„ Anogenital high-risk HPV prevalence and screening considerations in female transplant recipients: A cross-sectional study “

Dissertation

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Content

1. Comprehensive overview of the publication

1.1 Introduction

1.1.1 Human Papillomavirus (HPV)

HPV is a large and diverse group of viruses, with over 200 different types identified based on variations in their DNA sequences (Bzhalava et al., 2015).
HPV types can be divided into *high-risk* HPV (hrHPV) and *low-risk* HPV (lrHPV) types based on their oncogenic risk (Groves and Coleman, 2015). HrHPV have a high oncogenic potential and are associated with 4.8% of all cancer cases worldwide in 2008. Cervical cancer accounts for 86.9% of these cases. Infection with hrHPV is considered necessary for developing epithelial cervical cancer, as hrHPV types were detectable in almost 100% of cases (Forman et al., 2012). Several cofactors contribute to HPV infection and progression, including smoking and immunosuppression; however, the predominant determinant is sexual behavior, particularly multiple sexual partners and an early age at first sexual intercourse (Petry et al., 2013).

1.1.2 HPV Prevalence

Global prevalence estimates indicate that approximately 10–11% of women without cytological abnormalities are infected with HPV (Bruni et al., 2010).
HPV prevalence is strongly age-dependent, with the highest rates observed in women younger than 25 years (Smith et al., 2008). In the United States, Dunne et al. reported a prevalence of 44.8% among women aged 20–24 years, whereas Hariri et al. documented an even higher prevalence of 53.8% in the same age group (Dunne et al., 2007; Hariri et al., 2011). In Germany, a prevalence of 22% has been reported for women under the age of 30 (Iftner et al., 2010). Among older women, hrHPV prevalence declines substantially. The Wolfscreen study, which investigated nearly 20,000 women aged ≥35 years in the Wolfsburg area, identified an hrHPV prevalence of 6.2% (Luyten et al., 2014).

HPV16 is the most prevalent HPV type worldwide, followed by HPV31 and HPV18 in Europe; however, the distribution of individual types varies according to geographic region and the diagnostic methods applied. (Bruni et al., 2010; de Sanjosé et al., 2007).

Only a limited number of studies have investigated the prevalence of anal HPV infection in women without established risk factors, such as human immunodeficiency virus (HIV)

infection or cervical precancerous lesions. Hernandez et al. examined approximately 1,500 HIV-negative women in Hawaii without evidence of cervical precancerous lesions and reported an anal HPV prevalence of 27%, while concurrent cervical HPV prevalence was 29% (Hernandez, 2005). Similarly, Stier et al. (2015) observed an anal hrHPV prevalence of 22% among women aged 22–29 years (Stier et al., 2015).

1.1.3 Immunosuppressive treatment after transplantation

Organ transplant recipients require lifelong immunosuppressive medication to prevent graft rejection. Current guidelines recommend a triple-drug regimen consisting of a calcineurin inhibitor (CNI), an antiproliferative agent, and corticosteroids (Türk et al., 2010).

Chronic immunosuppressive therapy substantially increases cancer susceptibility; overall, transplant recipients exhibit a two- to fourfold higher risk of malignancies compared to the general population (Engels et al., 2011).

Anogenital cancers account for up to 3% of all post-transplant malignancies, with recipients showing a twofold increased risk of cervical cancer and a fivefold increased risk of anal cancer (Grulich et al., 2007; Liao et al., 2019).

Given this elevated cancer risk, regular screening examinations are recommended. For example, abdominal ultrasound and dermatological examinations should be performed at least annually (Schrem et al., 2009).

The current German S3 guideline on “Anal Cancer” recommends screening every 36 months for HIV-negative patients with increased immunological risk. In contrast, HIV-positive patients should undergo annual screening, including inspection, digital rectal examination, and anal cytology. However, for HIV-negative immunocompromised patients, no consensus exists regarding the optimal screening strategy, and the potential utility of anal hrHPV testing in this population remains uncertain (Aigner et al., 2021).

The German S3 guideline on “Cervical Cancer Prevention” does not recommend intensified screening for immunocompromised women compared to the general population (Hillemanns et al., 2020).

1.1.4 HPV Prevalence in transplanted patients

A systematic literature review on hrHPV prevalence in transplanted women was conducted between January and April 2021.

The search was limited to studies published between 2000 and 2021, including only those with a minimum of 20 patients. This threshold was chosen to improve statistical reliability and allow for meaningful comparisons across studies. Although a sample size of 20 is relatively small for a prevalence study, the limited availability of data made it impractical to set a higher minimum threshold without excluding a substantial number of relevant primary sources.

The following inclusion criteria were defined:

- Publication types: clinical study, epidemiologic study
- Patient population:
    - Female, age over 18 years
    - Solid organ transplantation or allogeneic stem cell transplantation
- Intervention:
    - HrHPV testing of the cervix and/or HrHPV testing of the anus

The literature search was carried out using Pubmed. The following keywords were used as search terms: (cervical human papillomavirus infection) AND (transplant recipient), (cervical human papillomavirus infection) AND (SOT), (cervical human papillomavirus) AND (stem cell transplantation), (cervicovaginal hpv infection) AND (transplantation), ((prevalence) AND (cervical human papillomavirus)) AND (female transplant recipient), ((prevalence) AND (cervical human papillomavirus)) AND (liver transplant recipient), (prevalence) AND (cervical human papillomavirus) AND (renal transplant recipient), ((prevalence) AND (cervical human papillomavirus) AND (transplantation)), (cervicovaginal hpv infection) AND (transplantation), ((prevalence) AND (human papillomavirus)) AND (lung transplant recipient), ((prevalence) AND (human papillomavirus)) AND (heart transplant recipient), (anal human papillomavirus infection) AND (renal transplantation), (anal human papillomavirus infection) AND (transplant recipient), (prevalence) AND (anal human papillomavirus) AND (transplant recipient), (prevalence) AND (anal human papillomavirus) AND (transplantation), (anal human papillomavirus infection) AND (stem cell transplantation), (anal human papillomavirus infection) AND (liver transplantation).

1.1.5 Findings

Using the combined search strategy, 528 studies were initially identified, of which 228 duplicates were removed. The remaining 300 records were screened according to predefined inclusion and exclusion criteria, resulting in 25 studies considered potentially relevant based on their abstracts. After full-text review, three additional studies were excluded as they did not meet the eligibility criteria.

The studies included in the systematic review reported heterogeneous results regarding anogenital HPV prevalence in female transplant recipients. Reported cervical HPV prevalence ranged from 6.9% to 40.4%. Across the included studies, cervical HPV prevalence was ≤10% in three studies, 10–20% in six studies, 21–30% in four studies, and >30% in five studies (see Appendix 13.4)

The anal hrHPV prevalence in transplanted women was between 8% and 45.5% (Grąt et al., 2014; Larsen et al., 2020).

The considerable variation in results may be explained by differences in study design, patient populations, geographic regions, and diagnostic procedures. Interpretation of the findings is further limited by the small sample sizes in most studies and using heterogeneous HPV testing methods with varying sensitivities. A detailed list of the included studies is provided in Appendix 13.4.

1.1.6 Objective

The objective of this study was to assess the age-dependent prevalence of anogenital HPV infection in liver and kidney transplant recipients and to compare these findings both between transplant groups and with prevalence data from the general female population in Germany. In addition, the study investigated potential determinants of HPV prevalence, including immunosuppressive therapy, sexual behavior, and HPV vaccination status.

1.2 Methods

1.2.1 Study design

In this cross-sectional study, patients were primarily recruited through the transplant outpatient clinic at the University Medical Center Hamburg-Eppendorf (UKE). Eligibility was determined using Cerner's Soarian Clinicals, and women meeting the inclusion criteria were informed about the study. In addition, all female liver and/or kidney transplant recipients registered at UKE received an invitation letter. Interested patients

were scheduled for a visit to the gynecological outpatient clinic. Following the provision of written informed consent, a quantitative and fully standardized interview was conducted (see Appendices 13.1–13.3). The study was approved by the Ethics Committee of the Hamburg Medical Association in June 2019 (approval number PV6011).
Both a cervical and an anal swab were obtained from each participant. The cervical swab was taken with the *Rovers® Cervex-Brush®* and preserved in *Roche Cell Collection Medium*. The *Bruker eSwab™ system* was used to preserve the anal smear. As not enough *eSwab™ swabs* were available due to the COVID-19 pandemic, the *MBT-010 Virus Transport Medium* from *Mantacc* was also used to preserve anal swabs.
The cervical samples were then examined with the *cobas® HPV test* using the *cobas® 6800 system*. This HPV test enables the detection of HPV 16 and 18, as well as 12 pooled hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) (Roche Deutschland Holding GmbH, 2021, 2021a).

If the test result was positive, the patients were informed and called in again. A further cervical and anal HPV test was performed for verification and genotyping. These HPV tests were preserved in *MBT-010 Virus Transport Medium* from *Mantacc* and analyzed using the *Anyplex™ II HPV28 Detection* System from *Seegene Inc*. This enables the detection of 19 hrHPV types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82). In addition, all HPV-positive women underwent a cervical brush smear, which was evaluated using the Papanicolaou method, along with a colposcopic examination of the cervix and vagina. A 5% acetic acid solution was applied to identify any abnormalities. If suspicious findings were observed, a colposcopy-guided biopsy was performed and examined histologically. Subsequent treatment followed the current S3 guideline on the prevention of cervical cancer, and the patients' gynecologists were informed of the results (Hillemanns et al., 2020).

The determined prevalence was compared with the HPV prevalence reported in the Wolfscreen study. Among the participants, 1,232 healthy women tested hrHPV-positive, corresponding to a prevalence of 6.2% (Luyten et al., 2014). Cervical samples were analyzed using the Digene *Hybrid Capture 2 high-risk HPV test* from *Qiagen*. In this study 1,232 healthy women tested hrHPV-positive, corresponding to a prevalence rate of 6.2% (Luyten et al., 2014).

Owing to its large sample size, the Wolfscreen study provides an appropriate comparison group representative of the general female population in Germany.

1.2.2 Inclusion and Exclusion criteria

Inclusion criteria required participants to be at least 18 years old, to have received treatment at the UKE transplant center, and to be at least one year post-organ transplantation. Patients who had undergone a total hysterectomy were excluded from participation.

1.2.3 Patient Questionnaire

In addition to cervical sampling, all participants completed a structured quantitative interview based on a standardized questionnaire, ensuring consistent data collection. The interview was designed to identify potential determinants of HPV prevalence and included demographic data (e.g., age, body mass index), transplant-related information (type and number of transplants), and detailed aspects of immunosuppressive therapy (duration, type, induction therapy, prior treatments, and complications such as infections or rejection episodes) Other areas covered were medical history, lifestyle factors, gynecological history, and sexual history.

Missing information was supplemented by reviewing patient records via the Soarian hospital system. The complete questionnaire is available in the appendix (Section 13.1).

1.2.4 Statistical analysis

Descriptive statistics were reported as medians and ranges for continuous variables, and as absolute numbers or percentages for categorical variables. To compare groups, the Kruskal-Wallis rank sum test was applied for continuous data, while Fisher's exact test was used for categorical data.

To investigate potential risk factors for hrHPV infection, we conducted a multiple logistic regression analysis. Smoking status, age, and type of organ transplantation were included as possible confounding variables based on their clinical relevance. Explanatory variables were selected based on clinical relevance. Multicollinearity among the predictors was assessed using Variance Inflation Factors (VIF), all of which were below 3, indicating no concerning levels of collinearity. We did not examine interaction effects between variables due to the limited sample size and lack of a strong theoretical rationale for such interactions in this context.

All statistical tests were two-sided, and a significance level of $\alpha = 0.05$ was used throughout the analysis. Statistical analysis was performed using R software (version 4.0.5, R Core Team, Vienna, Austria, 2021). Cases with missing data were excluded from the respective analyses. For patients with multiple transplantations, the duration of immunosuppression was defined as the time since their first transplant. Figures were generated using GraphPad Prism.

1.3 Results

For a detailed description of the results, please review the attached manuscript.

Between November 2019 and July 2021, a total of 201 transplant recipients (98 kidney transplant recipients, 93 liver transplant recipients, and 10 women who had received simultaneous kidney and liver transplants) were enrolled. Most participants were aware of their elevated cancer risk (65.2%) and the benefits of cervical screening (77.6%), with 92.5% reporting regular participation in screening programs.

At baseline, cervical hrHPV was detected in 15.9% (32/201) of participants, while anal hrHPV was found in 20.3% (40/197). As shown in Figure 1, hrHPV prevalence declined with increasing age. However, differences in cervical hrHPV prevalence across age groups did not reach statistical significance ($p = 0.068$), whereas anal hrHPV prevalence varied significantly by age group ($p = 0.038$). When comparing individuals aged ≤45 years with those >45 years, anal hrHPV prevalence was significantly higher in the younger group ($p = 0.020$). In contrast, cervical hrHPV prevalence showed a non-significant trend toward higher rates in the younger group ($p = 0.078$).

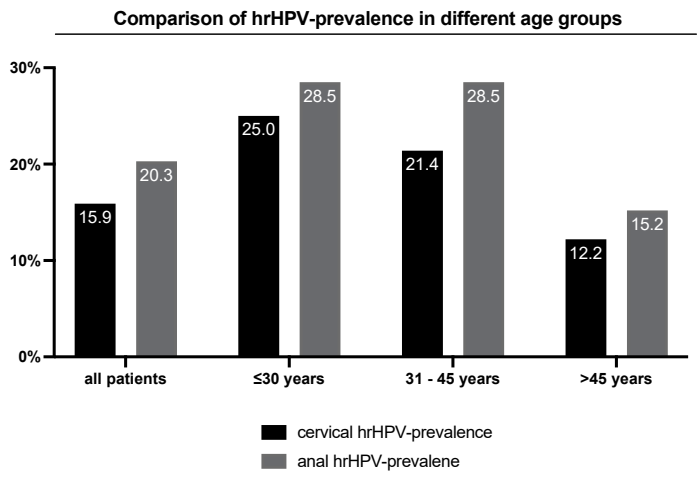

Figure 1 Comparison of hrHPV-prevalence in different age groups

Almost all participants (97.5%) were receiving immunosuppressive therapy, with 75% on CNI-based regimens. Differences in immunosuppressive regimens, duration or type of transplantation (kidney or liver) were noted, but did not translate into differences in hrHPV prevalence.

Behavioral factors associated with increased hrHPV risk in the general population were also analyzed. HrHPV-positive women reported more than twice the number of lifetime sexual partners compared to hrHPV-negative women (median 7 vs. 3, $p<0.001$), were younger at first sexual intercourse (p=0.025), and had more sexual partners since transplantation ($p<0.001$). Multivariable logistic regression confirmed these findings, identifying younger age ($p=0.018$) and a higher number of sexual partners ($p=0.001$) as independent predictors of cervical hrHPV infection.
HPV vaccination coverage was 12.4% overall, with most vaccinated patients being under 30 years of age. The majority was vaccinated before their first intercourse, and a few before transplantation. HrHPV-positive patients were somewhat more likely to have been vaccinated, though this was not statistically significant.

Follow-up was offered to hrHPV-positive women 6 to 18 months after initial testing, with a high participation rate (91%). Persistent cervical hrHPV infection was confirmed in 25 of 29 women, with 52% harboring multiple HPV types. Four women were diagnosed with high-grade cervical or vaginal lesions, three of whom had normal cytology results. Anal swab specimens also revealed multiple hrHPV genotypes in over half of the hrHPV-positive cases, with 11 high-risk types detected.

Co-infection at cervical and anal sites was common. Among cervical hrHPV-positive women, 68.8% also tested positive for anal hrHPV, compared to only 10.9% among those who were cervical hrHPV-negative (p<0.001). In 78% of cases with both cervical and anal genotyping available, at least one hrHPV type matched, with HPV 16 showing 100% concordance.

1.4 Discussion

1.4.1 HrHPV prevalence in transplant recipients compared to the general population

This study is one of the largest studies published to date investigating anogenital hrHPV prevalence in female transplant recipients.

The overall prevalence of cervical hrHPV was 15.9%, while the prevalence of anal hrHPV was 20.3%. Cervical hrHPV prevalence in transplant recipients was more than twice compared to the global general population (15.9% vs. 8.1%) (de Sanjosé et al., 2007). Given the regional variation in hrHPV prevalence, we compared our findings to data from a German population. In women over the age of 30, the WOLFSCREEN study assessed an hrHPV prevalence of 6.2% compared to 14.5% in our cohort.

When stratifying by age, no increase in hrHPV prevalence was observed among transplant recipients under 30 years of age compared to the general German population (25% in our cohort vs. 22% in the general population) (Iftner et al., 2010). However, this comparison has limited validity, as the reference data originate from a 2010 study conducted at a time when HPV vaccination was not yet widely implemented in Germany. U.S. trends have shown a decline in hrHPV prevalence since the introduction of the HPV vaccine (Rosenblum, 2021). More recent data—particularly considering increasing vaccination coverage—would be valuable to assess hrHPV prevalence among young women in Germany accurately.

1.4.2 Review of the literature

Studies from the literature search reported varying findings on anogenital HPV prevalence among transplanted women, with cervical HPV rates ranging from 6.9% to 40.4% and anal HPV rates ranging from 8% to 45.5%. (Ghazizadeh et al., 2011; Grąt et al., 2014; Larsen et al., 2020; Seshadri et al., 2001). The significant variability in results may be influenced by differences in study design, patient populations, or countries of origin. The studies used various testing methods, detecting between one and over 13 hrHPV types, and not all employed standardized assays. Overall, HPV prevalence was higher in most of the identified studies compared to the general population or control groups (see appendix 13.4), which is consistent with the findings of this study. Only three of the identified studies on cervical hrHPV prevalence included cohorts of transplant recipients with more than 100 participants. In these studies, hrHPV prevalence ranged from 11% to 16%, which aligns well with the prevalence observed in our study (Hinten et al., 2017a; Meeuwis et al., 2015; Paternoster et al., 2008).

1.4.3 Risk factors for hrHPV infection in transplanted patients

The significant influence of established risk factors for HPV, such as sexual behavior, was confirmed by our study. Nonetheless, these risk factors result in a higher hrHPV prevalence compared to the general population. This may be due to prolonged HPV persistence and reduced clearance rates in immunosuppressed patients.

Reactivation of HPV infection is also being discussed. This theory is supported by the findings of Hinten et al. and Cistjakovs et al. Both observed an increase in HPV prevalence within the first two years after transplantation, which could not be attributed to changes in patient behavior (Cistjakovs et al., 2018; Hinten et al., 2017b).

Interestingly, no study on cervical HPV prevalence in transplant recipients has found a significant correlation between the duration of immunosuppression and the incidence of HPV infections. Origoni et al. followed women over 10 years and observed no increase in HPV infections over time (Origoni et al., 2011). This finding is supported by Meeuwis et al., who also found no higher prevalence among patients who had been transplanted for more than 10 years (Meeuwis et al., 2015). This suggests that immunosuppression itself—rather than its duration—is the primary risk factor, an observation that was also confirmed in our study.

The elevated prevalence of HPV in organ transplant recipients is associated with a higher incidence of CIN. Given the high likelihood of HPV persistence, early referral for colposcopic evaluation may be beneficial for these patients.

1.4.4 Cervical hrHPV infection as a surrogate marker for anal hrHPV infection

Even if the risk of anal carcinoma is increased in transplant recipients, the overall incidence remains low. As a result, it is challenging to justify or establish structured screening programs in this population. The low absolute number of cases limits the potential impact of routine screening and raises concerns regarding cost-effectiveness, overdiagnosis, and unnecessary interventions. Further research is needed to identify subgroups of transplant recipients who may be at particularly high risk and who could benefit most from targeted surveillance strategies.

Our study identified a high rate of concurrent hrHPV infection at cervical and anal sites, with a co-infection rate of 72%. Among women who tested negative for cervical hrHPV,

10.9% were positive for anal hrHPV. Notably, all patients with cervical HPV 16 infection also tested positive for HPV 16 at the anal site.
The prevalence of anal high-grade squamous intraepithelial lesions (HSIL) is higher in individuals with cervical hrHPV positivity. In particular, women over the age of 45 with cervical HPV16 infection exhibit an anal cancer risk comparable to that of HIV-positive individuals, for whom annual anal cancer screening is currently recommended (Lin et al., 2019). Given the absence of standardized screening protocols for anal HSIL in transplant recipients, cervical hrHPV positivity may serve as a useful marker to identify patients at elevated risk, particularly since cervical HPV testing is already included in routine screening. Immunocompromised patients, especially those testing positive for HPV 16 and in case of hrHPV persistence, should be referred for anal cancer screening irrespective of the time since transplantation (Jacot-Guillarmod et al., 2022). In cases of abnormal anal cytology, high-resolution anoscopy should be performed (Stier et al., 2024).

1.4.5 Limitations

One limitation of this study is the absence of anal follow-up, which prevents assessment of the prevalence of anal HSIL among patients who tested positive for cervical hrHPV. Consequently, the hypothesis that solid organ transplant recipients may benefit from anal screening in the presence of cervical hrHPV infection cannot be evaluated within this study. Although this study represents one of the most extensive investigations of hrHPV prevalence in organ transplant recipients to date, and its findings are consistent with existing literature, the sample size remains insufficient to draw definitive conclusions about potential influencing factors, such as differences in immunosuppressive therapy regimens.

1.5 Conclusion

Transplanted patients show an elevated hrHPV prevalence compared to the general population, irrespective of the specific immunosuppressive regimen. Based on our findings,
reconsideration and potential adaptation of current screening strategies in this high-risk group can be discussed. In the presence of hrHPV, colposcopic examination should be conducted regardless of cytology results, due to the increased likelihood of HPV-related disease. Cervical hrHPV positivity may also serve as a surrogate marker to guide targeted

anal screening—particularly in cases of HPV16 detection, but also for other high-risk genotypes.

Article

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Anogenital high-risk HPV prevalence and screening considerations in female transplant recipients: a cross-sectional study

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Abstract

Purpose Organ transplant recipients receiving immunosuppressive therapy have a higher risk of developing anogenital HPV-related (pre)malignancies. This study aims to determine the age-dependent anogenital hrHPV prevalence in transplanted patients and to investigate various risk factors within this high-risk patient group.

Methods Women ($n = 201$) after kidney ($n = 98$), liver ($n = 93$), and combined ($n = 10$) transplantation were tested and genotyped for hrHPV in the anal and cervical regions. Medical records and a questionnaire assessed sexual behaviour, medical treatment history, and demographic data.

Results Among our cohort the median age was 52 years (range 18–78), the prevalence of cervical hrHPV infection was 15.9% (32/201), with no significant difference observed between liver and kidney transplant recipients. Increased hrHPV prevalence was not associated with transplant-specific risk factors such as type and duration of immunosuppressive therapy, whereas typical risk factors such as sexual behaviour conferred increased risk. Anal hrHPV had an overall prevalence of 20.3%, and the co-prevalence of hrHPV detected at both anal and cervical sites was 68.8%. 90% of the patients with cervical hrHPV infection (29/32) attended clinical follow-up and high-grade intraepithelial neoplasia was detected in four women (3x CIN2+/ 1x VaIN3).

Conclusion Compared to the general population, our study shows an increased cervical HPV prevalence in transplanted patients above 30 years. In addition, the baseline risk for infection with anal hrHPV is increased, suggesting that additional screening in cervical hrHPV-positive transplanted patients may be beneficial to detect (pre) invasive lesions in the anal region.

Take-home message
Female organ transplant recipients show a high genital hrHPV prevalence with an increased anal co-infection rate, suggesting additional screening for genitoanal lesions might be beneficial.

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Keywords Organ transplantation, Immunosuppressive therapy, High-risk HPV prevalence, Cervical HrHPV, Anal HrHPV, Kidney transplant recipients, Liver transplant recipients

Introduction

Persistent infection with high-risk Human Papillomavirus (hrHPV) is a prerequisite for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. The development of cervical cancer can be largely prevented through vaccination and screening [1]. The progression from infection to cancer usually takes decades, so detecting hrHPV or CIN at an early stage and, if necessary, initiating correct further treatment is highly beneficial for patients. HPV 16 and 18 have high oncogenic potential and are detected in 70% of cervical cancers [2]. Persistent hrHPV infection is also a major cause of anal cancer, with HPV16 playing a pivotal role. There is a strong correlation between cervical and anal HPV infections, so cervical HPV-based screening could improve screening for anal cancer risk by allowing patients with hrHPV positivity in the cervix also to receive screening for anal changes [3].

Transplanted patients receive lifelong immunosuppressive treatment to prevent rejection. However, drug treatment is associated with an elevated risk of developing anogenital (pre)malignancies related to HPV [4–6]. Given the increased incidence of genitoanal dysplasia, one might conclude that hrHPV prevalence is elevated in transplanted women. Nevertheless, previous studies regarding cervical and anal HPV prevalence have shown contradictory results: Reported cervical hrHPV prevalence in transplanted patients varies between 7% and 40% and anal prevalence between 8% and 46% depending on the testing method and study population [7–15]. The wide variation in reported prevalence might also be attributed to the small sample size and locoregional differences.

No screening algorithms beyond the guideline-based cervical cancer screening in the general population are currently recommended for organ transplant recipients (dependent on national programs, hrHPV testing from 30 to 35 years and cervical cytology is recommended) [16].

Early detection of high-grade squamous intraepithelial lesions (HSIL) is critical for the prevention of anal carcinoma, as the treatment of HSIL significantly reduces the risk of progression to anal cancer [17].To reduce the risk of anal cancer in transplanted patients, the International Anal Neoplasia Society (IANS) currently recommends screening through a digital rectal examination combined with anal cytology and/or HPV testing, beginning 10 years after transplantation [18]. An abnormal finding should then be followed by high-resolution anoscopy.

This study aims to determine the age-dependent genitoanal hrHPV prevalence in liver and kidney transplant recipients and to identify possible risk factors for HPV infection.

Methods

Study population

In this cross-sectional study, female patients who received kidney or liver transplantation were eligible for participation if they met the following criteria: (1) minimum age of 18 years, (2) time interval to organ transplantation of at least 12 months, (3) treatment at the Transplant Center of the university hospital. Patients with hysterectomies were excluded. The Hamburg Medical Association Ethics Committee approved the study in June 2019 (Ethics vote: PV6011). Patients were informed by telephone, in writing, or verbally at the transplant centre about possible study participation. After written informed consent was obtained, patients completed a standardized questionnaire, and cervical and anal swabs were collected. Medical records were used to gather information regarding medication and co-morbidities. All eligible patients, who were willing to participate in the study were enrolled between November 2019 and July 2021.

HPV-testing

Cervical and anal swab collection was performed by a gynecologist or trained personnel under supervision. The cervical swabs were collected with the Rovers CervexBrush and preserved in Roche Cell Collection Medium. For the anal swab, the Bruker eSwabTM system or Mantacc's MBT-010 Virus Transport Medium was used for preservation. The cervical specimens were then tested with the cobas HPV assay through the cobas 6800 system. This HPV assay detects HPV 16 and 18, and 12 pooled hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). If the test result was positive, the patients were informed. Further cervical and anal HPV testing were analyzed by Seegene's AnyplexTM II HPV28 Detection – System for verification and genotyping as this is the standard test in our center. This allows the simultaneous detection of 19 hrHPV types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and low risk (lr)HPV (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70). In this study, only the detection of hrHPV was investigated, and lrHPV was not considered in the statistical analysis. Testing of anal swabs for HPV-DNA is not validated by the manufacturer regarding clinical sensitivity and specificity and is performed as a research-use-only assay.

Follow-up

Patients who tested positive for hrHPV in the cervical area were readmitted to our dysplasia clinic, receiving cytology, colposcopy, and, if necessary, a biopsy of suspicious lesions. Follow-up was performed between 6 and 18 months after initial testing. Since the cobas HPV assay only provides pooled genotyping, HPV testing in the cervical and anal regions was repeated in cobas positive patients, and further genotyping was performed using Seegene's Anyplex™ assay. Patients who tested HPV positive only in the anal region were informed of the result and recommended follow-up with a practicing proctologist. HPV negative patients did not receive follow-up.

Questionnaire

All study participants were asked to complete a questionnaire created for this study (see supplements). This questionnaire included baseline data like age, type of transplantation, and medical history, focusing on immunosuppression, comorbidities, and sexual history. Where possible, we cross-checked patient information with hospital records to ensure accuracy and to fill in any missing information in the questionnaire.

Data and statistical analysis

Descriptive statistics were presented as medians and ranges for continuous data and counts or percentages for discrete data. Groups were compared using the Kruskal-Wallis rank sum test for continuous data and Fisher's exact test for discrete data. To evaluate risk factors of hrHPV infection we performed a multiple logistic regression analysis and included smoking, age and type of transplantation as potential confounders. Explanatory variables were selected based on clinical relevance. Multicollinearity was assessed using Variance Inflation Factors (VIF), all of which were below 3. We did not test for interactions among the independent variables included due to limited sample size and lack of theoretical justification. An alpha level of 0.05 was used for all statistical tests.

Statistical analysis was performed using R (version 4.0.5, Windows, R core group, Vienna, Austria, 2021). Missing answers were excluded from the analysis. In this study, the duration of immunosuppression refers to the time since the first transplant (for multiple transplant recipients). Graph Pad Prism was used to create figures.

Results

Between November 2019 and July 2021, 201 women were enrolled in the study. These included 98 kidney transplant recipients, 93 liver transplant recipients, and ten patients who received simultaneous kidney and liver transplantation. 65.2% of patients knew they were at increased risk for genitoanal cancers, and 77.6% knew cervical screening could reduce cancer risk. In addition, most patients (92.5%) reported regularly taking advantage of the cervical screening offer.

HrHPV prevalence

The baseline characteristics of the participants are shown in Table 1, which compares hrHPV positive and negative patients. Overall, 32 out of 201 (15.9%) patients tested positive for hrHPV at the cervical site. The anal hrHPV prevalence was 20.3% (40/197). No significant difference in cervical hrHPV prevalence was found between kidney and liver transplanted patients (see Table 2). The median age was 52 years (median 18–78), with cervical hrHPV-positive patients being, on average, eight years younger ($p = 0.029$). HrHPV prevalence declined with increasing age as shown in Fig. 1. However, the differences in cervical hrHPV prevalence across age groups were not statistically significant ($p = 0.068$), whereas anal hrHPV prevalence did show a significant difference across age groups ($p = 0.038$). When comparing individuals aged ≤ 45 years to those > 45 years, anal hrHPV prevalence was significantly higher in the younger age group ($p = 0.020$). In contrast, cervical hrHPV prevalence showed a non-significant trend towards higher rates in the younger group ($p = 0.078$).The median body mass index (BMI) was 23.4 in the cervical hrHPV-negative group and 21.4 in the cervical hrHPV-positive group ($p = 0.030$).

Immunosuppressive treatment

Overall, 97.5% of the patients were currently taking immunosuppressants, with most (75%) being on a calcineurin inhibitor (CNI) based immunosuppressive regimen consisting of more than two drugs. A comparison of immunosuppression and HPV risk factors is shown in Table 1. Neither the number of immunosuppressants nor the type of immunosuppression was significantly associated with hrHPV infection. Other transplant-specific variables, such as duration of immunosuppressive treatment, pretransplant immunosuppressant use, or graft rejections, did not correlate with hrHPV infection. A comparison of kidney and liver transplant recipients showed differences in immunosuppressive therapy (see Table 2). Compared to liver transplants, more kidney recipients took at least two immunosuppressants and had higher induction therapy rates (85.5% vs. 37%). However, cervical hrHPV prevalence showed no significant difference. Additionally, risk factors like sexual partners and age at first intercourse didn't differ between kidney and liver recipients.

Risk factors associated with increased HPV prevalence in the general population, i.e. sexual behaviour and younger age, are confirmed in transplanted patients in a multivariable logistic regression model, with adjusting for transplantation, nicotine use and age of first intercourse

Table 1 Baseline characteristics of the study population comparing cervical hr-HPV-positive and negative patients

	Total (*N* = 201)	Positive (*N* = 32)	Negative (*N* = 169)	*p*-value
Median Age in years (range)	52.0 (18.0, 78.0)	44.0 (19.0, 72.0)	52.0 (18.0, 78.0)	*
Median BMI (range)	23.2 (16.2, 38.4)	21.4 (18.3, 37.9)	23.4 (16.2, 38.4)	*
Kidneytransplantation	108 (53.7%)	18 (56.2%)	90 (53.3%)	NS
Livertransplantation	103 (51.2%)	15 (46.9%)	88 (52.1%)	NS
Combined transplantation	10 (5.0%)	1 (3.1%)	9 (5.3%)	NS
Years since first transplantation (range)	9.0 (1.0, 42.0)	8.5 (1.0, 23.0)	9.0 (1.0, 42.0)	NS
< 5 years	55 (27.4%)	7 (21.9%)	48 (28.4%)	NS
5 - <10 years	47 (23.4%)	10 (31.2%)	37 (21.9%)	NS
10 - <15 years	39 (19.4%)	6 (18.8%)	33 (19.5%)	NS
≥ 15 years	60 (29.9%)	9 (28.1%)	51 (30.2%)	NS
Patient knew about elevated cancer risk	131 (65.2%)	17 (53.1%)	114 (67.5%)	NS
Patient knew about cancer screening	156 (77.6%)	25 (78.1%)	131 (77.5%)	NS
Regularly participates in cancer screening examinations	186 (92.5%)	29 (90.6%)	157 (92.9%)	NS
Nicotine consumption	26 (12.9%)	5 (15.6%)	21 (12.4%)	NS
Consumes alcohol	73 (36.3%)	16 (50.0%)	57 (33.7%)	NS
(pre)cancerous lesion in history	72 (35.8%)	13 (40.6%)	59 (34.9%)	NS
HPV-associated cancers and precancerous lesions in history	36 (17.9%)	8 (25.0%)	28 (16.6%)	NS
Abnormal PAP smear in the history	28 (13.9%)	7 (21.9%)	21 (12.4%)	NS
Abnormal HPV smear in the history	16/200 (8.0%)	8/31 (25.8%)	8 (4.7%)	***
Vaccinated against HPV	25 (12.4%)	7 (21.9%)	18 (10.7%)	NS
Before first intercourse	17/25 (68.0%)	4/7 (57.1%)	13/18 (72.2%)	NS
Before transplantation	6/25 (24.0%)	1/7 (14.3%)	5/18 (27.8%)	NS
Currently taking immunosuppression	196 (97.5%)	32 (100.0%)	164 (97.0%)	NS
Number of immunosuppressants				NS
None	5 (2.5%)	0 (0.0%)	5 (3.0%)	
Single drug	45 (22.4%)	9 (28.1%)	36 (21.3%)	
Multiple drugs	151 (75.1%)	23 (71.9%)	128 (75.7%)	
CNI (Tacrolimus, Cyclosporin A)	177 (88.1%)	29 (90.6%)	148 (87.6%)	NS
mTOR-Inhibitor (Everolimus, Sirolimus)	55 (27.4%)	11 (34.4%)	44 (26.0%)	NS
Antiproliferative substances (Azathioprine, Mycophenolate Mofetil, Mycophenolsäure)	91 (45.3%)	13 (40.6%)	78 (46.2%)	NS
Prednisolone	68 (33.8%)	13 (40.6%)	55 (32.5%)	NS
Other immunosuppressants	2 (6.2%)	8 (4.7%)	10 (5.0%)	NS
Number of other drugs taken				**
None	3 (1.5%)	3 (9.4%)	0 (0.0%)	
0–2	65 (32.3%)	11 (34.4%)	54 (32.0%)	
3–5	51 (25.4%)	4 (12.5%)	47 (27.8%)	
>5	82 (40.8%)	14 (43.8%)	68 (40.2%)	
Induction therapy (Basiliximab, ATG, prednisolone)	90/137 (65.7%)	16/24 (66.7%)	74/113 (65.5%)	NS
Multiple transplantations	38 (18.9%)	6 (18.8%)	32 (18.9%)	NS
Rejection	95 (47.3%)	17 (53.1%)	78 (46.2%)	NS
Age at first intercourse				
Median (Range)	17.0 (12.0, 39.0)	16.0 (13.0, 24.0)	17.0 (12.0, 39.0)	*
Number of sexual partners				***
Nmiss	1	0	1	
Median (Range)	4.0 (0.0, 30.0)	7.0 (1.0, 30.0)	3.0 (0.0, 25.0)	
0–1	40/200 (20.0%)	1 (3.1%)	39/168 (23.2%)	***
2–5	92/200 (46.0%)	12 (37.5%)	80/168 (47.6%)	
6–10	50/200 (25.0%)	12 (37.5%)	38/168 (22.6%)	
>10	18/200 (9.0%)	7 (21.9%)	11/168 (6.5%)	
Number of sexual partners since Tx				
Median (Range)	1.0 (0.0, 15.0)	1.5 (0.0, 10.0)	1.0 (0.0, 15.0)	***
0–1	151 (75.1%)	16 (50.0%)	135 (79.9%)	***

Table 1 (continued)

	Total (*N* = 201)	Positive (*N* = 32)	Negative (*N* = 169)	*p*-value
2–5	41 (20.4%)	11 (34.4%)	30 (17.8%)	
6–10	8 (4.0%)	5 (15.6%)	3 (1.8%)	
>10	1 (0.5%)	0 (0.0%)	1 (0.6%)	
Anal hrHPV **infection**	40/197 (20.3%)	22 (68.8%)	18/165 (10.9%)	***

ATG = Anti-thymocyte globulin, CNI = Calcineurin inhibitors, HPV = human papillomavirus, hrHPV = high-risk human papillomavirus, mTOR-inhibitor = mammalian target of rapamycin- inhibitor, n = number, nmiss = number of missing information, Tx = Transplantation, NS = not significant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$

Table 2 Comparison of immunosuppressive treatment of liver transplant recipients, kidney transplant recipients and transplant recipients who received a simultaneous liver and kidney transplantation

	Kidney-Tx (*N* = 98)	Liver-Tx (*N* = 93)	Combined Tx (*N* = 10)	*p*-value
Years since first transplantation Median (Range)	9.0 (1.0, 42.0)	10.0 (1.0, 30.0)	7.0 (1.0, 13.0)	NS
Multiple transplantations	21 (21.4%)	17 (18.3%)	0 (0.0%)	NS
Number of transplantations Median (range)	1.0 (1.0, 5.0)	1.0 (1.0, 3.0)	2.0 (2.0, 2.0)	***
Rejection	43 (43.9%)	50 (53.8%)	2 (20.0%)	NS
Number of immunosuppressive drugs				***
none	5 (5.1%)	0 (0.0%)	0 (0.0%)	
Single	9 (9.2%)	36 (38.7%)	0 (0.0%)	
Multiple	84 (85.7%)	57 (61.3%)	10 (100.0%)	
CNI (Tacrolimus, Cyclosporin A)	79 (80.6%)	89 (95.7%)	9 (90.0%)	**
mTOR-Inhibitora (Everolimus, Sirolimus)	25 (25.5%)	22 (23.7%)	8 (80.0%)	***
Antiproliferative substances (Azathioprine, Mycophenolate Mofetil, Mycophenolsäure)	55 (56.1%)	35 (37.6%)	1 (10.0%)	***
Prednisolone	50 (51.0%)	17 (18.3%)	1 (10.0%)	***
Others	9 (9.2%)	0 (0.0%)	1 (10.0%)	**
Induction therapy (Basiliximab, Anti-thymocyte globulin, prednisolone)	65/76 (85.5%)	20/54 (37.0%)	5/7 (71.4%)	***
Cervical hrHPV	17 (17.3%)	14 (15.1%)	1 (10%)	NS
Anal hrHPV	21/95 (22.1%)	17/92 (18.5%)	2 (20.0%)	NS

CNI = Calcineurin inhibitors, HPV = human papillomavirus, hrHPV = high-risk human papillomavirus, mTOR-inhibitor = mammalian target of rapamycin- inhibitor, N = number, Tx = Transplantation, NS = not significant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$

(see Table 3). HrHPV-positive women were, on average, one year younger at the time of first sexual intercourse ($p = 0.025$) and had more than twice as many sexual partners as HPV- negative patients ($p < 0.001$). Likewise, the number of sexual partners since the first transplant was significantly higher among hrHPV-positive patients ($p < 0.001$).

HPV vaccination

In total, 12.4% (25/201) of patients had prior HPV vaccination. Among them, 80% (20/25) were under 30, while only 2.9% (5/173) of those over 30 were vaccinated ($p < 0.0001$). Most patients were vaccinated before their first sexual intercourse (17/25), and six were vaccinated before transplantation. The number of vaccinated patients was higher among HPV-positive patients compared with HPV-negative patients (see Table 1). Three HPV-positive women were vaccinated after their first sexual intercourse and six after their transplantation.

Follow-up

The participation rate in the follow-up offered 6 to 18 months after the initial HPV test for cervical hr-HPV positive patients was 91%, with 29 out of 32 patients returning. The positive hr-HPV result was confirmed in 25 cases. In 52% (13/25), more than one HPV type was determined by genotyping. A total of 14 different HPV-Types with oncogenic potential were detected in the cervical site (HPV 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73). High-grade squamous intraepithelial lesion (HSIL) was detected in four patients during follow-up in the dysplasia unit (1x CIN2, 2x CIN3, 1x VaIN3). Three out of four patients with precancerous lesions had normal pap smears (NILM).

In anal swab specimens more than one HPV genotype was detected in 52.5% of patients, and 11 different high-risk oncogenic genotypes were identified (HPV 16, 18, 31, 39, 45, 51, 52, 56, 58, 59, 68). The most common HPV-types are shown in Fig. 2.

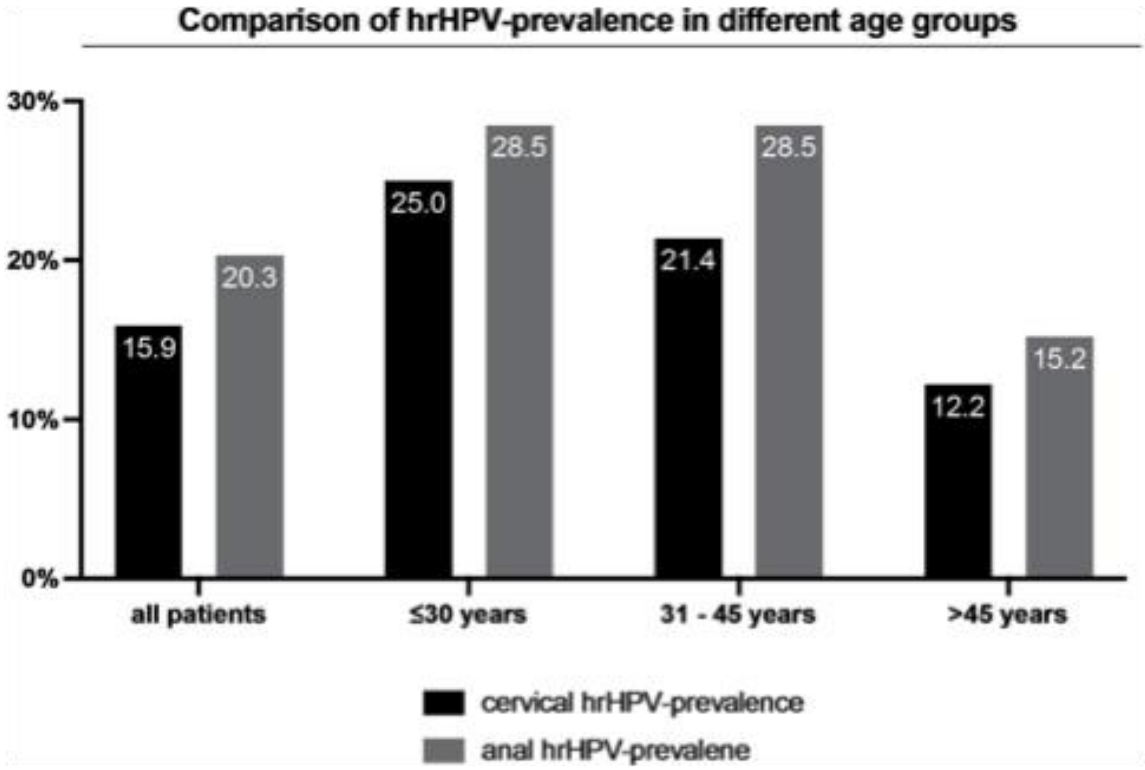

Fig. 1 hrHPV = high-risk human papillomavirus

Table 3 Multiple logistic regression of influencing factors on cervical HrHPV positvity

	HPV cervix		
Predictors	*Odds Ratios*	*CI*	*p-value*
Liver Tx	0.90	0.39–2.08	0.803
Kidney or combined Tx	1.00	0.05–7.12	0.998
Number of sexual partners	1.13	1.05–1.21	**0.001**
smoking	1.30	0.36–3.93	0.663
Age (in years)	0.97	0.94–0.99	**0.018**
Age at first intecourse	0.93	0.78–1.06	0.340
Observations	200		
R^2 Tjur	0.113		

Tx = transplantation, CI = confidence interval

Anal and cervical co-infection

For further investigation of co-infection in cervical hrHPV-positive patients, genotyping was performed at follow-up, whereas anal HPV testing involved genotyping at baseline and follow-up, and one positive test was considered sufficient for hrHPV positivity. All detected HPV types were included in the evaluation of co-infection, regardless of the time of examination. In patients with cervical hrHPV positivity, anal co-infection was detected in 68,8% (22/32), whereas in cervical HPV-negative patients, only 10.9% (18/165) had an anal hrHPV infection. In 18 of 23 patients, cervical and anal genotyping was available to compare HPV genotypes. Fifteen of these 18 patients were positive for more than one HPV type. There was a strong association at the HPV-specific level: 78% (14/18) of patients exhibited at least one concordant hrHPV type, while 22% (4/18) displayed different hrHPV genotypes. The highest concordance rate was found for HPV 16, with all 6 out of 6 patients (100%) showing a coinfection in the anal swab specimens.

Discussion

This study is one of the largest studies investigating genitoanal hrHPV prevalence in female transplant recipients published so far. Overall, the observed cervical hrHPV prevalence was 15.9%, and the anal hrHPV prevalence was 20.3%. Compared to the general population worldwide, cervical hrHPV prevalence is more than twice as high in transplant recipients (15.9% vs. 8.1%) [19]. In particular, patients older than 30 are at increased risk for hrHPV infection, with a prevalence of 14.5% compared to 6.2% in the general population in Germany, while transplanted women younger than 30 show no increased hrHPV prevalence [20, 21]. These findings are aligned with other larger studies that observed a cervical hrHPV

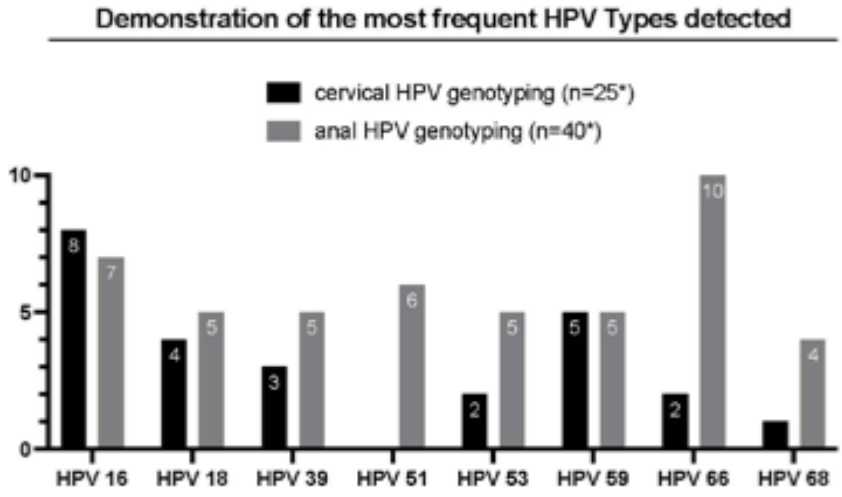

Fig. 2 * This refers to the number of tested patients; multiple HPV types can occur in a single patient. HPV = Human papillomavirus

prevalence of 15.2% and 17.4% in solid organ transplant recipients [14, 15].

The HPV prevalence data for patients under 30 used in this study were obtained from a 2010 publication. To the author's knowledge, there is no more recent data on hrHPV prevalence in the German population under 30 available. Yet, US trends show vaccination reduces HPV prevalence in young women [22]. Obtaining comparable data for the German population in the future could help evaluate hrHPV prevalence in young, transplanted patients compared to vaccinated women.

Encouragingly, the cervical screening participation rate was over 90%. Four out of 29 patients had undetected HSIL with three of them being over 30 years old. This raises the question of whether cervical screening should be intensified in transplant recipients. In our study, three out of four patients with precancerous lesions had normal pap smears. Currently, repeating co-testing after one year is recommended for women in Germany with hrHPV positivity and normal cytology. Immunosuppressed patients with hrHPV infection might benefit from direct referral to colposcopy considering the high probability of hrHPV persistence and increased prevalence of precancerous lesions [4].

Our findings suggest that neither the time since transplantation nor the type of iatrogenic immunosuppression were associated with increased hrHPV prevalence. Based on our results, the only significant transplantation-specific risk factor for HPV infection appears to be immunosuppression itself. This is consistent with the findings of other studies in transplanted patients, which showed that duration and intensity were only weak determinants for increased hrHPV prevalence [14, 23]. The significant influence of known risk factors for HPV like sexual behavior, was confirmed by the results of our study. Still, these risk factors lead to a higher prevalence of hrHPV than in the general population. The reasons might be a longer persistence of HPV and a lower clearance rate in immunosuppressed patients leading to a higher risk for precancerous lesions. This highlights the need for regular screening in a high-risk group to detect the development of precancerous lesions on time. Also, patients should be informed about the risk factors and transmission of HPV infection and the development of HPV associated diseases, as only 63% of patients were aware of their increased cancer risk.

Compared to cervical hrHPV prevalence, anal hrHPV prevalence is less well studied. Lin et al. reported an anal HPV prevalence of 9% for women who are cervical HPV negative, compared to a 43% co-infection rate for cervical hrHPV positive women [3]. Our study described an even higher rate of co-infection at cervical and anal sites of 69% in immunosuppressed women. The hrHPV prevalence in women who were cervical HPV negative was 10.9% and is comparable to the results of Lin et al.

Recently, it was shown that the prevalence of anal HSIL is higher in patients with cervical hrHPV positivity [3]. However, the transition from infection to dysplasia can take decades, and most anal HPV infections are thought to clear on their own. This is especially true for immunocompetent patients. HIV-infected patients have been shown to be less likely to clear HPV than HIV-negative patients [24]. The increased risk of anal cancer in transplanted patients is well known. The risks appear to increase with the number of years since transplantation [5]. Given the high prevalence of anal hrHPV infections, the patient groups at the highest risk should be identified to initiate targeted secondary prevention. Women

with cervical HPV16 infection over 45 years have a comparable anal cancer risk to HIV-positive patients, where anal cancer screening is recommended [3]. Our findings suggest cervical hrHPV positivity could be a surrogate marker for anal hrHPV co-infection that may help stratify transplanted patients and initiate screening. The extent to which other hrHPV types besides HPV16 can also serve as surrogate markers and how many cases of hrHPV infection lead to anal carcinoma in transplanted patients still needs to be investigated in further studies. Current guidelines recommend screening 10 years post-transplantation using digital rectal exam combined with anal cytology and/or anal HPV testing, which may be appropriate for patients without a history of HPV-related dysplasia or cancer [18]. However, transplant recipients with known HPV-related disease face a significantly higher risk of developing anal HPV associated disease including cancer [25]. In such cases, anal cancer screening should be recommended regardless of the time elapsed since transplantation. High resolution anoscopy should be performed in case of abnormal cytology or hrHPV positivity [18].

It could also be considered whether anal HPV testing should be integrated into cervical screening protocols, given its feasibility. With an estimated anal high-risk HPV (hrHPV) prevalence of approximately 20%, around one in five patients would qualify for referral to high-resolution anoscopy. However, the potential benefit of this strategy in terms of earlier detection of anal intraepithelial neoplasia (AIN) and anal carcinoma in transplant recipients remains uncertain and requires further evaluation in prospective studies before implementation can be recommended. This might be even more relevant for younger patients as our fings suggest that age-related differences in hrHPV prevalence may be more pronounced for anal than for cervical sites in this population.

The overall vaccination rate was only about 12%. One reason for the low vaccination rate in our study is the high age of the participating patients. Age was significantly lower in vaccinated patients (71.4% ≤30 years vs. 2.9% >30 years).

However, our results indicate that sexual behaviour is the leading risk factor for hrHPV infection regardless of age. Because the prevalence of hrHPV was increased in the age group over 30 years, vaccination of this patient group beyond 18 years can be discussed. In addition, vaccination rates were higher in hrHPV-positive women than in HPV-negative women. One reason for this is undoubtedly the younger average age of the hrHPV-positive cohort. Also, most of the HPV-positive patients were vaccinated after transplantation. Studies suggest that vaccination before transplantation is beneficial for immune response, so vaccination before transplantation should be considered [26].

Although the cross-sectional design limits definitive causal inference, cautious interpretation of the observed associations remains valuable, given the limited number of studies conducted in this patient group. However, the small sample size and lack of longitudinal data highlight the need for further research to conclusively assess influencing factors, such as variations in immunosuppressive therapy regimens. Unfortunately, following up on the number of anal (pre)malignancies was impossible, so risk factors related to anal carcinomas could not be evaluated. Two different HPV tests were used for cervical and anal testing (Cobas vs. Anyplex), but both tests show comparable sensitivity and specificity for detecting cervical HPV infections and are recommended for cancer screening [27]. To the authors' knowledge, there have been no extensive studies conducted to date on the sensitivity and specificity of HPV tests for the detection of anal intraepithelial neoplasia (AIN) and their comparability with one another. Still, using Anyplex Seegene for anal hrHPV detection is common clinical practice.

It should also be considered that many patients received an HPV test for the first time during the study since HPV testing was not included in regular screening in Germany until 2020. Some of the information evaluated here on sexual behavior, HPV vaccination status and parts of medical history (e.g. HPV-associated diseases) were provided only by patients. Verification of the information using medical records was not always possible.

Conclusions

Immunosuppressed patients represent a high-risk group for developing anogenital dysplasia and cancer. The risk of harboring an hrHPV infection is increased regardless of the immunosuppressive regimen. Based on our results, adjustment of current screening in this high-risk group can be discussed. If cervical hrHPV is detected, a colposcopic examination should be performed independently of cytology because of the high risk for HPV-dependent disease. Cervical hrHPV positivity can also serve as a surrogate marker for targeted anal screening, especially in the case of HPV16 detection, and possibly regarding other hr-HPV genotypes. Given the high prevalence of hrHPV, particularly in patients over 30, HPV vaccination should be considered, ideally before transplantation.

Abbreviations

AIN	Anal intraepithelial neoplasia
CIN	Cervical intraepithelial neoplasia
CNI	Calcineurininhibitor
HPV	Human papillomavirus
hrHPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
lrHPV	Low risk human papillomavirus
VaIN	Vaginal intraepithelial neoplasia

Author contributions
All authors contributed to the design of the study. Christoph Hillen and Charlotte Sachs were responsible for patient recruitment and inclusion. Laboratory analysis was performed by Marc Lütgehetmann and Charlotte Sachs. Data analysis was performed by Elik Vettorazzi and Charlotte Sachs. The first draft of the manuscript was written by Charlotte Sachs and Christoph Hillen. All authors commented on earlier versions. All authors have read and approved the final manuscript. The manuscript is part of a medical thesis at the Medical Faculty of Hamburg University.

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Declarations

Ethical approval
The Hamburg Medical Association Ethics Committee approved the study in June 2019 (Ethics vote: PV6011).

Competing interests
The authors of this manuscript have conflicts of interest to disclose. L Woelber has given talks or received honoraria from Roche, Eisai, Novartis, MSD, Seagen, GSK, Astra Zeneca, Pfizer, Lumenis, TEVA, pomedicis, and Omnilamed and has served as consultant or received consulting fees from GSK, Roche, Eisai, MSD, and Seagen. Her research was supported by grants from DKH, Hamburger Krebsgesellschaft, medac oncology, and Roche diagnostics. IK Prieske reports personal fees from AstraZeneca, MSD, Molecular health, GSK, Roche, and Clovis Oncology outside the submitted work. However, the opinions expressed in this article are those of the authors and do not reflect those of any of the companies mentioned above.

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References

1. Bouvard V, Wentzensen N, Mackie A, et al. The IARC perspective on cervical Cancer screening. N Engl J Med. 2021;385:1908–18. https://doi.org/10.1056/NEJMsr2030640.
2. Bzhalava D, Guan P, Franceschi S, et al. A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types. Virology. 2013;445:224–31. https://doi.org/10.1016/j.virol.2013.07.015.
3. Lin C, Slama J, Gonzalez P, et al. Cervical determinants of anal HPV infection and high-grade anal lesions in women: a collaborative pooled analysis. Lancet Infect Dis. 2019;19:880–91. https://doi.org/10.1016/S1473-3099(19)30164-1.
4. Liao JB, Fisher CE, Madeleine MM. Gynecologic cancers and solid organ transplantation. Am J Transpl Off J Am Soc Transpl Am Soc Transpl Surg. 2019;19:1266–77. https://doi.org/10.1111/ajt.15292.
5. Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. Int J Cancer. 2021;148:38–47. https://doi.org/10.1002/ijc.33185.
6. Madeleine MM, Finch JL, Lynch CF, et al. HPV-Related cancers after solid organ transplantation in the united States. Am J Transpl. 2013;13:3202–9. https://doi.org/10.1111/ajt.12472.
7. Ghazizadeh S, Lessan-Pezeshki M, Nahayati MA. Human papilloma virus infection in female kidney transplant recipients. Saudi J Kidney Dis Transpl Off Publ Saudi Cent Organ Transpl Saudi Arab. 2011;22:433–6.
8. Grąt M, Grąt K, Hołówko W, et al. Initial prevalence of anal human papilloma virus infection in liver transplant recipients. Transpl Int Off J Eur Soc Organ Transpl. 2014;27:816–23. https://doi.org/10.1111/tri.12339.
9. de Oliveira Martins CA, Guimarães ICCDV, Velarde LGC. Relationship between the risk factors for human papillomavirus infection and lower genital tract precursor lesion and cancer development in female transplant recipients. Transpl Infect Dis. 2017;19:e12714. https://doi.org/10.1111/tid.12714.
10. Larsen HK, Haedersdal M, Thomsen LT et al. (2020) Risk of anal High-grade squamous intraepithelial lesions among renal transplant recipients compared with immunocompetent controls. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa781
11. Eleutério J, Cavalcante LR, Gonçalves AKS, et al. Prevalence of high-risk HPV and atypia in liquid-based cytology of cervical and intra-anal specimens from kidney-transplanted women. Diagn Cytopathol. 2019;47:783–7. https://doi.org/10.1002/dc.24180.
12. Veroux M, Corona D, Scalia G, et al. Surveillance of human papilloma virus infection and cervical Cancer in kidney transplant recipients: preliminary data. Transpl Proc. 2009;41:1191–4. https://doi.org/10.1016/j.transproceed.2009.03.015.
13. Wielgos A, Pietrzak B, Sikora M, et al. Human papillomavirus (HPV) DNA detection using Self-Sampling devices in women undergoing long term Immunosuppressive therapy. Viruses. 2020;12. https://doi.org/10.3390/v12090962.
14. Meeuwis IKa, Hilbrands P, IntHout LB J, et al. Cervicovaginal HPV infection in female renal transplant recipients: an observational, Self-Sampling based, cohort study. Am J Transpl. 2015;15:723–33. https://doi.org/10.1111/ajt.13053.
15. Paternoster DM, Cester M, Resente C, et al. Human papilloma virus infection and cervical intraepithelial neoplasia in transplanted patients. Transpl Proc. 2008;40:1877–80. https://doi.org/10.1016/j.transproceed.2008.05.074.
16. Hillemanns P, Friese K, Dannecker C. (2020) S3-Leitlinie Prävention des Zervixkarzinoms. 240.
17. Palefsky JM, Lee JY, Jay N, et al. Treatment of anal High-Grade squamous Intraepithelial lesions to prevent anal Cancer. N Engl J Med. 2022;386:2273–82. https://doi.org/10.1056/NEJMoa2201048.
18. Stier EA, Clarke MA, Deshmukh AA, et al. International anal neoplasia society's consensus guidelines for anal cancer screening. Int J Cancer. 2024;154:1694–702. https://doi.org/10.1002/ijc.34850.
19. de Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007;7:453–9. https://doi.org/10.1016/S1473-3099(07)70158-5.
20. Iftner T, Eberle S, Iftner A, et al. Prevalence of low-risk and high-risk types of human papillomavirus and other risk factors for HPV infection in Germany within different age groups in women up to 30 years of age: an epidemiological observational study. J Med Virol. 2010;82:1928–39. https://doi.org/10.1002/jmv.21910.
21. Luyten A, Buttmann-Schweiger N, Luyten IK, et al. Early detection of CIN3 and cervical cancer during long-term follow-up using HPV/Pap smear co-testing and risk-adapted follow-up in a locally organised screening programme. Int J Cancer. 2014;135:1408–16. https://doi.org/10.1002/ijc.28783.
22. Rosenblum HG, Lewis RM, Gargano JW, et al. Declines in prevalence of human papillomavirus Vaccine-Type infection among females after introduction of Vaccine - United States, 2003–2018. MMWR Morb Mortal Wkly Rep. 2021;70:415–20. https://doi.org/10.15585/mmwr.mm7012a2.
23. Pietrzak B, Mazanowska N, Eklel AM, et al. Prevalence of high-risk human papillomavirus cervical infection in female kidney graft recipients: an observational study. Virol J. 2012;9:117. https://doi.org/10.1186/1743-422X-9-117.
24. Wei F, Goodman MT, Xia N, et al. Incidence and clearance of anal human papillomavirus infection in 16 164 individuals, according to human

immunodeficiency virus status, sex, and male sexuality: an international pooled analysis of 34 longitudinal studies. Clin Infect Dis Off Publ Infect Dis Soc Am. 2023;76:e692–701. https://doi.org/10.1093/cid/ciac581.
25. Freeman MJ, Yang Q, Chemey-Stafford L, et al. (2024) Analysis of >15 000 solid organ transplant recipients reveals Nonanal genitourinary HPV-related disease as highest risk predictor for anal squamous intraepithelial lesions/anal Cancer. Transplantation. https://doi.org/10.1097/TP.0000000000004930
26. Danziger-Isakov L, Kumar D, Practice TAIC. of (2019) Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 33:e13563. https://doi.org/10.1111/ctr.13563
27. Arbyn M, Simon M, Peeters E, et al. 2020 List of human papillomavirus assays suitable for primary cervical cancer screening. Clin Microbiol Infect. 2021;27:1083–95. https://doi.org/10.1016/j.cmi.2021.04.031.

Publisher's note

Summary

3.1. English summary

This study investigated the prevalence of anogenital hrHPV infections in female organ transplant recipients and explored relevant risk factors. Women who had undergone kidney and/or liver transplantation were included, and both cervical and anal swabs were tested for hrHPV genotypes, while demographic, clinical, and behavioral data were collected through questionnaires and medical records. The analysis of 201 women revealed that cervical hrHPV prevalence was 15.9 % and anal hrHPV prevalence was 20.3 %, with a high rate of co-infection, as nearly 69 % of women who were cervical hrHPV-positive also carried anal hrHPV. The study found no difference between kidney and liver transplant recipients and no association between hrHPV prevalence and transplant-specific factors such as the type, duration, or intensity of immunosuppressive therapy. The only risk-factor seems to be immunosuppression itself. Instead, established risk factors such as sexual behavior, a higher number of sexual partners, and younger age were confirmed as significant contributors to hrHPV infection. Follow-up examinations of cervical hrHPV-positive patients revealed four cases of high-grade intraepithelial neoplasia that had not always been detected by Pap smear alone, highlighting the limitations of cytology in this group. HPV vaccination coverage was very low, with only 12.4 % of participants reporting vaccination. Compared with the general population, cervical hrHPV prevalence in transplant recipients, particularly women over 30, was more than twice as high.
These findings suggest that current screening strategies may need adaptation for this high-risk population. Cervical hrHPV-positive transplant recipients could benefit from colposcopic evaluation regardless of cytology results. Cervical hrHPV positivity, especially with HPV16, could be used as a surrogate marker to guide targeted anal screening. Overall, female transplant recipients have an increased burden of hrHPV infections and intensive and tailored screening, combined with improved vaccination strategies, may be beneficial for this vulnerable group.

3.2. German summary

Diese Studie untersuchte die Prävalenz von anogenitalen hrHPV-Infektionen bei organtransplantierten Patientinnen und untersuchte relevante Risikofaktoren. Es wurden Frauen einbezogen, die sich einer Nieren- und/oder Lebertransplantation unterzogen hatten, und sowohl zervikale als auch anale Abstriche wurden auf HPV getestet, während demografische, klinische und Verhaltensdaten mittels Fragebögen und Krankenakten

erhoben wurden. Die Analyse von 201 Frauen ergab, dass die cervicale hrHPV Prävalenz bei 15,9 % und die anale hrHPV Prävalenz bei 20,3 % lag, wobei eine hohe Rate an Koinfektionen zu verzeichnen war, da fast 69 % der Frauen, die im Gebärmutterhals hrHPV-positiv waren, auch im Analbereich hrHPV trugen. Es konnte kein Zusammenhang zwischen der hrHPV-Prävalenz und transplantationsspezifischen Faktoren wie Art, Dauer oder Intensität der immunsuppressiven Therapie gezeigt werden. Der einzige Risikofaktor scheint die Immunsuppression selbst zu sein. Stattdessen wurden etablierte Risikofaktoren wie Sexualverhalten, eine höhere Anzahl von Sexualpartnern und ein jüngeres Alter als signifikante Faktoren für eine hrHPV-Infektion bestätigt. Bei Nachuntersuchungen von Patientinnen mit hrHPV-positiven Abstrichen wurden vier Fälle von hochgradiger intraepithelialer Neoplasie festgestellt, die durch den Pap-Abstrich allein nicht immer erkannt worden waren. Die HPV-Impfquote war sehr niedrig, nur 12,4 % der Teilnehmerinnen gaben an, geimpft zu sein. Im Vergleich zur Allgemeinbevölkerung war die Prävalenz von hrHPV im Gebärmutterhals bei Transplantationsempfängerinnen, insbesondere bei Frauen über 30, mehr als doppelt so hoch.

Diese Ergebnisse deuten darauf hin, dass die aktuellen Screening-Strategien für diese Hochrisikogruppe möglicherweise angepasst werden müssen. HrHPV-positive transplantierte Patientinnen könnten unabhängig von den zytologischen Ergebnissen von einer kolposkopischen Untersuchung profitieren. Eine hrHPV-Positivität im Gebärmutterhals, insbesondere mit HPV16, könnte als Grund für ein gezieltes Analscreening verwendet werden. Insgesamt haben transplantierte Patientinnen eine erhöhte Prävalenz von hrHPV-Infektionen und intensive Vorsorgeuntersuchungen in Kombination mit verbesserten Impfstrategien könnten für diese gefährdete Gruppe von Vorteil sein.

4. References

Aigner, F., Siegel, R., Esser, S., 2021. S3-Leitlinie Analkarzinom: Diagnostik, Therapie und Nachsorge von Analkanal- und Analrandkarzinomen. coloproctology 43, 1–2. https://doi.org/10.1007/s00053-021-00522-8

Bruni, L., Diaz, M., Castellsagué, X., Ferrer, E., Bosch, F.X., de Sanjosé, S., 2010. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J. Infect. Dis. 202, 1789–1799. https://doi.org/10.1086/657321

Bzhalava, D., Eklund, C., Dillner, J., 2015. International standardization and classification of human papillomavirus types. Virology 476, 341–344. https://doi.org/10.1016/j.virol.2014.12.028

Cistjakovs, M., Sultanova, A., Jermakova, O., Sokolovska, L., Chapenko, S., Lesina-Korne, B., Rozental, R., Murovska, M., Ziedina, I., 2018. Importance of High-Risk Human Papillomavirus Infection Detection in Female Renal Transplant Recipients in the First Year after Transplantation. Infect. Dis. Obstet. Gynecol. 2018, 9231031. https://doi.org/10.1155/2018/9231031

de Sanjosé, S., Diaz, M., Castellsagué, X., Clifford, G., Bruni, L., Muñoz, N., Bosch, F.X., 2007. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect. Dis. 7, 453–459. https://doi.org/10.1016/S1473-3099(07)70158-5

Dunne, E.F., Unger, E.R., Sternberg, M., McQuillan, G., Swan, D.C., Patel, S.S., Markowitz, L.E., 2007. Prevalence of HPV Infection Among Females in the United States. JAMA 297, 813–819. https://doi.org/10.1001/jama.297.8.813

Engels, E.A., Pfeiffer, R.M., Fraumeni, J.F., Kasiske, B.L., Israni, A.K., Snyder, J.J., Wolfe, R.A., Goodrich, N.P., Bayakly, A.R., Clarke, C.A., Copeland, G., Finch, J.L., Fleissner, M.L., Goodman, M.T., Kahn, A., Koch, L., Lynch, C.F., Madeleine, M.M., Pawlish, K., Rao, C., Williams, M.A., Castenson, D., Curry, M., Parsons, R., Fant, G., Lin, M., 2011. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 306, 1891–1901. https://doi.org/10.1001/jama.2011.1592

Forman, D., de Martel, C., Lacey, C.J., Soerjomataram, I., Lortet-Tieulent, J., Bruni, L., Vignat, J., Ferlay, J., Bray, F., Plummer, M., Franceschi, S., 2012. Global Burden of Human Papillomavirus and Related Diseases. Vaccine, Comprehensive Control of HPV Infections and Related Diseases 30, F12–F23. https://doi.org/10.1016/j.vaccine.2012.07.055

Ghazizadeh, S., Lessan-Pezeshki, M., Nahayati, M.A., 2011. Human papilloma virus infection in female kidney transplant recipients. Saudi J. Kidney Dis. Transplant. Off. Publ. Saudi Cent. Organ Transplant. Saudi Arab. 22, 433–436.

Grąt, M., Grąt, K., Hołówko, W., Malejczyk, M., Walter de Walthoffen, S., Lewandowski, Z., Kobryń, K., Patkowski, W., Majewski, S., Młynarczyk, G., Krawczyk, M., 2014. Initial prevalence of anal human papilloma virus infection in liver transplant recipients. Transpl. Int. Off. J. Eur. Soc. Organ Transplant. 27, 816–823. https://doi.org/10.1111/tri.12339

Groves, I.J., Coleman, N., 2015. Pathogenesis of human papillomavirus-associated mucosal disease. J. Pathol. 235, 527–538. https://doi.org/10.1002/path.4496

Grulich, A.E., van Leeuwen, M.T., Falster, M.O., Vajdic, C.M., 2007. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet Lond. Engl. 370, 59–67. https://doi.org/10.1016/S0140-6736(07)61050-2

Hariri, S., Unger, E.R., Sternberg, M., Dunne, E.F., Swan, D., Patel, S., Markowitz, L.E., 2011. Prevalence of Genital Human Papillomavirus Among Females in the United

States, the National Health and Nutrition Examination Survey, 2003–2006. J. Infect. Dis. 204, 566–573. https://doi.org/10.1093/infdis/jir341
Hernandez, B.Y., 2005. Anal Human Papillomavirus Infection in Women and Its Relationship with Cervical Infection. Cancer Epidemiol. Biomarkers Prev. 14, 2550–2556. https://doi.org/10.1158/1055-9965.EPI-05-0460
Hillemanns, P., Friese, K., Dannecker, C., 2020. S3-Leitlinie Prävention des Zervixkarzinoms 240.
Hinten, F., Hilbrands, L.B., Meeuwis, K. a. P., IntHout, J., Quint, W.G.V., Hoitsma, A.J., Massuger, L.F. a. G., Melchers, W.J.G., de Hullu, J.A., 2017b. Reactivation of Latent HPV Infections After Renal Transplantation. Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg. 17, 1563–1573. https://doi.org/10.1111/ajt.14181
Hinten, F., Hilbrands, L.B., Meeuwis, K.A., van Bergen-Verkuyten, M.C., Slangen, B.F., van Rossum, M.M., Rahamat-Langendoen, J., Massuger, L.F., de Hullu, J.A., Melchers, W.J., 2017a. Improvement of Gynecological Screening of Female Renal Transplant Recipients by Self-Sampling for Human Papillomavirus Detection. J. Low. Genit. Tract Dis. 21, 33–36. https://doi.org/10.1097/LGT.0000000000000270
Iftner, T., Eberle, S., Iftner, A., Holz, B., Banik, N., Quint, W., Straube, A.-N., 2010. Prevalence of low-risk and high-risk types of human papillomavirus and other risk factors for HPV infection in Germany within different age groups in women up to 30 years of age: An epidemiological observational study. J. Med. Virol. 82, 1928–1939. https://doi.org/10.1002/jmv.21910
Jacot-Guillarmod, M., Balaya, V., Mathis, J., Hübner, M., Grass, F., Cavassini, M., Sempoux, C., Mathevet, P., Pache, B., 2022. Women with Cervical High-Risk Human Papillomavirus: Be Aware of Your Anus! The ANGY Cross-Sectional Clinical Study. Cancers 14, 5096. https://doi.org/10.3390/cancers14205096
Larsen, H.K., Hædersdal, M., Thomsen, L.T., Hertzum-Larsen, R., Lok, T.T., Bonde, J., Sørensen, S.S., Hansen, J.M., Palefsky, J.M., Kjær, S.K., 2020. Risk of Anal High-grade Squamous Intraepithelial Lesions Among Renal Transplant Recipients Compared With Immunocompetent Controls. Clin. Infect. Dis. https://doi.org/10.1093/cid/ciaa781
Liao, J.B., Fisher, C.E., Madeleine, M.M., 2019. Gynecologic cancers and solid organ transplantation. Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg. 19, 1266–1277. https://doi.org/10.1111/ajt.15292
Lin, C., Slama, J., Gonzalez, P., Goodman, M.T., Xia, N., Kreimer, A.R., Wu, T., Hessol, N.A., Shvetsov, Y., Ortiz, A.P., Grinsztejn, B., Moscicki, A.-B., Heard, I., del Refugio González Losa, M., Kojic, E.M., Schim van der Loeff, M.F., Wei, F., Longatto-Filho, A., Mbulawa, Z.A., Palefsky, J.M., Sohn, A.H., Hernandez, B.Y., Robison, K., Simpson, S., Conley, L.J., de Pokomandy, A., van der Sande, M.A.B., Dube Mandishora, R.S., Volpini, L.P.B., Pierangeli, A., Romero, B., Wilkin, T., Franceschi, S., Hidalgo-Tenorio, C., Ramautarsing, R.A., Park, I.U., Tso, F.K., Godbole, S., D'Hauwers, K.W.M., Sehnal, B., Menezes, L.J., Heráclio, S.A., Clifford, G.M., 2019. Cervical determinants of anal HPV infection and high-grade anal lesions in women: a collaborative pooled analysis. Lancet Infect. Dis. 19, 880–891. https://doi.org/10.1016/S1473-3099(19)30164-1
Luyten, A., Buttmann-Schweiger, N., Luyten, K., Mauritz, C., Reinecke-Lüthge, A., Pietralla, M., Meijer, C.J.L.M., Petry, K.U., 2014. Early detection of CIN3 and cervical cancer during long-term follow-up using HPV/Pap smear co-testing and risk-adapted follow-up in a locally organised screening programme. Int. J. Cancer 135, 1408–1416. https://doi.org/10.1002/ijc.28783

Meeuwis, K. a. P., Hilbrands, L.B., IntHout, J., Slangen, B.F.M., Hendriks, I.M.P., Hinten, F., Christiaans, M.H.L., Quint, W.G.V., Kerkhof, P.C.M. van de, Massuger, L.F. a. G., Hoitsma, A.J., Rossum, M.M. van, Melchers, W.J.G., Hullu, J.A. de, 2015. Cervicovaginal HPV Infection in Female Renal Transplant Recipients: An Observational, Self-Sampling Based, Cohort Study. Am. J. Transplant. 15, 723–733. https://doi.org/10.1111/ajt.13053

Origoni, M., Stefani, C., Dell'Antonio, G., Carminati, G., Parma, M., Candiani, M., 2011. Cervical Human Papillomavirus in transplanted Italian women: A long-term prospective follow-up study. J. Clin. Virol. 51, 250–254. https://doi.org/10.1016/j.jcv.2011.05.017

Paternoster, D.M., Cester, M., Resente, C., Pascoli, I., Nanhorngue, K., Marchini, F., Boccagni, P., Cillo, U., Ribaldone, R., Amoruso, E., Cocca, N., Cuccolo, V., Bertolino, M., Surico, N., Stratta, P., 2008. Human papilloma virus infection and cervical intraepithelial neoplasia in transplanted patients. Transplant. Proc. 40, 1877–1880. https://doi.org/10.1016/j.transproceed.2008.05.074

Petry, K.U., Luyten, A., Justus, A., Iftner, A., Strehlke, S., Reinecke-Lüthge, A., Grunwald, E., Schulze-Rath, R., Iftner, T., 2013. Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84--results of WOLVES, a population-based epidemiological study in Wolfsburg, Germany. BMC Infect. Dis. 13, 135. https://doi.org/10.1186/1471-2334-13-135

Roche Deutschland Holding GmbH, 2021. cobas® 6800 und cobas® 8800 System – Roche.de [WWW Document]. URL https://www.roche.de/diagnostik-produkte/produktkatalog/systeme/cobas-6800-und-cobas-8800-system (accessed 9.12.21).

Roche Deutschland Holding GmbH, 2021a. The cobas® HPV Test [WWW Document]. Diagnostics. URL https://diagnostics.roche.com/global/en/products/params/cobas-hpv.html (accessed 9.12.21).

Rosenblum, H.G., 2021. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of Vaccine — United States, 2003–2018. MMWR Morb. Mortal. Wkly. Rep. 70. https://doi.org/10.15585/mmwr.mm7012a2

Schrem, H., Barg-Hock, H., Strassburg, C.P., Schwarz, A., Klempnauer, J., 2009. Aftercare for Patients with Transplanted Organs. Dtsch. Aerzteblatt Online. https://doi.org/10.3238/arztebl.2009.0148

Seshadri, L., George, S.S., Vasudevan, B., Krishna, S., 2001. Cervical intraepithelial neoplasia and human papilloma virus infection in renal transplant recipients. Indian J. Cancer 38, 92–95.

Smith, J.S., Melendy, A., Rana, R.K., Pimenta, J.M., 2008. Age-Specific Prevalence of Infection with Human Papillomavirus in Females: A Global Review. J. Adolesc. Health 43, S5.e1-S5.e62. https://doi.org/10.1016/j.jadohealth.2008.07.009

Stier, E.A., Clarke, M.A., Deshmukh, A.A., Wentzensen, N., Liu, Y., Poynten, I.M., Cavallari, E.N., Fink, V., Barroso, L.F., Clifford, G.M., Cuming, T., Goldstone, S.E., Hillman, R.J., Rosa-Cunha, I., La Rosa, L., Palefsky, J.M., Plotzker, R., Roberts, J.M., Jay, N., 2024. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int. J. Cancer 154, 1694–1702. https://doi.org/10.1002/ijc.34850

Stier, E.A., Sebring, M.C., Mendez, A.E., Ba, F.S., Trimble, D.D., Chiao, E.Y., 2015. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am. J. Obstet. Gynecol. 213, 278–309. https://doi.org/10.1016/j.ajog.2015.03.034

Türk, T.R., Witzke, O., Zeier, M., 2010. KDIGO-Leitlinien zur Betreuung von Nierentransplantatempfängern. Nephrol. 5, 94–107. https://doi.org/10.1007/s11560-009-0369-6

5. List of abbreviations

AIN – Anal intraepithelial neoplasia

Ca – Carcinoma

CIN – Cervical intraepithelial neoplasia

CNI – Calcineurin inhibitors

HIV – Human immunodeficiency virus

HSIL – High-grade squamous intraepithelial lesion

HPV – Human papillomavirus

HrHPV – High-risk human papillomavirus

LrHPV – Low-risk human papillomavirus

SOT – Solid organ transplantation

UKE – University Medical Center Hamburg-Eppendorf

VAIN – Vaginal intraepithelial neoplasia

VIN – Vulvar intraepithelial neoplasia

6. Figures

7. Personal contribution

This work was conducted at the Department of Gynecology, University Medical Center Hamburg-Eppendorf, under the direction of Professor Dr. med. Barbara Schmalfeldt. The study concept was developed by my doctoral supervisor and head of the dysplasia outpatient clinic, Professor Dr. med. Linn Wölber. I performed an independent literature review before initiating experiments and analyses. I independently collected the clinical data and performed all data management under the supervision of Dr. med. Christoph Hillen and PD Dr. med. Anna Jaeger. The follow-up examination was performed by PD Dr. Anna Jaeger. Evaluation of the HPV tests was carried out by me under the supervision of Dr. Marc Lütgehetmann with support from the medical-technical assistants in the microbiology laboratory. I conducted the descriptive statistical analyses with support from Dr. med. Christoph Hillen, Eik Vettorazzi, and Professor Dr. med. Linn Wölber; the multivariate analyses were performed by Mr. Eik Vettorazzi. I prepared the manuscript for publication, with feedback from Dr. med. Christoph Hillen and Professor Dr. med. Linn Wölber.

8. Eidesstaatliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Das gilt insbesondere auch für alle Informationen aus Internetquellen.
Soweit beim Verfassen der Dissertation KI-basierte Tools („Chatbots“) verwendet wurden, versichere ich ausdrücklich, den daraus generierten Anteil deutlich kenntlich gemacht zu haben. Die „Stellungnahme des Präsidiums der Deutschen Forschungsgemeinschaft (DFG) zum Einfluss generativer Modelle für die Text- und Bilderstellung auf die Wissenschaften und das Förderhandeln der DFG“ aus September 2023 wurde dabei beachtet.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich damit einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Datum Unterschrift

9. Acknowledgement

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I would also like to extend my sincere thanks to PD Dr. med. Anna Jaeger, who assisted me in collecting the samples and took over the follow-up examinations. My thanks also go to the nurses of the outpatient clinic, in particular Dimitra, Dana, and Isabella, who supported me with scheduling and conducting the examinations.

Finally, I would like to thank my parents, Dr. rer. medic. Judith Scholler-Sachs and Dr. med. Gernot Sachs, as well as my grandmother Maria Scholler, whose unconditional support, trust, and love have accompanied and strengthened me throughout my entire journey.

10. Appendix

10.1. Questionnaire

Zur Studie: „Prävalenz von genitoanalen HPV Infektionen bei Frauen nach Organtransplantation“

Patientennummer:

Sehr geehrte Patientin,
Sie helfen uns sehr, wenn Sie vor dem Gespräch im Rahmen unserer Studie folgende Fragen beantworten:
Wie groß sind Sie? cm
Wie viel wiegen Sie? kg

Anamnese zur Organtransplantation und Therapie
Welches Organ wurde bei Ihnen transplantiert? □ Niere □ Leber □beides

In welchem Jahr war Ihre Transplantation (falls mehrere erste Transplantation)?
:……
…….....

Wussten Sie, dass sie als Patientin mit einem Transplantationsorgan ein erhöhtes Krebsrisiko im Genitalbereich haben? □ Nein □ Ja

Fühlen Sie sich über gynäkologische Risiken und Vorsorgemaßnahmen ausreichend informiert? □ Nein □ Ja
Ist es jemals zu einer Abstoßungsreaktion gekommen? □ Nein □ Ja
□ weiß ich nicht
Wenn ja, wann ?
……
…….
Welche Immunsupressiva nehmen Sie aktuell ein?

Tacrolimus (Prograf, Modigraf, Advagraf,Envarsus) □

Cyclosporin (Sandimmun Optoral) □

Everolimus (Certican) □

Sirolimus (Rapamune) □

MMF (Cellcept, Mykophenolat) □

MPA (Myfortic , Mykophenolsäure) □

Azathioprin (Imurek) □

Prednisolon/Metynprednisolon (Decortin/Urbason) □

Belatacept (Nulojix) □

Nicht genannte Immunsupressiva □

……

……

Hatten Sie eine Induktionstherapie? □ Nein □ Ja

□ weiß ich nicht

Wenn ja, mit

Simulect (Basiliximab) □

Thymoglobulin □

Belatacept □

Weitere □

……

……

Haben Sie vor der Transplantation bereits Medikamente eingenommen,

die die Immunabwehr herabsetzen? □ Nein □ Ja

□ weiß ich nicht

Wenn ja, welche und seit ungefähr wann

……
…….

Leiden Sie unter Erkrankungen, z.B. autoimmune Erkrankungen wie Colitis ulcerosa, M. Crohn, rheumatische Erkrankung, Multiple Sklerose) die eine zusätzliche immunsuppressive Therapie notwendig machen? □ Nein □ Ja
□ weiß ich nicht
Wenn ja, welche ?
……
……

Allgemeine Anamnese

Leiden sie an kardiovaskulären Erkrankungen? □ Nein □ Ja
□ weiß ich nicht

Leiden Sie an einer Erkrankung der Schilddrüse? □ Nein □ Ja
□ weiß ich nicht

Leiden Sie an einer diabetischen Erkrankung? □ Nein □ Ja
□ weiß ich nicht

Wurde bei Ihnen schon einmal eine bösartige Erkrankung, bzw. die Vorstufe einer solchen Erkrankung diagnostiziert?
……
……
……
……

Leiden Sie unter wiederholten Infektionserkrankungen? □ Nein □ Ja
□ weiß ich nicht

Wenn ja,
welche……...

Nehmen Sie außer den Immunsuppressiva regelmäßig
Medikamente ein? □ Nein □ Ja
□ weiß ich nicht

Wenn ja, welche und in welcher Dosierung?
……
……
……

Sind bei Ihnen Allergien bekannt? □ Nein □ Ja
□ weiß ich nicht

Wenn ja,
welche:…….

Rauchen Sie? □ Nein □ Ja
Wenn ja, was und wie
viel?.....

Trinken Sie Alkohol? □ Nie □ gelegentlich □ häufig □ regelmäßig

Gibt es in Ihrer Familie Krebserkrankungen? □ Nein □ Ja
□ weiß ich nicht

Wenn ja,
welche?.....

Gynäkologische Anamnese
Gehen Sie regelmäßig zur Krebsfrüherkennungsuntersuchung
(=Vorsorge) beim Frauenarzt? □ Nein □ Ja
Wenn ja, wie häufig ?

……
……

Hatten Sie bereits einmal einen auffälligen Gebärmutterhalsabstrich? □ Nein □ Ja
□ weiß ich nicht

Wenn ja, wann und welche Therapie wurde durchgeführt?

……
……....

Leiden Sie an wiederholten genitalen Infektionen? □ Nein □ Ja
□ weiß ich nicht

Wenn ja,
welche……

Haben Sie eine HPV Impfung (Impfung gegen Gebärmutterhalskrebs)
erhalten? □ Nein □ Ja

Wenn ja:
In welchem Jahr haben Sie die HPV Impfung
erhalten?.....
Vor dem ersten GV? □ Nein □ Ja
□ weiß ich nicht

Vor/nach der Transplantation? □ Vor □ Nach
□ weiß ich nicht

Welche Vakzine und wie viele
Dosen?.....

Nehmen Sie Hormonpräparate ein? □ Nein □ Ja
□ weiß ich nicht
Wenn ja, welche?
……...

Haben Sie mal Hormonpräparate eingenommen? □ Nein □ Ja

□ weiß ich nicht

Wenn ja, wie

lange?.....

Wann hatte Sie als Mädchen Ihre erste Regelblutung (Menstruation)? Mit …. Jahren.

Wann hatten Sie Ihre letzte Regelblutung?

…….....

In welchem Alter hatten Sie ihren ersten

Geschlechtsverkehr?.....

Wie viele Sexualpartner hatten Sie insgesamt

bisher?.....……

Wie viele Sexualpartner hatten Sie seit ihrer

Transplantation?.....

Haben Sie Kinder geboren? Wenn ja, wie viele? Geburtsjahr

……

……

10.2. Informed consent form

Zur Studie: „Prävalenz von genitoanalen HPV Infektionen bei Frauen nach Organtransplantation“

Name,

Vorname:……....

Name des aufklärenden Arztes:……

Sehr geehrte Patientin,

das Universitätsklinikum Hamburg-Eppendorf möchte eine medizinische Versorgung auf hohem Niveau bieten und dieses Niveau konsequent verbessern. Daher ist zusätzlich zur Patientenversorgung die Forschung eine wichtige Aufgabe in unseren Kliniken. Hierzu erbitten wir nachfolgend Ihre Unterstützung.

In ihrer Vorgeschichte hatten Sie eine Organtransplantation und sind deshalb am UTC (Universitäres Transplantations Centrum) angebunden. Um eine Abstoßungsreaktion des Transplantats zu verhindern, erhalten Sie eine immunsupprimierende Therapie und befinden sich in regelmäßiger Nachsorge. Eine langfristige immunsupprimierende Therapie kann verschiedene Nebenwirkungen haben. Studien zeigen, dass ein erhöhtes Risiko für Krebserkrankungen, insbesondere für Gebärmutterhalskrebs, besteht. Dieser Krebs wird durch eine Virusinfektion, nämlich durch das sogenannte Humanen Papillomavirus (HPV) mit hervorgerufen. In dieser Studie möchten wir untersuchen, ob das Vorkommen von HPV Infektionen bei transplantierten Patientinnen im Vergleich zu nicht transplantierten Patientinnen erhöht ist. Hierzu würden wir bei Ihnen in unserer gynäkologischen Poliklinik jeweils zwei Abstriche vom Gebärmutterhals und einen Abstrich aus der Analregion entnehmen. Die Abstrichentnahme erfolgt im Rahmen einer Spiegeleinstellung des Gebärmutterhalses, einer gynäkologischen Routinemaßnahme, die nur wenige Minuten dauert (2-3 Minuten). Die Untersuchung wird von manchen Patientinnen als unangenehm empfunden, weitere Risiken bestehen bei dieser Untersuchung jedoch nicht. Die Abstriche werden dann sowohl in der Mikrobiologie des UKE als auch in der Charité Berlin auf das Vorkommen von HPV Infektionen untersucht. Zusätzlich würden wir Sie bitten, einen Fragebogen mit speziellen Fragen zu ihrer Krankengeschichte und Ihren Lebensgewohnheiten, von denen wir vermuten, dass sie mit

dem Auftreten der HPV Infektion in Zusammenhang stehen, auszufüllen. Das Ausfüllen des Fragebogens wird circa 20 Minuten dauern. Alle Daten werden vollständig anonymisiert in die Auswertung einfließen. Falls bei Ihnen ein auffälliger Befund festgestellt wird, werden Sie informiert und im Rahmen der Dysplasiesprechstunde des UKE weiter betreut. Ziel unserer Studie ist es die Ursachen für das erhöhte Vorkommen von HPV verursachten Krebserkrankungen bei transplantierten Patientinnen besser zu verstehen. Ein besseres Verständnis wird hoffentlich zu einer effektiveren Vorsorge führen und helfen Risiken für Krebserkrankungen frühzeitig zu

erkennen und zu behandeln. Deshalb würden wir uns freuen, wenn Sie an unserer Studie teilnehmen.

Ziel der Studie und Befragung

Ziel der Studie ist es das Vorkommen von HPV Infektionen bei leber- und nierentransplantierten Patientinnen zu untersuchen. Die Häufigkeit des Auftretens einer HPV Infektion soll dabei sowohl zwischen leber- und nierentransplantierten Patienten als auch mit der Normalbevölkerung verglichen werden. Außerdem sollen weitere Untersuchungen potentieller Marker für das Entstehen und Fortschreiten einer HPV bedingten Krebsvorstufe des Genitalbereiches untersucht werden. Die Fragebögen sollen helfen weitere Einflussgrößen für das Auftreten von HPV zu identifizieren.

Freiwillige Teilnahme

Die Teilnahme an dieser Untersuchung ist absolut freiwillig. Wenn Sie teilnehmen möchten, worüber wir uns sehr freuen würden, füllen Sie bitte die Einverständniserklärung aus. Wenn Sie sich nicht beteiligen möchten oder ihre Einwilligung später widerrufen möchte, entstehen Ihnen daraus keine Nachteile.

Datenschutz

Die im Rahmen der Studie erhobenen persönlichen Daten, insbesondere Befunde, unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen. Für die Auswertung im Rahmen der Studie werden ihre Daten zunächst in Papierform erfasst und

auf elektronischen Datenträgern pseudonymisiert[1] (verschlüsselt) für die Dauer von 5 Jahren gespeichert. Die Ergebnisse der Abstrichuntersuchung werden ebenfalls verschlüsselt auf diesem Datenträger gespeichert. Die Pseudonymisierung erfolgt direkt nach Einwilligung zur Teilnahme an der Studie. Bei der Pseudonymisierung (Verschlüsselung) werden der Name und andere Identifikationsmerkmale (z.B. Teile des Geburtsdatums) durch eine Patientinnennummer ersetzt, um die Identifizierung des Studienteilnehmers auszuschließen oder wesentlich zu erschweren. Zugang zu dem „Schlüssel", der eine persönliche Zuordnung der Daten des Studienteilnehmers ermöglicht, haben neben dem Studienleiter nur von diesem ausdrücklich dazu autorisierte Personen der Klinik für Gynäkologie des UKE. Sobald der Forschungszweck es zulässt, wird der Schlüssel gelöscht und die erhobenen Daten damit anonymisiert[2]. Die Nutzung der Daten erfolgt dann nur noch anonymisiert. Eine Weitergabe im Rahmen des Forschungszwecks erfolgt ebenfalls nur in anonymisierter Form. Eine Veröffentlichung wissenschaftlicher

Ergebnisse erfolgt ausschließlich in einer Weise, dass keine, Sie unmittelbar identifizierenden Daten (Name, Telefonnummer usw.), enthalten sind. Ihre Daten und Proben werden gegebenenfalls für eine

Anschlussstudie, die sich aus den Studienergebnissen ergeben könnte, weiter genutzt.

Im Falle des Widerrufs der Einwilligungserklärung werden die bereits erhobenen Daten gelöscht oder anonymisiert[2] und in dieser Form weiter genutzt. Eine Löschung bereits anonymisierter Daten ist nicht möglich.

Weitere Informationen und Rechte

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[1] Pseudonymisieren ist das Ersetzten des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Bestimmung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a BDSG).

[2] Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Absatz 6 BDSG)

Für die Verarbeitung ihrer Patientinnendaten verantwortlich ist Fr. Prof. Linn Wölber, Klinik für Gynäkologie des UKE (frauenklinik@uke.de).
Der zuständige Datenschutzbeauftragte des Universitätsklinikums Hamburg Eppendorf Herr Jaster ist erreichbar unter 040-741056890.
Sie haben die Möglichkeit, sich mit einer Beschwerde an die zuständige Datenschutzaufsichtsbehörde zu wenden. Dies ist im Regelfall die oder der Landesbeauftragte für den Datenschutz des Bundeslandes, in dem Sie behandelt wurden. Zudem haben Sie das Recht, Auskunft über die Sie betreffenden Patientendaten zu erhalten (auf Wunsch einschließlich einer unentgeltlichen Überlassung einer Kopie) sowie ggf. deren Berichtigung oder Löschung oder Einschränkung der Verarbeitung zu verlangen.Sie haben weiter das Recht, von Ihnen bereitgestellte Daten in einem standardisierten elektronischen Format zu erhalten oder an eine von Ihnen genannte Stelle übermittelt zu bekommen (Recht auf Datenübertragbarkeit).

Wenn Sie mit der beschriebenen Art und langfristigen Dauer der Nutzung ihrer Daten nicht in vollem Umfang einverstanden sind oder Ihre Rückfragen nicht alle zufriedenstellend beantwortet wurden, sollten Sie Ihre Einwilligung nicht erteilen.

Ethik-Kommission

06/19 positives Votum der Ethik-Kommission der Ärztekammer Hamburg.

Sollten Sie weitere Fragen zu dieser Befragung haben oder noch Unklarheiten bestehen, können Sie gerne mit unserem Team über folgende Telefonnummer Kontakt aufnehmen: **015222824626**

Mit herzlichem Dank für Ihre Unterstützung, Ihre

Prof. Dr. med. Linn Wölber Dr. med. Christoph Hillen

10.3. Consent form

Zur Studie: „Prävalenz von genitoanalen HPV Infektionen bei Frauen nach Organtransplantation“

Name:……
Geburtsname:……
Vorname:……
Geburtsdatum:…….....
Telefonnummer:……

_____ (Name des aufklärenden Arztes) hat mich umfassend über das Wesen und die Bedeutung der geplanten Studien aufgeklärt. Ich konnte dabei alle mich interessierenden Fragen stellen. Ferner hatte ich Gelegenheit, die Aufklärungsblätter genau durchzulesen und auch dazu Fragen zu stellen.

Maßnahmen:
Ich stimme den Maßnahmen, die im Rahmen der Studie durchgeführt werden, zu. Zu diesen zählen die gynäkologische Untersuchung mit Spekulumeinstellung und Abstrichentnahme vom Gebärmutterhals sowie von der Analregion und Untersuchung dieser Abstriche auf HPV Infektionen und weiterer möglicher Marker für das Entstehen und Fortschreiten einer HPV bedingten Krebsvorstufe. Zusätzlich stimme ich zu, den studienbedingten Fragebogen mit Fragen zu meiner Krankengeschichte und Lebensgewohnheiten auszufüllen.

Datenschutz:
Ich bin darüber aufgeklärt worden, dass die im Rahmen der Studie erhobenen persönlichen Daten und Befunde der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen unterliegen. Sie werden für die Studienauswertung zunächst in Papierform aufgezeichnet

und auf elektronischen Datenträgern pseudonymisiert[3] für die Dauer von 5 Jahren gespeichert. Die Ergebnisse der Abstrichuntersuchung werden ebenfalls verschlüsselt auf diesem Datenträger gespeichert. Die Pseudonymisierung erfolgt direkt nach Einwilligung zur Teilnahme an unserer Studie. Bei der Pseudonymisierung (Verschlüsselung) werden der Name und andere Identifikationsmerkmale (z.B. Teile des Geburtsdatums) durch eine mehrstellige Patientinnennummer ersetzt, um die Identifizierung des Studienteilnehmers auszuschließen oder wesentlich zu erschweren. Zugang zu dem „Schlüssel", der eine persönliche Zuordnung der Daten des Studienteilnehmers ermöglicht, haben neben dem Studienleiter nur von diesem ausdrücklich dazu autorisierte Personen der Klinik für Gynäkologie des UKE. Sobald es der Forschungszweck zulässt, wird der Schlüssel gelöscht und die erhobenen Daten damit anonymisiert[4]. Die Nutzung der Daten erfolgt dann anonymisiert. Eine Weitergabe im Rahmen des Forschungszwecks erfolgt nur in anonymisierter Form. Eine Veröffentlichung wissenschaftlicher Ergebnisse erfolgt ausschließlich in einer Weise, dass keine Sie unmittelbar identifizierenden Daten (Name, Telefonnummer usw.) enthalten sind. Ich bin außerdem darüber aufgeklärt worden, dass meine Daten und Proben gegebenenfalls für eine Anschlussstudie, die sich aus den Studienergebnissen ergeben könnte, weiter genutzt werden.

Meine Einwilligung ist freiwillig. Ich kann meine Einwilligung jederzeit ohne Angabe von Gründen vollständig oder in Teilen widerrufen, ohne dass mir irgendwelche Nachteile entstehen. Im Falle des Widerrufs der Einwilligungserklärung werden die bereits erhobenen Daten gelöscht oder anonymisiert[2] und in dieser Form weiter genutzt. Eine Löschung bereits anonymisierter Daten ist nicht möglich.

Weitere Informationen und Rechte

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[3] Pseudonymisieren ist das Ersetzten des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Bestimmung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a BDSG).

[4] Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Absatz 6 BDSG)

Für die Verarbeitung ihrer Patientinnendaten verantwortlich ist Fr. Prof. Linn Wölber, Klinik für Gynäkologie des UKE (frauenklinik@uke.de)
Der zuständige Datenschutzbeauftragte des Universitätsklinikums Hamburg Eppendorf Herr Jaster ist erreichbar unter 040-741056890.
Sie haben die Möglichkeit, sich mit einer Beschwerde an die zuständige Datenschutzaufsichtsbehörde zu wenden. Dies ist im Regelfall die oder der Landesbeauftragte für den Datenschutz des Bundeslandes, in dem Sie behandelt wurden.
Zudem haben Sie das Recht, Auskunft über die Sie betreffenden Patientendaten zu erhalten (auf Wunsch einschließlich einer unentgeltlichen Überlassung einer Kopie) sowie ggf. deren Berichtigung oder Löschung oder Einschränkung der Verarbeitung zu verlangen.
Sie haben weiter das Recht, von Ihnen bereitgestellte Daten in einem standardisierten elektronischen Format zu erhalten oder an eine von Ihnen genannte Stelle übermittelt zu bekommen (Recht auf Datenübertragbarkeit).

Ich wurde über die Nutzung meiner Patientendaten sowie die damit verbundenen Risiken informiert und erteile im vorgenannten Rahmen meine Einwilligung. Ich hatte ausreichend Bedenkzeit und alle meine Fragen wurden zufriedenstellend beantwortet.
Eine Kopie der Patienteninformation und der Einwilligungserklärung habe ich erhalten.

Ort, Datum	
Vor- und Nachname Patient/in (Druckbuchstaben)	Unterschrift Patient/Patientin
Ich habe das Aufklärungsgespräch geführt.	

Vor- und Nachname Mitarbeiter/in (Druckbuchstaben)	Unterschrift Mitarbeiter/in

10.4. Study overview

A total of 22 studies were identified that examined cervical and/or anal HPV prevalence in transplant recipients. All studies are primary literature. The study by Seshadri et al. could only be evaluated based on the abstract, as access to the full text was not possible (Seshadri et al., 2001). Prevalence is given as a percentage. For studies that did not specify a percentage, prevalence was calculated by dividing the number of cases by the total number and multiplying the result by 100. The same applies to the occurrence of cervicovaginal and anal dysplasia. Since different classifications were used in the individual studies, the following terms are summarized under cervicovaginal dysplasia for easier comparison: abnormal Pap smear (PAP), cervical intraepithelial dysplasia (CIN), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), vaginal intraepithelial dysplasia (VaIN), vulvar intraepithelial dysplasia (VIN), atypical squamous cells of undetermined significance (ASC-US), and atypical squamous cells cannot exclude HSIL (ASC-H). Anal dysplasia encompasses the changes ASC-US, LSIL, HSIL, anal intraepithelial lesion (AIN), and ASC-H.

Author	Research Question	Patient Cohort	HPV Test	Risk Factors	Duration/Type of Immunosuppression and HPV Prevalence	Incidence of Dysplasia	hrHPV Prevalence
Studies on cervical HPV Prevalence							
Aggarwal et al. 2014	HPV prevalence and genotyping in kidney transplant	40 NTx, median age 40; 80 controls, median age 38	23 hrHPV, 6 lrHPV; tested 6 mo postTx	Not recorded	No correlation between duration/type and HPV prevalence	No abnormal cytology	NTx: 32.5%; Controls: 17.5%

	patients in North India						
Cistjakovs et al. 2018	hrHPV prevalence in female kidney transplant recipients during first year postTx	43 NTx, median age 48; 79 controls, median age 48	EDTA blood: IgG-Ab to L1; Cervical: 19 hrHPV, 9 lrHPV; testing 2w, 6m, 12m	Not recorded	High viral load after 6 mo; 72% of NTx with rejection hrHPV+	NTx: 3 CIN1; Control: none	NTx hrHPV 24% (2w), 26% (6m), 36% (12m); Controls hrHPV 8%
de Oliveira Martins et al. 2017	Association between hrHPV and anogenital cancers in female kidney Tx	58 NTx, 3 LTx; mean age 46.2; mean 90.2 mo since Tx; mean partners 2.92	11 hrHPV, 9 lrHPV; ≥24 mo postTx	Hormone intake	No correlation between duration/type and HPV prevalence	16.4%; 7 HSIL, 1 VIN, 1 VAIN, 1 cervical cancer	hrHPV: 40%; <30y: 6.6%, 31–54y: 73.3%, >55y: 20%

Ghazizadeh et al. 2011	HPV prevalence in female kidney Tx	58 NTx, median age 37.2	Tested preTx and 1y postTx	Not recorded	Not recorded	No SIL/VIN; 2 genital warts	PreTx: 0%; 1y postTx: 6.9% (no typing)
Hinten et al. 2017	Improve screening in kidney Tx women by HPV self-testing	217 NTx, median age 56; Tx 3–37y ago	Self-sampling 25 HPV types; physician confirm	Not recorded	Not recorded	11 patients: 5 LSIL, 2 HSIL, 1 condyloma, 1 VIN, 1 VIN+VaIN, 1 LSIL+condyloma	Self-test: 16%; Clinical: 9.2%
Hinten et al. 2017	Reactivation of latent HPV after kidney Tx	59 NTx, median age 50; 33 controls awaiting Tx	Self-sampling 25 HPV types; 0–6 mo preTx and up to 29 mo postTx (median 15 mo)	None significant	Significant HPV increase; reactivation likely; no behavior change	No association with rejection; 8 abnormal cytologies: 3 LSIL, 5 HSIL	NTx self-test: 19%→31%; clinical: 10%→14%; Controls self-test:

							21%→27%; clinical: 16%
Long et al. 2018	Cervical cytology/histology after SOT	86 Tx women >30, median age 43.9	HPV per Danish guidelines	Not recorded	Not recorded	5 LSIL, 4 ASC-US, 1 AGUS	HPV: 12.8% (types not given)
Meeuwis et al. 2015	Cervicovaginal HPV in organ Tx women	218 NTx, mean age 55.4; Tx mean age 43.1; mean immunosuppression 8.5y	Self-test 25 HPV types; confirm in clinic	Young age, non-Dutch ethnicity, younger at Tx, # partners, recent sex	No correlation with duration/type	5 ASC-US, 4 LSIL, 6 HSIL	hrHPV: 17.4%; lrHPV: 9.6%

Origoni et al. 2011	HPV prevalence in Italian female Tx over 10y	48 Tx (50% NTx, 50% NTx+PTx), 200 controls; median age 37.9	13 hrHPV, 5 lrHPV; start 6 mo postTx; follow-up 10y	No significant RF	Peak prevalence at 6 mo postTx; no sig diff vs controls	CIN1: 14.5%; CIN2: 6.25%; CIN3: 2.08%	NTx: 10.5–27.7% in 10y; Controls: 16.8–18%
Paternoster et al. 2008	HPV and CIN in Tx patients	151 patients: 26 LTx, 119 NTx, 4 PTx, 2 LTx+NTx; mean age 40	Tested 6 mo pre/post Tx; hrHPV types 16,18,33,45,51,52,53,58,68, 73,82	Not recorded	Not recorded	Abnormal PAP 7.28%; 6 LSIL (4 hrHPV+), 5 HSIL (2 hrHPV+)	HPV 15.23%; hrHPV 11.2%; lrHPV 3.9%
Pietrzak et al. 2012	HPV prevalence in kidney Tx women	60 NTx (7 mo–20y postTx); 60 controls; median age 37	hrHPV-DNA (13 hrHPV); HPV-mRNA (E6/E7); tested 0 & 24 mo	HPV more frequent >2 partners	No correlation with immunosuppression	Abnormal PAP: 2 NTx, 2 controls	NTx hrHPV 18.33%; Controls 25%; Clearance 81.8% vs 93%

Roensbo et al. 2018	HPV prevalence/genotyping in Danish women postTx	Group1: 13 NTx+7 BMTR; Group2: 30 NTx+10 BMTR; median age 55.5	14 hrHPV; Group1 tested 1w,1m,3m; Group2 once	HPV more frequent >5 partners, 1st sex <17y	Higher prevalence BMTR vs NTx	Abnormal PAP 11.7%: LSIL 6.7%, HSIL 5%	hrHPV both groups: 15%; Group1: 15% clearance, 10% persistence
Seshadri et al. 2001	CIN and HPV in kidney Tx women	42 NTx, 41 controls; only HPV16	Not specified	Not specified	—	CIN: NTx 23.8%, Controls 7.3%	NTx HPV16 40.4%; Controls 23.3%
Veroux et al. 2009	HPV prevalence in kidney Tx women	35 NTx, median age 47	18 hrHPV, 8 lrHPV; tested preTx & 6 mo postTx	Not recorded	Not recorded	No abnormal cytology	hrHPV 37.1%; HPV total 62.8%

Wang et al. 2012	Cervical dysplasia after allo-SCT	43 allo-SCT; median age not given	Retrospective, registry data	Not recorded	Not recorded	ASC-US, LSIL, HSIL in 25.5%	HPV: 27.9%
Wielgos et al. 2020	HPV in immunosuppressed women	49 NTx, 31 LTx, 11 other (lupus, GN, heart Tx); mean age 46.2	Self-test 23 HPV types	HPV more frequent >2 partners	No difference between groups; hrHPV+ mostly on TAC+MMF+steroids	Not recorded	hrHPV: 28.9%; Multiple inf. 34.6%
Studies on cervical and anal HPV Prevalence							
Eleutério et al. 2019	Cervical/anal HPV in kidney Tx women	31 NTx, median age 42.6 (31–70)	14 hrHPV	Anal HPV correlated with cervical	Not recorded	Cervical: 2 ASC-US, 1 ASC-H, 4 LSIL, 1 carcinoma; Anal: 1 ASC-US, 7 LSIL	Cervical hrHPV: 22.5%; Anal hrHPV: 40.7%
Grąt et al. 2017	Cervical HPV & anal HPV in liver Tx	50 LTx, median age 55.5	Only HPV16/18; anal tested 12/50	>4 partners, MELD> 8, 1st	—	20% abnormal cytology: 6 ASC-US, 2	Cervical hrHPV: 10%; Anal

				sex <17y, age <50		ASC-H, 2 LSIL	hrHPV: 8.3% (1/12)
Studies on anal HPV prevalence							
Grat et al. 2014	HPV prevalence in liver Tx	25M + 25F LTx; mean age 48.5	Tested HPV6,11,16,18 within 3w postTx	HBV infection, >3 partners, 1st sex <19y	No correlation	Not recorded	hrHPV 8%; lrHPV 10%
Larsen et al. 2020	Anal neoplasia risk in kidney Tx	124M,123F NTx (median 52y); Controls:125F,124M	13 hrHPV; ≥6 mo postTx	Receptive anal sex, prior warts, >10 partners	Longer since Tx → trend to higher prevalence	HSIL NTx: F 15.4%, M 6.5%; Controls: F 4%, M 0.8%	NTx: F 45.5%, M 19.4%; Controls: F 27.2%, M 23.6%
Patel et al. 2010	HPV and anal dysplasia in kidney Tx	108 NTx (68M, 40F); median 75 mo postTx	Tested 1–385 mo postTx	Receptive anal sex, rejection	Higher HPV with rejection; higher with >5y	Dysplasia 5.8% (2 AIN1, 1 AIN2, 3 AIN3);	hrHPV 9.3%

				history, >5 partners	immunosuppression	Borderline 3.8%	
Roka et al. 2004	HPV prevalence in Tx patients	60 (43 NTx, 17 LTx; 40M, 20F; median age 52.5)	5 lrHPV, 13 hrHPV	Not recorded	Not recorded	Not recorded	hrHPV: LTx 17.6%; NTx 13.9%

Comparison of cervical or anal HPV prevalence in transplant patients compared to the control group

Study	HPV prevalence among the control group	HPV prevalence among the transplant cohort
Aggarwal et al. 2014	17,5%	32,5%
Cistjakovs et al. 2018 *	8%	36%
Hinten et al. 2017a	16%	14%
Origoni et al. 2011	18%	27,7%
Pietrzak et al. 2012	25%	18,8%
Seshadri et al. 2001	23,3%	40,4%
Larsen et al. 2020 *	27,2%	45,5%

* = significant difference