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This issue of Journal Club is hosted by the AHNS Cancer Prevention Service – contributors: Heather Edwards (service chair), James Gates (service vice-chair), Marisa Buchakjian, Varun Vendra, Kevin Wang & Thomas L Haupt.

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GLP-1RA Use and Thyroid Cancer Risk

Juan P. Brito, MD; Jeph Herrin, PhD; Kavya Sindhu Swarna, MPH; Naykky M. Singh Ospina, MD; Victor M. Montori, MD; David Toro-Tobon, MD; Guillermo E. Umpierrez, MD; Rodolfo J. Galindo, MD; Yihong Deng, PhD; Mindy M. Mickelson, MA; Hui Shao, MD; Eric C. Polley, PhD; Rozalina G. McCoy, MD, MS

from JAMA Otolaryngology Head & Neck Surgery, , March 1, 2025

Abstract

Importance: The increasing use of glucagon-like peptide-1 receptor agonists (GLP-1RA) demands a better understanding of their association with thyroid cancer.

Objective: To estimate the risk of incident thyroid cancer among adults with type 2 diabetes being treated with GLP-1RA vs other common glucose-lowering medications.

Design, setting, and participants: This was a prespecified secondary analysis of a target trial emulation of a comparative effectiveness study using claims data for enrollees in commercial, Medicare Advantage, and Medicare fee-for-service plans across the US. Eligible participants were adults with type 2 diabetes at moderate risk for cardiovascular disease and without history of thyroid cancer who had newly filled prescriptions for GLP-1RA, sodium-glucose cotransporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP4i), or sulfonylurea from January 1, 2014, to December 31, 2021. Data were analyzed February 1 to October 31, 2024.

Main outcomes and measures: Overall and piecewise (<1, 1-2, and ≥2 years since treatment initiation) hazard ratios (HRs) for thyroid cancer with use of GLP-1RA vs the other 3 drug classes were estimated using inverse propensity score weighted Cox proportional hazards models. Modified intention-to-treat (mITT) (primary) and as-treated (sensitivity) analyses were performed.

Results: Of 351 913 patients (mean [SD] age, 65.3 [8.5] years; 173 391 [49.3%] females and 178 522 [50.7%] males), 41 112 started treatment with GLP-1RA; 76 093, with DPP4i; 43 499, with SGLT2i; and 191 209, with sulfonylurea therapy. The numbers of patients diagnosed with thyroid cancer were 69 (0.17%) in the GLP-1RA group, 172 (0.23%) in the DPP4i group, 72 (0.17%) in the SGLT2i group, and 381 (0.20%) in the sulfonylurea group. In the mITT analysis, GLP-1RA initiation was not significantly associated with increased overall risk for thyroid cancer compared to the other 3 diabetes drugs (HR, 1.24; 95% CI, 0.88-1.76). However, the risk for thyroid cancer was significantly higher within the first year after GLP-1RA initiation (HR, 1.85; 95% CI, 1.11-3.08) and was amplified in the overall as-treated analysis that censored patients when therapy was discontinued or another medication was added (HR, 2.07; 95% CI, 1.10-3.95).

Conclusions and relevance: This secondary analysis of a target trial emulation of a comparative effectiveness study found that despite the low absolute risk of thyroid cancer among patients receiving GLP-1RA therapy, there was an increased risk of new thyroid cancer diagnoses within the first year of GLP-1RA initiation compared to 3 other diabetes drugs. This finding may have been due to enhanced early detection; therefore, further research is necessary to understand the underlying causes of this association.

Summary

The incidence of GLP-1 receptor agonist (GLP-1RA) use in the United States continues to rise, with an estimated 12% of Americans reporting use of these medications for diabetes management and/or weight loss. Given the public interest in GLP-1RA treatment and its potential health benefits it is imperative to better understand the risk of adverse events. Specifically, GLP-1RA medications come with a warning from the U.S Food and Drug Administration about the potential risk of thyroid C-cell tumors, more commonly known as medullary thyroid cancer (MTC). This warning stems from results of preclinical animal models and postmarketing case reports in patients. Currently, GLP-1RA medications are contraindicated in patients with a history of MTC or a diagnosis of Multiple Endocrine Neoplasia syndrome type 2 (MEN2). However, the true risk of MTC in the setting of GLP-1RA use is unclear, leaving some patients unsure of how to weigh the risks and benefits of GLP-1RA medication use.

A recent manuscript published in *JAMA Otolaryngology-Head & Neck Surgery* examined the risk of incident thyroid cancer using insurance claims data in patients with new prescriptions for GLP-1RA. The study group included patients with type 2 diabetes at moderate risk for cardiovascular disease and without a history of thyroid cancer. Importantly, the authors compared the risk of developing thyroid cancer in patients on GLP-1RA to those on three other non-GLP glucose-lowering medications, serving as control groups. Over 350,000 patients were analyzed, with 40,000 on GLP-1RA medications. A total of 69 (0.17%) of patients on GLP-1RA were diagnosed with thyroid cancer in this study, which was not significantly associated with an incidence overall risk of thyroid cancer compared to the non-GLP diabetes medications. Although the overall risk of thyroid cancer was not different between the groups, when examining timing of diagnosis there was found to be a significantly higher risk of thyroid cancer diagnosis within the first year after starting GLP-1RA treatment (Hazard Ratio 1.85, 95% Confidence Interval, 1.11-3.08). This suggests enhanced detection of thyroid cancer in GLP-1RA patients despite an overall low incidence, a hypothesis which is also supported by an increased

likelihood of undergoing thyroid ultrasonography after medication initiation in GLP-1RA patients compared to non-GLP-1RA patients.

Strengths
The strengths of this study include using a diverse patient population with well-balanced baseline characteristics between the GLP-1RA and non-GLP-1RA groups. The authors were also stringent in censoring patients when GLP-1RA medications were discontinued or additional glucose-lowering agents were added.

Weaknesses
As discussed by the authors, one weakness of the study was the inability to distinguish between MTC and other thyroid cancer subtypes, and it is possible that small differences in MTC incidence are present but unable to be detected without additional detailed information. Focusing specifically on MTC would be the next logical step for this type of study. Future studies should also focus on examining thyroid cancer characteristics at the time of diagnosis (size, presence of lymph node metastases, presence of extrathyroidal extension) as well as long-term cancer results between GLP-1RA and non-GLP-1RA patients.

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High Sugar-Sweetened Beverage Intake and Oral Cavity Cancer in Smoking and Nonsmoking Women

Gomez-Castillo L, Cushing-Haugen KL, Useche M, Norouzi A, Rizvi Z, Ferrandino R, Futran N, Marchiano E, Rodriguez T, Harris HR, Barber B.

from JAMA Otolaryngology Head & Neck Surgery, May 1, 2025

ABSTRACT
Importance: The incidence of oral cavity cancer (OCC) is increasing among nonsmokers and young individuals without traditional risk factors worldwide. High sugar-sweetened beverage (SSB) intake is associated with various gastrointestinal cancers, but its association with OCC has not been explored.

Objective: To evaluate the association between SSB intake and the risk of OCC among smoking and nonsmoking women participating in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Design, setting, and participants: This longitudinal cohort study analyzed data from women in the NHS (follow-up, 1986-2016) and NHSII (follow-up, 1991-2017) after excluding those with a history of cancer, implausible caloric intake, or missing SSB intake data. Participants were followed up until the diagnosis of OCC. Data analysis was performed from July 2023 to June 2024.

Exposure: SSB intake, quantified by frequency of consumption ranging from less than 1 SSB monthly to 1 or more SSBs daily.

Main outcome and measure: Cox proportional hazards regression models with age and questionnaire period as the time scale were used to estimate hazard ratios (HRs) and 95% CIs associated with the development of OCC for each category of SSB intake, with less than 1 SSB per month as the reference group.

Results: A total of 162 602 women (mean [SD] age, 43.0 [9.9] years) were evaluated. During 30 years of follow-up, 124 invasive OCC cases were documented. In multivariable-adjusted models, participants consuming 1 or more SSB daily (5 people per 100 000 population) had a 4.87 times (95% CI, 2.47-9.60 times) higher risk of OCC compared with those consuming less than 1 SSB monthly (2 people per 100 000 population), increasing the rate of OCC to 3 more people per 100 000 population. When restricted to both nonsmokers or light smokers and nondrinkers or light drinkers, the risk of OCC was 5.46 times (95% CI, 1.75-17.07 times) higher, increasing the rate of OCC to 3 more people per 100 000 population.

Conclusions and relevance: In this study, high SSB intake was associated with a significantly increased risk of OCC in women, regardless of smoking or drinking habits, yet with low baseline risk. Additional studies are needed in larger cohorts, including males, to validate the impact of these findings.

Summary

- An increased proportion of younger, non-smoker patients have been diagnosed with oral cavity cancer, and risk factors for these patients need investigation
- The risk of developing oral cancer was found to be 4.87 times (95% CI, 2.47-9.60 times) higher in females aged 30-55 that consume 1 or more sugar sweetened beverages (SSB) daily, than in those who consume less than 1 SSB per month
- This association remained elevated in the non or light smoker cohort (3.71 times (95% CI, 1.37-10.05 times)), and was elevated further in the non or light drinker cohort (5.38 times higher (95% CI, 2.23-12.97)), thus showing that cancer risk increased with daily SSB intake regardless of smoking or drinking habits

Strengths

- Sample size was large including over 200,000 females and demographic age range consistent with the target range of the hypothesis (30-55 years old)
- Dietary surveys and cancer incidence were assessed from participants prospectively, every 2 years throughout their participation of the studies
- Multivariable statistical models were utilized to assess the strength of association of the variables tested and confounding variables minimized

Weaknesses

- The study relied on survey data with potential recall bias
- This study was completed in females only and most respondents where Caucasian females

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Noninferiority of One HPV Vaccine Dose to Two Doses

Aimée R Kreimer, Carolina Porras, Danping Liu, Allan Hildesheim, Loretto J Carvajal, Rebeca Ocampo, Byron Romero, Mitchell H Gail, Bernal Cortes, Monica S Sierra, Karla Coronado, Joshua Sampson, Carolina Coto, Casey L Dagnall, Daniela Mora, Troy J Kemp, Michael Zuniga, Ligia A Pinto, Gloriana Barrientos, John Schussler, Yenory Estrada, Cristian Montero, Carlos Avila, Dave Ruggieri, Jean T Cyr, Stephen Chanock, Douglas R Lowy, John T Schiller, Rolando Herrero

From the New England Journal of Medicine, December 2025

Abstract

Background: Multidose human papillomavirus (HPV) vaccination is efficacious, yet the vaccine has been underused globally. Emerging data suggest that a single dose may provide protection. Whether a single dose of HPV vaccine would provide similar protection to two doses is uncertain.

Methods: In this trial, we assessed whether one dose of an HPV vaccine was noninferior to two doses. Girls 12 to 16 years of age were randomly assigned, in a 1:1:1:1 ratio, to receive one or two doses of a bivalent HPV vaccine or one or two doses of a nonavalent HPV vaccine. The primary end point was new HPV type 16 or 18 infection occurring from month 12 to month 60 and persisting for at least 6 months. The prespecified noninferiority margin was 1.25 infections per 100 participants. We also assessed vaccine effectiveness by comparing HPV16 or HPV18 infection among the trial participants with that among girls and women enrolled in a nonrandomized survey.

Results: A total of 20,330 participants were enrolled and underwent randomization, and 3005 unvaccinated participants were enrolled in the survey. The noninferiority analysis showed that one vaccine dose was noninferior to two doses in preventing HPV16 or HPV18 infection. The rate difference between one and two doses of the bivalent vaccine was -0.13 infections per 100 participants (95% confidence interval [CI], -0.45 to 0.15; P<0.001 for noninferiority), and the difference between one and two doses of the nonavalent vaccine was 0.21 infections per 100 participants (95% CI, -0.09 to 0.51; P<0.001 for noninferiority). The vaccine effectiveness was at least 97% in each of the four trial groups. No safety concerns were identified.

Conclusions: One dose of either a bivalent or nonavalent HPV vaccine provided protection against HPV16 or HPV18 infection and was not inferior to two doses. (Funded by the National Cancer Institute and others; ESCUDDO ClinicalTrials.gov number, NCT03180034.).

Summary

- This randomized controlled trial (ESCUDDO) enrolled 20,330 girls aged 12-16 years and demonstrated that **one dose of either bivalent or nonavalent HPV vaccine was noninferior to two doses** in preventing persistent HPV16 or HPV18 infection over 60 months, with vaccine effectiveness of at least 97% in all four trial groups. [1]
- The primary endpoint was new HPV16 or HPV18 infection occurring from month 12 to month 60 and persisting for at least 6 months, with a prespecified noninferiority margin of

1.25 infections per 100 participants; both vaccine formulations met this criterion with no safety concerns identified.
- The trial included a nonrandomized survey of 3,005 unvaccinated participants for comparison, providing additional evidence of vaccine effectiveness across all dosing groups.

Strengths
- Large sample size and rigorous design: The trial enrolled over 20,000 participants in a randomized 1:1:1:1 allocation across four groups, providing robust statistical power to assess noninferiority with a clearly defined margin.
- Comparison of two vaccine formulations: The study evaluated both bivalent and nonavalent HPV vaccines, enhancing generalizability and providing evidence applicable to different vaccine products currently in use globally.
- Clinically meaningful endpoint: The primary outcome of persistent HPV infection (lasting at least 6 months) is a validated surrogate marker for cervical precancer and cancer, making the findings clinically relevant for prevention strategies.

Weaknesses
- Limited follow-up duration: The 60-month follow-up period, while substantial, may not capture long-term durability of protection from a single dose, particularly given that HPV-related cancers typically long after initial infection.
- Surrogate endpoint rather than cancer outcomes: The study assessed persistent HPV infection rather than cervical intraepithelial neoplasia or cervical cancer, which are the ultimate clinical outcomes of interest, though this is a practical limitation given the long natural history of HPV-related disease.
- Limited age range: The trial enrolled only girls aged 12-16 years, so the findings may not be generalizable to other populations such as older adolescents, young adults, or males, who are also candidates for HPV vaccination.

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Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline

Douglas E Peterson, Shlomo A Koyfman, Noam Yarom, Charlotte Duch Lynggaard, Nofisat Ismaila, Lone E Forner, Clifton David Fuller, Yvonne M Mowery, Barbara A Murphy, Erin Watson, David H Yang, Ivan Alajbeg, Paolo Bossi, Michael Fritz, Neal D Futran, Daphna Y Gelblum, Edward King, Salvatore Ruggiero, Derek K Smith, Alessandro Villa, Jonn S Wu, Deborah Saunders

Journal of Clinical Oncology, May 2024

Abstract

Purpose: To provide evidence-based recommendations for prevention and management of osteoradionecrosis (ORN) of the jaw secondary to head and neck radiation therapy in patients with cancer.

Methods: The International Society of Oral Oncology-Multinational Association for Supportive Care in Cancer (ISOO-MASCC) and ASCO convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. PubMed, EMBASE, and Cochrane Library databases were searched for randomized controlled trials and observational studies, published between January 1, 2009, and December 1, 2023. The guideline also incorporated systematic reviews conducted by ISOO-MASCC, which included studies published from January 1, 1990, through December 31, 2008.
Results: A total of 1,539 publications were initially identified. There were 487 duplicate publications, resulting in 1,052 studies screened by abstract, 104 screened by full text, and 80 included for systematic review evaluation.
Recommendations: Due to limitations of available evidence, the guideline relied on informal consensus for some recommendations. Recommendations that were deemed evidence-based with strong evidence by the Expert Panel were those pertaining to best practices in prevention of ORN and surgical management. No recommendation was possible for the utilization of leukocyte- and platelet-rich fibrin or photobiomodulation for prevention of ORN. The use of hyperbaric oxygen in prevention and management of ORN remains largely unjustified, with limited evidence to support its practice. Additional information is available at www.asco.org/head-neck-cancer-guidelines.

Summary
ORN affects approximately 3% of patients treated with RT for HNC, and can result in serious morbidity (including pain, dysphagia, trismus, dysarthria, weight loss, poor oral hygiene, and psychosocial burden), and treatment-related costs. The article provides multidisciplinary expert panel guidelines based on available literature (80 articles included for review).

Clinicians should adopt the ClinRad staging system (Watson et al. 2024, *JCO*) with assessment based on intraoral exam and radiologic studies, with a recommendation against bone biopsy.

Radiation treatment planning should make efforts to limit dose to bone, particularly ≤50 Gy, without compromising tumor coverage. Dental assessment prior to treatment addressing at-risk dentition (moderate-severe periodontal disease, periapical disease, partially erupted third molars) should be performed with alternatives to extractions favored if possible. A two-week healing period is appropriate after extractions if it will not delay treatment. Patients should use prescription-strength fluoride. Modifiable risk factors should be abated including active smoking and poorly controlled diabetes. Routine use of prophylactic oral antibiotics, antimicrobial oral rinses, pentoxifylline/tocopherol, HBO is not supported prior to dental interventions.

There is limited evidence supporting non-surgical management of ORN including PENTOCLO protocols. The role of HBO is inconclusive.

Surgical management of ORN should be guided by partial-thickness vs full-thickness involvement of the affected bone. For partial-thickness defects transoral management is appropriate when all necrotic bone can be removed with low risk of fistula or iatrogenic fracture. For more advanced ORN lesions, segmental resection with free flap reconstruction is favored. Free flap success rates exceed 90% in the included literature. The extent of resection should result in vascularized bleeding bone edges. In cases employing prefabricating bone cutting

templates, flexibility is needed if the above is not achieved. Subtotal removal of necrotic bone for palliation of symptoms may be considered in patients who are not candidates for extensive operations.

The guideline identifies several areas of future investigation including prospective RCTs of non-surgical interventions, dental implantation outcomes in irradiated bone, predictive biomarkers for ORN, and cost-effectiveness of prevention strategies.

Strengths

- Rigorous methodology with multidisciplinary panel spanning radiation oncology, head and neck surgery, oral medicine and surgery, medical oncology etc. Broad endorsement by stakeholders (AHNS, ASTRO, AAOMS, AAOM). High rate of concordance (~98%) among respondents.
- Emphasis on evidenced-based treatments revising previous recommendations (e.g. HBO). Transparency regarding informal consensus recommendations versus evidenced-based.
- Emphasis on standardizing definitions of ORN for use in future investigation

Weaknesses

- Only 6 studies included were RCTs limiting strength of available evidence. All surgical intervention recommendations were based on retrospective data.
- Literature limited by heterogeneous definitions/staging of ORN
- Stratification of ORN of maxilla vs mandible would have been useful
- Additional future considerations may include outcomes with emerging adoption of re-irradiation, novel radiotherapy techniques (e.g. proton therapy), and immunotherapy

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Effect of Nicotinamide in Skin Cancer and Actinic Keratoses Chemoprophylaxis, and Adverse Effects Related to Nicotinamide: A Systematic Review and Meta-Analysis

Laurence Mainville, Anne-Sophie Smilga, Paul R Fortin

from Journal of Cutaneous Medicine and Surgery, February 8, 2022

Abstract

Background: Oral nicotinamide is recommended in individuals with a field of cancerization or with ≥1 previous cutaneous squamous cell carcinoma (cSCC). This systematic review and meta-analysis evaluated the effect of nicotinamide in the prevention of skin cancers across a broad population regardless of immunosuppression status.

Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted using Medline, EMBASE, CENTRAL, and Web of Science databases through October 2020. Two independent reviewers screened 4,730 citations. The primary outcome was new skin cancers of all types. Secondary outcomes included basal cell carcinomas (BCCs),

cutaneous squamous cell carcinomas (cSCCs), actinic keratoses (AKs), melanomas, and digestive, cutaneous, and biochemical adverse effects (AEs). Random-effects models were used for all pooled analyses.

Results: Twenty-nine RCTs enrolling 3,039 patients were included. Nicotinamide was associated with a significant reduction in overall skin cancers (rate ratio 0.50; 95% CI 0.29–0.85; moderate-quality evidence), BCCs (rate ratio 0.46; low-quality evidence), and cSCCs (rate ratio 0.48; moderate-quality evidence). No significant effect was observed for AKs or melanoma. Nicotinamide was associated with a significantly increased risk of digestive AEs (RR 1.78; 95% CI 1.30–2.45; very low-quality evidence), with no significant increase in cutaneous or biochemical AEs.

Conclusion: Oral nicotinamide 500 mg twice daily should be considered for chemoprophylaxis of BCC and cSCC in healthy patients or organ transplant recipients with a history of skin cancer (GRADE: weak recommendation; moderate-quality evidence). Further evaluation is needed regarding AK, melanoma, long-term safety, and post-discontinuation effects.

Summary Statements

- Nicotinamide (vitamin B3) may prevent skin cancers via UV-induced DNA repair and reduction of UV-mediated immunosuppression.
- Meta-analysis of 29 RCTs (3,039 patients): 50% reduction in new skin cancers vs. control (rate ratio 0.50; 95% CI 0.29-0.85).
- Significant reductions in BCCs (rate ratio 0.46; 95% CI 0.22-0.95) and cSCCs (rate ratio 0.48; 95% CI 0.26-0.88).
- No significant effect on actinic keratoses or melanoma.
- Increased digestive adverse effects (RR 1.78; 95% CI 1.30-2.45); resolved with dose reduction or discontinuation.
- Supports expanding nicotinamide indications to include BCC chemoprophylaxis alongside established cSCC prevention.
- Low cost and over-the-counter availability support use in at-risk patients, including organ transplant recipients.

Strengths

- Large, Broad Sample**:** 29 RCTs and 3,039 participants across diverse settings and indications enhance statistical power and generalizability.
- Rigorous Methodology**:** Followed PRISMA and Cochrane guidelines with duplicate review, RoB2 risk of bias assessment, and GRADE evidence grading.
- Comprehensive Outcomes**:** Evaluated BCCs, cSCCs, AKs, melanoma, and three adverse effect categories, providing a thorough efficacy and safety profile.
- A Priori Subgroup Analyses**:** Pre-specified analyses by dose, route, duration, and immunosuppression status allowed structured exploration of heterogeneity.
- Broad Eligibility Criteria**:** Including trials regardless of primary indication maximized data capture for both skin cancer outcomes and adverse effects.

Weaknesses

- Few Skin Cancer-Focused Trials**:** Only 5 of 29 trials were designed to evaluate skin cancer endpoints; most data were incidentally reported and limited to tertiary prevention.
- Substantial Heterogeneity**:** High I2 values (up to 67%) across outcomes were not fully explained by subgroup analyses, limiting confidence in pooled estimates.
- Narrow Adverse Effect Categorization**:** AEs were grouped into only three categories; retaining only the highest-count AE per study may overestimate effect sizes and obscure the full safety profile.
- Tertiary Prevention Only**:** All skin cancer trials enrolled patients with prior skin cancers; findings cannot be generalized to primary or secondary prevention populations.
- Inclusion of Topical Nicotinamide**:** Two trials used topical formulations with different pharmacokinetics from oral use; topical nicotinamide was not effective in subgroup analyses and may confound overall estimates.

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