Effect of GSDMB polymorphism on sensitivity to chemoradiation therapy for cervical cancer

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Background: To investigate the effects of GSDMB polymorphism on sensitivity to chemoradiation. *Methods*: 108 cervical cancer patients were selected and treated with a combination of radiotherapy and chemotherapy. After 2 cycles, patients were grouped into sensitive group and non-sensitive group based on the chemoradiation therapy outcomes. GSDMB polymorphism was assessed by high-resolution melting (HRM) analysis, and the GSDMB gene expression was detected using RT-qPCR. *Results*: Our results indicate that the allele and genotype distribution of GSDMB in patients from sensitivity group were significantly different as compared to non-sensitive group. Experimental analysis showed a close correlation between GSDMB polymorphism and sensitivity to chemoradiation therapy for cervical cancer. Moreover, ATT, GCC, GCT and GTC halotype of GSDMB gene was significantly different among sensitive and non-sensitive groups ($p < 0.05$). Finally we found that GSDMB polymorphism was associated with GSDMB gene expression ($p < 0.05$). *Conclusions*: Our study concluded that GSDMB polymorphism has a distinct impact on sensitivity to chemoradiation therapy for cervical cancer. Collectively, this analysis provides new insights into the genetic causes of cervical cancer, and influences the overall prevention and treatment of cervical cancer.

Keywords

Gene polymorphism; GSDMB; Cervical cancer; Sensitivity to chemoradiation therapy

1. Introduction

Cervical cancer is regarded as the most common gynecologic cancer in developing countries which ranks third among all cancer types [1–3]. Recent studies demonstrated that treatment of cervical epithelial atypical hyperplasia, a precancerous of cervical cancer, displays 1% and 0.5% decrease in the incidence and mortality, respectively [4]. The rise in the occurrence of cervical cancer in developing countries is associated with sexual behavior, such as multiple partners, multiple pregnancy with *Chlamydia psittaci* infection, and HIV-associated immunosuppression, which could increase the risk of HPV infection, therefore promote the occurrence of cervical cancer [5, 6]. The main therapy to treat cervical cancer is surgical operation and radiotherapy combined with chemotherapy [7–9]. The efficacy of chemoradiation therapy determines their prognosis and survival time among the patients who cannot receive radical operation [10, 11]. It has been established that the sensitivity to chemoradiation therapy for cervical cancer is associated with numerous factors, including immune state, neoplasm staging and genovariation [12, 13]. Among these, gene polymorphism has a close relationship with the efficacy of chemoradiation therapy for cervical cancer [14, 15]. However, the relationship between GSDMB polymorphism and sensitivity to chemoradiation therapy for cervical cancer has been unclarified yet. Therefore, we designed this study to investigate the effect of GSDMB polymorphism on sensitivity to chemoradiation therapy for cervical cancer. Briefly, this study analyzed the GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism combined with haplotype analysis and linkage disequilibrium analysis, and GSDMB gene expression analysis in patients with cervical cancer who are sensitive or non-sensitive to chemoradiation therapy.

2. Object and method

2.1 Participants

108 patients with cervical cancer registered in Chenzhou First People's Hospital (Chenzhou, China) from January 2019 till now were selected as participants. All of them were confirmed for cervical cancer, and the stage and grade of differentiation was assessed by an experienced histopathologist based on the International Federation of Gynecology and Obstetrics classification system and the World Health Organization. The possibility of other serious cancerous diseases, such as primary hepatic carcinoma and lung cancer, was ruled out. All patients had no previous history of any chemoradiation therapy, while they were also unsuitable for radical surgery. Based on the outcomes of radiotherapy and chemotherapy, patients were grouped into sensitive group (62 cases) and non-sensitive group (46 cases). The median age was 58.32 ± 3.84 and 57.27 ± 4.22 years old of sensitive group and non-sensitive group respectively. There is no significant difference in general information between patients from sensitive and non-sensitive group.

2.2 Chemoradiotherapy regimen

Radiation regimen: All participants were irradiate using a linear accelerator (Primus, Siemens Corporation, Beijing, China). Firstly, whole pelvic radiotherapy was given (36 Gy, four times per week), and then four weeks irradiation was performed (56 Gy, 30 times), and eventually brachytherapy was given (90 Gy). Chemotherapeutic regimen: Cisplatin was given at a dose of 30 mg/m^2 after the beginning of radiotherapy. Important indicators such as blood routine indexes were closely monitored.

2.3 Assessment of therapeutic efficacy

The therapeutic efficacy of chemoradiation therapy which is classified into complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD), was evaluated after 2 cycles of treatment according to RECIST1.1. Patients were grouped into sensitive group and non-sensitive group based on the therapeutic effect of chemoradiation therapy, i.e., CR and PR were grouped into sensitive group, while SD and PD were grouped into non-sensitive group.

2.4 Sample collection and DNA extraction

4–5 mL of peripheral blood was collected in tubes containing EDTA anticoagulant from all participants before chemoradiation therapy. Genomic DNA from whole blood was extracted by using DNA extraction kit (Tiangen, Nobleride Corporation, Beijing, China) following the manufacturer's protocol. Quality and quantity of extracted DNA was determined by using a spectrophotometer (Spectrum Instrument Co., Ltd., Shanghai, China).

2.5 Detection of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism

High-resolution melting (HRM) analysis was used to analyze GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism. PCR reactions were carried out in 10 μL volumes using 5 μL of Mix, 0.5 μL of primer and 2 μL of genomic DNA. The application conditions were 95 $^\circ$C for 1 min, followed by 45 $^\circ$C for 70 s and 55 $^\circ$C for 1 min. Then the melting curve was visualized as the temperature elevated gradually. Primers used in this study were designed using Primer 3, and synthesized and validated by Sangon Biotech (Shanghai, China). The amplification primers used for each polymorphic region of GSDMB gene are listed in Table 1.

2.6 Detection of GSDMB gene expression

RNA from peripheral blood cells was extracted by using Trizol, cDNA was synthesized via reverse transcription of total RNA, and the gene expression was detected by qPCR. GAPDH was used as housekeeping gene. Primer sequences used for RT-qPCR analysis are shown in Table 1.

2.7 Statistical analysis

SHEsis online program (http://analysis.bio-x.cn/) was used for polymorphism, haplotype and linkage disequilibrium analysis. The distinction in genotypic prevalence between the patients and controls, and their genotype deviation

Table 1. PCR primer sequences.

	Primer	Sequence
rs8067378	Sense	TGTGAGTGGAAAGCTTGACAG
	Anti-sense	AGCTTGCTACAGTGAGACCC
rs7216389	Sense	AGTTCTGTCGCTGTTGTTTGT
	Anti-sense	ACACATCCTCCACGAACCTG
rs11650680	Sense	CTTCCTTCCCTGCTAGTCCC
	Anti-sense	TCAAAAGACTTGAGGAGGTTCA
GSDMB	Sense	TGATTGCCGTTAGAAGCCTTG
	Anti-sense	TCCCGTTGAGTCTACATTATCCA
GAPDH	Sense	AGGTCGGTGTGAACGGATTTG
	Anti-sense	GGGGTCGTTGATGGCAACA

using the Hardy–Weinberg equilibrium was evaluated using a χ^2 test. The Cochran–Armitage p trend test (p trend) was used to test the correlations. The χ^2 and Fisher exact tests were used to determine the differences in genotypic distributions between different groups. The odds ratio (OR) and 95% confidence intervals (CIs) were also calculated. A logistic regression analysis was used to adjust the effect of confounders such as age, gender, pathological classification and tumor size. A bilateral p-value of <0.05 was considered statistically significant. Statistical analysis was evaluated by Dunnett's posthoc test. SPSS 22.0 (IBM, Guangzhou, China) was used for data analysis.

3. Results

3.1 Analysis on therapeutic efficacy of chemoradiation therapy

The ratio of CR, PR, SD and PD patients among all 108 patients with cervical cancer after chemoradiation therapy was 24% (26/108), 33.3% (36/108), 29.6% (32/108) and 12.9% (14/108) respectively, which showed an effective rate of 57.3%. Sensitive group comprising of CR and PR patients, which were sensitive to chemoradiation therapy, accounted for 54.7% (62/108). While SD and PD patients accounted for 42.6% (46/108), belong to non-sensitive group as they were not sensitive to chemoradiation therapy.

3.2 Analysis on general information of patients in sensitive and non-sensitive group

No significant difference was observed among the age (p = 0.236), pathology results (p = 0.168), stage distribution (p = 0.078), and histological grade (p = 0.069). However, the tumor size (p = 0.011) and CEA (p = 0.000) level showed a statistically significant difference between sensitive and non-sensitive group. This suggested that tumor size and CEA level contribute to the sensitivity of patients to chemoradiation therapy rather than age, pathology results, stage and histological grades (Table 2).

3.3 Correlation between general information and sensitivity to chemoradiation therapy of patients with cervical cancer

There was no significant association between age (p = 0.439), pathology results (p = 0.573), stage (p = 0.736) and sensitivity to chemoradiation therapy. However, tumor size (r = 0.263, p = 0.005) and CEA level (r = –0.548, p = 0.000)

Table 2. General information of patients in sensitive and non-sensitive group.

Parameters	Cases	Sensitive group	Non-sensitive group	p
Age (years)				0.236
<50	50	26	24	
≥50	58	36	22	
Pathology results				0.168
Squamous carcinoma	90	51	49	
Adenocarcinoma	18	11	7	
Tumor size (cm)				0.011
<4	70	52	18	
≥4	38	10	28	
CEA (ng/mL)				0.000
<5	66	50	16	
≥5	42	12	30	
Tumor stage				0.078
Stage IA	5	3	2	
Stage IB	7	4	3	
Stage IIA	30	13	17	
Stage IIB	31	26	5	
Stage IIIA	30	15	15	
Stage IIIB	5	1	4	
Stage IV	0	0	0	
Histological grade				0.069
G1	47	25	22	
G2	35	26	9	
G3	21	10	11	
G_X	5	1	4	

showed statistically significant association with chemoradiation therapy (Table 3).

Table 3. Correlation between general material and sensitivity to chemoradiation of patients.

Parameter	r	p
Age	0.017	0.439
Pathology results	0.105	0.573
Tumor size	0.263	0.005
CEA	−0.548	0.000
Stage	0.021	0.736
Histological grade	0.015	0.532

3.4 The allele distribution of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T sites

The values for the χ^2 test for Hardy–Weinberg equilibrium were 0.317 and 0.169 for the patients of sensitive group and non-sensitive group, respectively. The allele distribution of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T sites in patients of sensitive group was significantly different from that of non-sensitive group. The frequency of "A" allele of site rs8067378 A>G ($p = 0.000$), and "C" allele of site rs7216389 C>T ($p = 0.000$) was higher in patients from sensitive group (Table 4).

3.5 Genotypic distribution of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T sites

The genotypic distribution of GSDMB rs8067378 A>G ($p = 0.000$), rs7216389 C>T ($p = 0.000$) and rs11650680 C>T ($p = 0.007$) in patients of sensitive group were significantly different from that of non-sensitive group. Our results showed that the frequency of AA in rs8067378 A>G, TT in rs7216389 C>T and CT in rs11650680 C>T were higher in sensitive group (Table 5).

3.6 Analysis on correlation between GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism and sensitivity to chemoradiation therapy

Our further investigation revealed that there was a dramatic correlation between GSDMB rs8067378 A>G (r = 0.437, $p = 0.000$), rs7216389 C>T (r = −0.274, $p = 0.003$) polymorphism and sensitivity of chemoradiation therapy among patients with cervical cancer (Table 6).

3.7 Generation of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism model

The distribution of rs8067378 A>G in sensitive group was significantly different to that of non-sensitive group in a recessive model (as shown in Table 7). Our results indicated that the frequency of AG + GG was lower by a recessive model. We further observed a statistically significant difference in the distribution of rs7216389 C>T between sensitive and non-sensitive group in a dominant model which had a lower frequency of CC + CT.

3.8 Analysis on haplotype of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T

Our data showed ATT, GCC, GCT and GTC of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T were in sensitive group were significantly different as compared to non-sensitive group (Fig. 1).
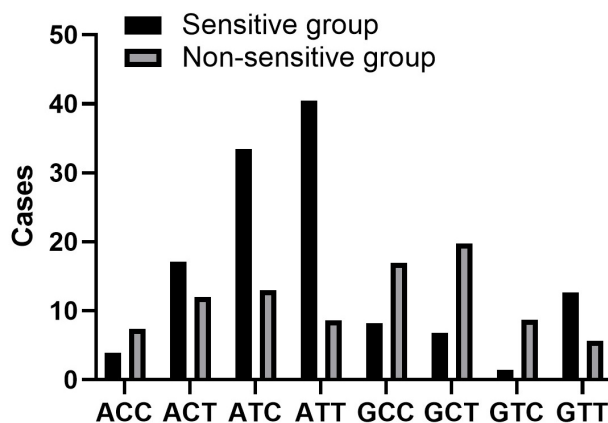

Fig. 1. Haplotype distribution of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T.

Table 4. Allele distribution of sensitive and non-sensitive group.

Site	Allele	Sensitive group	Non-sensitive group	OR value	95% CI	χ^2	p
rs8067378	A	95 (0.766)	41 (0.446)	4.07	2.27–7.31	23.26	0.000
	G	29 (0.234)	51 (0.554)				
rs7216389	C	36 (0.290)	56 (0.609)	0.26	0.14–0.46	21.89	0.000
	T	88 (0.710)	36 (0.391)				
rs11650680	C	47 (0.379)	46 (0.500)	0.61	0.35–1.05	3.15	0.075
	T	77 (0.621)	46 (0.500)				

Table 5. Genotype distribution of sensitive and non-sensitive group.

Site	Genotype	Sensitive group	Non-sensitive group	χ^2	p
rs8067378	AA	39 (0.629)	8 (0.174)	22.67	0.000
	AG	17 (0.274)	25 (0.543)		
	GG	6 (0.097)	13 (0.283)		
rs7216389	CC	8 (0.129)	17 (0.370)	19.15	0.000
	CT	20 (0.323)	22 (0.478)		
	TT	34 (0.548)	7 (0.152)		
rs11650680	CC	4 (0.065)	13 (0.283)	9.83	0.007
	CT	39 (0.629)	20 (0.435)		
	TT	19 (0.306)	13 (0.283)		
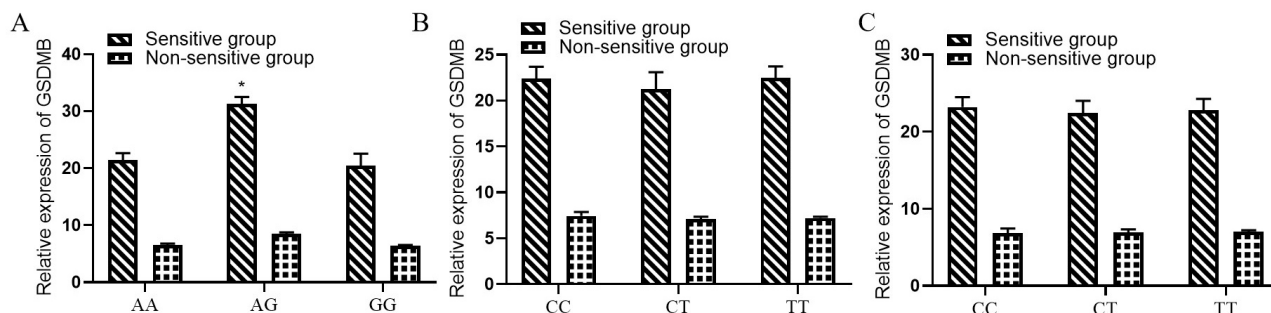
Fig. 2. Correlation between GSDMB rs8067378 A>G (A), rs7216389 C>T (B), rs11650680 C>T (C) polymorphism and gene expression (*compared with genotype of sensitive group, $p < 0.05$).

Table 6. Analysis on correlation between GSDMB polymorphism and sensitivity to chemoradiation therapy.

Polymorphism site	r	p
rs8067378 A>G	0.437	0.000
rs7216389 C>T	−0.274	0.003
rs11650680 C>T	0.178	0.064

3.9 Linkage disequilibrium analysis of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T

We further revealed that linkage disequilibrium was higher in GSDMB rs8067378 A>G and rs7216389 C>T (D' = 0.415, r^2 = 0.137) (Tables 8,9).

3.10 Relationship between GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism and gene expression

Finally, we found that GSDMB rs8067378 A>G polymorphism was correlated with GSDMB gene expression significantly ($p < 0.05$). Moreover, GSDMB gene expression level was remarkably increased in patients with AG genotype of sensitive group (Fig. 2).

4. Discussion

Cervical cancer is one of the most common malignant tumors in women. It has been estimated that the five-year survival rate of localized cervical cancer is 91.5%, while metastatic cervical cancer is 16.5% [16]. Cisplatin-based chemotherapy has long been the major treatment for intermediate and advanced cervical cancer. However, the survival rate shows no significant improvement as patients respond differently to chemotherapy. Adding of new therapeutical drugs, such as antiangiogenic agent, can greatly improve the outcome of curative capability [17]. However, the sensitivity of patients to chemoradiation varies because of tumor heterogeneity and individual difference, which directly impact the tumor prognosis and survival of patients [18, 19]. Therefore, identifying factors which are associated with the sensitivity to cervical cancer chemoradiation therapy could contribute to prolong the overall survival of patients. In this study, we analyzed a total 108 cases of cervical cancer after chemoradiation therapy. We discovered that 24% of total patients were CR, while the percentages of PR, SD and PD patients were

Table 7. Analysis on GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism model.

	Site	Genotype	Sensitive group	Non-sensitive group	χ^2	p
Dominant model						
	rs8067378	AA + AG	56 (0.903)	33 (0.717)	4.38	0.112
		GG	6 (0.097)	13 (0.283)		
	rs7216389	CC + CT	28 (0.452)	39 (0.848)	15.34	0.000
		TT	34 (0.548)	7 (0.152)		
	rs11650680	CC + CT	43 (0.694)	31 (0.717)	3.57	0.168
		TT	19 (0.306)	13 (0.283)		
Recessive model						
	rs8067378	AA	39 (0.629)	8 (0.174)	14.38	0.001
		AG + GG	23 (0.371)	38 (0.826)		
	rs7216389	CC	8 (0.129)	17 (0.370)	4.32	0.115
		CT + TT	54 (0.871)	29 (0.630)		
	rs11650680	CC	4 (0.065)	13 (0.283)	5.34	0.069
		CT + TT	58 (0.935)	33 (0.717)		
Hybrid model						
	rs8067378	AA	39 (0.629)	8 (0.174)	3.25	0.197
		AG	17 (0.274)	25 (0.543)		
	rs7216389	CC	8 (0.129)	17 (0.370)	4.28	0.118
		CT	20 (0.323)	22 (0.478)		
	rs11650680	CC	4 (0.065)	13 (0.283)	2.34	0.312
		CT	39 (0.629)	20 (0.435)		
Homozygous model						
	rs8067378	AA	39 (0.629)	8 (0.174)	3.85	0.146
		GG	6 (0.097)	13 (0.283)		
	rs7216389	CC	8 (0.129)	17 (0.370)	3.17	0.205
		TT	34 (0.548)	7 (0.152)		
	rs11650680	CC	4 (0.065)	13 (0.283)	2.84	0.242
		TT	19 (0.306)	13 (0.283)		

Table 8. Linkage disequilibrium analysis of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T (D').

D'	rs8067378	rs7216389	rs11650680
rs8067378	-	0.415	0.002
rs7216389	0.415	-	0.004
rs11650680	0.002	0.004	-

Table 9. Linkage disequilibrium analysis of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T (r^2).

r^2	rs8067378	rs7216389	rs11650680
rs8067378	-	0.137	0.001
rs7216389	0.137	-	0.001
rs11650680	0.001	0.001	-

33.3%, 29.6% and 12.9% respectively, with an effective ratio of 57.3%. Tumor size and CEA level were significantly different, meanwhile, age, pathology results, stage and histological grade distribution were not changed significantly between sensitive and non-sensitive group. Moreover, no significant correlation was found between age, pathology results, stage, histological grade, and sensitivity to chemoradiation therapy. Instead, tumor size and CEA were correlated

with chemoradiation sensitivity. These results suggested that tumor size and CEA level contribute to the sensitivity of patients to chemoradiation therapy rather than age, pathology results, stage and histological grades.

GSDMB belongs to the Gasdermin protein family, and these gene family members share conserved N- and C-terminal structural domain with a sequence homology of 45% [20, 21]. The Gasdermin protein family has five members in humans, which are termed as GSDMA, GSDMB, GSDMC, GSDMD and GSDME [22, 23]. GSDMB displays broader expression pattern as compared to other GSDM family members by showing higher tissue-specific expression in skin epithelium, gastrointestinal tract and immune cells [24, 25]. Genome-wide association study (GWAS) revealed a close relationship between GSDMB and susceptibility to inflammatory diseases such as Crohn's disease, asthma, and type I diabetes [26, 27]. A study on GSDMB transgenic mice indicated that GSDMB promotes the development of asthma, and increases airway responsiveness and remodeling [28, 29]. Besides, researchers have found that GSDMB was highly expressed not only in healthy tissues, but also in cancerous tissues from gastric cancer, metrocarcinoma, cervical cancer and breast cancer. GSDMB was located in amplicons which often amplified during the progression of cancer [30]. There-

fore, GSDMB might be involved in the occurrence, development and metastasis of cancer. However, the functions of GSDMB are still not studied well. Meanwhile, the effect of GSDMB on sensitivity to chemoradiation therapy in cervical cancer also remains undocumented. This study compared the GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism between sensitive group and non-sensitive group, and discovered the difference of allele distribution at GSDMB rs8067378 A>G ($p = 0.000$) and rs7216389 C>T ($p = 0.000$) sites. Moreover, we also found that the "A" allele frequency of rs8067378 A>G and the "C" allele frequency of rs7216389 C>T was higher in sensitive group. Genotype distribution of GSDMB rs8067378 A>G ($p = 0.000$), rs7216389 C>T ($p = 0.000$) and rs11650680 C>T ($p = 0.007$) in sensitive group was different from that of non-sensitive group. The frequency of AA in rs8067378 A>G, TT in rs7216389 C>T and CT in rs11650680 C>T was higher in sensitive group. There was significant correlation between GSDMB rs8067378 A>G (r = 0.437, $p = 0.000$), rs7216389 C>T (r = −0.274, $p = 0.003$) polymorphism and sensitivity to chemoradiation therapy in cervical cancer. In a recessive model, distribution of rs8067378 A>G was different between sensitive and non-sensitive group, with a lower frequency of AG + GG in sensitive group. A significant difference was observed in the distribution of rs7216389 C>T between sensitive and non-sensitive group in a dominant model, and sensitive group has a lower frequency of CC + CT. These results suggested a close relationship between GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism, and efficacy of chemoradiation therapy for cervical cancer. Overall, it was found that cervical cancer patients with specific genotype might be more sensitive to chemoradiation therapy. In clinics, sensitivity of patients to chemoradiation therapy can be assessed in advance by detecting GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism, so as to adjust regimen accordingly to enhance treatment efficacy.

By haplotype analysis and linkage disequilibrium analysis, we found that ATT ($p = 0.000$), GCC ($p = 0.008$), GCT ($p = 0.000$) and GTC ($p = 0.004$) of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T were different between sensitive and non-sensitive group. Linkage disequilibrium was higher in GSDMB rs8067378 A>G and rs7216389 C>T (D' = 0.415, $r^2 = 0.137$). These data indicate that GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T sites might influence the sensitivity to chemoradiation therapy in cervical cancer through haplotype. People with different haplotype in GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T might have different sensitivity to chemoradiation therapy.

We further concluded that GSDMB rs8067378 A>G polymorphism was associated with GSDMB gene expression ($p < 0.05$). Gene expression level of GSDMB was significantly increased in patients with AG genotype of sensitive group, suggesting that GSDMB polymorphism might affect GSDMB

expression, or the impact of GSDMB polymorphism on sensitivity to chemoradiation therapy for cervical cancer might be exerted through modulating gene expression, which needs further study.

The limitations of this study is that the sample size is not large enough to fully confirm the effect of GSDMB rs8067378 A>G, rs7216389 C>T and rs11650680 C>T polymorphism. Moreover, our study validated only one SNP, while other SNPs not included in this study which could also account for alternation of GSDMB expression. To achieve full gene coverage, a number of other tag SNP needed to be covered in further study. Therefore, our genetic study contains one Chinese cohort, and it should be replicated for rs8067378 and a number of other tag SNPs covering GSDMB in other independent ethnicities. However, our conclusion is defensible, and it supports further investigating to reveal the relationship between GSDMB gene and sensitivity to chemoradiation therapy for cervical cancer.

5. Conclusions

This analysis provides new insights into the genetic causes of cervical cancer and is of great significance for the prevention and treatment of cervical cancer.

Author contributions

NZ, YY and HL designed the research study. NZ performed the research. GHP, HC and QYT provided help and advice on the ELISA experiments. NZ, YY, HKL, QP, HZZ and YBZ analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Chenzhou First People's Hospital (Approval number: QZ6C11).

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Conflict of interest

The authors declare no conflict of interest.

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