RESEARCH ARTICLE

E-Selectin S128R Polymorphism is Associated with Cancer Risk: a Meta-analysis

Da-Ye Cheng*, Yi-Wen Hao, Wen-Ling Zhou, Yi-Ran Ma

Abstract

Background: Genetic factors have been shown to play an important role in the development of cancers. However, individual studies may fail to completely demonstrate complicated genetic relationships because of small sample size. Therefore, we performed a meta-analysis to evaluate the association of E-selectin Ser128Arg (S128R) with cancer risk. Materials and Methods: A literature search in PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure databases was carried out to identify studies of the association between E-selectin S128R polymorphism and cancer risk. The odds ratio (OR) with 95% confidence intervals (95%CIs) were used to assess the strength of association. Results: A total of eight studies involving 1,675 cancer cases and 2,285 controls were included in the meta-analysis. In overall populations, S128R polymorphism seemed to be associated with cancer risk (Arg allele *vs* Ser allele: OR=1.65, 95%CI =1.33-2.04, *p*<0.01; Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=1.87, 95%CI =1.48-2.36, *p*<0.01; Arg/Ser *vs* Ser/Ser: OR=1.80, 95%CI =1.51-2.14, *p*<0.01). Similarly, subgroup analysis by ethnicity and source of control also revealed that this polymorphism was related to cancer risk. Conclusions: Our meta-analysis revealed that there was association between the E-selectin S128R polymorphism and the risk of cancer. Further large and well-designed studies are needed to confirm this association.

Keywords: E-selectin - S128R - polymorphism - cancer - meta-analysis

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Introduction

Selectins, a family of mammalian lectins engaged in adhesion reactions, are expressed by leukocytes, endothelial cells, and platelets (Cummings and Smith, 1992; Ley, 2003). They belong to a family of intercellular adhesion molecules consisting of 3 members including E-, P-, and L-selectin (Bevilacqua and Nelson, 1993). They share a mosaic structure consisting of an N-terminal C-type lectin domain followed by an epidermal growth factor (EGF)-like domain, a variable number of complement regulatory repeats, a transmembrane domain and a short cytoplasmic tail (Ley, 2003; Barthel et al., 2007) . To date, sound evidence has demonstrated that cell adhesion molecules are involved in the progression of cancer and its metastatic migration (Zhang et al., 2012). E-selectin expressed by endothelial cells are activated by cytokines released during the inflammatory process, and plays an important role in adhesion and extravasation of leukocytes carrying the ligands sialyl-LewisX or sialyl-LewisA into injured areas of tissues (Krause and Turner, 1999). Numerous studies using tumor cell lines and mouse models suggest that E-selectin is also involved in tumor cell adhesion, migration and the development of metastases (Laferriere et al., 2001; Khatib et al., 2002). Moreover, many studies indicated that elevated levels of serum E-selectin occurred in the patients with ovarian cancer, breast cancer, and gastric cancer (Banks et al., 1993), and were significantly associated with poorer prognosis in gastric cancer (Alexiou et al., 2003; Ke et al., 2006), colorectal cancer (Alexiou et al., 2003; Dymicka-Piekarska and Kemona, 2009), papillary thyroid carcinomas (Bal et al., 2008).

Carcinogenesis is a consequence of complex genetic and environmental factors (Da et al., 2013). Numerous case-control studies and family-based studies have shown that inherited genetic factors have played important roles in the susceptibility to cancer (Tang et al., 2014). Currently, several single nucleotide polymorphisms (SNP) have been identified within the E-selectin gene. The most common polymorphism, S128R, is detected in exon 4 of the E-selectin gene resulting an amino acid substitution of serine (Ser) for arginine (Arg) within the extracellular domain of the receptor, which increases its affinity for ligands suggesting its role as a functional polymorphism (Wenzel et al., 1994; Revelle et al., 1996). The previous studies have revealed that E-selectin S128R polymorphism, to some extent, contributes to

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cancer susceptibility. However, individual study may fail to completely demonstrate the complicated genetic relationship because of the small sample size (Cheng et al., 2013). In order to provide strong evidence of the effects of E-selectin S128R polymorphism on cancer, we performed a meta-analysis by combining data from numerous published studies, by which can facilitate this disease prevention, diagnosis, and prognosis.

Materials and Methods

Search strategy

A literature search in PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure databases was carried out to identify studies investigating the association between E-selectin S128R polymorphism and cancer risk from Jan. 2000 to Oct. 2013. The search terms were as follows: E-selectin, CD62; cancer, carcinoma, tumor; polymorphism, variant, SNP. All languages were included.

Inclusive and exclusive criteria

The selection criteria of the retrieved articles in our meta-analysis were as follows: (1) a case-control design which evaluated the association between E-selectin S128R polymorphism and cancer risk; (2) sufficient data available to calculate an odds ratio (OR) with 95% confidence interval (CI); and (3) all cancers were diagnosed by histopathology. The exclusion criteria of the meta-analysis were: (1) case-control studies not focusing on the correlation between the E-selectin S128R polymorphism and cancer risk; (2) studies with duplicate data; (3) studies with incomplete data; and (4) meta-analyses, letters, reviews and editorial articles. If more than one study was published by the same author using the same patient population or overlapping case series, studies with the largest size of samples were included.

Data extraction

Data was extracted carefully from all eligible publications independently by two reviewers (Cheng and Hao), based on the inclusion criteria above. The following data were collected: name of first author, year of publication, country, ethnicity, cancer types, the source of control, number of cases and controls, and genotype frequency in cases and controls. According to the source of control, eligible studies were defined as hospital-based (HB) and population-based (PB). Ethnicity descents were simply categorized as Asian and Caucasian. Discrepancies were resolved by consensus.

Statistical analysis

The pooled ORs together with their corresponding 95% CIs were used to assess the strength of association between the E-selectin S128R polymorphism and cancer risk. The comparison models were as follows: allele model (Arg *vs* Ser), dominant model (Arg/Arg+Arg/Ser *vs* Ser/Ser), recessive model (Arg/Arg *vs* Arg/Ser+Ser/Ser), homozygote comparison (Arg/Arg *vs* Ser/Ser), and heterozygote comparison (Arg/Ser *vs* Ser/Ser). Between-study heterogeneity assumptions were assessed by chi-squarebased Q test (Wermuth and Cochran, 1979), and the heterogeneity was considered significant when $p<0.10$. When the p value was more than 0.10, the pooled OR was calculated by the fixed-effects model, otherwise, a random-effects model was used. Z test was applied to determine the significance of the pooled ORs, and $p<0.05$ was considered significant. Reliability of the results was evaluated by sensitivity analysis performed by sequential exclusion of individual study. Begg's funnel plots (Begg and Mazumdar, 1994) and Egger's linear regression test (Egger et al., 1997) were used to evaluate publication bias. All statistical analyses were performed using STATA version 12.0 (STATA Corporation, College Station, TX).

Results

Studies selection and characteristics

A total of 158 potentially relevant publications were identified from the databases. Of these, 150 publications were excluded because of case reports, or reviews, or non-relevance research, or duplicate data, or incomplete date. Finally, eight studies were included in this meta-analysis, with a total of 1,675 cancer cases and 2,285 controls (Alessandro et al., 2007; Bai, 2009; Hebbar et al., 2009; Panoussopoulos et al., 2010; Naidu et al., 2011; Xia et al., 2012; Kontogianni et al., 2013; Liarmakopoulos et al., 2013). A flow diagram schematized the process of selecting and excluding articles with specific reasons was shown in Figure 1, and the main characteristics of eligible studies were shown in Table 1.

Among 8 studies, three studies were performed in Asian populations and five studies were conducted in Caucasian populations. Five studies were population-based case-control studies and three was hospital-based case-control studies. The distribution of E-selectin S128R genotypes in the controls was consistent with Hardy-Weinberg equilibrium (HWE) ($p>0.05$) in all but one studies.

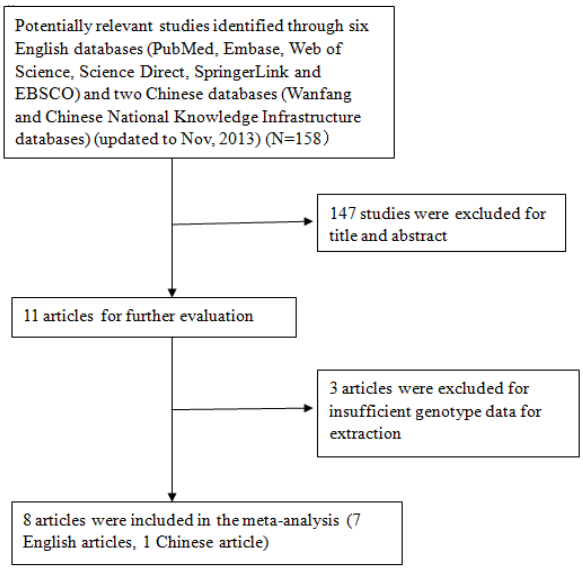

Figure 1. The Flow Diagram of Included and Excluded Studies

Quantitative synthesis

Table 2 listed the main results of this meta-analysis. Obviously, E-selectin S128R polymorphism was significantly associated with increase cancer risk in the allelic model (Arg allele *vs* Ser allele: OR=1.65, 95%CI =1.33-2.04, $p<0.01$), dominant model (Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=1.87, 95%CI =1.48-2.36, $p<0.01$), and heterozygous comparison (Arg/Ser *vs* Ser/Ser: OR=1.80, 95%CI =1.51-2.14, $p<0.01$) when all the available studies were pooled into the meta-analyses. However, no significant difference of cancer risk in other genotypic models (Arg/Arg *vs* Arg/Ser+Ser/Ser: OR=1.24, 95%CI =0.83-1.84, $p=0.30$; Arg/Arg *vs* Ser/Ser: OR=1.45, 95%CI =0.97-2.18, $p=0.07$).

In the further subgroup analysis by ethnicities, we found that E-selectin S128R polymorphism was significantly associated with an increase risk of cancer in Asian populations (Arg allele *vs* Ser allele: OR=1.80, 95%CI =1.36-2.39, $p<0.01$; Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=2.28, 95%CI =1.24-4.16, $p=0.008$, Figure 2; Arg/Ser *vs* Ser/Ser: OR=2.41, 95%CI =1.30-4.48, $p=0.005$) and in Caucasian populations (Arg allele *vs* Ser allele: OR=1.48, 95%CI =1.25-1.74, $p<0.01$; Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=1.66, 95%CI =1.36-2.02, $p<0.01$; Arg/

Table 1. Characteristics of Studies Included in the Present Meta-analysis

Studies	Year	Country	Ethnicity	Caner type	Source of controls	Sample size	Genotyping method	HWE
Hebbar M	2009	France	Caucasian	Colorectal	PB	264/310	PCR-sequencing	0.107
Kontogianni P	2013	Greece	Caucasian	Breast	HB	261/480	PCR-RFLP	0.951
Alessandro R	2007	Italy	Caucasian	Colon	PB	172/80	PCR-RFLP	0.638
Xia HZ	2012	China	Asian	Gastric	PB	311/425	MassARRAY	<0.01
Panoussopoulos G	2010	Greece	Caucasian	Colon	PB	80/160	PCR-RFLP	0.081
Naidu R	2011	Malaysia	Asian	Breast	PB	387/252	PCR-RFLP	0.092
Liarmakopoulos E	2013	Greece	Caucasian	Gastric	HB	88/480	PCR-RFLP	0.497
Bai Y	2009	China	Asian	Oral	HB	112/98	PCR-RFLP	0.211

*PB, population-based controls, HB, hospital-based controls. HWE, Hardy-Weinberg equilibrium. PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism

Table 2. Overall and Subgroup Analysis of the Associations of E-selectin S128R Polymorphism with Cancer Risk in All Genetic Comparisons

Comparison models	Pooled estimates			Heterogeneity	
	OR (95%CI)	*p* value	Model	PQ	I^2(%)
Overall studies					
Arg allele *vs* Ser allele (Allele model)	1.65 (1.33-2.04)	<0.01	Random	0.06	48%
Arg/Arg+Arg/Ser *vs* Ser/Ser (Dominant model)	1.87 (1.48-2.36)	<0.01	Random	0.10	42%
Arg/Arg *vs* Arg/Ser+Ser/Ser (Recessive model)	1.24 (0.83-1.84)	0.30	Fixed	0.16	35%
Arg/Arg *vs* Ser/Ser (Homozygous comparison)	1.45 (0.97-2.18)	0.07	Fixed	0.19	31%
Arg/Ser *vs* Ser/Ser (Heterozygous comparison)	1.80 (1.51-2.14)	<0.01	Fixed	0.11	41%
Group by ethinicity					
Asian					
Arg allele *vs* Ser allele (Allele model)	1.80 (1.36-2.39)	<0.01	Fixed	0.13	51%
Arg/Arg+Arg/Ser *vs* Ser/Ser (Dominant model)	2.28 (1.24-4.16)	0.008	Random	0.05	67%
Arg/Arg *vs* Arg/Ser+Ser/Ser (Recessive model)	1.22 (0.55-2.72)	0.63	Fixed	0.61	0%
Arg/Arg *vs* Ser/Ser (Homozygous comparison)	1.29 (0.58-2.89)	0.53	Fixed	0.60	0%
Arg/Ser *vs* Ser/Ser (Heterozygous comparison)	2.41 (1.30-4.48)	0.005	Random	0.06	65%
Caucasian					
Arg allele *vs* Ser allele (Allele model)	1.48 (1.25-1.74)	<0.01	Random	0.10	49%
Arg/Arg+Arg/Ser *vs* Ser/Ser (Dominant model)	1.66 (1.36-2.02)	<0.01	Fixed	0.32	15%
Arg/Arg *vs* Arg/Ser+Ser/Ser (Recessive model)	1.24 (0.56-2.77)	0.59	Random	0.06	56%
Arg/Arg *vs* Ser/Ser (Homozygous comparison)	1.51 (0.69-3.31)	0.30	Random	0.08	52%
Arg/Ser *vs* Ser/Ser (Heterozygous comparison)	1.67 (1.36-2.04)	<0.01	Fixed	0.37	6%
Group by control source					
Population-based controls					
Arg allele *vs* Ser allele (Allele model)	1.60 (1.30-1.98)	<0.01	Fixed	0.44	0%
Arg/Arg+Arg/Ser *vs* Ser/Ser (Dominant model)	1.79 (1.41-2.28)	<0.01	Fixed	0.73	0%
Arg/Arg *vs* Arg/Ser+Ser/Ser (Recessive model)	1.17 (0.68-1.99)	0.57	Fixed	0.22	30%
Arg/Arg *vs* Ser/Ser (Homozygous comparison)	1.39 (0.80-2.40)	0.25	Fixed	0.36	9%
Arg/Ser *vs* Ser/Ser (Heterozygous comparison)	1.86 (1.44-2.39)	<0.01	Fixed	0.57	0%
Hospital-based controls					
Arg allele *vs* Ser allele (Allele model)	1.74 (1.09-2.77)	0.02	Random	<0.01	79%
Arg/Arg+Arg/Ser *vs* Ser/Ser (Dominant model)	2.05 (1.15-3.65)	0.01	Random	<0.01	8%
Arg/Arg *vs* Arg/Ser+Ser/Ser (Recessive model)	1.40 (0.48-4.03)	0.54	Random	0.07	69%
Arg/Arg *vs* Ser/Ser (Homozygous comparison)	1.67 (0.50-5.61)	0.41	Random	0.04	75%
Arg/Ser *vs* Ser/Ser (Heterozygous comparison)	2.02 (1.16-3.51)	0.01	Random	0.01	77%

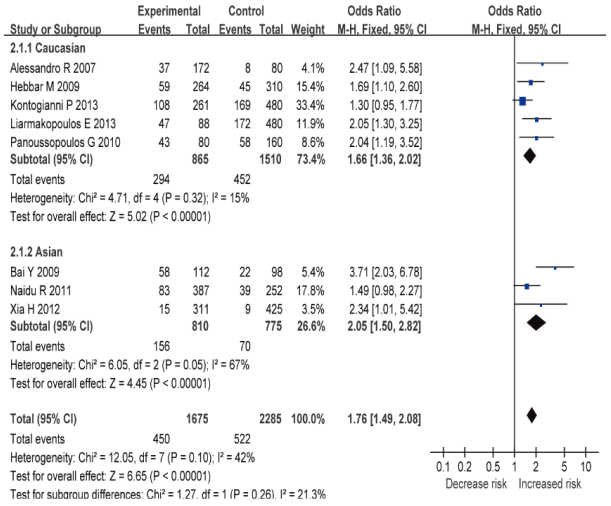

Figure 2. Meta-analysis for the Association between E-selectin S128R Polymorphismin and Cancer Risk Under Dominant Model (Arg/Arg+Arg/Ser *vs* Ser/Ser): Subgroup Analysis by Ethnicity

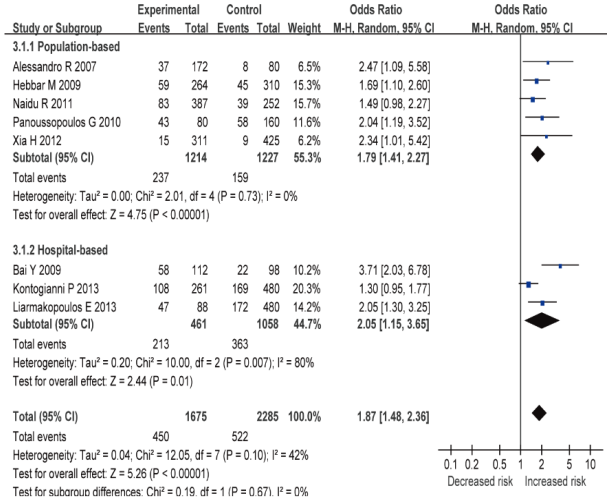

Figure 3. Meta-Analysis for the Association between E-selectin S128R Polymorphismin and Cancer Risk Under Dominant Model (Arg/Arg+Arg/Ser *vs* Ser/Ser): Subgroup Analysis by Source of Control

Ser *vs* Ser/Ser: OR=1.67, 95%CI =1.36-2.04, p<0.01). No significant associations were found in the other models in Asian populations and Caucasian populations.

In the further subgroup analysis by source of controls, we observed that E-selectin S128R polymorphism was significantly associated with an increase risk of cancer in population-based subgroup (Arg allele *vs* Ser allele: OR=1.60, 95%CI =1.30-1.98, p<0.01; Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=1.79, 95%CI =1.41-2.28, p<0.01, Figure 3; Arg/Ser *vs* Ser/Ser: OR=1.86, 95%CI =1.44-2.39, p<0.01) and in hospital-base subgroup (Arg allele *vs* Ser allele: OR=1.74, 95%CI =1.09-2.77, p=0.02; Arg/Arg+Arg/Ser *vs* Ser/Ser: OR=2.05, 95%CI =1.15-3.65, p=0.01; Arg/Ser *vs* Ser/Ser: OR=2.02, 95%CI =1.16-3.51, p=0.01). No significant associations were found in the other models in population-based subgroup and hospital-base subgroup.

Sensitivity analysis

In order to assess the stability of the results of the meta-analysis, sensitivity analysis was performed by sequentially excluding each study. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of this meta-analysis.

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of literatures. As shown in Figure 3, the shape of the funnel plots was symmetrical for E-selectin S128R polymorphisms under allele model and dominant model, and the results of Begg's test did not show any evidence of publication bias under allele model (p=0.256) and dominant model (p=0.157).

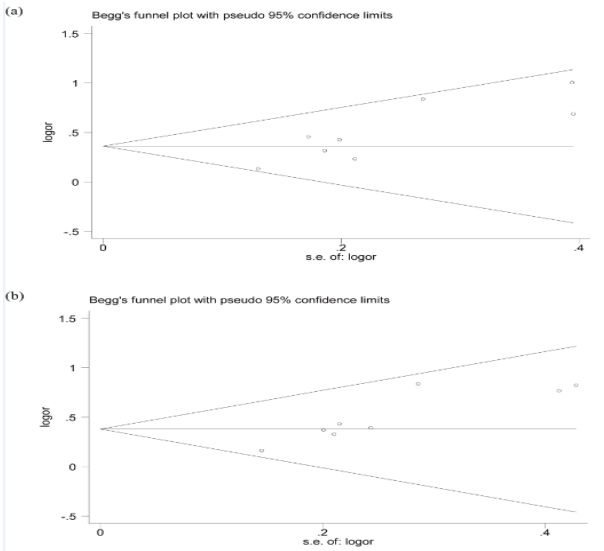

Figure 4. Begg's Funnel Plot of E-selectin S128R Polymorphism and Cancer Risk. A) allele model, **B)** dominant model

Discussion

Cancer is a complex disease, characterized by multiple molecular alterations triggered by genetic, environmental and lifestyle effects. Several reports in the last few years have indicated that besides the imbalance in regulatory pathways because of activation of oncogenes or loss of tumor suppressor genes, cancer progression and clinical outcomes may be greatly modulated by functional alteration in key proteins often determined by genetic polymorphisms (Houlston and Peto, 2004; Bond et al., 2005).

Strong evidence has indicted that E-selectin has a fundamental role in the recruitment of leukocytes during inflammation, and is normally downregulated when the initiating event subsides (Kontogianni et al., 2013). That tumor cells mimic and exploit similar mechanisms used by leukocytes in extravasation, through adhesive interactions with the vasculature, is substantiated by a number of recent studies (Laubli et al., 2009; Laubli and Borsig, 2010). Moreover, several studies strongly support the role of E-selectin-mediated adhesion of cancer cells to endothelial cells as an important determinant of cancer development (Sawada et al., 1994; Porquet et al., 2011). Thomas SN, also reported that CEA is an E-selectin ligand, and tumor cell CEA overexpression may enhance tumor development

depending on the supportive role of selectin protein (Bal et al., 2008). Therefore, alteration in the expression of E-selectin may influence the adhesion of cancer cells. Evidence has showed that E-selectin polymorphism may predispose to cancer.

The most common polymorphism, S128R, is the substitution of a serine by an arginine at position 128 (transversion A561C). The E-selectin S128R polymorphism has been demonstrated to have functional implications in terms of adhesiveness to endothelial cells. To date, many studies have investigated it by genetic and molecular approaches. The results of them have provided adequate statistical evidence for disease association and a plausible biological context supporting that S128R is an attractive candidate for a causal polymorphism leading to the risk of cancer. Due to small size in single study, we performed a meta-analysis to get more reliable results, including 8 case-control studies with1,675 cases and 2,285 controls, and the result demonstrated that E-selectin S128R polymorphism was associated with cancer susceptibility in overall analysis. Further, stratified analyses were performed to evaluate the effects of ethnicity and source of controls. Ethnicity is one of the important factors for the development of cancer; the pathogenesis of different cancer is inherited among different ethnic populations (Jia et al., 2013). In the subgroup analysis by ethnicities and sources of controls, we found an increase risk of cancer under allele model, dominant model, and heterozygous model in Asian populations, Caucasian population, PB subgroup, and HB subgroup. Therefore, E-selectin may be of potential diagnostic and therapeutic value in cancer by virtue of its expression profile. Besides, more studies with large sample size are needed to further assess the associations above.

The current meta-analysis has some limitations in spite of several advantages compared to individual studies. First, the meta-analysis was limited by a relatively small number of available studies. It is difficult to perform subgroup analysis for every type of cancers. Second, the gene-gene/gene-environment interaction was not evaluated in our meta-analysis, while lacking of the information for the date analysis may cause confounding bias. Third, only published studies in the selected databases were included in this meta-analysis. It is possible that some studies that were not included in these databases or some unpublished studies with null results were not identified, and this may have biased our results.

In conclusion, despite these limitations, this meta-analysis suggests that E-selectin S128R polymorphism is associated with cancer risk among Caucasians and Asians. Further investigations with larger sample sizes and rigorous matching criteria are required to overcome the above-mentioned limitations and confirm the association.

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