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Lack of association between *Cyclin D1* gene G870A polymorphism and esophageal cancer: evidence from a meta-analysis

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ABSTRACT. The association between the *Cyclin D1* gene (*CCND1*) G870A polymorphism and esophageal cancer has been widely evaluated, with conflicting results. As meta-analysis is a reliable approach to resolving discrepancies, we aimed to evaluate this association. Data were available from 9 study populations incorporating 1898 cases and 3046 controls. Overall, the allelic/genotypic association between the G870A polymorphism and esophageal cancer was nonsignificant [for allele: odds ratio (OR) = 1.14, 95% confidence interval (95%CI) = 0.94-1.38, P = 0.184; for genotype homozygous comparison: OR = 1.36, 95%CI = 0.90-2.06, P = 0.140; for dominant model: OR = 1.24, 95%CI = 0.88-1.75, P = 0.222; for recessive model: OR = 1.13, 95%CI = 0.90-1.43, P = 0.292]. Moreover, subgroup analyses according to study designs, geographic areas, types of esophageal cancer, genotyping methods, and ethnicities failed to demonstrate a significant association between this polymorphism and esophageal cancer. In addition, there was significant publication bias as reflected by funnel plots and the

Egger test (P = 0.042). Taken together, our results suggest that the *CCND1* G870A polymorphism might not be a potential candidate for predicting esophageal cancer risk.

Key words: Esophageal cancer; *CCND1* gene; Polymorphism; Meta-analysis; Genetic association

INTRODUCTION

Esophageal cancer, with a 5-year survival rate below 20%, is one of the most common and most deadly malignancies worldwide (Jemal et al., 2008). Although the mechanisms of esophageal carcinogenesis are not well understood, it is generally accepted that the development of esophageal cancer is a complex, multistep, and multifactorial process involving a variety of risk factors. Specifically, smoking, drinking, micronutrient deficiency, and exposure to dietary carcinogens have been reported to be the main contributors to this disease. However, only a small portion of at-risk individuals exposed to the above factors will develop esophageal cancer, and most patients do not carry these known risk factors (Hiyama et al., 2007), suggesting genetic involvement in esophageal carcinogenesis.

Cyclin D1, also known as *CCND1*, is located on chromosome 11q13 and is a key regulator of the G1 phase of the cell cycle (Fu et al., 2004). *CCND1* binds to and activates its kinase partners CDK4 and CDK6, which results in the phosphorylation of the retinoblastoma protein and further affects the transcription of genes that promote progression to the S-phase of the cell cycle (Mallya and Arnold, 2000). Experimental models showed that upregulation of *CCND1* expression enhanced the metastatic efficiency of esophageal cancer (Zhou et al., 2009), supporting the notion that *CCND1* plays a pivotal role in the development of esophageal cancer.

Many polymorphisms have been identified in *CCND1*. A common functional polymorphism, G870A (rs603965), which increased the frequency of alternative splicing and encoded a protein with an altered C-terminal domain and increased the stability or half-life of the protein, has garnered wide attention. It was proposed that DNA-damaged cells in individuals with the A allele may bypass the G1/S checkpoint, leading to an increased proportion of cells with DNA damage and genetic alterations (Betticher et al., 1995). Meanwhile, epidemiological studies have reported an association between the *CCND1* A/A genotype and increased risk of various cancers, including cervical (Jeon et al., 2005; Satinder et al., 2008; Thakur et al., 2009) and colorectal cancer (Ho-Pun-Cheung et al., 2007; Talseth et al., 2008; Tan et al., 2008). Although some studies have attempted to link this polymorphism with esophageal cancer, the results are often not reproducible. Generally, replication failure might result from genetic heterogeneity across different races or ethnicities, as well as individually underpowered studies. To address this issue, we investigated whether the *CCND1* G870A polymorphism is associated with esophageal cancer by meta-analysis and assessed whether this polymorphism shows genetic heterogeneity across different study designs, geographic areas, types of esophageal cancer, genotyping methods, or ethnicities.

MATERIAL AND METHODS

Literature search

We searched the MEDLINE, EMBASE, and Web of Science engines for studies

published before March 7, 2012. The key words used for searching were “Cyclin D1” or “CCND1” and “esophageal cancer” along with “polymorphism”.

We also checked the reference lists of all retrieved articles to ensure the comprehensiveness of this meta-analysis. If articles involved more than 1 geographic or ethnic heterogeneous group, we showed them separately. If more than 1 article shared the same sample, we removed the article with smaller sample size. Articles written in English and studies performed in humans were identified.

Inclusion and exclusion criteria

Articles were included if they evaluated the *CCND1* gene G870A polymorphism and esophageal cancer risk; if they were conducted in a case-control, nested case-control, or cross-sectional design; and if they provided sufficient information regarding genotype distributions between both cases and controls. Meanwhile, we only focused on esophageal cancer rather than other 2nd neoplasms. We excluded case reports or series, editorials, review articles, and non-English articles.

Extracted information

From each qualified articles, two authors (W.C. and Z.T.W.) independently drew the following information: 1st author’s last name, year of publication, ethnicity of the population studied, study design, number of subjects in each category, baseline characteristics of the study populations, and the number of persons with different genotypes in cases and controls. We resolved discrepancies by discussion until a consensus was reached.

Statistical analysis

In this meta-analysis, we used the allelic (870A *vs* 870G), homozygous (870AA *vs* 870GG), dominant (870AA plus 870GA *vs* 870GG), and recessive models (870AA *vs* 870GG plus 870GA). Hardy-Weinberg equilibrium was calculated by the χ^2 test.

The fixed-effect model was used if between-study heterogeneity was absent (I^2 statistics) and the random-effect model was used otherwise (Higgins et al., 2003). In this meta-analysis, only the random-effect model was applied since within a fixed-effect model, only sampling error contributes to the differences between the observed effect-size estimates across individual studies (Cohn and Becker, 2003; Borenstein et al., 2009). Between-study heterogeneity was quantified by the inconsistency index I^2 statistic, which ranged from 0 to 100%. The I^2 statistic was documented for the percentage of the observed between-study variability due to heterogeneity rather than chance, with higher values of this index suggesting the existence of heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). If between-study heterogeneity was significant, we examined the study characteristics that could stratify the studies into subgroups with homogeneous effects.

Publication bias was tested by funnel plots and the Egger test. The Egger test can detect funnel plot asymmetry by determining whether the intercept deviates significantly from 0 in a regression of the standardized effect estimates against their precision.

Significance was judged at $P < 0.1$ for the I^2 statistic and the Egger test. We managed the data and performed statistical analyses by using the STATA software (version 11.0 for Windows; StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics

After an extensive search, a total of 12 studies were collected based on our inclusion/exclusion criteria. If more than 1 geographical or ethnic group was included in the same study, then data from different populations were extracted. Therefore, 8 studies, including 9 populations (Yu et al., 2003; Zhang et al., 2003; Casson et al., 2005; Geddert et al., 2005; Jain et al., 2007; Akbari et al., 2009; Liu et al., 2010; Hussain et al., 2011) with 1898 patients with esophageal cancer and 3046 controls were finally identified: 4 populations were from East Asia [2 Chinese (Yu et al., 2003; Zhang et al., 2003) and 2 from India (Jain et al., 2007; Hussain et al., 2011)], 2 were from West Asia (Akbari et al., 2009), and 3 included Caucasians (Casson et al., 2005; Geddert et al., 2005; Liu et al., 2010). A flow diagram schematizing the process of selected and excluded articles with specific reasons for each is presented in Figure 1.

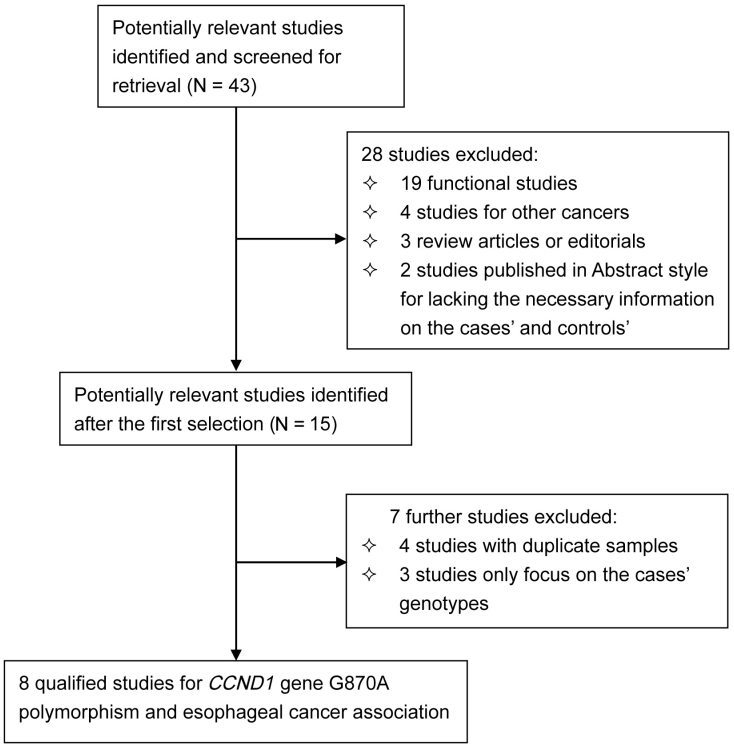

Figure 1. Flow diagram of search strategy and study selection.

With regard to the study design, 3 of these studies were population based (Yu et al., 2003; Zhang et al., 2003; Akbari et al., 2009), and 5 employed a hospital-based design (Casson et al., 2005; Geddert et al., 2005; Jain et al., 2007; Liu et al., 2010; Hussain et al., 2011). The baseline characteristics of all eligible studies are summarized in Table 1.

Table 1. Baseline characteristics from all eligible studies.

Study	Year	Histology types	Ethnicity	Genotyping methods	Study design	Number (case/control)	Age [mean (SD), years]		Number [males (%)]		870A allele frequency (%)	
							Cases	Controls	Cases	Controls	Cases	Controls
Zhang et al.	2003	ESCC	Chinese	PCR-based	Population	120/183	55.7 (13.1)	47.5 (11.7)	65.00	66.67	60.00	51.37
Yu et al.	2003	ESCC	Chinese	PCR-based	Population	321/345	NA	NA	NA	NA	54.36	57.54
Casson et al.	2005	EA	Canadian	PCR-based	Hospital	56/95	NA	NA	89.29	67.37	54.46	35.79
Geddert et al.	2005	EA	Germany	PCR-based	Hospital	56/253	61	43	82.14	68.38	48.21	48.22
Jain et al.	2007	ESCC	Indian	PCR-based	Hospital	151/201	56.4 (12.3)	56.6 (9.1)	75.50	71.00	60.26	53.98
Akbari et al.	2009	ESCC	Turkish	Array	Population	195/250	63.6	55.2	50.94	50.98	48.46	54.80
Akbari et al.	2009	ESCC	Mixed	Array	Population	549/1118	63.6	55.2	50.94	50.98	53.92	56.35
Liu et al.	2010	EA	American	Taqman	Hospital	299/450	64	64	89.42	87.44	47.83	47.67
Hussain et al.	2011	ESCC	Indian	PCR-based	Hospital	151/151	NA	NA	58.28	56.95	53.97	39.07

SD = standard deviation; ESCC = esophageal squamous cell carcinoma; EA = esophageal adenocarcinoma; NA = not available.

The frequencies of the *CCND1* gene +870A allele in patients ranged from 47.83 to 60.26%, and that of controls varied from 35.79 to 57.54%. No deviations from Hardy-Weinberg equilibrium were observed in the genotype distributions of controls at the significance level of 0.05.

Genetic association

The combined results based on all studies showed that there was no statistically significant link between the *CCND1* G870A polymorphism and esophageal cancer susceptibility in the allele model [odds ratio (OR) = 1.14, 95% confidence interval (95%CI) = 0.94-1.38, P = 0.184]. Since the test for heterogeneity among the studies was significant (P < 0.0005, I^2 = 78.1%; Figure 2), the random-effect model was conducted. Lack of significance persisted in homozygous models for comparison of 870AA with 870GG (OR = 1.36, 95%CI = 0.90-2.06, P = 0.140), as well as in dominant (OR = 1.24, 95%CI = 0.88-1.75, P = 0.222) and recessive (OR = 1.13, 95%CI = 0.90-1.43, P = 0.292) models.

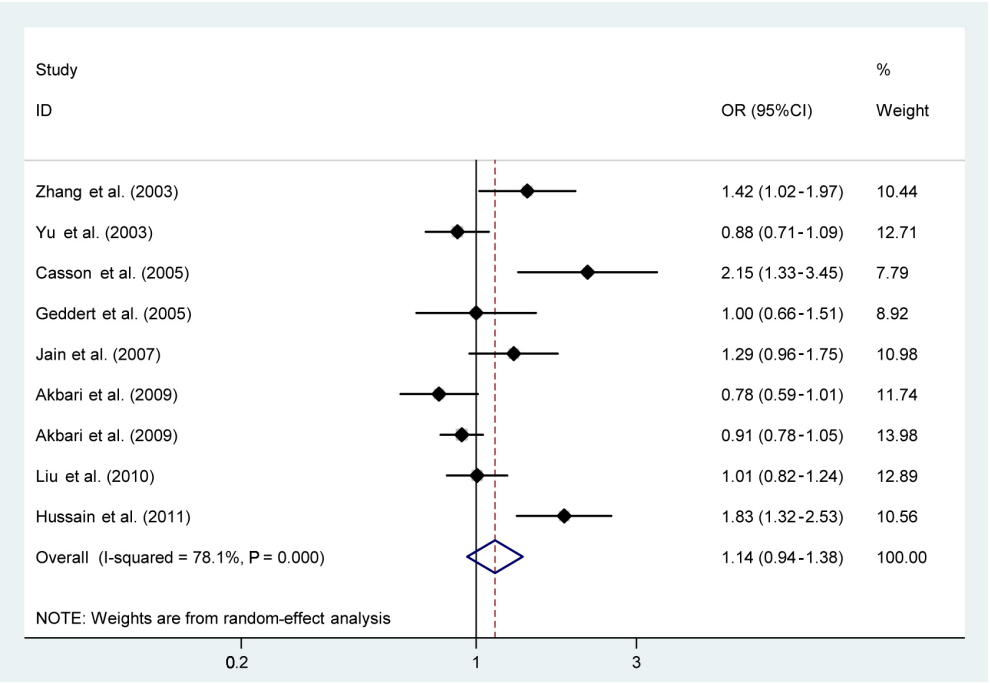

Figure 2. Contrast of the *CCND1* gene 870A allele versus the 870G allele. The combined results based on all studies showed that there was no statistically significant link between the *CCND1* G870A polymorphism and esophageal cancer susceptibility in allele model. Odds ratio (OR) = 1.14, 95% confidence interval (95%CI) = 0.94-1.38.

Subgroup analyses

Considering that the study design, the geographic difference, the type of esophageal cancer [esophageal adenocarcinoma (EA) or esophageal squamous cell carcinoma (ESCC)],

and the method of genotyping might bias the overall association results, we conducted separate analyses according to these factors.

In view of the study design, no obvious association existed in the population-based subgroup, although a significant association between the *CCND1* A870G polymorphism and esophageal cancer risk was observed for the allele model (OR = 1.35, 95%CI = 1.01-1.80, P = 0.04) and the homozygous genotype model (OR = 1.95, 95%CI = 1.02-3.75, P = 0.044) in the hospital-based subgroup.

When stratifying by the genotyping method, no obvious association existed in either the Taqman or Chip subgroup, while a significant increased risk was found in the PCR-based subgroup for the allele model (OR = 1.33, 95%CI = 1.01-1.76, P = 0.045). Similarly, there was a statistically significant increased risk in the PCR-based subgroup for the homozygous genotype model (OR = 1.98, 95%CI = 1.02-3.85, P = 0.043), as well as in the recessive model (OR = 1.42, 95%CI = 1.00-2.02, P = 0.047).

In the subgroup analysis based on geographic area, we still observed no material changes except in West Asian studies. For example, in populations from West Asia, the 870A allele and 870AA homozygous genotype had 13 and 23% reduced risk of esophageal cancer (for the 870A allele: OR = 0.87, 95%CI = 0.77-0.99, P = 0.041; for the 870AA genotype: OR = 0.77, 95%CI = 0.60-0.99, P = 0.043), respectively.

In the subgroup meta-analysis based on the type of esophageal cancer, nearly no changes in ORs were observed in the ESCC and EA subgroups for *CCND1* A870G polymorphisms.

Publication bias

As reflected by the funnel plot (Figure 3) and the Egger test, there was significant publication bias existing for the *CCND1* gene A870G polymorphism (t = 2.49, P = 0.042).

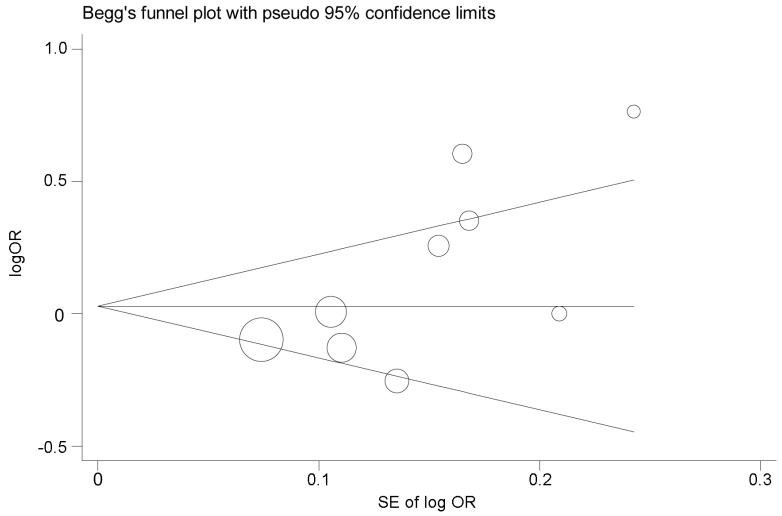

Figure 3. Begg's funnel plot of publication bias test for the *CCND1* A870G polymorphism. As reflected by the funnel plot, there was significant publication bias exiting for the *CCND1* gene A870G polymorphism. SE = standard error. OR = odds ratio.

DISCUSSION

Although some statistical biases could not be eliminated and the between-study heterogeneity was alarming, our results suggest that the *CCND1* A870G polymorphism is not significantly associated with esophageal cancer in general populations. This study, including 4944 subjects from 9 populations, to our knowledge, is the 1st meta-analysis examining the relationship between the *CCND1* A870G polymorphism and occurrence of esophageal cancer. This result requires further investigation, not only due to the relatively small sample size, but also because of genetic heterogeneity and the differences in the study design, genotyping method, and esophageal cancer type, which were identified as potentially significant sources of between-study heterogeneity in this study.

Firstly, genetic heterogeneity is an inevitable problem in any disease identification strategy (Hemminki et al., 2006). In our analyses by geographic areas, the *CCND1* A870G polymorphism showed significant heterogeneity in esophageal cancer across different subgroups, with the 870A allele and the 870AA genotype in West Asia presenting 13 and 23% reduced risk, respectively. However, we could not detect any significant esophageal cancer risk variation for all genetic models in East Asians or Caucasians. Different genetic backgrounds may cause this discrepancy or different populations may have different linkage disequilibrium patterns. A polymorphism may be in close linkage with another nearby causal variant in one ethnic population but not in another (Yu et al., 2010). Thus, it is reasonable to hypothesize that the *CCND1* A870G polymorphism might be in close linkage with different nearby causal variants in different populations. Moreover, this polymorphism might have a pleiotropic role in the pathogenesis of esophageal cancer or might interact with other genetic and environmental factors. However, considering the relatively small sample sizes in this study, we suggest that confirmation in large, well-designed studies is critical.

Secondly, study design and genotyping method might also be significant contributors to the *CCND1* A870G polymorphism and esophageal cancer risk. With regard to study design, although allele and homozygous genotype comparison of the A870G polymorphism generated a marginally significant association in hospital-based studies, we ran the risk of overestimating the magnitude of this association in view of the striking weaknesses of this type of design, such as population stratification and admixture. Contrastingly, no positive signal was identified in population-based studies, reinforcing the quality of our conclusion. For the genotyping method, a marginal association was noted with the PCR-based method, which was susceptible to genotypic misclassification errors. Likewise, a negative association was preserved in the Chip or Taqman method. Therefore, to obtain convincing evidence, well-designed studies using less error-prone methods are encouraged.

Thirdly, EA and ESCC are the 2 main histological types of esophageal cancer and have great differences in etiology and tumor biology (van Baal et al., 2008). For example, EA is quite common in Western countries, and it is widely believed that EA arises from Barrett esophagus, an acquired condition in which the normal esophageal squamous epithelium is replaced by a metaplastic columnar cell-lined epithelium (Williams et al., 2006). However, ESCC is the major subtype in the Asia-Pacific countries, and its development is reportedly attributed to smoking, alcohol consumption, and betel quid chewing (Chung et al., 2010). In view of this geographic distribution difference, we subgrouped studies according to the types of esophageal cancer and found that the magnitude of the association between the *CCND1*

A870G polymorphism and esophageal cancer was augmented in the EA group relative to the ESCC group across all genetic comparisons except in the dominant model (Table 2), although the pooled associations lacked statistical significance. Considering the relatively small sample sizes in each subgroup, additional research within the framework of genetics and biology is needed in various types of esophageal cancer.

Table 2. Subgroup analysis of the *CCND1* gene A870G polymorphism and esophageal cancer.

Subgroup	Study number	A *vs* G		AA *vs* GG		Dominant		Recessive	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Geographic area									
East Asians	4	1.29 (0.93-1.80)	0.128	1.85 (0.84-4.09)	0.129	1.74 (0.79-3.81)	0.169	1.22 (0.93-1.60)	0.159
West Asians	2	0.87 (0.77-0.99)	0.041	0.77 (0.60-0.99)	0.043	0.80 (0.60-1.07)	0.128	0.85 (0.70-1.04)	0.117
Caucasians	3	1.25 (0.81-1.91)	0.310	1.67 (0.64-4.34)	0.291	1.18 (0.77-1.81)	0.443	1.59 (0.68-3.70)	0.280
Study design									
Population	4	0.94 (0.78-1.14)	0.543	0.92 (0.59-1.42)	0.696	0.94 (0.63-1.40)	0.754	0.91 (0.77-1.06)	0.226
Hospital	5	1.35 (1.01-1.80)	0.040	1.95 (1.02-3.75)	0.044	1.56 (0.93-2.62)	0.092	1.48 (0.96-2.28)	0.078
Method of genotyping									
PCR-based	6	1.33 (1.01-1.76)	0.045	1.98 (1.02-3.85)	0.043	1.58 (0.89-2.80)	0.117	1.42 (1.00-2.02)	0.047
Chip or Taqman	3	0.91 (0.81-1.02)	0.111	0.83 (0.66-1.03)	0.084	0.89 (0.68-1.15)	0.361	0.87 (0.73-1.03)	0.103
Type of EC									
ESCC	6	1.10 (0.87-1.40)	0.409	1.28 (0.77-2.14)	0.336	1.27 (0.78-2.07)	0.330	1.04 (0.84-1.29)	0.713
EA	3	1.25 (0.81-1.91)	0.310	1.67 (0.64-4.34)	0.291	1.18 (0.77-1.81)	0.443	1.59 (0.68-3.70)	0.280

OR = odds ratio; 95%CI = 95% confidence interval; EC = esophageal cancer; ESCC = esophageal squamous cell carcinoma; EA = esophageal adenocarcinoma.

Lastly, some limitations of this meta-analysis should be addressed. First, only articles written in English were identified in this meta-analysis, which may be the major cause of the high probability of publication bias. Second, most of the studies included were limited by the small sample size. Moreover, the population from 8 studies was not uniform. As in other investigations, the source of heterogeneity may include geographic area, the study design, the geographic area, the type of esophageal cancer (EA or ESCC), as well as the method of genotyping used. Third, the single-locus-based nature of this meta-analysis precluded the possibility of gene-gene and gene-environment interactions, as well as haplotype-based effects, suggesting that additional studies assessing these aspects will be necessary. Furthermore, we only centered on the *CCND1* A870G polymorphism and did not evaluate other genes or polymorphisms. It seems likely that the A870G polymorphism individually makes a moderate contribution to risk prediction in esophageal cancer patients, although whether this polymorphism integrated with other risk factors will enhance the predictive power requires additional research. Thus, we must refrain from drawing a firm conclusion until large, well-performed studies confirm or refute our results.

Taken together, we expanded previous individually underpowered studies regarding esophageal cancer risk by suggesting that no obvious association was found between *CCND1* A870G and esophageal cancer susceptibility. In addition, our observations raise the question of a potential heterogeneous effect of A870G across different ethnic populations. Nevertheless, for practical reasons, we hope that this study will not remain just another endpoint of research, and instead will represent a beginning to establish the background data for further investigation of the association between the *CCND1* gene and esophageal cancer.

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