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The Prognosis Value of *CDH-1* Methylation – The Epigenetic Biomarker in Nasopharyngeal Carcinoma: Systematic Review and Meta-Analysis

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Abstract

Background: The phenome of *CDH-1* gene methylation has been reported to be associated with the nasopharyngeal tumorigenesis. **Objective:** Aiming to evaluate the association between the *CDH-1* gene methylation and nasopharyngeal cancer, and its correlation could be used as an epigenetic biomarker for nasopharyngeal cancer risk based on meta-analysis. **Materials and Methods:** Relevant articles were identified by searching MEDLINE database. The frequency and Odds Ratio (OR) were applied to estimate the effect of *CDH-1* methylation based on random-/fix-effects models. **Results:** Total of 12 studies, including 500 samples from NPC patients and 201 samples from non-cancerous samples, were enrolled in current study. Overall, the frequency of *CDH-1* gene methylation were 48.50% and 3.09% in the case and control group, respectively. The association between the *CDH-1* gene methylation and risk of NPC was also confirmed by calculating OR value of 15.33 (95% CI = 7.82-30.06), based on the fix-effects model. Additionally, the significant association was also found between the methylation of *CDH-1* gene and subgroups. **Conclusion:** this meta-analysis provides scientific evidences to suggest the *CDH-1* methylation was the potential biomarker for risk of NPC.

Keywords: *CDH-1,* Epigenetic Biomarker, Nasopharyngeal carcinoma, Meta-Analysis

1. Introduction

Nasopharyngeal Carcinoma (NPC), a malignant tumor of nasopharynx with remarkable differences in distribution according to geography and ancestry, gravitating toward Southern Asia, especially in China and Vietnam, processes the highest rate of head and neck cancer[1-6]. Updated to 2018, a total of 129,079 new nasopharyngeal cases were recorded in the world, of which 72,987 nasopharyngeal death cases were occurred[6]. Even though improvements in nasopharyngeal cancer treatment have been achieved, the diagnosis at an advanced stage led to reduce the success rate of treatment as well as the survival of patients. Therefore, the early diagnosis or screening is very important to increase the opportunities for cancer treatment. However, the major obstacle to prognosis and early screening of NPC is the different access due to the deeply seated location of nasopharynx, as well as the unclear presenting symptoms. Many efforts have been made for identification of early biomarkers, which

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involved in the pathogenesis of NPC, including the genetic and epigenetic alteration, in nasopharyngeal carcinoma patients. In recent years, a well-established etiology factor of NPC: the methylation of tumor suppressor gene, related to the pathogenesis and development of NPC, has been postulated. It is noted that the hypermethylation occurred in the tumor suppressor genes' promoter leads to gene inactivation, which inhibit the functions of those genes, resulting in the cancer development[7]. *CDH-1* (also known as E-cadherin), located on chromosome 16q 22.1, a prototype of the cadherin family, has been recognized as the tumor suppressor gene. Its encoded protein has been reported as the main key mediator of cell-cell adhesion in epithelial tissue by the forming of E-cadherin/catenin complex which is further linked to the actin cytoskeleton[8,9]. Recent studies indicated that the methylation of *CDH-1* plays a vital role in the development and progression of NPC and might be the potential biomarker for NPC patients. However, due to the different sensitivities and intra/inter-assay coefficients of variation of methods, the reported frequency of *CDH-1* methylation, and its prognostic value is highly variable, and also remain controversial. Therefore, we performed the present study to carry out a systematic review and a meta-analysis, notably, the systematic review and a meta-analysis, in order to summarize the previously published studies and to evaluate the methylation of *CDH-1* could be served as the prognosis and early screening for NPC risk.

2. Materials and Methods

2.1 Search Strategy and Inclusion/Exclusion Criteria

The guidelines of Preferred Reporting Items for Systematics reviews and Meta-Analyses (PRISMA) were applied to perform the current meta-analysis[10]. By using separation or combination of following keywords: "Nasopharyngeal carcinoma", "methylation", "*CDH-1*", "E-cadherin", "prognosis", "diagnosis", were applied to search related published articles in MEDLINE database (updated on December, 2019). Additional studies were also identified via the references listed in the articles.

Studies were deeply considered eligible only when they met all of the following inclusion criteria: 1. The articles were limited to studies written in English; 2. case-control study designed; 3. provided that data about the frequency of *CDH-1* methylation as well as the sample size in both case and control group. Exclusion criteria were as follows: 1. The articles were written in other languages; 2. abstracts, case reports, letter to editor or unpublished articles were eliminated; 3. studies were related to other tumors and not specific for NPC; 4. studies lacked vital information for analysis.

3. Data Extraction

The eligibility of each study, the relevant data from the eligible studies was independently retrieved by two authors. Disagreements were resolved through discussion within the third author or our research team. The relevant data were extracted from each study according to the data form, including first Author's last name, year of publication, country where the study was performed, sample type, experimental methods to assess the methylation of *CDH-1*, and number of cases and controls subjects.

4. Statistical Analysis

All data were statistically analyzed using the MedCalc® software by MedCalc Software Ltd. (https://www.medcalc.org/). The frequency of *CDH-1* methylation was calculated in both case and control group. The strength of association between *CDH-1* methylation and NPC was evaluated by Odds Ratio (OR) with 95% confidence intervals (95%CI). In present study, the heterogeneity among the included studies was estimated by the Cochran Q test and I^2 statistics[11]. The cut-off point: $p = 0.05$ for the Q test and I^2 were used to test the heterogeneity between studies[12,13]. The scale of I^2 value is classified as following: $I^2 < 25\%$: no heterogeneity, $25\% \leq I^2 \leq 50\%$: moderate heterogeneity, and $I^2 > 50\%$: strong heterogeneity[21,22]. The random-effects model was applied if the heterogeneity among studies existed ($p < 0.05$ for Q test, $I^2 > 50\%$). In the case of no between-study heterogeneity, a fixed-effects model was applied to compute the pooled ORs. In order to determine the presence of publication bias, the symmetry of the funnel plots in which ORs were plotted against their corresponding standard errors

were assessed by the Begg's funnel plot and Egger's test ($p < 0.05$ indicates statistically significant)[14,15].

5. Results

5.1 The Characteristic of Eligible Studies

A total of 148 articles were retrieved from the database of MEDLINE and related references. After exclusion of studies which do not meet the inclusion criteria, finally, eleven studies that included 701 samples, comprised of 500 samples from NPC patients and 201 samples from non-cancerous samples were enrolled in current systematic review and meta-analysis. The characteristics of included studies of *CDH-1* methylation. These patients came from: Asian countries (four countries: Hong Kong, Thailand, China, Singapore), Africa (one country: Tunisia). The various source case samples, including NPC biopsy tumor, plasma, buffy coat, nasopharyngeal swab, were used to evaluate the methylation of *CDH-1* in NPC. Of which, biopsy tumor sample was preferentially used in the evaluation of methylation of *CDH-1* in NPC. Among the included studies, Eleven studies used MSP method only one study used quantitative Realtime-PCR to explore the frequency of *CDH-1* methylation in NPC and corresponding controls (Table 1).

5.2 The Frequency of *CDH-1* Methylation, and the Association between *CDH-1* Methylation and Risk of NPC

Considering the significant heterogeneity between studies (Case: Q = 92.53, $p < 0,0001$, I^2 = 82.71%, 95%CI = 73.47-88.73; Control: Q = 9.50, $p = 0.66$, I^2 = 0.00%, 95% CI for I^2 = 0.00-45.30), the random-effects model, and the fix-effects model were applied to calculate the frequency of *CDH-1* methylation in NPC and corresponding controls (Figure 1&2). According to Figure 1&2, the frequency of *CDH-1* methylation in case and control group were 48.50% (95% CI = 37.97-59.10) and 3.09% (95% CI = 1.21-6.39) based on random-effects model, and the fix-effects model, respectively. The current meta-analysis results indicated that the frequency of *CDH-1* methylation in NPC patients was significantly higher than the control group. We also evaluated the association between the presence of *CDH-1* methylation and NPC by analysis OR. The presence of *CDH-1* methylation was associated with an increased NPC risk with a pooled OR of 15.33 (95% CI = 7.82-30.06), based on the fix-effects model (Q = 7.77, p = 0.80, I^2 = 0.00%, 95% CI for I^2 = 0.00-33.10) (Figure 3). The funnel plot of pooled analysis, which was quite symmetric, indicated that there was no significant bias among the included studies; therefore, there was no any factor of influence on the current meta-analysis (Figure 4).

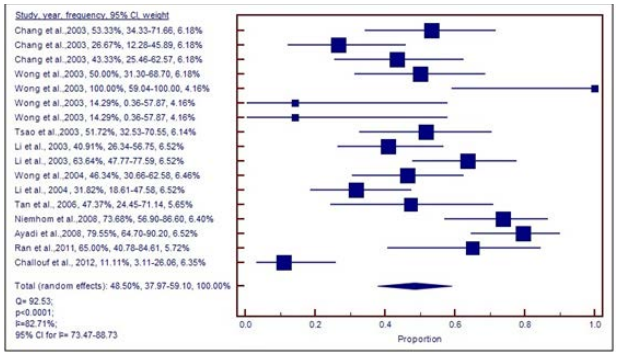

Figure 1. Forest plot of frequency of *CDH-1* gene methylation detected in NPC samples.

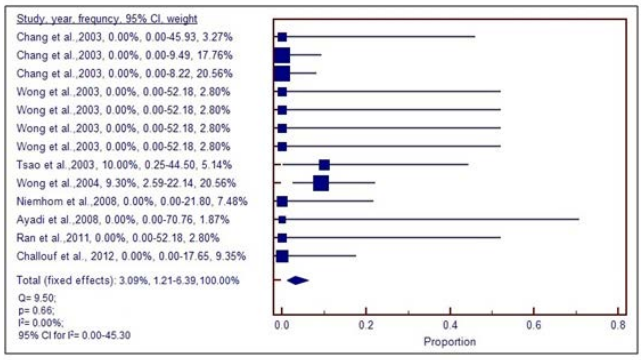

Figure 2. Forest plot of frequency of *CDH-1* gene methylation detected in non-cancerous samples.

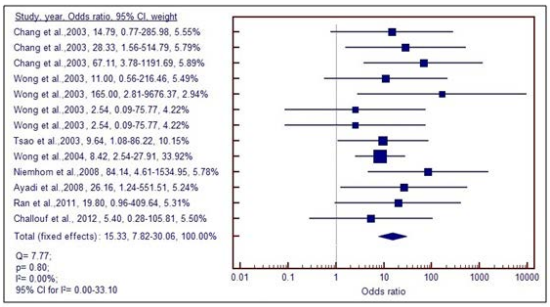

Figure 3. Forest plot of the association between the methylation of *CDH-1* gene and NPC through OR based on the fix-effects model.

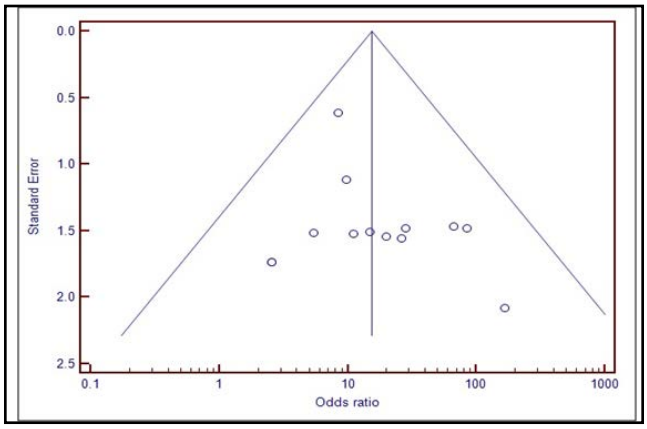

Figure 4. Funnel plot of *CDH-1* methylation and nasopharyngeal cancer risk based on the fix-effects model

Aiming to evaluate the stability and reliability of current enrolled database, the sensitivity analysis was performed according to the leave-one-out method by excluding one study. As shown in (Table 2), the pooled OR was ranged from 12.37, (95% CI = 5.89-25.95) to 18.72, (95% CI = 8.19-42.82) under the fix-effects model within the I^2 = 0.00 (Table 2). Therefore, the enrolled of present enrolled database of current meta-analysis, which was to evaluate the association between methylation of *CDH-1* and NPC risk, were stable and reliable.

We also performed subgroup analyses by region, testing-method, and source of case sample. The results indicated no heterogeneity was in among subgroup of region, testing-method, and source of case sample. Regarding to the subgroup of region, there was the significant association between *CDH-1* methylation and risk of NPC among group of Asian countries and non-Asian countries (Asian countries: OR = 15.00, 95% CI = 7.53-29.86; Non-Asian countries: OR = 26.16, 95% CI = 7.53-29.86). Considering the source of samples, the significant association between *CDH-1* methylation and NPC was observed among the NPC biopsy tissue group and non-biopsy group in the fix-effect model (biopsy tissue group: OR = 18.94, 95% CI = 6.86-52.29; non-biopsy group: OR = 12.53, 95% CI = 5.07-30.98). Additionally, significant association between CDH-1 methylation and NPC risk among test-method subgroup was found (MSP: OR = 18.72, 95% CI = 8.19-42.82; qRT-PCR: OR = 8.42, 95% CI = 2.54-27.91) (Table 3).

Table 1. The characteristics of studies included in the meta-analysis of *CDH-1* methylation and risk of NPC

Author, Reference	Region	Case		Control		Method	Source of	
		N	P	N	P		Case	Control
Chang et al., 2003[16]	Hong Kong	30	16	6	0	MSP	B	B
Chang et al., 2003[16]	Hong Kong	30	8	37	0	MSP	S	S
Chang et al., 2003[16]	Hong Kong	30	13	43	0	MSP	MT	MT
Wong et al., 2003[17]	Hong Kong	30	15	5	0	MSP	B	B
Wong et al., 2003[17]	Hong Kong	7	7	5	0	MSP	T	B
Wong et al., 2003[17]	Hong Kong	7	1	5	0	MSP	P	B
Wong et al.,2003[17]	Hong Kong	7	1	5	0	MSP	Bu	B
Tsao et al., 2003[18]	Hong Kong	29	15	10	1	MSP	B	B
Li et al., 2003[19]	China	44	18	-	-	MSP	B	-
Li et al., 2003[20]	China	44	28	-	-	MSP	B	-
Wong et al., 2004[21]	China	41	19	43	4	qRT-PCR	P	P
Li et al., 2004[22]	China	44	14	-	-	MSP	B	-
Tan et al., 2006[23]	Singapore	19	9	-	-	MSP	B	-
Niemhom et al., 2008[24]	Thailand	38	28	15	0	MSP	B	B
Ayadi et al., 2008[25]	Tunisia	44	35	3	0	MSP	B	B
Ran et al., 2011[26]	China	20	13	5	0	MSP	B	B
Challouf et al., 2012[27]	Tusinia	36	4	19	0	MSP	B	B

Note: B: NPC biopsy tissue; P: Plasma; S: Nasopharyngeal swab; Bu: Buffy coat; MT: mouth and rinse; MSP: methylation-specific PCR; qRT-PCR: Real-Time Quantitative Reverse Transcription PCR.

Table 2. Sensitivity analysis of methylation of *CDH-1* and NPC risk by the fix-effects model

	OR, 95% CI	Heterogeneity	
		I^2, 95% CI	p
Omitting Chang et al., 2003	12.37, 5.89-25.95	0.00, 0.00-43.61	0.74
Omitting Wong et al., 2003	17.01, 8.08-35.82	0.00, 0.00-36.52	0.82
Omitting Tsao et al., 2003	16.06, 7.90-32.63	0.00, 0.00-40.50	0.74
Omitting Wong et al., 2004	18.72, 8.19-42.82	0.00, 0.00-33.15	0.81
Omitting Niemhom et al., 2008	13.21, 6.56-26.59	0.00, 0.00-24.22	0.87
Omitting Ayadi et al., 2008	15.00, 7.53-29.86	0.00, 0.00-39.77	0.75
Omitting Ran et al., 2011	15.13, 7.59-30.18	0.00, 0.00-40.68	0.74
Omitting Challouf et al., 2012	16.31, 8.18-32.52	0.00, 0.00-38.31	0.76

Table 3. Summary of subgroup analysis in meta-analysis of CDH-1 methylation and NPC risk

Group	Case		Control		Model, OR, 95% CI (Fix-effects model)	Heterogeneity	
	N	P	N	P		I^2 (%)	p
Total	349	175	201	5	15.33, 7.82-30.06	0.00	0.80
Region							
Asia	305	140	198	5	15.00, 7.53-29.86	0.00	0.75
Non-Asia	44	35	3	0	26.16, 7.53-29.86	-	-
Source of sample							
Biopsy sample	234	133	68	1	18.94, 6.86-52.29	0.00	0.85
Non-biopsy	115	42	133	4	12.53, 5.07-30.98	0.00	0.44
Histological type of cancer							
MSP	308	156	158	1	18.72, 8.19-42.82	0.00	0.81
qRT-PCR	41	19	43	4	8.42, 2.54-27.91	-	-

Note: not recorded due to only study is recorded

6. Discussion

The inactivation of tumor suppressor genes, including *CDH-1* gene, through the methylation of its promoter, has been reported as the etiological factor of NPC development and progression[28,29]. *CDH-1*, a tumor suppressor gene, plays an important role in maintaining the differentiation of cell as well as the cell-cell adhesion based on the linkage between cell and the actin cytoskeleton through interactions with catenin in the cytoplasm[30,31].The current meta-analysis was done based on the previous published studies, included 500 samples from NPC patients and 201 samples from non-cancerous samples to evaluate the association between the methylation of *CDH-1* gene and NPC cancer risk as well as evaluate the potential of *CDH-1* methylation could be served as a biomarker for prognosis and early screening of NPC. The overall frequency of *CDH-1* gene promoter methylation in NPC was higher than control group (Case: 48.50% (95% CI = 37.97-59.10) and control: 3.09% (95% CI = 1.21-6.39, $p < 0.01$). Additionally, it could be suggested that the individuals with the methylation of *CDH-1* gene was significant associated with NPC (pooled OR = 15.33, 95% CI = 7.82-30.06, based on the fix-effects model (Q = 7.77, p = 0.80, I^2 = 0.00%, 95% CI for I^2 = 0.00-33.10). Those results supported the predictive function of *CDH-1* gene promoter could be served as the potential biomarker of NPC. Further subgroup analysis revealed that association between methylation of *CDH-1* and nasopharyngeal cancer was found among the Asian region. Notably, almost studies was performed in Asian region (11 of 12 studies), thus, one again confirmed the nasopharyngeal cancer is native to Asian region. Concerning to the test-method, MSP method was used in 11 of 12 studies,

counting for 91.67% It could be explained that MSP is the "gold standard method" of evaluation of methylation. The MSP shows the useful tool for the qualitative DNA methylation analysis within the ease of design and execution, sensitivity in the ability to detect small quantities of methylated DNA[32]. Moreover, in which MSP products are run on a gel, and the results are reported as methylated or unmethylated at the target DNA sequence[33]. In additionally, methylation in biopsy samples may be efficient and sensitive to detect the methylation of *CDH-1* when compared to other source of samples: nasopharyngeal swab, mouth and rinse, plasma (Biopsy: OR = 18.94, Non-biopsy: OR = 12.53). It indicated that the type of biopsy was more suitable to apply to evaluate the methylation of *CDH-1* gene. However, the source of non-biopsy samples, including nasopharyngeal swab, mouth and rinse, plasma – type of non/less-invasive source of sample, could be reflect alterations in the NPC and facility of collecting NPC samples led it a potential biomarker for prognosis and early screening of NPC. These results are in accordance with that documented *CDH-1* gene methylation to be the common and epigenetic event in the progression of NPC. However, the current meta-analysis exhibited some limitations due to the number of current enrolled studies of 12, the data of non-English language studies may contribute to some bias, as well as the evaluation of the correlation between methylation of *CDH-1* gene and clinicopathological features.

7. Conclusion

The frequency of *CDH*-1 gene (counting for 48.50%) and in the NPC samples was significantly higher than in control group (counting for 3.09%). Additionally, our findings underscore the correlation among *CDH-1* gene methylation and all subgroups, including region, source of samples, and test-method. It is worth emphasizing that the methylation of *CDH-1* gene was recorded as the early epigenetic event in the progression of nasopharyngeal tumorigenesis based on the literature-based meta-analysis.

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