GYNECOLOGY

Second primary anal and oropharyngeal cancers in cervical cancer survivors

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BACKGROUND: Human papilloma virus infection is responsible for approximately 31,500 new cancers in the United States annually. Almost all cervical cancers are linked to human papilloma virus infection. As early identification and treatment of cervical cancer improve, the incidence of cervical cancer has decreased and survival has improved. However, survivors continue to remain at risk for other human papilloma virus–related malignancies. The purpose of this study was to assess the risk of primary anal and oropharyngeal cancers among women with a history of squamous cell carcinoma of the cervix.

STUDY DESIGN: A population-based cohort of 21,060 women diagnosed with cervical squamous cell carcinoma from 1973 through 2014 was identified from the Surveillance, Epidemiology, and End Results Program-9 data. Standardized incidence ratios for anal and oropharyngeal cancers were calculated to estimate the risk of a second primary human papilloma virus–related malignancy based on incidence in the general population. Results were further stratified by age (20–53, 54 years old or older) and latency period (2–11, 12–59, 60–119, 120 months or longer). The number needed to screen for oropharyngeal and anal cancers was estimated using study results and Centers for Disease Control and Prevention–reported incidence rates.

RESULTS: Cervical squamous cell cancer survivors had a higher risk of being diagnosed with oropharyngeal cancer (standardized incidence ratio, 4.36, 95% confidence interval, 1.19–11.15) and anal cancer (standardized incidence ratio, 2.20, 95% confidence interval, 1.28–3.52). Patients diagnosed with cervical cancer between ages 20 and 53 years had an increased risk of anal cancer (standardized incidence ratio, 3.53, 95% confidence interval, 1.15–8.23). Age 54 years or older at cervical cancer diagnosis was associated with increased oropharyngeal cancer risk only (standardized incidence ratio, 5.04, 95% confidence interval, 1.37–12.91). Latency stratification was significant for increased OPC risk between 2–11 months and 12–59 months after diagnosis. At 120 months or longer, there was an increased risk of both oropharyngeal cancer (standardized incidence ratio, 7.97, 95% confidence interval, 2.17–20.42) and anal cancer (standardized incidence ratio, 2.60, 95% confidence interval, 1.34–4.54). The estimated number needed to screen for oropharyngeal cancer (number needed to screen for oropharyngeal cancer, 282) and anal cancer (number needed to screen for anal cancer, 1272) is significantly less than the number needed to screen for cervical cancer.

CONCLUSION: Squamous cell cervical cancer survivors have a substantially increased risk of anal and oropharyngeal cancers. This increased risk is significant 10 or more years after the cervical cancer diagnosis. Health care providers and survivors should be aware of this increased risk. The development of effective and economical surveillance methods for anal and oropharyngeal cancers in cervical cancer survivors is urgently needed.

Key words: anal cancer, anal intraepithelial neoplasia, cervical cancer, human papilloma virus, oropharyngeal cancer, screening tools, surveillance, anal Papanicolaou smears

Human papilloma virus (HPV) is a known cause of cancer of the cervix, vulva, vagina, oropharynx, anus, rectum, and penis.[1] According to data collected by the Center for Disease Control (CDC) from 2008 through 2012, approximately 30,700 new cancers per year in the United States can be attributed to HPV infection. Of these cases, 19,200 are diagnosed in women and 11,600 in men.[1] Screening for cervical cancer with cytology and HPV testing can detect premalignant lesions and can help prevent progression to cancer.

Guidelines for surveillance after the treatment of cervical cancer were developed by the National Comprehensive Cancer Center and are supported by the Society of Gynecologic Oncology.[2] Recommendations include follow-up every 3–6 months for the first 2 years after treatment, followed by every 6 months for 3 additional years, and annually thereafter. Surveillance visits should include speculum, bimanual, and rectovaginal examinations. Routine cytology for detecting vaginal or local recurrence is suggested; however, there is insufficient evidence regarding its benefit.[2]

As early identification and treatment of cervical cancer improve, the incidence of cervical cancer in the United States and worldwide has decreased, and progression-free survival has improved.[1,3] However, survivors continue to remain at risk for other HPV-related malignancies. Specifically, the incidence of oropharyngeal (OPC) and anal cancers has been slowly increasing.[4] A 3-fold increase in OPC incidence rates in the United States was noted between 1988 and 2004.[5]

In 2019, an estimated 53,000 people will develop OPC, many of which will be linked to HPV infection.[6] Furthermore, the same oncogenic HPV strains that are associated with squamous cell carcinoma of the cervix are associated with anal and oropharyngeal squamous cell carcinomas. A study by Crawford et al[7]

Cite this article as: Papatla K, Halpern MT, Hernandez E, et al. Second primary anal and oropharyngeal cancers in cervical cancer survivors. Am J Obstet Gynecol 2019;221:478.e1-6.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.05.025

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AJOG at a Glance

Why was this study conducted?

The study was conducted to determine the risk of anal and oropharyngeal cancers among cervical cancer survivors and to demonstrate the need for the development of screening guidelines and tools in this vulnerable population.

Key findings

There is a long latency (10 or more years) to the development of anal and oropharyngeal cancers after diagnosis of cervical cancer. Patients are at a particularly increased risk of oropharyngeal cancer. The estimated number needed to screen for oropharyngeal and anal cancers is significantly less than the number needed to screen for cervical cancer.

What does this add to what is known?

Our study reaffirms previous data on the increased risk of human papilloma virus–associated malignancies among cervical cancer survivors. Few studies have investigated the number needed to screen for anal and oropharyngeal cancers in this patient population.

analyzed 100 nonimmunocompromised women with abnormal cervical cytology. Results showed a high prevalence of HPV in all 3 sites (96.0% cervix, 91.4% anus, and 92.4% oropharynx), suggesting that HPV simultaneously exists in multiple anatomical sites after the infection is acquired.[7] Progression to anal cancer can be prevented if premalignant lesions are detected and treated early.[8]

The purpose of this study was to assess the risk of primary anal and oropharyngeal cancers among women with a history of squamous cell carcinoma of the cervix and to demonstrate the need for the development of screening tools for this high-risk patient population.

Materials and Methods

All patients were identified using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. This database includes incidence and population data stratified by race, sex, year of diagnosis, geographic area, and age. The collected data are thought to be representative of the general United States population.

The SEER-9 data ranges from 1973 to 2014 and includes approximately 9.4% of the entire US population based on 2010 census data. Regions covered include San Francisco–Oakland, Connecticut, Detroit (metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Atlanta.

Using the SEER*Stat software program (Surveillance Research Program, National Cancer Institute, Bethesda, MD), the SEER-9 registry data were utilized to estimate the incidence of secondary HPV-related malignancies among cervical squamous cell carcinoma survivors.

A population-based cohort of women diagnosed with cervical squamous cell carcinoma from 1973 through 2014 was identified from the SEER-9 program data. *International Classification of Diseases for Oncology*, third edition, histology classification codes for squamous cell carcinoma, not otherwise specified [8070/3], and site recoded as cervix uteri were utilized to identify the patient population. Cases reported on death certificate or autopsy as well as those with unknown age at diagnosis were excluded.

Standardized incidence ratios (SIRs) for anal cancer and OPC were calculated to estimate the risk of a second primary HPV-related malignancy based on incidence in the general population. Two separate categories were identified for OPC based on assigned diagnosis codes: oral cavity and pharynx and oropharynx.

SEER*Stat software was used to calculate SIR as a measure of the relative risk of developing a second primary malignancy. The statistical significance of the SIRs were assessed using exact confidence intervals (CI) based on the assumption that the observed number of second anal cancers and OPCs followed a Poisson distribution. A latency period of 2 months or greater between cancer diagnoses was required to exclude synchronous primary cancers.

The observed incidence of second primary malignancies among women with a history of squamous cell cervical cancer was compared with the expected incidence among the corresponding general US population. Results were further stratified by age at cervical cancer diagnosis (20–53, 54 years old or old) and latency period between first and second primary malignancies (2–11, 12–59, 60–119, 120 months or longer). An estimate of the number needed to screen (NNS) to prevent 1 case of OPC or anal cancer among cervical cancer survivors was calculated. We used the incidence of OPC and anal cancer in our study population (1973–2004) and the incidence rates reported by the CDC for women diagnosed with OPC and anal cancer between 2011 and 2015. The formula used is that used to calculate number needed to treat (see description in Results section below).

Results

A total of 21,060 women diagnosed with cervical squamous cell carcinoma from 1973 through 2014 were identified from the SEER-9 geographic areas. They were 20 years old or older at the time of cervical cancer diagnosis. Mean age at the time of cervical cancer diagnosis was 52 years.

A total of 2566 second primary malignancies were observed among the identified cohort. Of these, 76 were OPC and 17 were anorectal (Table 1). The observed to expected ratio (SIR) of both oropharyngeal and anal cancers was statistically larger than expected.

There were no cases in the database of women diagnosed with cervical cancer between 0 and 19 years of age. When stratified by age at initial cervical cancer diagnosis, the SIR of both

anal cancer and OPC remained statistically significant in patients diagnosed between 20 and 53 years old ($SIR_{oral\ cavity+pharynx}$, 2.56, 95% CI, 1.40–4.29; $SIR_{anus,\ anal\ canal,\ anorectum}$, 3.53, 95% CI, 1.15–8.23). Between 54 and 99 years old, only the SIR for OPC was significant ($SIR_{oropharynx}$, 5.04, 95% CI, 1.37–12.91; $SIR_{oral\ cavity+pharynx}$, 2.00, 95% CI 1.52–2.58).

Between 2 and 11 months after the cervical cancer diagnosis, patients were only at an increased risk of OPC ($SIR_{oral\ cavity+pharynx}$, 4.04, 95% CI 1.75–7.97). An increased risk of OPC was also noted between 12 and 59 months after cervical cancer diagnosis ($SIR_{oral\ cavity+pharynx}$, 2.43, 95% CI 1.41–3.89).

There was no statistically significant increase in the SIR of OPC or anal cancer between 60 and 119 months after initial cervical cancer diagnosis. However, at 120 months or longer after a cervical cancer diagnosis, a statistically significant increased risk for developing both OPC and anal cancer was seen ($SIR_{oropharynx}$, 7.97, 95% CI, 2.17–20.42; $SIR_{oral\ cavity+pharynx}$, 1.93, 95% CI, 1.35–2.67; $SIR_{anus,\ anal\ canal,\ anorectum}$, 2.60, 95% CI, 1.34–4.54).

The calculation of the NNS is shown in Tables 2 and 3. With an effective screening method, 282 cervical cancer survivors will need to be screened to potentially prevent 1 case of OPC, while 1272 will need to be screened to prevent 1 case of anal cancer.

Comment

In 2018, an estimated 51,540 and 8580 women were diagnosed with OPC and anal cancer, respectively, in the United States, while 13,240 women were diagnosed with cervical cancer.[9] The results of our study strongly support previous literature that has demonstrated the increased risk of OPC and anal cancer among cervical squamous cell cancer survivors. In particular, this risk persists and remains significant 10 or more years after their initial diagnosis of cervical cancer.

Multiple European studies have utilized national databases to perform similar analyses. Neumann et al[10] used cancer data from 10 districts in France to determine the SIR of any potentially HPV-associated malignancy after a first potentially HPV-related malignancy. HPV-related malignancies were defined as cancers of the cervix, vagina, anus, vulva (squamous cell and basaloid), base of tongue, lingual tonsil, oropharynx, and tonsil. Of the 4,234 women with primary cervical cancer, 87 second potentially HPV-related cancers were observed, of which 5 were head and neck, 5 were anus, 3 were vaginal, and 3 were vulvar ($P < .05$ for all).[10] Similar to our study, results were highly significant for the identified second potentially HPV-related malignancies despite small numbers.

A nationwide cohort study performed in Denmark followed up close to 2.8 million women for up to 34 years. For those women with cervical intraepithelial neoplasia (CIN)-3, there was an increased relative risk of anal cancer starting even 1 year after diagnosis of CIN-3. This risk was observed even 25 years after diagnosis (hazard risk, 4.8, 95% CI 3.3–7.0).[11]

Other observed second primary cancer sites included the vulva and vagina. Increased anal cancer risk was also noted in women with a history of CIN-2, although less so than for those with CIN-3.[11] Rectal cancer, which has no confirmed association with HPV infection, was used as a comparison; no increased risk was noted.[11] This study did not evaluate OPC risk.

Ebisch et al[12] followed up 89,018 women with CIN-3 in The Netherlands and found increased incidence rates (IRs) for anal cancer (IR, 3.85), anal

TABLE 1
Incidence of anal and oropharyngeal cancers after cervical squamous cell carcinoma

Site of second primary malignancy (total n = 21,060)	Number of observed	Number of expected	SIR (or O/E)	95% CI	Mean age at event, y
Oropharynx	4	0.92	4.36[a]	1.19–11.15	62.67
Oral cavity and pharynx	72	34.55	2.08[a]	1.63–2.62	63.41
Anus, anal canal, and anorectum	17	7.42	2.20[a]	1.28–3.52	61.73

CI, confidence interval; *E*, expected; *O*, observed; *SIR*, standardized incidence ratio.

[a] Statistically significant SIR ($P < .05$).

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TABLE 2
Number needed to screen to prevent 1 case of OPC

Variables	Cervical Cancer Survivors (N)	General population (N)
Oropharyngeal carcinoma, n	76	6.3
No oropharyngeal carcinoma, n	20,984	99,993.7
Absolute risk of OPC	0.00357479	0.000063
Absolute risk reduction ($AR_{cervical\ ca} - AR_{general\ population}$)	0.003547	
NNS (1/ARR)	281.9	

AR, absolute risk; *ARR*, absolute risk reduction; *NNS*, number needed to screen; *OPC*, oropharyngeal cancer.

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TABLE 3
Number needed to screen to prevent 1 case of anal cancer

Variables	Cervical cancer survivors (n)	General population (n)
Anal cancer, n	17	2.1
No anal cancer, n	21,043	99,997.9
Absolute risk of anal cancer	0.00080722	0.000021
Absolute risk reduction ($AR_{cervical\ ca} - AR_{general\ population}$)	0.000786	
NNS (1/ARR)	1272.3	

AR, absolute risk; *ARR*, absolute risk reduction; *NNS*, number needed to screen.

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intraepithelial neoplasia grade 3 (IR, 6.68), vulvar cancer (IR, 4.97), vulvar intraepithelial neoplasia grade 3 (IR, 13.66), vaginal cancer (IR, 86.08), vaginal intraepithelial neoplasia grade 3 (IR, 26.65), and OPC (IR, 5.51). This risk was observed even after 20 years of follow-up.[12]

Results of a similar nationwide cohort study performed in Sweden in 2007 were consistent with both the Dutch and Danish cohort studies.[13] Risks for anal, vulvar, and vaginal cancers were increased 10 or more years after a diagnosis of CIN-3 and were also age dependent.[13]

These European database studies demonstrate that a diagnosis of CIN alone can increase a woman's risk of future HPV-associated malignancies. However, while many of the European studies analyze anogenital second primary malignancies, few have included OPC in their analyses.

A number of population-based studies within the United States have also examined the incidence of HPV-associated malignancies after cervical cancer. Ragin and Taioli[14] showed that patients with cervical cancer were at highest risk of developing laryngeal (SIR, 2.7), oropharyngeal (SIR, 2.7), and tonsillar (SIR, 3.1) cancers.

Utilizing data from 13 population-based cancer registries in the United States, Denmark, Norway, Finland, and Sweden, Chaturvedi[4] showed an increased risk of both HPV-related malignancies and smoking-related malignancies among 104,760 cervical cancer survivors.[4] Similar to our study, they demonstrated the long latency of subsequent HPV-related cancers, with second cancers observed even after 40 years of follow-up.

A 2008 SEER database study by Balamurugan et al[15] analyzed the risk of in situ and invasive HPV-associated cancers after cervical cancer between 1992 and 2004. While this study showed a significantly increased risk of in situ vaginal and vulvar cancers as well as invasive cancers of the vagina, vulva, and rectum, the risk of OPC was not significant. The risk of anal cancer was not analyzed because of a lack of identified cases within the database.[16] In contrast to this 2008 SEER study, our study utilizes a larger SEER database and was able to demonstrate a significant risk of both OPC and anal cancer.

More recently, a SEER-database study by Matsuo et al[16] demonstrated the increased risk of metachronous vaginal, vulvar, and anal cancers among cervical cancer survivors, with 20-year cumulative incidence rates of 0.57%, 0.33%, and 0.16%, respectively, and poor 5-year survival rates after diagnosis. Associated risk factors included older age, squamous histology, radiotherapy, and black race. OPC was not examined.[16]

Despite multiple studies demonstrating the increased risk of HPV-related malignancies after cervical cancer, there are currently no evidence-based recommendations or guidelines for screening of cervical cancer survivors. As reviewed previously, the National Comprehensive Cancer Center provides detailed post-treatment surveillance for cervical cancer survivors to screen for recurrence but does not address other HPV-associated malignancies.[2] This reflects, in part, the difficulty in screening for OPC or anal cancer, even among high-risk populations. Given the lack of effective screening tools for anal carcinoma and OPC, funded research is needed to identify and validate new tools that are both specific and cost effective for this high-risk population.

To demonstrate the impact that effective screening tools could have in preventing premature death from OPC and anal cancer, we calculated the number of cervical cancer survivors needed to be screened to prevent 1 death. A concrete formula for NNS has not been determined, and this calculation has been approached in a number of different ways. One such approach utilizes the same formula used for the number needed to treat.[17]

It is important to note that application of this method to our data requires the assumption that ideal screening tools for OPC and anal cancer exist and can account for the differences in disease incidences between cervical cancer survivors and the general population. The calculations presented here are inferences and simply meant to demonstrate the benefit that potential screening tools may have in cervical cancer survivors. The specifics of these calculations can be found in Tables 2 and 3.

We used the incidence of OPC and anal cancers in our study population (1973–2004) and the reported CDC incidence rates of OPC and anal cancer per 100,000 women between 2011 and 2015. We recognize that these time frames are different; however, we assumed that in the 2 large populations followed up over long time intervals, the rates of OPC and anal cancers remained relatively stable despite the difference in the time frame.

Our estimated NNS to prevent 1 case of either OPC ($NNS_{OPC} = 282$) or anal cancer ($NNS_{anal} = 1272$) appears to be

less than the NNS to prevent cervical cancer. A 2016 British study showed that among women aged 20−64 years with borderline high risk, moderate dyskarosis or worse, the NNS to prevent 1 case of invasive cervical cancer was 2726 (95% CI, 2630−2826).[18]

Surveillance and screening guidelines for cervical cancer survivors should be updated to include awareness of the increased risk and long latency for development of anal and oropharyngeal cancers. At-risk populations such as those with HIV, women with multiple sexual partners and/or high risk sexual activity, cigarette smokers, older women, and women who have undergone radiation therapy should be considered for screening when effective methods become available.

Given the long latency demonstrated in our study, those who are poorly adherent with care may benefit from convenience screening whenever they see a health care provider. Additionally, investigating the roles of tobacco use and prior pelvic radiation in the development of second primary malignancies may also help identify subsets of cervical cancer survivors that are perhaps at the highest risk. This in turn can help to narrow the focus of future research and early detection and/or prevention efforts.

There are several limitations to our study. SEER data are thought to be representative of the general US population, and the SIR used in our analyses controls for a number of confounding factors including age and calendar time. However, while our SIR results were statistically significant, they were based on small numbers of women with second primary malignancies (76 for OPC and 17 for anal cancer, respectively). This small number may account for the nonsignificant increase in the SIRs between 60 and 119 months after the initial cervical cancer diagnosis despite significant SIRs before 60 months and after 119 months.

In addition, SEER does not include information on socioeconomic status and smoking status, so we could not control for these factors.[11] Further limitations of our study include the lack of information on prior cervical cancer treatment, particularly pelvic radiation therapy. Further studies are needed to evaluate the effect of prior radiation therapy to the pelvis on the development of second primary HPV-related malignancies within the irradiated field. Finally, our study assumes that the second primary anal cancers and OPC that were observed in our patient population can be attributed to persistent HPV infection. However, HPV status of the tumor is not specified in this retrospective database.

Conclusion

Squamous cell cervical cancer survivors have an increased risk of HPV-associated malignancies such as anal cancer and OPC. This increased risk is significant 10 or more years after the cervical cancer diagnosis. As cervical cancer treatment improves and patients survive longer, health care practitioners and survivors should be aware of this risk. Given that the estimated NNS for both OPC and anal cancer is less than the NNS for cervical cancer, research aimed at determining the most effective and economical screening methods for these diseases in cervical cancer survivors is warranted. ■

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Received Feb. 6, 2019; revised May 10, 2019; accepted May 17, 2019.

The authors report no conflict of interest.

Abstract presented as poster at 49th annual meeting of the Society of Gynecologic Oncology, New Orleans, LA, March 24—27 2018.

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