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Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States

Anil K Chaturvedi, Barry I Graubard, Tatevik Broutian, Robert K L Pickard, Zhen-Yue Tong, Weihong Xiao, Lisa Kahle, Maura L Gillison
From Journal of Clinical Oncology, 2018

Abstract:
Purpose: The incidence of human papilloma virus (HPV)-positive oropharyngeal cancers has risen rapidly in recent decades among men in the United States. We investigated the US population-level effect of prophylactic HPV vaccination on the burden of oral HPV infection, the principal cause of HPV-positive oropharyngeal cancers.

Methods: We conducted a cross-sectional study of men and women 18 to 33 years of age (N = 2,627) within the National Health and Nutrition Examination Survey 2011 to 2014, a representative sample of the US population. Oral HPV infection with vaccine types 16, 18, 6, or 11 was compared by HPV vaccination status, as measured by self-reported receipt of at least one dose of the HPV vaccine. Analyses accounted for the complex sampling design and were adjusted for age, sex, and race. Statistical significance was assessed using a quasi-score test.

Results: Between 2011 and 2014, 18.3% of the US population 18 to 33 years of age reported receipt of at least one dose of the HPV vaccine before the age of 26 years (29.2% in women and 6.9% in men; P < .001). The prevalence of oral HPV16/18/6/11 infections was significantly reduced in vaccinated versus unvaccinated individuals (0.11% v 1.61%; Padj = .008), corresponding to an estimated 88.2% (95% CI, 5.7% to 98.5%) reduction in prevalence after model adjustment for age, sex, and race. Notably, the prevalence of oral HPV16/18/6/11 infections was significantly reduced in vaccinated versus unvaccinated men (0.0% v 2.13%; Padj = .007). Accounting for vaccine uptake, the population-level effect of HPV

vaccination on the burden of oral HPV16/18/6/11 infections was 17.0% overall, 25.0% in women, and 6.9% in men.

Conclusion: HPV vaccination was associated with reduction in vaccine-type oral HPV prevalence among young US adults. However, because of low vaccine uptake, the population-level effect was modest overall and particularly low in men.

Summary Statements:

- This study provides some of the first population-level evidence that HPV vaccination reduces the prevalence of vaccine-type oral HPV infections, the causal precursor to HPV-related oropharyngeal cancers.
- Unlike cervical cancer, where randomized trials established efficacy by showing prevention of precancerous lesions, the oropharynx lacks a detectable precancerous phase; this study circumvents that limitation by using oral HPV prevalence as a surrogate.
- Among vaccinated individuals aged 18–33, the prevalence of oral HPV16/18/6/11 was significantly lower compared to unvaccinated peers, suggesting high efficacy of the vaccine in the oropharynx.

Strengths:

- Utilizes a large, nationally representative dataset (NHANES), enhancing generalizability to the U.S. population.
- Provides an important surrogate endpoint for vaccine efficacy in the oropharynx, where visualizable precancerous lesions are not detectable.
- Demonstrates a strong effect size—an estimated 88% reduction in vaccine-type oral HPV prevalence among vaccinated individuals—despite low uptake in men.

Weaknesses:

- Cross-sectional design precludes causal inference and is subject to confounding despite statistical adjustments.
- Reliance on self-reported vaccination status introduces potential misclassification bias.
- The analysis focused only on vaccine-covered HPV types and did not evaluate possible type replacement or broader oncogenic HPV coverage.

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Peri-operative tobacco cessation interventions: a systematic review and meta-analysis

S Harrogate, J Barnes, K Thomas, A Isted, G Kunst, S Gupta, S Rudd, T Banerjee, R Hinchliffe , R Mouton
from Anaesthesia, Nov 2023

Abstract
Tobacco smoking is associated with a substantially increased risk of postoperative complications. The peri-operative period offers a unique opportunity to support patients to stop tobacco smoking, avoid complications and improve long-term health. This systematic review provides an up-to-date summary of the evidence for tobacco cessation interventions in surgical patients. We conducted a systematic search of randomized controlled trials of tobacco cessation interventions in the peri-operative period. Quantitative synthesis of the abstinence outcomes data was by random-effects meta-analysis. The primary outcome of the meta-analysis was abstinence at the time of surgery, and the secondary outcome was abstinence at 12 months. Thirty-eight studies are included in the review (7310 randomized participants) and 26 studies are

included in the meta-analysis (5969 randomized participants). Studies were pooled for subgroup analysis in two ways: by the timing of intervention delivery within the peri-operative period and by the intensity of the intervention protocol. We judged the quality of evidence as moderate, reflecting the degree of heterogeneity and the high risk of bias. Overall, peri-operative tobacco cessation interventions increased successful abstinence both at the time of surgery, risk ratio (95%CI) 1.48 (1.20-1.83), number needed to treat 7; and 12 months after surgery, risk ratio (95%CI) 1.62 (1.29-2.03), number needed to treat 9. More work is needed to inform the design and optimal delivery of interventions that are acceptable to patients and that can be incorporated into contemporary elective and urgent surgical pathways. Future trials should use standardized outcome measures.

Summary statements

- Systematic review (n=38) and meta-analysis (n=26) including randomized controlled trials of patients undergoing surgery who received smoking cessation interventions, assessing abstinence from tobacco at the time of surgery and at 12 months post-surgery.
- Interventions were effective in promoting abstinence from tobacco at the time of surgery (RR 1.48, CI 1.20-1.83, NNT=7) and at 12 months (RR 1.62, CI 1.29-2.03, NNT=9).
- Intensive smoking cessation interventions were associated with greater likelihood of abstinence at 12 months (RR 2.35, CI 1.48-3.72) and possibly at the time of surgery (RR 4.35, CI 0.90-21.14), although the latter result was not statistically significant.

Strengths

- Nearly 6000 patients enrolled in randomized controlled trials were included for study, providing both high level of evidence and statistical power.
- Inclusion of 12-month data as a secondary outcome provides insight into durability of interventions in the perioperative period.
- Robust methodology for article selection and appropriate statistical measures.

Weaknesses

- Total duration of follow-up was limited, as some evidence suggests relapse rates of 49% and 20% at two and four years respectively, which may be unaccounted for in this study.
- The study pertains to surgical patients undergoing a variety of procedures, not limited to head and neck cancer operations. In fact, none of the included studies were limited to head and neck oncologic surgery. As head and neck cancer is often a tobacco-related illness, rates of abstinence may differ from those of the general surgical population.
- I^2 was 77% for the primary outcome assessed, indicating high levels of heterogeneity.

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Single-cell and spatial dissection of precancerous lesions underlying the initiation process of oral squamous cell carcinoma

Sun L, Kang X, Wang C, Wang R, Yang G, Jiang W, Wu Q, Wang Y, Wu Y, Gao J, Chen L, Zhang J, Tian Z, Zhu G, Sun S.
from Cell Discovery, March 2023

Abstract:
Precancerous lesions of the oral mucosa, especially those accompanied by moderate to severe dysplasia, contribute to the initiation of oral squamous cell carcinoma (OSCC). However, the cellular compositions and spatial organization of the precancerous stage and how these factors promote human OSCC initiation remain unclear. Here, we built a single-cell transcriptome atlas and a spatial transcriptome map after

obtaining data from pairwise human oral mucosal biopsies of 9 individuals consisting of very early-stage OSCC, adjacent precancerous lesions with moderate to severe dysplasia, as well as a matched normal region. An altered epithelial gene-expression profile was identified which favored OSCC initiation. This observation was coupled with distinct fibroblast, monocytic, and regulatory T-cell subclusters involved in reshaping the microenvironment. In particular, a unique immune-inhibitory monocyte subtype and spatial-switching regulation of VEGF signaling were observed surrounding precancerous lesions, concertedly strengthening activities in promoting cancer initiation. Collectively, our work elucidated the cellular landscapes and roles of precancerous lesions underlying OSCC initiation, which is essential for understanding the entire OSCC initiation process and helps inform therapeutic strategies for cancer intervention.

Summary statements

- In this study, dysplasia progression correlated to an increased transcription of eight genes that are known to upregulate production of epithelial cells, cancer associated fibroblasts(CAF) and an immune inhibitory monocyte subpopulation
- These "initiation-associated genes" were confirmed by spatial transcriptomics (ST) which mapped the locations of the genetic changes in the tissue; in addition ST showed increased VEGF, TGFB1 and immune inhibitory signals in severe dysplasia as compared to mild dysplasia, suggesting specific ways in which cell: cell communication modifies the tumor microenvironment (TME) during oral oncogenesis
- This investigation provides a framework of epithelial: mesenchymal interaction in oral cancer initiation whereby malignant epithelial changes occur in the setting of and likely at the direction of TME cell proliferation and an immune tolerant TME that promotes oral cancer initiation. The authors support surgical resection of moderate to severe dysplasia to remove this "immune inhibitory and proliferative ecosystem". In addition, they discuss potential for immune based therapies for this disease such as anti-PD1 and anti-TGFB-1 monoclonal antibodies

Strengths

- This study, and related work represent an important paradigm shift in oral cancer prevention research away from the search for broadly applicable, static, predetermined biomarkers toward the investigation of molecular changes that occur in transforming tissue
- The pairing of adjacent normal, dysplastic and early invasive specimens from the same person avoids genetic variability between individuals and is a great strength
- The combination of single cell RNA seq with spatial transcriptomics allows identification, confirmation and location of active genes in oral epithelium during the process of cancer initiation; the combined testing validates these findings greater than either test alone

Weaknesses

- This study examined 10 samples from 9 patients, expansion of this concept into larger clinical studies will help to validate this method for use as a biomarker for oral cancer initiation
- Regarding the suggestion of medical intervention, further investigation is needed to determine whether identification of initiation associated genes consistently identifies targetable mutations/pathways
- Immune based therapies such as anti-PD-1 and anti TGFB-1 have significant adverse effects and it will be a challenge to justify administration of these agents for prevention of oral cancer outside of the most high risk subset such as PVL; clinical trials are needed.

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Cannabis Use and Head and Neck Cancer

Tyler J Gallagher,, Ryan S Chung, Matthew E Lin, Ian Kim, Niels C Kokot
from **JAMA-OTO, December 2024**, *DATE*

Importance: Cannabis is the most commonly used illicit substance worldwide. Whether cannabis use is associated with head and neck cancer (HNC) is unclear.

Objective: To assess the clinical association between cannabis use and HNC.

Design, setting, and participants: This large multicenter cohort study used clinical records from a database that included 20 years of data (through April 2024) from 64 health care organizations. A database was searched for medical records for US adults with and without cannabis-related disorder who had recorded outpatient hospital clinic visits and no prior history of HNC. Propensity score matching was performed for demographic characteristics, alcohol-related disorders, and tobacco use. Subsequently, relative risks (RRs) were calculated to explore risk of HNC, including HNC subsites. This analysis was repeated among those younger than 60 years and 60 years or older.

Exposure: Cannabis-related disorder.

Main outcomes and measures: Diagnosis of HNC and any HNC subsite.

Results: The cannabis-related disorder cohort included 116 076 individuals (51 646 women [44.5%]) with a mean (SD) age of 46.4 (16.8) years. The non-cannabis-related disorder cohort included 3 985 286 individuals (2 173 684 women [54.5%]) with a mean (SD) age of 60.8 (20.6) years. The rate of new HNC diagnosis in all sites was higher in the cannabis-related disorder cohort. After matching (n = 115 865 per group), patients with cannabis-related disorder had a higher risk of any HNC (RR, 3.49; 95% CI, 2.78-4.39) than those without HNC. A site-specific analysis yielded that those with cannabis-related disorder had a higher risk of oral (RR, 2.51; 95% CI, 1.81-3.47), oropharyngeal (RR, 4.90; 95% CI, 2.99-8.02), and laryngeal (RR, 8.39; 95% CI, 4.72-14.90) cancer. Results were consistent when stratifying by older and younger age group.

Conclusions and relevance: This cohort study highlights an association between cannabis-related disorder and the development of HNC in adult patients. Given the limitations of the database, future research should examine the mechanism of this association and analyze dose response with strong controls to further support evidence of cannabis use as a risk factor for HNCs.

Summary statements

- Large, multi-center cohort study comparing patients with and without cannabis-related disorder to assess rates of head and neck cancers
- Cannabis-related disorders are defined by the excessive use of cannabis with associated psychosocial symptoms, such as impaired social and/or occupational functioning
- Patients with cannabis-related disorder had a higher risk of any head and neck cancer (RR, 3.49; 95% CI, 2.78-4.39)
- Patients with cannabis-related disorder had an elevated risk of oral, oropharyngeal and laryngeal cancer

Strengths

- Large study of 116 076 individuals including 20 years of data from 64 health care organizations

- Focus on heavy cannabis users (diagnosed with cannabis-related disorder) could improve the ability to detect an association, and use of physician diagnoses through electronic medical records may reduce the likelihood of recall and selection biases
- Controlled for alcohol use disorder and tobacco use

Weaknesses

- Lack of information on dosage and frequency of cannabis use
- Possibility for bias, as cannabis use disorder may be associated with alcohol and tobacco use (while authors controlled for alcohol use disorder and tobacco use, differences in dosage between groups may remain)

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Host-microbe computational proteomic landscape in oral cancer revealed key functional and metabolic pathways between Fusobacterium nucleatum and cancer progression

Camila Paz Muñoz-Grez, Mabel Angélica Vidal, Tamara Beatriz Rojas, Luciano Esteban Ferrada, Felipe Andrés Zuñiga, Agustin Andrés Vera, Sergio Andrés Sanhueza, Romina Andrea Quiroga, Camilo Daniel Cabrera, Barbara Evelyn Antilef, Ricardo Andrés Cartes, Milovan Paolo Acevedo, Marco Andrés Fraga, Pedro Felipe Alarcón-Zapata, Mauricio Alejandro Hernández, Alexis Marcelo Salas-Burgos, Francisco Tapia-Belmonte, Milly Loreto Yáñez, Erick Marcelo Riquelme, Wilfredo Alejandro González, Cesar Andrés Rivera, Angel Alejandro Oñate, Liliana Ivonne Lamperti, Estefanía Nova-Lamperti

from International Journal of Oral Science, January 2025

Objective: To investigate the role of Fusobacterium nucleatum in oral squamous cell carcinoma (OSCC) by evaluating the host-pathogen interactions through computational proteomics and functional assays, and to delineate the bacterial metabolic pathways contributing to tumor progression.

Methods: Secretome samples from OSCC patients and healthy controls were analyzed using mass spectrometry. Bacterial peptides were identified using PEAKS X+ software, and label-free quantification was conducted. Ingenuity Pathway Analysis (IPA) and Gene Ontology (GO) enrichment were used to identify host-pathogen pathways. Functional assays including Western blot, confocal microscopy, flow cytometry, and tumorsphere models were performed on HSC3 OSCC cells to assess the impact of F. nucleatum on L-glutamate transport, epithelial-mesenchymal transition (EMT), immune checkpoint expression, and tumor cell behavior.

Results: F. nucleatum was identified as the predominant bacterium in OSCC samples, contributing to 70% of bacterial peptides detected. Proteomic analysis revealed upregulation of host pathways related to LPS response, cell migration, and amino acid metabolism, and downregulation of complement cascade proteins. F. nucleatum activated the System xc- (SLC7A11/SLC3A2), promoting L-glutamate efflux which supports bacterial energy metabolism via the glutamate degradation pathway. In vitro, F. nucleatum induced EMT by upregulating MMP-9 and downregulating E-cadherin, promoted Galectin-9 expression, enhanced tumorsphere growth, and increased cell migration and detachment. Butyrate, a metabolite of glutamate degradation, stimulated tumor growth in a dose-dependent manner.

Conclusion: Fusobacterium nucleatum promotes a pro-tumorigenic microenvironment in OSCC by manipulating glutamate metabolism, inducing EMT, modulating immune checkpoints, and impairing

innate immune responses through complement suppression. These findings emphasize the importance of considering oral dysbiosis in OSCC pathogenesis and highlight potential targets for microbiome-based therapeutic strategies.

Summary Statement
A computational and functional proteomic investigation demonstrates that F. nucleatum plays a key role in OSCC progression through metabolic and immunomodulatory mechanisms.

Strengths
- Comprehensive integration of computational proteomics and functional assays
- Identification of specific metabolic pathways (e.g., L-glutamate degradation) enabling bacterial colonization
- Robust in vitro models (tumorspheres, confocal microscopy, transwell assays) to validate hypotheses
- Novel link between System xc- activity and bacterial-induced glutamate efflux

Weaknesses
- Lack of in vivo validation of mechanistic findings
- Study does not explore inter-bacterial interactions or microbiome complexity
- F. nucleatum was not quantified from patient periodontal plaque samples
- Observations are limited to one OSCC cell line (HSC3)