Int J Clin Exp Med 2015;8(8):12983-12988
www.ijcem.com /ISSN:1940-5901/IJCEM0009998

Original Article

Association of CCND1 gene polymorphism with cervical cancer susceptibility in Caucasian population: a meta-analysis

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Received May 7, 2015; Accepted August 3, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: Objective: To study G870A polymorphism in CCND1 gene and the risk of cervical cancer susceptibility in Caucasian population by meta-analysis. Methods: Search the correlative study of G870A polymorphism in CCND1 gene and cervical cancer susceptibility in PubMed and EMBASE database, and extract the reference data according to the including criteria. We used RevMan 5.2 software to merge the OR value and 95% confidence interval and to perform meta-analysis. Results: Five case-control studies were enrolled into the analysis, including 1665 patients with cervical cancer and 2511 healthy people as control. It was revealed by meta-analysis that, in the Caucasian population, there was no significant correlation between G870A polymorphism in CCND1 gene and the risk of cervical cancer (G allele vs. A: OR = 1.01, 95% CI = 0.80-1.27, P = 0.95; AA vs. GA + GG: OR = 1.13, 95% CI = 0.98-1.30, P = 0.10; (GA + AA) vs. GG: OR = 1.15, 95% CI = 0.72-1.85, P = 0.55). Conclusion: G870A polymorphism in CCND1 gene may be uncorrelated with the development of cervical cancer in Caucasian population.

Keywords: Cervical cancer, cyclin D1, polymorphism, meta-analysis

Introduction

Cervical cancer is the most common malignant tumor among women, and its incidence and mortality rank the third and fourth position, respectively [1, 2]. In 2008, 529.8 thousand new cases worldwide were diagnosed with cervical cancer and 275.1 thousand people died from cervical cancer, which severely threaten women's life and health [3]. Recent studies [4, 5] showed that cervical cancer is the result of interaction of various factors, such as down-regulation of host immunity, abnormal changes of cell apoptosis, unclean sexual behavior as well as infection of human papillomavirus (HPV) may be the causes of cervical cancer [6, 7].

It is confirmed by molecular epidemiology study that, the abnormal genetic mutations in certain genes of susceptible population may lead to a difference in the risk of cervical cancer among individuals. Cyclin D1 (CCND1) is an oncogene is located at human chromosome 11q13. The expressed protein controls the transition of cell cycle from G1 to S, which is a key regulator in cell cycle. CCND1 is specifically expressed in tumor tissues, thereby it is closely related to the development of cancer [8]. In 1995, Bittcher et al. [9] first identified G87A (rs9344) mutation on the terminal of the fourth exon of CCND1 gene. Although the mutation didn't affect the structure of amino acids, it caused the generation of two mRNA transcripts, leading to the increase in the half-life of encoded proteins as well as the abnormal proliferation of tumor cells.

In 2005, Catarino et al. [10] first conducted the case-control study among the Portugal population, and they investigated G870A polymorphism in CCND1 gene and the risk of cervical cancer among European population. Until now, several related studies have been reported. However, the results are inconsistent, even contradictory. In this study, we made a comprehen-

Table 1. The characteristics of the included studies

Author	Year	Country	Case	Control	Genotype					
					Case			Control		
					GG	GA	AA	GG	GA	AA
Catarino	2005	Portugal	143	103	35	64	44	9	55	39
Castro	2009	Sweden	952	1713	229	463	260	465	837	411
Warchol	2011	Poland	129	288	35	65	29	116	123	49
Djansugurova	2013	Kazakhstan	215	160	54	103	58	41	78	41
Catarino	2008	Portugal	226	247	60	103	63	40	138	69

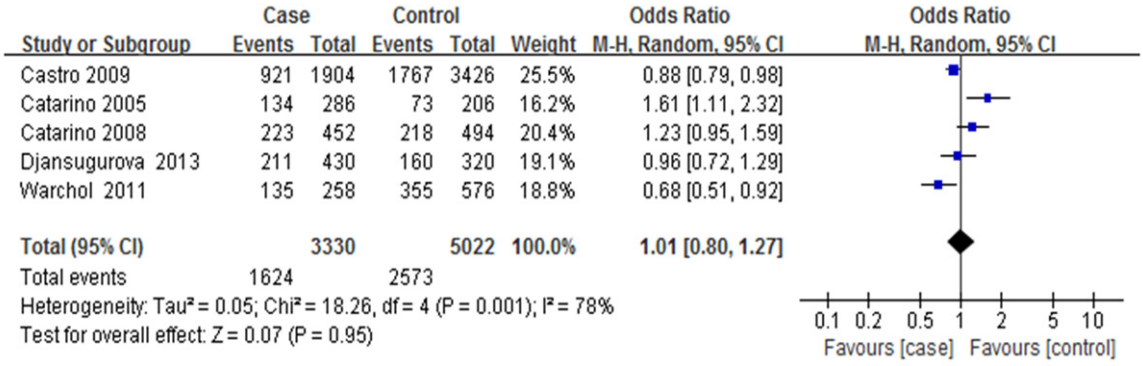


Figure 1. Forest plot of cervical cancer susceptibility and G870A polymorphism (G allele *vs.* A allele), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

sive quantitative evaluation on the previous results by meta-analysis, and assessed the correlation between G870A polymorphism in CCND1 gene and the risk of cervical cancer.

Material and methods

Search strategy

The PubMed and EMBASE data were searched, and the published correlative study of polymorphism in CCND1 gene and cervical cancer susceptibility was collected. The key words for searching included "cervical cancer", "cervical", "cancer", "Cyclin D1", and "polymorphism". The related data were traced through literatures.

Including criteria of literatures

All of the studies included should meet the following criteria: 1) The literature was the published case-control study on cervical cancer and CCND1 gene polymorphism, which was written in English; 2) The relevant data in the literature should be complete, or could be deduced according to the data in the literature; 3) When there was similarity or overlap in the data among several literatures, enroll the literature with the maximal data or the latest literature; 4) The patients were Caucasian population.

Exclusion criteria

We excluded the literatures if 1) not case-control study on cervical cancer and CCND1 gene polymorphism; 2) the patients were not Caucasian population.

Data extraction

Two investigators independently read and extracted relevant data from the literatures, confirmed by cross-checking. If there was inconsistency, it would be transferred to a third-party for solution. The information included: the name of the first author, published time, country (race) of subjects, data of genotype.

Statistical analysis

The odds ratio (OR) and 95% confidence interval (CI) derived from data merging were used to

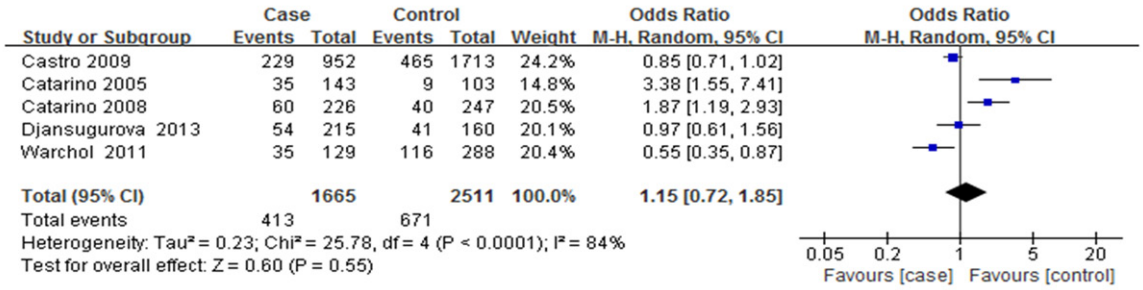


Figure 2. Forest plot of cervical cancer susceptibility and G870A polymorphism (GG vs. GA + AA), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

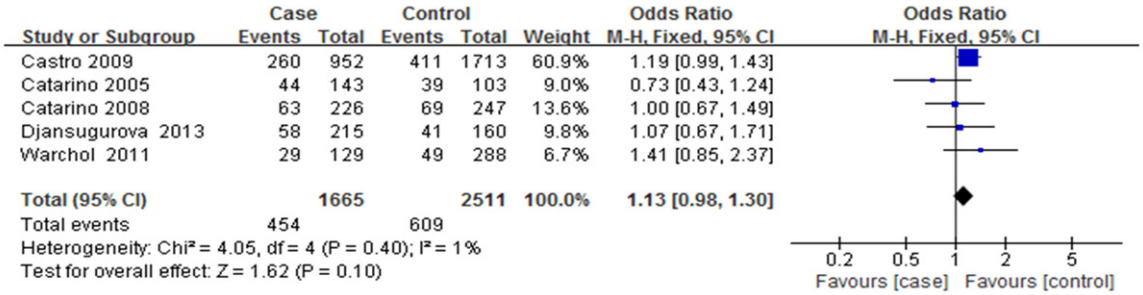


Figure 3. Forest plot of cervical cancer susceptibility and G870A polymorphism (AA vs. GG + GA), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

assess the relationship strength of G870A polymorphism in CCND1 gene and the risk of cervical cancer. The heterogeneity of the merged data was evaluated by Chi-square test and I^2 test, and the heterogeneity of inter-studies was evaluated by Cochran Q test. $I^2 < 25\%$ indicated a slight heterogeneity, 25%-50% indicated a moderate heterogeneity, and $I^2 > 50\%$ indicated a significant heterogeneity. If the heterogeneity of inter-studies was significant ($I^2 > 50\%$), random effect model should be applied for data merging, and if the heterogeneity of inter-studies was insignificant ($I^2 \leq 50\%$), then fixed effect model should be used. The publication bias was evaluated by funnel plot, and the data significance was evaluated by sensitivity analysis. RevMan 5.2 software was used for statistical analysis. $P < 0.05$ was considered as significant difference.

Results

Results of literature searching

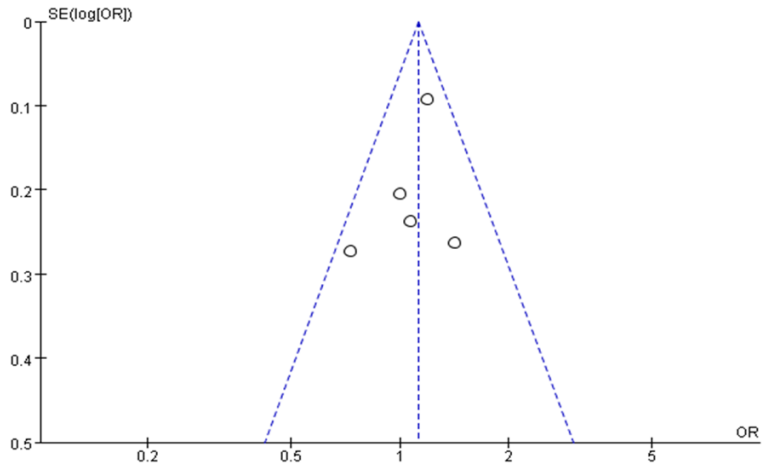
Through preliminary search, 38 literatures related to G870A polymorphism in CCND1 gene and the risk of cervical cancer were collected. After screening, 5 case-control studies were included [10-14], including 1665 patients with cervical cancer and 2511 healthy people as control. The genotyping methods applied were PCR-RFLP and TaqMan methods. The basic characteristics included in the study are shown in **Table 1**.

Results of meta-analysis

As shown in **Figures 1-3**, there was no significant correlation between G870A polymorphism in CCND1 gene and the risk of cervical cancer (G allele vs. A: OR = 1. 01, 95% CI = 0. 80-1. 27, P = 0.95; AA vs. GA + GG: OR = 1.13, 95% CI = 0.98-1.30, P = 0.10; (GA + AA) vs. GG: OR = 1.15, 95% CI = 0.72-1.85, P = 0. 55).

Results of publication bias

Through Begger's test, the funnel plot showed that, in all of the plots of genetic model, the distribution of the studies enrolled was fundamentally symmetric, without significant bias (**Figure 4**).



Figures 4. The funnel plot for publication bias.

Results of sensitivity analysis

The literatures included in the study were excluded one by one in each genetic model, and the sensitivity was analyzed. It revealed that the OR value and 95% CI of the corresponding model did not change substantially after exclusion, suggesting that the statistical result of our study was reliable.

Discussion

The latest epidemiology study has shown that the development of malignant tumors is a process involving various genes and factors and the interaction result of environmental factors and genetic factors [15-19]. Infection of HPV, unclean sexual behavior, smoking and drinking may be the main causes of cervical cancer. Individual genetic mutation, especially single nucleotide polymorphism (SNPs), may be the main cause for the difference in the risk of cervical cancer among individuals [20].

Cyclin D1 (CCND1) is an oncogene related to cell cycle, and its expressed protein is the key protein of proliferation signaling in G1 stage. CCND1 has been shown to play an important role in the development of malignant tumors and closely relate to the development, metastasis and prognosis of tumors. The G870A mutation in the transcription-splicing supply region located at the terminal of the fourth exon of CCND1 may cause the way of splicing to change and result in the generation of CCND1 protein with abnormal half-life. Consequently, CCND1 accumulated in cells, increasing the risk of malignant tumors.

In 2005, Catarino et al. [10] first conducted the case-control study among the Portugal population, and they found that the GG genotype of G870A loci in CCND1 gene might increase the risk of cervical cancer among European population (OR = 3.45, 95% CI = 1.47-7.56). And in 2009, Thakur et al. [11] found that AA genotype might increase the risk of cervical cancer among Indian population (OR = 2.40, 95% CI = 1.51-4.09). Catarino et al. [12] and Castro et al. [13] showed that the risk of population carrying A allele was 1.17 times of that of healthy people (95% CI = 1.02-1.27). While Warchol et al. [14] found that Poland population carrying (AA + AG) genotype had an obvious increase in the risk of cervical cancer (OR = 1.81, 95% CI = 1.15-2.85).

In this study, Begg's methods were applied to evaluate the publication bias and sensitivity of the literatures included in the study. No significant publication bias and substantial data deviation were found, indicating that the results were reliable. Meta-analysis could systemically integrate relevant studies. In this way, the sample size was increased, avoiding the systemic error because of relative small sample size and obtaining comparatively objective and reliable conclusion. This study still has some limitations: 1) The amount of studies included was inadequate, the population was confined to European and Asian population, and inadequacy of the data might result in uncertainty of the results; 2) This study only focused on G870A polymorphism in CCND1 gene, and there was no further study on other related locus and haploid; 3) The fundamental information of individuals included in the study was insufficient, and the lacking of information on smoking and drinking history as well as infection rate of HPV confined the study of environmental-genetic interaction and cervical cancer susceptibility.

The meta-analysis enrolled 5 case-control studies, including 1665 patients with cervical can-

cer and 2511 people as control. No significant correlation between G870A polymorphism in CCND1 gene and the risk of cervical cancer was found. Given the limits of the sample size and the scope of the study, further large-scale, multi-center and multi-race case-control studies are required to verify the conclusion of the meta-analysis and deeply investigate the correlation between G870A polymorphism in CCND1 gene and genetic-environmental interaction as well as the development of cervical cancer.

Disclosure of conflict of interest

None.

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