

BACKGROUND

- From the mid-1970s and early 1980s, survival among HPV-associated cancer patients has improved, while the incidence has increased among younger age cohorts.
- Among HPV-associated cancer survivors, persistent HPV infection may remain a risk factor for preventable HPV-associated second primary cancers (HPV-SPCs).
- Objective:** To determine the risk of HPV-SPCs among HPV-associated index cancer patients.

METHODS

- Study period:** Jan 1, 1973 – Dec 31, 2014
- Study population:** Persons (73 085 women and 40 187 men) with HPV-associated (cervical, vaginal, vulvar, oropharyngeal, anal and penile) cancers in the Surveillance Epidemiology and End Results (SEER) database.
 - Follow-up period: 644 691 person-years for women and 192 440 person-years for men
- Outcome:** Metachronous invasive solid HPV-SPCs developing ≥ 2 months after index HPV-associated cancers.
- Analyses:** Overall and stratified by cancer subtypes
 - The risk of second primary cancer by using the standardized incidence ratio (SIR) (observed cases/expected cases)
 - The expected cases were estimated based on reference rates in SEER-9 registries that were stratified by race, sex, age intervals, and the calendar year.
 - Excess absolute risks (EAR) were also calculated. (Observed cases-Expected cases)*10,000/ person-years at risk

RESULTS

Table 1. Standard incidence ratios of HPV-SPC after index HPV-associated cancers

Index HPV Cancers	Women			Men		
	Observed	SIR (95% CI)	EAR*	Observed	SIR (95% CI)	EAR*
All HPV related cancers	1397	6.2 (5.9-6.6)	18.2	1098	15.8 (14.9-16.8)	53.5
Cervical	362	2.4 (2.2-2.7)	4.5	NA	NA	NA
Vaginal	26	6.2 (4.0-9.0)	24.0	NA	NA	NA
Vulvar	265	12.7 (11.2-14.2)	50.5	NA	NA	NA
Oropharyngeal	669	19.8 (18.4-21.4)	80.6	1007	18.0 (16.9-19.1)	61.5
Anal	75	5.2 (4.1-6.5)	17.5	42	6.5 (4.7-8.8)	18.5
Penile	NA	NA	NA	49	7.0 (5.2-9.3)	22.7
Non-HPV related cancers	1757	0.8 (0.8-0.8)	-0.8	1355	0.7 (0.7-0.8)	-1.1
Prostate	NA	NA	NA	1315	0.7 (0.7-0.8)	-1.2
Breast	1651	0.8 (0.8-0.8)	-0.8	NA	NA	NA
Thyroid	106	0.6 (0.5-0.8)	-1.0	40	0.9 (0.6-1.2)	-0.3

Abbreviations: HPV-SPC, HPV-related second primary cancer; SIR, standard incidence ratio; EAR, excess absolute risk; NA, Not applicable; * EAR = (Observed count – Expected count) * 10,000 / Person-years at risk

Table 2. Standard incidence ratios of HPV-SPC occurring at sites different than index cancers

Index HPV Cancers	Women			Men		
	Observed	SIR (95% CI)	EAR*	Observed	SIR (95% CI)	EAR*
All HPV related cancers	485	3.5 (3.2-3.8)	5.4	44	2.1 (1.5-2.8)	1.2
Cervical	290	3.5 (3.1-3.9)	4.4	NA	NA	NA
Vaginal	19	4.8 (2.9-7.5)	16.6	NA	NA	NA
Vulvar	90	5.4 (4.4-6.7)	15.2	NA	NA	NA
Oropharyngeal	37	1.6 (1.1-2.2)	1.8	15	1.7 (1.0-2.8)	0.4
Anal	49	3.8 (2.8-5.1)	10.5	14	2.4 (1.3-4.0)	4.3

Abbreviations: HPV-SPC, HPV-related second primary cancer; SIR, standard incidence ratio; EAR, excess absolute risk; NA, Not applicable; * EAR = (Observed count – Expected count) * 10,000 / Person-years at risk

CONCLUSION

- The risk of developing HPV-SPC among HPV-associated cancer survivors is significant, implying that persistent HPV infection at multiple sites may be associated with SPCs.
- Future studies of HPV infection persistence occurring at all anatomic sites among HPV-associated cancer survivors are crucial to understand the role of HPV in SPC carcinogenesis.

Figure 1. Subsite-specific standard incidence ratios

