RESEARCH ARTICLE

Relationship Between the Prohibitin 3' Untranslated Region C > T Gene Polymorphism and Cancer Susceptibility - Results of a Meta-analysis

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Abstract

Objective: The results from the published studies on the association between prohibitin 3' untranslated region C > T gene polymorphism and cancer risk are conflicting. This meta-analysis was performed to evaluate the relationship with cancer susceptibility overall, and to explore whether the T allele or TT genotype could become a predictive marker for cancer risk. Methods: Association studies were identified from the databases of PubMed, Embase, and Cochrane Library as of March 1, 2012, and eligible investigations were synthesized using the meta-analysis method. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. Results: Six investigations were identified for the analysis of association between the prohibitin 3' untranslated region C > T gene polymorphism and cancer risk, covering of 1,461 patients with cancer and 1,197 controls. There was a positive association between the T allele and cancer susceptibility (OR=1.20, 95% CI: 1.03-1.39, P=0.02), and CC homozygous might play a protective role (OR=0.80, 95% CI: 0.68-6.11, P=0.95). In the sub-group analysis, prohibitin 3' untranslated region C > T gene polymorphism and cancer risk appeared associated with the risk of breast cancer, but not ovarian cancer. Conclusions: Our results indicate that T allele is a significant genetic molecular marker to predict cancer susceptibility and CC genotype is protective, especially for breast cancer. However, more investigations are required to further clarify the association of the prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility.

Keywords: Prohibitin - 3' untranslated region - C > T gene polymorphism - ovarian cancer - breast cancer - meta-analysis

Asian Pacific J Cancer Prev, **13**, 3319-3323

Introduction

Prohibitin, a ubiquitous and highly conserved protein, is thought to control the cell cycle, senescence, and tumor suppression and negatively controls the cell cycle in the early G1 phase and specifically inhibit initiation of DNA synthesis (Altus et al., 1995; Nadimpalli et al., 2000). Prohibitin genes appear to be expressed in many tissues and organisms, but with some modulation of expression consistent with a role in the cell cycle (Nadimpalli et al., 2000). Laser confocal microscopy results reveal that prohibitin co-localized with the expressions of tumor suppressor genes, such as c-myc, c-fos, p53, and Rb (Li et al., 2011). Prohibitin might be an important gene in the pathogenesis of cancer. Prohibitin 3' untranslated region C > T gene polymorphism consists of three genotypes: wild-type C/C, heterozygous C/T, and the mutant T/T genotype. Mutations or deletions of prohibitin are linked to some human breast and ovarian cancers, supporting the idea that prohibitin suppresses tumors as part of its antiproliferative function involving cell cycle control (Nadimpalli et al., 2000). At present, reports on the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer risk are mainly from breast and ovarian cancers. Cancers are the most risk diseases which threaten our health at present, and there is rare indicator for early diagnosis. Breast and ovarian cancers are the most two frequent cancers of women worldwide, and the most lethal gynecological malignancy worldwide (Yip et al., 2006; Yip & Anderson, 2007; Gao et al., 2009; Khokher et al., 2012; Zhang et al., 2012). Early diagnosis and better prognosis of breast and ovarian cancers is still a challenge, and genetic factors have established a role in pathogenesis of breast and ovarian cancers (Yip et al., 2009; Gao et al., 2012; Jeschke et al., 2012; Xu et al., 2012). Prohibitin can co-localize with the expressions of tumor suppressor genes, such as c-myc, c-fos, p53, and Rb (Li et al., 2011). Interestingly, c-myc, c-fos, p53, and Rb are very important in the pathogenesis of breast and ovarian cancers (Wang et al., 2010; Alshatwi et al., 2011; Kermani et al., 2011; Luparello et al., 2012; Szabova et al., 2012; Vijayaraman et al., 2012). Prohibitin might be associated with the risk of breast and ovarian cancers. In the past decade, there were some studies trying to find a indicator for early diagnosis of breast and ovarian cancers, and exploring the relationship between prohibitin

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3' untranslated region C > T gene polymorphism and the risk of breast and ovarian cancers. However, the results were controversial. The evidence from meta-analysis may be powerful when compared with the individual investigation. This meta-analysis was performed to investigate whether the prohibitin 3' untranslated region C > T gene polymorphism was associated with the onset of cancer, by widely collect the reported investigations.

Materials and Methods

Search strategy for the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer risk

The relevant studies were searched from the electronic databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Database) on March 1, 2012. The retrieval strategy of (prohibitin OR PHB) AND (polymorphism OR variant OR genotype) was entered into these databases mentioned above for search. Additional articles were identified through references cited in retrieved articles.

Inclusion and Exclusion Criteria for Cancer group vs Control group

Inclusion criteria: (1) The outcome had to be cancer; (2) There had to be at least two comparison groups (cancer group vs control group); (3) Investigation should provide the detailed data of prohibitin 3' untranslated region C > T genotype distribution.

Exclusion criteria: (1) Review articles and editorials; (2) Case reports; (3) Preliminary result not on prohibitin 3' untranslated region C > T gene polymorphism or outcome; (4) If multiple publications from the same study group occurred, we only recruited the most complete paper into our final analysis.

Data extraction and synthesis

Two investigators independently extracted the following information from each eligible study: first author's surname, year of publication, which country the study performed, and the number of cases and controls for prohibitin genotypes. Frequency of T allele was calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreement was resolved by discussion.

Statistical Analysis

Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each investigation. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the P value of heterogeneity test was less than 0.1 (Zhou et al., 2012) . Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $P < 0.05$ was required for the pooled OR to be statistically significant. I^2 was used to test the heterogeneity among the included studies. In order to avoid excessive comparisons, the OR was calculated by using three methods (Zhou et al., 2011): method 1, allele comparison (T allele vs I allele); method 2, comparing TT homozygous with the other two combinations (TT vs TC+CC); method 3, comparing CC genotype with the other two combinations (CC vs TT+TC). A chi-square (χ^2) test using a web-based program was applied to determine if genotype distributions of the control group reported conformed to Hardy-Weinberg equilibrium (HWE; $P < 0.05$ was considered significant). The gene distributions of the control group in the included studies were not in HWE, which might be an important reason for heterogeneity (Zhou et al., 2011; Zhou et al., 2011), and the study that the genotype distributions in the control group were significantly deviated from HWE was excluded from our sensitive analysis. The Begg adjusted rank correlation test (Begg & Mazumdar, 1994) and the Egger regression asymmetry test (Egger et al., 1997) were used for exploring publication bias ($P<0.1$ was considered significant), when the number of the included studies was more than five. All descriptive data were expressed as mean ± SD.

Results

Characteristics of included studies

Six studies (Campbell et al., 2003; Spurdle et al., 2003; Jakubowska et al., 2007; Grimm et al., 2008; Jakubowska et al., 2008; Karakus et al., 2008) were recruited into our investigation to study the relationship between prohibitin 3' untranslated region C > T gene polymorphism and cancer susceptibility. Three studies (Campbell et al., 2003; Jakubowska et al., 2007; Karakus et al., 2008) were performed in breast cancer and three studies (Spurdle et al., 2003; Grimm et al., 2008; Jakubowska et al., 2008) were conducted in ovarian cancer. The data of our interest were extracted: first author's surname, year of publication, which country the study performed, and the number of cases and controls for prohibitin genotypes (Table 1). Those six investigations contained 1461 patients with cancer and 1197 controls. The average distribution frequency of T allele in patients with cancer was 17.27% and the average frequency in controls was 15.29%. The average distribution frequency of T allele in cases was a

Table 1. Characteristics of the Studies Evaluating the Effects of PHB Gene Polymorphism on Cancer Risk

First author, year	Country	Type of cancer	Case			Control			T allele (%)		P (HWE)
			TT	TC	CC	TT	TC	CC	Case	Control	
Spurdle 2003	Australia	Ovarian cancer	20	161	362	8	87	196	18.51	17.7	0.654
Campbell 2003	England	Breast cancer	10	93	188	7	61	170	19.42	15.76	0.594
Jakubowska 2007	Poland	Breast cancer	5	77	176	2	45	211	16.86	9.5	0.813
Karakus 2008	Turkey	Breast cancer	3	36	67	6	47	101	19.81	19.16	0.856
Grimm 2008	Australia	Ovarian cancer	2	46	88	6	39	84	18.38	19.77	0.594
Jakubowska 2008	Poland	Ovarian cancer	1	25	101	0	25	102	10.63	9.84	0.219

Table 2. Meta-analysis of the Association of PHB Gene Polymorphism with Risk of Cancer

Genetic contrasts	Group and subgroups	studies Q test P value	Model seclected	OR (95%CI)	P
T vs C	Overall	6	0.10	Fixed	1.20(1.03,1.39)	0.02
	Ovarian cancer	3	0.83	Fixed	1.03(0.83,1.26)	0.81
	Breast cancer	3	0.09	Random	1.39(0.99,1.95)	0.06
TT vs (TC+CC)	Overall	6	0.50	Fixed	1.11(0.68,1.80)	0.68
	Ovarian cancer	3	0.22	Fixed	1.02(0.52,2.01)	0.95
	Breast cancer	3	0.52	Fixed	1.21(0.60,2.45)	0.60
CC vs (TT+TC)	Overall	6	0.11	Fixed	0.80(0.68,0.95)	0.01
	Ovarian cancer	3	1.00	Fixed	0.97(0.76,1.23)	0.80
	Breast cancer	3	0.13	Fixed	0.66(0.52,0.84)	0.0007

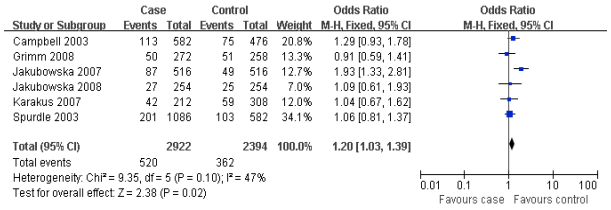

Figure 1. Association Between T Allele and Cancer Risk

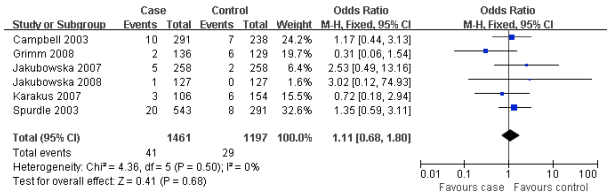

Figure 2. Association of TT Genotype with Cancer Risk

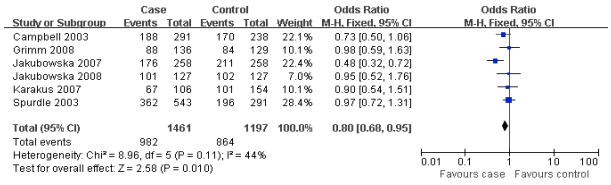

Figure 3. Association of CC Genotype with Cancer Risk

little increased when compared with that in control group (cancer/control = 1.13).

Association of prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility

In this meta-analysis, we found that T allele was associated with cancer risk (Figure 1, Table 1). However, the TT genotype was not associated with the cancer risk (Figure 2, Table 1). Interestingly, CC genotype seemed to play a protective role against cancer risk (Figure 3, Table 1).

We conducted a sensitivity analysis according to the gene distribution of control group in the included study not in HWE. The genotype distributions of the control population in all the recruited studies conform to HWE test, and the results in sensitivity analysis according to HWE test were same as those in non-sensitivity analysis. In this study, a sub-group analysis according to different type of cancer was also performed. In breast cancer, the pooled OR for T allele was markedly favourable to the cancer group, although the differences were not statistically significant (OR=1.39, 95% CI: 0.99-1.95, P=0.06; Table 2). TT genotype was not associated with the risk of breast cancer (OR=1.21, 95% CI: 0.60-2.45, P=0.60; Table 2). Interestingly, CC genotype seemed to play a protective role against breast cancer risk (OR=0.66, 95% CI: 0.52-0.84, P=0.0007; Table 2). However, for ovarian cancer, we found that prohibitin 3' untranslated region C > T gene polymorphism was not associated with and susceptibility of ovarian cancer (T: OR=1.03, 95% CI: 0.83-1.26, P=0.81; TT: OR=1.02, 95% CI: 0.52-2.01, P=0.95; CC: OR=0.97, 95% CI: 0.76-1.23, P=0.80; Table 2).

Evaluation of publication bias

No significant publication bias was showed for the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility (Begg P=0.462, Egger: P=0.216).

Discussion

Genetic origin of cancer had been a focus of research in the past years, and some studies found that the genetic alteration was associated with the susceptibility of cancer and might become an early diagnosis indicator to predict the risk of cancer (Sagae et al., 2002; Huo et al., 2009; Jeon et al., 2010; Arisawa et al., 2012; Xu et al., 2012). Prohibitin, acting as a tumor suppression gene, might play an important role in the pathogenesis of cancer. Prohibitin 3' untranslated region C > T gene polymorphism is the first and only reported mutation site of prohibitin at present. All the studies on the association of prohibitin 3' untranslated region C > T gene polymorphism with diseases were performed in breast cancer and ovarian cancer. This meta-analysis was performed to explore the association of prohibitin 3' untranslated region C > T gene polymorphism with the risk of cancer.

In our study, we found that T allele was associated with cancer risk, and CC genotype seemed to play a protective role against cancer risk. However, the TT genotype was not associated with the cancer risk. There was no notable heterogeneity among the included studies. Furthermore, there was no significant publication bias for the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility. The conclusion for the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility might be robust to some extent.

In the sub-group study for breast cancer, we found that prohibitin 3' untranslated region C > T gene polymorphism was associated with susceptibility of breast cancer. T allele was markedly favourable to the cancer group, although the differences were not statistically significant. When

fixed effects model was used for the relationship between T allele and susceptibility of breast cancer, we found that T allele was associated with breast cancer (OR=1.40, 95% CI: 1.14-1.73, P=0.002). Interestingly, CC genotype seemed to play a protective role against breast cancer risk. However, there only three studies were included for the meta-analysis for breast cancer. More studies on the association of prohibitin 3' untranslated region C > T gene polymorphism with susceptibility of breast cancer should be conducted in the future.

Jakubowska et al. (2007) reported that the 3' untranslated region C > T polymorphism of PHB was associated with breast cancer risk in Polish women, and suggested that the PHB 3'UTR T allele increased the risk of breast cancer. Manjeshwar et al. (2003) conducted a study in vivo and reported that: Clones expressing the C allele RNA (3'untranslated region/C) exhibited significant suppression of growth in cell proliferation assays, inhibition of colony formation in soft agar assays, and suppression of xenograft tumor growth when implanted on nude mice, compared with either T allele expressing or empty vector clones. Immunohistochemical analyses with Ki67 staining confirmed a significant reduction in proliferation of 3'untranslated region/C tumors. Thus, the C allele of prohibitin 3'untranslated region produced a functional RNA, whereas a single nucleotide polymorphism creates a null allele (T allele) of which the RNA product had lost activity. Those data demonstrated for the first time that an RNA molecule functioned as a tumor suppressor in human breast cancer. Our results in this meta-analysis were similar with the results form Jakubowska et al. (2007) and Manjeshwar et al. (2003). However, Campbell et al. (2003) didn't find the 3' untranslated region C > T gene polymorphism of PHB was associated with the risk of breast cancer. Karakus et al. (2008) reported that 3' UTR C > T gene polymorphism contributed to risk of breast cancer, and the PHB T variant was not associated with the risk of breast cancer in Turkish women.

In the sub-group study for breast cancer, we found that prohibitin 3' untranslated region C > T gene polymorphism was not associated with susceptibility of ovarian cancer. Grimm et al. (2008) found that the PHB 3' untranslated region polymorphism was not associated with risk and prognosis of ovarian cancer in Caucasian women. Jakubowska et al. (2008) performed a comparison of the genotype frequencies between cases and controls, and revealed no association of the PHB 3' untranslated region CT+TT genotypes with ovarian cancer risk in Polish women. Spurdle et al. (2003) reported that there was no evidence of an effect of the CT, TT, or pooled CT/TT genotype on risk of ovarian cancer, and the prohibitin T variant also did not appear to be associated with risk of ovarian cancer in Australian women. Our results in this meta-analysis were consistent with those studies mentioned above.

To sum up those mentioned above, we found that prohibitin 3' untranslated region C > T gene polymorphism was associated with susceptibility of cancer. Breast cancer might be responsible for this conclusion, and more studies in breast cancer should be conducted in the future. In this meta-analysis, the gene distributions of all the included studies were in HWE, and there was no significant publication bias for the association of prohibitin 3' untranslated region C > T gene polymorphism with cancer susceptibility. The conclusion from our meta-analysis might be robust to some extent. However, there were also some limitations in our meta-analysis. First, heterogeneities might be present, affecting the results of our meta-analysis, although a random effects model has been performed. Furthermore, the sample sizes in some studies are relatively small. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study supported that prohibitin 3' untranslated region C > T gene polymorphism was associated with the cancer susceptibility. However, more case-control association investigations on larger, stratified populations are required to further clarify the role of the prohibitin 3' untranslated region C > T gene polymorphism in cancer susceptibility, especially in breast cancer.

Acknowledgements

The authors would like to gratefully acknowledge the most helpful comments on this paper received from Professor Liang Rong, Department of Pediatric-neonatology, Baylor College of Medicine, Houston, texas, USA.

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