INPLASY PROTOCOL

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None declared.

PAI-1 polymorphisms have significant associations with cancer risk, especially endometrial and colorectal cancer

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Review question / Objective: **Background: The plasminogen activator inhibitor-1 (PAI-1) is found in many types of tumour cells, which involved in tumorigenesis. Some studies investigated the associations PAI-1 polymorphisms with various cancers, but the results were inconsistent. So this study did a meta-analysis to assess the strength of relationship between PAI-1 and cancer. Methods: Articles that meet the requirements were searched from PubMed and EMBASE electronic databases before May 1st 2020. Stata version 11.2 merged the odds ratios (ORs) values and calculated 95% confidence intervals (CIs). Stratified analyses were assessed on the basis of types of cancer, ethnicity and source of the control group. Heterogeneity and sensitivity were tested, and publication bias was also estimated.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 June 2021 and was last updated on 09 June 2021 (registration number INPLASY202160026).

INTRODUCTION

Review question / Objective: **Background: The plasminogen activator inhibitor-1 (PAI-1) is found in many types of tumour cells, which involved in tumorigenesis. Some studies investigated the associations PAI-1 polymorphisms with various cancers, but the results were inconsistent. So this study did a meta-analysis to assess the strength of relationship between PAI-1 and cancer. Methods: Articles that meet the requirements were searched from PubMed and EMBASE electronic databases before May 1st 2020. Stata version 11.2 merged the odds ratios (ORs) values and calculated 95% confidence intervals (CIs). Stratified analyses were assessed on the basis of**

types of cancer, ethnicity and source of the control group. Heterogeneity and sensitivity were tested, and publication bias was also estimated.

Rationale: Articles that meet the requirements were searched from PubMed, EMBASE, Scopus, CNKI, Wanfang and SinoMed electronic databases before May 1st 2021. Stata version 11.2 merged the odds ratios (ORs) values and calculated 95% confidence intervals (CIs). Stratified analyses were assessed on the basis of types of cancer, ethnicity and source of the control group. Heterogeneity and sensitivity were tested, and publication bias was also estimated.

Condition being studied: Cancer is a primarily public health issue and global problem with high mortality rates. Substantial and convincing evidences suggested that genetic factors were one indispensable factor of the pathogenesis of cancer. The study of genetic variation has had an enormous impact on the belief within the last 30 or so years that could directly or indirectly link specific variants with specific traits or diseases. The commonest type of gene mutation is single nucleotide polymorphism (SNP) at the genomic level, accounting for more than 90% of all known polymorphisms. SNPs could be applied to detect alleles at polymorphic sites for indirectly or directly physiological correlation with traits or disease. In other words, researchers have found that sorts of cancers, such as ovarian, breast and lung, are associated with genetic polymorphism via SNPs test. Plasminogen activator inhibitor type 1 (PAI-1) made a critical difference in tumour progression, involving in degradation of the basement membrane and tumor stroma. PAI-1 could inhibit the expression of active plasmin which degrades the fibrin, hence overexpression of PAI-1 might lead to fibrinolytic system dysfunction, thereby further increasing thrombosis risk. Therefore, PAI-1 expresses and regulates the growth, invasion and angiogenesis of many types of cancer cell in a dose-dependent manner. The level of PAI-1 expression had been found to be modulated by its own genetic polymorphism, of which the most relevant SNP is a single guanosine nucleotide insertion/deletion variation (4G/5G). The location of 4G allele of 4G/5G polymorphism was the promoter region -675 base pairs upstream, PAI-1 gene (rs1799889) could cause an increase in expression levels of PAI-1 in plasma, which suggested that PAI-1 gene (rs1799889) had an effect on the binding of nuclear proteins. This nuclear proteins participated in the regulation of PAI-1 gene transcription and conditioned a clear hypo-fibrinolytic state. In addition, the single nucleotide polymorphism identified in the promoter region -844 G/A (rs2227631) was be investigated. Up to now, the studies that have been published frequently focused on three variants of the PAI-1 gene including the rs1799889/rs2227631/rs2227667 polymorphisms. In order to get a farther understanding of the PAI-1 gene, many case-control reports have explored the correlation between the rs1799889/rs2227631/rs2227667 polymorphisms and risk to different types of cancers. Nevertheless, these reports also showed inconsistency findings. To address these issues, the meta-analysis was conducted to obtain a more precise verdict about the relationship between the rs1799889/rs2227631/rs2227667 polymorphisms and cancer risks.

METHODS

Search strategy: The studies about the relation between rs1799889, rs2227631, or rs2227667 polymorphisms and cancer risks were identified and two databases used in this study were PubMed and EMBASE. The searches identified the eligible publications using the following terms and keywords in the variety of ways: (1) “PAI-1"/ "plasminogen activator inhibitor-1”/ "SERPINE1"; (2) “polymorphism"/ "geneotype"/"gene mutation”/ "variant"/"variation"; (3) “carcinoma"/ "cancer"/ "tumor". The time cut-off point for this searching work was May1, 2021.

Participant or population: Participant who have these cancers, such as ovarian,

breast and lung, are associated with rs1799889/rs2227631/rs2227667 polymorphisms of PAI-1.

Intervention: A case-control study was conducted without intervention.

Comparator: Healthy people.

Study designs to be included: Case-control.

Eligibility criteria: The criteria including eligible articles: (1) evaluation of the link between at least one of these three polymorphisms (SERPINE1 rs1799889, rs2227631, rs2227667) and cancer risk; (2) published language: English, Chinese; (3) enough data to be available for odds ratios (OR) with the 95% confidence interval (95% CI) calculation; (4) study design: case-control; (5) If many studies from the same datum were available, only the studies with larger sample size or most recent studies were included in this study.

Information sources: Articles that meet the requirements were searched from PubMed, EMBASE, Scopus, CNKI, Wanfang and SinoMed electronic databases.

Main outcome(s): Crude ORs and 95% CI were applied to calculate and analyze the relationship between rs1799889 polymorphisms and cancer risk in four models (homozygous model: 4G/4G vs 5G/5G; heterozygous model: 4G/4G vs 4G/5G; recessive model: 4G/4G vs 5G/4G+5G/5G; dominant model: 4G/4G+5G/4G vs 5G/5G). Subgroup analyses were calculated by ethnicity, source of controls and cancer types respectively. Crude ORs and 95% CI were applied to calculate and analyze the association between rs2227631/rs2227667 polymorphisms and the susceptibility to cancer in homozygous model (AA vs GG), heterozygous model (AA vs AG), recessive model (AA vs AG+GG) and dominant genetic model (AA+AG vs GG).

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa Scale was selected for quality assessment.

Strategy of data synthesis: Crude ORs and 95% CI were applied to calculate and analyze the relationship between rs1799889/rs2227631/rs2227667 polymorphisms and cancer risk in four models (homozygous model; heterozygous model; recessive model; dominant model).

Subgroup analysis: Subgroup analyses were calculated by ethnicity, source of controls and cancer types respectively.

Sensitivity analysis: Heterogeneity was calculated and analyzed by using I2 value and P value. I2 statistic indicated the proportion of total variation which was caused by the variation between study and study. The random effects model was used when there were statistical differences found in heterogeneity ($P < 0.05$, $I2 > 50\%$), or else the fixed effects model was conducted when P value was more than 0.05 and I value was less than 50%. Publication bias was used to calculate statistically by the Egger's linear regression test. STATA version 11.2 (StataCorp, College Station, TX, USA) counted all the results, using the P values of two-sided ($P < 0.05$: statistical significance; $P \geq 0.05$: no statistical significance). In order to test the stability of the meta-analysis, a sensitivity analysis was performed by removing individual studies one by one.

Country(ies) involved: China.

Keywords: Cancer; Polymorphism; PAI-1; Meta-analysis.

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