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Vascular endothelial growth factor +936C/T polymorphism and cancer risk in Asians: a meta-analysis

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ABSTRACT. Vascular endothelial growth factor (VEGF), the most important regulator of angiogenesis and vascular permeability, is involved in various steps of carcinogenesis. The +936C/T polymorphism of the VEGF gene has been reported to affect the VEGF protein level and to be related to the susceptibility of cancer. However, the results of published studies, as well as the subsequent meta-analyses, remain contradictory. We investigated the association between VEGF +936C/T polymorphism and cancer risk in the Asian population. Twenty-one papers were selected from the PubMed database after a systematic search. Statistics on the frequencies of CC, CT, and TT genotypes of the VEGF +936C/T gene were collected from 8298 cases and 8053 controls. No significant associations between the VEGF +936C/T polymorphism and cancer risk were found for alleles T *vs* C [odd ratio (OR) = 0.99, 95% confidence interval (95%CI) = 0.93-1.05], TT *vs* CT/CC (OR = 1.05, 95%CI = 0.88-1.26), CC *vs* CT/TT (OR = 1.02, 95%CI = 0.96-1.10), and TT *vs* CC (OR = 1.05, 95%CI = 0.88-1.25). No significant associations were detected in the subgroup analysis by

cancer type either. The VEGF +936C/T polymorphism is not associated with risk of overall cancer among Asians.

Key words: Cancer; Vascular endothelial growth factor; Asian; Single nucleotide polymorphism

INTRODUCTION

As we all know, the malignancies are lethal largely due to their advanced stage at diagnosis. Thus, the discovery of genetic factors associated with cancer risk may help lower the stage and improve survival (Bosch et al., 2011; Jelovac and Armstrong, 2011).

Angiogenesis, which plays a pivotal role in carcinogenesis by influencing growth, invasion, and the formation of metastases, is regulated by a balance of pro- and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) is a crucial player in angiogenesis as it represents the principal pro-angiogenic factor. High VEGF levels have been proven to have association with many malignances such as ovarian cancer (Cooper et al., 2002), colorectal cancer (Alabi et al., 2009), and gastric cancer (Ohta et al., 2003).

The human VEGF gene is located on chromosome 6p21.3 and consists of 8 exons separated by 7 introns (Vincenti et al., 1996). Several single nucleotide polymorphisms have been shown to affect the expression of the VEGF gene, including the VEGF +936C/T polymorphism in the 3'-untranslated region of the VEGF gene. Renner et al. (2000) found that +936T allele carriers had significantly lower VEGF plasma levels, suggesting that it could be a genetic marker for angiogenesis-associated disease. To date, a large number of studies have focused on exploring the association between the VEGF +936C/T polymorphism and risk of various types of cancer, including oral, gastric, colorectal, breast, lung, prostate, cervical, and so on. However, the results are conflicting. Taking breast cancer as an example, similar frequencies of VEGF +936C/T genotypes between cases and controls were reported by Jacobs et al. (2006). In contrast, Krippl et al. (2003), Kataoka et al. (2006), and Jakubowska et al. (2008) suggested that VEGF +936T is a protective factor against breast cancer. However, Balasubramanian et al. (2007) found that VEGF +936C was associated with decreased breast cancer risk when combined with -460T and +405C. Meta-analyses also failed to confirm the protective role of VEGF +936T (Gu and Wang, 2011; Yang et al., 2011).

We conducted this meta-analysis to determine if the VEGF +936C/T polymorphism modulates susceptibility in Asians.

MATERIAL AND METHODS

Publication search

PubMed was searched using the terms “Vascular endothelial growth factor gene polymorphism” and “cancer”. Additional studies were included by a manual inspection of the references cited in the original studies and reviews. Only English-language papers were included.

Inclusion and exclusion criteria

All studies that met the inclusion criteria were included in this meta-analysis; if not,

the study was excluded: i) case-control study based on the association between the VEGF +936C/T polymorphism and cancer risk; ii) the study contained detailed information on the frequencies of the CC, CT, and TT genotypes in both cases and controls, and iii) all cases and controls involved were Asians. If the study had the same population resource, only the study reporting the largest population was selected.

Data extraction

We followed a standard protocol for data extraction. For each study, the following information was recorded: first author's surname, year of publication, country or region, numbers of genotyped cases and controls, and genotyping method.

Statistical analysis

The odds ratios (OR) with 95% confidence intervals (95%CIs) of allele T *vs* allele C in cases and controls were calculated to assess the strength of the association between the VEGF +936C/T polymorphism and cancer risk, as well as the recessive genetic model (TT *vs* CT/TT), dominant genetic model (CC *vs* CT/TT), and homozygote comparison (TT *vs* CC). Further stratified analyses were also performed in the subgroups sharing the same cancer type and consisting of more than two papers.

We used the Q-statistic to determine the degree of heterogeneity between the trials. $P < 0.05$ was interpreted as significant heterogeneity. When there was no statistical heterogeneity, we used a fixed-effect model (the Mantel-Haenszel method). If heterogeneity was present, we used a random-effect model (the DerSimonian and Laird method). All statistical analyses were performed with the Stata software (version 11; Stata Corporation, USA). All statistical tests were two-sided.

RESULTS

Characteristics of studies

In total, 21 studies (Abe et al., 2002; Kataoka et al., 2006; Hsiao et al., 2007; Amano et al., 2008; Bae et al., 2008a,b; Chae et al., 2006, 2008; Cheng et al., 2008; Ke et al., 2008; Hsing et al., 2008; Al-Moundhri et al., 2009; Tahara et al., 2009; Wu et al., 2009; Li et al., 2010; Kim et al., 2010; Bao et al., 2011; Beeghly-Fadiel et al., 2011; Kang et al., 2011; Li et al., 2011; Zhou et al., 2011) comprising 8298 cancer cases and 8053 controls were included in the meta-analysis. The VEGF allele +936T frequency was 17.78% in cases and 17.84% in controls. According to the cancer type, we performed subgroup analyses for 6 gastric cancer risk studies and 4 colorectal cancer risk studies. The other characteristics of the studies included in the present meta-analysis are listed in Table 1.

Quantitative synthesis

In the overall analysis, no association could be observed between the VEGF +936C/T polymorphism and cancer risk when all the eligible studies were pooled, as was shown in T *vs* C (fixed effects, OR = 0.99, 95%CI = 0.93-1.05, P= 0.178) (Figure 1), TT *vs* CT/CC (fixed

effects, OR = 1.05, 95%CI = 0.88-1.26, P= 0.090) (Figure 2), CC *vs* CT/TT (fixed effects, OR = 1.02, 95%CI = 0.96-1.10, P= 0.352) (Figure 3), and TT *vs* CC (fixed effects, OR = 1.05, 95%CI = 0.88-1.25, P= 0.082) (Figure 4). According to the subgroup analyses by cancer type, there were no significant associations between the VEGF allele +936C/T polymorphism and risk of colorectal cancer and gastric cancer in different genetic comparisons.

Table 1. Main characteristics of the eligible studies.

No	Reference	Region	Cancer type	Case Nos.	Control Nos.	Genotyping method
1	Abe et al., 2002	Japan	Renal cell carcinoma	145	145	PCR-RFLP
2	Chae et al., 2006[a]	Korea	Gastric cancer	413	413	PCR-RFLP
3	Kataoka et al., 2006	China	Breast cancer	1109	1195	TaqMan
4	Hisao et al., 2007	Taiwan	Thyroid cancer	288	232	TaqMan
5	Amano et al., 2008	Japan	Endometrial carcinoma	105	179	PCR-RFLP
6	Bae et al., 2008[b]	Korea	Colon cancer	262	229	PCR-RFLP
7	Bae et al., 2008[b]	Korea	Gastric Cancer	154	229	PCR-RFLP
8	Ke et al., 2008	China	Gastric cancer	540	561	PCR-RFLP
9	Hsing et al., 2008	China	Biliary Cancer	407	779	TaqMan
10	Chae et al., 2008[a]	Korea	Colorectal cancer	465	413	PCR/DHPLC
11	Cheng et al., 2008	Taiwan	Oral squamous cell carcinoma	218	121	PCR-RFLP
12	Al-Moundhri et al., 2009	Omani	Gastric Cancer	130	130	PCR-RFLP
13	Wu et al., 2009	China	Colorectal cancer	157	117	PCR-RFLP
14	Tahara et al., 2009	Japan	Gastric cancer	385	316	PCR-RFLP
15	Li et al., 2010	China	Epithelial ovarian cancer	303	303	PCR-RFLP
16	Kim et al., 2010	Korea	Cervical cancer	198	214	PCR-SSP
17	Bao et al., 2011	China	Glioma	160	320	PCR-RFLP
18	Zhou et al., 2011	China	Gastric cancer	150	150	PCR-RFLP
19	Beeghly-Fadial et al., 2011[cd]	China	Breast cancer	1901	1801	TaqMan
20	Li et al., 2011	China	Glioma	758	798	MassARRAY
21	Kang et al., 2011[c]	Korea	Colorectal cancer	50	50	PCR-RFLP

TaqMan (Applied Biosystems, Foster City, CA, USA) and MassARRAY (Sequenom, San Diego, CA, USA) are commercial systems for single nucleotide polymorphism genotyping; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; DHPLC = denaturing high-performance liquid chromatography. [a]Data of Chae et al. (2006) were combined in analyses, since the articles share the same control subjects. [b]Data of Bae et al. (2008) were combined in analyses, since the articles share the same control subjects. [c]Data of Beeghly-Fadial et al. (2011) and Kang et al. (2011) were obtained by e-mail contact. [d]Beeghly-Fadial et al. (2011) provided genotyping information of 2261 participants from the SBCS I (Shanghai Breast Cancer Study, 1996-1998) and 3702 participants from the SBCS II (2002-2005). Since Kataoka et al. (2006) reported larger population based on SBCS I, only 3702 participants of this article were involved in this meta-analysis.

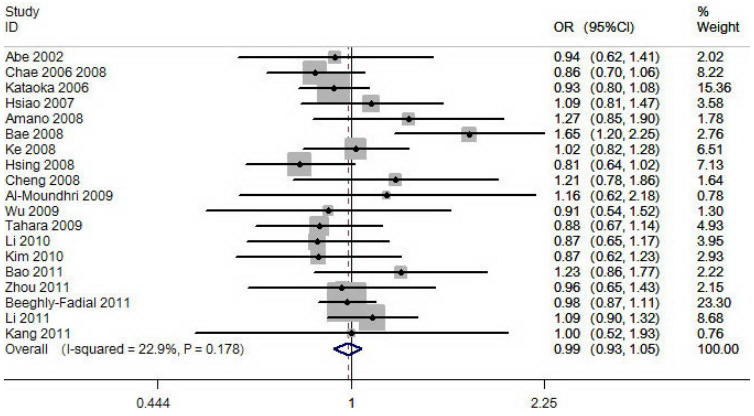

Figure 1. Forest plot of overall cancer risk associated with the VEGF +936C/T polymorphism (T *vs* C). OR = odds ratio; 95%CI = 95% confidence interval.

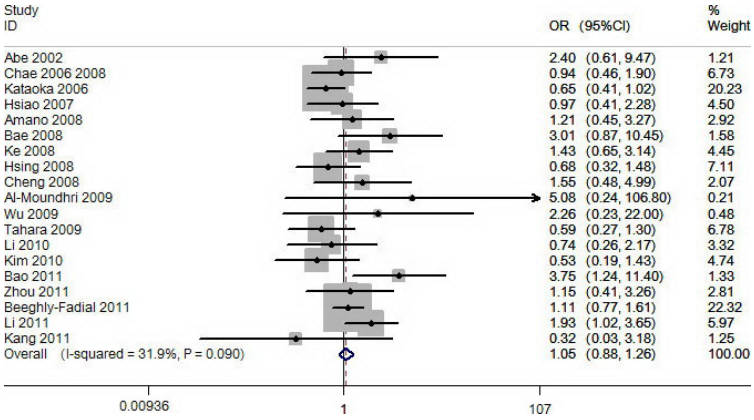

Figure 2. Forest plot of overall cancer risk associated with the VEGF +936C/T polymorphism (TT *vs* CT/CC). OR = odds ratio; 95%CI = 95% confidence interval.

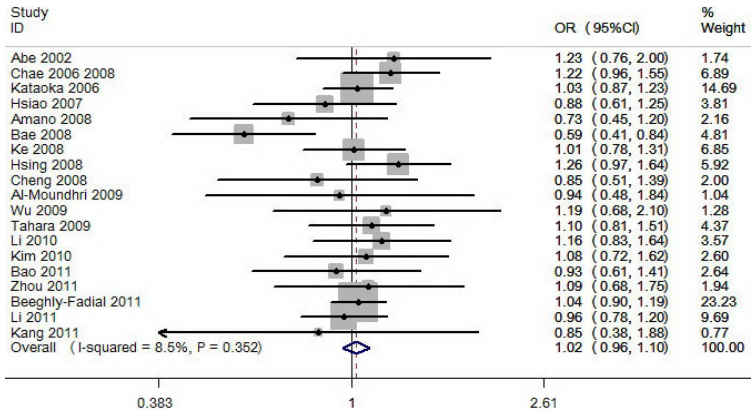

Figure 3. Forest plot of overall cancer risk associated with the VEGF +936C/T polymorphism (CC *vs* CT/TT). OR = odds ratio; 95%CI = 95% confidence interval.

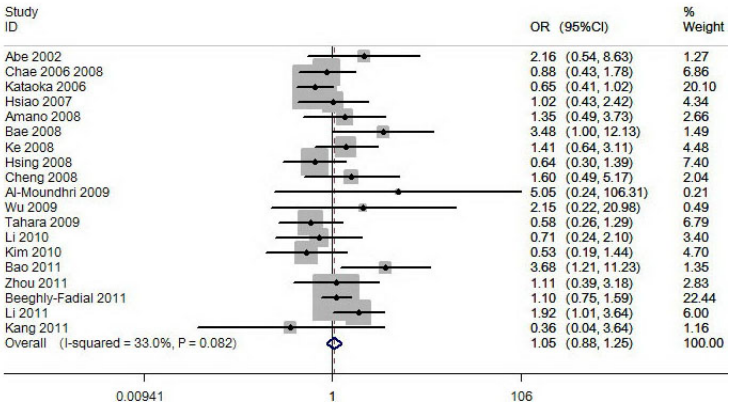

Figure 4. Forest plot of overall cancer risk associated with the VEGF +936C/T polymorphism (TT *vs* CC). OR = odds ratio; 95%CI = 95% confidence interval.

Publication bias

The publication bias of the studies was assessed by Begg's funnel plot and the Egger test. As shown in Figures 5-8, the shapes of the funnel plots did not reveal any obvious asymmetry, indicating the absence of publication bias in the studies. Subsequently, the Egger test was used to provide statistical evidence of the symmetry. As expected, the result revealed no obvious evidence of publication bias (t = 1.05, P = 0.307 in T *vs* C).

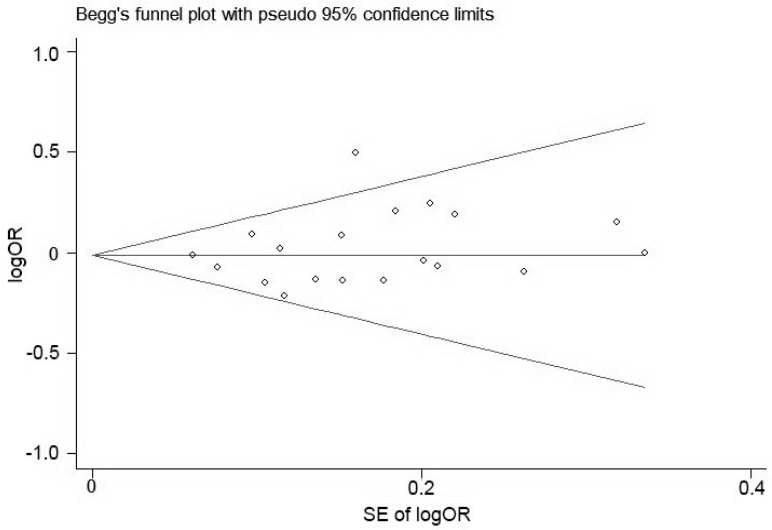

Figure 5. Begg's funnel plot for publication bias test (T *vs* C). SE = standard error; OR = odds ratio.

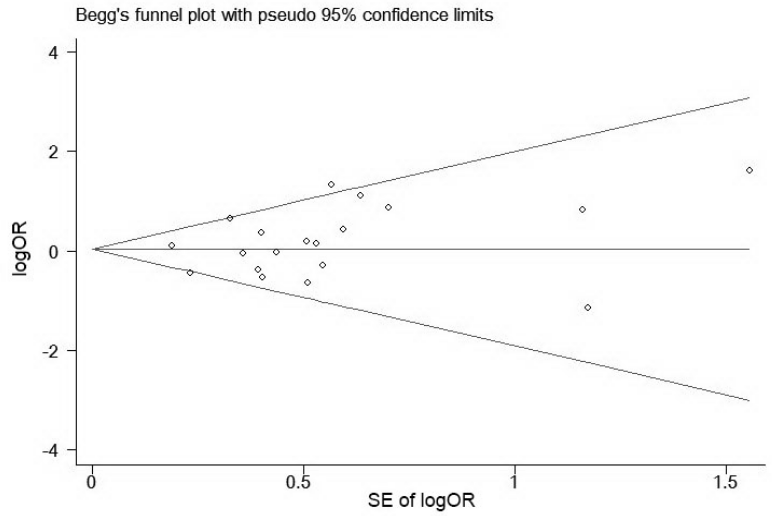

Figure 6. Begg's funnel plot for publication bias test (TT *vs* CT/CC). SE = standard error; OR = odds ratio.

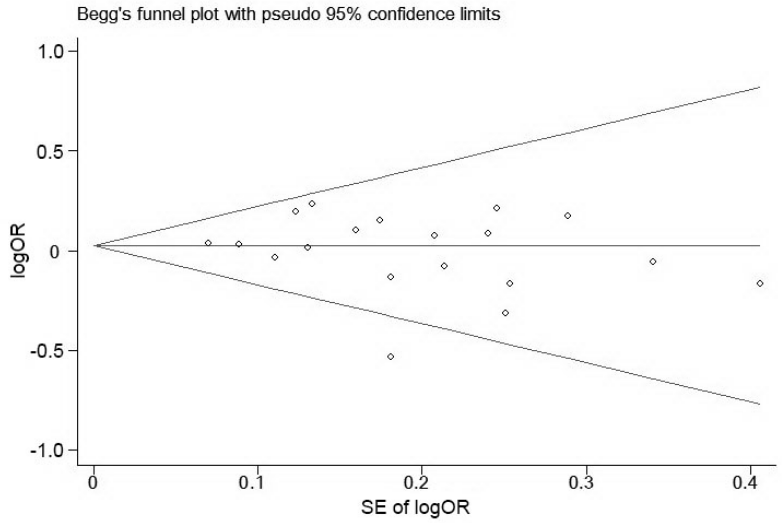

Figure 7. Begg's funnel plot for publication bias test (CC *vs* CT/TT). SE = standard error; OR = odds ratio.

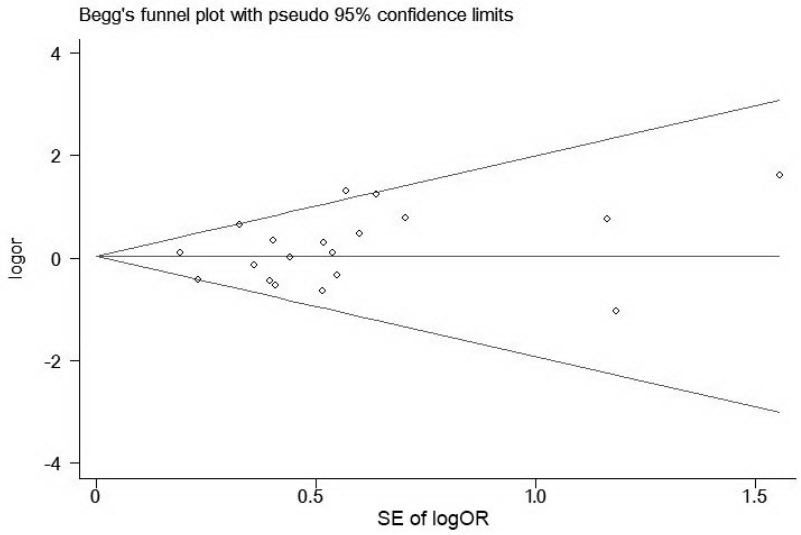

Figure 8. Begg's funnel plot for publication bias test (TT *vs* CC). SE = standard error; OR = odds ratio.

DISCUSSION

In our meta-analysis, no association between the VEGF +936C/T gene polymorphism with cancer risk was found among the Asian population. Subgroup analyses stratified by cancer type were also performed, and did not reveal any genotype differences between cases and controls (Table 2).

Table 2. Stratified analyses of the VEGF +936C/T polymorphism and cancer risk.

Cancer type		Gastric cancer	Colorectal cancer
Article numbers		6	4
Cases/controls		1772/1799	934/809
T *vs* C	OR (95%CI)	1.03 (0.84-1.26)	1.07 (0.90-1.27)
	P[a]	0.004	0.171
TT *vs* CT/CC	OR (95%CI)	1.06 (0.71-1.58)	1.36 (0.75-2.45)
	P	0.168	0.416
CC *vs* CT/TT	OR (95%CI)	1.00 (0.92-1.08)	0.94 (0.77-1.15)
	P	0.011	0.162
TT *vs* CC	OR (95%CI)	1.05 (0.70-1.56)	1.37 (0.76-2.49)
	P	0.095	0.396

[a]P = Q-statistic for heterogeneity. The random-effect model (DerSimonian-Laird method) was used when $P < 0.05$; the fixed-effect model (Mantel-Haenszel method) was used otherwise. OR = odds ratio; 95%CI = 95% confidence interval.

The exact mechanism for how VEGF +936C/T acted on the carcinogenic procedure was not clear. In recent years, intense genetic research efforts have been made in this field, and the results produced have been conflicting (Krippl et al., 2003; Jacobs et al., 2006; Kataoka et al., 2006; Balasubramanian et al., 2007; Jakubowska et al., 2008). The leading potential explanation for the association was that the DNA sequence variation may alter VEGF production and/or activity (Renner et al., 2000), thereby causing differences in the development of tumors (Kim et al., 2010). However, Bae et al. (2008b) believed that VEGF-related functions such as thrombosis (Verheul et al., 2000; Eroglu et al., 2007) made sense, instead of angiogenesis. The most confusing question was if the genetic association does exist, why could we not find the difference? First, the VEGF polymorphism may exert varying effects on various cancers, and the combined studies diminished the differences. Second, other VEGF genes could have interacted with VEGF +936C/T, thus affecting the VEGF serum level and being involved in the carcinogenesis. Third, as the pathogenesis of cancer is regulated by many factors, it is possible that other related genes and environmental factors (Xu et al., 2010) predominated in the development of cancer and obscured the role of VEGF +936C/T.

At the same time, Ke et al. (2008) suggested that VEGF is perhaps more likely to affect tumor biological behavior, such as tumor growth, invasion, and metastasis than it is in defining susceptibility to tumors. Thus, the VEGF +936C/T polymorphism appeared to be more effective in predicting the prognosis, rather than the cancer risk. In addition, Renner et al. (2000) believed that the 936C/T polymorphism could result in linkage disequilibrium with another yet unidentified functional polymorphism elsewhere and tolerated type II error in the studies. Moreover, the insufficient statistic power, stemming from the small sample size (Jain et al., 2009), also contributed to the inconsistence among the studies.

The limitations of this meta-analysis should be addressed. First, the controls in the studies included were not uniformly defined. As a result, the statistics presented here were based on unadjusted estimates. A more precise analysis could be conducted adjusted by other co-variants, such as age, gender, lifestyle, and environmental factors. Second, the size of each subgroup with the same cancer type was too small to provide adequate statistical power to detect further associations. Third, VEGF gene polymorphisms other than VEGF +936C/T may

have a combined effect with it, which we could not detect. The limited data available from studies on other gene polymorphisms were the main reason we restricted this meta-analysis to the VEGF +936C/T polymorphism.

In conclusion, the results of our meta-analysis provided evidence that the VEGF +936C/T polymorphism was not associated with overall cancer risk in Asians. Neither did the subgroups of colorectal and gastric cancer exhibit any associations between the VEGF allele +936T and cancer risk. Further, well-designed large epidemiological studies are warranted to validate our findings.

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