SECOND PRIMARY HEAD AND NECK TUMOR RISK IN PATIENTS WITH CERVICAL CANCER—SEER DATA ANALYSIS

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Abstract: Background. Human papillomavirus (HPV) causes >99% of cervical carcinomas and is associated with approximately 25% of head and neck squamous cell carcinomas (HNSCCs). The role of HPV infection in HNSCC development after a first diagnosis of cervical cancer is unknown.

Methods. Using the National Cancer Institute’s Surveillance, Epidemiology, and End Results data, the authors compared the risk of second primary cancer (SPC) HNSCC in patients with cervical cancer with the general population and with females with other primary cancers.

Results. The lifetime risk of SPC HNSCC for patients with cervical cancer was higher than in the general population (standardized incidence ratio [SIR]: 1.7). When compared with that in females with other cancers, the risk of anogenital and oropharyngeal SPC was in excess, but not of SPC in the oral cavity.

Conclusion. Patients with cervical cancer develop an excess SPC HNSCC in comparison with females with other cancers. A possible role of HPV is suggested.

Keywords: second primary tumors; cervical; head and neck cancer; relative risk

More than 90% of head and neck tumors are squamous cell carcinomas (SCC)1 that occur in the oral cavity, pharynx, and larynx. Approximately 45,660 new cases and 11,210 deaths from cancers of the oral cavity, pharynx, and larynx were expected in the United States in 2007.2 The age-adjusted incidence of head and neck squamous cell carcinoma (HNSCC) in males has declined between 1975 and 2002, whereas it varied very little in females.3

Human papillomaviruses (HPVs) are a family of small double-stranded DNA viruses that infect the basal cells of the epithelial mucosa. More than 100 types of HPV have been identified and are classified according to their ability to infect mucosal or cutaneous epithelial sites. Almost all cases of invasive cancers of the cervix and most other anogenital tract cancers are associated with high-risk HPV types (predominantly types 16, 18, 31, and 45).4,5 Although tobacco and alcohol use are the primary risk factors associated with HNSCC,6,7 we and others have shown that HPV may be an independent risk factor for a subset of head and neck tumors.8–11 A recent systematic review of worldwide HPV16 prevalence in HNSCC reported that overall the virus was detected in
about 31% of tumors from the oropharynx, 17% from the larynx, and 16% from the oral cavity. Among oropharyngeal tumors, HPV prevalence was found to be highest in the tonsils. The source of HPV infection to the oral mucosa is still unclear; however, a relationship between cervical and other HPV-related anogenital cancers and the development of second primary HNSCC has been reported using data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data. However, these studies have not determined whether the observed increased risk of second primary HNSCC in patients with anogenital cancers was more than what would be expected for patients with cancer in general. Further, these studies did not disentangle the effect of radiotherapy on the risk of second primary HNSCC in patients with an HPV-related anogenital cancer. We hypothesize that women with cervical cancer are at higher risk of HPV-related head and neck tumors in comparison with women with other types of cancers. SEER data from 1973 to 2002 were analyzed to assess whether patients with cervical cancer had an increased lifetime risk of second primary tumors at head and neck sites, in comparison with the general population, and with overall female patients with cancer. In addition, comparisons of the lifetime risk of second primary tumors in head and neck subsites were performed between cervical and urinary bladder and breast cancers.

MATERIALS AND METHODS

Study Population. We studied 2618 women (ages 19–97 years; mean, 55 years) who had a first diagnosis of cervical cancer between 1973 and 2002 and who developed a second primary cancer (SPC) at least 1 month subsequent to their cervical cancer diagnosis. An SPC is defined as a new event, rather than a metastasis or a recurrence of the first neoplasm based on time of occurrence, histological type, and site. Invasive cervical cancer is usually treated with surgery or radiation or both, as well as chemotherapy in some cases. To rule out the effect of radiotherapy on the SPC risk, the calculations were performed for all patients with cervical cancer as well as restricted to those who did not receive radiotherapy. The majority of the second primary cancers arising in head and neck sites (oral cavity, lip, salivary gland, oropharynx, nasopharynx, hypopharynx, and larynx) were SCCs (ICD-O-3: 8070, and 8071). There was one verrucous carcinoma (ICD-O-3: 8051) in the tonsil, 1 lymphoepithelial carcinoma (ICD-O-3: 8082) in the nasopharynx, and 1 mucoepidermoid carcinoma (ICD-O-3: 8430) arising in the oral cavity. In the SEER Stat software, the site grouping for tongue included tumors that occurred in the base of tongue and lingual tonsil. Subsequently, these subsites were categorized as oral cavity tumors instead of the oropharynx.

Relative Risk Comparisons with Breast and Bladder Cancer Women. The SEER data set does not provide information on smoking habits. To indirectly assess whether the risk of second primary tumors in head and neck subsites among patients with cervical cancer was to be mostly attributed to persistence of smoking, the relative risk of second primary tumors among females with cervical cancer was compared with that of female patients with breast and urinary bladder cancer. We expected that if SPCs in patients with cervical cancer that arose in head and neck subsites were primarily smoking-related, then the relative risk for these tumor sites should be similar to that of females with urinary bladder cancer (a smoking-related cancer) and higher than that for female patients with breast cancer (a cancer less related to smoking). Similar to the patients with cervical cancer, the subpopulation of breast and urinary bladder patients with SPCs was limited to patients that were of an age at diagnosis ranging from 19 to 97 years so as to create an appropriately matched comparison group.

Statistical Analysis.

Standardized Incidence Ratios. The Multiple Primary-Standardized Incidence Ratio (MP-SIR) program of the SEER Stat software was used to generate the relative risk of second primary cancers for all tumor sites using data from 1973 to 2002. The SIR (or relative risk) 30 years postdiagnosis was calculated for all females with a first diagnosis of cervical cancer to determine the lifetime risk associated with the development of an SPC at a particular tumor site. Person years of follow-up were counted from 1 month after initial diagnosis until the diagnosis of an SPC or death or end of the study (30 years after diagnosis). A single outcome analysis was used, so that the event (SPCs) caused individuals to exit the study contributing no further person time at risk subsequent to the event,
or any additional events they may have experienced. For each particular tumor site, the SIR was calculated as follows: observed number of cancer cases at a particular tumor site/expected number of cancer cases at that particular tumor site based on the incidence rates in the general population. The observed number of cancer cases refers to the exact count of SPCs counted for this cohort. The expected number of cases refers to the number of SPCs expected based on the cancer incidence rates in the general population. Cancer incidence in the general population was calculated using the United States standard population. Estimation of the 95% confidence intervals for the SIR was calculated using the Wilson and Hilferty\textsuperscript{21} approximation of chi-square percentiles.

Ratios of the risk of cervical:breast and cervical:urinary bladder were performed to assess differences in risk among cancer subtypes. As previously described, the 3 cohorts of patients with cervical, breast, and urinary bladder cancer were similarly selected (i.e., the cases among each cohort were all diagnosed at ages 19–97). The expected number of cases for each of the 3 case cohorts was computed according to the U.S. standard population.

**Excess Risk.** The excess risk was calculated to determine whether there is an excess in the number of cases of SPC in patients with cervical cancer compared with females with other cancers. This excess risk of SPC was calculated for patients with cervical cancer, and was compared with the referent population of age-matched female patients with cancer (excluding patients with cervical cancer). First, the expected number of cases of second primary tumors was determined by applying the stratum-specific incidence rates for the female cancer population to the stratum-specific person-years for the patients with cervical cancer (i.e., \([\text{observed number of cases in the female cancer population/female cancer population's person-years at risk}] \times \text{cervical cancer patient's person-years at risk}\) × cervical cancer patient's person-years at risk). The excess risk of second primary tumors per 10,000 persons per year for each tumor site was calculated as \((\text{observed number of cases of second primary tumors for patients with cervical cancer – expected number of cases of second primary tumors when females with other cancers is used as the reference group}) \times 10,000)/\text{cervical cancer patient's person years at risk}.\) Wald 95% confidence limits were calculated for the excess risk.

**RESULTS**

**Second Primary Tumors in Patients with Cervical Cancer.** Among the patients with cervical cancer \((n = 2618)\) that had an SPC, 2356 (90%) had an SPC that was a solid tumor. The overall incidence of SPC among these patients, for all sites combined, was 86/10,000 persons per year. Eighty-seven (4%) of these patients with cervical cancer had a second primary head and neck tumor (oral cavity \([n = 30]\), lip \([n = 4]\), salivary gland \([n = 5]\), oropharynx \([n = 12]\), tonsil \([n = 11]\), nasopharynx \([n = 2]\), hypopharynx \([n = 7]\), and larynx \([n = 25]\)), with an incidence rate of 3.2/10,000 persons per year. For the patients with cervical cancer treated without radiation therapy \((n = 978)\), there were 885 (91%) patients that had an SPC that was a solid tumor. The overall incidence of SPC (for solid tumors only) for these patients was 57/10,000 persons per year. Among these, 38 (6.6%) had a second primary head and neck tumor (oral cavity \([n = 10]\), lip \([n = 1]\), salivary gland \([n = 1]\), oropharynx \([n = 5]\); all occurred in the tonsil), nasopharynx \([n = 1]\), hypopharynx \([n = 6]\), other oral cavity and pharynx \([n = 2]\), and larynx \([n = 12]\)), with an incidence rate of 2.4/10,000 persons per year.

The SIRs or relative risk of SPC for all cancer sites among patients with cervical cancer are shown in Figure 1, and indicate that the lifetime risk of SPC in patients with cervical cancer was significantly higher in comparison with the general population, as expected (relative risk for solid tumors, all cancer sites combined = 1.3, 95% confidence interval \([CI] = 1.2–1.3\)). The lifetime risk of SPC in patients with cervical cancer for combined oral cavity and pharynx was higher than the risk of cancer for all sites \((SIR = 1.7, 95\% CI = 1.3–2.2)\).

The analysis of risk by cancer site shows an elevated risk of SPC in the vagina \((SIR = 16.9, 95\% CI = 13.2–21.5)\) and vulva \((SIR = 5.2, 95\% CI = 4.0–6.8)\). For each head and neck subsite, a significantly elevated lifetime relative risk was observed except for tumors on the lip \((SIR = 2.0, 95\% CI = 0.6–5.2)\), salivary gland \((SIR = 1.1, 95\% CI = 0.4–2.6)\), and nasopharynx \((SIR = 1.0, 95\% CI = 0.1–3.6)\). The highest risk was observed for the larynx \((SIR = 2.7, 95\% CI = 1.7–3.9)\) and oropharynx \((SIR = 2.7, 95\% CI = 1.4–4.7)\). The lifetime risk for patients with SPC in the tonsils only was even more significantly elevated \((SIR = 3.1, 95\% CI = 1.5–5.5)\) (data not shown). Other statistically significant increased risks were
FIGURE 1. Lifetime standardized incidence ratios (SIRs) or relative risk of second primary cancers developed post–cervical cancer diagnosis for all patients (■), and for patients without radiotherapy (x). All cases were diagnosed from 1973 to 2002. *The SIR for second primary vaginal cancer among patients treated without radiotherapy was 21.7; 95% confidence interval, 15.2–30.0.
observed for the lung and other respiratory organs; urinary bladder, renal pelvis, and other urinary organs; anus/anal canal; rectum; stomach; and ovary. A statistically significant decreased risk was associated with second primary tumors in the breast, cervix, corpus, uterus, and skin (melanomas).

When the analysis was restricted to women with cervical cancer who did not receive radiotherapy, overall there were no real differences in lifetime risk of SPC in the oral cavity and pharynx combined. However, there was a significant increased risk of SPC for tumors arising in the vagina (SIR = 21.7, 95% CI = 15.2–30.0), hypopharynx (SIR = 5.7, 95% CI = 2.1–12.3), and urinary bladder (SIR = 3.7, 95% CI = 1.8–6.5). The risk of tumors in the tonsils remained the same (SIR = 3.1, 95% CI = 1.0–7.3) (data not shown).

**Excess Risk of Second Primary Tumors.** We determined whether the increased lifetime risk of SPC observed in patients with cervical cancer was in excess of that observed for all other female patients with cancer (Figure 2). Overall the number of observed cases of SPC for the oral cavity and pharynx combined were not in excess of that which was expected among the general female cancer population which excluded patients with cervical cancer (excess risk = 1.0 cases/10,000).

Among the second primary head and neck cancer developed in patients with cervical cancer, only the oropharynx, hypopharynx, and larynx were in excess in number of cases compared with females with other cancers. For the tonsils, the excess number of cases was 0.1 cases/10,000. As expected, for patients with cervical cancer, SPC in the vagina, vulva, anus/anal canal, and other female genital organs were in excess compared with other female patients with cancer. The highest excess risk was associated with second primary cancers in lung (2.8 cases/10,000). However, when the analysis was limited to patients with cervical cancer who were not treated with radiotherapy, excess cases of SPC in the lung was not observed (−6.8 cases/10,000) (data not shown).

**FIGURE 2.** Lifetime excess risk/10,000 for second primary tumors in patients with cervical cancer, compared with females with other cancers. Lung includes bronchus, trachea, mediastinum, and other respiratory organs. *Breast: excess risk/10,000 = −26.9; 95% confidence interval, −26.9 to −27.0.*
The SPC in the oropharynx, hypopharynx, larynx, vagina, vulva, anus/anal canal, and other female urinary organs for these patients remained in excess. The SPC for the tonsils in these patients also remained at 0.1 cases/10,000.

**Table 1. Risk of second primary tumors in female patients (19–97 y) with cervical, breast, and urinary bladder cancer.**

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients with cervical cancer (19–97 y) (n = 2525)</th>
<th>Patients with urinary bladder cancer (19–97 y) (n = 3050)</th>
<th>Patients with breast cancer (19–97 y) (n = 36,709)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>1.5 (1.0–2.1)</td>
<td>0.7 (0.4–1.1)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>Lip</td>
<td>2.0 (0.6–5.2)</td>
<td>0.2 (0.3–3.0)</td>
<td>0.8 (0.6–1.2)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>1.1 (0.4–2.6)</td>
<td>0.4 (0.1–1.5)</td>
<td>1.5 (1.2–1.9)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>2.7 (1.4–4.7)</td>
<td>1.2 (0.4–2.8)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>3.1 (1.5–5.5)</td>
<td>1.2 (0.3–3.2)</td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>1.0 (0.1–3.6)</td>
<td>0.0 (0.0–2.5)</td>
<td>1.1 (0.7–1.6)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>2.8 (1.1–5.7)</td>
<td>1.2 (0.2–3.4)</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td>Larynx</td>
<td>2.7 (1.7–3.9)</td>
<td>2.4 (1.5–3.6)</td>
<td>0.8 (0.6–1.0)</td>
</tr>
<tr>
<td>Lung*</td>
<td>2.4 (2.2–2.6)</td>
<td>2.1 (1.9–2.3)</td>
<td>0.9 (0.9–1.0)</td>
</tr>
<tr>
<td>Vagina</td>
<td>16.9 (13.2–21.5)</td>
<td>2.0 (1.0–3.7)</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>Vulva</td>
<td>5.2 (4.0–6.8)</td>
<td>1.3 (0.8–1.9)</td>
<td>0.8 (0.7–0.9)</td>
</tr>
<tr>
<td>Anus, anal canal and ano rectum</td>
<td>2.9 (1.7–4.5)</td>
<td>1.3 (0.6–2.3)</td>
<td>0.9 (0.7–1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: SIR, standardized incidence ratio; CI, confidence interval.
*Includes bronchus, trachea, mediastinum, and other respiratory organs.

**Risk of Second Primary Head and Neck Tumors among Patients with Cervical Cancer Compared with Patients with Breast and Bladder Cancer.** The lifetime relative risk of second primary tumors among females with cervical, breast, and urinary bladder cancers of similar age are reported in Table 1. Both patients with cervical (SIR = 2.4, 95% CI = 2.2–2.6) and female patients with urinary bladder cancer (SIR = 2.1, 95% CI = 1.9–2.3) were at similar and increased risk of lung cancer as a second primary tumor. In contrast, female patients with breast cancer were at a reduced risk of developing lung cancer as a second primary tumor (SIR = 0.6, 95% CI = 0.4–0.9). The risk of SPC in the lung for patients with cervical cancer was almost 3 times higher than that for female patients with breast cancer. As expected, HPV-related second primary tumors arising in the vagina, vulva, and anus/anal canal were significantly increased for patients with cervical cancer (SIR = 16.9, 5.2, and 2.9, respectively), whereas for female patients with urinary bladder cancer the lifetime relative risk was slightly elevated but was not statistically significantly different from the general female population (SIR = 2.0, 1.3, and 1.3, respectively). The risk of vaginal cancer in patients with cervical cancer was 8.5 times higher than patients with urinary bladder cancer.

Patients with breast cancer were not at risk for second primary tumors in the vagina, vulva, or anus/anal canal, and their relative risk was 28, 6.5, and 3 times lower, respectively, than what was observed for patients with cervical cancer. For the development of second primary tumors in head and neck subsites, female patients with breast cancer were not at increased risk, except for the salivary gland (SIR = 1.5, 95% CI = 1.2–1.9). Female patients with urinary bladder cancer were at a reduced risk of developing lung cancer as a second primary tumor (SIR = 0.9, 95% CI = 0.7–0.9). The risk of vaginal cancer in patients with cervical cancer was 8.5 times higher than patients with urinary bladder cancer.

**DISCUSSION**

This analysis of the SEER data from 1973 to 2002 reported the lifetime risk of second primary cancers among females who had a first diagnosis of cervical carcinoma. The incidence of SPC of the head and neck subsites in this population was
compared with the incidence of all SPC in females in the general population to assess whether patients with cervical cancer had an excess risk of second primary tumors at head and neck sites. Our results indicate that second to anogenital sites of the vagina, vulva, and anus/anal canal, patients with cervical cancer had the highest risk of developing SPC in the pharynx. This pattern did not change when the analysis was repeated with a subset of patients with cervical cancer that did not receive radiotherapy as a form of treatment for their cervical cancer. Our study agrees with earlier studies that have reported patients with cervical cancer as having an increased risk of developing SPCs in the upper aerodigestive tract. Frisch and Biggar have also reported an etiological parallel with HPV-associated anogenital cancer and the development of tonsillar cancers. In addition to what was previously reported, we show that the observed number of cases of tonsillar and other pharyngeal tumors among patients with cervical cancer is in excess of what is expected among female patients with other types of cancers.

Our results are consistent in showing an increase in HPV-related cancers (vagina, vulva, anus/anal canal, and to a lesser extent, oropharynx, hypopharynx, and larynx) after a cervical cancer diagnosis, suggesting the etiologic involvement of HPV in the development of these SPCs. The prevalence of HPV in head and neck tumors is reported to be about 24% for all head and neck subsites combined, but for the oropharynx (which includes the tonsils), the prevalence is about 31%. The direct involvement of HPV infection in the risk of HNSCC as second primary cancers among patients with cervical cancer cannot be demonstrated in these preliminary data. However, the increased risk observed for pharynx and more so the tonsils, ranked second to that of other HPV-related anogenital cancers (vagina: SIR = 16.9; oropharynx SIR = 2.7; tonsils SIR = 3.1; hypopharynx SIR = 2.8), suggesting a possible involvement of HPV.

Studies have suggested that the increased risk of head and neck cancer among patients with cervical cancer is tobacco-related, and this is clearly shown by the increased risk of SPC at other tobacco-related sites such as the lung and urinary bladder; however, the relative risk for the pharynx and tonsils was approximately 3 times higher than what was observed for another tobacco-related cancer, bladder cancer. Among female patients with urinary bladder cancer, the lifetime relative risk for SPC in the oropharynx, hypopharynx, and tonsil was 1.2. For patients with cervical cancer, the lifetime relative risk for SPC was 2.8 and 2.7 for the oropharynx and hypopharynx, respectively, and 3.1 for the tonsils. One limitation of the SEER data base is that no direct data on smoking are available; therefore, determination of whether a subset of SPC at head and neck sites among patients with cervical cancer might occur in the absence of tobacco use cannot be determined. The data suggest that the increased risk of SPC in head and neck subsites in patients with cervical cancer may be attributed to tobacco. Slightly elevated risks of SPC in the lung and larynx for patients with cervical cancer was comparable to that of patients with urinary bladder cancer. However, the comparisons of lifetime relative risk of SPC in HPV-related head and neck subsites such as the tonsils and other pharynx shows an excess risk for patients with cervical cancer compared with patients with urinary bladder cancer. Therefore, other risk factors besides tobacco must be present in patients with cervical cancer who develop an excess head and neck SPC. Altogether, our results suggest that further investigation of the role of HPV in the development of SPC of head and neck in patients with cervical cancer is warranted. Problems in immune function caused by treatment of chemotherapy in patients may also affect the risk of second primary head and neck cancer among the patients with cervical, bladder, and breast cancer. We used the SEER public-use database for this analysis. Another limitation of this database is that the public-use file does not have data on chemotherapy. Nonetheless, we performed the analysis for all patients, patients treated with surgery only (no radiation), and all patients treated with radiation to see whether there might be a difference in SPC based on treatment. We found no significant differences in these results.

The source of HPV infection to the oral mucosa is still unclear. Studies of oral HPV infection in women with past or present genital HPV infection reported a low prevalence of oral HPV infection in cytologic scrapings of the buccal mucosa using cotton tip swabs. These results did not support the hypothesis that women with genital HPV infection would be at risk for oral HPV infections. However, true HPV prevalence relies on the collection of basal epithelial cells, thus the results of this study may have been underestimated because of their sample collection method. In contrast to these prior studies, another study has
shown a correlation between the HPV types detected in cervicovaginal smears from patients with HPV-positive head and neck tumors.\textsuperscript{27}

In studies of cervical carcinoma, behaviors such as early age of sexual intercourse, multiple sex partners, and lifetime number of partners demonstrate that sexual transmission is the predominant mode of acquisition of HPV.\textsuperscript{28} For HNSCC, some studies have also reported a relationship between sexual behavior and HPV-infection, suggesting that oral HPV infection may be acquired through sexual behavior,\textsuperscript{9,29–32} whereas others do not find such an association.\textsuperscript{10,33,34}

Although some evidence suggests that sexual behavior may be associated with HPV acquisition in the oral mucosa, the route of transmission is still unclear and lack of sexual behavior information for the subjects included in this analysis was also a limitation.

Nonetheless, our data, in conjunction with the lack of information on the direct association between HPV genital infection and HPV-positive HNSCC, suggest that further studies are needed to determine whether the increased risk of HPV-positive HNSCC is associated with a prior diagnosis of other HPV-related cancers.

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**REFERENCES**


