

# FAS-670 gene polymorphism and cervical carcinogenesis risk: A meta-analysis

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Abstract. FAS is a cell surface receptor that plays an important role in the etiology of cancer. Previous studies on the association between FAS-670 polymorphism and cervical carcinogenesis failed to reach a consensus; therefore, this meta-analysis was conducted to estimate the association of FAS-670 polymorphism and the risk of cervical cancer. This meta-analysis included 10 studies on FAS-670 genotyping, including a total of 2,901 cases and 2,831 controls. The complete overdominant model was applied in our meta-analysis [AB vs. AA: odds ratio (OR)=0.879, 95% confidence interval (CI): 0.775-0.998, P=0.046; BB vs. AA: OR=0.903, 95% CI: 0.775-1.052, P=0.190]. The random effects OR was 1.13 (95% CI: 0.95-1.34,  $I^2$ =52.7%,  $P_{heterogeneity}$ =0.03). An ethnic subgroup analysis was subsequently performed. The OR for Asians was 1.25 (6 comparisons, 95% CI: 1.05-1.48, I<sup>2</sup>=23.5%, P<sub>heterogeneity</sub>=0.03), whereas for Caucasians, no significant association was observed between FAS-670 polymorphism and cervical carcinogenesis (4 comparisons, OR=0.96, 95% CI: 0.75-1.24, I<sup>2</sup>=45.9%, P<sub>heterogeneity</sub>=0.14).

## Introduction

Apoptosis is a physiological process that regulates normal homeostasis and alterations of the apoptosis-related genes are likely to contribute to the pathogenesis of malignant tumors (1-3) and autoimmune diseases (4). FAS is a type of cell surface apoptotic signal transmission receptor. When combined with its natural ligand CD95L to initiate the death signal cascade, the complex leads to apoptosis (5,6). The human FAS gene is one of members of the tumor necrosis factor receptor superfamily (7) and is located in chromo-

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some 10q24.1, involving 9 exons and 8 introns. Previous studies (8-10) reported that the downregulation of FAS may result in resistance to death signals in several types of cancer. Nunobiki *et al* (11) reported that the transcriptional expression of the FAS gene was regulated by a number of genetic elements located in the 5' upstream promoter region of the gene. In the promoter region, Huang *et al* (12) reported that the polymorphism involved an A-to-G substitution at the -670 nucleotide position in the enhancer region (FAS-670 A>G, rs1800682) and the heterozygous A/G alleles were observed in 52% of the normal population, with a frequency of the G and A alleles of 0.49 and 0.51, respectively.

The FAS-670 polymorphism consists of the variant genotypes FAS-670 G/G and FAS-670 A/G and the wild-type A/A. The frequency range of FAS-670 A/A among healthy controls was reported to be 25.5-43.6% and the frequency of the homozygous G/G variant ~12%, whereas the frequency range of the heterozygous A/G was reported to be 44.2-60.5% (13,14).

Cervical cancer is the second most common cancer among women worldwide (11,15), with a high incidence (>80%) in developing compared to developed countries (15,16). Cervical cancer is on the increase in Asia (17) and exhibits relatively higher incidence and mortality rates in Hungary compared to those in other European Union countries (18). Moreover, cervical cancer was reported to constitute 23.3% of all cancers among African women (19).

Human papillomavirus (HPV) is widely considered as the key etiological agent in cervical carcinogenesis. A meta-analysis of cross-sectional high-risk HPV type distribution in 115,789 HPV-positive women was performed, with HPV16 positivity in particular increasing steeply from normal/atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion (LSIL)/cervical intraepithelial neoplasia (CIN)1 (20-28%), through CIN2/high-grade squamous intraepithelial lesion (HSIL) (40/47%) to CIN3/invasive cervical cancer (58/63%) in different regions (20). Furthermore, previous epidemiological studies investigated the etiology of cervical cancer in order to recommend preventive measures to reduce the incidence of cervical carcinogenesis and identified certain important environmental factors. Cervical cancer is considered to be a multifactorial disease, with smoking and age being important etiological factors contributing to increased risk (21,22). Therefore, genetic as well as environmental factors may contribute to cervical carcinogenesis.

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Previous studies, including the 10 studies that we included in the present meta-analysis, were conducted to estimate the incidence of cervical carcinogenesis in association with the FAS-670 polymorphism; however, a consensus was not reached (13,23-31). Zhang *et al* (32) conducted a meta-analysis on FAS promoter polymorphisms and cancer risk, but failed to demonstrate a significant association with FAS-670 polymorphism. Since then, no confirmed outcomes based on small sample sizes or potential publication bias from the previous studies was obtained. Therefore, an updating meta-analysis was performed, using the accumulated data, to re-examine the association between the risk of cervical carcinogenesis and FAS-670 polymorphism.

#### Materials and methods

Search strategy. A search for eligible studies was conducted in PubMed, Embase and HuGNet electronic databases, using the following key words and word combinations: 'uterine cervical neoplasm', 'cervical cancer', 'cervical', 'cervix', 'FAS' and 'FAS-670'. The last update of retrieval was March 25, 2012. The search was limited to English language papers. Additional studies were identified through the reference lists of the original studies. We selected the articles with more information regarding the origin of cases and controls and the ones with the largest number of subjects among the overlapping reports.

Selection and exclusion criteria. The detailed selection criteria were as follows: i) case-control studies evaluating the association between FAS-670 polymorphism and the risk of cervical carcinogenesis; ii) case population including patients with precancerous lesions and cervical cancer patients; iii) control population comprising healthy individuals and not malignant tumor patients. The exclusion criteria were as follows: i) if similar studies included overlapping populations, only the most recent articles were included and the remaining were excluded; ii) insufficient data; iii) Hardy-Weinberg equilibrium (HWE) did not reach statistical significance (P<0.05).

*Data extraction*. The information was extracted from the eligible studies, including first author, year of publication, ethnicity, area, sample size of cases and controls, source of cases and controls, mean age of cases and controls and genotype frequency in cases and controls.

Statistical analysis. The ORs with their corresponding 95% CIs were used as the metric of choice. Based on the individual ORs, the pooled OR was estimated. First, we investigated the distribution of genotypes in the control groups under HWE to obtain evidence of population stratification (HWE; P>0.05) (33). We also estimated the association with cervical carcinogenesis risk with a complete overdominant genotypic model (G/G + A/A vs. A/G). Second, to assess the P<sub>heterogeneity</sub> among different studies, a statistical test for heterogeneity was conducted using the I<sup>2</sup> statistic, with values between 0 and 100%, with higher values leading to greater heterogeneity (no heterogeneity, I<sup>2</sup>: 0-25%; moderate heterogeneity, I<sup>2</sup>: 25-50%; significant heterogeneity, I<sup>2</sup>: 50-75%; and extreme heterogeneus among the studies, the fixed effects model was used to

estimate the overall effect size. Otherwise, a random effects model was used. Random effects may incorporate an estimate of between-study variance to a great extent and provide wider 95% CI.

To further investigate the source of heterogeneity, we performed a subgroup analysis by grouping studies with similar characteristics, such as ethnicity and sample size. The ethnic subgroups were categorized into Caucasian and Asian. In addition, a sensitivity analysis was employed. In the sensitivity analysis, studies was excluded one at a time to determine the magnitude of their effect on the overall summary estimate (35). Finally, publication bias was assessed using funnel plots and Begg's rank correlation test (36). All the P-values were two-sided. The statistical analysis was performed using Metagen and Stata software, version 11.0 (Stata Corp, College Station, TX, USA).

# Results

*Identification and characteristics*. A total of 140 abstracts were retrieved through searching PubMed, Embase and HuGNet databases. We identified 16 relevant studies that described the association between the FAS-670 polymorphism and cervical carcinogenesis. However, after reading the full articles, one study was excluded as a letter (37), one as a review (11) and two due to the lack of raw data (5,38). Two studies were overlapped (13,39) and one was retained (13) according to the criteria mentioned above. After calculating the HWE for each of the remaining studies, one more was excluded (14) and a total of 10 studies were finally included in this meta-analysis.

All the articles were case-control studies. Among the eligible studies, 6 were conducted on Asian (13,24,25,27,28,30) and 4 on Caucasian populations (23,26,29,31). Two studies were classified as LSIL and HSIL (28,30) and one study included HSIL and cervical cancer (27), whereas others exclusively included cervical cancer patients (13,23-26,29,31). Only one study reported the clinical stages (26). In all the studies, the majority of the patients were recruited from hospitals by blood samples or tissue specimens. Six studies mentioned the mean age of the patients (13,23,24,27,29,30) and the remaining 4 studies did not (25,26,28,31). All the studies used polymerase chain reaction. Other detailed information is presented in Table I.

*Main results and subgroup analysis*. In total, the eligible studies included 3,247 cases and 2,944 controls and a total of 2,901 cases and 2,831 controls were genotyped. The summary ORs and 95% CIs for the FAS-670 polymorphism and the subgroup analysis are presented in Table II. The results indicated that FAS-670 was not associated with the risk of cervical carcinogenesis. The summary OR was 1.13 (95% CI: 0.95-1.34), with between-study heterogeneity (I<sup>2</sup>=52.7%, P<sub>heterogeneity</sub>=0.03). All the analyses were based on pooling of data from different populations. Therefore, a subgroup analysis according to different ethnicities was performed. The OR for Asians was 1.25 (6 comparisons, 95% CI: 1.05-1.48, I<sup>2</sup>=23.5%, P<sub>heterogeneity</sub>=0.03), whereas for Caucasians, no significant association was observed between FAS-670 polymorphism and the risk of cervical carcinogen-

	Selection/charact and controls (m	teristics of cases tean age ± SD)		Eligible	subjects	Control		
Investigator (year)	Cases	Controls	Race	Cases	Controls	of controls	Method	Refs.
Zucchi et al (2009)	Histologically confirmed diagnosis (52.5±11.9)	Randomly selected healthy subjects (43.8±11.7)	Caucasian	91	176	Population	PCR-RFLP	(23)
Sun <i>et al</i> (2005)	Histological and gynecological diagnosis (43.5±9.8)	Randomly selected healthy subjects (44.0±10.1)	Asian	314	625	Population	<b>PCR-RFLP</b>	(13)
Kang <i>et al</i> (2008)	Histologically confirmed diagnosis (47.8)	Age-matched healthy subjects (48.2)	Asian	155	160	Hospital	PCR-RFLP	(24)
Ueda <i>et al</i> (2006)	Histologically confirmed diagnosis	Healthy subjects	Asian	259	95	Population	PCR	(25)
Zoodma <i>et al</i> (2005)	Histologically confirmed diagnosis	Randomly selected healthy subjects	Caucasian	985	607	Population	PCR	(26)
Lai <i>et al</i> (2005)	Histological and cytological diagnosis $(45.7\pm12.9)$ $(HSIL 45.5\pm13.0)$ $(CC 54.2\pm12.9)$	Age-matched to patients	Asian	318	318	Hospital	PCR	(27)
Ueda <i>et al</i> (2005)	Histologically confirmed diagnosis	Normal patients from hospital	Asian	216	63	Hospital	<b>PCR-RFLP</b>	(28)
Dybikowska <i>et al</i> (2004)	Histologically confirmed diagnosis (53.7)	Healthy women (29.5)	Caucasian	51	65	Hospital	PCR-RFLP	(29)
Lai <i>et al</i> (2003)	Histological and cytological selected diagnosis (41.6±11.0)	One to one matched to patients (within 3 years)	Asian	411	411	Hospital	PCR-RFLP	(30)
Chatterjee et al (2009)	Histologically confirmed diagnosis	Without cervical cancer from hospitals and clinics	Caucasian	447	424	Hospital	Total nucleic acid extraction technologies	(31)
SD, standard deviation; PCR- with non-malignant disease.	RFLP, polymerase chain reaction-re	estriction fragment length polym	orphism; HSIL, h	igh-grade sq	lamous intraepi	thelial lesion; CC, c	cervical cancer; Normal patients.	, patients

Table I. Summary of the studies of cervical cancer risk and FAS-670 polymorphism.



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Subgroups and FAS-670 polymorphism	Comparisons (no.)	Genotype cases (no.)	Genotype controls (no.)	Random effects OR (95% CI)	P <sub>heterogeneity</sub>	$I^{2}(\%)$
Population						
Asians	6	1,496	1,662	1.25 (1.05, 1.48)	0.03	23.5
Caucasians	4	1,405	1,169	0.96 (0.75, 1.24)	0.14	45.9
Sample						
>200	6	2,522	2,335	1.13 (0.91, 1.41)	0.01	69
<200	4	290	496	1.13 (0.86, 1.48)	0.42	0.0
Overall	10	2,901	2,831	1.13 (0.95, 1.34)	0.03	52.7

Table II. Summar	y ORs and 95%	CIs for FAS-670	polymorphism a	nd subgroup analysis.
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OR, odds ratio; CI, confidence interval.



Figure 1. Effect of FAS-670 phenotype studies (first author, year of publication) on the risk of cervical cancer and combined estimate of odds ratio (OR) and 95% confidence interval (CI) by the complete overdominant effects model. Also shown is the summary random effects estimate for the comparison along with the respective 95% CI. Asian: Chi-squared test for heterogeneity = 6.54 (df=5), P=0.257, I<sup>2</sup>=23.5%; test of OR=1:z=2.51 (P=0.012). Caucasian: Chi-squared test for heterogeneity = 5.54 (df=3), P=0.136, I<sup>2</sup>=45.9%; test of OR=1:z=0.3 (P=0.761). df, degree of freedom.

esis (4 comparisons, OR=0.96, 95% CI: 0.75-1.24, I<sup>2</sup>=45.9%, P<sub>heterogeneity</sub>=0.14) (Fig. 1).

#### Discussion

In the sensitivity analysis, we applied the random effects model (Fig. 2) to estimate the risk of cervical cancer (OR=1.13, 95% CI: 0.95-1.34, I<sup>2</sup>=52.7%, P<sub>heterogeneity</sub>=0.03). However, in the funnel plot analysis of publication bias, the funnel plot appeared to be symmetrical and the Egger's test (P=0.343) revealed no evidence of publication bias (Fig. 3).

This meta-analysis, involving the comparison of a total of 3,247 cases and 2,944 controls, investigated 10 case-control studies on FAS-670 and assessed the association of FAS-670 polymorphism with the risk of cervical carcinogenesis. There was no significant evidence supporting an association between FAS-670 polymorphism and cervical cancer risk.





Figure 2. Summary plot for FAS-670 phenotype studies (first author, year of publication) and combined estimate of odds ratio (OR) and 95% confidence interval (CI) by the complete overdominant effects model. Chi-squared test for heterogeneity = 19.04 (df=9), P=0.025,  $I^2=52.7\%$ ; test of OR=1:z=1.40 (P=0.161).



Figure 3. Funnel plot of the association of FAS-670 genotype polymorphism with cervical carcinogenesis. In Begg's test, z=0.18, (continuity corrected), P>|z|=0.858 (continuity corrected). In Egger's test, t=1.01, P>|t|=0.343, (95% CI: -1.651001-4.215824).

In the meta-analysis, heterogeneity was always estimated in a statistical analysis. However, the tests appeared to be of low statistical power. Thus, a subgroup meta-analysis was conducted based on ethnicity and sample size. In the ethnicity subgroups, a positive association between FAS-670 polymorphism and cervical cancer was observed in Asian, but not in Caucasian populations. However, the negative result in Caucasian must be assessed with caution, as the relatively high between-study heterogeneity may due to a mixture of populations of different races and from different geographical regions. Moreover, regarding sample size subgroups, no association between FAS-670 polymorphism and cervical cancer was observed in the smaller or in the larger size subgroups.

Regarding our results, several limitations must be mentioned. First, of all the eligible studies, there was inherent bias in the study design. Selection bias is a possible major source of heterogeneity in the acquisition of cancer samples and hospital controls. Moreover, only two studies (27,30) matched the number of subjects between the case and the control groups and this lack of symmetry in the included subjects may lead to deviations. All these factors may result in bias.

Second, the pathological classification and clinical stages were not consistent. For example, some of the studies only included samples of cervical cancer, whereas others included cervical cancer and LSIL or HSIL. The potential deviation may produce different outcomes.

Finally, the combined analysis of different ages and races may lead to deviations. The mean age range of the eligible subjects was 29-55 years in the case and control groups. However, one study reported that the risk of cervical cancer increases with advancing age (23). Thus, age may be the cause of heterogeneity. Moreover, the incidence of cervical cancer differs among different ethnicities (14,17,18); therefore, a subgroup analysis according to race is required. However, our meta-analysis was only focused on Asians and Caucasians, which may have affected the outcome of the ethnicity subgroup analysis.

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