Implications of the Oropharyngeal Cancer Epidemic

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Chaturvedi et al,[1] analyzing specimens back to 1984, validate the long-held hypothesis that infection with human papillomavirus (HPV) has increased oropharyngeal squamous cell carcinoma (OPSCC) incidence in the US. They find the incidence of OPSCC in men—who have higher risks of both HPV-positive and HPV-negative OPSCC than women—similar to that of cervical cancer in women. From 1988 to 2004, incidence of HPV-negative OPSCC decreased in parallel with smoking whereas incidence of HPV-positive OPSCC increased at about 7.5% per year, so the percentage of OPSCC that was HPV-positive went from less than 20% to more than 70%.

HPV-positive and HPV-negative OPSCC are etiologically and clinically distinct,[2,3] with HPV-positive disease having better outcome.[4-6] In the current study,[1] the hazard ratio of 0.3 for HPV-positive/HPV-negative in survival analysis essentially balances the difference in prevalence so each form of OPSCC now accounts for a similar number of deaths. Notably, the authors found that outcomes for HPV-positive OPSCC have improved over time, whereas outcomes for HPV-negative OPSCC are as dismal as they were 25 years ago. The authors argue convincingly that vaccination to prevent oral HPV infections should be evaluated and that better treatments for both types of OPSCC should be developed.

We are unlikely to get a better picture of the recent history of OPSCC in the United States. This study used all available OPSCC specimens from the three Surveillance, Epidemiology, and End Results (SEER) registries that participate in the Residual Tissue Repositories Program, analyzed them in several ways, adjusted for loss of detectability over time, corrected for demographic differences between the analyzed cases and all registry cases, and extrapolated the results from these three registries to the US population so far as possible (given that nearly half of specimens came from the small island state of Hawaii and none came from states east of the Mississippi River). The authors' predictions—that the number of specifically HPV-positive OPSCC will surpass cervical cancers by 2020 and that OPSCC will be a majority of all head and neck cancers by 2030—are acknowledged as being on less solid ground. We do not know where we are in the course of the epidemic of oral HPV leading to OPSCC, whether currently increasing incidence of HPV-positive OPSCC will continue as projected, level off, accelerate, or eventually diminish (eg, with HPV vaccination). In any event, during the next decade, we can expect some 10,000 to 15,000 patients with OPSCC per year in the United States, with the great majority having HPV-positive OPSCC.

These findings have three important implications for clinical practice. First, with cancers related to HPV now affecting both men and women and with present vaccines only effective before infection is established,[7] primary care providers should inform parents of boys (not only girls) about risks of HPV-associated tumors and the likely reduction in risk provided by vaccination. The HPV quadrivalent (types 6, 11, 16, 18) vaccine is approved by the US Food and Drug Administration for patients through age 26 years for prevention of genital warts and anal cancer,[8] although the Centers for Disease Control and Prevention do not yet recommend HPV vaccination of males,[9] and the efficacy of vaccination for reducing oral HPV infection or OPSCC, although expected,[1,10] is not yet documented. Direct tests of this efficacy are needed, given that prevention through vaccination will almost certainly be the ultimate solution to HPV-positive OPSCC. As Chaturvedi et al recommend,[1] prior cost-benefit analyses of vaccinating males, which underlie Centers for Disease Control and Prevention recommendations, must be reconsidered in light of the growing incidence of male HPV-positive OPSCC demonstrated in the current report. Second, with significant risk factors for both HPV-positive and HPV-negative OPSCC well-known,[11] patients should be encouraged to minimize behaviors that put them at risk for either form of OPSCC. Third, oncologists should routinely test all patients with OPSCC for HPV status, if for no other reason than to refine prognosis. Nodal involvement in HPV-positive OPSCC typically leads to a high TNM stage that does not represent disease risk relative to other head and neck cancers.[12,13] Chaturvedi et al[1] found that several analytic methods provided similar results for identifying HPV-positive tumors, including the readily available surrogate marker of high immunohistochemical p16 protein expression.[14] Such testing is already part of OPSCC clinical study design[15] with the hope that the HPV-positive/HPV-negative distinction (in practice, perhaps the closely associated p16-positive/p16-negative distinction) may soon assist in selecting treatments.

The major difference in outcome between HPV-positive and HPV-negative OPSCC, in particular the lack of change of outcome of HPV-negative OPSCC over two decades, requires serious re-evaluation of prior work on head and neck squamous cell carcinoma (HNSCC). Patients who have HPV-positive OPSCC tend to have different associated health-endangering behaviors than those who have HPV-negative OPSCC[11] and are probably less likely to show field cancerization.[16] Their tumors, arising from the epithelium of lymphoid tissue[17] and with viral proteins instead of a long history of somatic mutations disrupting tumor suppressor mechanisms[18] may respond differently to genotoxic therapy[19] and have different tendencies for extracapsular spread, perineural invasion, and metastasis. Many clinical studies on HNSCC in the past two decades were done in the context of an increasing prevalence of HPV-positive OPSCC within a mix of HNSCC subsites. Interpretation of these studies might have been misled by what we now know to have been the substantially different tumor biology of undetermined numbers of patients with HPV-positive OPSCC. For example, it may be that the benefit of adding cetuximab to radiotherapy in HNSCC[20] is restricted to HPV-positive OPSCC[21] and that racial disparity in treatment outcomes after chemoradiotherapy for HNSCC represents racial differences in the prevalence of better-outcome HPV-positive OPSCC.[22] Such re-evaluation of other HNSCC studies in light of the increasing prevalence of HPV-positive OPSCC over these decades may be important for better understanding and treatment of both HPV-positive OPSCC and other HNSCC.

The challenge for future research on therapy differs between these two forms of OPSCC. For HPV-negative OPSCC, this study shows that

decades of trials have yet to improve outcome; development and adoption of more effective treatments are still required. For HPV-positive OPSCC, the combination of increasing incidence, young age at presentation, and substantial long-term survival[2] presents an urgent need for lower-intensity therapy that maintains control of disease while avoiding the significant short- and long-term morbidity of current therapy.[12,21,23] Within both HPV-positive and HPV-negative OPSCC, additional biomarker-based delineations of tumor subtypes[24,25] may contribute to development of better individualized therapy.

Unfortunately, the nature of current clinical trials may not provide useful treatment comparisons in a reasonable time frame. Of 100 patients with OPSCC as might be seen per year in an academic referral center, about 70 patients will have HPV-positive disease versus 30 patients with HPV-negative disease, and about 15 recurrence-related deaths are expected in each group at 2 to 3 years. With these numbers of events, distinguishing treatment outcomes in a clinical trial on either HPV-positive or HPV-negative OPSCC requires hundreds of patients per treatment group, particularly if there is additional stratification of patients by additional biomarkers. For example, the recently activated RTOG-1016 trial design for comparing cetuximab versus cisplatin in combination with radiation therapy for p16-positive OPSCC[15] anticipates enrollment of more than 700 patients. Yet expected rates of patient accrual combined with necessary follow-up time may mean no definitive results for 7 years. In principle, results could be obtained more quickly if more of the 10,000 patients with OPSCC in the United States each year were involved in trials, but that would require a major increase in the number of participating institutions, substantial success at obtaining patient consent, and an unprecedented level of cooperation and coordination in study design, execution, and analysis. It is noteworthy that this trial was developed and approved within the new National Cancer Institute framework for extramural trials[26] in response to the Institute of Medicine report.[27] Without additional funding and a mechanism in place to effect broader participation beyond cooperative group head and neck committee members, however, a substantive increase in accrual rate may be slow in coming.

The current study[1] illustrates how difficult such interinstitutional cooperation can be. During the two decades examined, there were approximately 200,000 patients with OPSCC nationwide. With the limits of the SEER network, only three SEER Residual Tissue Repositories Program registries and fewer than 5% of patients in those three registries having available specimens, this reconstruction of the history of OPSCC in the United States is based on only 271 patients. We need much more complete representation of patients with OPSCC in future studies and trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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