Secondary Neoplasms of the Female Lower Genital Tract After Hematopoietic Cell Transplantation

Howard A. Chang, BA^a; Saro H. Armenian, DO, MPH^a; and Thanh H. Dellinger, MD^b

Abstract

Hematopoietic cell transplantation (HCT) results in long-term survival (≥ 10 years) in 85% of patients who survive transplant-related complications within the first 2 years posttransplant. Transplant survivors, however, are at an increased risk of chronic health conditions compared with the general population, including the emergence of secondary malignant neoplasms. In particular, female transplant survivors may face a greater risk of lower genital tract (cervical, vulvar, or vaginal) neoplasms due to chronic immune dysregulation in the peritransplant and posttransplant environment. Persistent immune suppression may facilitate the carcinogenesis of human papillomavirus (HPV), the causative agent of nearly all cervical cancers and most vulvar and vaginal cancers. Nevertheless, the risk of these cancers has not been sufficiently quantified in female transplant survivors. Small clinical studies have shown that the rate of cervical cytological abnormalities increases after allogeneic HCT, but large population-based studies have not consistently demonstrated an increased risk of secondary cervical cancer after transplant compared with the general population; the risk of developing secondary vulvar or vaginal cancer after transplant remains unclear. A better understanding of the natural history of HPV-associated lower genital tract neoplasms and their transplant-related risk factors would help delineate optimal long-term follow-up protocols in this population. In this systematic review, we summarize the current literature on this topic and discuss the implications for cervical cancer screening and vaccination in female transplant recipients.

J Natl Compr Canc Netw 2018;16(2):211–218
doi: 10.6004/jnccn.2018.7005

The female lower genital tract (cervix, vulva, vagina) is a common cancer site within the general population.¹ Cervical cancer is the second most common cancer among women worldwide, while vulvar and vaginal cancers are much rarer, accounting for 7% of all gynecologic malignancies.^{2,3}

More than 90% of cervical cancers and at least 60% to 70% of vulvar and vaginal cancers are caused by the human papillomavirus (HPV), the most common sexually transmitted infection.^{4–6} Because of the viral etiology of most lower genital tract cancers, women who are immunocompromised and thus unable to eliminate HPV or suppress its activity may be at a higher risk of developing these cancers.^{7,8} For example, solid organ transplant recipients who are on prolonged immunosuppressive therapy are more likely to develop lower

genital tract precancers and cancers, and these diseases are more aggressive, advance more quickly, and occur earlier in life than in immune-competent women.^{9–11}

Hematopoietic cell transplantation (HCT) entails immune dysregulation in both recipients of autologous HCT (auto-HCT)^{12,13} and allogeneic HCT (allo-HCT).^{14,15} Allo-HCT recipients in particular are susceptible to graft-versus-host disease (GvHD), a serious inflammatory condition resulting from the immunologic attack of recipient tissue by donor T cells.¹⁶ Both the acute and chronic manifestations of GvHD play a role in impeding immunologic recovery following HCT.^{14,15} Moreover, patients who develop chronic GvHD often require years of immunosuppressive therapy to treat the condition.¹⁷ The immune dysregulatory effects of GvHD and the prolonged immunosuppressive therapy used to treat it may provide a physiological milieu condu-

From the ^aDepartment of Population Sciences, Division of Outcomes Research, and ^bDepartment of Surgery, Division of Gynecologic Surgery, City of Hope National Medical Center, Duarte, California.
Submitted November 13, 2017; accepted for publication January 9, 2018.
The authors have disclosed that they have no financial interests,

arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Thanh H. Dellinger, MD, Department of Surgery, Division of Gynecologic Surgery, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010-3000. E-mail: tdellinger@coh.org

cive to the reactivation, progression, or acquisition of HPV.⁷ Auto-HCT recipients do not experience the same degree of immune dysregulation because GvHD does not occur in these patients; however, the immune system may still be impaired for at least a year after auto-HCT.¹³ These biological underpinnings substantiate a model in which impaired immune surveillance of viral latency facilitates HPV replication en route to progressive lower genital tract disease.⁷

Ninety percent of immune-competent females infected with HPV will mount an effective immune response to clear the infection within 2 years.¹⁸ Those who are unable to do so may develop cervical, vulvar, or vaginal dysplasia. Screening with Papanicolaou (Pap) smears detects cytologic abnormalities such as low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively). Histology-confirmed koilocytic changes found on colposcopic biopsy are denoted, in increasing severity, as cervical intraepithelial neoplasia grades 1, 2, and 3 (CIN1, CIN2, and CIN3, respectively). Upon incident HPV infection, the transition from cervical dysplasia to invasive cancer is fairly low and slow: only 1%, 5%, and 12% of CIN1, CIN2, and CIN3, respectively, progress to cervical cancer,¹⁹ with a time frame of at least 5 to 10 years from the incident infection.²⁰ Vulvar intraepithelial neoplasia progresses to cancer in 2.7% to 8.5% of women.²¹ Limited data are available on the rate of progression from vaginal intraepithelial neoplasia to cancer, due to the rarity of primary vaginal cancer. Importantly, because these low transition rates are reported in immune-competent women, rates of progression to cancer may be higher in female HCT recipients. Prompt detection of lower genital tract neoplasms is therefore paramount to providing clinicians with early intervention opportunities in this high-risk population.

The primary goal of this review is to summarize the current literature describing female lower genital tract neoplasms (dysplasias and cancers) after HCT. This information can provide key information on the potential for HCT-related risk and potentially assist in clinical decision-making on long-term follow-up strategies after HCT.

Methods

A comprehensive literature review was performed via PubMed encompassing the years 1994 to 2016 to search for articles covering 2 separate but related

topics: first, all clinical and population-based studies on occurrence (presentation, incidence, or risk) of cervical, vulvar, and vaginal neoplasms after HCT, and second, all such studies broadened to include any kind of secondary neoplasm after HCT. A standard strategy using advanced search keywords was used with variations of terms (eg, “cervical dysplasia,” “cervical neoplasm,” “secondary cancers”) to incorporate wording differences in the literature. The initial search, along with additional articles identified from published reviews, yielded 355 articles, which were reviewed and screened to exclude 312 articles. Among the remaining 43 articles, 20 were excluded due to lack of cervical, vulvar, or vaginal cases, leaving 23 articles eligible for this review (Figure 1).

Results

Cervical Dysplasia After HCT

Our search yielded 4 studies assessing cervical dysplasia after HCT (Table 1). Sasadeusz et al²² were the first to show an increased occurrence of abnormal cervical cytology in women after undergoing allo-HCT. They conducted a retrospective analysis of all available pre-HCT and post-HCT Pap smears in 40 recipients of auto-HCT and 24 recipients of allo-HCT at a single center, finding that allo-HCT recipients had a 6.8-fold increased risk of LSIL or HSIL post-HCT compared with the age-matched general population. However, there was no increased risk of cervical dysplasia among auto-HCT recipients compared with the general population. The authors concluded that factors unique to the allogeneic setting—chronic GvHD and/or the requirement of long-term immunosuppressive therapy—likely exacerbated the risk of cervical dysplasia. However, the study was limited by the absence of both data on chronic GvHD severity and details regarding the intensity and duration of immunosuppressive therapy.

In another study of only allo-HCT recipients, Savani et al²³ similarly found that patients had greater rates of cervical dysplasia post-HCT compared with pre-HCT. In this study, 35 women who had normal cervical cytology pre-HCT were followed for a median of 7 years after HCT. During the follow-up period, 43% developed cervical dysplasia, including 20% with HSIL and 14% with LSIL, all of which were biopsy-confirmed to be HPV-related (HPV DNA testing was not performed). The au-

Female Genital Tract Neoplasms After HCT

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the systematic review of secondary cervical, vulvar, and vaginal neoplasms after hematopoietic cell transplantation.

thors also recorded the duration of post-HCT immunosuppressive therapy administered to the patients, finding that prolonged (>3 years) exposure to immunosuppressive agents for management of chronic GvHD resulted in a 4.6-fold increased risk of HPV-associated cervical HSIL or LSIL compared with shorter (<3 years) use of immunosuppressive therapy.

A subsequent study by Wang et al²⁴ followed a larger cohort of allo-HCT recipients (89 women) for a longer period (11 years) post-HCT, and also showed an increased rate of cervical dysplasia post-HCT compared with pre-HCT. All patients were screened on a standardized schedule after HCT and received an average of 6.5 Pap smears per patient during the follow-up period. Compared with pre-HCT smears, there was a 3-fold increase in the proportion of patients with abnormal smears at any time during the post-HCT follow-up. Among 69 patients who had normal cytology pre-HCT, 16 (23%) showed HSIL and 6 (9%) showed LSIL post-HCT. Most patients (57%) with persistent HSIL had biopsy-confirmed CIN3. HPV DNA testing in a small subset of patients revealed that 7 of 12 (58%) with HSIL were HPV-positive, but none of the 6 tested patients with LSIL were HPV-positive, implicating non-specific therapy-related changes. Significant risk factors for the development of HSIL (regardless of HPV status) included unrelated human leukocyte antigen-matched donor and vulvovaginal GvHD.

Most recently, Negri et al²⁵ described how in 54 patients with normal cytology pre-allo-HCT, 13 (24%) showed abnormal cytology post-HCT, including LSIL that persisted on cytologic follow-up 3 to 6 months later in 11% of the entire cohort. However, they also found that among 3 patients whose initial cytology after HCT revealed atypical squamous cells cannot exclude HSIL (ASC-H), all had negative results on follow-up testing (2 had negative histologic follow-up; 1 had cytologic follow-up and a high-risk

Table 1. Studies on Cervical Cytology After HCT (1994–2016)

Study	HCT Period (Location)	Patients, N	HCT Type	Median Age at HCT, y (range)	Median Follow-Up, y (range)	Patients With Normal Pre-HCT Cytology With Abnormal Post-HCT Cytology, n (%) ^a	Key Finding ^b
Sasadeusz et al, ²² 2001	1989–1998 (Australia)	64	Allo or auto	43 (22–66)	Auto: 2.6 (0.5–7.5) Allo: 3.5 (0.3–8.8)	Not reported	Allo-HCT recipients, but not auto-HCT recipients, had a significant increase in rate of LSIL or HSIL post-HCT vs pre-HCT
Savani et al, ²³ 2008	1993–2003 (USA)	38	Allo	33 (9–60)	7.1 (3.8–13.6)	Total: 15/35 (≈43%) ^c LSIL: 5/35 (≈14%) ^c HSIL: 7/35 (≈20%) ^c	Chronic GvHD requiring systemic immunosuppressive therapy ≥3 years was the only risk factor for HPV-positive HSIL or LSIL after HCT
Wang et al, ²⁴ 2012	1985–2005 (Norway)	89	Allo	39 (15–59)	11 (5–25)	Total: 44/69 (64%) LSIL: 6/69 (8.7%) HSIL: 16/69 (23%)	Vulvovaginal GvHD was the only risk factor for CIN2–3 after HCT
Negri et al, ²⁵ 2014	NR (Italy)	54	Allo	NR	NR	Total: 13/54 (24%) LSIL: 6/54 (11%) ASC-H: 3/54 (5.6%)	Follow-up was histologically normal for all 3 patients showing ASC-H on first cytology post-HCT

Abbreviations: allo, allogeneic; ASC-H, atypical squamous cells (cannot exclude high-grade lesion); auto, autologous; CIN, cervical intraepithelial neoplasia; GvHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NR, not reported.

^aColumn omits percentages of atypical squamous cells of undetermined significance detected on post-HCT cytology.

^bNo cases of cervical cancer were histologically confirmed during the follow-up period in any study.

^cApproximations. Cytology was performed after transplant in 35 adult patients only. Authors state that “most patients had normal cervical cytology testing prior to transplantation.”

HPV test, both of which were negative). These initial smears showing ASC-H demonstrated morphology worrisome for invasive cancer, but the authors later recognized these as being false-positives, because the patients had all received high-dose busulfan, a well-known cause of cell atypia appearing on cytology and histology. Therefore, they concluded that even though post-HCT smears may indicate cervical atypia suspicious for cancerous changes, clinicians should wisely determine whether histologic follow-up is warranted to validate these findings.

Despite cohort and treatment differences, all of the aforementioned clinical studies provide evidence that the rate of abnormal cervical cytology increases after allo-HCT. But these studies are limited in important ways. First, small patient populations (38–89 patients) with no detected cervical cancers restricts the ability to draw conclusions about the risk of these cancers post-HCT. Second, the absence of HPV DNA cotesting alongside Pap smears (now standard in the general population) in most of the participants limits the ability to distinguish true cervical dysplasia from transient cytologic atypia. The high HPV negativity rate among patients who were tested implies that significantly larger patient numbers are needed to detect cervical cancer post-HCT.

Demonstrating whether cervical dysplasia tends to progress more readily in HCT recipients compared with the general population may provide further insight into the epidemiology of HPV in immunocompromised women. The evidence suggests that immunocompromised HCT recipients may indeed be more susceptible to cervical progression, because risk factors for cervical dysplasia after HCT include immunologic features such as vulvovaginal GvHD,²⁴ unrelated donor,²⁴ and long-term use of systemic immunosuppressive therapy.²³ Future research should seek to compare dysplastic progression and regression rates in HCT recipients using standardized screening schedules with Pap smears and HPV DNA cotesting to minimize detection bias during the follow-up period. Studies should compare these rates with those in the general population, and elucidate the role of HCT-related risk factors in promoting the development of cervical dysplasia.

Cervical Cancer After HCT

Although few studies have examined cervical dysplasia after HCT, several large cohort studies assessing

the risk of secondary cancers after HCT have determined the occurrence of cervical cancer post-HCT (Table 2). Studies by Bhatia et al²⁶ and Shimada et al²⁷ followed 919 and 324 women, respectively, who received either allo-HCT or auto-HCT and discovered a 13.3-fold and 8.6-fold elevated risk of cervical cancer compared with the general population. However, in much larger cohorts (range, 1,765–11,752 women) comprising only allo-HCT recipients, there was no increased risk of cervical cancer post-HCT compared with the general population.^{28–33}

The explanation for Bhatia et al²⁶ and Shimada et al's²⁷ discovery of an increased cervical cancer risk in a mixed cohort of auto- and allo-HCT recipients presents a challenge in light of the average risk found in studies involving only allo-HCT recipients, who are hypothesized to have the highest risk relative to auto-HCT recipients or the general population. Their positive findings could be explained by their relatively small cohort sizes, in which a small number of detected cervical cancer cases may drive the risk toward significance. Only 4²⁶ and 2²⁷ women in these studies, respectively, developed cervical cancer after HCT. Additionally, neither of the 2 patients who developed cervical cancer in Shimada et al's²⁷ study had chronic GvHD or were receiving immunosuppressive therapy—the most salient HCT-related risk factors for cervical cancer—when they were diagnosed. Although these findings do not disconfirm the influence of allogeneic factors on HPV progression in the cervix, they nevertheless indicate that allo-HCT may not—at least patently—increase the risk of cervical cancer. Notably, each study in Table 2 is limited by a lack of data on HPV types among HCT recipients, which may contribute in a crucial manner toward determining which individuals are most affected by allo-HCT (eg, those with high-risk HPV) versus those who are not (eg, those with low-risk or no detectable HPV).

One possible explanation for why studies have generally not found an increased risk of cervical cancer in allo-HCT recipients is that the duration of follow-up was not sufficiently long enough to detect cervical cancer. The incidence of secondary solid tumors has been shown to peak at approximately 6.8 years after allo-HCT,³⁴ and this incidence continues to increase linearly with time for at least 2 decades post-HCT.³¹ The long latency period of secondary solid tumors, particularly cervical cancer, may mean that longer follow-up would allow more time for

Female Genital Tract Neoplasms After HCT

Table 2. Cervix-Related Findings on Secondary Cancers After HCT (1994–2016)

Study Details					Cervix-Related Findings				
Study	HCT Period	Patients, N	HCT Type	Median Age at HCT, y (range)	Median Follow-Up, y (range) ^a	Cervical Cancers Post-HCT, n (% of All Patients)	SIR (95% CI)	Time to Diagnosis of Cervical Cancer Post-HCT, y (Number of Cases)	Cervical Dysplasia Cases Post-HCT, n (Type)
Bhatia et al, ²⁶ 2001	1976–1998	919	Allo or auto	33.9 (1.5–71.5)	3.3 (0.1–21.1)	4 (0.44)	13.3 ^b (3.5–29.6)	Median: 3.3 Range: 1.6–9.7	0
Shimada et al, ²⁷ 2005	1981–2000	324	Allo or auto	34 (15–70)	5.3 (1–19.9)	2 (0.62)	8.6 ^b (1.04–31.01)	3.8 (1) 4.9 (1)	0
Ringden et al, ²⁸ 2014	1995–2006	1,765	Allo	53 (<1–79)	6 (0.1–15.7)	1 (0.057)	2.1 (0.05–11.93)	NR	0
Atsuta et al, ²⁹ 2014	1990–2007	7,149	Allo	40 (16–85)	69,465 person-years	7 (0.098)	1.5 (0.6–3.0)	<1 (1) 1–4 (4) 5–9 (1) ≥10 (1)	0
Majhail et al, ³⁰ 2011	1986–2006	1,903	Allo	29 (<1–60) or 36 (<1–60) ^c	7 (<1–21) or 8 (<1–19) ^c	3 (0.16)	2.3 (0.48–6.77)	<1 (1) 1–4 (1) 5–9 (1)	0
Rizzo et al, ³¹ 2009	1964–1994	11,752	Allo	27 (0.1–72.4)	36,252 person-years for women	5 (0.043)	1.7 (0.54–3.85)	<1 (1) 1–4 (3) ≥15 (1)	3 (CIS)
Curtis et al, ³² 1997	1964–1990	7,851	Allo	25.5	3.5 (1–25)	1 (0.013)	1.7 (0.54–3.85)	1–4 (1)	0
Lowsky et al, ³³ 1994	1970–1993	248	Allo	(17–55)	1,608 person-years ^d (1–24)	0	–	–	5 (CIN)
Kolb et al, ³⁵ 1999	pre-1986	433	Allo or auto	21 (1–51.9)	10.7 (5–22.1)	0	–	–	5 (CIS)
Danner-Koptik et al, ³⁶ 2013	1987–2003	592	Auto	8 (<1–21)	8 (<1–21)	1 (0.17)	48 ^b (1.2–270)	<1 (1)	0
Seshadri et al, ³⁷ 2009	1987–2006	164	Auto	50 (19–70)	4.8	1 (0.61)	NR	NR	0
Brown et al, ³⁸ 2005	1982–1997	254	Auto	44	9.5	0	–	–	1 (HSIL)
Ruiz-Soto et al, ³⁹ 2005	1993–2002	60	Auto	46 (18–69)	3 (0.5–12)	1 (1.7)	NR	9.8 (1)	0

Abbreviations: allo, allogeneic; auto, autologous; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; HCT, hematopoietic cell transplantation; HSIL, high-grade squamous intraepithelial lesion; NR, not reported; SIR, standardized incidence ratio.

^aDetermined by the authors for the entire cohort including both male and female patients, except where specified.

^bStatistically significant.

^cStudy included 2 groups of patients, those with either acute myeloid leukemia in first complete remission or chronic myeloid leukemia in first chronic phase, with their medians and ranges listed respectively.

^dTwo patients were aged 12 and 13 years. Median age of sample was not provided.

HCT-related factors to exert their maximal influence on cervical HPV. Indeed, some cases of cervical cancer have been diagnosed ≥10 years post-HCT (Table 2). However, insufficient follow-up duration may not entirely explain the apparent absence of increased cervical cancer risk post-HCT, as evidenced by other studies that have shown a relatively short latency (0–4 years) for secondary cervical cancers (Table 2).

Collectively, these findings argue against an elevated risk of cervical cancer among female recipients of allo-HCT. However, this conclusion needs to be regarded cautiously, because young children (<10 years of age) comprised a substantial fraction of the HCT population in several studies that did not identify an elevated risk. In the largest cohort study by Rizzo et al,³¹ 4,058 of 28,874 total HCT recipients (14%) were <10 years of age. Majhail et al³⁰ reported 6% of total HCT recipients <10 years of age, and

Kolb et al³⁵ included 15% of female HCT recipients aged ≤10 years. Bhatia et al²⁶ and Ringden et al²⁸ also included very young children, but the proportion of those aged 0 to 10 years was not specified. Furthermore, all of these studies included HCT recipients as young as infants (≤1 year of age). Because children between the ages of 0 and 10 years are unlikely to contract HPV during the follow-up period, the number of cervical cancer cases may have been underestimated. These and future studies should therefore consider performing separate analyses for cervical cancer risk after excluding very young patients unlikely to have reached sexual debut.

Finally, the outcomes of small studies suggest no increased risk of cervical cancer after auto-HCT compared with the general population (Table 2).^{36–39} The only study that found an increased risk was based on only 1 case in a pediatric sample.³⁶

Vulvar and Vaginal Neoplasms After HCT

Minimal information is available on vulvar and vaginal neoplasms after HCT; studies have been limited by small numbers detected post-HCT and by heterogeneity of follow-up (Table 3). Although an elevated risk of vulvar cancer post-HCT was found in 2 studies, these were based on the occurrence of only 1 case⁴⁰ and 2 cases,²⁸ respectively. Other studies have also identified single cases of vulvar dysplasia or cancer, without risk determination.^{33,34,41} There are no available risk assessments for vaginal cancer after HCT due to its rarity; among all the studies we reviewed, only 1 case of vaginal cancer was detected post-HCT.⁴² We are unaware of any studies reporting on the rate of vulvar or vaginal dysplasias after HCT or identifying HCT-related risk factors for their occurrence.

Implications for Screening and Vaccination After HCT

Existing studies of Pap-detected cervical abnormalities after HCT have not captured any cervical cancers during their respective follow-up periods.^{22–25} This may be due to small sample sizes or the long latency from HPV infection to cervical cancer. Nonetheless, one may question whether abnormal Pap smears post-HCT reliably predicts cancer in HCT recipients without HPV DNA cotesting, because abnormal cytology can occur transiently from non-HPV-related causes such as conditioning therapy.²⁵ Important but unaddressed impli-

cations exist regarding screening schedules in HCT recipients and whether these should differ from those recommended for the general population. The HPV DNA test is now incorporated into general cervical screening recommendations (Table 4).⁴³ We contend that this test should also be part of screening for HCT survivors, potentially replacing cytology-only screening.

Currently, there are no official guidelines for cervical screening in women post-HCT, although consensus-based recommendations suggest Pap smears every 1 to 3 years,^{44–46} which is in contrast to the official recommendations of 3 to 5 years for the general population.⁴³ It is unknown whether screening every 1 to 3 years is optimal in HCT survivors, or whether certain subsets of women—for example, those who have extensive vulvovaginal GvHD or who are on protracted immunosuppressive therapy post-HCT—would benefit from more regular screening, and how HPV DNA testing should be incorporated into follow-up strategies for high-risk individuals. For instance, should women who develop vulvovaginal GvHD—which affects at least 25% to 49% of women within 2 years after allo-HCT—be screened more regularly, given that the condition may increase the risk of HPV-associated neoplasms?^{72,47,48} A modified evidence-based cervical screening schedule already exists for immunocompromised women who are HIV-positive (Table 4).⁴⁹ In a similar fashion, we hope that further research will help guide an evidence-based process to establish guidelines in HCT survivors.

Table 3. Vulva- and Vagina-Related Findings on Secondary Cancers After HCT (1994–2016)									
Study Details						Vulva- and Vagina-Related Findings			
Study	HCT Period	Patients, N	HCT Type	Median Age at HCT, y (range)	Median Follow-Up, y (range) ^a	Cancers Post-HCT, n (% of All Patients)	SIR (95% CI)	Time to Cancer Diagnosis After HCT, y (No. of Cases)	Dysplasia Cases Post-HCT, n (Type)
Vulva-related									
Oddou et al, ⁴⁰ 1998	1985–1995	65	Auto	38 (11–61)	4.3 (1.8–13)	1 vulvar (1.5%)	287 ^b (3.73–552)	3 (1)	0
Ringden et al, ²⁸ 2014	1995–2006	1,765	Allo	53 (<1–79)	6 (0.1–15.7)	2 vulvar (0.11%)	18.6 ^b (2.25–67.02)	NR	0
Deeg et al, ⁴¹ 1996	1970–1993	283	Allo	18 (1.8–67)	1,498 person-years for women	1 vulvar (0.35%)	NR	NR	0
Lowsky et al, ³³ 1994	1970–1993	248	Allo	(17–55)	(1–24)	0	–	–	1 (VIN)
Gallagher & Forrest, ³⁴ 2007	1985–2003	416	Allo	39 (12–65)	1.8 (0–19.2)	0	–	–	1 (VIN3)
Vagina-related									
Shimoni et al, ⁴² 2013	1999–2011	385	Allo	50 (17–76)	4.6 (1–13)	1 vaginal (0.26%)	NR	NR	0

Abbreviations: allo, allogeneic; auto, autologous; HCT, hematopoietic cell transplantation; NR, not reported; SIR, standardized incidence ratio; VIN, vulvar intraepithelial neoplasia.
^aDetermined by the authors for the entire cohort including both male and female patients, except where specified.
^bStatistically significant.

Female Genital Tract Neoplasms After HCT

Table 4. Official Cervical Screening Guidelines for Women With Routine Normal Findings^a

Age Group	General Population ^b	HIV-Positive Women ^c
<21 years	No screening	Begin cytologic screening at time of HIV diagnosis <ul style="list-style-type: none"> • If normal, screen again at 12 and 24 months • If all 3 screens are normal, screen every 3 years
21–29 years	Cytology alone every 3 years	Same as for <21 years of age
30–65 years	Cytology alone every 3 years (acceptable) Cytology and HPV DNA cotest every 5 years (preferred)	Begin cytologic screening at time of HIV diagnosis (with optional HPV DNA cotest) If screening by cytology alone: <ul style="list-style-type: none"> • If normal, screen again at 12 and 24 months • If all 3 screens are normal, screen every 3 years If screening by cytology and HPV DNA cotest: <ul style="list-style-type: none"> • If normal, screen every 3 years
>65 years	No screening if: <ul style="list-style-type: none"> • Negative prior screening^d • No history of CIN2+ in past 20 years 	Same as for 30–65 years of age

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

^aAdditional follow-up diagnostic measures are recommended in the event of any positive cytological screening or HPV testing results, including colposcopic follow-up in certain cases (guidelines not listed).

^bRecommendations from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (ACS-ASCCP-ASCP) Cervical Cancer Guideline Committee.⁴³

^cRecommendations from the Centers for Disease Control and Prevention, National Institutes of Health, and the HIV Medicine Association (CDC-NIH-HIVMA) Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents.⁴⁹

^dDefined as 3 consecutive negative cytology results or 2 consecutive negative cotest results within the previous 10 years, with the most recent tested performed within the past 5 years.

Finally, we highlight that a clearer understanding of the role of HCT in HPV acquisition and progression will inform vaccination guidelines in HCT survivors, for whom there are presently no immunogenicity or safety data regarding the HPV vaccine. Significant declines in the occurrence of high-grade cervical, vulvar, and vaginal neoplasms in multiple populations around the world have been attributed to the HPV vaccine.⁵⁰ However, the rate of HPV vaccination has remained low in childhood cancer survivors, a group that may experi-

ence significant long-term benefits from the vaccine.² A study in Texas found that female pediatric cancer survivors aged 13 to 17 years do not begin the 3-dose HPV vaccine series as commonly as the general population (36% vs 57%).^{51,52} Another study in Tennessee found that female pediatric cancer survivors aged 9 to 17 years were less likely to initiate (32.6%) or complete (17.9%) the HPV vaccine series compared with healthy age-matched controls (34.3% initiated and 20.0% completed).⁵³ Thus, the effort to elucidate the incidence, risk, and risk factors associated with female lower genital tract neoplasms may provide clinical evidence of HCT-related risks critical to improving the rate of vaccine uptake among young eligible women.

Conclusions

Small clinical studies suggest that cervical dysplasia increases in women after allo-HCT. This observation is supported by our current understanding of the HPV-related causes of cervical carcinogenesis, a process that may be facilitated by immune dysregulation in the peri- and post-allo-HCT setting. But despite this finding, large population-based studies generally do not show a greater risk of subsequent cervical cancer in allo-HCT recipients compared with the general population. Post-HCT cervical dysplasia may indeed be the transient result of transplant conditioning rather than HPV progression, and even true HPV-related dysplasias often revert to a normal presentation upon HPV clearance.¹⁸ The occurrence of vulvar and vaginal neoplasms, being much rarer than their cervical counterparts, has not been adequately studied post-HCT. Further elucidating the role of HCT in the progression of female lower genital tract neoplasms will be an important step towards clarifying optimal screening and vaccination measures in vulnerable patients.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. Klosky JL, Gamble HL, Spunt SL, et al. Human papillomavirus vaccination in survivors of childhood cancer. *Cancer* 2009;115:5627–5636.
3. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2014 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2017. Available at: www.cdc.gov/uscs. Accessed January 12, 2018.
4. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
5. Monk BJ, Burger RA, Lin F, et al. Prognostic significance of human papillomavirus DNA in vulvar carcinoma. *Obstet Gynecol* 1995;85(5 Pt 1):709–715.
6. Alemany L, Saunier M, Tinoco L, et al. Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples. *Eur J Cancer* 2014;50:2846–2854.
7. Maglennon GA, Doorbar J. The biology of papillomavirus latency. *Open Virol J* 2012;6:190–197.
8. Maglennon GA, McIntosh PB, Doorbar J. Immunosuppression facilitates the reactivation of latent papillomavirus infections. *J Virol* 2014;88:710–716.

9. Hinten F, Meeuwis KA, van Rossum MM, de Hullu JA. HPV-related (pre)malignancies of the female anogenital tract in renal transplant recipients. *Crit Rev Oncol Hematol* 2012;84:161–180.
10. Meeuwis KA, van Rossum MM, van de Kerkhof PC, et al. Skin cancer and (pre)malignancies of the female genital tract in renal transplant recipients. *Transpl Int* 2010;23:191–199.
11. Chin-Hong PV, Kwak EJ. Human papillomavirus in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):189–200.
12. Porrata LF, Litzow MR, Markovic SN. Immune reconstitution after autologous hematopoietic stem cell transplantation. *Mayo Clin Proc* 2001;76:407–412.
13. Steingrimsdottir H, Gruber A, Bjorkholm M, et al. Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications. *Haematologica* 2000;85:832–838.
14. Williams KM, Gress RE. Immune reconstitution and implications for immunotherapy following haematopoietic stem cell transplantation. *Best Pract Res Clin Haematol* 2008;21:579–596.
15. Fujimaki K, Maruta A, Yoshida M, et al. Immune reconstitution assessed during five years after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001;27:1275–1281.
16. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol* 2012;12:443–458.
17. Garnett C, Apperley JF, Pavlu J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol* 2013;4:366–378.
18. Plummer M, Schiffman M, Castle PE, et al. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis* 2007;195:1582–1589.
19. Schiffman MH, Brinton LA. The epidemiology of cervical carcinogenesis. *Cancer* 1995;76(10 Suppl):1888–1901.
20. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2012;18:348–371.
21. van de Nieuwenhof HP, Massuger LF, van der Avoort IA, et al. Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. *Eur J Cancer* 2009;45:851–856.
22. Sasadeusz J, Kelly H, Szer J, et al. Abnormal cervical cytology in bone marrow transplant recipients. *Bone Marrow Transplant* 2001;28:393–397.
23. Savani BN, Stratton P, Shenoy A, et al. Increased risk of cervical dysplasia in long-term survivors of allogeneic stem cell transplantation—implications for screening and HPV vaccination. *Biol Blood Marrow Transplant* 2008;14:1072–1075.
24. Wang Y, Brinch L, Jebsen P, et al. A clinical study of cervical dysplasia in long-term survivors of allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2012;18:747–753.
25. Negri G, Herz M, Deola S, et al. Abnormal cervical cytology after allogeneic bone marrow transplantation. *Am J Clin Pathol* 2014;142:222–226.
26. Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol* 2001;19:464–471.
27. Shimada K, Yokozawa T, Atsuta Y, et al. Solid tumors after hematopoietic stem cell transplantation in Japan: incidence, risk factors and prognosis. *Bone Marrow Transplant* 2005;36:115–121.
28. Ringden O, Brazauskas R, Wang Z, et al. Second solid cancers after allogeneic hematopoietic cell transplantation using reduced-intensity conditioning. *Biol Blood Marrow Transplant* 2014;20:1777–1784.
29. Atsuta Y, Suzuki R, Yamashita T, et al. Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease. *Ann Oncol* 2014;25:435–441.
30. Majhail NS, Brazauskas R, Rizzo JD, et al. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. *Blood* 2011;117:316–322.
31. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. *Blood* 2009;113:1175–1183.
32. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. *N Engl J Med* 1997;336:897–904.
33. Lowsky R, Lipton J, Fyles G, et al. Secondary malignancies after bone marrow transplantation in adults. *J Clin Oncol* 1994;12:2187–2192.
34. Gallagher G, Forrest DL. Second solid cancers after allogeneic hematopoietic stem cell transplantation. *Cancer* 2007;109:84–92.
35. Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med* 1999;131:738–744.
36. Danner-Koptik KE, Majhail NS, Brazauskas R, et al. Second malignancies after autologous hematopoietic cell transplantation in children. *Bone Marrow Transplant* 2013;48:363–368.
37. Seshadri T, Pintilie M, Kuruvilla J, et al. Incidence and risk factors for second cancers after autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Leuk Lymphoma* 2009;50:380–386.
38. Brown JR, Yeckes H, Friedberg JW, et al. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 2005;23:2208–2214.
39. Ruiz-Soto R, Sergeant G, Gisselbrecht C, et al. Estimating late adverse events using competing risks after autologous stem-cell transplantation in aggressive non-Hodgkin lymphoma patients. *Cancer* 2005;104:2735–2742.
40. Oddou S, Vey N, Viens P, et al. Second neoplasms following high-dose chemotherapy and autologous stem cell transplantation for malignant lymphomas: a report of six cases in a cohort of 171 patients from a single institution. *Leuk Lymphoma* 1998;31:187–194.
41. Deeg HJ, Socie G, Schoch G, et al. Malignancies after marrow transplantation for aplastic anemia and fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood* 1996;87:386–392.
42. Shimoni A, Shem-Tov N, Chetrit A, et al. Secondary malignancies after allogeneic stem-cell transplantation in the era of reduced-intensity conditioning: the incidence is not reduced. *Leukemia* 2013;27:829–835.
43. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin* 2012;62:147–172.
44. Nguyen ML, Flowers L. Cervical cancer screening in immunocompromised women. *Obstet Gynecol Clin North Am* 2013;40:339–357.
45. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2012;18:348–371.
46. Bhatia S, Armenian SH, Landier W. How I monitor long-term and late effects after blood or marrow transplantation. *Blood* 2017;130:1302–1314.
47. Spinelli S, Chiodi S, Costantini S, et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica* 2003;88:1163–1168.
48. Zantomio D, Grigg AP, MacGregor L, et al. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. *Bone Marrow Transplant* 2006;38:567–572.
49. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Available at: http://aidsinfo.nih.gov/contentfiles/vguidelines/adult_oi.pdf. Accessed November 10, 2017.
50. Castle PE, Maza M. Prophylactic HPV vaccination: past, present, and future. *Epidemiol Infect* 2016;144:449–468.
51. Hoffman L, Okcu MF, Dreyer ZE, et al. Human papillomavirus vaccination in female pediatric cancer survivors. *J Pediatr Adolesc Gynecol* 2012;25:305–307.
52. Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among adolescents aged 13–17 years—United States, 2012. *MMWR Morb Mortal Wkly Rep* 2013;62:685–693.
53. Klosky JL, Russell KM, Canavera KE, et al. Risk factors for non-initiation of the human papillomavirus vaccine among adolescent survivors of childhood cancer. *Cancer Prev Res (Phila)* 2013;6:1101–1110.