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The association between codon72 polymorphism of p53 gene and the risk of endometrial cancer: an updating meta-analysis

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Abstract
Objective Controversy still exists in the relationship between p53 codon72 polymorphism and the risk of endometrial cancer.
Materials and methods In order to figure out this inconsistency, database on HuGE Navigator, PubMed and Web of Science about the case–control studies were compiled in the present work. Statistic analysis was performed by STATA 12.0.
Results Total 11 eligible publications were selected in this meta-analysis including 1086 endometrial cancer and 1403 controls. There was no significant relationship between codon72 polymorphism of p53 gene and the risk of endometrial cancer under allele model [Pro versus Arg: OR 0.99, 95 % CI (0.87, 1.15)], dominant model [Arg-Pro + ProPro versus ArgArg: OR 0.88, 95 % CI (0.67, 1.15)], recessive model [ProPro versus ArgArg + ArgPro: OR 1.09, 95 % CI (0.84, 1.42)] and addictive model [ProPro versus ArgArg: OR 0.97, 95 % CI (0.72, 1.29)]. Samples from endometrial tissue with homozygous ArgArg have the increased risk of EC [allele model: OR 0.71, 95 % CI (0.53, 0.96); addictive model: OR 0.46, 95 % CI (0.24, 0.87)].
Conclusion This meta-analysis revealed a weak association between the codon72 polymorphism of p53 gene and the risk of endometrial cancer. Women with homozygous Arg72 may be more susceptible to endometrial cancer than others with heterozygotes and homozygous Pro72.

Keywords p53 · Polymorphism · Endometrial cancer · Meta-analysis

Introduction

Endometrial cancer (EC) is one of the most common cancers in female, which mainly afflicts women in menopausal and postmenopausal period even in young age. Since 2008, the incidence of endometrial cancer has increased 21 % [1], and its death rate has also increased. In USA, annual incidence of endometrial cancer was 0.243 ‰ [2], and 0.194 ‰ in UK [3]. However, compared with developed countries, the morbidity of endometrial cancer is lower in several developing countries, such as the lowest rates in Africa and West Asia (0.6 %) [4], which may be related to poor medical care. All those statistics indicate, along with popularity of screening and the development of diagnostic techniques of cervical cancer that endometrial cancer has become the most common gynecological malignant tumor, occupying the fourth most common cancer in European and North America [5].

The pathogenesis of endometrial cancer remains unclear yet, but closely related to hormone as well as interactions with environment element and genetic factor. Women with colorectal cancer (CRC) are more susceptible to endometrial cancer due to the same inheritance pattern [6]. However, the endometrial cancer in those without colorectal cancer exhibit familial aggregation [7]. A meta-

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analysis found out that women who had a first-degree family history of EC or CRC are more likely to suffer from developing EC than those without a family history [8].

The inactivation of anti-oncogenes may also play one of the important pathogenesis mechanisms of EC. Anti-oncogenes induce terminal differentiation, maintain genomic stability, trigger cell aging, regulate cell growth and inhibit against protease activity [9]. The p53 gene is one of the anti-oncogenes. The initiation and progression of estrogen-independent EC are associated with the mutation of p53 gene [10]. p53, encoded by the TP53 gene on the short arm 17p13.1 of chromosome 17, is composed of 11 exons and 10 introns. As a suppressor gene, it prevents genetic anomalies transmission to daughter cells [11]. It plays a key role in regulation of cell-cycle, preventing chromosomes from damage. Moreover, p53 recognizes DNA damage, promotes DNA repair and induces senescence and programmed cell death [12]. Animal studies verified variance of p53 gene may cause permanent cell damage and neoplastic transformation, even malignance ultimately [13].

For human beings, p53 is associated with breast cancer, lung cancer and high-grade ovarian tumors, including EC as well [14]. Wild-type p53 gene regulates normal cell growth process and inhibits cell transformation, and tumorigenesis occurs in case of its mutation [15]. Several variants in p53 gene have been figured out, with codon72 which is located in exon 4, leading to a CGC-to-CCC transition. The postulate is by far the most relevant polymorphisms in EC association studies. However, all these studies remained inconsistent. In order to figure out these unsolved conflicting results, we conducted a meta-analysis of published genetic association studies of the polymorphisms and risk of EC.

Materials and methods

Search strategy

A combined search was performed from PubMed, HuGE Navigator and Web of Science SCI electronically. The search in PubMed updated on May 1st, 2015, using free words and medical subject headings (MeSH) terms were as follows: (p53 OR TP53) and [(endometrial cancer) or (endometrial carcinoma)] and (polymorphism or genetic or variation). HuGE navigator is an integrated, searchable knowledge database of genetic associations and human genome epidemiology. We also conducted a search on HuGE Navigator up to May 1st 2015, using the Gene Prospector tool with phenotype indexing terms: "endometrial cancer" or "endometrial carcinoma". Then we collected studies in the TP53 gene. In addition, Web of Science SCI was included in the search. All results were limited to English publications.

Selection criteria and data extraction

We performed all the eligible studies selection and data extraction independently by two investigators (first author and second author). Inconsistency was resolved by adjudication and discussion. A third investigator would intervene if any discrepancy still exist. We followed the inclusion criteria as: (a) publications were published on association p53 gene codon72 polymorphism with risk of EC; (b) case–control studies and (c) all the eligible articles contained useful information especially the genotype frequencies. Case-only studies, review articles and researches on animals were excluded. The information of first author's surname, study year, ethnicity, sample size, frequency of genotypes and genotyping method were extracted.

Statistical analysis

First of all, we used the χ^2 analysis to test whether the genotype frequencies of p53 gene codon72 polymorphism in control groups conformed to Hardy–Weinberg equilibrium (HWE), and $p < 0.05$ was considered as departure from HWE. Then the strength of association between codon72 polymorphism of p53 gene and EC risk was assessed by crude odds ratios (ORs) with the corresponding 95 % CI under allele model (Pro versus Arg), dominant model (ArgPro + ProPro versus ArgArg), recessive model (ProPro versus ArgArg + ArgPro) and addictive model (ProPro versus ArgArg), respectively. The significance of the pooled OR was determined by the Z test and the heterogeneity among studies was assessed by the I^2 statistic proposed by Higgins and Thompson [16]. If $I^2 \leq 50$ %, a fixed effect model would be used as the pooling method. Otherwise, a random effect model would be adopted if there was substantial heterogeneity ($I^2 > 50$ %). A χ^2-base Q test was applied to estimate the heterogeneity between subgroups. Potential publication bias was assessed through Begg's funnel plot and Egger's test. All statistical analyses were performed with the STATA software (version 12.0; Stata Corporation, College Station, TX, USA). All the p values were two-sided analysis.

Results

Search outcomes

We obtained 11 potential studies after excluding 132 duplicates, 374 ineligibles and one study lack of complete genotypes. Thus, 11 case–control studies, containing 1086

EC cases and 1403 controls, were selected by reading abstract and full text as shown in Fig. 1. The detailed characteristics of the studies included in this meta-analysis were summarized in Table 1. These eligible studies were performed in eight different countries, containing two main ethnicities in general. The sample source for p53 genotyping determination was varying in three specimens: endometrial tissue, peripheral blood cells and both of the two above. Sample sizes of the 11 studies ranged from 39 to 556.

Meta-analysis

The pooled results are shown in Table 2. Overall, there was no evidence of an association between the increased risk of EC and the p53 gene codon72 polymorphism under allele model [Pro versus Arg: OR 0.99, 95 % CI (0.87, 1.15)], dominant model [ArgPro + ProPro versus ArgArg: OR 0.88, 95 % CI (0.67, 1.15)], recessive model [ProPro versus ArgArg + ArgPro: OR 1.09, 95 % CI (0.84, 1.42)] and addictive model [ProPro versus ArgArg: OR 0.97, 95 % CI (0.72, 1.29)].

Considering the potential discrepancy of the association between p53 condon72 polymorphism and the risk of EC, we pooled five articles in each subgroup after excluding an article without description of ethnicity. No significant association was observed either in Caucasians or Asians. As sample size and sample source would also influence the reliability of the pooled results, we categorized the studies into two subgroups. In the stratified analysis of sample source subgroups, homozygous ArgArg has the increased risk of EC [allele model: OR 0.71, 95 % CI (0.53, 0.96); addictive model: OR 0.46, 95 % CI (0.24, 0.87)].But results in sample size subgroups were negative. However, significantly increased risk of EC in people with ArgArg genotype was identified among studies deviated from HWE in dominant model [OR 0.63, 95 % CI (0.42, 0.94)].

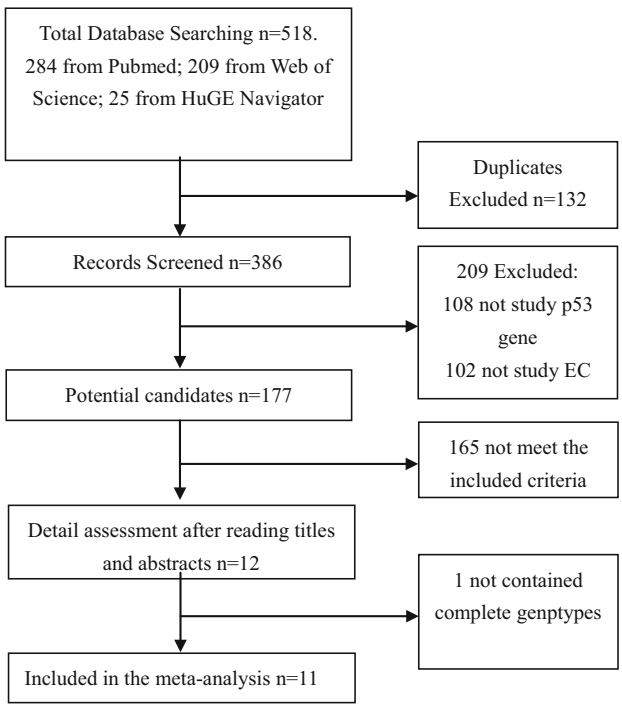

Fig. 1 Flow chart of relative studies

Publication bias

Both Begg's test and Egger's test were applied to evaluate the publication bias of these studies. No significant publication bias was detected in all the aforementioned inherited models (as shown in Table 3).

Discussion

Endometrial cancer is a common female malignancy which has its morbidity ascended to the top spot in Occident. Although multiple studies proved that genetic variant is somehow associated with the risk of cancer, the mechanism of initiation and progression of cancer still remains unclear. Single nucleotide polymorphisms (SNPs) exist throughout people's DNA, sometimes involving susceptibility to several diseases. When SNPs occur within a gene or in proximity to a gene, they may directly affect the gene's function, and subsequently trigger diseases. Mounting evidence suggested the risk of EC is related to genetic polymorphisms in various genes. The p53 gene is proved to be involved in malignant tumorigenesis, such as breast cancer [17], ovarian cancer [18], esophagus cancer [19] and other tumor genesis. The polymorphism of codon72 of p53 gene has become a research hotspot. With the transition CGC to CCC encoded by codon 72, this mutation results in an arginine-to-proline amino-acid substitution. Arg72 and Pro72 genotypes belong to wild-type. However, their molecular biological behaviors and functions are totally different. Arg allele suppresses the growth of transformed cell, induces cell apoptosis and repairs the injured cell [20]. Whereas the Pro allele plays a role in binding with several transcription factors which seems to activate transcription more efficiently in up-regulation of downstream gene, indicating that the Arg72 variant is more efficient than p53 Pro in suppressing transformation [21]. In the comparison of apoptosis induction, one study reported that the Arg72 form of p53 was at least five times efficient than the Pro72 form was [22]. In addition, the Pro genotype appears to induce a higher level of G1 arrest than the Arg genotype [23]. As for the development of human papilloma-virus-associated (HPV) cancer, the Arg72

Table 1 The characteristics of eligible studies

References	Year	Country	Ethnicity	Genotyping method	Sample source	Total numbers of case/control	Genotypes ArgArg/ArgPro/ProPro		Allele Arg/Pro		*P* value for HWE
							Case	Control	Case	Control	
Esteller et al. [35]	1997	Spain	Caucasian	RFLP	Endometrial tissue	80/60	36/36/8	29/23/8	108/52	81/39	0.328
Peller et al. [36]	1999	Israel	Not stated	PCR	Endometrial tissue and peripheral blood cells	26/13	17/7/3	8/5/0	41/13	21/5	0.390
Agorastos et al. [37]	2004	Greek	Caucasian	PCR-ASP	Endometrial tissue	56/30	24/28/4	6/19/5	76/36	31/29	0.142
Niwa et al. [38]	2005	Japan	Asian	PCR-CTPP	Peripheral blood cells	114/442	37/66/11	178/210/54	140/88	566/318	0.509
Ueda et al. [39]	2006	Japan	Asian	RFLP	Peripheral blood cells	108/95	55/45/8	34/54/7	155/61	122/68	0.021
Ashton et al. [32]	2009	Australia	Caucasian	TaqMan	Peripheral blood cells	191/291	101/75/15	166/107/17	277/105	439/141	0.965
Nunobiki et al. [40]	2009	Japan	Asian	RFLP	Peripheral blood cells	102/95	44/48/10	34/54/7	136/68	122/68	0.021
Zubor et al. [41]	2009	Slovak	Caucasian	PCR	Peripheral blood cells	102/95	69/44/8	200/113/17	182/60	513/147	0.841
Ghasemi et al. [42]	2010	Iran	Caucasian	RFLP	Peripheral blood cells	30/32	2/15/13	4/21/7	19/41	29/35	0.067
Yoneda et al. [43]	2013	Japan	Asian	RFLP	Peripheral blood cells	125/200	52/55/18	75/102/23	159/91	252/148	0.184
Zajac et al. [14]	2013	Poland	Caucasian	RFLP	Endometrial tissue	152/50	50/39/63	7/21/22	139/165	35/65	0.586

variant was found to be more susceptible to degradation by the HPV-18 E6 protein, revealing that people with homozygous Arg72 are much more susceptible to HPV-associated tumorigenesis than heterozygotes [24]. The carriers of Arg allele of codon 72 TP53 gene may have an increased risk for development of cervical carcinoma [25]. A meta-analysis deduced that homozygote genotype of Arg allele was of higher frequency among high grade endometrial cancer compared with low grade one [26]. In contrast, Pro allele might be related to some carcinogenesis, which significantly increased the risk of EC [27]. Similarly, the results of a meta-analysis confirmed that Pro72 was significantly related with EC risk, especially in Asians [28]. Although there is no consensus regarding the effect of the codon 72 polymorphism on susceptibility to endometrial cancer, the SNPs of p53 gene may lead to different cellular subsequence–programmed death or immortalization.

Our meta-analysis did not reveal any significant association between p53 codon72 polymorphism and endometrial cancer risk in either the Asians or the Caucasians. However, several studies hold various conclusions. A meta-analysis about the association of codon72 polymorphism with cancer risk demonstrated that significantly increased cancer risk was observed among Asians in homozygous and recessive models, while in Americans increased cancer risk was observed only in dominant and recessive models [29], suggesting that people with Pro allele would be more susceptible to EC. Interestingly, in our study, the pooled ORs under allele model and addictive model prompted homozygous Arg72 might represent a risk factor in the development of endometrial cancers, wherein discrepancy maybe involved in the various sensitivity and specific degrees from different specimens, or somewhat likely be related to sample size.

Two studies deviated from HWE, appeared to be significantly associated with ArgArg genotype. Departure from HWE involves not sample size but study quality, genetic reasons as well as methodological reasons [30]. As those two studies contained small sample size relatively, the results might not be reliable.

TP53 gene has reported to be an independent prognostic factor in endometrioid EC [31]. However, the combination of other genetic variant maybe a higher grade of EC relevant [32]. TP53 gene mutations occur in some of endometrioid endometrial cancers in the presence of PTEN gene mutations, suggesting that both these genes participate in the development of breast tumors and endometrioid EC [33]. Mutations in PIK3CA and FBXW7 were also proved to correlate with high tumor grade of endometrial cancer [34].

From the analytical results of our work, it can be concluded that the p53 gene codon72 polymorphism may not

Table 2 Pooled results of different models

Subgroup	Number of literatures	Allele model[a]				Recessive model[a]				Dominant model[a]				Addictive model[a]			
		OR (95 % CI)	*P*[*Z*]	I^2 (%)	*P*(*Q*)	OR (95 % CI)	*P*[*Z*]	I^2 (%)	*P*(*Q*)	OR (95 % CI)	*P*[*Z*]	I^2 (%)	*P*(*Q*)	OR (95 % CI)	*P*[*Z*]	I^2 (%)	*P*(*Q*)
Total	11	0.99 (0.87, 1.15)	0.81	36.4		1.09 (0.84, 1.42)	0.51	0.00		0.88 (0.67, 1.15)[r]	0.34	51.2		0.97 (0.72, 1.29)	0.82	17.7	
Ethnicity					0.60				0.78				0.48				0.81
Asian	4	0.95 (0.79, 1.14)[r]	0.84	5.20		1.05 (0.83, 1.40)	0.82	0.00		0.85 (0.57, 1.27)[r]	0.43	61.3		1.00 (0.65, 1.53)[r]	0.99	0.00	
Caucasian	6	0.97 (0.72, 1.30)[r]	0.57	58.5		0.99 (0.68, 1.44)	0.60	20.1		0.87 (0.56, 1.35)[r]	0.53	60.4		0.87 (0.45, 1.68)[r]	0.69	54.2	
Sample source					0.02				0.12				0.05				0.01
Endometrial tissue	3	0.71 (0.53, 0.96)	0.03	33.7		0.76 (0.46, 1.27)	0.30	0.00		0.53 (0.22, 1.29)[r]	0.16	69.6		0.46 (0.24, 0.87)	0.02	6.70	
Peripheral blood cells	7	1.05 (0.92, 1.20)	0.50	17.4		1.22 (0.90, 1.65)	0.20	0.00		0.99 (0.76, 1.28)[r]	0.92	43.1		1.18 (0.84, 1.64)	0.34	0.00	
Sample size					0.79				0.63				1				0.76
≤200	6	1.01 (0.82, 1.24)	0.93	36.2		1.22 (0.77, 1.91)	0.40	20.0		0.92 (0.65, 1.31)[r]	0.64	23.0		1.05 (0.64, 1.75)	0.84	28.1	
>200	5	0.97 (0.83, 1.13)	0.72	48.9		1.03 (0.75, 1.43)	0.84	0.00		0.83 (0.54, 1.27)[r]	0.40	72.2		0.93 (0.65, 1.32)	0.67	21.6	
Status of HWE					0.12				0.82				0.03				0.81
Yes	9	1.03 (0.90, 1.18)	0.66	36.8		1.08 (0.82, 1.43)	0.60	2.30		1.02 (0.85, 1.23)	0.82	47.8		0.98 (0.72, 1.34)	0.90	32.0	
No	2	0.80 (0.59, 1.07)	0.13	0.00		1.18 (0.57, 2.45)	0.65	0.00		0.63 (0.42, 0.94)	0.02	0.00		0.89 (0.42, 1.91)	0.77	0.00	

P(Q) for heterogeneity between subgroups; *P[Z]* for the strength of association; *r* random model

[a] Allele model: Pro allele versus Arg allele; recessive model: ProPro versus ArgArg + ArgPro; dominant model: ArgPro + ProPro versus ArgArg; addictive model: ProPro versus ArgArg

Table 3 Publication bias of the genetic models

Genetic model	Begg's test *p* value	Egger's test *p* value
Allele model	0.350	0.539
Recessive model	0.755	0.470
Dominant model	0.276	0.197
Addictive model	0.640	0.938

be associated with the risk of endometrial cancer, though, discrepancies of different studies still exist. The inconsistency maybe due to following aspects: (a) difference of ethnicity and geographical characteristics of study population. (b) The inclusion criteria variants contributed to the differences in study design. (c) The detected sample sources were collected from peripheral blood, fresh tissue and tissue fixed in formalin, resulting in difference of DNA quality and quantity. (d) Genotyping method variant and small sample size may lead to bias. In conclusion, well-designed large studies are anticipated in further research in association of p53 gene and EC.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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