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Clinical effects of p53 overexpression in squamous cell carcinoma of the sinonasal tract

A systematic meta-analysis with PRISMA guidelines

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Abstract

Background: The level of p53 protein expression in sinonasal squamous cell carcinoma (SNSCC) has been estimated, but the results remain inconsistent and the point of consensus has not been reached. This study was first determined to evaluate the clinical effects of p53 expression in SCC of the sinonasal tract.

Methods: According to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement criteria, the potential literature was searched from diverse databases. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to assess the strength of association between p53 expression and SNSCC.

Results: Final 17 eligible studies were included in a total of 258 cases and 748 controls. The result of p53 expression was shown to be notably higher in SNSCC than in benign sinonasal papillomas and normal sinonasal mucosa (OR = 26.93, $P < 0.001$; OR = 39.79, $P < 0.001$; respectively). Subgroup analyses of ethnicity revealed that p53 expression had significant association with SNSCC in Asian and Caucasian populations in cancer versus benign sinonasal papillomas or normal sinonasal mucosa. The expression of p53 was notably higher in moderately or poorly differentiated SNSCC than in well-differentiated SNSCC (OR = 3.51, $P = 0.021$), while p53 expression was not associated with histological type.

Conclusion: The results suggested that p53 overexpression may be correlated with the carcinogenesis and progression of SNSCC. The p53 gene may become a novel drug target of SNSCC. Additional studies on the correlation of p53 expression with clinicopathological features are needed.

Abbreviations: 95% CI = 95% confidence interval, IHC = immunohistochemistry, KSCC = keratinizing squamous cell carcinoma, NKSCC = nonkeratinizing squamous cell carcinoma, OR = odds ratio, SNSCC = sinonasal squamous cell carcinoma.

Keywords: benign papilloma, p53, sinonasal squamous cell carcinoma, tumor differentiation

1. Introduction

As one of the most uncommon malignant diseases, malignant neoplasms of the sinonasal tract account for approximately 0.3% of all cancers, and about 3% of head and neck carcinomas,[1,2] with an overall incidence rate of 0.5 to 1.0 cases per 100,000 population annually.[3] The most common histological subtypes in the nasal sinuses are squamous cell carcinoma (SCC) and adenocarcinoma. Sinonasal squamous cell carcinoma (SNSCC) is the most common type and accounts for approximately 60% to 75% of sinonasal cancer cases.[4,5] Due to the relatively asymptomatic pattern of tumor growth, the majority of SNSCC patients are diagnosed at an advanced stage. Patients have a low average 5-year survival rate and poor outcomes.[6,7]

Although the existence of many factors are correlated with SNSCC, such as cigarette smoking, wood dust, nickel, and leatherworking, these risk factors do not necessarily associate with a late stage of SNSCC.[8] Recently, accumulating evidence suggests that a number of genetic alterations may contribute to the initiation and progression of SNSCC.[9–12] The *p53* gene is a tumor suppressor gene mapped to chromosome 17p13, encodes the p53 protein, which involves in the regulation of the cell cycle, the inhibition of DNA synthesis, the function of DNA repair and apoptosis.[13–15] The *p53* mutation is the most commonly found genetic alterations in various human carcinomas,[16,17] and the overexpression of p53 detected by immunohistochemistry (IHC) in most of cases (85%) is consistent with an underlying mutation.[18] Thus, p53 expression may be considered as an indicator of *p53* gene mutation.

Due to the small sample size problem of individual studies with the low statistical power in SNSCC, therefore, we first performed a comprehensive meta-analysis of all published articles to determine the association between p53 expression and SNSCC by comparing cancer cases with benign sinonasal papillomas and normal sinonasal mucosa. In addition, we also evaluated the

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correlation of p53 expression with clinicopathological characteristics in SNSCC.

2. Materials and methods

2.1. Search for eligible studies

We identified eligible studies by searching a range of online electronic databases (PubMed, EMBASE, EBSCO, and Cochrane Library) prior July 27, 2016, without language or date-of-publication limitations. The keywords and search terms included the following: (sinonasal OR nasal OR paranasal sinuses) AND (cancer OR carcinoma OR tumor OR squamous cell OR SCC OR papilloma) AND (p53 OR p53 protein) AND (expression OR overexpression OR hyperexpression). In addition, we manually scanned the reference lists of the identified articles to identify the other potential studies.

2.2. Selection criteria

Eligible articles included in this meta-analysis must meet the following inclusion criteria: the patients were limited to SNSCC by histopathological confirmation; control groups were divided into benign sinonasal papillomas and normal sinonasal mucosa; case–control or cohort studies had to provide the sufficient information regarding the frequency of p53 expression to evaluate the correlation between p53 expression and SNSCC for this study; if more than one article using the same sample data were published, only most recent article or article with the largest sample size was included in the present study. Studies excluded did not meet the above selection criteria.

2.3. Ethical review from patients

Although this meta-analysis was not primary research involving human specimens, this research was a secondary analysis with regard to human subject data published in the public domain.

2.4. Data extraction

The following data were retrieved from eligible studies: the first author's surname, year of publication, country, ethnicity, control type, detection method, number of case and control samples, frequency of p53 expression in cases and controls, and clinicopathological parameters such tumor differentiation and histological type. Two reviewers (Fang Qi and Zhiqiang Gao) independently extracted relevant data from each study. To resolve disagreements between 2 reviewers, any disagreements about study selection and data extraction were discussed by all authors.

2.5. Statistical analysis

This meta-analysis was carried out using the STATA software (version 12.0, Stata Corporation, College Station, TX). The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and summarized to estimate the strength of association between p53 expression and SNSCC in case versus controls. Additionally, we also determined whether the expression of p53 protein was correlated with tumor differentiation and histological type in cancer. Between-study heterogeneity was examined using the Chi-square test and Q statistics.[19] The pooled OR was calculated under the random-effects model. If substantial heterogeneity was found in this study ($P < 0.1$), a sensitivity analysis was performed to estimate the influence of a single study on the pooled OR and the effect of deleting a single study on the stability of the results.[20,21] The potential publication bias was identified by Egger test.[22] P-value <0.05 was considered to be statistically significant for the pooled ORs and 95% CIs with more than 1 or less than 1.

3. Results

3.1. Characteristics of eligible studies

Figure 1 shows the detailed procedure of included studies selection. Three hundred thirty-four studies were identified from an original literature search of electronic databases and a manual search. Ultimately, a total of 17 studies fulfilled the above select criteria and were included in the current meta-analysis.[9,23–38] Among the 17 articles published in English, the publication years ranged from 1998 to 2015. Sixteen studies including 229 SNSCC and 675 benign papilloma patients evaluated the relationship between p53 expression and SNSCC in cancer versus benign sinonasal papillomas.[9,23–30,32–38] Five studies involving 112 SNSCC patients and 73 normal sinonasal mucosa estimated the relationship between p53 expression and SNSCC in cancer versus normal sinonasal mucosa.[30,34,35,37,38] Three studies with 72 SNSCC patients evaluated the correlation between p53 expression and tumor differentiation in cancer.[27,32,35] Three studies with 83 SNSCC patients evaluated the correlation between p53 expression and histological type in cancer.[31,32,35] Their baseline characteristics are summarized in Table 1.

3.2. Correlation of p53 expression in cancer versus control groups

In this study, the random-effects model was applied to make the results more reliable. The pooled OR indicated that the level of p53 expression in SNSCC tissues was notably higher than in

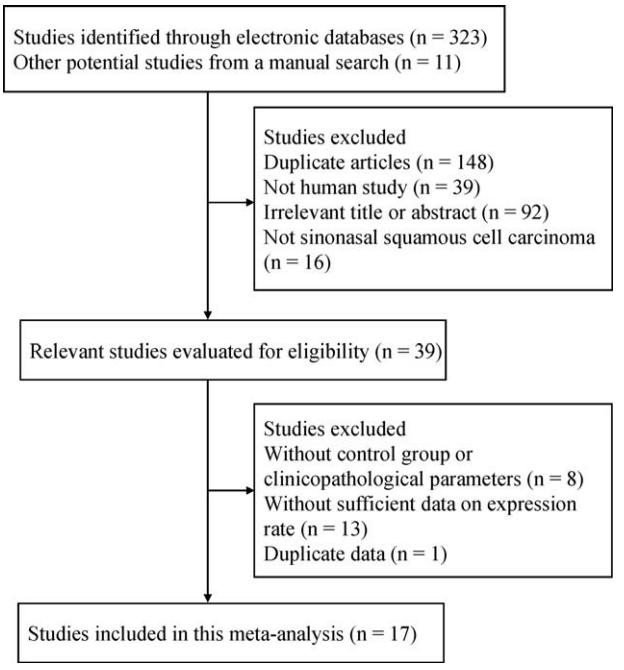

Figure 1. Flow diagram of the literature search strategy.

Table 1

The baseline characteristics of eligible studies.

Refs.	Country	Ethnicity	Method	Sample type	SNSCC N (E %)	Benign papillomas N (E %)	Normal mucosa N (E %)	Mod/ poorly E+/N	Well E+/N	KSCC E+/N	NKSCC E+/N	p53+ value
Fang et al[38]	China	Asians	IHC	Tissue	42 (57.1)	26 (0)	15 (0)	—	—	—	—	>10%
Franzmann et al[37]	Denmark	Caucasians	IHC	Tissue	5 (60)	25 (0)	7 (0)	—	—	—	—	>5%
Finkelstein et al[36]	USA	Caucasians	IHC	Tissue	9 (88.9)	4 (0)	—	—	—	—	—	NA
Saegusa et al[35]	Japan	Asians	IHC	Tissue	48 (58.3)	74 (0)	34 (0)	20/29	8/19	11/23	17/25	>30%
Schwerer et al[34]	Germany	Caucasians	IHC	Tissue	5 (100)	26 (53.8)	7 (0)	—	—	—	—	>15%
Gujrathi et al[33]	Canada	Caucasians	IHC	Tissue	5 (80)	10 (0)	—	—	—	—	—	NA
Keles et al[32]	Turkey	Caucasians	IHC	Tissue	6 (50)	15 (0)	—	2/3	1/3	2/5	1/1	>25%
El-Mofty and Lu[31]	USA	Caucasians	IHC	Tissue	29 (37.9)	—	—	—	—	8/21	3/8	>0%
Katori et al[30]	Japan	Asians	IHC	Tissue	12 (66.7)	29 (31)	10 (10)	—	—	—	—	NA
Bura et al[29]	Croatia	Caucasians	IHC	Tissue	8 (87.5)	41 (4.9)	—	—	—	—	—	NA
Cheung et al[28]	China	Asians	IHC	Tissue	5 (100)	60 (5)	—	—	—	—	—	>10%
Kim et al[27]	Korea	Asians	IHC	Tissue	18 (44.4)	63 (0)	—	8/15	0/3	—	—	>10%
Oncel et al[26]	Turkey	Caucasians	IHC	Tissue	9 (33.3)	22 (4.5)	—	—	—	—	—	>10%
Yoon et al[25]	Korea	Asians	IHC	Tissue	5 (100)	68 (8.8)	—	—	—	—	—	>10%
Lin et al[24]	USA	Mix	IHC	Tissue	21 (61.9)	135 (33.3)	—	—	—	—	—	>5%
Tsou et al[23]	China	Asians	IHC	Tissue	10 (100)	60 (58.3)	—	—	—	—	—	>10%
Yamashita et al[9]	Japan	Asians	IHC	Tissue	21 (52.4)	17 (5.9)	—	—	—	—	—	>25%

"—" = stands for no data, E or E+ = p53 positive expression, IHC = immunohistochemistry, KSCC = keratinizing squamous cell carcinoma, Mod/poorly = moderately or poorly differentiated SNSCC, N = the total number of samples, NA = not applicable, NKSCC = nonkeratinizing squamous cell carcinoma, p53+ value = p53 positive expression status was defined as more than a value of percentage, SNSCC = sinonasal squamous cell carcinoma, well = well-differentiated SNSCC.

benign sinonasal papillomas and normal sinonasal mucosa by using IHC (OR = 26.93, 95% CI = 11.41–63.55, $P < 0.001$; OR = 39.79, 95% CI = 10.60–149.36, $P < 0.001$; respectively) (Fig. 2). This analysis suggested that p53 overexpression was significantly correlated with an increased risk of SCC of the sinonasal tract.

3.3. Subgroup analyses of ethnicity in cancer versus control groups

According to ethnic population, subgroup analyses were applied to explore the difference of correlation in different subgroups. When SNSCC was compared to benign sinonasal papillomas, subgroup ethnicity analyses indicated that there was significant correlation between p53 expression and SNSCC in Asians, Caucasians, and mixed population (OR = 36.20, 95% CI = 11.10–118.06, $P < 0.001$; OR = 35.17, 95% CI = 11.53–107.29, $P < 0.001$; OR = 3.25, 95% CI = 1.26–8.41, $P = 0.015$; respectively) (Fig. 3).

When SNSCC was compared to normal sinonasal mucosa, subgroup ethnicity analyses demonstrated that significant association was observed between p53 expression and SNSCC in Asians and Caucasians (OR = 37.33, 95% CI = 7.96–174.99, $P < 0.001$; OR = 47.42, 95% CI = 3.67–613.03, $P = 0.003$; respectively) (Fig. 4). Especially, the result of mixed population subgroup should be carefully considered as only one study was analyzed in our study.

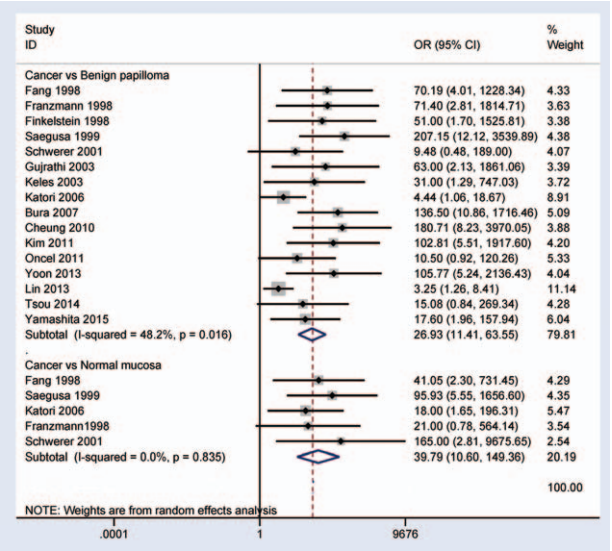

Figure 2. Forest plot of p53 expression in SNSCC versus benign sinonasal papillomas and normal sinonasal mucosa, SNSCC versus benign sinonasal papillomas: OR = 26.93, 95% CI = 11.41–63.55, $P < 0.001$; SNSCC versus normal sinonasal mucosa: OR = 39.79, 95% CI = 10.60–149.36, $P < 0.001$.

3.4. A sensitivity analysis of p53 expression in cancer versus benign sinonasal papillomas

A substantial heterogeneity was measured in cancer versus benign sinonasal papillomas ($P = 0.016$). Thus, we conducted a sensitivity analysis by omitting an individual study to assess the stability of the pooled result and change of heterogeneity. Therefore, we deleted this study by Lin et al,[24] recalculated the pooled OR from remaining 15 studies and shown in Fig. 5. Our result revealed that the overall OR of p53 expression was not notably changed (OR = 30.00, 95% CI = 14.65–61.44, $P < 0.001$). *P*-value of the heterogeneity dramatically increased to 0.359, indicating that the heterogeneity was very low. Our analysis suggested that the result of p53 expression was stable in the comparison of SNSCC and benign sinonasal papillomas.

3.5. Correlation of p53 expression with clinicopathological characteristics in cancer

The association of p53 expression with clinicopathological features was also further evaluated in this study. The overall OR including 3 studies with 47 moderately or poorly differentiated SCC patients and 25 well-differentiated SCC patients showed

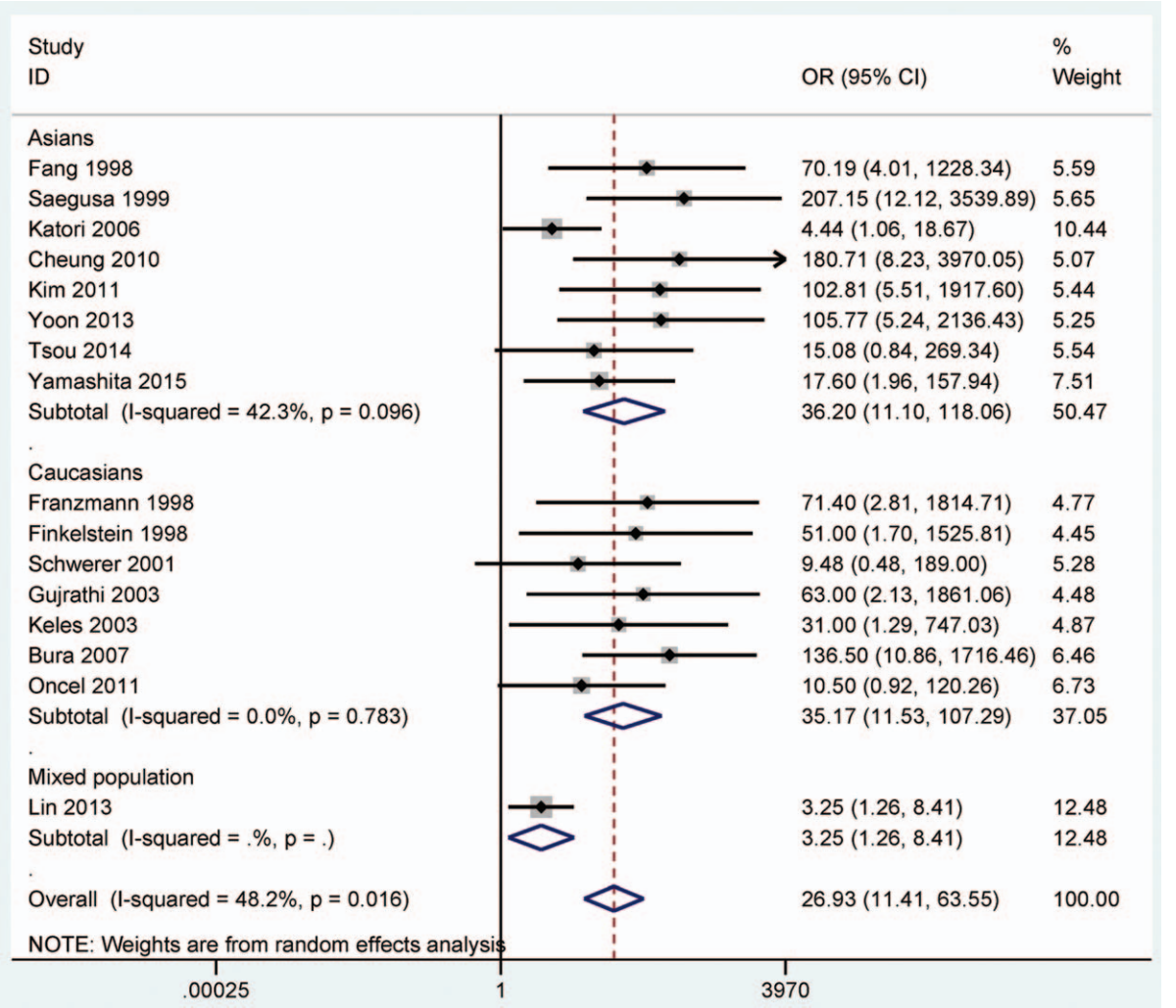

Figure 3. Forest plot of p53 expression based on subgroup ethnicity analyses in SNSCC versus benign sinonasal papillomas, Asians: OR = 36.20, 95% CI = 11.10–118.06, $P < 0.001$; Caucasians: OR = 35.17, 95% CI = 11.53–107.29, $P < 0.001$; mixed population: OR = 3.25, 95% CI = 1.26–8.41, $P = 0.015$.

that p53 expression was significantly higher in moderately or poorly differentiated SNSCC than in well-differentiated SNSCC (OR = 3.51, 95% CI = 1.21–10.18, $P = 0.021$) (Fig. 6A). The overall OR including 3 studies with 49 keratinizing squamous cell carcinoma (KSCC) and 34 nonkeratinizing squamous cell carcinoma (NKSCC) showed that p53 expression was not correlated with histological type (OR = 0.54, 95% CI = 0.21–1.37, $P = 0.194$) (Fig. 6B). However, the analyses of p53 expression with clinicopathological features were cautious due to smaller sample sizes.

3.6. Publication bias

Egger test was performed to identify the possible publication bias. There was a substantial evidence of publication bias in SNSCC versus benign sinonasal papillomas ($P < 0.001$) (Fig. 7A), however, no evidence of significant publication bias was found in SNSCC versus normal sinonasal mucosa ($P = 0.260$) (Fig. 7B).

4. Discussion

In human malignant tumors, p53 is the most frequently inactivated tumor suppressor gene.[17] Reduction of expression of wild-type p53 can contribute to abnormal cell proliferation and carcinogenesis, while mutant p53 may facilitate cell migration, cell invasion, and cell metastasis.[39] Some studies show that positive/high p53 expression is correlated with the development and progression of tumor in several human cancers.[40,41] However, the results of p53 expression are still inconsistent and controversial in SNSCC. Different expression levels of the p53 gene were reported in different studies, ranging from 33.3%[26] to 100%[23] in SNSCC. In addition, the expression levels of the p53 gene were different benign sinonasal papillomas, with a range from 0%[27] to 58.3%.[23] Therefore, the present study was first determined whether p53 expression was significantly associated with the risk of SNSCC. Furthermore, we also determined whether p53 expression was correlated with clinicopathological characteristics in SNSCC.

Sinonasal papillomas are benign epithelial neoplasms of the paranasal sinuses, generally with local invasiveness, higher recurrence rate, could be transformed to SNSCC.[28,42] The p53 expression by using immunohistochemistry (IHC) was shown to be significantly higher in SNSCC than in benign sinonasal papillomas and normal sinonasal mucosa, which suggested that p53 overexpression plays an important role in the tumorigenesis of SNSCC. However, when cancer was compared

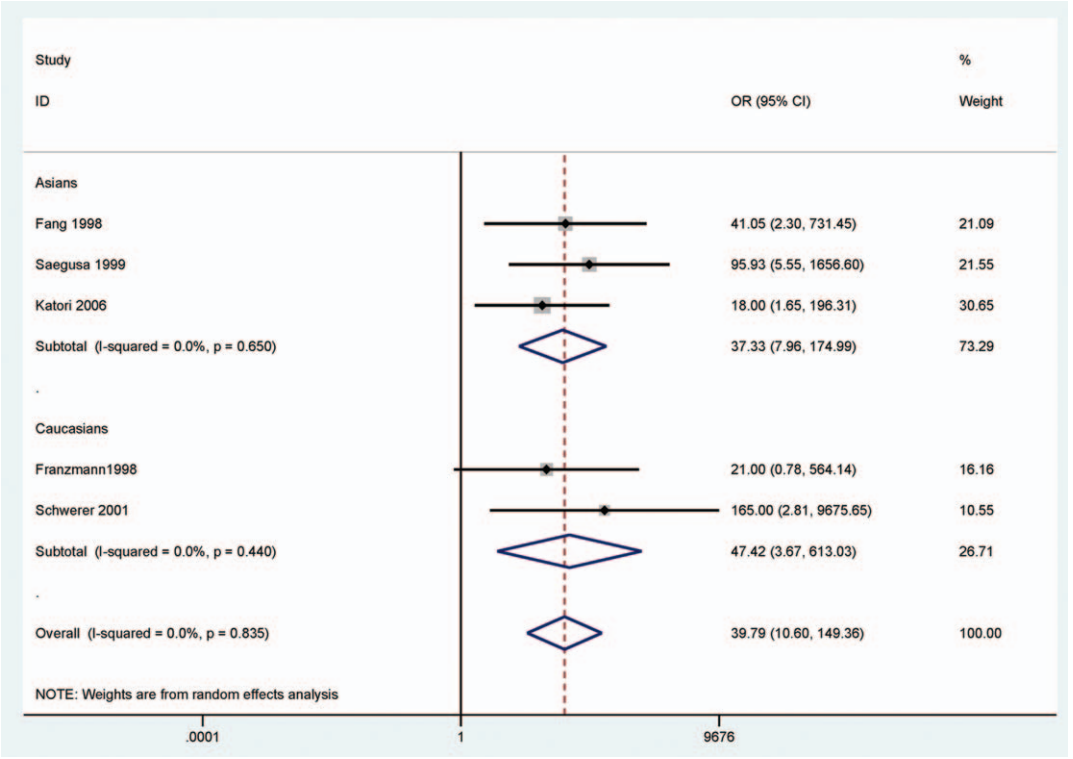

Figure 4. Forest plot of p53 expression based on subgroup ethnicity analyses in SNSCC versus normal sinonasal mucosa, Asians: OR = 37.33, 95% CI = 7.96–174.99, $P < 0.001$; Caucasians: OR = 47.42, 95% CI = 3.67–613.03, $P = 0.003$.

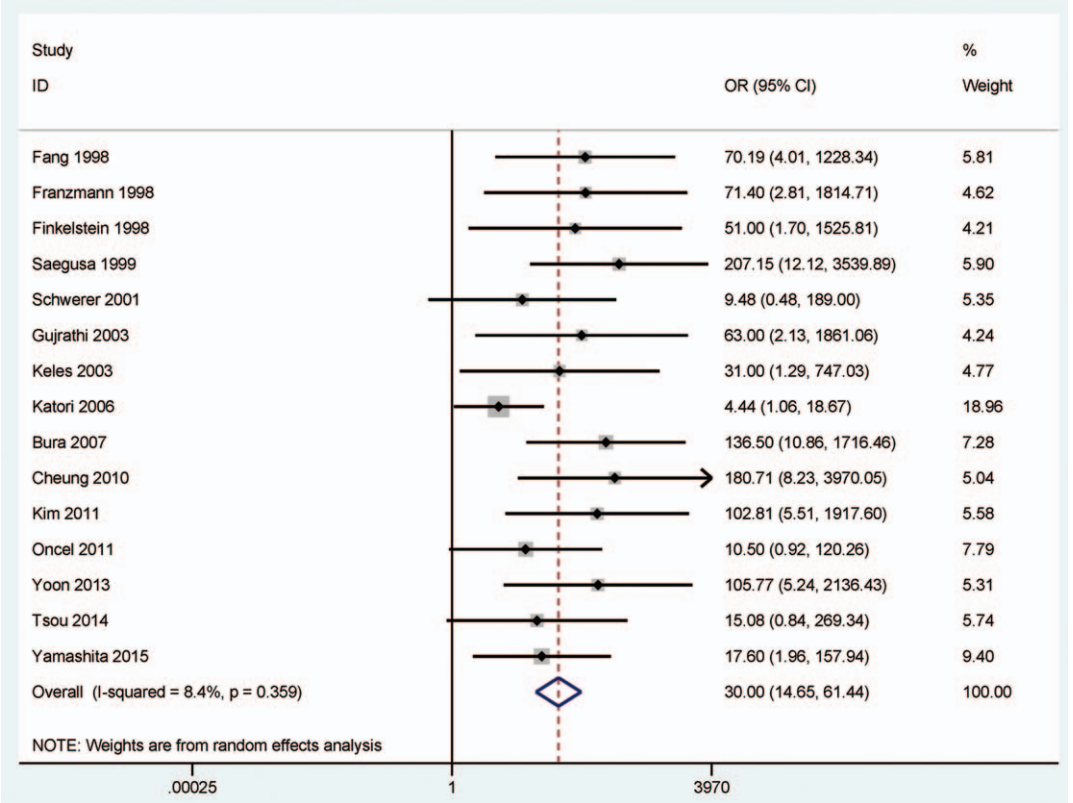

Figure 5. Forest plot of p53 expression based on a sensitivity analysis in SNSCC versus benign sinonasal papillomas, OR = 30.00, 95% CI = 14.65–61.44, $P < 0.001$, with the absence of heterogeneity ($P = 0.359$).

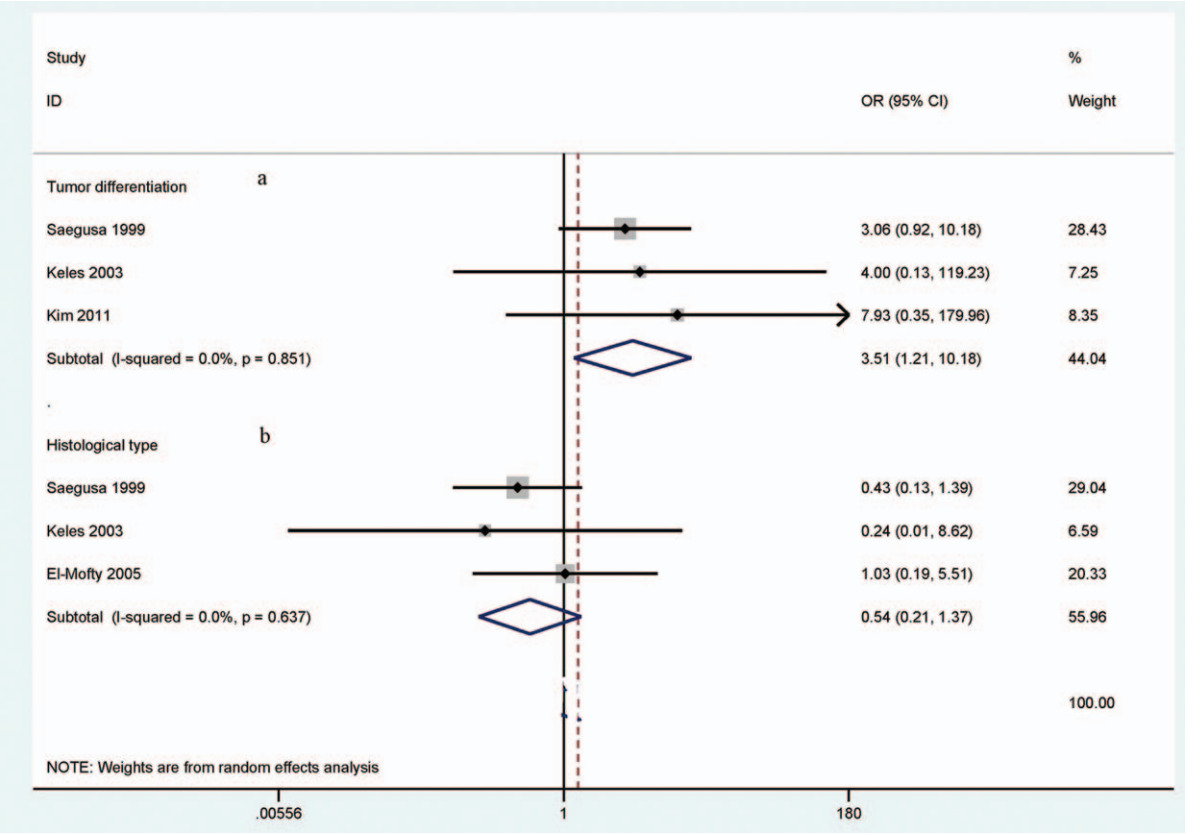

Figure 6. Forest plot of p53 expression with clinicopathological features, (A) (tumor differentiation: OR = 3.51, 95% CI = 1.21–10.18, $P = 0.021$); (B) (histological subtype: OR = 0.54, 95% CI = 0.21–1.37, $P = 0.194$).

to benign sinonasal papillomas, a significantly heterogeneity was found ($P = 0.016$). Thus, a sensitivity analysis was performed to evaluate the stability of the result and change of heterogeneity by deleting this study by Lin et al.[24] The result showed that the pooled OR of p53 expression was not significantly changed. Additionally, a *P*-value of the heterogeneity was very low ($P = 0.359$), indicating that the stability of our analysis.

Next, when cancer was compared to benign sinonasal papillomas or normal sinonasal mucosa, subgroup analyses of ethnicity were conducted to find the significant difference of association in different subgroups. Our findings revealed that p53 expression was significantly correlated with SNSCC in Asian and Caucasian populations. Meanwhile, the pooled OR of Asian population and Caucasian population subgroups was not significantly different in our study. The results suggested that Asian and Caucasian populations were susceptible to the p53 gene. However, the results should be careful with caution as only small subjects were analyzed in the comparison of cancer and

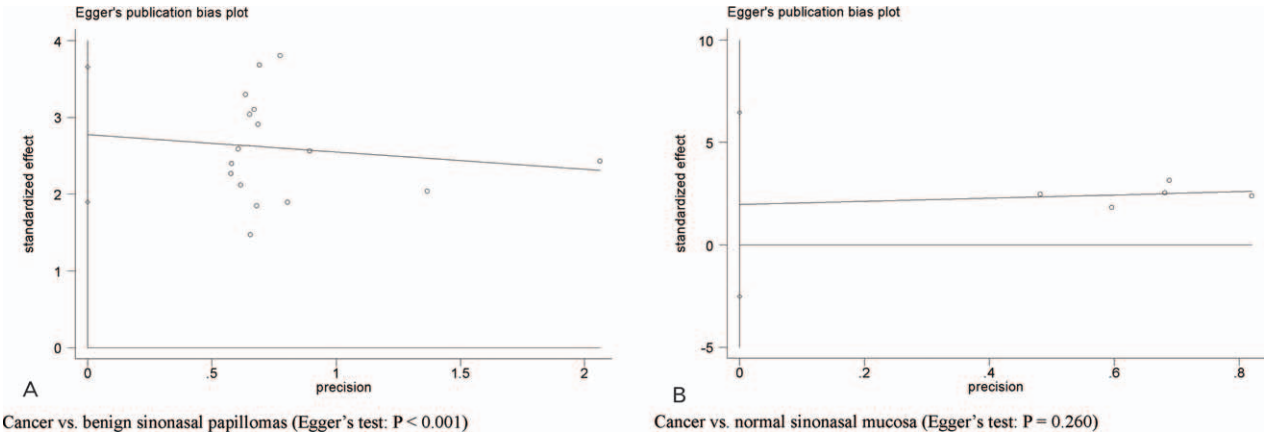

Figure 7. Forest plot of publication bias based on Egger test in SNSCC versus benign sinonasal papillomas and normal sinonasal mucosa, (A) (SNSCC vs benign sinonasal papillomas: $P < 0.001$), (B) (SNSCC vs normal sinonasal mucosa: $P = 0.260$).

normal sinonasal mucosa, especially in subgroup ethnicity analyses.

We further determined whether p53 expression was correlated with clinicopathological parameters in SNSCC. We found that the expression of p53 was not correlated with histological subtype of SNSCC. However, the expression of p53 was correlated with tumor differentiation, and higher in moderately or poorly differentiated SNSCC than in well-differentiated SNSCC (OR = 3.51, $P = 0.021$), which suggested that p53 overexpression may play a key role in the progression of SNSCC. While the analyses of p53 expression with clinicopathological parameters should be carefully considered because of small sample size were included in our study. Additional studies with larger sample size are very necessary to further validate the results of p53 expression with more clinicopathological parameters, such as tumor stage in the future.

There were several limitations in the present meta-analysis. First, although we try to search the above databases as completely as possible, a publication bias was detected in SNSCC versus benign sinonasal papillomas. Articles published in Chinese and other language were excluded due to the fact that they were easily unreadable content, in addition, unpublished papers or conference abstracts were excluded based on insufficient information. Second, Asian and Caucasian populations were included in this study, but other ethnicities, such as Africans, were lacking. Third, because of the limitation of studies with sufficient data, we did not analyze the correlation of p53 expression status with other clinicopathological features, such as tumor stage and gender status etc. Thus, large-scale studies with larger subjects should be essential to confirm the results in the future.

In conclusion, our findings suggested that p53 overexpression was significantly associated with an increased risk of SNSCC, in addition, p53 overexpression was significantly higher in moderately or poorly differentiated SNSCC than in well-differentiated SNSCC. The overexpression of p53 was not correlated with histological subtype. Further large-scale researches are needed to provide more insight into the clinical effects of p53 overexpression in SNSCC patients.

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References

[1] Bell D, Hanna EY, Agaimy A, et al. Reappraisal of sinonasal undifferentiated carcinoma: SMARCB1 (INI1)-deficient sinonasal carcinoma: a single-institution experience. Virchows Arch 2015;467:649–56.
[2] Barham HP, Said S, Ramakrishnan VR. Colliding tumor of the paranasal sinus. Allergy Rhinol 2013;4:e13–6.
[3] Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. Am J Surg Pathol 2014;38:1282–9.
[4] Sanghvi S, Khan MN, Patel NR, et al. Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4994 patients. Laryngoscope 2014;124:76–83.
[5] Porceddu S, Martin J, Shanker G, et al. Paranasal sinus tumors: Peter MacCallum Cancer Institute experience. Head Neck 2004;26:322–30.
[6] Youlden DR, Cramb SM, Peters S, et al. International comparisons of the incidence and mortality of sinonasal cancer. Cancer Epidemiol 2013;37:770–9.
[7] Ansa B, Goodman M, Ward K, et al. Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009. Cancer 2013;119:2602–10.
[8] Unsal AA, Dubal PM, Patel TD, et al. Squamous cell carcinoma of the nasal cavity: a population-based analysis. Laryngoscope 2016;126:560–5.
[9] Yamashita Y, Hasegawa M, Deng Z, et al. Human papillomavirus infection and immunohistochemical expression of cell cycle proteins pRb, p53, and p16(INK4a) in sinonasal diseases. Infect Agents Cancer 2015;10:23.
[10] Jung YG, Lee HW, Kim MG, et al. Role of Wnt signaling pathway in progression of sinonasal inverted papilloma to squamous cell carcinoma. Am J Rhinol Allergy 2015;29:e81–6.
[11] McBride SM, Rothenberg SM, Faquin WC, et al. Mutation frequency in 15 common cancer genes in high-risk head and neck squamous cell carcinoma. Head Neck 2014;36:1181–8.
[12] Lopez F, Llorente JL, Garcia-Inclan C, et al. Genomic profiling of sinonasal squamous cell carcinoma. Head Neck 2011;33:145–53.
[13] Soussi T. The p53 pathway and human cancer. Br J Surg 2005;92:1331–2.
[14] Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997;88:323–31.
[15] Kastan MB, Onyekwere O, Sidransky D, et al. Participation of p53 protein in the cellular response to DNA damage. Cancer Res 1991;51(23 Pt 1):6304–11.
[16] Toledo F, Wahl GM. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. Nat Rev Cancer 2006;6:909–23.
[17] Hollstein M, Sidransky D, Vogelstein B, et al. p53 mutations in human cancers. Science 1991;253:49–53.
[18] Baas IO, Mulder JW, Offerhaus GJ, et al. An evaluation of six antibodies for immunohistochemistry of mutant p53 gene product in archival colorectal neoplasms. J Pathol 1994;172:5–12.
[19] Zintzaras E, Ioannidis JP. HEGESMA: genome search meta-analysis and heterogeneity testing. Bioinformatics 2005;21:3672–3.
[20] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[21] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.
[22] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[23] Tsou YA, Huang HJ, Wang TC, et al. Evaluation of correlation of cell cycle proteins and Ki-67 interaction in paranasal sinus inverted papilloma prognosis and squamous cell carcinoma transformation. Biomed Res Int 2014;2014:634945.
[24] Lin GC, Scheel A, Akkina S, et al. Epidermal growth factor receptor, p16, cyclin D1, and p53 staining patterns for inverted papilloma. Int Forum Allergy Rhinol 2013;3:885–9.
[25] Yoon BN, Chon KM, Hong SL, et al. Inflammation and apoptosis in malignant transformation of sinonasal inverted papilloma: the role of the bridge molecules, cyclooxygenase-2, and nuclear factor kappaB. Am J Otolaryngol 2013;34:22–30.
[26] Oncel S, Cosgul T, Calli A, et al. Evaluation of p53, p63, p21, p27, ki-67 in paranasal sinus squamous cell carcinoma and inverted papilloma. Indian J Otolaryngol Head Neck Surg 2011;63:172–7.
[27] Kim SG, Lee OY, Choi JW, et al. Pattern of expression of cell cycle-related proteins in malignant transformation of sinonasal inverted papilloma. Am J Rhinol Allergy 2011;25:75–81.
[28] Cheung FM, Lau TW, Cheung LK, et al. Schneiderian papillomas and carcinomas: a retrospective study with special reference to p53 and p16 tumor suppressor gene expression and association with HPV. Ear Nose Throat J 2010;89:E5–12.
[29] Bura M, Seiwerth S, Vladika I, et al. Possible prognostic significance of p53 and Ki 67 in inverted sinonasal papilloma. Coll Antropol 2007;31:545–9.
[30] Katori H, Nozawat A, Tsukuda M. Relationship between p21 and p53 expression, human papilloma virus infection and malignant transformation in sinonasal-inverted papilloma. Clin Oncol 2006;18:300–5.
[31] El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. Am J Surg Pathol 2005;29:1367–72.
[32] Keles N, Erdamar B, Kaur A, et al. p21, p53, and p27 Kip1 alterations in benign and malignant tumors of sinonasal epithelium. Otolaryngol Head Neck Surg 2003;129:77–84.
[33] Gujrathi C, Pathak I, Freeman J, et al. Expression of p53 in inverted papilloma and malignancy associated with inverted papilloma. J Otolaryngol 2003;32:48–50.
[34] Schwerer MJ, Sailer A, Kraft K, et al. Patterns of p21(waf1/cip1) expression in non-papillomatous nasal mucosa, endophytic sinonasal papillomas, and associated carcinomas. J Clin Pathol 2001;54:871–6.
[35] Saegusa M, Nitta H, Hashimura M, et al. Down-regulation of p27Kip1 expression is correlated with increased cell proliferation but not expression of p21waf1 and p53, and human papillomavirus infection

in benign and malignant tumours of sinonasal regions. Histopathology 1999;35:55–64.
[36] Finkelstein SD, Tiffee JC, Bakker A, et al. Malignant transformation in sinonasal papillomas is closely associated with aberrant p53 expression. Mol Diagn 1998;3:37–41.
[37] Franzmann MB, Buchwald C, Jacobsen GK, et al. Expression of p53 in normal nasal mucosa and in sinonasal papillomas with and without associated carcinoma and the relation to human papillomavirus (HPV). Cancer Lett 1998;128:161–4.
[38] Fang SY, Yan JJ, Ohyama M. Assessment of p53 protein expression in normal mucosa and benign and malignant lesions of the nasal cavity. Oncology 1998;55:168–73.
[39] Muller PA, Vousden KH, Norman JC. p53 and its mutants in tumor cell migration and invasion. J Cell Biol 2011;192:209–18.
[40] Du J, Wang SH, Yang Q, et al. p53 status correlates with the risk of progression in stage T1 bladder cancer: a meta-analysis. World J Surg Oncol 2016;14:137.
[41] Wei K, Jiang L, Wei Y, et al. The prognostic significance of p53 expression in gastric cancer: a meta-analysis. J Cancer Res Clin Oncol 2015;141:735–48.
[42] Vorasubin N, Vira D, Suh JD, et al. Schneiderian papillomas: comparative review of exophytic, oncocytic, and inverted types. Am J Rhinol Allergy 2013;27:287–92.