Stepped Behavioral and Biological Screening for Oral Oncogenic HPV DNA in Middle-aged and Elderly Adults: A Feasibility Study

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ABSTRACT

Novel preventive interventions are needed to address the rising incidence of human papillomavirus (HPV)-mediated oropharyngeal cancer (HPV+ OPC). This pilot study evaluated the feasibility of a stepped, behavioral and biological screening program for oral oncogenic HPV infection, an intermediate HPV+ OPC outcome.

This was a cross-sectional, feasibility study. Eligible 45–74 years old adults identified from three clinical research registries were administered a behavioral risk survey (step 1). Participant tobacco use and sexual behavior history were translated into a quantifiable risk of oral oncogenic HPV DNA, according to prior National Health and Nutrition Examination Survey analyses. Females with >2% risk and males with >7% risk were offered biological screening for oral oncogenic HPV DNA (step 2) via an oral rinse and gargle specimen.

A total of 292 individuals were contacted, but only 144 (49%) were reached. Among these, 56 individuals (19%) were uninterested and 18 (13%) were ineligible. Seventy individuals began the survey and 66 completed it (step 1), among whom 46 were classified as low-risk. Among the remaining 20 participants classified as high-risk for an oral oncogenic HPV infection, 5% were current smokers and the median participant had performed oral sex on 10 unique partners. During step 2 (biological screening), 45% (9/20) completed testing, all of whom tested negative for oral oncogenic HPV DNA.

In this pilot of a stepped, oral oncogenic HPV screening program, enrollment and study completion were suboptimal. These barriers to screening should be characterized and addressed before reevaluating the feasibility of this program.

Prevention Relevance: Novel preventive interventions are needed to address the rising incidence of HPV+ OPC. In this feasibility study, we characterized barriers to a two-step, behavioral and biological screening program for oral oncogenic HPV infection, an intermediate outcome for HPV+ OPC.

Introduction

Current strategies to prevent and control human papillomavirus (HPV)-mediated oropharyngeal cancer (HPV+ OPC) are inadequate. Approximately 13,500 individuals are diagnosed with HPV+ OPC annually in the United States (1). Despite this, only 59% of adolescents are up to date with HPV vaccination (2). Decades will elapse before at-risk middle-aged and elderly cohorts will be protected by the vaccine (3). In the next 10 years alone, the incidence of oropharyngeal cancer is expected to rise by almost 50% (4).

Novel secondary preventive interventions for HPV+ OPC are needed (1). In 2014, the U.S. Preventive Services Task Force determined that evaluation of "the health effect of screening persons who are (oral) HPV-16 positive," the most common oral oncogenic HPV genotype, may be warranted (5). To our knowledge, two ongoing trials seek to address this gap in understanding. The Throat and other HPV-Related cancers IN men: Identifying Them earlY trial aims to screen 1,500 middle-aged men using oral and blood-based biomarkers (6). Participants deemed biologically high-risk for an HPV-mediated cancer undergo longitudinal clinical evaluations. However, skeptics of this age- and sex-based screening approach cite the relatively low incidence of HPV+ OPC in the target screening group and thus, a high number needed to screen to detect a case (7).

To identify an even higher-risk target screening group, another trial also applies sexual behavior as an eligibility criterion. Prior investigators have established a significant correlation between higher lifetime number of oral sex partners or vaginal sex partners and risk of HPV+ OPC (3). In the Men and Women Offering Understanding of Throat HPV (MOUTH) trial, men

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Cancer Prev Res 2023;16:127–32

doi: 10.1158/1940-6207.CAPR-22-0371

without other risk factors must have had at least two lifetime oral sex partners to be eligible for biological screening (8). The MOUTH trial identifies participants with oral oncogenic HPV, an intermediate outcome for HPV+ OPC, and follows them for oral oncogenic HPV persistence (8).

The concept of using demographic, behavioral, and biological inputs in an HPV+ OPC screening program is supported by the research literature. Tota and colleagues developed a promising oropharyngeal cancer risk prediction model incorporating lifetime number of sexual partners, oral oncogenic HPV status, and other patient-level factors (9). Individuals in the highest risk decile comprised 99% of incident HPV+ OPCs (9). In this model, individuals with an oral oncogenic HPV infection exhibited 38–60 times increased odds of developing HPV+ OPC in the next year (depending on sex and smoking status) compared with individuals without an oral oncogenic HPV infection.

Despite its promise, the feasibility of this approach has not been comprehensively assessed. In this study, we aimed to evaluate the feasibility of implementing a stepped, behavioral and biological screening approach for oral oncogenic HPV infections in middle-aged and elderly adults. An improved understanding of the screening process for this key intermediate outcome may inform future HPV+ OPC screening trials.

Materials and Methods

Study design and ethics

We performed a cross-sectional feasibility study. We obtained written informed consent from patients and all enrolled patients were administered the intervention. Neither randomization nor blinding was applied in the study design. The study was conducted in accordance with the Belmont Report and was approved by the University of Texas Southwestern (UTSW) Medical Center Institutional Review Board (STU 2018-0330).

Population, inclusion, and exclusion criteria

As described in **Fig. 1**, we screened 45–74 years old adults within three clinical research registries: Research Match, the UTSW Patient Volunteer Registry, and the UTSW Community Registry. Eligibility criteria included the absence of a prior history of HPV-associated cancer, head and neck radiation, organ transplant, and cancer therapy or blood transfusion in the past 6 months. Participants also had to be willing to complete a questionnaire regarding their sexual history and provide an oral rinse sample for biological testing.

Behavioral screening (step 1)

The first step of the screening approach involved the administration of a behavioral risk survey assessing tobacco use and sexual history by telephone. Each individual received a $10 gift card. The survey was adapted from the D'Souza and colleagues risk-stratified prediction model for an oncogenic oral HPV infection (10). This model was derived from 2009–2014 National Health and Nutrition Examination Survey data describing the prevalence of oral oncogenic HPV infections in 13,089 people ages 20–69 (10).

Individuals with greater than "low-risk" for an oral oncogenic HPV infection (females: >2%; males: >7%) were deemed eligible for the second step—biological screening. Specifically, females eligible for biological screening exhibited the following behaviors: current smoker (2.1% prevalence of an oral oncogenic infection), ever performed oral sex on a woman (3.5%), or performed oral sex on ≥5 and ≥10 partners in her lifetime (2.5%, 3.0%, respectively; ref. 10). Males eligible for biological screening exhibited "medium" (7.3%) or "elevated" risk (14.9%) of an oral oncogenic HPV infection. Medium-risk males were current smokers and performed oral sex on two to four partners in their lifetimes or nonsmokers and performed oral sex on ≥ 5 partners in their lifetimes (10). Elevated risk males were current smokers and performed oral sex on ≥ 5 partners in their lifetimes (10).

Biological screening (step 2)

The second step of screening involved the biological analysis of an oral rinse and gargle specimen. Fasting participants rinsed and gargled 15 mL of sterile saline for 15 seconds and then expectorated the specimen. Specimens were centrifuged at 800 × *g*/2,000 rpm at 4°C for 15 minutes, the supernatant was decanted, the pellet resuspended in 1 mL of prechilled 1X PBS and 0.25 mL of sample added to 1 mL of Thinprep. Samples were analyzed for oncogenic HPV DNA (14 high-risk types) via PCR and nucleic acid hybridization using the Roche Cobas HPV assay. Four findings were reported: detection of HPV16 DNA, HPV18 DNA, other high-risk HPV DNA (alone or in combination), or no high-risk HPV DNA. Each individual received an additional $10 gift card to participate in the second step.

Power analyses and study discontinuation

Notably, the protocol was originally designed to identify and enroll 10 oral oncogenic HPV DNA-positive individuals in a longitudinal study involving procurement of serial specimens to evaluate for oral HPV DNA, oropharyngeal HPV DNA and cytology, serum HPV E-antibodies, and circulating HPV DNA. According to our power analyses, we estimated that screening 225 individuals would yield 8 males and 2 females with oral oncogenic HPV infections. However, the longitudinal study was discontinued at the onset of the COVID-19 pandemic due to institutional protocols prohibiting in-person contact for noninterventional trials. As the pandemic and risk to participants and study staff persisted, we decided to permanently close the study after receiving a subsequent grant to fund a larger-scale, multi-institutional HPV+ OPC screening trial.

Statistical methods

RStudio 1.2.5033 was used for descriptive statistical analyses including Pearson χ^2, Fisher exact, and Wilcoxon–Mann Whitney tests. The "openxlsx" package (v4.1.2; CRAN, RRID: SCR_019185) was used to import data into R DataFrame. Statistical significance was defined as $P < 0.05$. All P values were reported as two sided.

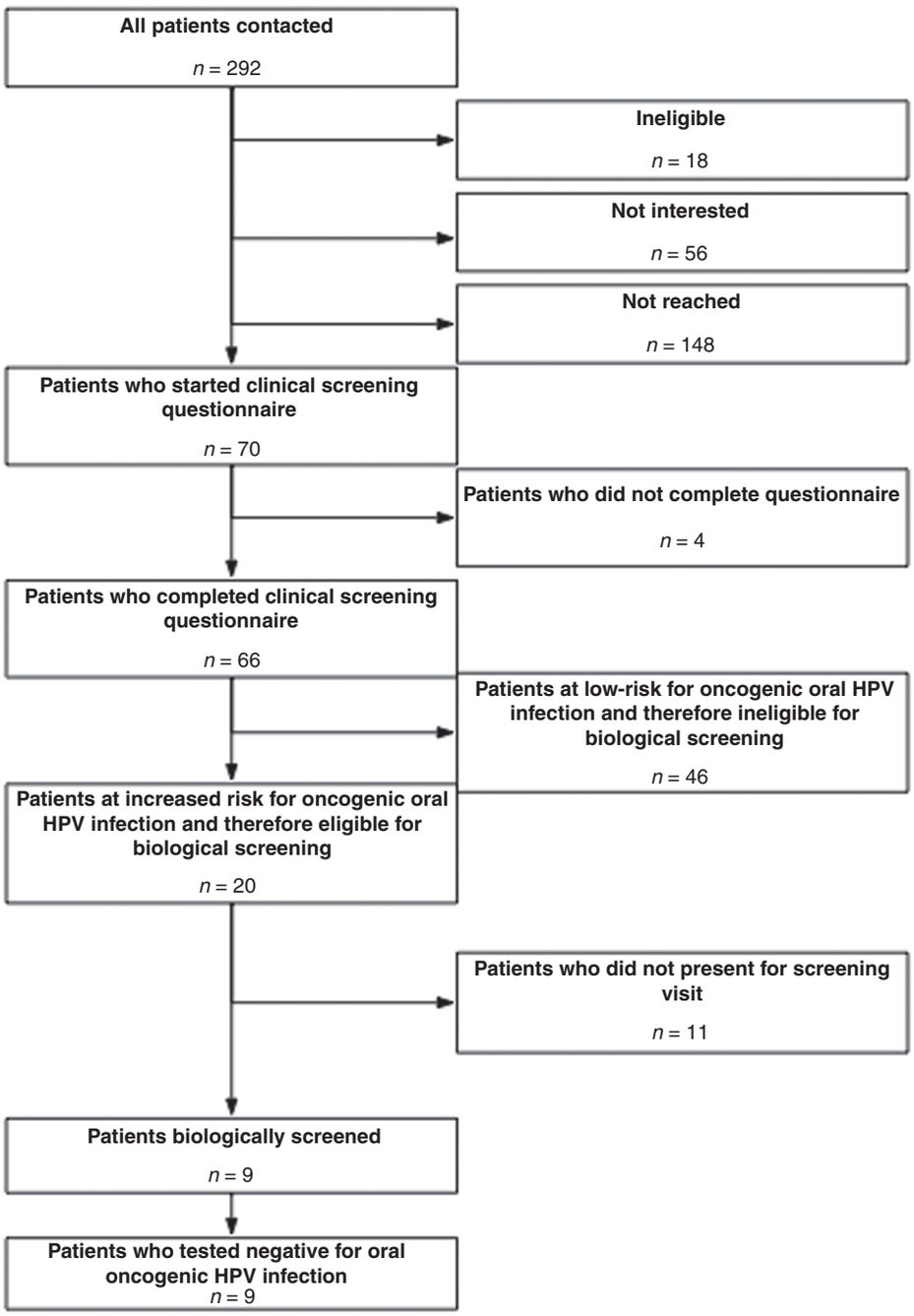

Figure 1.
Among the 292 individuals contacted, 144 were reached, 70 consented to participate in the study, and 66 completed the clinical questionnaire. Among these 66 participants, 20 were identified as high-risk for an oral oncogenic HPV infection and were therefore eligible for biological testing. Nine participants underwent testing, all of whom were negative for infection.

Data availability

Data were generated by the authors and are available upon request.

Results

Progression through screening

Screening was limited by sequential missing data at each step (**Fig. 1**). In step 1 (behavioral risk assessment), we attempted to enroll 292 registry members. After making up to six telephone calls per individual, 148 (51%) were not reached. Among the 144 individuals who were reached, 18 (13%) were ineligible and 56 (39%) declined to participate. Among the 70 individuals who began the behavioral risk assessment, four (6%) did not complete the survey.

Among the 66 individuals who completed step 1, 46 were classified as low-risk, and the remaining 20 were classified as high-risk and proceeded to step 2. During the biological screening phase, 55% ($n = 11/20$) of the participants did not undergo biological testing.

Table 1. Cohort characteristics stratified by clinical risk for oncogenic oral HPV infection and biological screening status.

Patients, *n* (%)							
	Completed (*n* = 66)	**Clinical low-risk (*n* = 46)**	**Clinical high-risk (*n* = 20)**	***P*[a]**	**High-risk, biologically screened (*n* = 9)**	**High-risk, not biologically screened (*n* = 11)**	***P*[a]**
Sex							
M	21 (32)	9 (20)	12 (60)	0.001	8 (89)	4 (36)	0.028
F	45 (68)	37 (80)	8 (40)		1 (11)	7 (64)	
Age							
45–54	17 (26)	9 (20)	8 (40)	0.175	3 (33)	5 (45)	0.603
55–64	27 (41)	19 (41)	8 (40)		3 (33)	5 (45)	
65–74	22 (33)	18 (39)	4 (20)		3 (33)	1 (10)	
Race/ethnicity							
Non-Hispanic White	18 (27)	10 (22)	8 (40)	0.166	6 (67)	2 (18)	0.040
Non-Hispanic Black	39 (59)	30 (65)	9 (45)		2 (22)	7 (64)	
Hispanic	8 (12)	6 (13)	2 (10)		0 (0)	2 (18)	
Other	1 (2)	0 (0)	1 (5)		1 (11)	0 (0)	
Smoking							
Never	41 (62)	31 (68)	10 (50)	0.393	3 (33)	7 (64)	0.265
Former	22 (33)	13 (28)	9 (45)		5 (56)	4 (36)	
Current	3 (5)	2 (4)	1 (5)		1 (11)	0 (0)	
Insurance							
Yes	60 (91)	41 (89)	19 (95)	0.659	8 (89)	11 (100)	0.450
No	6 (9)	5 (11)	1 (5)		1 (11)	0 (0)	
Lifetime number of sexual partners, any type (oral, vaginal, or anal)							
Median	5.5 (3.0–10.0)	5 (2.0–7.0)	20 (10.0–24.8)	<0.001	20 (20.0–23.0)	11 (8.5–25.0)	0.303
Lifetime number of oral sexual partners (giving oral sex only)							
Median	3 (2.0–9.0)	2 (1.0–3.0)	10 (5.0–16.3)	<0.001	13 (5.0–20.0)	11 (5.0–10.0)	0.424
Same-sex partners							
Yes	5 (8)	1 (2)	4 (20)	0.030	3 (33)	1 (9)	0.285
No	61 (92)	45 (98)	16 (80)		6 (67)	10 (91)	

[a]Categorical variable data were compared using χ^2 test of independence or Fisher exact test of independence (if $n < 5$ in any cell). All continuous variable data were not normally distributed and hence comparisons were made using Wilcoxon–Mann–Whitney test.

Characteristics of participants who began step 1

Participants completing behavioral screening ($n = 66$) were diverse: 68% were women, 73% were of minority race/ethnicity, and 8% reported a previous same-sex partner (**Table 1**). Among the 20 high-risk participants, 40% were female, 5% were current smokers, and 20% had a prior same-sex partner. The median behaviorally high-risk participant reported 20 lifetime sex partners and had performed oral sex on 10 unique partners.

Four individuals (1 man and 3 women) started but did not complete behavioral screening: two discontinued screening after the mention of oral sex, one declined to provide their ethnicity, and one declined to proceed due to the possible need for oral rinse testing. Similarly, there were no sociodemographic or behavioral differences between eligible participants who completed biological screening and those who did not.

Characteristics of participants eligible for step 2

Nine participants completed biological screening and all nine tested negative for oral oncogenic HPV DNA. Apart from sex ($P = 0.028$) and race/ethnicity ($P = 0.040$), no sociodemographic or behavioral factors predicted whether participants would complete biological screening. Relative to males and non-Hispanic White individuals, females, non-Hispanic Black, and Hispanic individuals were less likely to complete biological screening.

Discussion

Our pilot data demonstrate that a stepped behavioral and biological screening program for oral oncogenic HPV infection can be conducted in a diverse population. However, the loss of potential participants throughout the screening process, especially during the behavioral screening step, requires further evaluation.

The feasibility of triaging individuals for guideline-recommended cancer screening based on sexual behavior history has not yet been established. Current cancer screening interventions require surveying patients about less "charged" topics such as age, sex, and smoking status (11–14). Our pilot study demonstrated that a portion of eligible individuals were willing to answer sensitive questions about sexual behavior via telephone followed by in-person procurement of an oral rinse and gargle sample.

To our knowledge, the MOUTH trial is the only other ongoing study evaluating a stepped screening approach for

oncogenic oral HPV infection (8). MOUTH enrolls men 35–69 years of age with two or more lifetime oral sex partners, women with a history of cervical dysplasia and their partners, and partners of patients with HPV+ oropharyngeal squamous cell carcinoma (OPSCC; ref. 8). While this study has behaviorally and biologically screened 261 individuals, MOUTH investigators did not describe upstream screening participation prior to identification of a behaviorally screened cohort.

Our pilot study addresses this knowledge gap. Although feasible, missing data in approximately 50% of potential participants throughout the behavioral screening phase critically constrain the stepped screening program. Most importantly, 39% of individuals reached by telephone declined to participate in the program. Capturing the rationale for nonparticipation among these individuals was not within the scope of this study; however, it will be necessary to advance stepped HPV+ OPC screening programs.

Ultimately, the use of our stepped screening program in the service of screening for HPV+ OPC, consistent with the approach proposed by Tota and colleagues (9), warrants restrained enthusiasm. Despite narrowing the demographically eligible population by 2/3, there were no oral oncogenic HPV infections in our behaviorally screened population. While this finding is of little significance in our feasibility study (because only nine participants were tested), it aligns with MOUTH results wherein only 3% of biologically screened participants exhibited an oral oncogenic HPV infection (8).

The mediocre performance characteristics of oral oncogenic HPV DNA as a biomarker for HPV+ OPC further limit this approach. In a recent meta-analysis, oral HPV16 DNA was only 72% sensitive and 92% specific for HPV+ head and neck squamous cell carcinoma (15). According to a nested case–control analysis of a cancer epidemiology cohort, oral HPV16 DNA infection conferred a high, yet insufficiently remarkable, 22 times increased risk of OPSCC (16). These findings are not unexpected. While over 10 million individuals in the United States currently have an oral oncogenic HPV infection (17), a substantially lower 13,500 people will develop HPV+ OPC annually. High, rapid clearance rates are the most likely explanation for this phenomenon: the median individual will clear their incident oral oncogenic HPV infection in 6.3 months (18). In light of this, investigators continuing to use oral oncogenic HPV testing in screening should explore (i) more convenient, mailed oral rinse and gargle specimen collection protocols or (ii) pairing this biomarker with more valid, blood-based HPV E-antibodies or circulating HPV DNA (6, 19).

Limitations and future directions

In their landmark report, "Fulfilling the Potential of Cancer Prevention and Early Detection," the National Research Council of the National Academies of Science, Engineering and Medicine, along with the Institute of Medicine, applied a four-part model of behavioral change to describe barriers to cancer screening (20). Here, we apply this model and discuss possible oral oncogenic HPV or HPV+ OPC screening barriers related to participant knowledge, attitudes, ability, and reinforcement.

First, layperson knowledge of HPV+ OPC is deficient. In a population-based survey of 1,200 individuals in the United Kingdom, only 37% had ever heard of HPV and only 14% "recognized HPV as a risk factor" for oropharyngeal cancer (21). In our pilot study, we introduced the topic of HPV and HPV+ OPC to provide a rationale for the study. However, we did not evaluate the study participants' knowledge of HPV or HPV+ OPC, which we now recognize as an unfortunate omission.

Second, eligible individual attitudes toward stepped oral oncogenic HPV or HPV+ OPC screening may impede participation. This may include a preference for privacy or embarrassment regarding sexual history. Notably, sexual behavior screening for MOUTH study enrollment was available online—unlike our interviewer-based approach. Experts have advocated for a computer-assisted approach to sexual behavior surveys over an interviewer-administered approach (22). This finding should be considered in the design of future feasibility studies. Other attitudes impeding participation may have included fear of drawing blood and the inconvenience of in-person procurement of specimens. In addition, because "only" 0.9% of men will develop oropharyngeal cancer in their lifetime (10), individuals may believe they are low-risk and perceive screening to be insufficiently useful.

Third, potential participants may not have the ability to undergo HPV+ OPC screening. They may lack transportation, be unable to take a day off work to provide oral rinse and gargle specimens in person, or lack insurance and subsequent access to healthcare to work-up abnormal results. Fourth, individuals may require reinforcement in the form of reminders or additional education to complete biological screening or participate in the longitudinal follow-up of abnormal results. An improved understanding of these barriers to screening participation may facilitate the design and development of interventions to enhance stepped HPV+ OPC screening.

Conclusion

In conclusion, two-step screening for oncogenic oral HPV infections is technically feasible. However, identifying and addressing barriers to completion of the behavioral risk assessment and biological testing should be performed prior to reevaluating this approach in a larger-scale trial. In addition, oral HPV DNA testing may be an inefficient mechanism to screen for HPV+ OPC.

Authors' Disclosures

A.T. Day reports CPRIT Individual Investigator Research Award (8/19/2020-8/18/2023).

Establishment of a prospective cohort at high-risk for HPV-associated cancers: using HPV testing at oropharyngeal and anogenital mucosal site and blood-based assays for risk stratification in men.

Co-Investigator. D. Oliver reports grants from Simmons Developmental Funds for Translational Research Pilot Studies during the conduct of the study; and CPRIT Individual Investigator Research Award 8/19/2020-8/18/2023.

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Role: Co-Investigator. K.R. Dahlstrom reports non-financial support from Roche Diagnostics outside the submitted work. E.M. Sturgis reports non-financial support from ROCHE Diagnostics outside the submitted work. J.A. Tiro reports grants from Cancer Prevention & Research Institute of Texas during the conduct of the study; grants from NCI/NIH 2P30CA142543, NCI/NIH UM1CA221940, and NCI/NIH 1R01CA240375 outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

A.T. Day: Conceptualization, resources, formal analysis, supervision, funding acquisition, visualization, methodology, writing–original draft, writing–review and editing. **R.A. Sample:** Formal analysis, investigation, visualization, writing–review and editing. **J.R. Salley:** Writing–review and editing. **D. Oliver:** Resources, data curation, investigation, writing–review and editing. **K.R. Dahlstrom:** Writing–review and editing. **E.M. Sturgis:** Writing–review and editing. **J.A. Tiro:** Investigation, visualization, methodology, writing–original draft, writing–review and editing.

Acknowledgments

A.T. Day was awarded the Simmons Comprehensive Cancer Center Developmental Funds for Translational Research Pilot Studies, which supported this study.

Received August 7, 2022; revised November 7, 2022; accepted December 30, 2022; published first January 3, 2023.

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