

Original Article

Current evidence on the relationship between two common polymorphisms in *NPAS2* gene and cancer risk

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Abstract: The relationship between neuronal PAS domain protein 2 (NPAS2) gene polymorphisms and cancer risk has been widely investigated. However, the results are conflicting. We performed this meta-analysis to derive a more precise estimation on the relationship. We searched Pubmed, and Web of Knowledge databases until Dec, 2014 to identify eligible studies. Case-control studies containing available genotype frequencies of the NPAS2 polymorphisms were chosen. The odds ratios (ORs) with 95% confidence interval (CI) were used to assess the strength of association. Eight independent case-control studies with 3,857 cancer patients and 4,525 cancer-free controls were selected for this meta-analysis. Two NPAS2 gene polymorphisms were identified (rs2305160 and rs17024926). The results showed statistically significant associations of rs2305160 with cancer risk (AA+GA vs. GG: OR = 0.84, 95% CI = 0.72-0.98, $P = 0.02$; AG vs. GG: OR = 0.81, 95% CI = 0.68-0.96, $P = 0.02$). Stratified analysis by cancer type indicated that rs2305160 may decrease the risk of breast cancer (A vs. G: OR = 0.87, 95% CI = 0.76-0.96, $P = 0.006$; AA+GA vs. GG: OR = 0.77, 95% CI = 0.67-0.88, $P < 0.001$; AG vs. GG: OR = 0.74, 95% CI = 0.64-0.86, $P < 0.001$), whereas negative results were obtained for prostate cancer. For rs17024926 polymorphism, there was no significant association in any genetic model. This meta-analysis suggests that NPAS2 rs2305160 polymorphism may reduce cancer susceptibility, especially in breast cancer.

Keywords: NPAS2, polymorphism, cancer risk, meta-analysis

Introduction

Disruption of circadian rhythms or clock gene expression is emerging as a novel and potentially modifiable cancer risk factor, although the pathophysiological mechanism is incompletely understood [1-3]. Neuronal PAS domain protein 2 (NPAS2), the largest human core circadian gene, maps on chromosome 2 at 2q11.2 and encodes for a member of the basic helix-loop-helixPAS class of transcription factors [4]. NPAS2 regulates multiple biological processes by running 24-h circadian rhythm [5]. Previous evidence has suggested that NPAS2 is a putative tumor suppressor playing an important role in biological pathways that regulate DNA damage response, cell cycle control and apoptosis by activating different downstream genes [6-8].

Single nucleotide polymorphisms (SNPs) are the most frequent sequence variations in the human genome. Many studies have been conducted in recent years to evaluate the association between NPAS2 polymorphisms and cancer risk [9-16]. However, the results are inconsistent. Rana et al. reported that NPAS2 rs2305160 polymorphism does not appear to have any association with risk of chronic lymphocytic leukemia (CLL) in Pakistani population [9]. In a nested case-control study of Norwegian nurses comprising 563 breast cancer cases and 619 controls within a cohort of 49,402 Norwegian nurses, results indicated that NPAS2 rs2305160 polymorphism had no significant association with breast cancer risk, while rs17024926 polymorphism was associated with a reduced risk of breast cancer (OR =

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Table 1. Characteristics of the eligible studies included in this meta-analysis

First author	Year	Country	Cancer type	Ethnicity	Study design	Genotyping method	Source of control	Case/Control	SNP	HWE
Rana [9]	2014	Pakistan	CLL	Asian	CC	ARMS-PCR	Pop	37/37	rs2305160	0.14
Madden [10]	2014	USA	Glioma	Caucasian	CC	GoldenGate	Hosp	522/546	rs2305160	0.18
									rs17024926	0.36
Zienolddiny [11]	2013	Norway	BC	Caucasian	NCC	iPLEX	Pop	535/584	rs2305160	0.23
									rs17024926	0.25
Monsees [12]	2012	USA	BC	Mixed	CC	GoldenGate	Pop	436/872	rs2305160	0.61
Zhu [13]	2009	USA	PC	Caucasian	CC	SNPlex	Pop	1248/1239	rs2305160	0.42
									rs17024926	0.50
Chu [14]	2008	China	PC	Asian	CC	Taqman	Pop	187/242	rs2305160	0.43
Zhu [15]	2008	USA	BC	Mixed	CC	Taqman	Hosp	437/478	rs2305160	0.14
Zhu [16]	2007	USA	NHL	Mixed	CC	Taqman	Hosp	455/527	rs2305160	0.89

CLL: chronic lymphocytic Leukemia; BC: Breast Cancer; PC: Prostate Cancer; NHL: non-Hodgkin's Lymphoma; CC: case-control study; NCC: Nested case-control study; Pop: population based; Hosp: hospital based; SNP: single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium.

Table 2. NPAS2 polymorphisms genotype distribution and allele frequency in cases and controls

Study	Genotype (N)						Genotype (N)						MAF
	Case			Control			Case		Control				
	total	AA	AB	BB	total	AA	AB	BB	A	B		A	
rs2305160													
Rana 2014	37	22	9	6	37	17	13	7	53	21	47	27	0.28
Madden 2014	522	221	232	69	546	253	227	66	674	370	733	359	0.35
Zienolddiny 2013	535	238	224	73	584	233	261	90	700	370	727	441	0.35
Monsees 2012	436	207	173	56	872	351	410	111	587	285	1112	632	0.33
Zhu 2009	1248	530	578	140	1239	533	569	137	1638	858	1635	843	0.34
Chu 2008	187	119	49	19	242	140	91	11	287	87	371	113	0.23
Zhu 2008	437	225	161	51	478	207	226	45	611	263	640	316	0.30
Zhu 2007	455	233	182	40	527	218	243	66	648	262	679	375	0.29
rs17024926													
Madden 2014	607	278	267	62	615	255	290	70	823	391	800	430	0.32
Zienolddiny 2013	533	206	257	70	601	244	288	69	669	397	776	426	0.33
Zhu 2009	1246	499	594	153	1238	563	536	139	1592	900	1662	814	0.36

A: The major allele; B: The minor allele; MAF: Minor allele frequencies.

0.33, 95% CI = 0.13-0.84) [11]. In the study by Zhu et al, they found that women with the heterozygous Ala394Thr (rs2305160) genotype were significantly associated with breast cancer risk compared to those with the common homozygous Ala394Ala (OR = 0.61, 0.46-0.81) [15].

It is important to summarize inconclusive results from different studies to provide evidence on the association of polymorphisms with cancer risk [17]. To clarify the effect of the NPAS2 polymorphisms on cancer risk, we performed a meta-analysis on all eligible case-control studies to estimate the overall cancer risk

of the NPAS2 polymorphisms. Furthermore, we conducted the subgroup analysis by stratification according to the ethnicity and cancer type.

Materials and methods

Literature searching strategy

A comprehensive literature search without language restrictions was performed by two authors in PubMed, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases. The keywords were as follows: cancer/carcinoma/tumor/neoplasm, neuronal PAS domain protein 2/NPAS2, and polymorphism/genotype/variation. We also manu-

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Table 3. Meta-analysis of the association between NPAS2 polymorphism and cancer risk

SNP	Subtype	N	Case/ Control	Comparisons	OR	95% CI	P value	Heterogeneity		Effect model
								I ²	P value	
rs2305160	overall	8	3857/45 25	A vs. G	0.91	0.82-1.01	0.08	54%	0.03	R
				AA vs. GG	0.94	0.76-1.15	0.52	44%	0.08	R
				AA vs. GA+GG	1.00	0.88-1.15	0.95	35%	0.15	F
				AA+GA vs. GG	0.84	0.72-0.98	0.02	63%	0.009	R
				AG vs. GG	0.81	0.68-0.96	0.02	66%	0.005	R
	BC	3	1408/19 34	A vs. G	0.87	0.76-0.96	0.006	0%	0.99	F
				AA vs. GG	0.87	0.70-1.09	0.23	0%	0.64	F
				AA vs. GA+GG	1.01	0.82-1.24	0.95	0%	0.38	F
				AA+GA vs. GG	0.77	0.67-0.88	<0.001	0%	0.71	F
				AG vs. GG	0.74	0.64-0.86	<0.001	0%	0.41	F
	PC	2	1435/148 1	A vs. G	1.01	0.91-1.13	0.81	0%	0.91	F
				AA vs. GG	1.11	0.86-1.42	0.43	62%	0.11	F
				AA vs. GA+GG	1.43	0.63-3.24	0.39	76%	0.04	R
				AA+GA vs. GG	0.95	0.76-1.20	0.69	34%	0.22	F
				AG vs. GG	0.84	0.53-1.33	0.45	76%	0.03	R
	Caucasian	5	3197/337 4	A vs. G	0.92	0.80-1.05	0.23	70%	0.01	R
				AA vs. GG	0.91	0.72-1.15	0.43	51%	0.08	R
				AA vs. GA+GG	0.97	0.84-1.13	0.71	29%	0.23	R
				AA+GA vs. GG	0.87	0.71-1.06	0.18	74%	0.004	F
				AG vs. GG	0.87	0.70-1.06	0.17	73%	0.005	R
Asian	2	224/279	A vs. G	0.93	0.70-1.25	0.64	0%	0.35	R	
			AA vs. GG	1.49	0.78-2.86	0.23	54%	0.14	F	
			AA vs. GA+GG	1.75	0.93-3.30	0.09	52%	0.15	F	
			AA+GA vs. GG	0.75	0.52-1.07	0.12	0%	0.55	F	
			AG vs. GG	0.62	0.42-0.92	0.02	0%	0.77	F	
rs17024926	overall	3	2305/23 69	C vs. T	1.04	0.89-1.22	0.62	70%	0.04	R
				CC vs. TT	1.11	0.92-1.34	0.26	42%	0.18	F
				CC vs. TC+TT	0.94	0.79-1.11	0.46	46%	0.59	F
				CC+TC vs. TT	1.05	0.83-1.34	0.67	75%	0.02	R
				TC vs. TT	1.05	0.83-1.33	0.69	72%	0.03	R

BC: Breast Cancer; PC: Prostate Cancer; F: Fixed-effects model; R: Random-effects model.

ally searched the reference cited in the retrieved articles to identify additional potential studies. The literature search was finally conducted on Dec 30, 2014.

Selection criteria

The following criteria were used to select studies for further meta-analysis: (1) case-control study design; (2) investigation of the association between NPAS2 polymorphisms and cancer risk; (3) provision of detailed genotyping data; (4) cancer cases diagnosed and confirmed by histopathology; (5) fulfilling Hardy-Weinberg equilibrium ($P > 0.05$).

Data extraction and synthesis

Articles were performed independently by two reviewers and data with discrepancies in identification were discussed by all authors. The following information was collected: first author, year of publication, country, ethnicity, source of control, genotyping method, cancer type, number of cases and controls, genotype distribution in cases and controls. Different ethnicity descents were categorized as Caucasian, Asian, African, and "mixed". All the case and control groups were well controlled. The non-cancer controls without evidence of any malignant disease.

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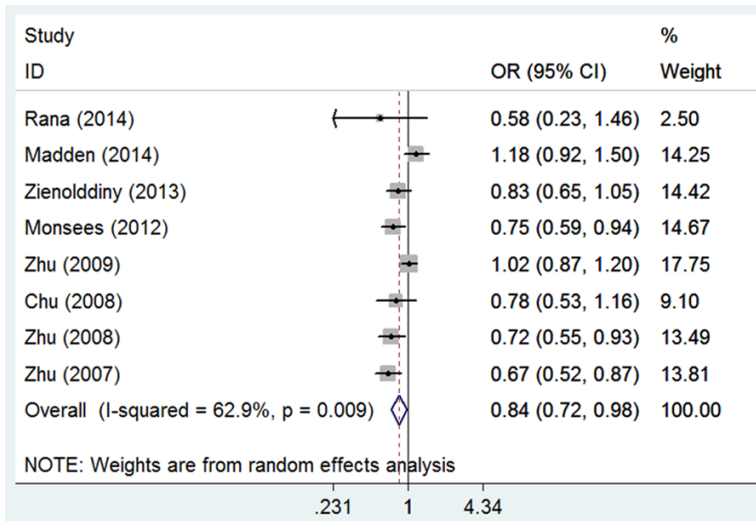


Figure 1. Forest plots of NPAS2 rs2305160 polymorphism and cancer risk (AA+GA vs GG). The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

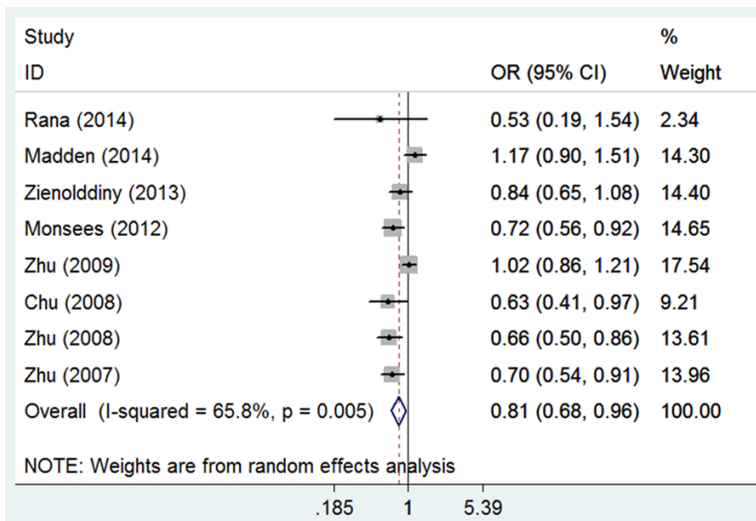


Figure 2. Forest plots of NPAS2 rs2305160 polymorphism and cancer risk (GA vs GG). The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were used to evaluate the associations between NPAS2 polymorphisms and cancer risk [18]. The significance of the pooled OR was determined by the Z test. The heterogeneity among different studies was assessed with the Q and I^2 statistics. The Q test and I^2 were claimed to test the variation which was due to heterogeneity or by random error. When P value

of heterogeneity tests was no more than 0.1 ($P \leq 0.1$), we used random effects model. When P value of heterogeneity test was more than 0.1 ($P \geq 0.1$), we used fixed effects model. Sensitivity analysis was also tested by removing one study at a time to calculate the overall homogeneity and effect size. Publication bias were evaluated by both Begg's test and Egger's regression test. $P < 0.05$ was considered the existence of statistically significant publication bias. The HWE of controls was calculated using Pearson χ^2 -test. The genotypes and allele frequencies of controls were considered in HWE if $P > 0.05$. All statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of studies

We identified 8 studies according to the eligible criteria, with 3,857 cancer patients and 4,525 cancer-free control. The characteristics of the included studies are listed in **Table 1**. All the 8 articles were published in English. There were 5 studies of Caucasians, 2 of Asians and 1 of mixed. All studies were case-control studies, including 3 breast cancer studies, 2 prostate cancer studies, one chronic lymphocytic leukemia study, one glioma study, and one non-Hodgkin's lymphoma study. All cancers were confirmed by histology or pathology. Moreover, controls were mainly matched on age, sex and ethnicity, of which 5 were population-based and 3 were hospital-based.

Meta-analysis results

Two NPAS2 gene polymorphisms were identified (rs2305160 and rs17024926). The minor

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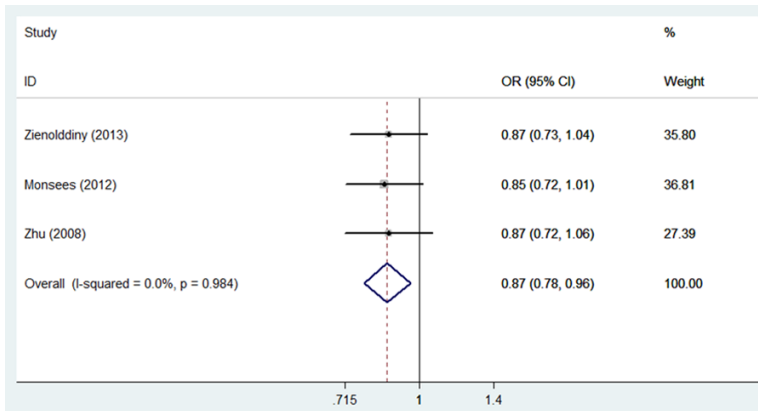


Figure 3. Forest plots of NPAS2 rs2305160 polymorphism and breast cancer risk (A vs G). The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

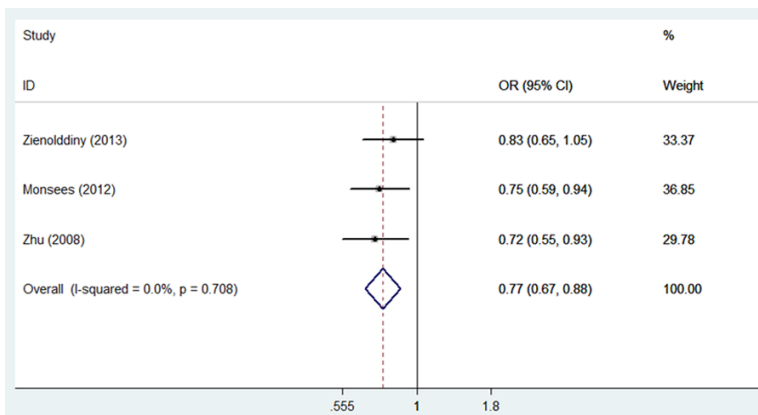


Figure 4. Forest plots of NPAS2 rs2305160 polymorphism and breast cancer risk (AA+GA vs GG). The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

allele frequencies (MAF) of rs2305160 varied widely across the eight studies, ranging from 0.23 to 0.35 (Table 2). The average MAF in overall population, Caucasian population and Asian population were 0.33, 0.33, and 0.24, respectively. There was significant difference between Asians and Caucasians ($P < 0.05$). The average MAF of rs17024926 in the three Caucasian studies was 0.35.

The main results of this meta-analysis were listed in Table 3. There was statistically significant associations of NPAS2 rs2305160 polymorphism with decreased cancer risk in the overall population based on two genotypes (AA+GA vs. GG: OR = 0.84, 95% CI = 0.72-0.98, $P = 0.02$, Figure 1; AG vs. GG: OR = 0.81, 95%

CI = 0.68-0.96, $P = 0.02$, Figure 2). However, negative results were obtained in other genetic models (A vs. G: OR = 0.91, 95% CI = 0.82-1.01, $P = 0.08$; AA vs. GG: OR = 0.94, 95% CI = 0.76-1.15, $P = 0.52$; AA vs. GG+GA: OR = 1.00, 95% CI = 0.88-1.15, $P = 0.95$).

Stratified analysis by cancer type indicated that rs2305160 may decrease the risk of breast cancer (A vs. G: OR = 0.87, 95% CI = 0.76-0.96, $P = 0.006$, Figure 3; AA+GA vs. GG: OR = 0.77, 95% CI = 0.67-0.88, $P < 0.001$, Figure 4; AG vs. GG: OR = 0.74, 95% CI = 0.64-0.86, $P < 0.001$). There was no significant association in prostate cancer in all genotypes (A vs. G: OR = 1.01, 95% CI = 0.91-1.13, $P = 0.81$; AA vs. GG: OR = 1.11, 95% CI = 0.86-1.42, $P = 0.43$; AA vs. GA+GG: OR = 1.43, 95% CI = 0.63-3.24, $P = 0.39$; AA+GA vs. GG: OR = 0.95, 95% CI = 0.76-1.20, $P = 0.69$; AG vs. GG: OR = 0.84, 95% CI = 0.53-1.33, $P = 0.45$, Table 3).

Further subgroup analysis by ethnicity revealed that rs2305160 polymorphism has association with cancer risk in Asians only in heterozygote comparison (OR = 0.62,

95% CI = 0.42-0.92, $P = 0.02$), but not in other genetic models. For Caucasians, all genetic models failed to detect significant correlations (A vs. G: OR = 0.92, 95% CI = 0.80-1.05, $P = 0.23$; AA vs. GG: OR = 0.91, 95% CI = 0.72-1.15, $P = 0.43$; AA vs. GA+GG: OR = 0.97, 95% CI = 0.84-1.13, $P = 0.71$; AA+GA vs. GG: OR = 0.87, 95% CI = 0.71-1.06, $P = 0.18$; AG vs. GG: OR = 0.87, 95% CI = 0.70-1.06, $P = 0.17$, Table 3).

For NPAS2 rs17024926 polymorphism, our meta-analysis contained three studies with 2,305 cases and 2,369 controls. Overall, the rs17024926 polymorphism was not associated with cancer risk (C vs. T: OR = 1.04, 95% CI = 0.89-1.22, $P = 0.62$; CC vs. TT: OR = 1.11, 95% CI = 0.92-1.34, $P = 0.26$; CC vs. TC+TT: OR =

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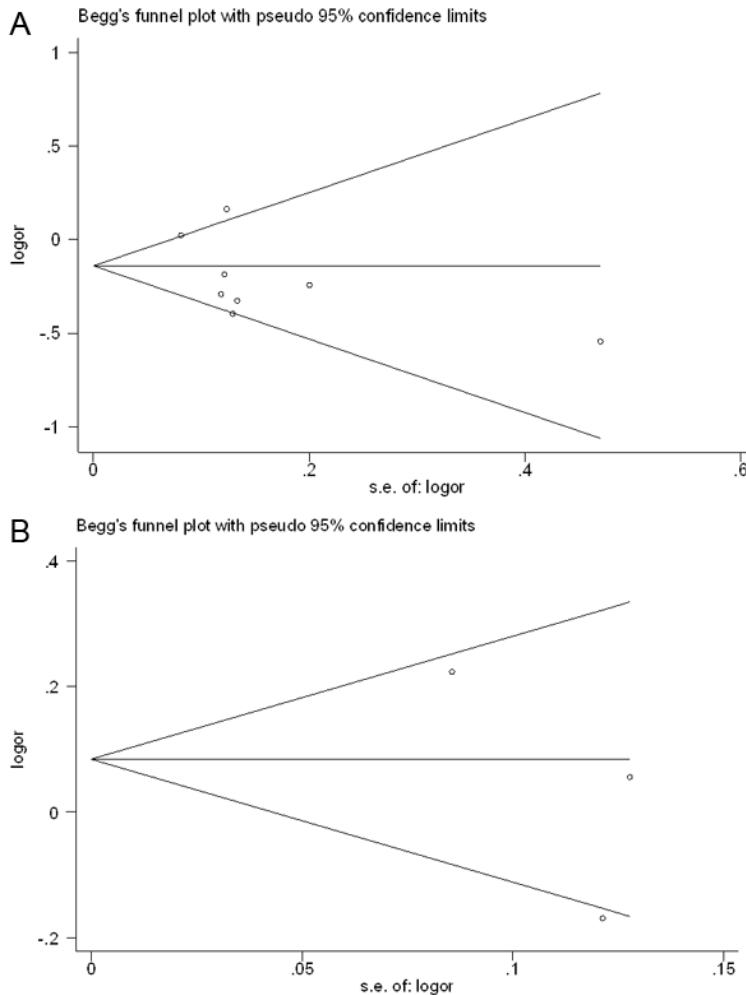


Figure 5. Funnel plot assessing evidence of publication bias from the included studies (A: rs2305160; B: rs17024926).

0.94, 95% CI = 0.79-1.11, $P = 0.46$; CC+TC vs. TT: OR = 1.05, 95% CI = 0.83-1.34, $P = 0.67$; TC vs. TT: OR = 1.05, 95% CI = 0.83-1.33, $P = 0.69$).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. As shown in **Figure 5**, the funnel plots did not reveal any obvious asymmetry in all genotypes in overall population, and the results of Egger's test revealed no publication bias ($P = 0.238$ for rs2305160, $P = 0.392$ for rs17024926).

Discussion

The current meta-analysis including 8 case-control studies was in an effort to clarify the

relationship between NPAS2 gene polymorphisms and cancer risk. The overall results indicated that the NPAS2 rs2305160 polymorphism was associated with susceptibility of cancer. Epidemiologic studies suggest disruption of circadian rhythms could increase cancer risk, especially for breast cancer, in night and rotating female shift workers [19]. The circadian genes may affect cancer susceptibility through effects on biological pathways that regulate DNA damage and repair, carcinogen metabolism and/or detoxification, cell growth and cell death [6].

NPAS2 is a product of the circadian clock gene. An animal study has also shown that the loss of normal NPAS2 may cause defects in several aspects of the circadian system, such as patterns of sleep and behavior [20]. Previous reports indicated the involvement of NPAS2 in tumorigenesis, by regulating PER2 that can act as tumor suppressor [21], and by suppressing transcription of c-Myc that is an oncogene [22]. In epidemiological studies including the

NHS2 cohort, night workers have been consistently found to have an increased risk of breast cancer [23]. To our knowledge, this is the first meta-analysis providing comprehensive insights into the effects of NPAS2 gene polymorphisms on the risk of cancer. The results indicated that rs2305160 may decrease the risk of breast cancer (A vs. G: OR = 0.87, 95% CI = 0.76-0.96; AA+GA vs. GG: OR = 0.77, 95% CI = 0.67-0.88; AG vs. GG: OR = 0.74, 95% CI = 0.64-0.86). However, there was no significant association between rs2305160 and prostate cancer risk in any genetic model.

Because of gene polymorphism of ethnic differences, different ethnicities have different gene-environment interplay models [24]. In the subgroup analysis based on ethnicity, compared

with GG genotype, a significantly decreased risk of cancer is associated with GA genotype in Asians (OR = 0.62, 95% CI = 0.42-0.92). However, there was no significant association in any genetic models in Caucasians.

Meta-analysis is considered a powerful tool for integrating conflicted results from different studies [25]. Nevertheless, some limitations of this meta-analysis should be noted. Firstly, this meta-analysis was based on pooled data and no individual data was available; thus, we could not assess the risk of cancer according to stratification of age, environment factors, and other risk factors of cancer. Secondly, in the stratified analysis by cancer type, we only analyzed breast cancer and prostate cancer. Limited study number made it impossible to perform subgroup analysis for other cancers. Thirdly, there were only 2 studies with 503 subjects based on Asian population [9, 14]. Larger scale multicenter studies are warranted to further validate the findings. Finally, only 3 published studies for rs17024926 were included in this meta-analysis [10, 11, 13]. We found the rs17024926 polymorphism was not associated with cancer risk. However, this negative finding may result from a lack of statistical power.

Conclusion

In conclusion, our present meta-analysis provides evidence for the association between NPAS2 polymorphisms and cancer risk. NPAS2 rs2305160 polymorphism plays a possible protective effect in cancer, especially in breast cancer.

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Disclosure of conflict of interest

None.

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