Association of the rs2430561 polymorphism of the interferon-γ gene with cervical cancer susceptibility and prognosis in Han Chinese women

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Objectives: To investigate IFN-γ rs2430561 polymorphisms in Han women in northeast China and the relationship between the rs2430561 polymorphisms and the risk of cervical cancer. Methods: PCR-ASP was used for genotyping. IFN-γ rs2430561 polymorphism was detected in 173 cases of cervical invasive carcinoma and 422 healthy controls in Han women in northeast China. Results: The allele and genotype distributions of the IFN-γ rs2430561 polymorphism were not significantly different between each of the groups (P > 0.05). There was no significant relationship between rs2430561 polymorphism and invasive cervical cancer (TT vs AA, OR = 1.321, 95% CI: 0.05). The polymorphism had no significant effect on overall survival (P = 0.071) or progression free survival (P = 0.632). The rs2430561 genotype was not associated with major clinicopathological features of invasive cervical cancer and 422 healthy controls in Han women in northeast China. Results: The allele and genotype distributions of the IFN-γ rs2430561 polymorphism were not significantly different between each of the groups (P > 0.05). The polymorphism had no significant effect on overall survival (P = 0.071) or progression free survival (P = 0.632) of invasive cervical carcinoma. Conclusions: Rs2430561 polymorphism had no effect on invasive cervical cancer susceptibility in Han females in northeastern China, and was not associated with the prognosis of invasive cervical carcinoma.

Keywords
Cervical cancer, Single nucleotide polymorphism, Genetic susceptibility, IFN-γ

1. Background
Cervical cancer is one of the most common malignancies in women, and its incidence is still increasing in developing countries [1]. Infection with the human papillomavirus (HPV) is an important risk factor for developing cervical cancer [2]. The malignant transformation mechanism after HPV infection is complex; it has been shown that the immune response induced by HPV infection plays an important role in the development of cervical cancer [3]. Many of the cytokines associated with immune modulation have been proven to be involved in the oncogenesis and progression of cervical cancer [4].

Interferon (IFN)-γ is a T helper (Th)1 cell pro-inflammatory cytokine that has important regulatory functions in almost all immune responses, such as differentiation and proliferation of T cells, antitumor, and antiviral activity [5, 6]. IFN-γ is mainly produced by activated lymphocytes and natural killer (NK) cells. IFN-γ is an important cytokine affecting the differentiation of T cells to Th1 and Th2 cells [7]. IFN-γ promotes T cells to differentiate into Th1 cells to activate cellular immunity. There is some evidence that IFN-γ has anti-proliferative and anti-angiogenic effects on a variety of tumor cells [8, 9]. Additionally, it has been found that cellular immunity can control HPV infection, and modulate cervical intraepithelial neoplasia (CIN) associated with HPV infection [10].

Previous studies suggest that IFN-γ expression is affected by the rs2430561 polymorphism (also known as the +874 locus) of the IFN-γ gene [11]. Given the role of IFN-γ in antitumor processes, it has been speculated that the rs2430561 polymorphism may be associated with genetic susceptibility to cervical cancer. Several studies have tried to answer this question; however, the relationship between the rs2430561 polymorphism and cervical cancer risk has not been confirmed [12–15]. The purpose of this study was to investigate the effect of the rs2430561 polymorphism on cervical cancer susceptibility and prognosis in females of Han descent.

2. Materials and methods
2.1 Study subjects
Patients in the case group were randomly selected from patients diagnosed with invasive cervical carcinoma by pathology in the Department of Obstetrics and Gynecology of Shengjing Hospital of China Medical University from August 2011 to April 2014. There were 173 cases of invasive cervical carcinoma enrolled in the study. Healthy women (n = 422) who took physical examinations in our hospital were selected to constitute the control group. Control group requirements included no history of CIN or other tumors, and no abnormalities detected by cervical cytology examination. All participants were Han women from Northeastern China. HPV
infection status was tested according to previously described methods [16]. The case group was followed from the first to the 60th month after definitive diagnosis. Endpoint events included death and disease progression; overall survival and progression-free survival were recorded. This study was reviewed and approved by the Ethics Committee of Shengjing Hospital.

2.2 Sample collection

For each participant, 5 mL of peripheral venous blood was collected using an EDTA anticoagulation blood tube (BD Biosciences, San Jose, CA, USA), aliquoted, and stored in a 1.5 mL centrifuge tube.

2.3 Genotyping

Genomic DNA was extracted using the Tiangen Blood Genome Kit (China) according to the manufacturers’ instructions. The PCR-ASP method [17] was used for rs2430561 genotyping. Primers used in the study are listed in Table 1. A 10 µL reaction was prepared according to manufacturers’ instructions. The annealing temperature was 55 °C–57 °C. Reactions were run on a Takara (Japan) TP600 PCR machine, and amplified products were analyzed by electrophoresis on a 2.5% agarose gel. The T allele and A allele were amplified using specific primers to obtain a 264 bp product. Control primers generated a 476 bp product that was used as an internal reference (Fig. 1).

Table 1. Primers used in the study.

| Primer          | Sequence                  | Fragment length |
|-----------------|---------------------------|-----------------|
| Sense primer    |                           |                 |
| Control primer  | 5′-GGAACTCTCGTTGCTCACT-3′  | 476 bp          |
| A allele primer | 5′-TTCTTACAAACACAAATCAATCA-3′ | 264 bp          |
| T allele primer | 5′-TTCTTACAAACACAAATCAATCCT-3′ | 264 bp          |
| Antisense primer|                           |                 |
| Common primer   | 5′-TCAACAAAGCTGATACTCCA-3′ |                 |

2.4 Statistical analyses

Multivariate logistic regression was used to analyze the association of genotype with cervical cancer risk. The odds ratio (OR) was calculated using a multivariate logistic regression model and adjusted for age, smoking history, pregnancy history, and HPV infection status. A chi-square test was used to test for Hardy–Weinberg equilibrium. The frequency of basic patient characteristics was tested using the Fisher exact test. A P-value < 0.05 was considered statistically significant. The Kaplan–Meier method was used to compare survival differences, and the log-rank method was used for significance testing. Multivariate survival analysis was performed using the Cox model. SPSS (version 13.0; SPSS, Inc., Chicago, IL, USA) was used for all analyses.

3. Results

3.1 Patient characteristics

The basic characteristics of the participants are shown in Table 2. There were no significant differences in age distribution, smoking history, and pregnancy history (P = 0.117, 0.106 and 0.106 respectively). Therefore, these factors were not associated with cervical cancer susceptibility.

PCR-ASP genotyping results are shown in Table 3. The genotype frequencies of the included subjects met Hardy–Weinberg equilibrium (P > 0.05). The frequencies of the A allele of the rs2430561 locus was 0.54 in the case group and 0.613 in the control group. The corresponding frequencies of the T allele in the case and control groups were 0.46 and 0.387, respectively. Compared with the A allele, the T allele was associated with a slight increase in cervical cancer susceptibility risk (OR = 1.232, 95% CI: 1.032–1.470). Although this increase was statistically significant (P = 0.023), it may not have practical or clinical significance. Multivariate logistic regression adjusted for age, smoking history, pregnancy history, and HPV infection status indicated that the various genotypes of rs2430561 did not significantly affect cervical
Fig. 2. Overall survival (OS).

Fig. 3. Progression-free survival (PFS). Kaplan-Meier survival curves of patients with cervical cancer according to rs2430561 genotype.

cancer susceptibility. The ORs of the TT genotype and TA genotype relative to the AA genotype were 1.321 (95% CI: 0.423–4.121, \(P = 0.632\)) and 0.439 (95% CI: 0.145–1.324, \(P = 0.144\)), respectively. Thus, the rs2430561 polymorphism of the IFN-\(\gamma\) gene had no significant effect on susceptibility to cervical invasive carcinoma or cervical cancer more generally.

3.2 Association of the rs2430561 genotype with clinicopathological features of cervical cancer

The distribution data of rs2430561 genotypes and clinicopathological features are shown in Table 4. For the 173 cases of cervical invasive carcinoma tested, the rs2430561 genotype was not associated with differentiation grade (\(P = 0.675\)), lymph node metastasis (\(P = 0.149\)), vascular cancerous embolus (\(P = 0.772\)), tumor size (\(P = 0.685\)), or infiltration depth (\(P\))
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not significantly different from one another (\( P = 0.457 \)). Kaplan–Meier analysis showed that the cumulative progression rates (\( \text{P}cure \) = 0.470). Overall, rs2430561 genotype did not show a significant association with any major clinicopathological feature of cervical cancer.

### 3.3 Association of rs2430561 genotype with patient prognosis

We followed 173 patients in the case group for 60 months. There were 59 patients who died during the follow up period (34.1% mortality). Disease progression occurred in 100 patients (57.8%). Kaplan–Meier analysis showed that the cumulative survival rates of the AA, TA and TT genotypes were not significantly different from one another (\( P = 0.457 \)), nor were the cumulative progression rates (\( P = 0.374 \)). Multivariate analyses of OS (Overall Survival) and PFS (Progression Free Survival) in relation to clinical parameters and genotype are shown in Table 5. The Cox model was used to analyze the effect of multiple factors on patient prognosis including age, smoking history, pregnancy history, HPV infection status, clinical stage, differentiation grade, lymph node metastasis, tumor size, tissue, and lymphatic vessel infiltration. The rs2430561 polymorphism was not associated with both OS (Fig. 2) and PFS (Fig. 3) (\( P = 0.071 \) and 0.067). However, HPV status, lymph node metastasis, and tumor size significantly affected OS and PFS (\( P < 0.05 \) for all).

### 4. Discussion

IFN-\( \gamma \) has important functions in both innate and adaptive immunity. Our previous study suggests that the rs2430561 polymorphism of the IFN-\( \gamma \) gene is associated with the risk of cervical HPV infection in Han women in Northeastern China [17]. The A allele and AA genotype both increase the HPV infection risk, and AA genotype carriers are prone to persistent and recurrent HPV infection. Taking into account the critical role of HPV infection in cervical cancer, we hypothesized that the polymorphism at this locus may be associated with cervical cancer susceptibility. In this study we did not identify a significant association between rs2430561 polymorphism and cervical cancer susceptibility.

The IFN-\( \gamma \) gene, located at 12q24, is \(-5.4 \text{ kb} \) in length and contains four exons. Like other cytokines, IFN-\( \gamma \) coding regions tend to be conserved [18]. Currently, there are no reported single nucleotide polymorphisms in the coding regions of the IFN-\( \gamma \) gene. Some studies have found an association between the rs2430561 polymorphism and IFN-\( \gamma \) expression levels [11, 17]. The transcription factor NF-\( \kappa B \) tends to bind to the the protein variant expressed by the T allele, which accounts for the effect of the rs2430561 polymorphism on IFN-\( \gamma \) expression [19]. The high expression of IFN-\( \gamma \) induced by the binding of NF-\( \kappa B \) to the T allele has also been demonstrated by an in vitro study [11]. Meanwhile, the A allele of rs2430561 and the AA genotype are associated with relatively low expression of IFN-\( \gamma \). It has been reported that the A allele is associated with an increased risk for infectious diseases such as tuberculosis, hepatitis B, and parvovirus infections [20–22]. Thus, the low expression of IFN-\( \gamma \) associated with the A allele may attenuate the body’s antiviral capabilities, and thus facilitate tumor transformation. A study suggests that AA homozygosity at the rs2430561 locus may increase cervical cancer risk in Chinese women [23]. However, a study in South Africa obtained the opposite result [14]. Our study selected Han females in Northeastern China as study subjects, and used a larger sample size than previous studies. However, we did not find a significant association between the rs2430561 polymorphism and cervical cancer susceptibility.

Based on our previous findings, we hypothesized that IFN-\( \gamma \) has a dual protective effect on HPV-associated CIN and cervical cancer [17]. However, studies in Brazilian women failed to show that the polymorphism at this locus affects susceptibility to HPV-associated CIN [15]. We did not

### Table 2. Clinical characteristics of cases and controls.

|                     | Patients (n = 173) | Control (n = 422) | \( p \)  |
|---------------------|--------------------|-------------------|--------|
| Age                 |                    |                   |        |
| ≤35                 | 34 (19.7)          | 103 (24.4)        | 0.117  |
| 36–50               | 92 (53.2)          | 235 (55.7)        |        |
| >50                 | 47 (27.2)          | 84 (19.9)         |        |
| Smoking             |                    |                   |        |
| Never               | 162 (93.6)         | 409 (96.9)        | 0.106  |
| Ever                | 11 (6.4)           | 13 (3.1)          |        |
| Pregnancy           |                    |                   |        |
| Never               | 3 (1.8)            | 30 (7.1)          | 0.106  |
| 1–2                 | 158 (91.3)         | 362 (85.8)        |        |
| >2                  | 12 (6.9)           | 30 (7.1)          |        |
| HPV status          |                    |                   |        |
| HPV+                | 153 (88.4)         | 0 [0]             | 0.000  |
| HPV-                | 20 (11.6)          | 422 [100]         |        |
| Clinical stage\( b \) |                   |                   |        |
| Stage I             | 132 (76.3)         |                    |        |
| Stage II            | 33 (19.1)          |                    |        |
| Stage III           | 7 (4.0)            |                    |        |
| Stage IV            | 1 (0.6)            |                    |        |
| Differentiation     |                    |                   |        |
| Well                | 56 (33.0)          |                    |        |
| Moderate            | 67 (39.4)          |                    |        |
| Poorly              | 50 (27.7)          |                    |        |
| Lymphatic metastasis|                    |                   |        |
| No                  | 134 (77.5)         |                    |        |
| Yes                 | 39 (22.5)          |                    |        |
| Tumor size          |                    |                   |        |
| ≤4 cm               | 119 (68.8)         |                    |        |
| >4 cm               | 54 (31.2)          |                    |        |
| Invasive interstitial depth |        |                   |        |
| <1/2                | 109 (63.0)         |                    |        |
| ≥1/2                | 64 (37.0)          |                    |        |
| Vascular invasion   |                    |                   |        |
| No                  | 127 (73.4)         |                    |        |
| Yes                 | 46 (26.6)          |                    |        |

\( a \) Two-sided Fisher’s Exact test.

\( b \) According to the International Federation of Gynecology and Obstetrics (FIGO) classification.
Table 3. Genotype frequencies of IFN rs2430561 among patients and controls and their association with SCCUC.

| Genotype | Patients (n = 173) | Controls (n = 422) | OR (95% CI) | P |
|----------|-------------------|-------------------|-------------|---|
|          | No. (%)           | No. (%)           |             |   |
| Allele frequency (n=346) (n=844) |                 |                 |             |   |
| T allele | 159 (46.0)        | 327 (38.7)        | 1.232 (1.032–1.470) | 0.023 |
| A allele | 187 (54.0)        | 517 (61.3)        | reference   |   |
| TT       | 38 (22.0)         | 67 (15.9)         | 1.321 (0.423–4.121) | 0.632 |
| TA       | 83 (48.0)         | 193 (45.7)        | 0.439 (0.145–1.324) | 0.144 |
| AA       | 52 (30.1)         | 162 (38.4)        | reference   |   |

a Data were calculated by multivariate regression analysis, adjusting for age, HPV status, pregnancy and smoking history.

Table 4. Genotypes distribution of differentiation.

| Genotype | Differentiation (n = 173) | P |
|----------|----------------------------|---|
|          | Well No. (%) | Moderate No. (%) | Low No. (%) |   |
| TT       | 12 (21.4) | 17 (25.4) | 9 (22.0) | 0.675 |
| TA       | 30 (53.6) | 28 (41.8) | 25 (48.0) |   |
| AA       | 14 (25.0) | 22 (32.8) | 16 (30.1) |   |

Lymphatic metastasis

|          | No No. (%) | Yes No. (%) | P |
|----------|------------|-------------|---|
| TT       | 25 (18.7) | 13 (33.3) | 0.149 |
| TA       | 68 (50.7) | 15 (38.5) |   |
| AA       | 41 (30.6) | 11 (28.2) |   |

Tumor size

|          | ≤4 cm No. (%) | >4 cm No. (%) | P |
|----------|---------------|---------------|---|
| TT       | 24 (20.2) | 14 (25.9) | 0.685 |
| TA       | 58 (48.7) | 25 (46.3) |   |
| AA       | 37 (31.1) | 11 (28.2) |   |

Invasive interstitial depth

|          | ≤1/2 No. (%) | ≥1/2 No. (%) | P |
|----------|--------------|--------------|---|
| TT       | 23 (21.1) | 15 (23.4) | 0.470 |
| TA       | 56 (51.4) | 27 (42.2) |   |
| AA       | 30 (27.5) | 22 (34.4) |   |

Vascular invasion

|          | No No. (%) | Yes No. (%) | P |
|----------|------------|-------------|---|
| TT       | 27 (21.3) | 19 (23.9) | 0.772 |
| TA       | 63 (49.6) | 13 (43.5) |   |
| AA       | 37 (29.1) | 9 (32.6) |   |

a Two-sided Fisher’s Exact test.

include CIN patients in this study, and the association of the rs2430561 polymorphism with CIN susceptibility will be investigated in future studies.

The ethnic background of the population is an important factor that should not be overlooked in genetic susceptibility studies. In a meta-analysis, Sun et al. systematically reviewed the association of rs2430561 with cervical cancer risk. They found that rs2430561 was significantly associated with cervical cancer susceptibility in the Asian population; however, this association was not observed in other races. This is may be due to differences in the genotype frequency of rs2430561 between different races [24, 25]. Our study did not correspond with results from other studies in Han women [23]. One reason for this discrepancy may be that while all study subjects were selected from the Han population, the study subjects were from different regions. The participants in our study came from northeastern China, while participants in former studies came mainly from northwestern China, in which more racial diversity was characterized. Thus, the genetic background may be different in our study. Secondly, our study included a larger sample than previous studies, and this variation in sample size may cause different results. Thirdly, the etiology of cervical cancer is complex, and gene-gene and gene-environment interactions can both affect the oncogenesis of cervical cancer, complicating study design and increasing the uncertainty of results.

We have found that AA genotype carriers were more likely to have persistent and relapsing HPV infections [17], and we speculated that the AA genotype may be associated with cervical cancer prognosis. In this study, we investigated whether the rs2430561 polymorphism of the IFN-γ gene was associated with the recurrence of invasive cervical cancer. We found that rs2430561 genotype of was not a factor affecting the prognosis of invasive cervical cancer. There was no significant difference in either OS or PFS among the various genotypes. Gangwar et al. [12] reported that the rs2430561 polymorphism was associated with cervical cancer prognosis in Indian women, and that this effect may be caused by low expression of IFN-γ associated with the AA genotype. However, our study did not indicate any such association. Treatment approach may also influence the prognosis, in our study all patients were treated following cervical cancer guideline. We will balance the treatment factor in different genotype group with larger sample in the future. Future studies using larger sample sizes may be helpful for clarifying this issue.

5. Conclusions

In conclusion, the rs2430561 polymorphism of the IFN-γ gene had no effect on cervical cancer susceptibility in Han females in Northeastern China, and was not associated with the prognosis of invasive cervical carcinoma.
Table 5. Multivariate analyses of OS and PFS in relation to clinical parameters and Genotype.

|                    | \( p \) | RR   | 95% CI     | \( p \) | RR   | 95% CI     |
|--------------------|--------|------|------------|--------|------|------------|
| Genotype           | 0.071  | 1.397| 0.972–2.010| 0.067  | 1.326| 0.981–1.792|
| Age                | 0.53   | 1.132| 0.769–1.667| 0.588  | 0.917| 0.669–1.256|
| Smoking            | 0.148  | 0.386| 0.107–1.399| 0.634  | 0.813| 0.347–1.904|
| Pregnancy          | 0.51   | 1.399| 0.515–3.800| 0.863  | 0.938| 0.454–1.939|
| HPV status         | 0.651  | 1.24 | 0.488–3.148| 0.461  | 1.319| 0.632–2.755|
| Clinical stage     | <0.001 | 4.223| 2.784–6.404| <0.001 | 4.055| 2.812–5.848|
| Differentiation    | 0.103  | 1.347| 0.941–1.928| 0.068  | 1.289| 0.981–1.693|
| Lymphatic metastasis| <0.001 | 3.314| 1.892–5.807| <0.001 | 4.188| 2.615–6.708|
| Tumor size         | 0.001  | 2.372| 1.392–4.041| 0.001  | 2.114| 1.372–3.746|
| Invasive interstitial depth | 0.591  | 1.269| 0.737–2.186| 0.136  | 1.372| 0.905–2.080|
| Vascular invasion  | 0.952  | 1.018| 0.572–1.810| 0.41   | 1.209| 0.770–1.896|

*Genotype 0.071 1.397 0.972–2.010 0.067 1.326 0.981–1.792
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Abbreviations
HPV, human papillomavirus; IFN, interferon; Th, T helper; NK, natural killer; CIN, cervical intraepithelial neo-plasia; OR, odds ratio; PCR-ASP, polymerase chain reaction-allele specific primer; OS, Overall Survival; PFS, Progress Free Survival.

Author contributions
HW and YZ Conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft, writing review and editing, project administration. QZ was involved in conceptualization and formal analysis. YML was involved in resources and data curation. YLH was involved in resources and data curation. NW was involved in conceptualization, funding acquisition, investigation, methodology, project administration and review & editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethical approval for human subjects was obtained from the research ethics committee of ShengJing Hospital (approved No.2012PS45K). Written informed consent was obtained by all patients.

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Conflict of interest
The authors declare no conflict of interest.

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