
IV	2 (0.5)		
Unknown	26 (6.4)		

[a] Information was available in 403 cases and 401 controls

[b] Information was available in 231 cases and 256 controls

[c] Information was available in 399 cases and 377 controls

Table 2 IL-1β levels and cervical cancer risk

Variable	Cases (n = 404) N (%)	Controls (n = 404) N (%)	P value	OR (95% CI)	OR (95% CI)[a]
Plasma IL-1β levels (pg/ml) (mean ± SD)	42.19 ± 31.55	34.86 ± 22.68	0.0002		
Plasma IL-1β level cutoff by the control quartile (pg/ml)					
IL-1β < 20.07	86 (21.3)	101 (25.0)		1.00	1.00
20.07 ≤ IL-1β < 35.56	89 (22.0)	101 (25.0)		1.04 (0.69–1.55)	1.01 (0.67–1.54)
35.56 ≤ IL-1β < 46.94	79 (19.6)	101 (25.0)		0.92 (0.61–1.39)	0.88 (0.58–1.35)
IL-1β ≥ 46.94	150 (37.1)	101 (25.0)	0.004	1.74 (1.19–2.56)	1.68 (1.13–2.48)
Dichotomized plasma IL-1β level					
IL-1β < 46.94	254 (62.9)	303 (75.0)		1.00	1.00
IL-1β ≥ 46.94	150 (37.1)	101 (25.0)	0.0002	1.77 (1.31–2.40)	1.74 (1.28–2.36)

[a] Adjusted for age, smoking status, menopausal status, family history of cancer and parity

53% significantly increased risk (adjusted OR, 1.53; 95% CI, 1.09–2.15), while the combined genotypes (–511CT/TT) were associated with a 52% significantly elevated risk (adjusted OR, 1.52; 95% CI, 1.10–2.09). However, there were no significant associations between *IL-1RN* genotypes and risk of cervical cancer (Table 3).

Table 3 *IL1* polymorphisms and cervical cancer risk

Variable	Cases (n = 404) N (%)	Controls (n = 404) N (%)	OR (95% CI)	OR (95% CI)[a]
IL-1B T-31C				
TT	94 (23.3)	128 (31.7)	1.00	1.00
TC	221 (54.7)	193 (47.8)	1.56 (1.12–2.17)	1.65 (1.17–2.31)
CC	89 (22.0)	83 (20.5)	1.46 (0.98–2.18)	1.50 (0.99–2.26)
TC/CC	310 (76.7)	276 (68.3)	1.53 (1.12–2.09)	1.60 (1.16–2.21)
IL-1B C-511T				
CC	94 (23.3)	124 (30.7)	1.00	1.00
CT	228 (56.4)	202 (50.0)	1.49 (1.07–2.07)	1.53 (1.09–2.15)
TT	82 (20.3)	78 (19.3)	1.39 (0.92–2.09)	1.47 (0.97–2.24)
CT/TT	310 (76.7)	280 (69.3)	1.46 (1.07–2.00)	1.52 (1.10–2.09)
IL-1RN				
I/I	354 (87.6)	352 (87.1)	1.0	1.0
I/II	45 (11.1)	47 (11.6)	0.95 (0.62–1.47)	0.94 (0.60–1.47)
I/III	1 (0.2)	1 (0.2)	0.99 (0.06–15.96)	0.74 (0.04–12.57)
I/IV	4 (1.0)	2 (0.5)	1.99 (0.36–10.93)	1.54 (0.27–8.64)
II/II	0 (0)	2 (0.5)	–	–

[a] Adjusted for age, smoking status, menopausal status, family history of cancer and parity

In the stratified analyses, we found that the effect of C-511T variant genotypes was more prominent in the strata of high plasma IL-1β levels (OR, 2.22; 95% CI, 1.27–3.90; P for heterogeneity test = 0.088). However, it seems no difference among subgroups by age, smoking status, age at menarche, age at first live birth, parity and family history of cancer for the associations of *IL-1B* −31TC/CC and −511CT/TT variant genotypes with cervical cancer risk (Table 4).

Furthermore, the difference of IL-1β concentration between cervical cancer cases and controls was observed only among carriers of *IL-1B* T-31C and C-511T variant genotypes, although the correlations between the genotypes (*IL-1B* T-31C and C-511T) and phenotypes (IL-1β levels) were not significant in both cases and controls as suggested by the general linear model (Table 5).

In addition, we performed a stepwise multivariate analysis for the effects of demographic characteristics (age, smoking status, menopausal status, family history of cancer and parity), genotypes of *IL-1B* T-31C and C-511T, and plasma IL-1β levels on cervical cancer risk. Five variables (menopausal status, family history of cancer, parity, T-31C, plasma IL-1β level) were selected into the regression model with a significance level of 0.05 for entering and 0.10 for removing a variable (Table 6).

Discussion

In this case–control study, we investigated the associations of plasma IL-1β levels, *IL-1B* T-31C, C-511T and *IL-1RN* polymorphisms, and cervical cancer risk in Chinese women. We found, for the first time, that both elevated plasma IL-1β levels and *IL-1B* T-31C and C-511T variant genotypes were significantly associated with increased risk of cervical cancer, and more importantly, the genetic effects on cervical cancer were more evident among subjects having higher plasma IL-1β concentration and the differences of IL-1β concentrations between cervical cancer cases and controls were observed only among subjects carrying *IL-1B* variant genotypes.

The functional relevance of the two *IL-1B* polymorphisms were evaluated previously in different disease models, especially for the T-31C (Chang et al. 2005; Chen et al. 2006; El-Omar et al. 2000; Francis et al. 1999; Lind et al. 2007). The variant alleles of the two SNPs (−31C and −511T) were usually reported to be associated with decreased (−31C) and increased (–511T) transcriptional activities (Chang et al. 2005; Chen et al. 2006; Lind et al. 2007), but it is not simply the case in terms of circulating IL-1β levels. In the current study, we found a decrease of plasma IL-1β levels associated with −31TC/CC variant genotypes, and −31CC and −511TT were correlated with a higher IL-1β level in the cases (Table 5), which was consistent with the observation that both variant genotypes and elevated IL-1β levels were associated with cervical cancer risk. Furthermore, increased plasma IL-1β levels were associated with an increased trend of advanced cervical cancer in our study (data not shown). However, we cannot evaluate IL-1β levels and cervical cancer progression without disease prognosis and survival information in the current study. For cervical carcinogenesis, inherited genetic polymorphisms contribute to cervical cancer

Table 4 Stratified analyses of *IL-1B* genotypes and cervical cancer risk

	IL-1B T-31C (cases/controls)				*IL-1B* C-511T (cases/controls)			
	TT	TC + CC	Adjusted OR (95% CI)[a]	P^b	CC	CT + TT	Adjusted OR (95% CI)[a]	P^b
Age				0.337				0.423
<55	48/70	164/148	1.86 (1.19–2.91)		48/66	164/152	1.71 (1.09–2.68)	
≥55	46/58	146/128	1.35 (0.84–2.18)		46/58	146/128	1.31 (0.82–2.11)	
Smoking status				0.829				0.871
Non-smoker	88/124	288/262	1.63 (1.17–2.27)		87/120	289/266	1.56 (1.12–2.17)	
Smoker	6/4	22/14	1.23 (0.10–15.79)		7/4	21/14	2.00 (0.10–39.17)	
Menopausal status				0.323				0.438
Premenopausal	41/54	130/91	1.90 (1.14–3.16)		42/52	129/93	1.73 (1.04–2.87)	
Postmenopausal	53/74	180/185	1.36 (0.89–2.08)		52/72	181/187	1.33 (0.87–2.05)	
Age at menarche				0.492				0.540
≤16	59/63	191/146	1.44 (0.94–2.21)		59/64	191/145	1.41 (0.92–2.15)	
>16	35/65	119/130	1.82 (1.09–3.04)		35/60	119/135	1.74 (1.03–2.92)	
Age at first live birth				0.564				0.440
<25	74/62	243/145	1.44 (0.96–2.15)		75/60	242/147	1.36 (0.90–2.04)	
≥25	20/66	67/131	1.78 (0.98–3.23)		19/64	68/133	1.81 (1.00–3.31)	
Parity				0.462				0.730
0–1	35/56	118/134	1.38 (0.83–2.28)		34/55	119/135	1.45 (0.87–2.40)	
>1	59/72	192/142	1.77 (1.15–2.71)		60/69	191/145	1.63 (1.06–2.51)	
Family history of cancer				0.356				0.278
Negative	71/103	223/227	1.47 (1.02–2.11)		70/99	224/231	1.39 (0.96–2.01)	
Positive	23/25	87/49	2.13 (1.06–4.29)		24/25	86/49	2.16 (1.07–4.38)	
Plasma IL-1β level				0.229				0.088
<46.94 pg/ml	60/90	194/213	1.44 (0.97–2.13)		62/86	192/217	1.23 (0.84–1.80)	
≥46.94 pg/ml	34/38	116/63	2.23 (1.23–4.03)		32/38	118/63	2.22 (1.27–3.90)	

[a] Adjusted for age, smoking status, menopausal status, family history of cancer and parity

[b] *P* value for homogeneity test

Table 5 Stratified analyses of plasma IL-1β levels on cervical cancer risk by *IL-1B* genotypes

Variable		Plasma IL-1β levels (pg/ml)		*P* value
		Cases ($n = 404$)	Controls ($n = 404$)	
IL-1B T-31C	TT ($n = 222$)	41.55 ± 36.03	38.06 ± 24.87	0.419
	TC ($n = 414$)	40.94 ± 27.62	32.49 ± 22.51	0.0007
	CC ($n = 172$)	45.94 ± 35.49	35.45 ± 18.84	0.016
		$P = 0.329$[a]	$P = 0.295$[a]	
IL-1B C-511T	CC ($n = 218$)	39.99 ± 30.93	35.88 ± 21.02	0.270
	CT ($n = 430$)	41.50 ± 29.93	34.11 ± 23.48	0.004
	TT ($n = 160$)	46.61 ± 36.28	35.17 ± 23.35	0.019
		$P = 0.152$[a]	$P = 0.779$[a]	

[a] Adjusted for age, smoking status, menopausal status, family history of cancer and parity in general linear model

susceptibility suggest IL-1β could also be etiological factor. As shown in Table 5, although plasma IL-1β levels were not simply determined by the two *IL-1B* polymorphisms, the observed differences between cases and controls were more evident among variant genotypes carriers (risk carriers). Therefore, variant genotypes of the two *IL-1B* polymorphisms may be associated with an increased response to carcinogens (like HPV infection), rather than regulation the basal expression in cervical carcinogenesis.

There is an increasing volume of literatures published to date on the role of cytokines in regulating a variety of cellular functions in tumor cells (Dinarello 1991; Dinarello and Wolff 1993), including the surveillance of HPV-related cervical neoplasia (Noqueira de Souza et al. 2006). Accumulative evidences showed that the levels of IL-1β were

Table 6 Stepwise logistic analyses of plasma IL-1β levels, IL polymorphisms and selected variables on cervical cancer risk

Variables	β	SE	OR	95% CI	*P*
Menopausal (yes vs. no)	−0.6333	0.1678	0.53	0.38–0.74	0.0002
Family history of cancer (yes vs. no)	0.4865	0.1752	1.63	1.15–2.29	0.0055
Parity[a]	0.2274	0.0534	1.26	1.13–1.39	<0.0001
IL-1B T-31C (CT/CC vs. TT)	0.4923	0.1647	1.64	1.19–2.26	0.0028
IL-1β levels (high vs. low)[b]	0.5760	0.1581	1.78	1.31–2.43	0.0003

[a] Parity was included as continuous variable

[b] Up quartile of IL-1β level in controls was used as the cut-off value

increased in the cervicovaginal washings of patients with cervical cancer (Tjiong et al. 2001) and elevated vaginal lavage IL-1β was associated with a higher risk of cervical dysplasia (Behbakht et al. 2002). Our study was among the largest ones to provide evidence, in the population level, that plasma IL-1β level is a risk factor for cervical cancer. Of course, the proven of the causal role of IL-1β in cervical carcinogenesis warrant perspective studies and also biological characterizations.

Since El-Omar et al. (2000) reported that the polymorphisms in *IL-1B* and *IL-1RN* were associated with risk of gastric cancer, many studies investigated the associations between these SNPs and cancers at different sites, such as the lung (Hu et al. 2006; Zienolddiny et al. 2004), breast (Liu et al. 2006), liver (Hirankarn et al. 2006) and cervical (Kang et al. 2007). However, the results remain controversial in different populations and different disease models. For the only published paper on cervical cancer, Kang et al. (2007) reported that the carriers with −511CT/TT genotypes were at a higher risk of cervical cancer with an odds ratio of 2.42 (95% CI, 1.31–4.46) in a small case–control study of 182 cases and 364 age-matched controls in Korean women, which was similar to the findings in our study. Although the plasma IL-1β levels were not simply predicted by *IL-1B* genotypes, these SNPs could still play a low penetrance role in cervical carcinogenic process, which may be useful in identifying at risk people for HPV-related cervical cancer. The *IL1RN*2* allele were characterized to predispose to a variety of human diseases primary of epithelial or endothelial cell origin (Arend 2002). Several studies have been reported to evaluate the associations between *IL-1RN* gene VNTR polymorphism and risk of cancers (especially gastric cancer) and the results were conflicting rather than conclusive (Chang et al. 2005; El-Omar et al. 2000; Fujiwaki et al. 2003; Hu et al. 2006; Machado et al. 2003; Zeng et al. 2003). Studies from Caucasian population have shown that the homozygous carriage of the *IL1RN*2* allele was associated with an increased risk of gastric cancer (El-Omar et al. 2000; Machado et al. 2003), however, this association was not replicated in Asian populations (Chang et al. 2005; Zeng et al. 2003) and we reported that the *IL1RN*2* allele was protective against lung cancer in a Chinese population (Hu et al. 2006). In addition, the *IL1RN*2* allele was extremely uncommon in Chinese (3.5%, $n = 361$; 8.3%, $n = 1024$; 6.3% among 404 controls in the current study) (Hu et al. 2006; Zeng et al. 2003) compared with that in Caucasians (26.9%) (El-Omar et al. 2000).

It needs to be pointed out that there were several limitations in this study. First, although we observed significant main effects of both *IL-1B* variant genotypes and plasma IL-1β levels, the limited sample size may restrict us to identify genotype–phenotype correlations. Second, our study lacked the measurement of IL-1β levels in the local environment of cervix and the representative of circulating IL-1β levels need to be investigated in further study. Third, the lack of cervical cancer tissues restricted the detection of HPV virus DNA, however, it is demonstrated that HPV-negative carcinoma is extremely uncommon, if it exists at all (Walboomers et al. 1999).

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