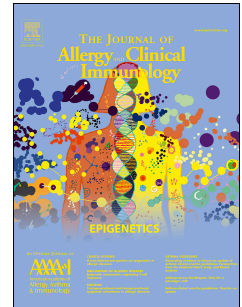


Journal Pre-proof

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PII: S0091-6749(19)31106-6

DOI: <https://doi.org/10.1016/j.jaci.2019.08.015>

Reference: YMAI 14151

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 23 July 2019

Revised Date: 15 August 2019

Accepted Date: 19 August 2019

Please cite this article as: Eschenbacher WH, Borish L, Nasal polyposis and future risk of sinonasal malignancy, *Journal of Allergy and Clinical Immunology* (2019), doi: <https://doi.org/10.1016/j.jaci.2019.08.015>.

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Nasal polyposis and future risk of sinonasal malignancy

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Disclosure Statements:

*Will Eschenbacher reports no conflicts of interest relevant to this editorial.

**Larry Borish reports to conflicts of interest relevant to this editorial. Unrelated to this editorial he received medical school research grants from Astra Zeneca and Glaxo Smith Kline (all funds go to the University of Virginia) and he has served on advisory boards to Astra Zeneca, Novartis, Genzyme, Sanofi, and Regeneron

Key words: Nasal polyposis, cancer, neoplastic development, chronic rhinosinusitis, neutrophilic

Nasal polyposis (NP) is a disease where abnormal hyperplastic inflammatory lesions originate from the sinus and paranasal sinus mucosa. Historically nasal polyps have not been felt to either represent a pre-cancerous condition or to confer additional risk for the development of nasal cavity/paranasal sinus (NCPS), or nasopharyngeal cancers. There have been studies which have suggested such a relationship, however, these have been primarily case-control studies and their small sample size has limited the ability to assess future risk for head and neck cancers.¹⁻⁴ Also in the recent literature are two larger database analyses, one looking at the relationship between chronic sinusitis and head and neck cancer and another looking at nasopharyngeal cancer in a Taiwanese population. These prior studies were limited by having only a small number of nasal polyp patients or from being unable to control for smoking history as a risk factor.⁵⁻⁶

A key feature in understanding nasal polyposis as it may pertain to risk for neoplasia is the nature of the underlying inflammatory pathology. NP, especially in Western countries and North America, are more often an eosinophilic disease associated with type 2 inflammation and occurring in the setting of asthma, allergic rhinitis and concomitant atopic disease.⁷⁻⁸ Whereas in a smaller subset of subjects in these countries but *most* subjects in China and other Asian countries, NP is characterized by neutrophilic inflammation in the setting of robust innate immunity with or without type 1 (interferon- γ)/type 3 (interleukin-17) inflammation – but not eosinophilia⁷. Several of these recent studies regarding neoplastic development in NP patients draw from populations that are enriched for tobacco abuse/exposure and/or are populations where there is a predominance of neutrophilic inflammatory polyposis. Properly determining

the risk for the development of neoplasia in patients with NP is extremely important as this will both guide physicians in performing appropriate clinical investigations regarding the basis of this and will determine how best to counsel and treat patients with NP.

In the current issue of *The Journal of Allergy and Clinical Immunology*, Kim et al.⁹ investigated a comprehensive database in Korea and their data suggest a small but significant increase in the prevalence of nasal cavity/paranasal sinus and nasopharyngeal cancers in this cohort. As noted, studies in this area had previously been lacking in sample size or appropriate control of confounding variables. This study does an excellent job of improving on prior work with a sample size that comprised the entire population of the South Korea. More importantly, this study was strengthened by having a longitudinal design. This involved recruiting patients without a diagnosis of NP or head and neck cancer and following them for the development of NP and subsequent malignant diagnoses. This study's contribution is important as it suggests that NP in certain cohorts may indeed increase the risk for the subsequent development of head and neck cancers in certain populations and that NP patients may merit additional screening.

There are, however, several salient points to keep in mind as we incorporate this study into our understanding of NP and risk for development of NCPS or nasopharyngeal cancers. Previous studies identifying a risk for neoplastic development in NP, as well as this one, focused on analyses of populations in Taiwan, Japan, China and Korea.²⁻⁵ This could suggest the possibility of a genetic predisposition to the development of NCPS or nasopharyngeal malignancy. Alternatively, these are populations more likely to be associated with NP having an eosinophil^{low}, type 1/3^{high} process, that is, by the presence

of a chronic neutrophilic state. (In Asian populations, ~80% of NPs are non-eosinophilic compared to 20-60% in European and North American cohorts.) It is well recognized that chronic neutrophilic inflammation is a risk factor for malignant transformation. Several risk factors are associated with development of nasopharyngeal cancers including viral infections (EBV and HPV) and genetic predisposition. This again raises the question as to whether the prevalence of neoplasia could be related to these unique risk factors being present in the Korean population. However, this possibility was mitigated as the prevalence of nasopharyngeal cancer in this population, cancers that are often virally-induced, was only modestly increased when compared to the development of NCPS malignancy.

Another potential pitfall which needed to be addressed was the possibility of a patient being initially labeled as having “benign” nasal polyposis *prior* to having a diagnostic biopsy or endoscopic evaluation, which, had the biopsy been performed, might have changed the diagnosis from benign NP to a nasal malignancy. In order to control for this, the study utilized a wash-out period of up to 5-years after initial nasal polyposis diagnosis to preclude an incidental or inaccurate initial diagnosis. Finally, another consideration for the observed surprising high prevalence of neoplastic development was that this could be reflective of the increased prevalence of tobacco use, smoking, and other carcinogenic exposures in this population. These exposures could be driving both an increased incidence of irritant/smoking related NPs as well as local carcinogenesis. The authors nicely addressed this by controlling for individually reported smoking histories in the database – although it is possible that this could underestimate actual exposure. However, that this could not explain the prevalence of NCPS cancers

was the authors' analysis of prevalence of non-nasopharyngeal or NCPS head and neck cancers, such as hypo-pharyngeal and laryngeal cancers. Within the NP group there was no significant difference in the rates of either of these subtypes, both of which have strong associations with smoking-driven carcinogenesis. This finding would have been observed had smoking been the basis for the observed prevalence of NCPS.

In addition to inflammatory (non-eosinophilic) polyps possibly driving neoplastic transformation, another consideration for a lower risk for neoplasia in a non-Korean population could be that eosinophilia may have a protective role in modulating malignancy risk.¹⁰ However, no studies have been performed to compare the relative risk of these cancers in different countries. The authors addressed this consideration utilizing the diagnosis of asthma or allergic rhinitis as a stand in for eosinophilic or type 2 inflammatory polyps. (Although it is important to recognize that asthma and allergic rhinitis are not ideal markers of polyp eosinophilia and that even in patients with known eosinophilic polyps, comorbid asthma only occurs ~50% of the time.⁷) Intriguingly, the data in this paper do bear out that in the cohort likely enriched for eosinophilic polyps (the asthmatic sub-group) the risk for NCPS and nasopharyngeal cancers appeared to be mitigated.⁹ Future studies should be performed to properly compare measurements of eosinophilia and markers of type 2 inflammation to better understand the risk profiles of different types of polyps when considering the possibility of future malignancy.

Naturally, when considering the implications of this study, it is important to keep in mind that an increase in screening for the rare development of neoplasia in this population will generate additional risks as well as the obvious benefits. These risks include the increased stress of delivering to a NP patient the potential for a future malignant

116 diagnosis, the increased risk of false positive screening, and the burden both on the
117 patient and health system of the costs of additional screening – both financial and
118 personal. This paper highlights some extremely interesting areas for future study and
119 has the potential to impact how patients are counseled and screened in the future
120 (Table I). The available data primarily suggest that, especially in populations that are
121 enriched for non-eosinophilic polyp disease, nasal polyps may be prone to conferring
122 risk for future NCPS cancers. However, further study is necessary to help elucidate if
123 the relationship hinges significantly on the underlying polyp pathology or, as is so often
124 the case, if the picture is more complex.

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Table I: Important Findings on Nasal Polyposis and Cancer Risk

1. Smoking Exposure	Increased rates of cancer could be associated with a chronic inflammatory epiphenomenon related to the higher prevalence of smoking and smoke exposure in certain geographic regions/populations
2. Polyp Pathology	Eosinophilic and Type 2 inflammatory polyps are far more prevalent in Europe and North America compared to many parts of Asia. ⁷⁻⁸ These types of polyps appear to have a lower risk of – and may even protect against – neoplastic transformation.
3. Unique Populations	Studies so far have focused on NP and neoplastic development in Korea, Japan, China and Taiwan. ²⁻⁵ Unique risk factors including genetic predisposition could create challenges when extending these results to all populations.
4. Risk/Benefit	Discussing the risk of developing cancer is not a benign subject with patients and should be approached with care. This study lays excellent groundwork for further research.

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130 Bibliography

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- 132 1. Brinton LA, Blot WJ, Becker JA, Winn DM, Browder JP, Farmer JC, Jr., et al. A
 133 case-control study of cancers of the nasal cavity and paranasal sinuses. *Am J*
 134 *Epidemiol* 1984; 119:896-906.
- 135 2. Fukuda K, Shibata A. A case-control study of past history of nasal diseases and
 136 maxillary sinus cancer in Hokkaido, Japan. *Cancer Res* 1988; 48:1651-2.
- 137 3. Zheng W, Blot WJ, Shu XO, Diamond EL, Gao YT, Ji BT, et al. A population-
 138 based case-control study of cancers of the nasal cavity and paranasal sinuses in
 139 Shanghai. *Int J Cancer* 1992; 52:557-61.
- 140 4. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other
 141 nondietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J*
 142 *Cancer* 1990; 45:1033-9.
- 143 5. Tsou Y-A, Lin C-C, Tai C-J, Tsai M-H, Tsai T-C, Chen C-M. Chronic
 144 rhinosinusitis and the risk of nasopharyngeal cancer in a Taiwanese health study.
 145 *Am J Rhinol Allergy* 2014; 28:e168-e72.
- 146 6. Beachler DC, Engels EA. Chronic Sinusitis and Risk of Head and Neck Cancer in
 147 the US Elderly Population. *JAMA Otolaryngol Head Neck Surg* 2017; 143:25-31.
- 148 7. Tomassen P, Vandeplas G, Van Zele T, Cardell L-O, Arebro J, Olze H, et al.
 149 Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of
 150 biomarkers. *J Allergy Clin Immunol* 2016; 137:1449-56.

- 151 8. Wang X, Zhang N, Bo M, Holtappels G, Zheng M, Lou H, et al. Diversity of TH
152 cytokine profiles in patients with chronic rhinosinusitis: a multicenter study in
153 Europe, Asia, and Oceania. *J Allergy Clin Immunol* 2016; 138:1344-53.
- 154 9. Kim HJ, HS Ahn, T Kang, C Bachert, and W-J Song, et al. Nasal Polyps and
155 Future Risk of Head and Neck Cancer: A Nationwide Population based Cohort
156 Study. *J Allergy Clinical Immunology* 2019 (in press).
- 157 10. Jensen-Jarolim E, Bax H, Bianchini R, Capron M, Corrigan C, Castells M, et al.
158 AllergoOncology—the impact of allergy in oncology: EAACI position paper. *Allergy*
159 2017; 72:866-87.