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The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium

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Background: Poor oral hygiene has been proposed to contribute to head and neck cancer (HNC) risk, although causality and independency of some indicators are uncertain. This study investigates the relationship of five oral hygiene indicators with incident HNCs.

Methods: In a pooled analysis of 8925 HNC cases and 12 527 controls from 13 studies participating in the International Head and Neck Cancer Epidemiology Consortium, comparable data on good oral hygiene indicators were harmonized.

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These included: no denture wear, no gum disease (or bleeding), <5 missing teeth, tooth brushing at least daily, and visiting a dentist ≥once a year. Logistic regression was used to estimate the effects of each oral hygiene indicator and cumulative score on HNC risk, adjusting for tobacco smoking and alcohol consumption.

Results: Inverse associations with any HNC, in the hypothesized direction, were observed for <5 missing teeth [odds ratio (OR) = 0.78; 95% confidence interval (CI) 0.74, 0.82], annual dentist visit (OR = 0.82; 95% CI 0.78, 0.87), daily tooth brushing (OR = 0.83, 95% CI 0.79, 0.88), and no gum disease (OR = 0.94; 95% CI 0.89, 0.99), and no association was observed for wearing dentures. These associations were relatively consistent across specific cancer sites, especially for tooth brushing and dentist visits. The population attributable fraction for ≤ 2 out of 5 good oral hygiene indicators was 8.9% (95% CI 3.3%, 14%) for oral cavity cancer.

Conclusion: Good oral hygiene, as characterized by few missing teeth, annual dentist visits, and daily tooth brushing, may modestly reduce the risk of HNC.

Key words: head and neck neoplasms, oral neoplasms, pharyngeal neoplasms, oral hygiene, pooled analyses

introduction

Primary head and neck cancer (HNC) is estimated to exceed 500 000 cases worldwide per year [1]. Geographic differences in HNC incidence rates persist among [2] and within some countries [3]. Although the prevalence of alcohol and tobacco use varies, regional variations in HNC incidence rates cannot be explained by these risk factors alone [4].

HNCs include cancers originating in the oral cavity, oropharynx, hypopharynx, or larynx. Oral hygiene indicators, such as missing teeth [5], denture use [6], bleeding gums [7], infrequent dental visits [8], and tooth brushing infrequency [5, 7, 8], have been suspected to contribute to the etiology of HNCs. The causal and independent role of oral hygiene in HNC development has thus been inconclusive due to the limited numbers of cases as well as a lack of available detailed information on more than one oral hygiene indicator for most studies [9–11]. Oral hygiene is not an established risk factor for HNCs and the population attributable fraction (PAF) of oral hygiene to HNCs has not been assessed.

In separate analyses of Latin American and central European case–control studies, poor condition of the mouth, regular mouthwash use, and lack of tooth-brushing were associated with HNC risk [8]. Our study expands the scope of this analysis to include countries from five continents and explores the role of oral hygiene indicators. We pooled oral hygiene and HNC data from studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. This pooled analysis describes the largest and most comprehensive assessment of the association between oral hygiene indicators and HNCs to date, including oral cavity, laryngeal, hypopharyngeal, and oropharyngeal cancers.

methods

studies and participants

The pooled analysis consisted of 8925 incident cases and 12 527 controls from 13 INHANCE case–control studies (data version 1.5) (http://www.inhance.utah.edu) [12, 13]. Data pooling and questionnaire harmonization methods have been described previously [12, 13]. Our investigation included studies from the United States ($n = 8$), Central Europe ($n = 1$), Latin America ($n = 2$), Japan ($n = 1$), and one international multicenter study (supplementary Table S1, available at *Annals of Oncology* online). Subjects with missing information on all oral hygiene variables were excluded ($n = 1013$).

Incident cases included patients with invasive tumors of the overall head and neck ($n = 8925$), oral cavity ($n = 2858$), oropharynx ($n = 2402$), hypopharynx ($n = 738$), larynx ($n = 2086$), and oral cavity/pharynx not otherwise specified ($n = 841$), as defined by International Classification of Disease, 2nd edition (ICD-O2) or ICD 9th or 10th edition as previously described [13]. Results for some oral hygiene variables have been previously published for 4 out of the 13 studies [8, 14, 15]. Written informed consent was obtained from study subjects, and investigations were approved by the institutional review board at each institution involved [16].

oral hygiene variables

Oral hygiene data were obtained from questionnaires administered by dentists in the central Europe study and self-report by face-to-face questionnaire interviews in other studies. Self-reported oral hygiene has been shown to be reliable [17–20]. Gum disease (which included periodontal disease and/or gingivitis) and wearing dentures were defined dichotomously. The number of missing teeth was defined as <5 or ≥ 5 teeth missing. Tooth brushing was categorized by frequency as ≥once/day versus <once/day, and dentist visit frequency as ≥once/year versus <once/year. These data were also coded categorically: for tooth-brushing frequency 1 = <once/day, 2 = once-to-twice/day, or 3 = ≥twice/day, regularity of dental visits (never or seldom, <once/year, ≥once/year); and number of missing teeth number (1 = <5, 2 = 5–15, and 3 = ≥16). The Puerto Rico, Latin America, and international multicenter studies contained all five oral hygiene variables.

covariates

Covariates included age (5-year age categories above age 40), sex, race/ethnicity (White, Black, Hispanic, Asian and Pacific Islander, Brazilian, and other), and education level (≤high school versus >high school, to adjust for educational level across countries with varying access to education). For individuals not reporting education level (0.1%), multiple imputation was applied to predict education level for each geographic region separately using logistic regression models with terms for age, sex, race/ethnicity, study center, and case–control status under the assumption that data were missing at random [21]. Alcohol consumption was calculated as the number of drinks/day based on average cumulative lifetime consumption, assuming one standardized drink contains 15.6 ml of pure ethanol (non-drinker, 0.1–0.9, 1.0–2.9, 3.0–4.9, and 5.0+, and missing drinks/day) [13]. Cumulative tobacco smoking was categorized as those who smoked 0–10.0, 10.1–20.0, 20.1–30.0, 30.1–40.0, 40.1–50.0, and 50.0+ pack-years. Missing data on race/ethnicity (0.4%), tobacco smoking (6.3%), and alcohol drinking (3.1%) were included in separate categories in models.

statistical analysis

Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations of oral hygiene indicators and incident HNCs. All ORs were adjusted for study (and center for multicenter studies), sex, age, race, education, alcohol consumption, and tobacco smoking.

P values for monotonic trends were derived from the fitted models of oral hygiene indicators as continuous variables. Interactions between each oral hygiene indicator and alcohol drinking, tobacco smoking, and geographical region were assessed with likelihood-ratio tests.

To determine the PAF of poor oral hygiene, an oral hygiene score was calculated for studies that included all oral hygiene indicators. Scores ranged from 5 to 0 on a best-to-worst oral health scale. The sum of the indicators was combined: denture wear: yes = 1, no = 0; gum disease: yes = 0, no = 1; missing teeth: '≥5' = 0, '<5' = 1; regular dental visit: yes = 1, no = 0; teeth brushing frequency: '≥once per day' = 1, '<once per day' = 0. The referent category for OR was defined as those with the best scores for oral hygiene (score ≥4). The PAF was calculated using the formula $P_{EC} \times (OR - 1)/OR$ [22], where OR is the adjusted OR and P_{EC} is the proportion of cases exposed to the worst oral hygiene. The definition of exposure for calculating PAF estimates considered subjects exposed when the oral hygiene score ≤2, and unexposed when the score was ≥3. PAF confidence limits were calculated with the command aflogit [23].

Harmonization and PAF calculation were completed using the Stata Statistical Software (Release 12.2; StataCorp LP, College Station, TX) and all other analyses were carried out using the SAS Statistical Software (Version 9.4; SAS Institute Inc., Cary, NC).

results

Selected characteristics of HNC incident cases and controls, including known risk factors, are displayed in supplementary Table S2, available at *Annals of Oncology* online. After multivariable adjustment, inverse associations were observed between HNC and no gum disease, missing <5 teeth, brushing teeth ≥once/day, and visiting a dentist ≥once/year (Table 1). No association was found between wearing dentures and HNC.

Table 1. Association of head and neck cancer risk overall and by subsite with oral hygiene indicators, INHANCE Consortium

Exposure	Outcome[a]	Case (exposed/unexposed)	Control (exposed/unexposed)	Odds ratio (95%CI)
Wear denture (yes versus no)	Head and neck	2223/2804	2067/3604	1.00 (0.95, 1.05)
	Oral cavity	653/1047	2067/3604	0.96 (0.90, 1.03)
	Pharynx	725/904	2067/3604	0.98 (0.91, 1.05)
	Oropharynx	559/747	2067/3604	0.98 (0.91, 1.06)
	Hypopharynx	166/157	1631/2441	0.95 (0.84, 1.09)
	Larynx	584/452	1362/2286	1.10 (1.01, 1.21)
Gum disease (no versus yes)	Head and neck	5533/1201	6778/1161	0.94 (0.89, 0.99)
	Oral cavity	1690/387	6778/1161	0.83 (0.77, 0.89)
	Pharynx	1933/403	6778/1161	1.04 (0.96, 1.11)
	Oropharynx	1522/333	6778/1161	1.01 (0.93, 1.10)
	Hypopharynx	411/70	5365/1049	1.12 (0.96, 1.30)
	Larynx	1020/235	3912/713	0.92 (0.83, 1.02)
Number of missing teeth (<5 versus ≥5)	Head and neck	934/4170	1731/3706	0.78 (0.74, 0.82)
	Oral cavity	251/1356	1732/3706	0.69 (0.64, 0.76)
	Pharynx	353/1203	1733/3706	0.88 (0.81, 0.94)
	Oropharynx	287/961	1383/3084	0.87 (0.80, 0.94)
	Hypopharynx	66/242	1733/3706	0.93 (0.79, 1.09)
	Larynx	174/1052	1062/2318	0.75 (0.68, 0.84)
Tooth brushing (≥once/day versus <once/day)	Head and neck	6067/1344	9470/863	0.83 (0.79, 0.88)
	Oral cavity	1863/336	9401/862	0.81 (0.75, 0.88)
	Pharynx	2113/392	9401/862	0.86 (0.80, 0.93)
	Oropharynx	1706/299	9470/863	0.87 (0.80, 0.95)
	Hypopharynx	463/108	7984/754	0.80 (0.70, 0.92)
	Larynx	1068/412	6272/679	0.78 (0.72, 0.85)
Visit dentist (≥once/year versus <once/year)	Head and neck	1703/3551	2486/2748	0.82 (0.78, 0.87)
	Oral cavity	428/1114	2486/2748	0.82 (0.76, 0.89)
	Pharynx	547/1038	2486/2748	0.78 (0.72, 0.84)
	Oropharynx	454/772	2486/2748	0.78 (0.72, 0.86)
	Hypopharynx	93/266	2242/2015	0.74 (0.64, 0.87)
	Larynx	443/915	2163/1573	0.83 (0.76, 0.91)

Odds ratios (95% CIs) were estimated using logistic regression models adjusting for study (and center for multicenter studies), age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), sex, race (Black, Hispanic, Asian and Pacific Islanders, Brazilian and Others), education level (≤high school, >high school), amount of alcohol drinking (non-drinker, 0.1–0.9, 1.0–2.9, 3.0–4.9, and 5.0+ drinks/day), and cumulative tobacco smoking (never smoker, smoked 0–10.0, 10.1–20.0, 20.1–30.0, 30.1–40.0, 40.1–50.0, 50.0+ pack-years). Cases and controls from studies with no data for a given oral hygiene variable were excluded from analyses of that exposure, as follows: wear dentures, 3898 cases and 6856 controls; gum disease, 2191 cases and 4588 controls; missing teeth, 3821 cases and 7090 controls; tooth brushing, 1514 cases and 2194 controls; and visit dentist, 3671 cases and 7293 controls.

[a]ICD-O-2 codes: oral cavity, C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, C06.9; oropharynx, C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, C10.9; hypopharynx, C12.9, C13.0–13.2, C13.8, C13.9; larynx, C32.0–C32.3, C32.8–C32.

Table 2. Association of oral hygiene indicators in terms of association with risk of head neck cancer and oral cavity cancer restricted to Puerto Rico ($n = 733$), Latin America ($n = 2938$), International Multicenter ($n = 1635$), INHANCE Consortium

Exposure	Head and neck Odds ratio (95% CI)	Oral cavity Odds ratio (95% CI)	Pharynx Odds ratio (95% CI)	Oropharynx Odds ratio (95% CI)	Hypopharynx Odds ratio (95% CI)	Larynx Odds ratio (95% CI)
Wear denture (yes versus no)	0.65 (0.57, 0.75)	0.58 (0.48, 0.72)	0.63 (0.51, 0.78)	0.62 (0.49, 0.78)	0.67 (0.46, 0.96)	0.93 (0.73, 1.18)
Gum disease (no versus yes)	0.48 (0.37, 0.63)	0.32 (0.23, 0.44)	0.78 (0.51, 1.18)	0.66 (0.45, 1.02)	0.75 (0.32, 1.79)	0.82 (0.45, 1.47)
Number of missing teeth (<5 versus ≥5)	0.38 (0.32, 0.46)	0.28 (0.21, 0.36)	0.51 (0.39, 0.66)	0.51 (0.38, 0.68)	0.48 (0.30, 0.79)	0.53 (0.38, 0.75)
Tooth brushing (≥once/day versus <once/day)	0.83 (0.68, 1.00)	0.79 (0.60, 1.04)	0.82 (0.62, 1.14)	0.84 (0.62, 1.14)	0.68 (0.41, 1.28)	0.99 (0.73, 1.33)
Visit dentist (≥once/year versus <once/year)	0.86 (0.73, 1.01)	0.91 (0.72, 1.16)	0.64 (0.50, 0.83)	0.69 (0.52, 0.90)	0.54 (0.33, 0.89)	0.95 (0.73, 1.23)

Results were based on populations from the following three studies, who had all five markers available: Puerto Rico ($n = 733$), Latin America ($n = 2938$), International Multicenter ($n = 1635$). Odds ratios (95% CIs) were estimated when put all five markers into one logistic regression model, which adjusted for study (and center for multicenter studies), age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), sex, race (Black, Hispanic, Asian and Pacific Islanders, Brazilian and Others), education level (≤high school, >high school), amount of alcohol drinking (non-drinker, 0.1–0.9, 1.0–2.9, 3.0–4.9, and 5.0+ drinks/day), and cumulative tobacco smoking (never smoker, smoked 0–10.0, 10.1–20.0, 20.1–30.0, 30.1–40.0, 40.1–50.0, 50.0+ pack-years).

Table 3. Association of head neck cancer overall and by site with oral hygiene score, INHANCE Consortium

	Head and neck		Oral cavity	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95%CI)
Oral hygiene score (worst to best oral hygiene)				
≤1	184/127	1.98 (1.68, 2.35)	57/127	3.12 (2.08, 4.68)
2	951/823	1.79 (1.50, 2.13)	287/823	2.42 (1.87, 3.15)
3	1171/940	1.98 (1.48, 2.65)	496/940	2.45 (1.93, 3.12)
≥4	366/744	1.0 (referent)	118/744	1.0 (referent)
P for trend		<0.0001		<0.0001

Oral hygiene score is the sum of the five following items: wear denture: yes = 0, no = 1; gum disease: yes = 0, no = 1; missing teeth: '≥5' = 0, '<5' = 1; regular visit dentist: yes = 1, no = 0; teeth brushing frequency: '≥once/day' = 1, '<once/day' = 0. Oral hygiene scores range from 0 to 5, corresponding to worst to best oral hygiene.

Odds ratios (95% CIs) were estimated using logistic regression models adjusted for age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), sex, race (Black, Hispanic, Asian and Pacific Islanders, Brazilian and Others), education level (≤high school, >high school), amount of alcohol drinking (non-drinker, 0.1–0.9, 1.0–2.9, 3.0–4.9, and 5.0+ drinks/day), and cumulative tobacco smoking (never smoker, smoked 0–10.0, 10.1–20.0, 20.1–30.0, 30.1–40.0, 40.1–50.0, 50.0+ pack-years).

Stratified associations between oral hygiene and HNC persisted among participants with risk profiles defined by smoking, alcohol drinking, and geographic region for gum disease, tooth brushing, and number of missing teeth with consistent directions of association with non-stratified results (supplementary Table S3, available at *Annals of Oncology* online). Supplementary Table S4, available at *Annals of Oncology* online, displays associations with HNC and oral cavity cancer after restricting the study to never smokers and never drinkers.

When all oral hygiene variables were adjusted for each other (38% of the pooled study population that included: Puerto Rico, the Latin American multicenter, and the international multicenter), all good oral hygiene indicators were inversely associated with HNC and oral cancer (Table 2). Magnitudes of associations between missing teeth and the risk of both HNC and oral cancer increased 75% and 107%, respectively, compared with models unadjusted for other oral hygiene indicators. No gum disease increased 95% for HNC and 160% for oral cancer risk compared with unadjusted models. Associations of dental visits with HNC and oral cavity cancer were attenuated. However, HNC attenuation was modest and within the CI of the unadjusted analysis.

oropharyngeal, hypopharyngeal, and pharyngeal cancers

Oropharyngeal and pharyngeal cancers were inversely associated with <5 missing teeth, tooth brushing ≥once/day, and regular dentist visit after multivariable adjustments. Hypopharyngeal cancers were inversely associated with brushing teeth ≥once/day and regular dentist visit. After mutual oral hygiene variable adjustment, strengths of association for cancers of the oropharynx, pharynx, and hypopharynx cancers were strongest for missing teeth and wearing dentures.

laryngeal cancers

Laryngeal cancer was inversely associated with <5 missing teeth, brushing ≥once/day, regular dentist visit, and wearing dentures. Strengths of association with laryngeal cancer were attenuated for regular dentist visits, tooth brushing, no gum disease, and

wearing dentures once all five variables were included in mutually adjusted logistic regression models.

oral hygiene score

Associations of cancer risk with oral hygiene scores mutually adjusted for all oral hygiene indicators ranged from 5 to 0 (from best to worst oral hygiene, respectively) are displayed in Table 3. The PAF for a suboptimal oral hygiene score ≤2 was 8.9% (95% CI 3.3%, 14%) for oral cavity cancer and 5.4% (95% CI 0.36%, 10%) for HNCs.

discussion

Associations were observed between oral hygiene indicators and HNC, independent of alcohol drinking and tobacco smoking. Having ≤2 indicators of good oral hygiene contributes to an estimated 8.9% of oral cavity cancers. Among the specific HNCs, the associations with oral hygiene were greatest for oral cavity cancers, strengthening the possibility of a causal role. Having <5 missing teeth demonstrated the greatest magnitude of association in the inverse direction for HNC, in addition to all subsites.

The mechanisms by which poor oral hygiene is associated with HNCs fall into categories of trauma and inflammation. Causes of trauma and inflammation are due to coexisting disease and/or negligence of oral hygiene. Thus, these indicators may be indicative of dysbiotic shifts in the commensal oral microbiome [24, 25], tooth wear [26], mechanical trauma [27, 28], and general health maintenance, all of which are linked to cancer.

Tooth loss is directly related to each of the other four oral hygiene indicators ($P < 0.001$ for interaction with each), and is supported by a magnitude of association increase for both HNC and all subsites when adjusted for all other oral hygiene indicators. It is biologically plausible that missing teeth reflects poor oral health maintenance (irregular tooth brushing and dental visits), mechanical trauma, inflammation (secondary to diabetes, nutritional deficits), infection (secondary to periodontitis or gingivitis), and exposures such as nitrosamines [29], tobacco use [30], and alcohol [30] which also result in tooth loss. Missing teeth may be causally related to dentures and inflammation, resulting in gingiva trauma in addition to receding gums, jawbone weakening, and teeth collapsing [31].

Dental visits had a 26% reduced risk association with oral cancer ($P < 0.001$) when adjusted for wearing dentures alone. To obtain dentures, a patient must visit a dentist more than once for diagnosis and denture fittings [32]. These necessary dental visits indirectly lead to treatment for any mechanical trauma or inflammation that resulted in the need for dentures and had a significant interaction with wearing dentures ($P = 0.005$). Adjusting for regular dental visits resulted in a 20% reduction in association between wearing dentures and HNCs (OR = 0.81; 95% CI 0.74, 0.89).

In addition to denture fittings, dental visits are also related to regular teeth cleaning, preventive diagnoses of dental carries, and an overall better quality of life [32]. In adjusted models, annual dental visits were associated with a 26% reduction in HNC for patients with gum disease. Because dental visits were found to interact with missing teeth ($P < 0.001$), gum disease ($P = 0.004$), and wearing dentures ($P < 0.001$), the inverse association of dental visits was attenuated after adjustment for all oral hygiene indicators.

Gum diseases develop either secondarily to chronic disease or as a result of neglected health maintenance [33] and was independently associated with increased risk of HNC. Previous observational studies have shown that gum diseases are also associated with poorly controlled diabetes and smoking [33]. These host-compromising factors may also lead to a strong association between gum disease and HNCs.

Our analysis is limited by factors influencing oral hygiene indicators and behaviors that could not be adjusted for. Control and management of diabetes [34], in addition to past and present medical history of inflammatory oral and/or systemic conditions such as osteoporosis and cardiovascular diseases [35], can increase the risk of gum disease and tooth loss which can increase HNC risk. The consortium, however, previously found a weak association with diabetes and HNC risk (OR = 1.09; 95% CI 0.95–1.24) [30]. Our study also includes only a small proportion of the age group (over the age of 75) in which osteoporosis is most prevalent (6% cases and 6% controls) and most cases were men. Another concern is that oral hygiene behaviors such as dental visits, wearing dentures, and tooth brushing may be influenced by socioeconomic status (SES) [36] and relative deprivation [37] within and between countries with access to dental care depending upon national healthcare system infrastructures and gross national income per capita [37]. Models in this study were adjusted for SES measured by educational level and regional disparities measured by study center. However, SES effects may be slightly underestimated or overestimated due to absent data on individual income levels, cultural class systems, and insurance status. We carried out stratified analysis for each study center (data not shown) and for four main regions. The stratified analysis was consistent with overall findings. Likewise, risk for HNCs was predictably lower for higher educated individuals. Additionally, although frequency data were measured, we have no data on the duration of teeth brushing over a year. However, it is reasonable to assume that the habits of tooth brushing, similar to other daily human hygiene or grooming rituals, are relatively consistent throughout one's life.

As with all case–control studies, a possibility of recall bias exists. Using newly diagnosed (incident) cases, recall of past events in personal histories tends to be more accurate than prevalent cases and cases were less likely to have changed their habits as a result of the cancer [38]. Because this study also selected representative controls from the case population, we were able to investigate the effect of oral hygiene on HNC cases, much like a cohort study [38]. Only two studies (2.4% cases and 2.2% controls with variables) utilized non-cancer hospital controls. These studies had data available for tooth brushing (both HOTSPOT and Baltimore) and denture wear (Baltimore). Although the magnitude of the inverse relationship between HNCs and tooth brushing was stronger for these two studies, exclusion from the analysis resulted in an OR of 0.84; 95% CI 0.65, 0.98.

This study has several strengths. It encompasses a large population of low-incidence cancer cases, resulting in more precise effect estimates and the ability to extend analysis to HNC subsites. Four geographical regions are also included, strengthening external validity. This study also incorporates multiple oral hygiene variables using primary data and is able to stratify oral

hygiene indicators by specific subgroups, eliminating possible confounders of alcohol drinking and tobacco smoking.

In conclusion, good oral hygiene is associated with lower risk of HNC. Improvements in oral hygiene by increasing oral hygiene literacy, particularly for annual dentist visits and daily tooth brushing, may be protective against HNC, although the extent of risk reduction is modest.

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disclosure

The authors have declared no conflicts of interest.

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Adjuvant treatment with pegylated interferon α-2a versus low-dose interferon α-2a in patients with high-risk melanoma: a randomized phase III DeCOG trial†

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Background: Adjuvant treatment with interferon (IFN)-α-2a improved disease-free survival (DFS) and showed a trend for improving overall survival (OS) in melanoma. This trial was designed to examine whether PEG-IFN is superior to IFN with regard to distant metastasis-free survival (DMFS), DFS and OS.

Patients and methods: In this multicenter, open-label, prospective randomized phase III trial, patients with resected cutaneous melanoma stage IIA(T3a)–IIIB (AJCC 2002) were randomized to receive PEG-IFN (180 μg subcutaneously 1×/week; 24 months) or IFN α-2a (3MIU subcutaneously 3×/week; 24 months). Randomization was stratified for stage,

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