Title: Human papillomavirus (HPV)-associated malignancies as second cancers in childhood cancer survivors: a report from the Childhood Cancer Survivor Study

Working Group: This report will be written within the Second Malignancy Working Group.

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1. Background and rationale

Second malignant neoplasms (SMN) are the leading cause of non-relapse mortality in childhood cancer survivors, occurring in 5-15% of long term survivors[1,2,3,4,5,6]. It is important to characterize SMN, including risk factors associated with their development, so that survivors at high risk can be identified and early surveillance and intervention can be implemented. Major risk factors for SMN include treatment-related risk factors (specifically, chemotherapeutic and radiation exposures) and genetic predisposition. In other chronic disease models, such as HIV and rheumatoid arthritis, investigators have identified increased rates of HPV-associated cervical, head and neck, and anal cancers[7,8,9,10]. These are hypothesized to be a consequence of the increased inflammation that can occur with HPV infection. Ojha and colleagues used the SEER Cancer Registries to determine that childhood cancer survivors indeed have a 1.4-fold increased risk of HPV associated SMN as compared to the general population.[6] However, this study was limited in its ability to examine specific treatment and behaviorally associated risk factors.

Human papillomavirus (HPV) infection is a necessary cause of cervical cancer[11,12]. HPVs also causes vaginal and vulvar cancers, anal cancers, and is the cause of a significant proportion of tonsillar and base of tongue malignancies. While HPV infection is a precondition for these malignancies, most HPV infections do not result in cancer. Indeed, in western society, the lifetime risk of a genital HPV infection is 70 to 80%[13,14]; however, only a small proportion (perhaps as low as 1%, depending on the HPV type) of people with anogenital HPV infections go on to develop HPV-associated anogenital malignancies[15]. Similarly, while the lifetime risk of oral HPV infection is high (the prevalence of oral HPV infection in males ranges between 4%-6.9%)[16,17], the lifetime risk of oropharyngeal cancer is only 1.1%[18]. Why only a small proportion of patients with HPV infection develop HPV-associated malignancies while the majority clears their infections spontaneously is unknown. Epidemiological risk factors

for progression from benign to malignant disease in patients with HPV infection are well described, and include early sexual debut, multiple sexual partners, HIV infection, smoking, and immunosuppression[19,20].

We have identified 68 SMN in 68 survivors in the childhood cancer survivor study that are HPV-associated cancers, including cervical, vaginal and vulvar, anal, tonsillar and base of tongue cancers (See Appendix A). Further understanding of the magnitude of the risk and risk factors, both treatment and health behavior related, of HPV-associated cancers in childhood cancer survivors would provide a unique opportunity to potentially reduce the SMN-associated risk in childhood cancer through promotion of HPV vaccine in childhood cancer survivors, development of more aggressive surveillance recommendations, and provide the basis for studies examining what aspects of the host response (e.g. expression of specific cytokines), host behaviors (e.g. sexual practices), and co-infections (e.g. with adenoviruses, with Epstein-Barr virus, with adeno-associated virus, or with bacterial pathogens, such as chlamydia) contribute to progression of HPV-associated infections to malignancies. While the investigators are cognizant that HPV infection, Pap smear results and history of genital warts, and sexual history are not available through the questionnaire data, we believe an understanding of the cumulative incidence, risk, and treatment related risk factors of these second cancers is in and of itself important as if we see an elevated rate, these data will impact cancer screening in this population, will support the use of preventive HPV virus-like particle vaccines, and may suggest that these patients have an underlying biologic reason for carcinogenesis requiring further investigation.

2. Specific Aims and Research Hypotheses:

Aim 1: To describe the cumulative incidence, standardized incidence ratio and absolute excess risk of potentially HPV-associated second malignant neoplasms (SMN) among childhood cancer survivors.

Hypothesis: Childhood cancer survivors have an increased risk of HPV-associated SMN as compared to the general population.

Aim 2: To describe the risk factors (treatment related, behavioral) associated with the development of HPV-associated second cancers among childhood cancer survivors.

Hypothesis: HPV-associated second cancers in childhood cancer survivors are associated with previous radiation therapy, history of smoking and alcohol use.

3. Analysis Framework:

1. Outcome of interest: Potentially HPV-associated second cancers (see Appendix)

2. Population: Overall CCSS cohort (Original + Expansion)

3. Predictor variables to be analyzed

a. Previous diagnosis

b. Age at previous diagnosis

c. History of radiation therapy (yes/no)
d. History of pelvic radiation (yes/no)
e. History of head and neck radiation (yes/no)
f. Chemotherapy
    i. Type (Alkylators, Heavy Metals (Platinum based drugs), Anti-Metabolites, Anthracyclines, Anti-Tumor Antibiotics (Bleomycin), Corticosteroids, Enzymes, Plant Alkaloids, Epipodophyllotoxins,
    ii. Dose
g. Tobacco History (Answers to baseline survey questionnaire O1, O2, O3, O4, O5, O6, O7, O8)
h. Hematopoietic stem cell transplant (Yes/No)

4. Analysis

a. The analytic plan will be to determine age, gender, and calendar year adjusted standardized incidence ratios, and absolute excess risk for subsequent HPV-associated cancers among childhood cancer survivors, using SEER rates to estimate expected numbers of HPV-associated cancers from Poisson regression models. Cumulative incidence of HPV-associated second cancers will be evaluated from entry to the cohort (5 years post diagnosis), treating death as a competing risk event.
b. To the extent possible, we will evaluate the association between previously discussed predictor variables, treatment modalities (radiation therapy, chemotherapy, and stem cell transplant) with HPV-associated cancer examined as the outcome examined in total and individually as cervical and oropharyngeal cancers, in multivariable piecewise Poisson models. Due to the small number of events, the primary focus will be on evaluate impact of treatment, with additional predictor variables included in sequential pairwise models to determine the most important confounders.

Tables/Figures

a. Table 1. Characteristics of the CCSS cohort, including separately for survivors who have and have not developed a HPV-associated cancer

Characteristic	Patients with secondary HPV-associated cancer (N; %)	Cohort Members without secondary HPV-associated cancer (N; %)
Median age at last follow-up, years (Range)		
Median duration of follow-up, years (Range)		
Sex Male Female		
Race White Black Other Unknown		
Age at Primary Diagnosis, years Mean (SD) Median (Range)		
Current Age Mean (SD) Median (Range)		
Primary Diagnosis Leukemia Brain/CNS Tumor Hodgkin disease Non-Hodgkin Lymphoma Kidney Tumor Neuroblastoma Soft Tissue Sarcoma Bone Tumor		
Radiation Therapy		

Yes No		
Smoking History Never Former Current		
Chemotherapy for Primary Malignancy Alkylators Heavy Metals (Platinum based drugs) Anti-Metabolites Anthracyclines Plant Alkaloids Epipodophyllotoxins		
Radiation Therapy for Primary Malignancy In-Field Out of Field		
Family History of any cancer Yes No		
Stem Cell Transplant for Primary Malignancy Yes No		
Other Second Malignant Neoplasm Yes No		
Treatment Era 1970-1974 1975-1979 1980-1986		
Vital Status Alive Deceased		
Median Time from primary diagnosis to diagnosis of HPV-associated cancer, years (Range)		N/A

Age at diagnosis of HPV-associated cancer, years Quartiles to be determined		N/A
Site of HPV-associated cancer Oropharynx Penis Cervix Vulva Rectum Anus Other		N/A
Radiation Exposure for Treatment of Primary Cancer HPV-associated Cancer in radiation field HPV-associated Cancer distant from radiation field No radiation from primary cancer Unknown primary radiation data Unknown site of HPV-associated Cancer		N/A
Cause of Death of HPV-Associated Second Cancer Participants Primary Cancer HPV-Associated Cancer Late Effects Toxicities Other Unknown		N/A

b. Figure 1 Cumulative Incidence Curve in entire cohort.

c. Table 2 Standardized Incidence Ratios and Excess Absolute Risks for Development of HPV-associated cancers

	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
All subjects with HPV-associated second cancers - Cervical Cancers - Oropharyngeal Cancers - Vulvar Cancers - Anal Cancers				
Sex Male Female				
Age at Primary Diagnosis (years)				
Time since primary diagnosis to HPV-associated second cancer				
History of Radiation Therapy Yes No Unknown				
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma				
Tobacco Use Never Smoker Former Smoker Current Smoker				
Family history of cancer Yes No				

d. Table 3. Risk Factors for the Development of HPV-associated Cancers: Univariate Analysis

Variable	Relative Risk (95% CI)	*P* Value
Sex		
Race White Black Hispanic Other		
Age at Primary Diagnosis		
Current age		
Primary Cancer Diagnosis		
Radiation Therapy		
Chemotherapy		
Alkylator score		
Antimetabolite (yes/no)		
Anthracycline dose tertile		
Epipodophyllotoxins		
Family History of GI Cancer		
Tobacco Use* Never Smoker Former Smoker Current Smoker		
History of Stem Cell Transplant for Primary Diagnosis Yes No		
Treatment Era 1970-1974 1975-1979 1980-1986		

***Incorporated as a time-dependent covariate**

e. Multivariate Rate Ratios for the development of HPV-associated malignancies

Variable	RR (95% CI)	*P* Value

Appendix: Seer coding for HPV-associated cancers

Site Group	ICD-O-2 Site	ICD-O-2 Histology (Type)	Recode
Oral Cavity and Pharynx			

Lip	C000-C009	excluding 9590-9989, and 9050-9055, 9140+	20010
Tongue	C019-C029		20020
Salivary Gland	C079-C089		20030
Floor of Mouth	C040-C049		20040
Gum and Other Mouth	C030-C039, C050-C059, C060-C069		20050
Nasopharynx	C110-C119		20060
Tonsil	C090-C099		20070
Oropharynx	C100-C109		20080
Hypopharynx	C129, C130-C139		20090
Other Oral Cavity and Pharynx	C140, C142-C148		20100
Anus, Anal Canal and Anorectum	C210-C212, C218		21060
Male Genital System			
Penis	C600-C609		28030
Female Genital System			
Cervix Uteri	C530-C539	excluding 9590-9989, and 9050-9055, 9140+	27010
Vagina	C529		27050
Vulva	C510-C519		27060

Appendix A.

SEER Recode category name				
SEER Recode Category	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
Tongue	13	19.12	13	19.12
Salivary Gland	1	1.47	14	20.59
Gum and Other Mouth	7	10.29	21	30.88
Nasopharynx	1	1.47	22	32.35
Tonsil	2	2.94	24	35.29
Oropharynx	1	1.47	25	36.76
Hypopharynx	1	1.47	26	38.24
Rectum	10	14.71	36	52.94
Cervix Uteri	23	33.82	59	86.76
Vulva	9	13.24	68	100.00

Reduction in early cervical lesion size in women who gave up smoking after diagnosis has been reported[21]. In addition, smokers have a 3-fold increased risk of treatment failure of CIN compared to non-smokers, necessitating more intensive follow-up after treatment[22].

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