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HPV vaccination coverage for pediatric, adolescent and young adult patients receiving care in a childhood cancer survivor program

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ABSTRACT

Pediatric, adolescent and young adult patients undergoing cancer treatment and/or hematopoietic stem cell transplant are at increased risk for developing a secondary human papillomavirus (HPV)-associated malignancy. The objective of this study was to determine HPV vaccination coverage among individuals participating in a childhood cancer survivor program (CCSP). A retrospective cohort study was conducted among CCSP patients age 11–26 years attending a CCSP visit between 2014 and 2019. Survivors were age-, sex-, and race-matched 1:2 with controls without cancer. Data were abstracted from the electronic health record and state-based vaccination registry. Analysis was limited to Minnesota residents to minimize missing vaccination data. Survivorship care plans (SCPs) were reviewed for vaccine recommendations.

592 patients were included in the analyses (200 CCSP patients; 392 controls). By study design, mean age (18.4 years), race (72 % white), and sex (49 % female) were similar in the two groups. Among CCSP patients 22 % resided in a rural area compared to 3.8 % of controls. Vaccination coverage among CCSP patients was not statistically significantly different from controls [60.0 % vs 66.3 %, OR = 0.82, 95 % CI: (0.55, 1.23), p = 0.35]. Completion of 3 doses was not different between groups even though 3 doses is recommended for all CCSP patients regardless of age at initiation (28.5 % vs 30.1 %, p = 0.09). Only 8.0 % of SCPs recommended HPV vaccination.

Although patients participating in a CCSP did not have significantly different HPV vaccination coverage compared to controls, HPV vaccination initiation and 3-dose series completion are still suboptimal in a patient population at high-risk of a secondary HPV-associated cancer.

1. Introduction

In 2020, an estimated 41 200 children, adolescents, and young adults younger than 30 years of age were diagnosed with cancer (American Cancer Society Key Statistics for Childhood Cancers, 2020). Among long-term pediatric, adolescent, and young adult cancer survivors, secondary cancers are a leading cause of early mortality (Yeh et al., 2020). Specifically, cancer survivors are 2.8 times more likely to develop a human papillomavirus (HPV)-associated malignancy compared to the general population (Ojha et al., 2013; Castellino et al., 2019). Further, these cancers are often diagnosed at younger ages with a median age of cervical cancer diagnosis of 27 years (Ojha et al., 2013; Castellino et al., 2019) compared to 49 years in the general population (Centers for Disease Control and Prevention). Oropharyngeal and cervical cancers are the most common HPV-associated cancers, followed by anal cancer; vaginal, vulvar and penile cancers are less common yet still cause significant morbidity (Centers for Disease Control and Prevention).

The HPV vaccine is highly effective at preventing HPV-associated

Abbreviations: CCSP, Childhood Cancer Survivor Program; EHR, electronic health record; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplant; IRB, institutional review board; MIIC, Minnesota Immunization Information Connection; SCP, survivorship care plan; TDaP, tetanus, diphtheria, and pertussis.

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cancers (Lei et al., 2020; Lehtinen et al., 2021; Falcaro et al., 2021; Kjaer et al., 2021). Whether HPV vaccination will achieve the same cancer risk reduction in immunosuppressed populations is currently unknown. Nonetheless, a Phase I study of patients who have undergone hematopoietic stem cell transplant (HSCT), the most immunosuppressive therapy, showed the vaccine to be safe; further, it induced an antibody response similar to that of healthy controls (Stratton et al., 2020). National Comprehensive Cancer Network Adolescent and Young Adult Oncology guidelines recommend HPV vaccination for male and female cancer survivors 9–26 years of age with consideration of vaccination up to 45 years in concordance with the Advisory Committee on Immunization Practices (Meites et al., 2020; Coccia et al., 2018). Unlike recommendations for the general population for whom only two doses of the vaccine are recommended if vaccination is initiated prior to 15 years of age, Centers for Disease Control and Prevention recommend three doses of the HPV vaccine regardless of age at initiation for all individuals who have received immunosuppressive therapy, including cancer therapy. Additionally, re-vaccination is recommended for patients who were vaccinated prior to hematopoietic stem cell transplant, or for those who were vaccinated during cancer therapy (Rubin et al., 2014; Centers for Disease Control and Prevention). Despite these recommendations and the elevated risk of HPV-associated cancers, observational studies have shown HPV vaccination coverage among pediatric, adolescent and young adult cancer survivors is even lower than coverage in the general population (Castellino et al., 2019; Klosky et al., 2013; Klosky et al., 2017). A study linking cancer registry data with 2014 state immunization data showed HPV vaccine initiation was only 24 % (34.1 % among female survivors and 16.8 % among male survivors) (Castellino et al., 2019). For those diagnosed with cancer prior to age 10 years, and thus eligible for on-time HPV vaccination, vaccination coverage for female cancer survivors was only one-third (HR: 0.32, 95 % CI: 0.12–0.89) and coverage for male cancer survivors was only one-quarter (HR: 0.25, 95 % CI: 0.06–0.98) that of the general population after adjusting for age, race and ethnicity. Furthermore, among those who initiated the vaccine, only 68.1 % of females and 56.9 % of males received at least 2 doses of vaccine. Notably, those who received only 2 doses of the vaccine may still have been incompletely vaccinated given the recommendation for 3 doses in this population (Rubin et al., 2014; Centers for Disease Control and Prevention, 2019). Unfortunately, these findings support results of other observational studies showing lower HPV vaccine coverage among cancer survivors (Klosky et al., 2017; Hardin et al., 2020).

Pediatric, adolescent and young adult cancer survivors may have additional and unique barriers to HPV vaccine initiation and completion, including potential ineligibility for HPV vaccination at the on-time vaccination age (9–12 years of age) due to cancer treatment or recovery, missed care due to ineffective care transitions between oncology and general practice pediatric providers once therapy is complete, and competing health issues resulting in suboptimal adherence due to care coordination challenges (Klosky et al., 2013; Cherven et al., 2019; Klosky et al., 2016; Klosky et al., 2015). Other studies have shown that similar to the general population, an oncologist recommendation for HPV vaccination is a strong predictor for vaccination among cancer survivors (Klosky et al., 2016; Klosky et al., 2012; Klosky et al., 2009). Practices vary widely as to whether the oncologist or the primary care provider is responsible for this aspect of care (Klosky et al., 2015).

These data highlight the unique challenges of providing HPV vaccination to pediatric, adolescent and young adult cancer survivors. The primary objective of this study was to determine the HPV vaccination coverage among patients participating in a childhood cancer survivorship program (CCSP), inclusive of survivors of pediatric, adolescent and young adult cancers and patients who had received a HSCT for a non-malignant hematologic condition, in comparison to a population of patients within the same health system who were matched by sex, age, and race. The secondary objective of this study was to determine if inclusion of a recommendation for HPV vaccination in the survivorship care plan (SCP) was associated with increased HPV vaccination coverage. We hypothesized that voluntary participation in a survivorship program focused on longitudinal healthcare post-cancer treatment and provision of a SCP, a summary document meant to be shared with the primary care provider, would be associated with increased HPV vaccination coverage among CCSP patients compared coverage previously reported in the literature, but that vaccination coverage would still be lower than that in the general population.

2. Patients and methods

2.1. Study design and population

In this retrospective cohort study, CCSP patients were matched 1:2 with non-cancer controls based on age (within 1 year), race, and sex. CCSP patients comprised individuals 11–26 years of age who had at least one visit in the University of Minnesota CCSP clinic between January 1, 2014 and December 31, 2019. Patients residing out of state were subsequently omitted from both groups to minimize missing vaccination data due to inability to collect data from out-of-state vaccination registries. Eligible CCSP patients were identified through the CCSP research database. Criteria for participation in the CCSP include having a diagnosis of cancer, or having a non-malignant condition treated with a HSCT, prior to age 25 years. CCSP participants are at least 5 years post diagnosis or 3 years post-HSCT. Thus, all age-appropriate patients seen in the CCSP clinic are eligible for HPV vaccination based on interval since completion of cancer treatment. Participation in the CCSP is voluntary and includes annual survivor-focused clinic visits and receipt of the SCP in the form of a detailed patient-friendly written document that is shared with the patient/family/caregivers and their primary care provider and other healthcare providers involved in their care. Age-, sex- and race-matched controls without a documented history of cancer who had at least one visit within the MHealth Fairview system during the study period were identified by the Clinical and Translational Science Institute Clinical Data Repository at the University of Minnesota. MHealth Fairview is a partnership between University of Minnesota, University of Minnesota Physicians and Fairview Health services, comprising 12 hospitals and medical centers, 56 primary care clinics, and the CCSP clinic (Fairview Health Services, 2021). Controls were matched by age, sex and race since differences in HPV vaccination coverage are known to be associated with these variables. The study was approved by the University of Minnesota Institutional Review Board (IRB; #00008330). A waiver of consent was approved by the IRB for this minimal risk study.

2.2. Data collection and study measures

Cancer diagnosis and treatment data were abstracted from the CCSP database. Data included age at first cancer diagnosis, date of initiation and completion of treatment; cancer type (subsequently coded as hematologic, solid tumor, or non-malignant condition), treatments received (chemotherapy or other systemic therapy; surgery; radiation therapy; HSCT), and duration of therapy. Relapses, secondary malignancies or hematologic disorders as well as the subsequent treatment(s) received were recorded. For participants enrolled in the CCSP, SCPs were manually reviewed and recommendations for vaccinations in general and HPV vaccination specifically were recorded.

Demographic and immunization data were abstracted from the electronic health record (EHR) through the CTSI Clinical Data Repository. The following data were abstracted: demographic data (age, sex, race, ethnicity, zip code of residence); HPV vaccination data (number of HPV vaccine doses received; date of HPV vaccine series initiation; date(s) of subsequent HPV vaccine doses). These data were supplemented by a manual chart review for vaccination data available through the Minnesota Immunization Information Connection (MIIC) which is integrated with the electronic health record but which cannot be abstracted through the automated data query. MIIC is the state

immunization registry which combines all immunization data for an individual into a single record even if vaccines are administered by different healthcare providers throughout the state. Almost all (91 %) providers in Minnesota routinely submit vaccination data to MIIC; furthermore, vaccines administered to Minnesota residents in the states of Wisconsin or North Dakota area are also recorded in MIIC (Minnesota Department of Health. Minnesota Immunization Information Connection).

2.3. Statistical analysis

Descriptive statistics were used to summarize patient demographic and clinical characteristics. Urban/rural status was defined by Rural Urban Commuting Area codes based on participants' residential ZIP codes. The primary outcome of interest for this analysis was receipt of at least one dose of the HPV vaccine. HPV vaccination coverage in CCSP patients was compared to age-, sex- and race-matched controls using a conditional logistic regression model accounting for the matched pairs and urban/rural status (Swiecki-Sikora et al., 2019). We did not adjust for ethnicity due to the small number of Hispanic or Latino/a patients in this population, however we did conduct a sensitivity analysis restricting the population to those who were non-Hispanic or non-Latino/a. Sub-group analyses were conducted with stratification by demographic characteristics including sex, race and cancer treatment characteristics including age of cancer diagnosis and age at last treatment (prior to age 11 vs age 11–14 years vs 15 + years), type of cancer (hematologic malignancy vs solid tumor vs non-malignant hematologic condition), type of cancer treatment (surgery vs radiation therapy vs chemotherapy vs HSCT) and duration of therapy. Odds ratios (OR) and associated 95 % confidence intervals (CI) were presented for all scenarios. Data analysis was performed using SAS 9.4 (Cary, NC).

3. Results

3.1. Study participants

A total of 592 patients were included in the data analysis (200 CCSP patients, 392 matched control patients; 8 of the CCSP patients from Minnesota only had 1 Minnesota resident control). Mean age was 18.4 ± 4.5 years, 48.6 % were females and 51.4 % were males (Table 1). Racial distribution as documented in the EHR was predominantly white (72.1 %), with 7.4 % identified as Asian, and 5.4 % identified as Black. By study design, these demographic characteristics were well-matched between CCSP patients and controls. Few patients identified as Hispanic or Latino/a (7.0 % of CCSP patients and 3.3 % of controls, $p = 0.11$). CCSP patients were more likely to live in rural Minnesota than controls (22.0 % vs 3.8 %, $p < 0.0001$).

3.2. HPV vaccination coverage

HPV vaccination coverage was not statistically significantly different among CCSP patients (60.0 %) compared to controls (66.3 %) [OR: 0.82, 95 % CI: (0.55, 1.23), $p = 0.35$]. The proportions receiving 2 doses (CCSP patients 21.5 % vs controls 20.7 %) and 3 doses (28.5 % vs 30.1 %) were comparable between CCSP patients and controls despite the fact that 3 doses are recommended for patients who have received immunosuppressive therapy regardless of age, but only for immunocompetent individuals initiating vaccination at 15 years of age or older. Table 2 shows HPV vaccination of CCSP patients compared to control patients stratified by sex. Consistent with national HPV vaccination trends, male CCSP patients were less likely to be vaccinated against HPV than female cancer survivors (53.4 % vs 67.0 %), though these trends held similarly for both CCSP patients and controls. The conclusions were the same when limiting to non-Hispanic or Latino/a patients.

Most CCSP patients were diagnosed at an age younger than 11 years (86.5 %) and last received treatment prior to 11 years of age (80.5 %; Table 3). A majority received chemotherapy (87.0 %); just over one-quarter (28.0 %) had received HSCT. We did not observe any cancer or treatment characteristics significantly associated with initiation of

Table 1
Demographic characteristics[1] (N = 592).

Characteristic	CCSP patients (N = 200)		Controls (N = 392)[2]	
	N	Mean (SD)	N	Mean (SD)
Age, years	200	18.4 (4.5)	392	18.4 (4.4)
	N	(%)	N	(%)
Sex				
Female	97	(48.5)	191	(48.7)
Male	103	(51.5)	201	(51.3)
Race				
Asian	15	(7.5)	29	(7.4)
Black, African, African American	11	(5.5)	21	(5.4)
White	144	(72.0)	283	(72.2)
Other, including > 1 race	2	(1.0)	4	(1.0)
Unknown	28	(14.0)	55	(14.0)
Ethnicity				
Hispanic or Latino/a	14	(7.0)	13	(3.3)
Not Hispanic or Latino/a	177	(88.5)	356	(90.8)
Unknown	9	(4.5)	23	(5.9)
Residence				
Rural	44	(22.0)	15	(3.8)
Urban	156	(78.0)	377	(962)

CCSP, Childhood Cancer Survivorship Program
1CCSP patients matched 2:1 to controls without cancer by age, race, and sex.
[2]8 controls in the Minnesota-only cohort were omitted since they were not residents of Minnesota and vaccine registry data were not available for review.

Table 2
HPV vaccination status of CCSP patients[1] versus controls (N = 592).

	CCSP patients (N = 200)		Controls (N = 392)		Odds Ratio (95 % CI)[2]	p-value
	N	(%)	N	(%)		
HPV vaccination status						
No	80	(40.0)	132	(33.7)	Ref	
Yes[3]	120	(60.0)	260	(66.3)	0.82 (0.55, 1.23)	0.35
Number of HPV vaccine doses						
0	80	(40.0)	132	(33.7)		
1	20	(10.0)	61	(15.6)		
2	43	(21.5)	81	(20.7)		
3	57	(28.5)	118	(30.1)		
Females						
HPV vaccination status						
No	32	(33.0)	46	(24.1)	Ref	
Yes[3]	65	(67.0)	145	(75.9)	0.75 (0.40, 1.41)	0.37
Males						
HPV vaccination status						
No	48	(46.6)	86	(42.8)	Ref	
Yes[3]	55	(53.4)	115	(57.2)	0.88 (0.52, 1.49)	0.63

CCSP, Childhood Cancer Survivorship Program; HPV, human papillomavirus; TDaP, tetanus, diphtheria and pertussis
[1]Among CCSP patients, 6 received HPV vaccination prior to their cancer diagnosis, 3 were revaccinated with at least 1 dose after cancer treatment.
[2] Conditional logistic regression accounting for matched pairs and urban/rural residence status.
3Received at least 1 of 2 (immunocompetent, initiated < 15 years of age) or 3 (cancer survivors any age or initiated 15 + years of age) recommended doses.

Table 3
HPV vaccination coverage (at least 1 dose) among PAYA cancer survivors by clinical characteristics (N = 200).

Clinical characteristic	Total N	(%)	HPV Vaccination No N	(%)	HPV Vaccination Yes N	(%)	p-value
Diagnosis							0.74
Solid tumor	79	(39.5)	34	(42.5)	45	(37.5)	
Heme malignancy	94	(47.0)	35	(43.8)	59	(49.2)	
Non-malignant disorder[1]	27	(13.5)	11	(13.8)	16	(13.3)	
Age at Diagnosis							0.60
<11 years	173	(86.5)	69	(86.3)	104	(86.7)	
11–14 years	20	(10.0)	7	(8.8)	13	(10.8)	
15–20 years	7	(3.5)	4	(5.0)	3	(2.5)	
Age at last treatment							0.99
<11 years	161	(80.5)	64	(80.0)	97	(80.8)	
11–14 years	27	(13.5)	11	(13.8)	16	(13.3)	
15–20 years	12	(6.0)	5	(6.3)	7	(5.8)	
Chemotherapy							0.86
No	26	(13.0)	10	(12.5)	16	(13.3)	
Yes	174	(87.0)	70	(87.5)	104	(86.7)	
Surgery							0.60
No	82	(41.0)	31	(38.8)	51	(42.5)	
Yes	118	(59.0)	49	(61.3)	69	(57.5)	
Radiation therapy							0.59
No	128	(64.0)	53	(66.3)	75	(62.5)	
Yes	72	(36.0)	27	(33.8)	45	(37.5)	
Hematopoietic stem cell transplant							0.65
No	144	(72.0)	59	(73.8)	85	(70.8)	
Yes	56	(28.0)	21	(26.3)	35	(29.2)	
SCP							0.72
No	8	(4.0)	4	(5.0)	4	(3.3)	
Yes	192	(96.0)	76	(95.0)	116	(96.7)	
Vaccination recommendations in SCP							0.82
No	105	(52.5)	41	(51.3)	64	(53.3)	
Yes	87	(43.5)	35	(43.8)	52	(43.3)	
N/A	8	(4.0)	4	(5.0)	4	(3.3)	
HPV vaccination recommendation in SCP							0.43
No	176	(88.0)	72	(90.0)	104	(86.7)	
Yes	16	(8.0)	4	(5.0)	12	(10.0)	
N/A	8	(4.0)	4	(5.0)	4	(3.3)	
Immunization review documented in SCP							0.57
No	72	(36.0)	31	(38.8)	41	(34.2)	
Yes	120	(60.0)	45	(56.3)	75	(62.5)	
N/A	8	(4.0)	4	(5.0)	4	(3.3)	

HPV, human papillomavirus; PAYA, pediatric, adolescent and young adult; SCP, survivorship care plan.
[1]Patients with non-malignant disorders have bone marrow disorders for which they have received hematopoietic stem cell transplant and therefore a similar increased risk of developing an HPV-associated malignancy.

HPV vaccination. Only 6 CCSP patients were vaccinated against HPV prior to cancer treatment, and 3 of these patients received at least 1 additional dose after completion of cancer therapy. Almost all (n = 192; 96.0 %) CCSP patients had a documented SCP. A review of the SCPs found that 60.0 % (n = 120) documented immunizations received, and 43.5 % (n = 87) included at least one vaccination recommendation. However, only 8.0 % (n = 16) of SCPs included a recommendation specifically for HPV vaccination. HPV vaccination coverage was not statistically significantly increased among those with a SCP recommendation for vaccinations in general or HPV vaccination specifically, though numbers are small.

For reference, the groups were also compared across other adolescent vaccinations, meningococcal and tetanus, diphtheria and pertussis (TDaP) (Table 4). TDaP vaccination coverage among CCSP patients (94.5 %) was higher than HPV vaccination coverage, and not statistically significantly different from coverage among controls (OR: 0.72, 95 % CI: 0.32, 1.63, p = 0.44). Meningococcal vaccination coverage among CCSP patients (75.0 %) was also higher than HPV vaccination coverage, however, it was statistically significantly lower than coverage among controls (OR: 0.43, 95 % CI: 0.25, 0.72, p = 0.002).

4. Discussion

We found patients participating in a well-established childhood cancer survivor care program had similar HPV vaccination coverage

Table 4
TDaP and Meningococcal vaccination status of PAYA cancer survivors versus controls (N = 592).

	PAYA Cancer Survivor (N=200) N	(%)	Controls (N=392) N	(%)	Odds Ratio (95% CI)[2]	p-value
Meningococcal vaccination						
No	50	(25.0)	56	(14.3)	Ref	
Yes[1]	150	(75.0)	336	(85.7)	0.43 (0.25, 0.72)	<0.01
Number of meningococcal vaccine doses						
0	50	(25.0)	56	(14.3)		
1	80	(40.0)	198	(50.5)		
2	58	(29.0)	132	(33.7)		
3	6	(3.0)	4	(1.0)		
4	6	(3.0)	2	(0.5)		
TDaP vaccination						
No	11	(5.5)	16	(4.1)	Ref	
Yes	189	(94.5)	376	(95.9)	0.72 (0.32,1.63)	0.44
Females						
Meningococcal vaccination						
No	22	(22.7)	27	(14.1)	Ref.	
Yes[1]	75	(77.3)	164	(85.9)	0.47 (0.23, 1.00)	0.05
TDaP vaccination						
No	6	(6.2)	10	(5.2)	Ref	
Yes	91	(93.8)	181	(94.8)	0.83 (0.28, 2.51)	0.74
Males						
Meningococcal vaccination						
No	28	(27.2)	29	(14.4)	Ref	
Yes[1]	75	(72.8)	172	(85.6)	0.38 (0.18, 0.80)	0.01
TDaP vaccination						
No	5	(4.9)	6	(3.0)	Ref	
Yes	98	(95.2)	195	(97.0)	0.61 (0.19, 2.03)	0.42

PAYA, pediatric, adolescent and young adults; TDaP, tetanus, diphtheria and pertussis
[1]Received at least 1 of 2 recommended doses.
[2]Conditional logistic regression accounting for matched pairs and urban/rural residence status.

compared to age-, race-, and sex-matched controls receiving care in the same healthcare system. While most patients will receive primary care at a clinic close to their residence, many patients have to travel great distances and across state lines to receive specialized cancer care. Since United States vaccine registries are state-based and not collected at the national level, true vaccination coverage among cancer survivors receiving out-of-state cancer care may be underestimated, and may partially explain the differences in our study findings (limited to patients residing in a single state with a robust state immunization registry) compared to those of previously published studies.

In this retrospective cohort study, we are unable to determine if the similar HPV vaccination coverage in cancer survivors and the general population is due to their participation in a clinic focused on survivorship care, a component of which is ensuring that all survivors have a medical home, or if it is indicative of the healthcare motivation of patients who choose to participate in a dedicated survivorship program. Results from a 2016 survey study of females participating in a childhood cancer survivorship clinic also showed similar reported HPV vaccination initiation and completion among cancer survivors and controls without a cancer history (Klosky et al., 2016). HPV vaccination coverage among CCSP patients in our study (60.0 %) was higher than that previously reported in this population, with the literature reporting coverage of 23.8 % to 38.4 % (Castellino et al., 2019; Klosky et al., 2017; Hardin et al., 2020). This is likely representative of the general increase in HPV vaccination coverage over time, especially since vaccination coverage was similar among cancer survivors and controls. While this increase in HPV vaccination coverage is encouraging, less than half (47.5 %) of the survivors initiating the vaccine series received the recommended 3 doses; this is comparable to a previous study showing that among those who initiated HPV vaccination, only 43 % of male and 53 % of female CCSP patients received at least 2 doses (Castellino et al., 2019). Despite data in the general population suggesting one dose of HPV vaccine may be sufficient (Brotherton et al., 2019), these data cannot be extrapolated to cancer survivors without further research given the potential for decreased immunogenicity of the vaccine following immunosuppressive cancer therapy and the unknown long-term impact of novel immunotherapies now being used to treat childhood cancers.

Creation of a SCP is an important aspect of survivor-focused care, yet in our study only 8 % of CCSP patients' SCPs included a specific recommendation for HPV vaccination. While it is possible that HPV vaccination was verbally recommended by the oncologist but not documented in the SCP, another study showed that childhood cancer survivors were less likely to report receiving a recommendation for HPV vaccination compared to controls without cancer (Klosky et al., 2016). This highlights an area for improvement in our CCSP at the University of Minnesota, and likely across the United States. While numbers are small, among the 16 SCPs in which HPV vaccination was recommended, three-quarters of these CCSP patients subsequently received at least one dose of the HPV vaccine, which is encouraging. It is notable that coverage of the other adolescent vaccines (TDaP, meningococcal) was higher than for HPV vaccination. Additional investigation is needed to determine the impact of recommendations for vaccinations in general and HPV vaccination specifically in SCPs. Previous studies have shown that receipt of a SCP is associated with improvement in uptake of screening tests and other recommended healthcare behaviors (Hill et al., 2020; Shay et al., Jun 2017). Other studies among pediatric, adolescent and young adult cancer survivors have shown an association between a physician recommendation for HPV vaccination, perceived severity of HPV infection and positive attitudes toward the HPV vaccine and increased HPV vaccination coverage (Klosky et al., 2016). Specifically, a cross-sectional study of female cancer survivors and caregivers at St. Jude Children's Research Hospital showed HPV vaccination intention was increased 8-fold among those who received a physician recommendation for vaccination (Hardin et al., 2020), and other studies have shown similar increased vaccination initiation (Cherven et al., 2019; Klosky et al., 2016). These published studies suggest that increasing HPV vaccination coverage among vulnerable pediatric, adolescent and young adult cancer survivors may require both a written recommendation in the SCP as well as a verbal recommendation and discussion with oncology healthcare providers, especially regarding the importance of completing the 3-dose vaccine series.

Limitations of this study are inherent to its retrospective design, including the possibility of misclassification of vaccination status due to missing vaccination data. We were unable to control for insurance status since current insurance coverage may not reflect coverage at the time of potential vaccination, but most patients in the study should have had coverage for the HPV vaccine through private insurance (coverage for dependents up to age 26 years per the Affordable Care Act) or programs such as Vaccines for Children. CCSP patients classified as vaccinated included individuals vaccinated prior to cancer treatment, although since this occurred in only 3 % of patients it suggests there is a role for inclusion of HPV vaccination in survivorship care. One of the objectives of the study was to determine if inclusion of a recommendation for HPV vaccination was associated with vaccination uptake, but analysis was limited by the small number of SCPs including this recommendation. Lastly, the study was conducted among a study population within a single health system with a predominantly white population. While this limits generalizability of our results, we were able to identify potential areas for improvement in survivorship care among a population which is most likely to receive high-level care; it is likely that similar deficiencies exist in other care settings, but that there may competing and more immediate barriers to care which may need to be addressed. Despite these limitations, our study was strengthened by the large number of CCSP patients for whom we had detailed diagnosis and treatment data. All study subjects were eligible for HPV vaccination based on age and interval since treatment completion. CCSP patients were matched by age, race, and sex to controls without cancer to minimize confounding from these factors which are known to be associated with HPV vaccination coverage. We also had reliable vaccination data available through both the EHR and a state-based immunization registry.

5. Conclusions

In summary, we found that patients who chose to participate in a well-established cancer survivorship program have similar HPV vaccination coverage to age-, race-, and sex matched controls. However, HPV vaccination coverage and especially vaccine series completion is still suboptimal for this population which is at increased risk for a secondary HPV-associated cancer. Further, a specific recommendation for HPV vaccination was rarely included in the SCP despite secondary malignancies being a leading cause of death in long-term pediatric, adolescent and young adult cancer survivors. Recent research suggests that earlier vaccination results in a lower risk of HPV-associated invasive cervical cancer compared to vaccination after the age of 17 years (Lei et al., 2020); adolescent vaccination may be even more important among pediatric, adolescent and young adult cancer survivors who have a higher risk of developing a secondary HPV-associated malignancy in the third- to fourth-decades of life (Ojha et al., 2013). Further research is needed to determine how to best incorporate HPV vaccination initiation and 3-dose completion into pediatric, adolescent and young adult cancer survivorship care.

Declarations

6. Ethics approvalss

This retrospective cohort study utilizing chart review of human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The University of Minnesota Institutional Review Board approved this study (IRB #00008330).

7. Consent to participate

A waiver of consent was approved by the Institutional Review Board for this minimal risk study that does not adversely affect the rights or welfare of the subjects.

8. Consent for publication

A waiver of consent was approved by the Institutional Review Board for this minimal risk study that does not adversely affect the rights or welfare of the subjects.

9. Implications and contribution

Patients who chose to participate in a well-established cancer survivorship program had similar HPV vaccination coverage to that of the general population. However, HPV vaccination initiation and especially series completion is still suboptimal for this population which is at increased risk for a secondary HPV-associated cancer.

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CRediT authorship contribution statement

Lauren Thomaier: Conceptualization, Methodology, Writing – review & editing. **Danielle A. Aase:** Conceptualization, Methodology, Writing – review & editing. **Rachel I. Vogel:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Helen M. Parsons:** Conceptualization, Methodology, Writing – review & editing. **Karim T. Sadak:** Conceptualization, Methodology, Writing – review & editing. **Deanna Teoh:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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