The Asn680Ser polymorphism of the follicle stimulating hormone receptor gene and ovarian cancer risk: a meta-analysis

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Abstract

Purpose The purpose of this study was to conduct a meta-analysis to assess the association between FSHR Asn680Ser polymorphism and ovarian cancer susceptibility.

Methods A literature search was conducted in PubMed, Embase and the China National Knowledge Infrastructure (CNKI) for all relevant studies published up to September 2013. The pooled odds ratios (ORs) with the corresponding 95 % confidence intervals (95 % CIs) were calculated to evaluate the association.

Results Four case–control studies including 474 ovarian cancer cases and 659 controls met the inclusion criteria. The pooled analyses showed that FSHR Asn680Ser polymorphism was

associated with the risk of ovarian cancer (Ser vs Asn: OR=1.295, 95 % CI 1.057–1.498, $P=0.01$; Ser/Ser + Asn/Ser vs Asn/Asn: OR=1.611, 95 % CI 1.027–2.528, $P=0.038$). Sub-group analyses by ethnicity (Caucasian and Asian) further revealed significant associations among Asians (Ser vs Asn: OR=1.386, 95 % CI 1.066–1.802, $P=0.015$; Ser/Ser + Asn/Ser vs Asn/Asn: OR=1.893, 95 % CI 1.329–2.689, $P=0.000$) but not Caucasians. There was no obvious risk of publication bias.

Conclusions The meta-analysis suggests that FSHR Asn680Ser polymorphism may be a risk factor for ovarian cancer in Asians. Due to the limited quantity of the included studies, further studies are needed to validate the above conclusions.

Keywords Follicle-stimulating hormone receptors · Polymorphism · Ovarian cancer · Meta-analysis

Capsule It has been speculated that FSHR Asn680Ser polymorphism is probably involved in susceptibility to cancer. This meta-analysis found that FSHR Asn680Ser polymorphism may be a risk factor for ovarian cancer in Asians.

Xue Qin, Liping Ma and Shi Yang contributed equally to this study and should be considered as co-first authors.

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Introduction

Ovarian cancer is a type of cancer that affects one or both ovaries, the glands on either side of the uterus. Ovarian cancer often goes undetected until it has spread within the pelvis and abdomen. At this late stage, ovarian cancer is difficult to treat and is often fatal. Approximately 225,500 new cases and 140,200 deaths of ovarian cancer reported annually [1, 2]. Identifying the risk factors for ovarian cancer is critical to the development of potential interventions and the understanding of the disease biology. However, little is known about the complex aetiology of ovarian cancer. Studies have suggested that a variety of environmental factors, such as smoking and exposure to chemical toxins, may increase the risk of ovarian cancer [3, 4]. However, some women exposed to the same risk factors may not develop ovarian cancer. This suggests that genetic predisposition may contribute to inter-individual differences in susceptibility.

Follicle stimulating hormone (FSH) is a significant female sex hormone and plays an important role in a variety of ovarian activities, including follicular maturation, selection of the dominant follicle and ovulation. FSH transduces signals to target cells by binding to follicle stimulating hormone receptors (FSHRs), which are expressed on granulosa cells in the ovaries [5, 6]. FSHRs belong to the large family of G protein-coupled receptors, whose members have a transmembrane domain that consists of seven-membrane traversing α -helices connected by three extracellular and three intracellular loops [7]. The FSHR genes are located on chromosome 2p21-p16 [8]. Several single nucleotide polymorphisms (SNPs) are present in the FSHR genes. The most frequent polymorphisms are in exon 10, Thr307Ala (G919A) and Asn680Ser (G2039A) [9]. The two polymorphisms Ala307Thr (A307 T) and Ser 680Asn (S680 N) are in linkage disequilibrium, resulting in two discrete combinations of FSH receptor isoforms (Thr307-Asn680 and Ala307-Ser680). In recent years, these polymorphisms have attracted widespread attention. However, the majority of studies have focused almost exclusively on polymorphisms at codon 680. Since 1998, several studies have been conducted to evaluate the association between FSHR (Asn680Ser, rs6166) polymorphism and ovarian cancer risk, but the results remain inconsistent and inconclusive [10–12]. These controversial results may relate to the small sample sizes in the individual studies, which have low statistical power. To overcome the limitations and to obtain comprehensive evidence for the possible association, a meta-analysis of case–control studies was performed.

Materials and methods

Search strategy

All relevant studies published up to September 2013 were searched in PubMed, Embase and the China National Knowledge Infrastructure (CNKI), using a search strategy based on combinations of the key phrases ‘ovarian cancer or ovarian carcinoma’ and ‘FSHR or follicle stimulating hormone receptor or FSH receptor’ and ‘polymorphism or mutation or variant or genotype’. The reference lists of the retrieved articles were hand-searched to obtain other relevant publications that were not identified using the above strategy. The results were limited to studies conducted in humans. No language restriction was specified.

Inclusion and exclusion criteria

A study was eligible for inclusion if it met the following criteria: (1) used case–control method; (2) assessed the association between FSHR Asn680Ser polymorphism and ovarian cancer risk; (3) included detailed genotyping data to estimate an odds ratio (OR) with 95 % CI; and (4) included participants

of any age. A study was excluded based on any of the following criteria: (1) was conducted on animals; (2) did not use case–control method; (3) included systematic reviews; (4) examined mutually overlapping populations.

Data extraction

Information was carefully extracted from all eligible studies by two independent investigators according to the inclusion and exclusion criteria listed above. Any differences were resolved by discussion between the two reviewers (Ma and Qin). The following data were extracted from each included study: the first author, year of publication, ethnicity studied, types of cancer, genotyping method, sample sizes of the ovarian cancer cases and controls and genotype distribution of Asn/Asn, Asn/Ser and Ser/Ser in the cases and controls.

Statistical analysis

The pooled odds ratio (OR) and its corresponding 95 % confidence interval (95 % CI) were used to assess the strength of the association between the polymorphism of FSHR Asn680Ser and ovarian cancer risk. The significance of the pooled OR was determined by the *z*-test. Asn680Ser genotypes were examined using four models: the allele (Ser vs Asn); co-dominant (Ser/Ser vs Asn/Asn and Asn/Ser vs Asn/Asn); dominant (Ser/Ser + Asn/Ser vs Asn/Asn) and recessive (Ser/Ser vs Asn/Ser + Asn/Asn) models.

The Chi-square test (assessing the *P* value) based on the *Q*-statistic and the I^2 statistic was performed to evaluate the between-study heterogeneity. If $P < 0.10$ and $I^2 > 50$ %, indicating the presence of heterogeneity, a random-effect (Mantel-Haenszel method) model was selected to pool the data. Otherwise, a fixed-effect (DerSimonian and Laird method) model was employed [13, 14]. At the conclusion of this meta-analysis, the subgroup analyses were done based on ethnicity (Caucasian or Asian), to explore the effect of heterogeneity among the studies. Potential publication bias was investigated by using a funnel plot, and the degree of asymmetry was tested by Egger’s test [15]. All of the statistical tests used in this meta-analysis were performed by the Stata package version 9.2 (StataCorp LP, College Station, TX, USA). All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Literature search and characteristics of the studies

Based on the search criteria, 35 records were preliminarily identified for further detailed evaluation. Only eight articles on the association of FSHR Asn680Ser polymorphism and ovarian cancer risk were identified and screened for data retrieval. Four

of these articles were excluded; one was a comment article [16], one was not designed as case-control [17] and two did not provide allele or genotyping data [18, 19]. As a result, 4 studies with a total of 474 ovarian cancer cases and 659 controls were included in this meta-analysis; one was written in Chinese [20] and three in English [10–12]. Among the eligible studies, two were performed with Asian and two with Caucasian women. The genotype frequencies for the control groups in the four studies were conformed to the Hardy-Weinberg equilibrium. The study characteristics are listed in Table 1, and the genotype distribution and risk allele frequency are summarized in Table 2.

Meta-analysis

Table 3 lists the summary results of this meta-analysis and the heterogeneity tests. The meta-analysis revealed that FSHR Asn680Ser polymorphism was associated with the risk of ovarian cancer (Ser vs Asn: OR=1.295, 95 % CI 1.057–1.498, $P=0.01$, $I^2=2$, $PQ=0.382$; Ser/Ser + Asn/Ser vs Asn/Asn: OR=1.611, 95 % CI 1.027–2.528, $P=0.038$, $I^2=53$, $PQ=0.103$) in all populations. When stratifying by ethnicity, significant associations between FSHR (Asn680Ser, rs6166) polymorphism and ovarian cancer risk were found in Asian women (Ser vs Asn: OR=1.386, 95 % CI 1.066–1.802, $P=0.015$; Ser/Ser + Asn/Ser vs Asn/Asn: OR=1.893, 95 % CI 1.329–2.689, $P=0.000$), but not Caucasian women.

Publication bias

Begg's funnel plot and Egger's linear regression tests were performed to assess the publication bias of the literature, and the funnel plot did not show obvious asymmetry in any of the four genetic models. In addition, all the P values of Egger's tests suggested no publication bias ($P<0.1$) (Fig. 1).

Discussion

Studies have reported that FSHR is expressed in human ovarian surface epithelium [21, 22] and at a higher level in

ovarian cancers [23, 24]. In addition, the overexpression of FSHR may be associated with enhanced levels of potential oncogenic pathways and increased proliferation in preneoplastic ovarian surface epithelial cells [25]. It has been suggested that FSH could be an important ovarian epithelial cell growth-promoting factor [26]. To date, the National Center for Biotechnology Information (NCBI) SNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) indicates that there are 731 SNPs in the FSHR gene, some of which are associated with a susceptibility to cancer [27]. The most frequent polymorphisms are in exon 10, Thr307Ala (G919A) and Asn680Ser (G2039A). The Thr307Ala (rs6165) polymorphism is situated at the extracellular domain of the receptor, the site responsible for high affinity hormone binding [28], while Asn680Ser (rs6166) is placed in the intracellular domain of the receptor, which may influence the uncoupling from adenylyl cyclase [29]. Amino acid substitutions within the coding region may affect the post-translational modifications of the FSHR protein, which may influence the function of the receptor, including FSH efficacy [30]. FSHR Asn680Ser polymorphism has been associated with a different sensitivity in the FSHR in previous studies. Perez-Mayorga et al. [31] demonstrated a fine-tuning in the feedback regulation of FSH, dependent on the FSHR genotype. The Ser/Ser genotype is more resistant to FSH action, while the Asn/Asn genotype seems to confer a higher activity to the FSHR. Greb et al. [32] found that the FSH receptor Ser/Ser genotype is associated with longer menstrual cycles. Hence, it has been speculated that FSHR Asn680Ser polymorphism is probably involved in susceptibility to cancer.

In recent years, many studies have assessed the association between FSHR Asn680Ser polymorphism and ovarian cancer risk, but the results remain controversial. Yang et al. [11] reported that 680Ser carriers had higher risk of developing serous and mucinous tumours compared to the control group (OR=1.74, 95 % CI 1.19–2.54, $P<0.004$, adjusted for age respectively). In their study on granulosa cell tumours, Fuller et al. [10] suggested that there was no clear association of the codon 680 allele with the occurrence of ovarian cancer. To knowledge, this meta-analysis was the first to investigate the

Table 1 Main characteristics of studies included in this meta-analysis

Author	Publication	Country	Geographic Location	Types of cancer	Detection Method	Sample size		HWE P value
	Year					Case	Control	
Fuller	1998	Australia	Caucasians	Sex cordstromal tumors, EOC	PCR	22	22	0.435
Yang	2006	China	Asian	EOC	PCR-RFLP	202	266	0.731
Ludwig	2009	Poland	Caucasians	EOC, others	PCR	215	349	0.694
Xu	2009	China	Asian	EOC	PCR-RFLP	35	22	0.157

EOC epithelial ovarian cancer, HWE Hardy-Weinberg equilibrium in control population

Table 2 The genotype distribution and risk allele frequency of all studies included

Author	Genotype distribution									
	Cases					Controls				
	No.	Asn/Asn	Ser/Asn	Ser/Ser	Ser allele	No.	Asn/Asn	Ser/Asn	Ser/Ser	Ser allele
Fuller	22	4	14	4	0.500(%)	22	5	9	8	0.568(%)
Yang	202	73	114	15	0.365(%)	266	131	113	22	0.295(%)
Ludwig	215	68	99	48	0.453(%)	349	121	172	56	0.407(%)
Xu	35	11	23	1	0.357(%)	22	15	5	2	0.205(%)

effect of FSHR Asn680Ser genotype on ovarian cancer risk. The overall results indicated that FSHR codon 680 polymorphism was a potential risk factor for ovarian cancer.

Several limitations should be acknowledged when interpreting the results of this meta-analysis. First, there was a potential language bias, because the PubMed, Embase and CNKI search engines were used to identify articles and to exclude articles written in languages other than English and Chinese. This might not have prevented the researchers from accessing all relevant studies. Second, relatively few eligible studies, all with small sample sizes, were included in this meta-analysis, which could increase the risk of random error. To conduct a more precise analysis of FSHR Asn680Ser polymorphism and the risk of ovarian cancer, further investigations with larger sample sizes and higher quality are needed. Third, the overall outcomes were based on individual unadjusted ORs; a more precise estimation should be adjusted by menstrual status, age, environmental and other confounding

factors. Finally, this meta-analysis could not address the gene-gene and gene-environmental interactions in the association between FSHR Asn680Ser polymorphism and ovarian cancer risk. Future studies that include detailed information on exposures to various carcinogens and individual-level data to assess the possible gene-gene and gene-environment interactions in the association between FSHR Asn680Ser polymorphism and ovarian cancer risk are needed.

This meta-analysis of four relevant studies suggested that FSHR Asn680Ser polymorphism is associated with an increased risk of ovarian cancer in allele and dominant genetic models. However, the functional significance of FSHR polymorphism is currently unclear. To understand the association between the FSHR polymorphism and the mechanism for ovarian cancer, additional studies with a greater number of patients should be performed. These studies should also examine how the FSHR variants interact with other risk loci to influence ovarian cancer risk.

Table 3 Meta-analysis of the association between FSHR Asn680Ser and ovarian cancer

Comparison	Population	Test of association			Heterogeneity		Effects
		OR	95%CI	P Value	I ² (%)	P Value	
Ser vs Asn	overall	1.259	1.057–1.498	0.01	2	0.382	Fixed
	Asian	1.386	1.066–1.802	0.015	7.9	0.297	Fixed
	Caucasians	1.167	0.924–1.473	0.195	7.9	0.297	Fixed
SerSer vs AsnAsn	overall	1.342	0.912–1.975	0.136	0	0.726	Fixed
	Asian	1.168	0.578–2.323	0.658	0	0.662	Fixed
	Caucasians	1.431	0.896–2.286	0.134	0	0.343	Fixed
AsnSer vs AsnAsn	overall	1.788	0.979–3.265	0.058	69.5	0.020	Random
	Asian	2.913	0.891–9.520	0.077	71.5	0.061	Random
	Caucasians	1.063	0.731–1.547	0.749	0.0	0.434	Fixed
SerSer vs AsnAsn + AsnSer	overall	1.152	0.861–1.627	0.421	46	0.135	Fixed
	Asian	0.818	0.425–1.578	0.55	0	0.369	Fixed
	Caucasians	0.904	0.250–3.268	0.878	70	0.068	Random
SerSer + AsnSer vs AsnAsn	overall	1.611	1.027–2.528	0.038	53	0.094	Random
	Asian	1.893	1.329–2.689	0	62.4	0.103	Fixed
	Caucasians	1.477	1.152–1.895	0.417	0	0.853	Fixed

OR odds ratio, 95 % CI 95 % confidence interval

Fig. 1 Begg's funnel plot and the Egger test of publication bias for the association between FSHR Asn680Ser polymorphism and ovarian cancer risk were detected on the comparison of Ser versus Asn allele (Egger regression test: $t=-0.07$, $P=0.951$, 95 % CI=-5.483–5.663)

Conflicts of interest None.

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