Genetic polymorphism (rs246079) of the DNA repair gene uracil N-glycosylase is associated with increased risk of cervical carcinoma in a Chinese population

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Abstract
The aim of this case-control study was to clarify the relationship between uracil N-glycosylase (UNG) rs246079 genotypes and risk of cervical squamous cell cancer (CSCC). Modified polymerase chain reaction-mismatch amplification ( MA-PCR) was applied for genotyping UNG rs246079 (A/G) and UNG rs246079 (A/G) polymorphisms in 400 CSCC, 400 cervical intraepithelial neoplasia (CIN) III, and 1200 normal controls. We observed no association between the UNG rs246079 (A/G) polymorphism and risk of CIN III or CSCC. However, risk of CIN III (odds ratio [OR] = 1.58) and CSCC (OR = 2.08) was significantly increased in cases with the homozygous GG genotype of UNG rs246079. At the UNG rs246079 (A/G) locus, individuals with the G allele or G carrier (GG + AG) genotype were at higher risk for CIN III (OR = 1.34) and CSCC (OR = 1.56). In the high-risk HPV (HR-HPV) positive group, homozygous GG of the UNG rs246079 genotype was associated with significantly increased risk of CSCC (OR = 2.37) and CIN III (OR = 1.81). Meanwhile, the proportion of G allele was significantly increased in CIN III (49.2%, OR = 1.33) and CSCC (52.5%, OR = 1.50) groups. G allele or G carrier (GG + AG) genotype was identified as a high-risk factor in CSCC (OR = 1.67) while in the CIN III group, no major differences were evident relative to the control group (OR = 1.45). A particularly high level of enrichment grouping was evident according to the number of sexual partners in the CIN III (P = .036) and CSCC (P = .001) groups. Our data clearly suggest an association between UNG rs246079 (A/G) and CSCC carcinogenesis, supporting the potential application of this polymorphism as a genetic biomarker for early prediction of cervical carcinoma.

Abbreviations: BER = base excision repair, CIN = cervical intraepithelial neoplasia, CI = 95% confidence intervals, CSCC = cervical squamous cell carcinoma, ESCC = esophageal squamous cell carcinoma, HC II = Hybrid Capture II, HPV = human papillomavirus, HR-HPV = high-risk HPV, MA-PCR = modified polymerase chain reaction-mismatch amplification, NER = nucleotide excision repair, OR = odds ratio, RA = rheumatoid arthritis, ROS = reactive oxygen species, SNP = single nucleotide polymorphisms, UNG = uracil N-glycosylase.

Keywords: cervical squamous cell carcinoma, Chinese population, cervical intraepithelial neoplasia III, human papillomavirus infection, uracil N-glycosylase polymorphism

Highlights
1. For the first time, we discovered the genetic correlation between cervical carcinoma and the DNA repair gene UNG rs246079 (A/G) polymorphism.
2. High ratio and large scale normal controls made the results more reliable (1:3; 1200 normal controls).
3. There was association between the UNG rs246079 (A/G) polymorphism with CSCC carcinogenesis.

1. Introduction
Cervical cancer (CC) is the fourth most common cancer type among women worldwide, accounting for an estimated 529,572 newly diagnosed cases and 274,967 deaths each year.[1] CC is the third leading cause of death from women neoplasia, with rising morbidity rates in recent years.[2] Combination treatment options for cervical cancer are currently available, which involve surgery and chemoradiotherapy, but in approximately half the cases, the disease continues to persist or recurs.[3] Although several potential contributory factors in CC development have been
identified, mainly intrinsic (genetic) and extrinsic factors belonging to the human papillomavirus (HPV) genetic factor family show potential as susceptibility or prognostic markers. Genetic polymorphisms play critical roles in cervical carcinogenesis. Associations have been established between multiple genetic variants, including immune-related and DNA repair genes, and risk of cervical cancer.

Deficiencies of the DNA repair system are implicated in cancer development. In humans, ~150 DNA repair genes involved in several pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair, and double-strand break repair, have been identified. Among these enzymes, those involved in the BER pathway are associated with cancer risk.

Uracil N-glycosylase (UNG) is a member of the uracil DNA glycosylase family of enzymes, which initiate BER of uracil resulting from deamination of cytosine or misincorporation of uracil or other thymidine analogs during DNA replication. UNG is located in the chromosome 12q24.11 region. Escherichia coli uracil glycosylase, which removes deaminated cytosines and misincorporated uracils from DNA, was the first BER enzyme discovered by Tomas Lindahl about 40 years ago. Increased incidence of B cell lymphoma in UNG-deficient mice has additionally been reported.

Researchers have documented significant correlations between single nucleotide polymorphisms (SNP) of UNG and susceptibility to rheumatoid arthritis (RA), glioblastoma, and esophageal cancer. However, no studies have focused on the potential association between cervical carcinoma and UNG SNPs to date. Here, we examined the relationship between UNG rs3219218 and UNG rs246079 genotypes and risk of cervical squamous cell carcinoma (CSCC) in a case-control study involving 400 CSCCs, 400 precursor lesions CIN III, and 1200 normal controls from a Chinese population.

2. Materials and methods

2.1. Participants

In total, 400 CSCCs, 400 CIN III, and 1200 normal controls were recruited from Zhejiang Province, China. Diagnoses were performed by 2 pathologists. Normal controls were recruited from healthy women volunteers subjected to gynecologic examinations from June 2004 to December 2008. Selection criteria for healthy controls included no positive cytological examinations from June 2004 to December 2008. Overall, 201 patients with CIN III, and 609 normal controls agreed to provide cervical brush-off samples for the HR-HPV test. This study was approved by the Medical Ethical Committee of Women’s Hospital, School of Medicine, Zhejiang University (No. 2004002). All patients signed informed consent forms to permit molecular research on the samples obtained.

2.2. DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood using a specific DNA extraction kit according to the manufacturer’s protocol (Sangon Bioengineering Co., Shanghai, China). All DNA samples were dissolved in water and stored at −20°C.

SNPs of UNG were determined via modified polymerase chain reaction-mismatch amplification (MA-PCR) as described previously. The forward primer sequences for UNG rs3219218 (A/G) were 5’-ATCTGTGAAATGACATAGT-3’ for the A allele and 5’-ATCTGTGAAATGACATAGTG-3’ for the G allele, which differed only in the last base. The same reverse primer was used (5’-GTTCCTGATCCTTCGAGCC-3’). The length of the amplified product was 351bp (UNG gene DNA Reference Sequence: NG_007284.1).

PCR was performed in a 25 µL reaction volume containing 50 ng genomic DNA, 5.0 pmol each primer, 0.2 mM each deoxynucleoside triphosphate and 1.0 unit Taq DNA polymerase (TAKARA, Dalian, China). Amplification reactions were conducted under the following conditions: initial denaturation at 94°C for 5 minutes, followed by 40 cycles of 94°C for 30 seconds, 57°C for 40 seconds, and 72°C for 40 seconds, and a final elongation step of 72°C for 8 minutes. Amplified products were examined via 1.5% agarose gel electrophoresis, stained with ethidium bromide, and visualized with a Typhoon™ 9410 Imaging System (GE Healthcare, Pennsylvania, USA). To determine the reproducibility of the results, all samples were examined twice by 2 technicians and the results agreed for all masked duplicate sets. Data reproducibility was 100%.

2.3. HR-HPV detection

HR-HPV infection was identified using the Hybrid Capture II (HC II) assay (Digene Diagnostics Inc., Gaithersburg, MD) using probe B, which includes a pool of RNA probes for HR-HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Cervical sampling for HR-HPV DNA was performed with the Digene Cervical Sampler.

2.4. Statistical analysis

Stratified analyses of lifestyle habits and genotype frequencies were conducted with the Kruskal-Wallis H test. For examination of associations between genotypes and risk of cervical carcinoma, odds ratio (OR), 95% confidence intervals (CI), and P-values were obtained via binary logistic regression analysis. The control set was set as the reference group. All reported values are two-tailed. The level of significance was set at P ≤ 0.05. All analyses were performed using SPSS version 18.0 (IBM, Amund City, New York) for Windows.

3. Results

3.1. Clinical features of cases and controls

In the control, CIN III and carcinoma groups, 602/598, 258/142, and 160/240 individuals were ≤40/>40 years of age, respectively, as shown in Table 1. The carcinoma group contained a significantly higher number of patients >40 years of age (P < 0.01) while the CIN III group contained more individuals ≤40 years (P < .001), compared with the control group. Moreover, relative to the control group, a higher proportion of patients in the CIN III and carcinoma groups had >3 sexual partners. The HR-HPV infection rate was 88.6% in carcinoma and 86.8% in CIN III groups but only 31.4% in the control group, clearly signifying higher infection rates in both patient groups (P < .001). Data presented in Table 1 are quoted from our self-previous publication.
Table 1
Frequency distribution of select features by case control status.

| Variable                      | Control N=1200 | CIN III N=400 | CSCC N=400 |
|-------------------------------|---------------|--------------|------------|
|                               | N (%)         | N (%)        | χ²          | P           | N (%) | χ²          | P           |
| Age at the first intercourse  |               |              |            |            |       |            |            |
| ≤20 years                     | 359 (29.9)    | 130 (32.5)   | 0.943      | 0.331      | 125 (31.3) | 0.253      | 0.615 |
| >20 years                     | 841 (70.1)    | 270 (67.5)   | 275 (68.8) | 0.799      |        |            |            |
| Number of sexual partners     |               |              |            |            |       |            |            |
| ≤1                            | 963 (80.3)    | 316 (79.0)   | 0.797      | 0.376      | 309 (77.3) | 1.657      | 0.198 |
| >1                            | 237 (19.8)    | 84 (21.0)    | 91 (22.8)  | 1.000      |        |            |            |
| Number of parities           | ≤3            | 548 (45.7)   | 158 (39.5) | 4.627      | 0.031  | 131 (32.8) | 20.49      | <.001 |
| >3                            | 652 (54.3)    | 242 (60.5)   | 269 (67.3) | 1.000      |        |            |            |
| Age at the first birth        | ≤22 years     | 235 (19.6)   | 91 (22.8)  | 1.854      | 0.173  | 89 (22.3)  | 1.321      | <.001 |
| >22 years                     | 965 (80.4)    | 309 (77.3)   | 311 (77.8) | 1.000      |        |            |            |
| Smoking status                |               |              |            |            |       |            |            |
| Smoker                        | 4 (0.3)       | 2 (0.5)      | 0.223      | 0.637      | 2 (0.5) | 0.223      | 0.637 |
| Nonsmoker                     | 1196 (99.7)   | 398 (99.5)   | 398 (99.5) | 1.000      |        |            |            |
| HR-HPV infection              | Positive      | 191 (31.4)   | 510 (86.8) | 277.107    | <.001  | 178 (88.6) | 199.315    | <.001 |
| Negative                      | 418 (68.6)    | 47 (13.2)    | 23 (11.4)  | 1.000      |        |            |            |
| Total                         | 609           | 357          | 201        |            |        |            |            |

Bold values show statistical data with significant difference.

2 Two-sided χ² test.

3 Parities including full-term pregnancy and abortion at or after 26 weeks.

3.2. Correlation analysis of UNG rs3219218 (A/G) and UNG rs246079 (A/G/T) with risk of CSCC
The genotypic and allelic frequencies of UNG rs3219218 (A/G) and UNG rs246079 (A/G/T) are depicted in Table 2. Genotype distributions were in Hardy-Weinberg equilibrium. The AA, AG, and GG frequencies of UNG rs3219218 (A/G) were 51.9%, 41.8%, and 6.3% in the control, 54.2%, 38.3%, and 7.5% in the CIN III, 55.8%, 35.7%, and 8.5% in the CSCC groups, respectively, suggesting no significant association of UNG rs3219218 (A/G) polymorphisms with risk of CINIII or CSCC.

The AA, AG, and GG frequencies of UNG rs246079 (A/G/T) were determined as 32.6%, 52.1%, and 15.3% in control, 26.5%, 53.7%, and 19.8% in CIN III, and 23.8%, 53.0%, and 23.2% in CSCC groups, respectively. Our data suggest that women bearing the homozygous GG genotype of UNG rs246079 have significantly increased risk of CIN III (OR = 1.58, CI = 1.13–2.23, P = .008) and CSCC (OR = 2.08, CI = 1.49–2.91, P = .000).

The incidence of the G allele at UNG rs246079 (A/G/T) was significantly higher in CIN III (373/800, 46.6%) and CSCC (398/800, 49.7%) groups, compared with the normal control (993/2400, 41.4%). The increased risk of G allele occurrence in CIN III and CSCC was estimated at 1.24 (1.05–1.45) and 1.40 (1.20–1.65), respectively. Moreover, individuals with G allele or G carrier (GG+AG) genotype at UNG rs246079 (A/G/T) were at higher risk of CIN III (OR = 1.34, CI = 1.04–1.73, P = .023) and CSCC (OR = 1.55, CI = 1.20–2.01, P = .001).

As shown in Table 3, in the HR-HPV positive group, homozygous GG of the UNG rs246079 (A/G/T) genotype was

Table 2
Association between UNG rs3219218 and UNG rs246079 variants and the risk of CIN and cervical carcinoma.

| Genotypes       | Control N=1200 | CIN III N=400 | adjusted OR* (95% CI) | P     | CSCC N=400 | adjusted OR* (95% CI) | P     |
|-----------------|---------------|--------------|-----------------------|-------|------------|-----------------------|-------|
| UNG rs3219218   |               |              |                       |       |            |                       |       |
| AA              | 623 (51.9)    | 217 (54.2)   | 1.00 (ref)            |       | 223 (55.8) | 1.00 (ref)            |       |
| AG              | 502 (41.8)    | 153 (38.3)   | 0.88 (0.69–1.11)      | 0.271 | 143 (35.7) | 0.80 (0.63–1.01)      | 0.063 |
| GG              | 75 (6.3)      | 30 (7.5)     | 1.15 (0.73–1.80)      | 0.547 | 34 (8.5)   | 1.27 (0.82–1.95)      | 0.285 |
| Allele frequency|               |              |                       |       |            |                       |       |
| Allele A        | 1748 (72.8)   | 587 (73.4)   | 1.00 (ref)            |       | 589 (73.6) | 1.00 (ref)            |       |
| Allele G        | 652 (27.2)    | 213 (26.6)   | 0.97 (0.81–1.17)      | 0.765 | 211 (26.4) | 0.96 (0.80–1.15)      | 0.662 |
| UNG rs246079    |               |              |                       |       |            |                       |       |
| AA              | 391 (32.6)    | 106 (26.5)   | 1.00 (ref)            |       | 95 (23.8)  | 1.00 (ref)            |       |
| AG              | 625 (52.1)    | 215 (53.7)   | 1.27 (0.97–1.65)      | 0.782 | 212 (53.0) | 1.40 (1.06–1.83)      | 0.017 |
| GG              | 184 (15.3)    | 79 (19.8)    | 1.58 (1.13–2.23)      | 0.008 | 93 (23.2)  | 2.08 (1.49–2.91)      | 0.000 |
| Allele frequency|               |              |                       |       |            |                       |       |
| Allele A        | 1407 (58.6)   | 427 (53.4)   | 1.00 (ref)            |       | 402 (50.3) | 1.00 (ref)            |       |
| Allele G        | 993 (41.4)    | 373 (46.6)   | 1.24 (1.05–1.45)      | 0.009 | 398 (49.7) | 1.40 (1.20–1.65)      | 0.000 |

Bold values show statistical data with significant difference.

* All P-values are adjusted for age, number of sexual partners, age at first intercourse, parities (including full-term pregnancy and abortion at or after 28 weeks) and age at first full-term pregnancy.
Allelic frequency

**Age at the first intercourse, number of parities, and age at first parity**

In terms of HR-HPV infection, the UNG rs246079 (A/G/T) polymorphism in the HR-HPV positive group was not significantly enriched relative to the HR-HPV negative group of CIN III ($\chi^2 = 0.194, P = .660$) or CSCC ($\chi^2 = 0.329, P = .566$).

### 4. Discussion

The BER pathway repairs the majority of endogenous DNA damage, including deamination, depurination, alkylation, and a plethora of oxidative damage (~30,000 per human cell per day)[19] and is highly conserved in a range of species, from bacteria to humans.[20–22] DNA damage plays a critical role in tumor development. Several DNA-damaging agents have been shown to cause genome instability, which would be an overwhelming problem for cells and organisms in the absence of an effective repair system.[23] Reactive oxygen species (ROS) consistently associated with markedly increased risk of CSCC (OR = 2.37, CI = 1.29–4.35, $P = .005$) and CIN III (OR = 1.81, CI = 1.07–3.15, $P = .027$). Meanwhile, the G allele proportion was significantly increased in both CIN III (305/620, 49.2%, $P = .036$) and CSCC (186/356, 52.5%, $P = .100$, CI = 1.12–2.01, $P = .006$) groups, compared with the control (161/382, 42.1%) group. G allele or G carrier (GG + AG) genotype at rs246079 was determined as a high risk factor in CSCC (OR = 1.67, CI = 1.05–2.67, $P = .031$). In the CIN III group, the OR value was increased but not to a statistically significant extent (OR = 1.45, CI = 0.97–2.15, $P = .071$).

### 3.3. UNG rs246079 (A/G/T) polymorphisms in relation to sexual or reproductive history of CSCC and CIN III patients

As shown in Table 4, participants were classified into 2 groups according to sexual/reproductive history (age, number of sexual partners, age of first sexual intercourse, number of parities, and age at first parity), and stratified analysis conducted in relation to the UNG rs246079 (A/G/T) genotype. We did not detect a particularly high level of enrichment among the groups, except the number of sexual partners in both CIN III ($\chi^2 = 4.397, P = .036$) and CSCC groups ($\chi^2 = 10.278, P = .001$).

**Table 3**: Association between UNG rs246079 variants and the risk of HPV-positive cervical carcinoma and CIN.

| UNG rs246079 | Control N = 191 | CIN III N = 310 | Adjusted OR* (95% CI) | P | CSCC N = 178 | Adjusted OR* (95% CI) | P |
|--------------|-----------------|-----------------|-----------------------|---|--------------|-----------------------|---|
| AA           |                 |                 |                       |   |              |                       |   |
| AG           |                 |                 |                       |   |              |                       |   |
| GG           |                 |                 |                       |   |              |                       |   |
| **Allelic frequency** |                 |                 |                       |   |              |                       |   |
| **Allele A**  |                 |                 |                       |   |              |                       |   |
| **Allele G**  |                 |                 |                       |   |              |                       |   |

**Bold values show statistical data with significant difference.**

*All P-values are adjusted for age, number of sexual partners, age at first intercourse, parities (including full-term pregnancy and abortion at or after 28 weeks) and age at first full-term pregnancy.

**Table 4**: Association between UNG rs246079 variants and the risk for CIN and cervical carcinoma stratified by various environmental factors.

| High risk exposure | Controls | CIN | Carcinoma |
|--------------------|----------|-----|-----------|
|                    | AA N (%) | AG N (%) | GG N (%) | $\chi^2$ | P | AA N (%) | AG N (%) | GG N (%) | $\chi^2$ | P | AA N (%) | AG N (%) | GG N (%) | $\chi^2$ | P |
| Age ≤40            | 197 (32.7) | 314 (52.2) | 91 (15.1) | 0.031 | .860 | 73 (28.3) | 138 (53.5) | 47 (18.2) | 1.751 | .186 | 36 (22.5) | 84 (52.6) | 40 (25.0) | 0.509 | .476 |
| >40                | 194 (32.4) | 311 (52.0) | 93 (15.6) | 33 (23.2) | 77 (54.2) | 32 (22.6) | 59 (24.6) | 128 (53.3) | 53 (22.1) | .056 | .476 |
| Number of sexual partners ≤1 | 304 (31.8) | 507 (52.6) | 152 (15.8) | 2.411 | .120 | 89 (28.2) | 171 (54.1) | 56 (17.7) | 4.397 | .036 | 82 (26.5) | 165 (53.4) | 62 (20.1) | 10.278 | .001 |
| >1                 | 87 (36.7) | 118 (49.8) | 32 (13.5) | 17 (20.2) | 44 (52.4) | 23 (27.4) | 13 (14.3) | 47 (51.6) | 31 (34.1) | .711 | .399 |
| Age at the first intercourse ≤20 | 120 (33.4) | 183 (51.9) | 56 (15.6) | 0.053 | .817 | 36 (27.7) | 71 (54.6) | 23 (17.7) | 0.429 | .512 | 31 (24.8) | 69 (55.2) | 25 (20.0) | 0.711 | .399 |
| >20                | 272 (32.0) | 442 (52.6) | 128 (15.4) | 70 (23.9) | 144 (53.3) | 56 (20.8) | 64 (23.3) | 143 (52.0) | 66 (24.7) | .056 | .476 |
| Number of parities ≤3 | 173 (31.6) | 288 (52.6) | 87 (15.8) | 0.552 | .457 | 44 (27.8) | 82 (51.9) | 23 (20.3) | 0.048 | .826 | 26 (28.4) | 73 (55.7) | 30 (22.9) | 0.171 | .679 |
| >3                 | 218 (33.4) | 337 (51.7) | 97 (14.9) | 62 (25.6) | 133 (55.0) | 17 (49.4) | 67 (24.9) | 139 (51.7) | 63 (23.4) | .342 | .068 |
| Age at the first parity ≤22 | 80 (43.0) | 121 (61.5) | 34 (15.4) | 0.353 | .552 | 22 (24.2) | 46 (50.5) | 23 (25.3) | 1.513 | .219 | 17 (17.9) | 45 (50.6) | 27 (30.3) | 3.342 | .068 |
| >22                | 311 (22.2) | 504 (52.2) | 150 (15.6) | 84 (27.2) | 169 (64.7) | 16 (16.1) | 76 (25.1) | 167 (53.7) | 66 (21.2) | .056 | .476 |
| HR-HPV infection status Positive | 61 (31.9) | 99 (51.8) | 31 (16.3) | 0.002 | .967 | 76 (24.5) | 163 (52.6) | 71 (22.9) | 0.194 | .660 | 39 (21.9) | 92 (51.7) | 47 (26.4) | 0.329 | .566 |
| Negative           | 137 (32.8) | 210 (50.2) | 71 (17.0) | 12 (25.5) | 26 (55.3) | 9 (19.2) | 6 (26.1) | 12 (52.2) | 5 (21.7) | .056 | .476 |

**Bold values show statistical data with significant difference.**

Stratified analyses were applied by the Kruskal-Wallis H-Test. A P-value < .05 was considered significant.
trigger considerable DNA damage and miscoding by DNA polymerase.[24] BER functions to remove DNA damaged by various carcinogens, such as ionizing radiation or ROS.[25] This system has additionally evolved to cope with mutagenic and cytotoxic hydrolytic, oxidative, and alkylidylation damage. BER is proposed to be associated with cancer progression, in view of the mutations and altered expression patterns of BER genes during carcinogenesis.[26]

Earlier, Zhang et al.[33] conducted a meta-analysis on genetic polymorphisms of cervical cancer that involved screening of a total of 5605 publications. The group reported that 14 genetic variants of 11 genes increased the risk of cervical cancer while 5 variants of 3 genes decreased the risk. These related genes mainly included immune-related and DNA repair genes, such as HLA DQB and XRCC3. Our findings indicate that polymorphisms of immune-related and DNA repair genes play important roles in susceptibility to cervical cancer. Consistently, previous studies by our group revealed significant associations between genetic polymorphisms in DNA repair genes, such as PARP-1 Val762Ala, MLH3 Pro844Leu, and Thr942Ile, and susceptibility to cervical cancer.[17,18]

The first mammalian DNA glycosylase gene identified, human UNG, was shown to be closely related to the ung gene of E. coli.[27,28] In humans, UNG encodes a nuclear version of uracil glycosylase, UNG2, whose primary role is to remove misincorporated uracils, and a mitochondrial version, UNG1.[29–31] This alternative spliceosome is generated using different promoters and alternative splicing, resulting in different N-terminal sequences but identical catalytic domains.[29,32] Both UNG1 and UNG2 are highly selective for uracil in DNA and have a moderate to weak preference for uracil in single-stranded DNA over U:G mismatches and U:A pairs, with turnover rates in the order of 1000 per min.[33] Cao et al.[34] examined the activity and function of UNG, and SMUG1 play a role in colorectal cancer susceptibility. Lo et al.[14] determined the effects of UNG SNPs (rs3219218 and rs246079) on rheumatoid arthritis (RA) in 183 patients and 192 controls. The group showed significant variations in genotype frequency distributions at rs246079 SNP between RA patients and controls. The G allele at rs246079 SNP was identified as a high-risk factor in RA development (OR = 1.77). Yin et al.[15] additionally studied the potential association of UNG rs3219218 (A/G) and UNG rs246079 (A/G/T) genotypes with esophageal cancer in a total of 380 esophageal squamous cell carcinoma (ESCC) cases and 380 controls. Using the UNG rs246079 GG homozygote genotype as the reference group, the GA genotype was associated with significantly decreased risk of ESCC (OR = 0.67) and the UNG rs246079 (A/G/T) polymorphism was correlated with ESCC risk among women, younger patients, non-smokers, and non-drinkers, but not the UNG rs3219218 (A/G) polymorphism. The documented literature suggests that UNG rs3219218 (A/G) SNP participates in the progression of a number of immune diseases and solid tumors.

The development of cervical carcinoma involves reversible changes in cervical tissue leading to various cellular abnormalities. Several well-defined stages of cervical neoplasia are described, including precursor lesion cervical intraepithelial neoplasia (CIN) and carcinoma.[17] In the present study, the homozgyous GG genotype of UNG rs246079 (A/G/T) was associated with significantly increased risk of CSCC (OR = 2.08, CI = 1.49–2.91, P = .000). We additionally observed a similar association between the UNG rs246079 (G/G) genotype and increased risk of CIN III (OR = 1.58, CI = 1.13–2.23, P = .008), supporting the involvement of this polymorphism in the early molecular events of carcinogenesis. Moreover, individuals with G allele or G carrier (GG + AG) genotype of UNG rs246079 (A/G/T) locus were at higher risk of CIN III and CSCC. Within the HR-HPV-positive group, homozygous GG of the UNG rs246079 (A/G/T) genotype was linked to significantly increased risk of CSCC and CIN III. In contrast, we observed no association between the UNG rs3219218 (A/G) polymorphism and CIN III or CSCC risk.

We analyzed enrichment of the rs246079 (A/G/T) genotype grouped by clinical features (number of sexual partners, age of first sexual intercourse, number of parities, and age at first parity). High level of enrichment between these groups was not evident, except the number of sexual partners in the CIN III (χ² = 4.397, P = .036) and CSCC (χ² = 10.278, P = .001) groups. Numerous studies have reported that HR-HPV participates in the development and progression of cervical carcinoma.[35] However, we did not observe significant differences in risk of disease between genotypes of UNG rs246079 (A/G/T) within the HR-HPV positive group. Based on these findings, we propose that the UNG rs246079 (A/G/T) SNP plays a role in initiation and development of cervical carcinoma or precancerous lesions but does not contribute to susceptibility to HR-HPV.

To our knowledge, the present study is the first to uncover associations between UNG rs246079 (A/G/T) and cervical carcinoma or CIN III. In general, SNP loci that affect the functions of genes are located in the promoter, coding or 3′ UTR regions. However, UNG rs246079 (A/G/T) is located in the intron. Although the precise function of UNG rs246079 (A/G/T) has not been elucidated in this study, one possibility is that it is in linkage disequilibrium with other functional variants and serves as a genetic marker of susceptibility. Another theory is that this SNP at rs246079 influences splicing and regulation, affecting UNG protein expression.[14]

Our study has a number of limitations that need to be addressed. The OR values were not particularly high (maximum of only 2.08), which may reflect the small sample size. Further investigations should therefore be performed on expanded sample sets. In addition, since cervical cancer is a multi-gene and multi-locus genetic disease, more loci need to be detected for linkage analysis to further confirm our conclusions. Moreover, is located within an intron region, which is weak in functional changes of the gene. Further comprehensive studies on important functional regions of the gene are warranted.

In summary, the current study has yielded novel information on UNG rs246079 (A/G/T) polymorphisms associated with cervical carcinoma and CIN III development that may be effectively utilized as molecular biomarkers. Future research will focus on their biological functions in carcinogenesis of cervical carcinoma.
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