Article

Risk Factors for Dysplasia in Recurrent Respiratory Papillomatosis in an Adult and Pediatric Population

Annals of Otology, Rhinology & Laryngology
2016, Vol. 125(3) 235–241

DOI: 10.1177/0003489415608196
aor.sagepub.com
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Abstract

Aim: Recurrent respiratory papillomatosis (RRP) is classically described as a benign neoplasm of the larynx caused by the low-risk human papillomavirus (HPV) viral subtypes. Nevertheless, transformation to dysplasia and invasive carcinoma can occur. We aimed to assess the prevalence of dysplasia and carcinoma-ex-papilloma in both adult-onset and juvenile-onset RRP and identify patient risk factors for this dysplastic transformation.

Material and Methods: Ten-year retrospective chart review of a tertiary otolaryngology referral center. Patients with papilloma were identified from a review of a pathology database and clinical records. Patient demographics, pathologic data, and treatment history, including use of cidofovir as an adjunctive therapy for papilloma, were extracted from electronic medical records.

Results: One hundred fifty-nine RRP patients were identified, 96 adult-onset (AORRP) and 63 juvenile-onset (JORRP) cases. Of this cohort, 139 (87%) had only benign papilloma as a pathologic diagnosis. In the AORRP cohort, 10 patients (10%) were diagnosed with dysplasia or carcinoma in situ in addition to papilloma, and 5 patients (5%) had malignant transformation to invasive carcinoma-ex-papilloma. There was a significantly higher age of disease onset for those with dysplasia or carcinoma versus those without dysplasia or carcinoma (56 vs 45 years old; $P = .0005$). Of the 63 JORRP patients, there were no cases of dysplasia but 3 (5%) cases of invasive carcinoma-ex-papilloma, all involving pulmonary disease. The JORRP patients with carcinoma-ex-papilloma had a younger average disease onset (2 vs 6 years old; $P = .009$) and a higher rate of tracheal involvement than those without carcinoma. Gender, smoking history, number of operations, or use of cidofovir showed no association with the development of dysplasia or carcinoma-ex-papillomatosis in either the AORRP or JORRP population.

Conclusion: In a large series of RRP, age of disease onset is the strongest predictor of dysplastic transformation in the adult and pediatric population. Carcinoma-ex-papillomatosis was uniformly associated with pulmonary disease in the JORRP population in this series. No other demographic or behavioral factors, including adjunctive therapy with cidofovir, were statistically associated with dysplasia or carcinoma-ex-papilloma.

Keywords

larynx, papilloma, dysplasia, laryngeal papillomatosis, recurrent respiratory papillomatosis, HPV, low-risk HPV, carcinoma ex-papilloma

Introduction

Respiratory recurrent papillomatosis (RRP) is for the most part a benign but chronic disease of viral etiology that occurs in both children and adults. The disease has significant impact on quality of life due to airway obstruction, dysphonia, and the need for serial operations to remove papillomas from the upper aerodigestive tract. Caused by low-risk human papillomavirus (HPV) subtypes 6 and 11, RRP has long been known to follow a different natural history than infection with high-risk subtypes, due to the reduced transforming capacity of the low-risk viral oncoproteins E6 and E7.[1]

Nevertheless, despite the designation as "low risk," the viral oncoproteins in HPV 6 and 11 have biologic functions

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Table 1. Rates of Dysplasia in AORRP and JORRP.

Disease Type	Study	Year	Patient No.	Moderate Dysplasia or Greater, %
AORRP	Johnson et al[23]	1981	22	55
	Preuss et al[24]	2007	135	16
	Blumin et al[13]	2009	73	22
	Gupta et al[19]	2010	13	37
	Sanchez et al[5]	2012	129	13
	Moore et al[14]	2013	25	41
	Omland et al[7]	2014	172	20
	Davids et al[3]	2014	85	24
	Karatayli et al[26]	2015	96	10
JORRP	Lindsay et al[20]	2008	17	0
	Sajan et al[25]	2010	20	5
	Omland et al[7]	2014	49	10
	Karatayli et al[26]	2015	63	0

Abbreviations: AORRP, adult-onset recurrent respiratory papillomatosis; JORRP, juvenile-onset recurrent respiratory papillomatosis.

that drive cellular proliferation,[2] and over time, transformation to dysplasia and carcinoma can occur in RRP. The literature reports a wide range of rates of dysplasia in adult-onset RRP (AORRP) and juvenile-onset RRP (JORRP), as seen in Table 1. Possible factors contributing to such a wide range include differing definitions of pathologic changes classified as dysplasia between studies, small sample sizes given the rarity of disease, interrater variability in pathologic diagnosis among pathologists,[4] co-infection with high-risk subtypes,[5] or behavioral/environmental contributions such as tobacco use. The true incidence of dysplasia in RRP is therefore difficult to assess, and few risk factors have been identified as factors in this dysplastic transformation. Proposed risk factors include tobacco use, HPV-negative papilloma, or use of cidofovir as adjunctive therapy for RRP.[8]

The primary concern with dysplastic changes in papillomatosis is the risk of developing invasive carcinoma-ex-papillomatosis. Unlike high-risk HPV types, it does not appear that RRP follows a well-described neoplastic transformation, necessarily progressing from dysplastic epithelium to eventual invasive carcinoma.[9] However, malignant carcinoma-ex-papillomatosis is a well-described entity, occurring at a rate in adult RRP between 2% to 4% in large series and much higher in some smaller series.[6] The rate of malignant transformation is not well characterized in JORRP.

Therefore, using a large cohort of RRP patients at a single institution, we sought to examine rates of dysplasia and carcinoma-ex-papillomatosis in the AORRP and JORPP population. We further aimed to assess the risk factors associated with dysplasia and carcinoma-ex-papilloma, including gender, age, disease severity, smoking, and cidofovir usage.

Materials and Methods

Patient Population

In an Institutional Review Board–approval protocol, the pathology archives of the Johns Hopkins Hospital and clinical records of patients of the Department of Otolaryngology–Head and Neck Surgery were reviewed to identify patients with a diagnosis of "papilloma" or "papillomatosis" between July 2005 and December 2013. Only patients with histopathologically confirmed RRP were included in the study, and all pathology records were cross-checked with clinical records to ensure accurate diagnoses. Patients with papillary carcinoma of the larynx or benign papilloma infecting only the palate, tongue, or other portions of the aeordigestive tract other than the larynx were excluded.

Clinical Chart Review

All patient records were then reviewed to extract relevant clinical data, including age, gender, age of disease onset, smoking history, and adjuvant treatment with cidofovir. Cidofovir usage was noted as positive if a patient received cidofovir in at least 1 of his or her operations (2.5 or 5 mg/ml; 1 to 4 mL per patient use depending on the preference of the surgeon). Pathology reports were reviewed for the definitive pathologic diagnosis assigned to each surgical procedure. If multiple pathology reports were available for a patient, all reports were reviewed, and the highest grade of dysplastic or neoplastic was used for purposes of data analysis. The pathologic status of the disease (transformation to carcinoma or existence of dysplasia [mild/moderate/severe/carcinoma in situ]) and the total number of operations a patient underwent for RRP was recorded. If the patient was diagnosed as carcinoma-ex-papillomatosis, the total number of operations

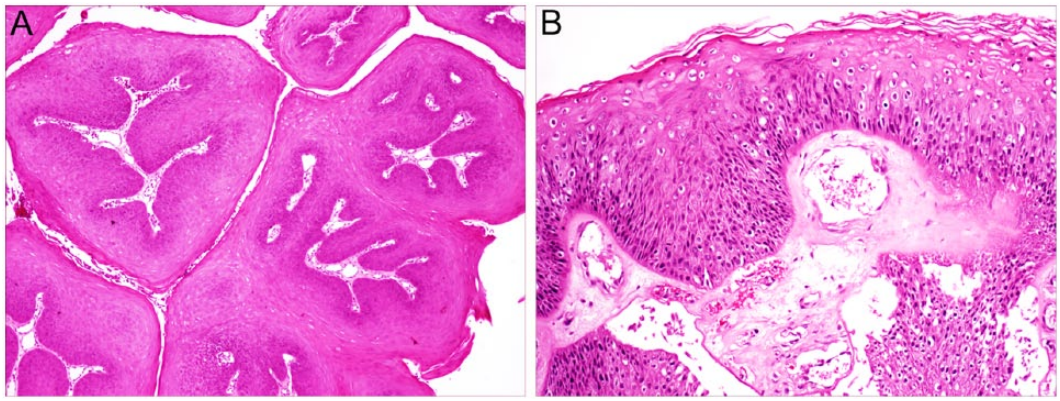

Figure 1. (A) A typical papilloma consists of fibrovascular cores lined by squamous epitehlium. (B) Papillomas often exhibit some degree of nuclear atypia reflecting human papillomavirus infection (so-called viral atypia), but it is mild, and squamous epithelium matures well from base to surface.

included the operations for RRP until diagnosis of carcinoma-ex-papillomatosis.

Data Analysis

For statistical analysis of risk factors, dysplasia and carcinoma-ex-papillomatosis were grouped together due to low numbers of patients in these groups and the biologically similar process being analyzed. For binary variables, Fisher's exact test was employed, and unpaired *t* test was used for continuous variables. Age of onset for JORRP showed significant skew, and therefore Welch's unpaired *t* test was performed for this continuous variable. Significance was attributed to a *P* value of less than .05.

Results

Overall, 159 RRP patients were identified: 96 AORRP and 63 JORRP. Taken as an entire cohort, 141 (89%) of these patients had a pathologic diagnosis of benign papilloma (Figure 1), 10 (6%) patients had dysplasia or carcinoma in situ (Figure 2), and 8 (5%) patients had invasive carcinoma-ex-papillomatosis (Figure 3). Out of the 10 AORRP patients with dysplasia, 1 had mild dysplasia, 8 had moderate dysplasia, and 1 had carcinoma in situ.

The rate of dysplasia varied significantly between the adult- and juvenile-onset RRP populations. In the AORRP cohort (Table 2) of 96 patients, 10 (10%) were diagnosed with dysplasia or carcinoma in situ, and 5 (5%) were diagnosed with invasive carcinoma-ex-papillomatosis. Of the 63 JORRP patients (Table 3), there were no pathologic diagnoses of dysplasia or carcinoma in situ but 3 (5%) patients with invasive pulmonary carcinoma-ex-papillomatosis. This rate of dysplasia is statistically significant between the 2 populations ($P = .006$), but there is no difference in the rate of carcinoma-ex-papillomatosis ($P \geq .999$). There was a difference between the 2 groups when examining the incidence of benign papilloma, with AORRP having a higher rate of pre-malignant or malignant changes than JORRP (16% vs 5%; $P = .04$). Risk factors for the diagnosis of benign papilloma versus pre-malignant or malignant diagnoses were then examined for the AORRP and JORRP populations independently, given the known differences in the biologic and clinical characteristics in these populations.

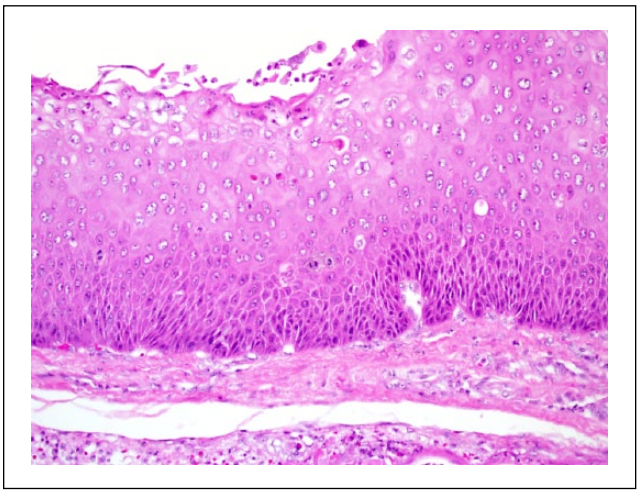

Figure 2. This papilloma with moderate dysplasia exhibtis atypia in the form of mitotic figures above the basillar layer, dyskeratosis, and nuclear pleomorphism beyond what is encountered in a typical papilloma.

As expected for AORRP, there was a significant gender skew in the population examined,[10] with a male to female gender ratio of 3:1 (Table 2). With a male to female ratio of 2:1 in the dysplasia or carcinoma-ex-papillomatosis group,

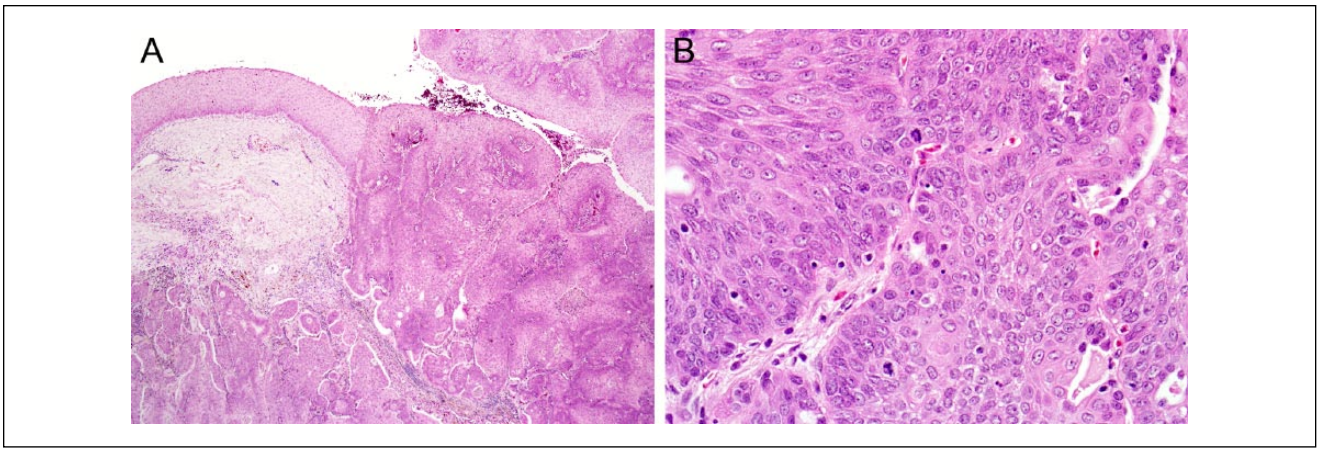

Figure 3. (A) This papilloma has undergone malignant transformation, with carcinoma frankly invading the submucosal soft tissues. (B) The carcinoma exhibits cellular atypia and an elevated mitotic rate.

Table 2. Adult-Onset Recurrent Respiratory Papillomatosis (AORRP) Patient Demographics and Characteristics.

Patient Demographics	All Papilloma n = 96	Without Dysplasia n = 81	Dysplasia/Carcinoma n = 15	*P* Value
Gender, n (%)				.53
Male	71 (74)	61 (76)	10 (67)	
Female	25 (26)	20 (24)	5 (33)	
Number of surgeries				.01
Mean (SD)	5 (6)	6 (6)	3 (2)	
Range	1-36	1-36	1-9	
Age of disease onset (y)				.0005
Mean (SD)	46 (16)	45 (16)	56 (9)	
Range	19-92	19-92	40-71	
Smoking history, n (%)	23 (24)	17 (21)	6 (40)	.18
Cidofovir, n (%)	41 (43)	37 (46)	4 (27)	.26

Table 3. Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP) Patient Demographics and Characteristics.

	All Papilloma n = 63	Without Dysplasia n = 60	Carcinoma n = 3	*P* Value
Gender, n (%)				>.999
Male	29 (46)	28 (47)	1 (33)	
Female	34 (54)	32 (53)	2 (67)	
Number of surgeries				.45
Mean (SD)	18 (30)	17 (30)	40 (35)	
Range	1-180	1-180	10-89	
Age of disease onset (y)				.009
Mean (SD)	5 (4)	6 (4)	2 (1)	
Range	1-13	1-13	1-3	
Tracheal involvement, n (%)	13 (21)	10 (17)	3 (100)	.007
Pulmonary involvement, n (%)	3 (5)	0 (0)	3 (100)	<.0001
Cidofovir, n (%)	15 (24)	15 (25)	0 (0)	>.999

there was no association between gender and pre-malignant or malignant changes (P = .53). The number of surgical interventions for the group ranged from 1 to 36 for those without dysplasia or carcinoma-ex-papillomatosis and 1 to 9

for those with. The mean number of surgeries was actually statistically less for those with dysplasia or carcinoma-ex-papillomatosis than for those with only benign papilloma (3 vs 6; $P = .01$).

The range of age of onset in the AORRP group was 19 to 92, with a median onset age of 46 years old. The average age of onset was a decade higher in the AORRP patients with dysplasia or carcinoma-ex-papillomatosis compared to those with only benign papilloma (56 vs 45 years old; $P = .0005$). Tobacco use was more prevalent in thes group with dysplasia or carcinoma-ex-papillomatosis compared to benign papilloma (41% vs 20%), but this was not statistically significant ($P = .18$). Finally, the use of cidofovir showed no association with dysplasia or carcinoma-ex-papillomatosis and was actually lower in this group than the benign papilloma group (27% vs 46%; $P = .26$).

A similar analysis was performed for JORRP (Table 3) between the 60 JORRP patients with benign papilloma and the 3 patients with carcinoma-ex-papillomatosis. The gender balance in the JORRP cohort was evenly divided and was not associated with carcinoma-ex-papillomatosis ($P \geq .999$). There was a very large range in the number of interventions for papilloma in the JORRP group, with no difference in the mean number of operations between groups (17 vs 40 operations; $P = .45$). The age of disease onset did show difference between the 2 groups, with those who eventually developed invasive carcinoma-ex-papillomatosis presenting at younger age than those with only benign papilloma (2 vs 6 years old; $P = .009$).

All 3 JORRP patients with carcinoma-ex-papillomatosis had malignant transformation in the setting of long-standing pulmonary disease associated with tracheal disease. The rate of tracheal involvement (17% vs 100%; $P = .007$) and pulmonary disease (0% vs 100%; $P \leq .0001$) was significantly lower in patients without malignant transformation compared to those with carcinoma-ex-papillomatosis. The use of cidofovir was not associated with malignant transformation, as none of the patients with carcinoma-ex-papillomatosis had received cidofovir, and there was no dysplasia or carcinoma in the 15 JORRP patients who had been exposed to cidofovir.

Discussion

In this large series of 159 adult- and juvenile-onset RRP patients, we report that the substantial majority (87%) of patients did not have dysplastic or malignant changes in their pathologic diagnosis. A small minority of patients were diagnosed with dysplasia (6%) or carcinoma-ex-papillomatosis (5%)—results that should be encouraging for practitioners who commonly field questions from patients about the risk of malignant changes in chronic HPV infections.

In the AORRP population, our reported rate of dysplasia (10%) is on the low end of reported results in the literature (Table 1), where rates of dysplasia can reach as high as 55%. However, when examining these series, it can be seen that the 4 largest series (including the current study) report rates of dysplasia that are less than 20% in AORRP patients. The HPV virus induces a wide range of pathologic atypia that could have been labeled dysplastic in other studies, and it is possible that in institutions that treat large cohorts of RRP patients these changes are accepted as "viral atypia" rather than "dysplasia." Review of all slides by a single pathologist was not performed in this study, but a recently published series where all cases were re-reviewed mainly resulted in a changed grade of dysplasia rather than detecting its presence.[3] While we cannot discount the possibility that our population has a uniquely low rate of dysplastic transformation, it seems more likely that carefully examining a large cohort of RRP patients reveals that the rate of dysplastic transformation is quite low, consistent with the known biology of low-risk HPV subtypes.

Our findings of no dysplasia in the JORRP population are consistent with multiple reports (Table 1) documenting a lower rate of dysplasia in this population compared to AORRP. Not all studies confirm this finding,[7] but it is interesting to note that the average duration of follow-up was actually a decade longer for the JORRP population (age of presentation = 5 years old; current age = 26 years old) than the AORRP population in our study (age of presentation = 46 years old; current age = 57 years old). Rather than increased duration of chronic infection leading to higher rates of dysplasia, this finding suggests that there may be a true difference in the disease progression or biology of HPV infections acquired at different ages.

We further aimed to define risk factors for dysplastic or malignant degeneration in laryngeal papillomatosis. We report the novel finding that age of disease onset is predictive for dysplasia or carcinoma-ex-papillomatosis in both the AORRP and JORRP population. Adults who were eventually diagnosed with dysplastic or malignant degeneration initially presented over a decade later in life. Blumin et al[13] reported the same tendency with no significance (56 vs 48 years old; $P < .09$), whereas in our larger series with almost identical ages of presentation, the difference between the 2 groups was highly significant (56 vs 45 years old; $P = .0005$). Furthermore, development of carcinoma-ex-papillomatosis was associated with a younger age of disease presentation in children, consistent with the known correlation between age of presentation and disease severity.

Gender was not a risk factor for dysplasia or carcinoma-ex-papillomatosis in either the AORRP or JORRP cohort. This result is consistent with previous published reports, although as in essentially all studies of AORRP and oral HPV infection in general,[10] we report a significant male preponderance in the AORRP cohort. While not a risk factor for dysplasia or carcinoma-ex-papillomatosis, the reason why

men have such a higher rate of acute and chronic oral HPV infection is not well understood.

As is well described, the average number of operations required in the clinical course of JORRP significantly exceeds that of AORRP, and our experience is no different.[11] In the JORRP group, there was no association between the number of operations and development of carcinoma-ex-papillomatosis. Notably however, in our AORRP cohort, there were statistically fewer surgeries performed in those patients with dysplasia or carcinoma-ex-papillomatosis compared to benign papilloma. The differences between these groups is likely methodological because while dysplasia can persist without progression in AORRP,[15] we chose to record only the number of surgeries up until the time of diagnosis of dysplasia or carcinoma as it is possible that the change in diagnosis could have altered the surgical or treatment plan. At the very least, the hypothesis that increased aggressiveness in AORRP, as measured by surgical interventions required, will then lead to dysplasia or carcinoma is not supported by our data.

There was no association between tobacco use and the development of dysplasia or carcinoma-ex-papillomatosis in our study, consistent with previously published reports. These data mirror the epidemiologic characteristics seen in the HPV-associated oropharyngeal cancer patient population, where tobacco use is not strongly associated with development of malignancy.[16]

Cidofovir is an acyclic nucleotide phosphonate antiviral medication that has been used for RRP and advocated for years.[17] However, this drug is a known carcinogen,[18] and a case report from Iowa reported dysplastic transformation of the laryngeal papilloma of a 28-year-old woman while undergoing cidofovir treatment.[8] It is therefore of great concern for practitioners who treat RRP patients if cidofovir is associated with dysplastic transformation or development of carcinoma-ex-papillomatosis. We identify no association with cidofovir use, and the development of dysplasia or carcinoma in this report and multiple other series support this conclusion.

Carcinoma-ex-papillomatosis is a rare event, occurring in 5% of patients in our series. This falls within the expected range of 2% to 4% in the literature, although a series from Taiwan reports an unusually high rate of 23%.[6] All pediatric cases in our series were associated with long-standing pulmonary disease,[21] whereas all AORRP cases had transformation in the larynx. All adults in our series were salvaged with total laryngectomy. Conversion to malignancy in pulmonary disease is an extremely difficult problem to manage with a poor prognosis, as there is usually widespread parenchymal disease separate from the cancer.

Drawbacks to our study include the lack of HPV typing, which would allow us to draw conclusions about the true incidence of low-risk HPV infection in our cohort. While it is clearly documented in the literature that malignant degeneration can occur in "low-risk" subtypes, the findings reported in multiple studies that "HPV negative" papilloma has a higher rate of conversion to dysplasia should be viewed with some suspicion. If the "typical" patient who progresses to dysplasia is a male presenting in his 50s, as a new diagnosis of AORRP has an average number of 3 surgeries before dysplasia or carcinoma is diagnosed and is low-risk HPV-negative, the diagnosis of benign papilloma as opposed to papillary squamous cell carcinoma[22] should perhaps be questioned. The very low rate of dysplasia in JORRP even with prolonged observation, where the diagnosis of RRP is more secure due to a lack of any viable alternative diagnoses, may more actually reflect the natural history of the disease.

Conclusions

In a large series of AORRP and JORRP patients, age of disease onset was predictive of eventual transformation to dysplasia or carcinoma-ex-papillomatosis in both the adult and pediatric populations. No other demographic or behavioral factor was associated with this transformation, including gender, average number of operations, smoking, or cidofovir use. The overall rate of dysplasia (10%) is lower than many studies but consistent with the largest contemporaneous series of RRP patients.

Authors' Note

This work was presented at the 10th Congress of the European Laryngology Society, April 9-12, 2014, Antalya, Turkey, and won Lichtenberger Prize.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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