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Risk of subsequent malignant neoplasms after an index potentially-human papillomavirus (HPV)-associated cancers

Maggie Wang[a], **Arun Sharma**[b], **Nosayaba Osazuwa-Peters**[c,d], **Matthew C. Simpson**[c], **Mario Schootman**[e], **Jay F. Piccirillo**[f], **Warner K. Huh**[g], **Eric Adjei Boakye**[h,i,j,*]

[a]Saint Louis University School of Medicine, 1402 S Grand Blvd, St. Louis, MO 63104, USA

[b]Department of Otolaryngology–Head and Neck Surgery, Southern Illinois University School of Medicine, 720 N. Bond Street, Springfield, IL 62702, USA

[c]Department of Otolaryngology–Head and Neck Surgery, Saint Louis University School of Medicine, 3660 Vista Ave, St. Louis, MO 63110, USA

[d]Saint Louis University Cancer Center, 3685 Vista Ave, St. Louis, MO 63110, USA

[e]Center for Clinical Excellence, SSM Health, 10101 Woodfield Ln., St. Louis, MO 63132, USA

[f]Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110, USA

[g]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 1201 11th Ave S, Birmingham, AL 35205, USA

[h]Department of Population Science and Policy, Southern Illinois University School of Medicine, 201 E. Madison Street, P. O. Box 19664, Springfield, IL 62794-9664, USA

[i]Department of Internal Medicine, Southern Illinois University School of Medicine, 751 N Rutledge St, Springfield, IL 62702, USA

[j]Simmons Cancer Institute at SIU, Southern Illinois University School of Medicine, 315 W Carpenter St, Springfield, IL 62702, USA

Abstract

[*]Corresponding author at: Southern Illinois University School of Medicine, Department of Population Science and Policy, 201 E. Madison Street, P. O. Box 19664, Springfield, IL 62794, USA. eadjeiboakye49@siumed.edu (E. Adjei Boakye).

Author contributions

Maggie Wang: Writing–original draft, writing–review and editing.
Arun Sharma: Methodology, writing–original draft.
Nosayaba Osazuwa-Peters: Conceptualization, writing–review and editing.
Matthew C Simpson: Data curation, formal analysis.
Mario Schootman: writing–review and editing, supervision.
Jay F Piccirillo: writing–review and editing, supervision.
Warner K Huh: writing–review and editing, supervision.
Eric Adjei Boakye: Conceptualization, data curation, formal analysis, writing–original draft, writing–review and editing, and supervision.

All authors gave approval for the final version of the article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101649.

Background: Since the number of cancer survivors is increasing, it is imperative that we better understand the long-term consequences of these survivors. We assessed the risk of developing a second primary malignant neoplasm (SPMN) after an index potentially-HPV-associated cancers (P-HPV-AC).

Methods: We constructed a population-based cohort of patients with P-HPV-AC using Surveillance, Epidemiology, and End Results registry data (2000–2015). We limited patients to those with invasive P-HPV-AC [cervical, vagina, vulva, penile, anal, and oropharynx] based on the International Classification of Diseases for Oncology, 3rd edition. Excess SPMN risks were calculated based on standardized incidence ratios (SIRs) and excess absolute risks (EARs) per 10,000 person-years at risk (PYR).

Results: A total of 105,644 patients with an index P-HPV-AC were identified, and 7.8 % developed a SPMN. In all P-HPV-AC patients, the overall SIR was 1.73 (95 % CI: 1.69–1.77) and EAR of 70.72 per 10,000 PYR. All index P-HPV-AC sites showed statistically significant increases in the risk of SPMN, except for anal cancer among men, compared with the general population. The greatest increase in risk of SPMN was observed among patients diagnosed with an index P-HPV-oropharyngeal cancer (SIR = 1.83; 95 % CI, 1.70–1.82 and SIR = 2.29; 95 % CI, 2.12–2.47 for men and women, respectively). Men developed SPMN mostly in aero-digestive tract whiles women developed SPMN both in aero-digestive tract and other HPV-associated cancer sites.

Conclusions: P-HPV-AC survivors experienced excess risk of SPMN. These findings have the potential to affect future surveillance practices and improve preventive healthcare for survivors of P-HPV-ACs.

Keywords

HPV-associated cancers; Second primary malignancies; Cancer survivors; Second cancers; Human papillomavirus; Risk and burden; SEER

1. Background

In the United States, human papillomavirus (HPV) is the most common sexually transmitted infection. Annually, approximately 39,000 people are diagnosed with a potentially-HPV-associated cancer (P-HPV-AC) [1]. Nearly all cervical cancers, 95 % of anal cancers, more than 70 % of oropharyngeal, 65 % of vaginal, 50 % of vulva and 35 % of penile cancers can be attributed to oncogenic HPV infection [2,3].

Improvements in cancer prevention, screening, and treatment has contributed to an increase in the number of cancer survivors. As of January 2016, there were an estimated 15.5 million cancer survivors in the United States. This is expected to increase to 20 million by the year 2024 [4]. As the number of survivors with P-HPV-AC increase, they face significant medical, psychosocial and economic challenges, including the development of secondary primary malignant neoplasms (SPMN) and other competing causes of death [5–8]. SPMN's are associated with lower five year survival rates for all age groups compared to primary malignancies [9].

We hypothesize that cancer survivors with primary P-HPV-AC continue to be exposed to risk factors that also increase their risk of future aerodigestive tract and HPV-related cancers. Studies have shown that patients continue to consume tobacco after diagnosis of head and neck cancer (HNC) [10,11]. Smoking has also been shown to decrease the clearance of low grade lesions [12]. Research has also demonstrated tobacco may be related to the increased incidence and persistence of high-risk HPV in the oropharynx [13]. These might suggest that among survivors of P-HPV-AC, the risk of a second primary aerodigestive tract cancer may be as high if not higher than the risk of a second primary P-HPV-AC.

Given the increase in P-HPV-AC prevalence and improved survivorship, we need to better understand the long-term consequences of P-HPV-AC. Identifying patients at increased risk of developing SPMN may inform survivorship recommendations for those diagnosed with P-HPV-AC. We analyze all SPMNs among survivors of P-HPV-AC in the US adult population. We assessed the risk of developing a SPMN after an index P-HPV-AC, and analyzed the sites where SPMN (HPV-AC vs. non-HPV-AC) most frequently occurred in these patients.

2. Materials and methods

2.1. Data source and population

We constructed a retrospective cohort using data from the Surveillance, Epidemiology, and End Results (SEER) Program database, which covers approximately 30 % of the US population [14]. SEER is a nationally representative, publicly available, population-based cancer database that contains over 8 million cancer cases and covers about 97% of all incident cancers in its registry areas [15,16]. All primary and subsequent cancers, occurring among residents of SEER areas are reportable, and the program has near-universal follow-up [17]. The National Cancer Institute does not require institutional review board approval for use of this de-identified data set.

We identified all patients (age > 20 years) diagnosed with an index P-HPV-AC between 2000 and 2015 (i.e., oropharynx, anal, cervical, vaginal, vulva, and penile). P-HPV-AC were defined as invasive cancers of specific anatomic sites comprising specific cell types in which HPV DNA is frequently found [18–20]. Oropharyngeal (which included oropharynx, tonsil, base of tongue and Waldeyer's ring), anal, vaginal, vulvar and penile cancers comprised of squamous cell carcinomas, and cervical cancer comprised of all carcinomas. P-HPV-AC were defined using the SEER site recode per International Classification of Diseases for Oncology third edition [21] primary site and histology codes (eTable 1).

2.2. Definition of SPMN

Coding of multiple primaries followed the rules of the International Agency for Research on Cancer (IARC). These rules define multiple primaries as two or more tumors arising in different sites, or at the same site when the histology is different [22]. A SPMN was defined as the first subsequent primary cancer occurring at least 2 months after first cancer diagnosis [6,8,23–25]. As a result, the person-year at risk (PYR) for each individual started at 2 months of follow-up and ended at the date of SPMN diagnosis, last known vital status,

death, or the end of the study period of follow-up (December 2015), whichever came first. Extensions, recurrences, metastasis, third and subsequent cancers were excluded. We conducted a sensitivity analyses using the 6-month definition of SPMN, which provided very similar results to our main analyses.

2.3. Statistical analysis

The standard "person-year approach" to calculate relative and absolute excess risk of developing SPMN was used [23,26]. Following this method, the number of observed SPMNs (Observed) is compared to the number of expected cancers (Expected) if patients with a first cancer had experienced the same rates as the general population. The number of expected cancers was calculated for a cohort of patients of identical age, sex, race, and time period. The expected number of SPMNs was calculated by multiplying sex-, age-, race-, and calendar year-specific SEER cancer incidence rates (available at http://seer.cancer.gov) with the accumulated person-years at risk. Standardized incidence ratios (SIR) [27], based on cancer registry data [28], are a relative measure of the strength of the association between two cancers. SIR was defined as the ratio of the observed to expected (Observed/Expected) cancers. Confidence intervals (95 %) for SIR were calculated with Byar's approximation to the Poisson distribution [26]. SIRs whose 95 % CI excluded the value of 1.0 suggested that the observed number of SPMNs were considered statistically significantly higher than the expected number of SPMNs (2-sided $P < .05$).

The excess absolute risk (EAR) [23] is an absolute measure of the burden of additional cancer occurrences in a population and was calculated as the excess (Observed – Expected) number of SPMNs per 10,000 PYR. SIR and EAR values were calculated in SEER*Stat version 8.3.4 (Surveillance Research Program, National Cancer Institute). Other analyses were performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC).

3. Results

3.1. Patient population

We identified 105,644 patients (68,202 women and 37,442 men) with index P-HPV-ACs diagnosed between 2000 and 2015, 8,203 of whom (7.8 %) developed SPMN. Mean age at index cancer diagnosis was 55.2 ± 14.8 years, and the median follow-up duration was 3.2 years (interquartile range = 1.0–7.6 years). Table 1 shows that 64.6 % of patients with index P-HPV-ACs were women, 86.5 % were white and 47.6 % were married. Among 33,712 men with index P-HPV-ACs, the majority presented with an index oropharynx cancer (89.6 %). Among 63,710 women with index P-HPV-AC, 73.1 % presented with an index cervical cancer.

3.2. Risk and burden of SPMN by index P-HPV-ACs characteristics

Among men, the risk of SPMN was significantly increased for all patient and tumor characteristics (age, race, marital status, year of diagnosis, stage, and grade; [the SIRs ranged from 1.35 to 2.65]) (Table 2). Similarly, among women, the risk of SPMN was significantly increased for all patient and tumor characteristics (age, race, marital status, year of diagnosis, stage, and grade; [the SIRs ranged from 1.56 to 2.25]).

3.3. Risk and burden of SPMN

Table 3 shows that a total of 8,203 patients developed a SPMN, resulting in a SIR of 1.73 (95 % CI, 1.69–1.77) and EAR of 70.7 cases per 10,000 PYR relative to the general population. Among men, the relative risk of developing SPMN (3,719 observed) was (SIR = 1.71; 95 % CI: 1.66–1.77), corresponding to (EAR = 100.1 cases per 10,000 PYR). All index P-HPV-AC sites showed statistically significant increases in the risk of SPMN, except for anal cancer. The greatest increase in risk and burden of SPMN existed among patients diagnosed with an index potentially-HPV-associated oropharyngeal (SIR = 1.76; 95 % CI, 1.70–1.82; EAR = 103.4 per 10,000 PYR), followed by penile (SIR = 1.41; 95 % CI, 1.27–1.57; EAR = 76.8 per 10,000 PYR) cancers.

Among women, the relative risk of developing SPMN (4,484 observed) was (SIR = 1.74; 95 % CI: 1.69–1.79), corresponding to (EAR = 57.1 cases per 10,000 PYR) compared with the general population. All index P-HPV-AC sites showed a statistically significant increase in the risk of SPMN. The greatest increases in risk of SPMN were among patients diagnosed with an index potentially-HPV-associated oropharyngeal (SIR = 2.29; 95 % CI, 2.12–2.47) and vulvar (SIR = 2.29; 95 % CI, 2.16–2.44), followed by vaginal (SIR = 1.85; 95 % CI, 1.57–2.15); cervical (SIR = 1.50; 95 % CI, 1.44–1.56); and anal (SIR = 1.41; 95 % CI, 1.15–1.72) cancers. The highest burden was also among patients diagnosed with an index potentially-HPV-associated vulvar (150 per 10,000 PYR), followed by oropharynx (142 per 10,000 PYR), and vaginal (104 per 10,000 PYR) cancers.

3.4. Incidence and location of SPMNs

The location of common SPMNs with significant risk and EAR ≥ 0.5 are detailed in Tables 4 and 5. Among men, there was an increased risk of developing a SPMN in any site associated with HPV (oropharynx, tonsil, penile and anal) [Table 4]. However, the majority of the common SPMNs were non-HPV-associated. There were secondary cancers of the aerodigestive tract (lung and bronchus, tongue, esophagus, larynx, hypopharynx), kidney and renal pelvis, acute myeloid leukemia, and soft tissue including heart.

Women also presented with an increased risk of SPMN of the aerodigestive tract (lung and bronchus, tongue, esophagus, larynx, hypopharynx) in addition to kidney and renal pelvis, colorectal, liver and acute myeloid leukemia (Table 5). There was also an increased risk of developing a SPMN in a site strongly associated with HPV (vulvar, vaginal, cervical, anal, tonsil, and oropharynx). Detailed information on location of common SPMNs by each index potentially-HPV-associated cancer and stratified by sex is provided in eTable 2.

3.5. Risks and burden of SPMN by latency interval and year of index cancer diagnosis

Overall and for both sexes, the risk of SPMN was significantly elevated for all latency periods compared with the general population except for index potentially HPV-associated anal cancer (the SIR for latency periods ranges from 1.17 to 2.47) and individual cancer risk declined with increasing latency (Table 6). Similarly, the risk of SPMN was significantly elevated for year of diagnosis of index cancers among both sexes and overall except anal cancer (the SIR for latency periods ranges from 1.28 to 2.68). Risk of SPMN was stronger among patients diagnosed between 2010–2015 overall and for both sexes.

4. Discussion

Our results show that patients with P-HPV-AC experienced an increased risk of SPMN relative to the general population, with a SIR of 1.73 and 71 excess second cancers developing per 10,000 PYR. Both men and women were at highest risk for SPMN with initial diagnosis of an index potentially-HPV-oropharyngeal cancer diagnosis. Our findings confirm that both women and men experienced an elevated risk of SPMNs among patients with index potentially-HPV-oropharyngeal cancer [24,29]. There was an increased risk of SPMN development of the aerodigestive tract as well as other HPV-associated SPMNs among both sexes. Lung and bronchus secondary cancers had the highest burden in both sexes. We also showed a persistently elevated risk of SPMNs across latency intervals and year of diagnosis. It should be noted that HPV is difficult to differentiate from the confounding risks of alcohol and tobacco consumption in oropharyngeal cancer. However, since the 1990's, rates of tobacco-related HNC cases have decreased while HPV-related HNCs have increased, leading to a viral cancer epidemic [30,31]. Patients with initial diagnosis of HNC frequently receive chemoradiotherapy, which places them at higher risk of secondary malignancy to the local area exposed [32].

Among men, SPMN were most commonly found in the aerodigestive tract whereas for women, SPMN were still localized to the aerodigestive tract and other HPV-associated sites. The increased risk of aerodigestive tract SPMN can potentially be attributed to concurrent tobacco/alcohol use or chemoradiation exposure [8,32]. Our research builds on previous work by Neumann et al. conducted in France which showed that after primary P-HPV-AC, a higher incidence of SPMN in the aerodigestive tract for males and in both the aerodigestive tract and other HPV sites for females [24]. Other studies have suggested a higher incidence of aerodigestive tract tumors in HNC, anal cancer, and cervical cancer [6,33–35]. To the best of our knowledge, this is the first study to establish increased risk of aerodigestive tract SPMN in penile, vaginal and vulva cancer. The smoking-cervical cancer hypothesis was first proposed in 1977 after researchers saw a strong geographic correlation between cervical cancer in women and lung cancer in men [36]. Since 1977, new research has shown that smokers have a significantly higher level of carcinogens found in the cervix that are potentially associated with the intracellular integration of the HPV virus into the human genome, and decreased regional immunity [37,38]. We hypothesize that patients with aerodigestive tract and HPV-associated cancers including penile, vaginal and vulva cancer may also share the common risk factor of tobacco use.

Risk of SPMN was greater among patients diagnosed 2010–2015 compared to those diagnosed between 2000 and 2004. The increase of SPMN in 2010–2015 can perhaps be attributed to the rising disease burden of P-HPV-AC related to high risk sexual activity [39]. Also, for both genders, almost all P-HPV-AC sites presented with a significant increase in the risk of SPMN relative to the general population within the first 5 years (with the exception of anal cancer) and individual cancer risk declined with increasing latency. Future work could focus on long term outcomes and risks of SPMN in patients with P-HPV-AC.

4.1. Clinical implications

Clinical guidelines recommend that patients diagnosed with HPV-related HNC are counselled on smoking cessation and alcohol use [40]. Screening for aerodigestive tract secondary malignancy using low dose computed tomography for the chest is still only recommended for patients with HNC and over 20 years of a pack-per-day history [40]. Few clinical guidelines have incorporated consideration for SPMN in the post-treatment surveillance of HPV-AC, especially because SPMN can arise in distant sites. There are few guidelines for screening for local area non-HPV secondary malignancy. For cervical cancer, vagina and vulva cancer, guidelines only describe local surveillance, despite increased incidence of aerodigestive tract SPMN [41,42]. Furthermore, for anal and penile cancer, follow-up guidelines terminates at 5 years, although secondary malignancy SIR does not decrease significantly after 5 years [43,44]. Given the increased risk of secondary aerodigestive tumors in survivors of P-HPV-AC, lifestyle counselling may be indicated for all survivors of P-HPV-AC. Guidelines that considers the results of studies such as ours may need to be adjusted to better address the increasing burden of SPMN.

4.2. Limitations & strengths

The inability to confirm HPV status in tumors through the SEER database is an important limitation. We consequently restricted selection of primary tumor, defined as P-HPV-AC, to morphological and topographical codes for which it is well established that HPVs are involved [18–20]. This potential misclassification could have underestimated our SPMNs. Because the SEER database does not include risk factors such as tobacco, alcohol, recreational drug use, and sexual activity, we were unable to control for these factors into our analysis. Another potential limitation is the two-month lag used to define SPMN, but this is based on established conventions analyzing SPMN [6,8,23–25,29]. We also performed sensitivity analyses using the 6-month definition, which showed very similar results to our main results. Moreover, although histological diagnosis of cancer and medical coding have improved, there is a chance a SPMN could have been a coded as recurrence which could lead to overestimation of SPMNs. Despite the aforementioned limitations, strengths of our study include a large national sample size with near complete follow-up and high-quality control as part of the SEER program. Risks were based on the large SEER reference cohort thereby maximizing both internal and external validity.

5. Conclusions

P-HPV-AC survivors are at increased risk of developing SPMNs, with about 1-in-12 patients developing SPMN. For both sexes, patients with index-oropharyngeal cancer had the highest increased risk of SPMN. Men developed SPMN mostly in aero-digestive tract while women developed SPMN both in aero-digestive tract and other HPV-associated cancer sites. Public health policy-makers and oncology care providers should focus on multidisciplinary preventive medicine and improved surveillance for the increasing population of P-HPV-AC survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

[1]. Viens LJ, Human papillomavirus–associated cancers—United States, 2008–2012, MMWR Morb. Mortal. Wkly. Rep. (2016) 65.

[2]. Gillison ML, Chaturvedi AK, Lowy DR, HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women, Cancer 113 (S10) (2008) 3036–3046. [PubMed: 18980286]

[3]. Ljubojevic S, Skerlev M, HPV-associated diseases, Clin. Dermatol. 32 (2) (2014) 227–234. [PubMed: 24559558]

[4]. American Cancer Society Cancer Facts & Figures 2017, American Cancer Society, Atlanta, 2017https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf.

[5]. Lin SS, Massa ST, Varvares MA, Improved overall survival and mortality in head and neck cancer with adjuvant concurrent chemoradiotherapy in national data-bases, Head Neck 38 (2) (2016) 208–215. [PubMed: 25225171]

[6]. Adjei Boakye E, Buchanan P, Hinyard L, Osazuwa-Peters N, Schootman M, Piccirillo JF, Incidence and risk of second primary malignant neoplasm after a first head and neck squamous cell carcinoma, JAMA Otolaryngol. Head Neck Surg. 144 (8) (2018) 727–737.

[7]. Simpson MC, Massa ST, Boakye EA, et al., Primary cancer vs competing causes of death in survivors of head and neck cancer, JAMA Oncol. 4 (2) (2018) 257–259. [PubMed: 29285537]

[8]. Adjei Boakye E, Buchanan P, Hinyard L, et al., Trends in the risk and burden of second primary malignancy among survivors of smoking-related cancers in the United States, Int. J. Cancer 145 (1) (2019) 143–153. [PubMed: 30613963]

[9]. Keegan THM, Bleyer A, Rosenberg AS, Li Q, Goldfarb M, Second primary malignant neoplasms and survival in adolescent and young adult cancer survivors, JAMA Oncol. 3 (11) (2017) 1554–1557. [PubMed: 28426850]

[10]. Duffy SA, Khan MJ, Ronis DL, et al., Health behaviors of head and neck cancer patients the first year after diagnosis, Head Neck 30 (1) (2008) 93–102. [PubMed: 17685451]

[11]. Osazuwa-Peters N, Adjei Boakye E, Chen BY, Tobo BB, Varvares MA, Association between head and neck squamous cell carcinoma survival, smoking at diagnosis, and marital status, JAMA Otolaryngol. Head Neck Surg. 144 (1) (2017) 43–50.

[12]. Matsumoto K, Oki A, Furuta R, et al., Tobacco smoking and regression of low-grade cervical abnormalities, Cancer Sci. 101 (9) (2010) 2065–2073. [PubMed: 20626752]

[13]. Fakhry C, Gillison ML, D'Souza G, Tobacco use and oral HPV-16 infection, JAMA 312 (14) (2014) 1465–1467. [PubMed: 25291584]

[14]. Surveillance E, End Results (SEER) Program, Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2016 Sub (2000–2014) < Katrina/Rita Population Adjustment > - Linked To County Attributes - Total U.S., 1969–2015 Counties, National Cancer Institute D, 2019 Surveillance Research Program, ed2017.

[15]. National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2015 Sub (2000–2013) - Linked To County Attributes – Total U.S., 1969–2014 Counties,

National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission, (2016).

[16]. Zippin C, Lum D, Hankey BF, Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute, Cancer 76 (11) (1995) 2343–2350. [PubMed: 8635041]

[17]. Harlan LC, Hankey BF, The surveillance, epidemiology, and end-results program database as a resource for conducting descriptive epidemiologic and clinical studies, J. Clin. Oncol. 21 (12) (2003) 2232–2233. [PubMed: 12805320]

[18]. Viens LJ, Henley SJ, Watson M, et al., Human papillomavirus-associated cancers - United States, 2008–2012, MMWR Morb. Mortal. Wkly. Rep. 65 (26) (2016) 661–666.

[19]. Saraiya M, Unger ER, Thompson TD, et al., US assessment of HPV types in cancers: implications for current and 9-Valent HPV vaccines, J. Natl. Cancer Inst. 107 (6) (2015).

[20]. Watson M, Saraiya M, Ahmed F, et al., Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods, Cancer 113 (10 Suppl) (2008) 2841–2854. [PubMed: 18980203]

[21]. Fritz A, Percy C, Jack A, Shanmugarathan S, Sobin L, Parkin DM, Whelan S, International Classification of Diseases for Oncology (ICD-O-3), 3 ed., World Health Organization, Geneva, 2000.

[22]. Muir CS, Percy C, Cancer registration: principles and methods. Classification and coding of neoplasms, IARC Sci. Publ. (95) (1991) 64–81. [PubMed: 1894333]

[23]. Curtis RE, Freedman DM, Ron E, et al., New Malignancies among Cancer Survivors: SEER Cancer Registries, 1973–2000, Institute NC, Bethesda, MD, 2019.

[24]. Neumann F, Jegu J, Mougin C, et al., Risk of second primary cancer after a first potentially-human papillomavirus-related cancer: a population-based study, Prev. Med. 90 (2016) 52–58. [PubMed: 27370167]

[25]. Adjei Boakye E, Buchanan P, Hinyard L, et al., Risk and outcomes for second primary human papillomavirus-related and -unrelated head and neck malignancy, Laryngoscope 129 (8) (2019) 1828–1835. [PubMed: 30582167]

[26]. Breslow NE, Day NE, Statistical methods in cancer research. Volume II–the design and analysis of cohort studies, IARC Sci. Publ. (82) (1987) 1–406.

[27]. Schoenberg BS, Myers MH, Statistical methods for studying multiple primary malignant neoplasms, Cancer 40 (4 Suppl) (1977) 1892–1898. [PubMed: 907991]

[28]. Begg CB, Zhang ZF, Sun M, Herr HW, Schantz SP, Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the Surveillance, Epidemiology, and End Results (SEER) program, Am. J. Epidemiol. 142 (6) (1995) 653–665. [PubMed: 7653476]

[29]. Suk R, Mahale P, Sonawane K, et al., Trends in risks for second primary cancers associated with index human papillomavirus–associated cancers, JAMA Netw. Open 1 (5) (2018) e181999–e181999.

[30]. Sturgis EM, Cinciripini PM, Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer 110 (7) (2007) 1429–1435. [PubMed: 17724670]

[31]. Martel M, Alemany L, Taberna M, et al., The role of HPV on the risk of second primary neoplasia in patients with oropharyngeal carcinoma, Oral Oncol. 64 (2017) 37–43. [PubMed: 28024722]

[32]. Tubiana M, Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review, Radiother. Oncol. 91 (1) (2009) 4–15. [PubMed: 19201045]

[33]. Shah BK, Budhathoki N, Second primary malignancy in anal carcinoma–a US population-based study, Anticancer Res. 35 (7) (2015) 4131–4134. [PubMed: 26124366]

[34]. Teng C-J, Huon L-K, Hu Y-W, et al., Secondary primary malignancy risk in patients with cervical cancer in Taiwan: a nationwide population-based study, Medicine 94 (43) (2015).

[35]. Chaturvedi AK, Engels EA, Gilbert ES, et al., Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk, J. Natl. Cancer Inst. 99 (21) (2007) 1634–1643. [PubMed: 17971527]

[36]. Winkelstein W Jr., Sacks ST, Ernster VL, Selvin S, Correlations of incidence rates for selected cancers in the nine areas of the Third National Cancer survey, Am. J. Epidemiol. 105 (5) (1977) 407–419. [PubMed: 871117]

[37]. Prokopczyk B, Cox JE, Hoffmann D, Waggoner SE, Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers, J. Natl. Cancer Inst. 89 (12) (1997) 868–873. [PubMed: 9196253]

[38]. Alam S, Conway MJ, Chen H-S, Meyers C, The cigarette smoke carcinogen benzo[a]pyrene enhances human papillomavirus synthesis, J. Virol. 82 (2) (2008) 1053–1058. [PubMed: 17989183]

[39]. Marur S, D'Souza G, Westra WH, Forastiere AA, HPV-associated head and neck cancer: a virus-related cancer epidemic, Lancet Oncol. 11 (8) (2010) 781–789. [PubMed: 20451455]

[40]. Roman BR, Goldenberg D, Givi B, AHNS Series–do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors, Head Neck 38 (2) (2016) 168–174. [PubMed: 25916656]

[41]. Rollo D, Colombo N, Carinelli S, Colombo A, Marini C, Sessa C, Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 23 (suppl_7) (2012) vii27–vii32. [PubMed: 22997451]

[42]. Salani R, Backes FJ, Fung MF, et al., Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: society of Gynecologic Oncologists recommendations, Am. J. Obstet. Gynecol. 204 (6) (2011) 466–478. [PubMed: 21752752]

[43]. Glynne-Jones R, Nilsson PJ, Aschele C, et al., Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. (2014) 25 Suppl 3:iii10–20. [PubMed: 25001200]

[44]. Van Poppel H, Watkin NA, Osanto S, Moonen L, Horwich A, Kataja V, Penile cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (suppl._6) (2013) vi115–vi124. [PubMed: 23975666]

Table 1

Patient and tumor characteristics of the study cohort, overall and stratified by sex, SEER 2000–2015.

	N (Percentage)				
		Men		Women	
	All patients (n = 105,644)	Index malignancy (n = 33,712)	SPMN (n = 3,730)	Index malignancy (n = 63,710)	SPMN (n=4,492)
Second primary malignant neoplasm					
No	97,441 (92.2)				
Yes	8,203 (7.8)				
Sex					
Women	68, 202 (64.6)				
Men	37,442 (35.4)				
Age at diagnosis of first malignancy, y					
< 55	51,157 (48.4)	11,760 (34.9)	989 (26.5)	36,576 (57.4)	1,832 (40.8)
55–64	26,789 (25.4)	12,495 (37.1)	1,519 (40.7)	11,659 (18.3)	1,116 (24.8)
65+	27,698 (26.2)	9,457 (28.0)	1,222 (32.8)	15,475 (24.3)	1,544 (34.4)
Race					
White	85,675 (86.5)	29,182 (89.5)	3,266 (90.0)	49,650 (84.7)	3,577 (84.9)
Black	12,582 (12.7)	3,190 (9.8)	361 (9.9)	8,397 (14.3)	634 (15.0)
Other	788 (0.8)	214 (0.7)	3 (0.1)	567 (1.0)	4 (0.1)
Marital status at diagnosis of index malignancy					
Married	50,318 (47.6)	19,322 (57.3)	2,276 (61.0)	26,805 (42.1)	1,915 (42.6)
Divorced/separated/widowed	25,194 (23.9)	6,118 (18.2)	675 (18.1)	16,971 (26.6)	1,430 (31.8)
Never married	23,866 (22.6)	6,409 (19.0)	605 (16.2)	15,979 (25.1)	873 (19.4)
Unknown	6,266 (5.9)	1,863 (5.5)	174 (4.7)	3,955 (6.2)	274 (6.1)
Year of diagnosis of index malignancy					
2000–2004	30,479 (28.9)	7,322 (21.7)	1440 (38.6)	19,715 (30.9)	2,002 (44.6)
2005–2009	32,883 (31.1)	10,118 (30.0)	1,400 (37.5)	19,776 (31.1)	1,589 (35.4)
2010+	42,282 (40.0)	16,272 (48.3)	890 (23.9)	24,219 (38.0)	901 (20.0)
Grade of index malignancy					
Well	9,646 (9.1)	1,809 (5.4)	257 (6.9)	6,977 (11.0)	603 (13.4)

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	N (Percentage)				
		Men		Women	
	All patients (n = 105,644)	Index malignancy (n = 33,712)	SPMN (n = 3,730)	Index malignancy (n = 63,710)	SPMN (n=4,492)
Moderate	33,604 (31.8)	10,942 (32.4)	1,312 (35.2)	19,805 (31.1)	1,545 (34.4)
Poor	32,782 (31.1)	12,640 (37.5)	1,363 (36.5)	17,655 (27.8)	1,124 (25.1)
Undifferentiated/unknown	29,497 (28.0)	8,321 (24.7)	798 (21.4)	19,164 (30.1)	1,214 (27.1)
Stage of index malignancy					
Localized	35,819 (33.9)	4,439 (13.2)	695 (18.6)	28,513 (44.8)	2,172 (48.4)
Regional	51,388 (48.7)	22,460 (66.6)	2,400 (64.3)	24,682 (38.8)	1,846 (41.1)
Distant	14,404 (13.6)	5,833 (17.3)	512 (13.7)	7,789 (12.2)	270 (6.0)
Unknown/unstaged	4,009 (3.8)	980 (2.9)	123 (3.3)	2,704 (4.2)	202 (4.5)
Index potentially HPV-associated cancer site					
Oropharynx	40,505 (38.3)	30,195 (89.6)	3,327 (89.2)	6,288 (9.9)	695 (15.5)
Anal	1,988 (1.9)	555 (1.7)	40 (1.1)	1,295 (2.0)	98 (2.2)
Penile	3,325 (3.2)	2,962 (8.8)	363 (9.7)	NA	NA
Cervical	49,038 (46.4)	NA	NA	46,550 (73.1)	2,488 (55.4)
Vulvar	8,902 (8.4)	NA	NA	7,855 (12.3)	1,047 (23.3)
Vaginal	1,886 (1.8)	NA	NA	1,722 (2.7)	164 (3.6)

SEER = Surveillance, Epidemiology, and End Results; HPV = Human papillomavirus, SPMN = Second primary malignant neoplasm.

Table 2:

Risk of SPMN according to the characteristics of the index cancer, stratified by sex, SEER 2000–2015.

	Men			Women		
	Observed SPMN	**SIR (95 % CI)**	**EAR per 10000 PYR**	**Observed SPMN**	**SIR (95 % CI)**	**EAR per 10000 PYR**
Age at diagnosis of index malignancy, y						
< 49	424	2.65 (2.40, 2.91)	75.32	1,270	1.86 (1.76, 1.97)	31.96
50–59	1,333	1.90 (1.80, 2.00)	100.86	1,149	1.86 (1.75, 1.97)	76.09
60–69	1,312	1.58 (1.50, 1.67)	120.35	1,042	1.67 (1.57, 1.77)	93.82
70+	661	1.35 (1.25, 1.46)	101.70	1,031	1.56 (1.47, 1.66)	103.09
Race						
White	3,266	1.68 (1.62, 1.74)	96.04	3,577	1.69 (1.64, 1.75)	55.47
Black	361	2.06 (1.86, 2.29)	169.34	634	2.10 (1.94, 2.27)	82.10
Other	100	2.13 (1.74, 2.59)	104.48	277	1.82 (1.61, 2.04)	47.18
Marital status at diagnosis of index malignancy						
Married	2,276	1.61 (1.54, 1.67)	86.80	1,915	1.68 (1.61, 1.76)	48.80
Divorced/separated/widowed	675	1.84 (1.71, 1.99)	130.36	1,430	1.73 (1.65, 1.83)	79.58
Never married	605	2.08 (1.92, 2.26)	129.68	873	1.90 (1.77, 2.03)	52.45
Unknown	174	1.62 (1.39, 1.88)	87.43	274	1.72 (1.53, 1.94)	55.79
Year of diagnosis of index malignancy						
2000–2004	1,440	1.65 (1.57, 1.74)	96.26	2,002	1.52 (1.45, 1.58)	40.10
2005–2009	1,400	1.72 (1.63, 1.81)	98.76	1,589	1.86 (1.77, 1.95)	65.65
2010+	643	1.79 (1.65, 1.93)	106.36	651	2.25 (2.08, 2.43)	97.81
Grade of index malignancy						
Well	257	1.74 (1.53, 1.96)	122.26	603	1.89 (1.74, 2.05)	70.41
Moderate	1,312	1.88 (1.78, 1.99)	121.86	1,545	1.90 (1.80, 2.00)	71.61
Poor	1,363	1.59 (1.51, 1.68)	83.22	1,124	1.66 (1.56, 1.75)	53.68
Undifferentiated/unknown	798	1.66 (1.54, 1.78)	92.87	1,214	1.58 (1.49, 1.67)	41.33
Stage of index malignancy						
Localized	695	1.74 (1.61, 1.87)	119.58	2,172	1.61 (1.55, 1.68)	42.46
Regional	2,400	1.63 (1.57. 1.70)	86.41	1,846	1.85 (1.77, 1.94)	76.25
Distant	512	2.12 (1.94, 2.31)	154.75	270	1.98 (1.75, 2.23)	86.35

	Men			Women		
	Observed SPMN	**SIR (95 % CI)**	**EAR per 10000 PYR**	**Observed SPMN**	**SIR (95 % CI)**	**EAR per 10000 PYR**
Unknown/unstaged	123	1.80 (1.50, 2.15)	111.74	202	1.95 (1.69, 2.24)	77.72

SPMN = Second primary malignant neoplasm; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized incidence ratio; EAR = Excess absolute risk; PYR = Person-year at risk; CI = Confidence interval; HPV = Human papillomavirus.

Table 3

Risk and burden of SPMN after an index potentially-HPV-associated cancer, by sex and site of index cancer, SEER 2000–2015.

	Index potentially HPV-associated cancer	Observed SPMN	SIR (95 % CI)	EAR per 10000 PYR
Overall				
	All index potentially HPV-associated cancer	8,203	1.73 (1.69, 1.77)	70.72
Both men and women				
	Oropharynx	4,001	1.83 (1.78, 1.89)	109.78
	Anal	138	1.37 (1.15, 1.61)	45.32
Men				
	All men index potentially HPV-associated cancer	3,719	1.71 (1.66, 1.77)	100.16
	Oropharynx	3,318	1.76 (1.70, 1.82)	103.41
	Anal	40	1.28 (0.91, 1.74)	39.73
	Penile	361	1.41 (1.27, 1.57)	76.78
Women				
	All women index potentially HPV-associated cancer	4,484	1.74 (1.69, 1.79)	57.10
	Oropharynx	683	2.29 (2.12, 2.47)	142.42
	Anal	98	1.41 (1.15, 1.72)	47.76
	Cervical	2,498	1.50 (1.44, 1.56)	32.56
	Vulvar	1,045	2.29 (2.16, 2.44)	150.28
	Vaginal	164	1.85 (1.57, 2.15)	103.70

SPMN = Second primary malignant neoplasm; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized incidence ratio; EAR = Excess absolute risk per 10000 person-year at risk; CI = Confidence interval.

Table 4

Anatomic sites at elevated risks of SPMN[#] according to site of index potentially HPV-associated cancer, Men, SEER 2000–2015.

Site of index potentially HPV-associated cancer	Site of SPMN	Observed SPMN	SIR 95 % CI	EAR per 10000 PYR
All men potentially HPV-associated cancer				
	Non-HPV-associated SPMN			
	Lung and Bronchus	940	3.15 (2.95, 3.36)	41.52
	Tongue	271	11.19 (9.90, 12.60)	15.96
	Esophagus	138	4.02 (3.38, 4.75)	6.71
	Pharynx	101	9.04 (7.36, 10.98)	5.81
	Larynx	80	3.00 (2.38, 3.73)	3.45
	Thyroid	71	3.18 (2.48, 4.01)	3.15
	Hypopharynx	47	9.20 (6.76, 12.23)	2.71
	Kidney and Renal Pelvis	123	1.36 (1.13, 1.62)	2.10
	Floor of Mouth	33	8.41 (5.79, 11.81)	1.88
	Nasopharynx	22	8.20 (5.14, 12.42)	1.25
	Acute Myeloid Leukemia	29	1.69 (1.13, 2.43)	0.77
	Soft Tissue including Heart	23	1.81 (1.15, 2.72)	0.67
	Lip	14	2.90 (1.58, 4.86)	0.59
	HPV-associated SPMN			
	Penile	60	17.56 (13.4, 22.61)	3.66
	Tonsil	59	3.69 (2.81, 4.76)	2.78
	Oropharynx	32	9.46 (6.47, 13.36)	1.85
	Anal	63	1.32 (1.01, 1.69)	0.98
Oropharynx				
	Non-HPV-associated SPMN			
	Lung and Bronchus	849	3.33 (3.11, 3.57)	42.87
	Tongue	268	12.27 (10.85, 13.84)	17.76
	Esophagus	135	4.51 (3.78, 5.34)	7.58
	Pharynx	100	10.06 (8.18, 12.23)	6.50
	Larynx	77	3.28 (2.59, 4.10)	3.86
	Thyroid	70	3.47 (2.71, 4.39)	3.60

Site of index potentially HPV-associated cancer	Site of SPMN	Observed SPMN	SIR 95 % CI	EAR per 10000 PYR
	Hypopharynx	47	10.41 (7.65, 13.84)	3.06
	Floor of Mouth	31	8.80 (5.98, 12.50)	1.98
	Kidney and Renal Pelvis	104	1.30 (1.06, 1.58)	1.74
	Nasopharynx	21	8.79 (5.44, 13.44)	1.34
	HPV-associated SPMN			
	Anal	54	1.29 (0.97, 1.68)	0.87
	Penile	3	1.03 (0.21, 3.01)	0.01
	Cervical	NA	NA	NA
	Vaginal	NA	NA	NA
	Vulvar	NA	NA	NA
Anal				
	Non-HPV-associated SPMN			
	Acute Myeloid Leukemia	3	11.48 (2.31, 33.55)	12.57
	HPV-associated SPMN			
	Oropharynx	0	0.00 (0.00, 82.02)	−0.21
	Penile	0	0.00 (0.00, 68.92)	−0.24
	Cervical	NA	NA	NA
	Vaginal	NA	NA	NA
	Vulvar	NA	NA	NA
Penile				
	Non-HPV-associated SPMN			
	Lung and Bronchus	83	2.12 (1.69, 2.63)	31.89
	Kidney and Renal Pelvis	18	1.91 (1.13, 3.02)	6.23
	HPV-associated SPMN			
	Anal	7	1.35 (0.54, 2.77)	1.31
	Oropharynx	0	0.00 (0.00, 12.43)	−0.21
	Cervical	NA	NA	NA
	Vaginal	NA	NA	NA
	Vulvar	NA	NA	NA

SPMN = Second primary malignant neoplasm; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized incidence ratio; EAR = Excess absolute risk; PYR = Person-year at risk; CI = Confidence interval.

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#Only non-HPV-associated SPMNs with statistically significant risk are shown (full list of SPMNs are shown in supplemental data).

Table 5

Anatomic sites at elevated risks of SPMN* according to site of index potentially HPV-associated cancer, Women, SEER 2000–2015.

Site of index potentially HPV-associated cancer	Site of SPMN	Observed SPMN	SIR 95 % CI	EAR per 10000 PYR
All women potentially HPV-associated cancer				
	Non-HPV-associated SPMN			
	Lung and Bronchus	888	2.73 (2.55, 2.91)	16.82
	Tongue	87	7.58 (6.07, 9.35)	2.26
	Kidney and Renal Pelvis	123	1.83 (1.52, 2.19)	1.67
	Thyroid	147	1.49 (1.25, 1.75)	1.44
	Colorectal	217	1.22 (1.06, 1.39)	1.17
	Esophagus	50	4.29 (3.18, 5.66)	1.15
	Pharynx	34	7.22 (5.00, 10.09)	0.88
	Soft Tissue including Heart	44	2.97 (2.16, 3.99)	0.87
	Liver	49	2.17 (1.60, 2.86)	0.79
	Acute Myeloid Leukemia	43	2.32 (1.68, 3.12)	0.73
	Larynx	29	3.56 (2.38, 5.11)	0.62
	Stomach	53	1.59 (1.19, 2.08)	0.59
	Floor of Mouth	17	7.85 (4.57, 12.56)	0.44
	Hypopharynx	16	10.19 (5.82, 16.54)	0.43
	HPV-associated SPMN			
	Vulva	409	26.76 (24.23, 29.48)	11.78
	Vagina	171	36.36 (31.11, 42.23)	4.98
	Cervical	144	3.36 (2.83, 3.95)	3.02
	Anal	73	1.56 (1.22, 1.96)	0.78
	Tonsil	18	4.03 (2.39, 6.37)	0.41
	Oropharynx	12	9.93 (5.13, 17.35)	0.32
Oropharynx				
	Non-HPV-associated SPMN			
	Lung and Bronchus	189	4.36 (3.76, 5.02)	53.90
	Tongue	76	55.68 (43.87,69.69)	27.62
	Esophagus	33	22.66 (15.59, 31.82)	11.68

Site of index potentially HPV-associated cancer	Site of SPMN	Observed SPMN	SIR 95 % CI	EAR per 10000 PYR
	Pharynx	23	44.93 (28.47, 67.42)	8.32
	Larynx	17	16.94 (9.86, 27.12)	5.92
	Floor of Mouth	14	51.34 (28.01, 86.14)	5.08
	Liver	9	3.41 (1.56, 6.48)	2.36
	Nasopharynx	4	23.66 (6.37, 60.59)	1.42
	Soft Tissue including Heart	5	3.19 (1.03, 7.45)	1.27
	HPV-associated SPMN			
	Vulvar	4	2.22 (0.60, 5.68)	0.81
	Cervical	5	1.53 (0.49, 3.56)	0.64
	Vaginal	2	3.64 (0.41, 13.13)	0.54
	Anal	4	0.77 (0.21, 1.98)	−0.44
	Penile	NA	NA	NA
Anal				
	Non-HPV-associated SPMN			
	Soft Tissue including Heart	3	8.15 (1.64, 23.81)	4.40
	HPV-associated SPMN			
	Vaginal	3	22.63 (4.55, 66.11)	4.79
	Vulva	2	4.59 (0.52, 16.58)	2.61
	Cervix Uteri	2	2.74 (0.31, 9.89)	2.12
	Oropharynx	0	0.00 (0.00, 107.21)	−0.06
	Penile	NA	NA	NA
Cervical				
	Non-HPV-associated SPMN			
	Lung and Bronchus	478	2.49 (2.27, 2.72)	11.23
	Urinary Bladder	101	3.22 (2.62, 3.92)	2.73
	Thyroid	117	1.53 (1.27, 1.84)	1.60
	Kidney and Renal Pelvis	77	1.79 (1.41, 2.24)	1.33
	Ovary	76	1.52 (1.20, 1.90)	1.02
	Colorectal	131	1.24 (1.03, 1.47)	0.99
	HPV-associated SPMN			
	Vaginal	122	41.32 (34.31, 49.33)	4.67

Site of index potentially HPV-associated cancer	Site of SPMN	Observed SPMN	SIR 95 % CI	EAR per 10000 PYR
	Vulva	45	4.80 (3.50, 6.43)	1.40
	Anal	50	1.63 (1.21, 2.14)	0.76
	Oropharynx	3	3.88 (0.78, 11.33)	0.09
	Penile	NA	NA	NA
Vulvar				
	Non-HPV-associated SPMN			
	Lung and Bronchus	178	2.66 (2.28, 3.08)	28.30
	Kidney and Renal Pelvis	26	2.20 (1.44, 3.22)	3.62
	Liver	9	2.24 (1.02, 4.25)	1.27
	Soft Tissue including Heart	7	2.84 (1.14, 5.84)	1.16
	Tongue	6	2.97 (1.08, 6.47)	1.02
	HPV-associated SPMN			
	Vagina	29	32.54 (21.79, 46.74)	7.17
	Cervix Uteri	16	3.42 (1.95, 5.56)	2.89
	Anal	9	1.10 (0.50, 2.09)	0.21
	Oropharynx	1	4.70 (0.06, 26.17)	0.20
	Penile	NA	NA	NA
Vaginal				
	Non-HPV-associated SPMN			
	Lung and Bronchus	29	2.19 (1.47, 3.15)	21.74
	Colorectal	14	1.84 (1.01, 3.09)	8.82
	HPV-associated SPMN			
	Vulva	22	37.98 (23.79, 57.50)	29.55
	Cervix Uteri	3	3.38 (0.68, 9.86)	2.91
	Oropharynx	0	0.00 (0.00, 88.37)	−0.06
	Anal	1	0.62 (0.01, 3.47)	−0.83
	Penile	NA	NA	NA

SPMN = Second primary malignant neoplasm; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized incidence ratio; EAR = Excess absolute risk; PYR = Person-year at risk; CI = Confidence interval.

* Only non-HPV-associated SPMNs with statistically significant risk are shown (full list of SPMNs are shown in supplemental data).

Table 6

Risk of SPMN according to latency interval and year of diagnosis, stratified by sex, SEER 2000–2015.

	SIR (95 % Confidence Interval)						
	Latency interval				Year of diagnosis		
Index P-HPV-AC	< 1year	1–5 year	5–10 year	10+ year	2000–2004	2005–2009	2010–2015
Overall							
All index P-HPV-AC	1.93 (1.83, 2.04)	1.81 (1.75, 1.87)	1.59 (1.52, 1.65)	1.44 (1.34, 1.56)	1.57 (1.52, 1.63)	1.79 (1.73, 1.85)	1.99 (1.90, 2.08)
Both men and women							
Oropharynx	1.85 (1.71, 2.00)	1.93 (1.84, 2.01)	1.72 (1.62, 1.83)	1.60 (1.42, 1.80)	1.79 (1.70, 1.88)	1.85 (1.75, 1.94)	1.89 (1.77, 2.01)
Anal	1.10 (0.65, 1.74)	1.48 (1.15, 1.87)	1.50 (1.09, 2.03)	0.82 (0.33, 1.70)	1.06 (0.78, 1.41)	1.45 (1.08, 1.90)	1.91 (1.36, 2.61)
Men							
Oropharynx	1.76 (1.62, 1.92)	1.86 (1.77, 1.95)	1.67 (1.56, 1.78)	1.51 (1.32, 1.72)	1.73 (1.63, 1.82)	1.76 (1.66, 1.86)	1.82 (1.70, 1.95)
Anal	0.89 (0.29, 2.09)	1.14 (0.66, 1.82)	1.34 (0.64, 2.47)	1.34 (0.27, 3.91)	1.18 (0.66, 1.95)	1.36 (0.78, 2.22)	1.33 (0.61, 2.52)
Penile	1.60 (1.24, 2.02)	1.39 (1.19, 1.62)	1.34 (1.07, 1.64)	1.41 (0.94, 2.02)	1.28 (1.09, 1.49)	1.45 (1.20, 1.72)	1.72 (1.36, 2.15)
Women							
Oropharynx	2.36 (1.96, 2.82)	2.39 (2.14, 2.65)	2.10 (1.79, 2.44)	2.22 (1.66, 2.92)	2.14 (1.89, 2.41)	2.42 (2.13, 2.73)	2.36 (2.00, 2.77)
Anal	1.21 (0.64, 2.06)	1.64 (1.23, 2.15)	1.39 (0.92, 2.01)	0.64 (0.17, 1.64)	1.01 (0.69, 1.43)	1.49 (1.01, 2.06)	2.20 (1.48, 3.14)
Cervical	2.21 (2.02, 2.42)	1.54 (1.45, 1.64)	1.28 (1.19, 1.39)	1.17 (1.03, 1.32)	1.34 (1.27, 1.42)	1.55 (1.45, 1.66)	2.00 (1.82, 2.19)
Vulvar	1.86 (1.56, 2.19)	2.40 (2.20, 2.62)	2.37 (2.11, 2.66)	2.28 (1.83, 2.82)	1.95 (1.77, 2.14)	2.56 (2.32, 2.83)	2.68 (2.34, 3.05)
Vaginal	2.17 (1.51, 3.02)	1.85 (1.46, 2.32)	1.44 (1.00, 2.02)	2.47 (1.46, 3.90)	1.58 (1.24, 2.01)	2.19 (1.68, 2.79)	1.96 (1.33, 2.78)

SPMN = Second primary malignant neoplasm; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized incidence ratio; EAR = Excess absolute risk per 10000 person-year at risk; CI = Confidence interval; P-HPV-AC = Potentially human papillomavirus associated cancers.