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Review

Lower Genital Tract Precancer and Cancer in Hematopoietic Cell Transplant Survivors and the Role of HPV: A Systematic Review and Future Perspectives

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ABSTRACT

Female recipients of hematopoietic cell transplant (HCT) may develop lower genital tract (LGT) dysplasia or new malignancies. A comprehensive systematic review to delineate the occurrence and risk factors for post-HCT LGT precancer and cancer in women was conducted via electronic search of the Cochrane Library, PubMed, Embase, Wiley Online Library, from 1990 to 2018. All studies on the risk, presentation, or incidence of LGT (cervix, vulva, vagina) precancer or cancer post-HCT were included. Reviews, case reports, meta-analysis, book chapters, and studies without the relevant clinical outcomes were excluded. Post-HCT incidence and risk factors for developing LGT precancer or cancer were assessed and determined. Twenty-two out of the original 344 studies met the selection criteria. The risk of LGT cancers in allo-HCT recipients was found to be significantly higher than in the general population, with the standardized incidence ratios of 1.5–48 for cervical cancer and from 19 to 287 for dysplasia. Our review portrays an increased risk of premalignant and malignant neoplasms of female LGT, which have an incompletely described epidemiology and outcomes. Similar to other immunocompromised states, HCT recipients require specific cervical screening guidelines and can greatly benefit from HPV vaccinations. However, there is a lack of prospective data regarding optimum cervical screening in HCT recipients and limited programs offer HPV vaccinations worldwide.

1. INTRODUCTION

Each year, malignancies, genetic diseases, hemoglobinopathies, and immunodeficiencies require hematopoietic cell transplantation (HCT) as potentially curative therapy for tens of thousands of patients. Eighty-five percent of patients who survive transplant-related complications in the first two years have a good prognosis for long-term survival (10 years) [1]. Female survivors are at a risk of developing chronic health conditions, including lower genital tract (LGT) precancer and cancer, premature menopause, and problems with sexual health. These women benefit from gynecologic care and follow-up post-HCT. An essential part of this care is screening for human papillomavirus (HPV)-related lower genital and cervical dysplasia/cancer, which includes cervical cytology and HPV testing and inspection of the LGT for HPV disease at pelvic exams. As in other populations, assessment of abnormalities noted on testing and biopsy of lesions enables early identification and treatment of premalignant lesions which, in turn, could decrease the risk of cervical and other LGT cancers in long-term survivors of allo-HCT [2].

HPV is the most common sexually transmitted infection, with a 27% estimated overall prevalence in women aged 14–59 years in North American and European populations [3,4]. The HPV prevalence increases from 20% in teenagers to 45% in women aged 20–24 years and declines to 5% in women over 50 years [5–7]. Ninety percent of HPV infections clear spontaneously within 2 years, but persistent HPV confers a significant risk of development of high-grade lesions and cancer. Additionally, HPV may reactivate and cause neoplasms later in life [8]. HPV-related disease typically takes 10 to 30 years to progress from initial epithelial changes to invasive cancer [9], illustrating how screening to identify and treat premalignant lesions in the general population can enable prevention of cervical cancer. Whether the time to these cancers is shorter in women post-HCT is not known.

Cervical cancer is the second most common cancer worldwide in women [10]. Vulvar and vaginal cancer are rare and account for only 7% of all gynecological malignancies [10] and HPV plays an important role in their development. High-risk HPV types (16, 18, 31, 33, 34, 45, 52, and 58) are responsible for 95% of cervical

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intraepithelial neoplasia (CIN) and invasive carcinomas [11,12] as illustrated by finding HPV genetic sequences in nearly all cervical cancers [12–14]. Primary vulvar and vaginal cancers are relatively rare in the LGT, but evidence of HPV DNA in precursor lesions (vulvar and vaginal intraepithelial neoplasia) has been reported with HPV 16 being the most common type detected [15]. Persistent infection with any of the oncogenic HPV types is essential for tumor cell transformation of cervical and other LGT cells [16–18]. Other immune compromised populations like HIV-infected women and those postrenal or other solid organ transplant are at risk of HPV-related disease throughout the LGTt.

HCT recipients may be at a higher risk of developing HPV-related neoplastic changes due to a number of factors. First, exposure to ionizing radiation and chemotherapy as part of treatment and conditioning regimens prior to HCT may lead to an increased risk due to their detrimental effects on immunity, making one more prone to infection or reactivation of HPV. Second, delayed immune recovery or prolonged immunosuppressive therapy (IST) for graft *versus* host disease (GVHD) increases the risk, as evidenced by an accelerated progression from cervical dysplasia to invasive carcinoma and a more aggressive disease course in immunocompromised patients [19]. Third, HPV and GVHD may be interrelated, as illustrated by a report of HPV reactivation in a post-HCT patient following use of topical immunosuppression and vaginal dilators [20]. Other gynecologic factors, like history of HPV-related disease and whether the woman has ever been and is currently sexually active also impacts the risk. Additionally, transplant-related factors related to the conditioning regimen and recovery including HPV vaccinations may alter this risk as well.

Given the growing literature on HPV and LGT cancers in recipients of HCT, many questions regarding the burden and risks of these complications have arisen in the practicing community. Herein, we conducted a systematic review of published peer-reviewed literature on the risk of HPV-related cervical and LGT precancer and cancer in HCT recipients. A meta-analysis could not be conducted due to the differences in both the selection of patients and the primary outcomes reported in various studies.

2. METHODS

A literature search was conducted on articles published from 1990 to 2018, indexed in the Cochrane Library, PubMed, Embase, Wiley Online Library.

2.1. Search Terms

These encompassed cervical abnormality, cervical dysplasia, cervical atypia, cervical cancer, cervical precancer, cervical neoplasia, squamous intraepithelial lesion (SIL), vulvar neoplasm, vulvar neoplasia, vulvar cancer, vaginal neoplasm, vaginal neoplasia, vaginal cancer, HPV, cervical cytology, bone marrow transplantation, HCT, stem cell transplantation, chronic graft *versus* host disease (cGVHD), GVHD, female genital tract (FGT), and female reproductive tract.

2.2. Inclusion Criteria

Clinical trials, prospective, retrospective, and cross-sectional observational studies, case-control studies, nested case control studies, and case series published in English regarding female subjects that described LGT (cervix, vulva, vagina) precancer or cancer post-HCT were included. Cohort studies of long-term risk of secondary neoplasms after HCT which included LGT cancers were also screened. Outcomes of interest included any LGT dysplasia or new (secondary) cancer after HCT and identification of risk factors that could lead to their development. These risk factors encompassed extensive chronic or genital GVHD (cGVHD, gGVHD), requirement for IST >3 years, transplant factors including unrelated human leukocyte antigen (HLA)-matched donors, allo-HCT recipients who had a relapse of the primary malignancy, extensive or genital chronic GVHD (as it a poses risk of prolonged IST), abnormal cervical cytology testing (Papanicolaou smears) prior to HCT which includes atypical squamous cells of undetermined significance (ASCUS), and pretransplant dysplasia.

2.3. Exclusion Criteria

Any language other than English, systematic reviews, review articles, meta-analysis, case reports, book chapters, and preclinical studies were excluded.

3. RESULTS

Of the 344 articles identified, 27 provided LGT precancer and cancer information in posttransplant recipients. Removing redundancies and review articles, only 22 remained. Of these 22, five studies (two prospective cohort and three retrospective cohort studies) included cervical cytology results and examined the risk factors for cervical or LGT precancer. Thirteen retrospective cohort studies reporting the incidence of secondary cancers post-HCT included cervical cancer and six retrospective cohort studies reported on vulvar or vaginal cancer incidence.

3.1. Study Characteristics

3.1.1. Cervical and lower genital tract dysplasia

Characteristics of individual studies are presented in Table 1 [21–26] which include four studies reporting on cervical and one study reporting on lower genital neoplasia.

Sasaduesz *et al.* [21] conducted a retrospective study of all available pap smears before and after HCT and reported a 6.8-fold increase in risk for cervical abnormality (low-grade squamous intraepithelial lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) before (age-adjusted odds ratio [OR] 2.2, $P = 0.02$) and after HCT (OR 7.0, $P < 0.0001$), with a greater incidence occurring in allogeneic *versus* Autologous HCT (auto-HCT) recipients post-HCT (OR 2.6, $P = 0.02$). A higher rate of abnormalities was only found in Allogeneic HCT (allo-HCT) recipients when comparing pre- and post-HCT status (allogeneic, OR 6.8, $P = 0.004$). No increased risk was reported among auto-HCT recipients. The risk factors for abnormal cytology identified among allo-HCT recipients included cGVHD and/or prolonged immunosuppressive therapy (>3 years). That study was limited by a lack of information on GVHD severity, intensity, and duration of immnosuppressive therapy.

Table 1 | Studies on cervical cytology in HCT recipients.

Study	Study Design	HCT Period	Patients, *N*	HCT Type	Median Age at HCT, Years (Range)	Median Follow-up, Years(Range)[a]	Conditioning Regimen	Immuno suppressive Therapy Duration, Months	GVHD Prophylaxis	Normal Pre-HCT Cytology/ Abnormal Post-HCT Cytology, *n* (%)	Key Findings
Sasaduesz *et al.*, 2001 [21]	Retrospective review	1989–1998	64	Allo or auto	Allo: 39(29–52) Auto: 43 (22–66)	Auto: 2.6 (0.5–7.5) Allo: 3.5 (0.3–8.8)	NR	NR	NR	NR	Significant increase in the rate of LSIL or HSIL in allo-HCT recipients, post-HCT, not auto-HCT recipients
Savani *et al.*, 2008 [22]	Prospective study	1993–2003	38[b]	Allo	33 (9–60)	7.1 (3.8–13.6)	9 RIC:Fludarabine + Cyclophosphamide 29 TBI + Cyclophosphamide (+/- Fludarabine)	>18 mo : 6 (17%)[c]	38 Cyclosporine	Total: 15/≈35[b] (≈43%) LSIL: 5/≈35[b] (≈14%) HSIL: 7/≈35[b] (≈20%)	Chronic GVHD requiring IST for ≥ 3 years was the only risk factor for HPV-related HSIL or LSIL after HCT
Wang *et al.*, 2012 [23]	Retrospective review	1985–2005	89	Allo	39 (15–59)	11 (5–25)	87 Busulfan + Cyclophosphamide 2 TBI + Cyclophosphamide	12 (0–78)	88 Cyclosporine + MTX	Total: 44/69 (64%) LSIL: 6/69 (8.7%) HSIL: 16/69 (23%)	Vulvovaginal GvHD was identified as the only risk factor was cervical dysplasia
Negri *et al.*, 2014 [26]	Retrospective review	NR	54	Allo	NR	NR	16 TBI-Cyclophosphamide 8 Treosulfan-Fludarabine 5 Busulfan-Fludarabine 4 Busulfan-Cyclophosphamide	NR	NR	Total: 13/54 (24%) LSIL: 6/54 (11%) ASC-H: 3/54 (5.6%)	Busulfan associated cervical atypia. ASC-H patients had normal cytology on first follow-up post-HCT
Shanis *et al.*, 2012 [24]	Prospective study	NR	82	Allo	36 (10–68)	9.4 (NR)	NR	NR	93% Myeloablative T-cell depleted	NR	Extensive chronic GvHD or genital GvHD increased the risk of post-HCT cervical dysplasia. Pre-HCT dysplasia was identified as a risk factor for HPV infections and the strongest factor for persistent HPV infection, post-HCT. Pre-HCT hysterectomy was a risk factor for multifocal HPV infections.

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; MTX, Methotrexate; NR, not reported; RIC, Reduced Intensity Conditioning; TBI, Total Body Irradiation.
(a) Determined by the authors for both males and females in the cohort. (b) Savani *et al.* only assessed 35 of the 38 patients.

Savani *et al.* [22] reported a retrospective study in 38 allo-HCT recipients, followed for a median of 7 years post-HCT, and found biopsy-confirmed HPV-related cervical dysplasia in 43% of patients. On a multivariate logistic regression, the only risk factor significantly associated with HPV-related cervical dysplasia (HSIL or LSIL) post-HCT was a prolonged usage of IST (>3 years) for cGVHD management, which showed a risk 4.6 times higher than that posed by a shorter duration of IST (OR 4.6, 95% confidence interval [CI] 1.1–16.4; P 5 .019). No significant association was found between HPV-related dysplasia and genital cGVHD ($P = 0.37$), but genital cGVHD was not uniformly assessed.

Wang *et al.* [23] followed a cohort of 89 allo-HCT recipients for 11 years post-HCT in which patients averaged 6.5 Pap smears during follow-up. Among 69 patients who had normal cervical cytology pre-HCT, 23% developed HSIL and 9% LSIL post-HCT. HPV DNA testing was conducted in 12 HSIL patients, 7 (58%) of whom were HPV positive. None of the six patients with LSIL tested for HPV DNA had a positive result. They identified unrelated HLA-matched donors and vulvovaginal cGVHD as independent risk factors for HSIL diagnosed on cervical cytology testing post-HCT compared with pre-HCT. Vulvovaginal cGVHD conferred the greatest risk for developing HSIL post-HCT (OR, 31.97; 95% CI, 1.33–769.42) and was the only independent risk factor significantly associated with histologically confirmed cervical dysplasia (adjusted OR, 47.7; 95% CI, 1.83–1234.65; $P = 0.02$).

Shanis *et al.* [24] in a prospective cohort study, found an increase in the cumulative rate of genital HPV infection over time. They identified having abnormal cervical cytology testing prior to HCT as a risk factor for having post-HCT HPV infection (OR = 6.5, $P = 0.008$) and the strongest risk factor for persistent HPV (OR = 23.2, $P < 0.001$). Having either genital cGVHD or extensive cGVHD conferred a higher risk of developing cervical dysplasia and for HPV disease, post-HCT (CIN II-III / VIN II-III; OR = 13.1, $P = 0.017$). Pre- or post-HCT hysterectomy was associated with an increased risk of multifocal HPV infections (OR = 7.9, $P = 0.01$). Pre-transplant dysplasia was also identified as an important risk factor on univariate analysis ($P = 0.018$) and confirmed with multivariate analysis (OR 10.3; $P = 0.013$). Time to abnormal cervical cytology testing was significantly associated with the utilization of vulvar steroids (hazard ratio [HR] 0.2, $p < 0.01$) and pre-transplant dysplasia (HR 0.26, $p < 0.05$).

Yu *et al.* [25] reported that among those with early cervical cytology testing, cervical atypia mimicking the appearance of cancer was more prevalent within 100 days after HCT in patients receiving busulfan containing conditioning regimens (before day +100, 80%, *versus* after day +100, 2.56%; $P = .0002$). Biopsy evaluation of these abnormalities showed that the atypia was related to busulfan and not to HPV-related neoplasia. Negri *et al.* [26] reported a higher rate of abnormal cervical smears and cytologic HPV-related SIL compared to the overall SIL rate in allo-HCT recipients in their institution ($P < 0.001$). They also described busulfan-related cervical atypia post allo-HCT, mimicking cancer, which was interpreted as a false-positive result.

In summary, the aforementioned studies suggest that HCT recipients are more susceptible to the progression of cervical dysplasia, due to prolonged immunosuppression as a result of vulvovaginal GvHD, and long-term use of systemic IST. There is also evidence to suggest a higher rate of abnormal cervical cytology after allo-HCT. Future studies with larger patient populations having detectable cervical cancer and HPV DNA co-testing will provide greater insight into the risk of cervical cancer development post-HCT, and help distinguish true from transient cervical atypia, minimizing detection bias.

3.1.2. Cervical cancer

Study characteristics are presented in Table 2 [27–39].

Thirteen studies allowed the assessment of the development of secondary cancer after HCT, including cervical cancer. Three of these studies followed recipients of either auto- or allo-HCT, four of only auto-HCT and the remaining six studies had patients who received allo-HCT only.

Previous studies have identified GVHD as a risk factor for secondary solid cancers after allo-HCT, with recipients developing new solid cancers at twice the rate of the general population, with a 3-fold greater risk among patients followed for 15 years or longer after transplant [37]. GVHD increased the risk of squamous cell carcinomas, and total body irradiation was the major risk factor for developing nonsquamous cell carcinomas. Also, LGT dysplasia was common among solid organ transplant recipients [40–42]. HPV has also been detected in 70%–90% of cutaneous squamous cell cancers [43,44] . Similarly, new (or secondary) neoplasms are a serious long-term complication after allo-HCT [32,33]. In a long-term prospective cohort of allogeneic HCT survivors, Bhatia *et al.* [33] reported an increased risk of developing oral and cervical squamous cell carcinomas. Although true for other sites, the relationship between HPV infection and second cancers of the cervix in HCT survivors is not known.

Bhatia *et al.* [33] (919 females) and Shimada *et al.* [35] (324 females) reported a 13.3- and 8.6-fold increase, respectively, in the risk of developing cervical cancer as compared with the general population, whereas Kolb *et al.* [32] (433 females) failed to show any significant risk increase. The studies with the largest cohorts (range, 1,765–11,752 females) followed recipients of allo-HCT and did not find an increase in the risk of developing cervical cancer compared with the general population [27,28,30,31,37,39]. Rizzo *et al.* [37] who followed the largest cohort of 11,752 women only reported five cases of cervical cancer post-HCT. Studies following women who received auto-HCT had relatively smaller cohorts (range: 60–592), and also did not show an increase in the risk of developing cervical cancer secondary to HCT compared with the general population [29,34,36,38]. Danner-Koptik *et al.* [29] reported an increase in risk based on a single case of cervical cancer in a pediatric population of patients.

In conclusion, for both auto-HCT and allo-HCT recipients, the findings collectively suggest no elevation in the risk of developing cervical cancer. However, it is difficult to draw any conclusions due to the shortcomings of the reviewed papers. A substantial portion of the collective cohort of these studies included patients aged 0–10 years, with infants being included in each individual study.

3.1.3. Vulvar and vaginal cancer

Study characteristics are presented in Table 3 [27,30,45–48].

Table 2 | Studies on cervical cancer after HCT.

Study	Study Design	HCT Period	Patients, *N*	HCT Type	Median Age at HCT, Years (Range)	Median Follow-Up, Years (Range)[a]	Cervical Cancers Post-HCT, *n* (% of Total Patients)	SIR (95% CI)	Time to Diagnosis of Cervical Cancer Post-HCT, Years (Number of Cases)	Cervical Dysplasia Cases Post-HCT, *n* (Type)
Lowsky *et al.*, 1994 [24]	Retrospective cohort	1970–1993	248	Allo	(17–55)	1,608 person-years[b]	0	-	-	5 (CIN)
Curtis *et al.*, 1997 [28]	Retrospective cohort	1964–1990	7,851	Allo	25.5	3.5 (1–25)	1 (0.013)	1.7 (0.54–3.85)	1–4 (1)	0
Kolb *et al.*, 1999 [32]	Retrospective cohort	pre-1986	433	Allo or auto	21 (1–51.9)	10.7 (5–22.1)	0	-	-	5 (CIS)
Bhatia *et al.*, 2001 [33]	Retrospective cohort and nested case-control	1976–1998	919	Allo or auto	33.9 (1.5–71.5)	3.3 (0.1–21.1)	4 (0.44)	13.3[c] (3.5–29.6)	Median: 3.3 Range: 1.6–9.7	0
Brown *et al.*, 2005 [34]	Retrospective Cohort	1982–1997	254	Auto	44	9.5	0	-	-	1 (HSIL)
Shimada *et al.*, 2005 [35]	Retrospective cohort	1981–2000	324	Allo or auto	34 (15–70)	5.3 (1-19-9)	2 (0.62)	8.6[c] (1.04–31.01)	3.8 (1) 4.9 (1)	0
Ruiz-Soto *et al.*, 2005 [36]	Retrospective cohort	1993–2002	60	Auto	46 (18–69)	3 (0.5–12)	1 (1.7)	NR	9.8 (1)	0
Rizzo *et al.*, 2008 [37]	Retrospective cohort	1964–1994	11,752	Allo	27 (0.1–72.4)	36,252 female person-years	5 (0.043)	1.7 (0.54–3.85)	<1 (1) 1–4 (3) ≥15 (1)	3 (CIS)
Seshadri *et al.*, 2009 [38]	Retrospective cohort	1987–2006	164	Auto	50 (19–70)	4.8	1 (0.61)	NR	NR	0
Majhail *et al.*, 2011 [39]	Retrospective cohort	1986–2006	1,903	Allo	29 (<1–60) or 36 (<1–60)[c]	7 (<1–21) or 8 (<1–19)[b]	3 (0.16)	2.3 (0.48–6.77)	<1 (1) 1–4 (1) 5–9 (1)	0
Danner-Koptik *et al.*, 2013 [29]	Retrospective cohort	1987–2003	592	Auto	8(<1–21)	8 (<1–21)	1 (0.17)	48[c] (1.2–270)	<1 (1)	0
Ringden *et al.*, 2014 [30]	Retrospective cohort	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.*, 2014 [31]	Retrospective cohort	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

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.
(a) Determined by the authors for both males and females in the cohort. (b) Two separate study groups of patients, those with either acute myeloid leukemia in first complete remission or chronic myeloid leukemia in first chronic phase, with their respective medians and ranges. (c) Statistically significant.

Table 3 | Studies on vulvar and vaginal dysplasia and cancer after HCT.

Study	Study Design	HCT Period	Patients, *N*	HCT Type	Median Age at HCT, Years (Range)	Median Follow-Up, Years (Range)[a]	Cancers Post-HCT, *n* (% of Total Patients)	SIR (95% CI)	Time to Diagnosis Post-HCT, Years (Number of Cases)	Dysplasia Cases Post-HCT, *n* (Type)
Lowsky *et al.*, 1994 [27]	Retrospective cohort	1970–1993	248	Allo	(17–55)	(1–24)	0	-	-	1 (VIN)
Deeg *et al.*, 1996 [46]	Retrospective cohort	1970–1993	283	Allo	18 (1.8–67)	1,498 female person-years	1 vulvar (0.35%)	NR	NR	0
Oddou *et al.*, 1998 [47]	Retrospective cohort	1985–1995	65	Auto	38 (11–61)	4.3 (1.8–13)	1 vulvar (1.5%)	287[b] (3.73-552)	3 (1)	0
Gallagher *et al.*, 2007 [48]	Retrospective cohort	1985–2003	416	Allo	39 (12–65)	1.8 (0–19.2)	0	-	-	1 (VIN3)
Shimoni *et al.*, 2013 [49]	Retrospective cohort	1999–2011	385	Allo	50 (17–76)	4.6 (1–13)	1 vaginal (0.26%)	NR	NR	0
Ringdén *et al.*, 2014 [30]	Retrospective cohort	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

Abbreviations: allo, allogeneic; auto, autologous; HCT, hematopoietic cell transplantation; NR, not reported; SIR, standardized incidence ratio; VIN, vulvar intraepithelial neoplasia.
(a) Determined by the authors for both males and females in the cohort. (b) Statistically significant.

In the case of vulvar and vaginal cancer post-HCT, limited information about the risk factors and incidence is available. Ringdén *et al.* [30] reported one case of vulvar cancer in 1,765 allo-HCT recipients (SIR, 18.6; 95% CI, 3.73–552; $P = 0.01$) and Oddou *et al.* [46] reported two cases in 65 auto-HCT recipients (SIR, 287; 95% CI, 3.73–552; $P = 0.01$). These are the only two studies which found an elevated risk of vulvar cancer post-HCT and neither attributed any factors underlying such risk. Deeg *et al.* [45] reported one case of vulvar cancer out of 283 allo-HCT recipients, without mentioning any change in the risk for that. Lowsky *et al.* [27], along with Gallagher and Forrest [47] each reported one case of vulvar dysplasia (VIN I and VIN III, respectively), without any risk determination. We were unable to find any studies which prospectively assessed the risk factors or rates of vaginal cancer post-HCT in allo-HCT recipients. Shimoni *et al.* [48] are the only authors who reported a single case of vaginal cancer out of 385 allo-HCT recipients but did not provide any risk determination data. Unfortunately, it is difficult to draw any conclusions regarding post-HCT vulvar and vaginal dysplasia or cancer, due to their rarity in the current literature. Most studies report small numbers post-HCT and lack any risk assessment.

4. RISK FACTORS AND MECHANISMS

Most studies to date in allo-HCT recipients have focused on cervical dysplasia rather than specifically on HPV-related LGT disease, and have shown that cervical HSIL and cervical dysplasia occur at a higher rate post-HCT than in general population. Women undergoing allo-HCT have an increased risk, due to chemotherapies and IST which come with the treatment of malignancy and cGVHD, respectively. The peak incidence for HPV disease appears to be years after HCT, suggesting HPV reactivation or new infection through a new sexual contact. Additionally, the conditioning regimen for HCT can potentially predispose the recipients to cervical dysplasia [33]. Finally, GVHD results in mucosal lesions involving genital tissues and may result in dysplasia either independently or synergistically with HPV involvement [49].

Besides quantitative risks, papers included in our review also identified that genital GVHD has various manifestations [50]. It can present as scarring or narrowing of the vaginal canal leading to shortening of the canal, with or without the presence of arcuate ridges or synechiae. It can also cause the formation of ulcers, or tender, inflamed erosions of the vulvar mucosa. Topical corticosteroid is the preferred treatment for mucocutaneous GVHD as systemic immunosuppression does not decelerate the course of genital GVHD progression. Topical estrogen may complement the effects of corticosteroids in some cases, as it promotes the growth of mucosa and may limit scarring [51]. But care must be taken, as IST and the usage of vaginal dilators has the potential to lead to widespread HPV infection [20].

HPV invokes both an antibody and cell-mediated response from the immune system, with evidence suggesting a central role of T-cells [52]. Posttransplant cell-mediated immunity is decreased, affecting T-cells, natural killer cells, and antibody production, which can be made worse by cGVHD and prolonged IST [53]. Cancer progression in active HPV infections can be affected by genetic factors, disease type, cGVHD, conditioning regimens, and treatments [54]. Aldabagh *et al.* [52] also highlighted an increased risk of multifocal HPV disease in immunocompromised women.

Since allo-HCTs carry a purportedly higher risk than auto-HCTs for developing new cancers post-HCT, these results present a challenge, as they collectively argue against this notion. The average risk described in allo-HCT recipients may be due to an insufficient follow-up period for cervical cancer, which has a long latency period, with some cases having been diagnosed after a decade. Secondary solid tumor development peaks at approximately 6.8 years post allo-HCT [47], and the incidence increases linearly over at least 20 years [37]. Longer follow up periods would allow the maximum influence of HCT-related factors to manifest on the cervix. All 13 studies on new cancers post-HCT lack HPV data (high risk *versus* low risk HPV infections) which can help identify which allo-HCT recipients are at an increased risk. Overall, the number of cervical cancer patients reported may have been underestimated, due to a significant fraction of children (<10 years at the time of HCT) included in the cohorts, who are unlikely to contract HPV during the latency period of cervical cancer. Rizzo *et al.* [37], Majhail *et al.* [39], and Kolb *et al.* [32] reported 14%, 6%, and 15% of total HCT recipients being under the age of 10, respectively. Ringdén *et al.* [30] and Bhatia *et al.* [33], did not specify the number, but did include young children in their cohorts. Additionally, the increased risk discovered by Bhatia *et al.* [33] and Shimada *et al.* [35] could be explained by their relatively small cohort sizes, where the small number of cervical cancers (four and six, respectively) could make the risk appear significantly elevated.

The exact relationship between GVHD and HPV reactivation and spread is uncertain. It is difficult to ascertain whether viral reactivation leads to GVHD or if GVHD and the IST associated with it, leads to HPV reactivation. IST hinders the ability of the immune system to clear HPV and increases the risk of dysplastic and neoplastic changes. Viral reactivation increases the likelihood of developing a pro-inflammatory microenvironment which promotes allo-immune activation, potentially leading to GVHD. The context of antigen presentation influences the immune response and the presence of self-antigens alone is enough to mount it [55]. Molecular patterns associated with pathogens and tissue damage are more likely to induce a pro-inflammatory response rather than anergy or an anti-inflammatory response [55]. Thus, when host self-antigens are presented to the donor immune system in this microenvironment, immune activation and local GVHD may become more likely. The need for the combination of both, alloantigen and an inflammatory stimulus, to be sufficient for GVHD to occur is exhibited by the association of viral reactivation and GVHD in other mucosal environments. Sri *et al.* [20], described a 30-year-old woman, two years post-HCT for aplastic anemia, receiving systemic cyclosporine for cGVHD. Topical estrogen and corticosteroids, along with vaginal dilators were also used for the treatment of vaginal cGVHD. Condylomatous cervicitis was discovered upon colposcopy and biopsy for abnormal cervical cytology testing. Continued dilator therapy over the next 4 months resulted in the development of linear verrucous lesions in the vagina and vulva, which were then treated with laser therapy. Following the same patient, Buchan *et al.* [56] reported an outbreak of genital warts following the use of topical IST. This HPV reactivation limited the use of local IST and a vaginal estrogen ring was only able to delay vaginal scarring and necessitated a cruciate incision in the cervico-vaginal scar to relieve the hematocolpos that developed due to GVHD. This case highlights a mode of spread of HPV that might be easily missed. The use of local IST and dilator therapy for genital GVHD can enhance the spread of HPV, and could explain why

vulvovaginal GVHD is a risk factor for cervical dysplasia in some papers. It also highlights the need for novel management of vaginal GVHD, and the interrelationship of GVHD and HPV.

5. ROLE OF HPV VACCINATIONS

Vaccination recommendations are provided in Table 4.

A limited number of HCT programs offer HPV vaccination post-HCT to provide protection to immunodeficient individuals against the pathogenic strains of HPV. Three vaccines are approved by the Food and Drug Administration to prevent HPV infection: Gardasil, Gardasil 9, and Cervarix. These vaccines are noninfectious, nonreplicating, subunits of viral-like particles. All three prevent infections with HPV types 16 and 18, two high-risk HPVs that cause about 70% of cervical cancers [57], 90% of anal cancers in men and women, 65% of vaginal cancers, and 78% of HPV-related vulvar cancers. Gardasil also prevents infection with HPV types 6 and 11, which cause 90% of genital warts. Gardasil 9 prevents infection with the same four HPV types plus five additional high-risk HPV types (31, 33, 45, 52, and 58).

For immunocompetent individuals, most guidelines recommend vaccinating females aged 9–14 years, before the onset of sexual activity, with a catch up period of 26 years. In many countries, a two-dose regimen is recommended for those under the age of 15 years with an interval of 6 months and a standard, three-dose regimen for those aged 15 years or older and the immunocompromised [58].

In the immunocompromised, including those who are HCT recipients, antibody titers are often lower when compared to the immunocompetent [59–62]. It was also noted that titers differ according to the immune therapy received, with mycophenolate producing lower HPV vaccine titers when compared to other drugs [63]. Nonetheless, these studies do not attribute any adverse effects to the HPV vaccine, nor do they alter the course of the original disease, demonstrating its safety [53,64,65]. Results from a recent large study on women posttransplant on low dose IST or not on any IST showed that they can mount a response to HPV vaccine and, thus, vaccination will likely become a recommended strategy in the future [66].

Female HCT recipients between the ages of 9 and 26 can ideally receive three doses of the HPV vaccine if there are no contraindications present. However, in sexually active women above the age of 26, vaccinations can be considered based on individual bases. Long-term safety and immunogenicity data is still lacking regarding the HPV vaccine post-HCT. Thus, further clinical research into understanding the course of LGT dysplasia, incidence of cancer, and the role of HPV is essential in guiding the establishment of HCT specific vaccination schedules in the future.

6. CHALLENGES

Due to the relative shortage of prospective trials on this topic and lack of relevant data, there are a number of challenges facing clinicians and researchers alike. A long-term follow-up period is needed to study the progressive changes associated with cervical precancer and cancer. Unfortunately, due to the age of the patients and the response to HCT, a significant number are lost to follow-up. Most of the reviewed publications describe their small cohorts as a

Table 4 | HPV vaccination recommendations.

Age/Situation	Schedule	Notes (Plus Specific Recommendations for HCT Patients)
9–14 years[a]	Routine vaccination for all adolescents at 11–12 years (can start at age 9) and through age 18 if not previously adequately vaccinated. Number of doses dependent on age at initial vaccination:	
	Age 9–14 years at initiation: 2-dose series at 0 and 6–12 months.	Minimum interval: 5 months (repeat a dose given too soon at least 12 weeks after the invalid dose and at least 5 months after the 1st dose).
	Age 15 years or older at initiation: 3-dose series at 0, 1–2 months, and 6 months.	Minimum intervals: 4 weeks between 1st and 2nd dose; 12 weeks between 2nd and 3rd dose; 5 months between 1st and 3rd dose (repeat dose(s) given too soon at or after the minimum interval since the most recent dose).
HCT recipients aged 9–26 years	3 doses, if no contraindications are present.	Consider vaccination on individual bases in sexually active females above the age of 26.
Immunocompromised (including HIV) aged 9–26 years[a]	3-dose series at 0, 1–2 months, and 6 months.	HCT recipients fall into this category
Pregnancy[a]	Vaccination not recommended, but there is no evidence the vaccine is harmful. No intervention is needed for women who inadvertently received a dose of HPV vaccine while pregnant. Delay remaining doses until after pregnancy. Pregnancy testing not needed before vaccination	
19–26 years[b]	2–3 doses depending on age of initial dose	
27–64 years[b]	No recommendations available	In sexually active females post HCT, HPV vaccination may be considered on individual basis
≥65 years[b]	No recommendations available	

Persons who have completed a valid series with any HPV vaccine do not need any additional doses.

HCT, hematopoietic cell transplant; HIV, human immunodeficiency virus; HPV, human papillomavirus.

(a) CDC, NCRID. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, UNITED STATES, 2018 Approved by the Advisory Committee on Immunization Practices American Academy of Family Physicians [Internet]. 2018 [cited 2019 Jan 2]. Available from: www.acog.org. (b) American Center for Disease Control and Prevention-Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2018, cited 2019 Jan 2]. Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-compliant.html#f6

limitation, warranting a large-scale study to be conducted. Although the Bethesda classification scale is used to identify the amount of dysplasia throughout these studies, there is a lack of consistency in the other variables being tested, which makes it extremely difficult to compile any meaningful numerical data, particularly the lack of pre and post-HCT HPV testing.

Cervical screening guidelines are provided in Table 5.

The timing and frequency of cervical screening in women undergoing HCT is still debatable, given the lack of prospective data. Frequent screening bears the risk of finding self-limiting, transient lesions which do not have any effect on treatment. The screening and management guidelines for cervical HPV disease in women post-HCT have not been formulated based on evidence. Instead they have mirrored what is advised for those with other immunodeficiencies. Established cervical screening programs for healthy populations require 3- or 5-year cervical cytology testing in sexually active females. However, this time frame is inappropriate for the immunocompromised patients and, additionally, the cytology testing alone may be insufficient for this group of patients. Based on individual risk factors, such as use of corticosteroids, duration of IST, time since coitarche and each woman's fertility goals, treatment of abnormalities should be individualized.

The same guidelines for cervical cancer screening and treatment in women with solid organ transplantation and HIV can be considered in post-HCT patients in the absence of substantial evidence. HPV-related disease screening starts earlier and occurs more frequently in HIV-positive women than in the general population, due to several reasons. Women infected with HIV have a greater risk of contracting high-risk HPV infections and CIN [67–69]. Sexually active adolescents who are HIV-positive have a higher rate of progression to abnormal cervical cytology [70]. These women have higher rates of vaginal, vulvar, and perianal neoplasia [71,72]. They also have higher rates of anal intraepithelial neoplasia and anal cancer, compared with the general population [73]. Abnormal cervical screening results and SIN lesions in HIV-positive women should be managed according to the ASCCP and The Panel on Opportunistic Infections guidelines and algorithms. Since these guidelines have recently changed, does it beckon a change in post-HCT cervical screening as well? In most of the articles reviewed, pre-HCT screening was generally ineffective in identifying women at an increased risk of developing cervical dysplasia, warranting the need for intense post-HCT monitoring. Cervical cancer screening is recommended every 1–3 years in HCT survivors from the ages of 21 to 65 years [74–76]; however, for nonsexually active females who have had three negative pap smears, discontinuation of screening may be considered on individual bases. Initiating annual gynecological screening is supported by the occurrence of HPV infection within the first few years after transplant, and in agreement with current transplant screening guidelines [53]. Women without extensive or genital GVHD, immunocompromised status, or malignancy relapse may be considered for longer screening intervals of 2–3 years if they have normal cytology testing in the first few years. Challenges also exist in finding the correct balance in treating GVHD and HPV. Genital HPV limits the use of local immunosuppression which may worsen scarring of the genital tract. As observed by Buchan *et al.* [56], only an estrogen ring was able to aid the healing of denuded vaginal mucosa as estrogen plays a role in the support and growth of mucosal surfaces [77], with limited effects on vaginal GVHD.

7. CONCLUSIONS

Our systematic review was conducted to compile relevant data regarding LGT precancer and cancer amongst HCT survivors and clearly suggests that good quality data regarding this topic are lacking and that further research is required. All studies show an increase in the amount of cervical dysplasia post-HCT, ranging from ASCUS to HSIL, with treatment-associated dysplasia occurring earlier in the course of the disease, and spontaneously resolving in some cases. The limited amount of progression data available shows either complete resolution of dysplasia or persistence until conization/hysterectomy. However, most of the published studies do not portray long-term outcomes of the complications or its interventions. Many allo-HCT recipients may require prolonged IST for GVHD and, thus, are at a higher risk for persistent HPV

Table 5 | Official cervical screening guidelines in the general population and HCT recipients with normal findings.[a,b]

Age Group	Type of Screening	Frequency of Testing	HCT Recipients(Not Official Recommendations)
<21	No screening	-	
21–29 years	Cervical cytology testing alone	Every 3 years	Every 1–3 years
30–65 years	Cervical cytology testing alone	Every 3 years	Every 1–3 years however, for nonsexually active females who have had three negative pap smears, discontinuation of screening may be considered on individual bases
	Cervical cytology and HPV DNA cotesting	Every 5 years	
>65 years	No screening required if: -Negative previous screening results[c] -No CIN2+ history in the past 20 years	-	

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
(a) If a positive result is detected on any cervical cytology testing of HPV DNA testing, additional follow-up testing is recommended (guidelines not stated). (b) Recommendations 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. (c) Defined as three consecutive negative cytology results or two consecutive negative cotest results within the previous 10 years, with the most recent tested performed within the past 5 years.

infections [22] and abnormal cervical smears [21]. Unrelated HLA-matched donor transplants are also associated with an increased risk for gGVHD among allo-HCT survivors [78] and, thus, confer an increased risk of cervical dysplasia [23]. Reports on new (secondary) cancer with LGT cancer data, following cohorts of allo and auto-HCT recipients, do not report consistent results. There is a lack of large prospective studies that follow post-HCT women to study the progression of LGT dysplasia to cancer.

Additionally, due to the absence of postvaccination efficacy studies, and to increased risk of disease from non-HPV vaccine strains, patients require intense gynecologic care post-HCT with dedicated gynecologists as part of survivorship program, and most countries recommend more frequent screening for these women compared to the general population [79–81]. Further research on this topic will help clarify screening measures and risk factors to effectively identify high-risk individuals and preemptively uncover any high-grade cervical precancer and cancer.

CONFLICTS OF INTEREST

None relevant.

AUTHORS' CONTRIBUTIONS

MST and SKH designed the study. All authors played a significant role in each step of manuscript writing and vouch for the accuracy and contents of the manuscript. All authors approved the final version of the draft.

DISCLOSURES

SKH: Honorarium Mallinckrodt, Janssen, Novartis, Pfizer

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