Human papillomavirus (HPV)-associated malignancies as subsequent malignant neoplasms (SMN) in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS)

Henderson, TO, MD, MPH[1], Nathan, PC, MD, MSc[2], Whitton, J, MS[3], Leisenring, W, ScD[3], Neglia, J, MD[4], MPH, Fowler, B, MPH[1], Arnold, MA, MD, PhD[5], Howell, RM, PhD[6], Robison, LL, PhD[7], Armstrong, GT, MD, MSCE[7], Alexander, K, MD[8]

[1]University of Chicago, Chicago, IL, [2]The Hospital for Sick Children, Toronto, Ontario, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, [4]University of Minnesota, Minneapolis, MN, [5]Nationwide Children's Hospital and The Ohio State University, Columbus, OH, [6]MD Anderson Cancer Center, Houston, TX, [7]St. Jude Children's Research Hospital, Memphis, TN, [8]Nemours Children's Hospital, Orlando, FL

Character count – 1948 not counting spaces (Maximum is 2000).

Background: It is not known whether childhood cancer survivors (CCS) develop human papillomavirus (HPV)-associated malignancies more frequently than the general population.

Methods: We assessed the cumulative incidence of SMN in sites typically associated with HPV (HPV-SMN) and evaluated Standardized Incidence Ratios (SIR) using age-, sex- and calendar-year specific rates from the Surveillance, Epidemiology and End Results (SEER) program. Multivariate Cox regression models identified associations between key risk factors and HPV-SMN development.

Results: Among 27,620 CCS, 42 developed an HPV-SMN at a median age of 28 years (range: 8-42) and a median of 16 years (range: 5-30) after their primary cancer. The 30-year cumulative incidence of an HPV-SMN was 0.25% (95% confidence interval [CI]: 0.16%-0.34%). HPV-SMN locations included oral cavity/pharynx (N=26, 62%), rectum (N=10, 21%), cervix/uteri (N=3, 7%), and vulva (N=3, 7%). The incidence of HPV-SMN was over 2-fold higher among CCS than the general population (SIR=2.54, 95% CI 1.8-3.6) with an absolute excess risk (AER) of 6.5/100,000 person-years. Rates were elevated in those exposed (SIR=3.02, CI 2.01-4.53) and not exposed to radiotherapy (RT; SIR=2.19, CI 1.21-3.95). Risk of oral cavity/pharynx SMN was elevated in both those exposed (SIR=7.26, CI 3.87-13.64) and not exposed (SIR=4.23, CI 2.20-8.12) to head or neck RT, whereas, risk in GU locations was elevated in those exposed (SIR=4.04, CI 2.10-7.78) but not in those not exposed to pelvic RT (SIR=0.77, CI 0.34-1.71). Male sex (RR=2.7, CI 1.4-5.5), exposure to head/neck/pelvic RT (RR=2.1, CI 1.0-4.3), platinum chemotherapy (RR=5.0, CI: 2.2-11.1), and alkylating agents (RR=3.1, CI 1.0-9.2) increased the risk. Survivors with an HPV-SMN were more likely to be deceased than those without (40.8% vs. 12.7%, p<0.01); 11/17 (65%) of deceased cases died of their SMN.

Conclusions: While the overall incidence is low, CCS are at increased risk for developing malignancies in locations commonly associated with HPV infection in the

general population. Further research examining the impact of HPV in the etiology of these SMN is warranted. As HPV-SMNs are potentially preventable, promotion of HPV vaccination efforts should be considered in this population.

Corresponding Author:

Tara Henderson, MD, MPH

Department of Pediatrics, University of Chicago, Chicago, IL

773-702-2501 – office

773-702-9881 - fax

thenderson@peds.bsd.uchicago.edu