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Skin cancer and (pre)malignancies of the female genital tract in renal transplant recipients

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Summary

Immunosuppressive therapy in renal transplant recipients (RTRs) is associated with an increased risk for the development of (pre)malignancies involving the skin and the female lower genital tract. We assessed whether yearly cervical screening was performed and evaluated the development of skin cancer and gynaecological (pre)malignancies in RTRs. Female RTRs ($n = 224$), transplanted between 1991 and 1995, were analysed retrospectively. Sociodemographic patient characteristics, frequency and results of cervical smears and prevalence of cutaneous, cervical, vaginal or vulvar (pre)malignancies were investigated and compared with that in the general population. A mean of 0.2 cervical smears per patient per year was found to have been performed in RTRs, which is significantly less than the recommended screening ratio of 1.0 for female RTRs ($P < 0.001$). The risk for RTRs to develop malignancies of the female lower genital tract was increased: twofold to sixfold for cervical intraepithelial neoplasia, threefold for cervical carcinoma and 50-fold for vulvar carcinoma. Cervical screening is not performed in accordance with the advised yearly intervals, and the risk for RTRs to develop vulvar and cervical (pre)malignancies is increased. More attention should be paid to the vulvar and cervical surveillance of RTRs by both medical specialists and general physicians.

Introduction

Each year, more than 800 renal transplantations (RT) are performed in the Netherlands according to the Netherlands Organ Transplantation Registration (NOTR). Solid organ transplantation requires the administration of lifelong intense immunosuppressive therapy. The strategies to reduce graft rejection have improved considerably since the first successful kidney transplantation in 1954 [1,2]. At present, most immunosuppressive regimens combine a calcineurin inhibitor (ciclosporin or tacrolimus) with an adjunctive agent (azathioprine, mycophenolate mofetil or sirolimus) and corticosteroids, resulting in a remarkable increase of patient survival [2]. The current immunosuppressive regimes have led to a 1-year patient and graft survival of more than 90% and the incidence of acute rejection has fallen to 10–15% [2]. This high survival rate has made it incumbent on the medical specialists to pay increasing attention to the long-term side-effects of immunosuppressive medication.

It is known that renal transplant recipients (RTRs) have at least a threefold to fivefold increase of risk to develop any kind of cancer compared with the general population [1,3–5]. The relative risk with respect to specific cancers, such as skin cancer, post-transplant lymphoproliferative disorders, Kaposi's sarcoma and human papillomavirus (HPV)-related malignancies of the lower

genital tract e.g. cervix, vulva and anus may be even higher [4,6–8].

The appearance of malignancies after RT is obviously related to the duration and dose of immunosuppressive medication [6,9–11]. Immunosuppressants may influence different mechanisms resulting in an increased risk for the development of cancer after RT. Immunosuppressive medication can directly affect DNA by inhibiting repair mechanisms and by causing chromosome strand breaks. This may lead to irreversible DNA alterations and subsequent cancer development [6,12]. Additionally, an immunosuppressive state potentiates oncogenic stimuli such as ultraviolet (UV) light, viruses and chemical carcinogens. UV-radiation can lead to mutations in proto-oncogenes and tumour-suppressor genes. Moreover, it can suppress the local cutaneous immune response by depletion of Langerhans' cells with less antigen presentation and recognition as a result [13–15]. HPV is an important factor in the development of lower genital tract malignancies and might also play a role in the development of cutaneous malignancies [13,15–18] (http://www.rivm.nl). The viral E6 protein inactivates p53 (a tumour-suppressor protein), which results in chromosomal instability and diminished apoptosis. The E7 protein suppresses the retinoblastoma protein pathway, which leads to enhanced cell proliferation [17,19]. In the pathogenesis of skin cancer, E6-proteins can inhibit UV-induced apoptosis by a p53-independent mechanism, which results in accumulation of UV-induced mutations [13,15–17].

Skin cancer is the most commonly encountered malignancy in RTRs, with 37.4–63% of all post-transplantation tumours [1,4,6,12,20]. In countries with a temperate climate, the incidence of skin cancer within 10 years after RT is 10–15%. After 20 years, this percentage increases to 40% [7,21]. More than 90% of all skin cancers are non-melanoma skin cancers, which are predominantly squamous cell carcinomas (SCCs) (up to 250-fold increased risk), followed by basal cell carcinomas (BCCs) (up to 10-fold increased risk) [3,7,11,22,23]. As BCCs prevail in the general population, the SCC/BCC ratio is reversed in RTRs [7,24] (http://www.rivm.nl).

It is generally accepted that lower genital tract neoplasms in female RTRs are fully related to high-risk HPV (hrHPV). Accordingly, immunosuppressed female RTRs are at a significantly increased risk for abnormal cervical smears, cervical/vulvar intraepithelial neoplasia (CIN/VIN) and lower genital tract malignancies. As a consequence, prevention and early treatment of (pre)malignancies is important. Earlier publications have suggested conducting physical examinations and cervical smears with smaller intervals than common in the national screening programmes (target population in the Netherlands: 30–60 years of age; interval 5 years), although there is a lack of evidence for this policy [25–27]. In 2000, The American Society of Transplantation advised yearly cervical screening for female RTRs [26].

In our study, we investigated whether cervical smears were performed in accordance with the advised yearly interval. In addition, we analysed the development of vulvar, vaginal and cervical (pre)malignancies in female RTRs to determine their prevalence in our RTR-population. Moreover, as both cutaneous and female lower genital tract (pre)malignancies are probably associated with HPV infections, we studied the correlation between these (pre)malignancies in the RTR-population. We formulated recommendations to optimize the follow-up concerning lower genital tract (pre)malignancies in female RTRs.

Patients and methods

Data on all consecutive female patients who underwent a RT between January 1991 and December 1995 at the Radboud University Nijmegen Medical Centre, the Netherlands, were included in this analysis. Identities of all 224 patients were extracted from the local RT registry of this academic centre. Clinical data of the patients were abstracted from the patient hospital charts and the electronic patient files, up to the first of August 2008. To complete the histo- and cytopathological data, we used PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), which is a nationwide histo- and cytopathology network and archive that achieved complete national coverage since 1991 [28]. All patients started with triple immunosuppressive therapy (calcineurin inhibitor, mycophenolate mofetil and prednisolone). Six months after transplantation, almost all patients were treated with double immunosuppressive therapy [in most instances azathioprine (2–3 mg/kg) and prednisolone (10 mg)].

The follow-up period was defined as the period between transplantation and any of the following dates whichever is earlier: the first of August 2008, date of death or date denominated as 'lost to follow-up'. Patients with failure of renal graft function ($n = 73$) and therefore restart of dialysis were also followed until the first of August 2008. Variables recorded included sociodemographic patient characteristics (i.e. race, age at transplantation, decease) and background information on renal medical history, transplantation, and restart of haemodialysis.

We collected the dates and results of cervical smears and the development of skin cancer and cervical, vaginal or vulvar (pre)malignancies after RT. Whenever a malignancy developed, we registered additional clinical and pathological data. The duration of immunosuppression

was calculated from the date of transplantation to either the end of the study period, the date of death, or the date of definitive transplant failure when dialysis was resumed. When a patient used immunosuppression during more than one period, the durations of all such periods were aggregated.

We counted the total number of cervical smears performed in female RTRs from their 18th year of life. As the advised screening frequency is once a year, we excluded the patients with less than 1 year of follow-up after their transplantation from further analysis. To calculate the number of patient-years after transplantation, we also corrected the years after the transplantation for incomplete follow-up, death, and childhood (<18 years). The mean number of cervical smears per patient per year was calculated by dividing the total number of cervical smears by the total number of patient-years after transplantation. We compared this ratio with the advised ratio of 1.0 smear per patient-year. The ratio of cervical smears performed before the first low- or high-grade squamous intraepithelial lesion (SIL; after which patients get more frequent follow-up smears according to national guidelines) was calculated by dividing the total number of cervical smears until the first pathological smear by the number of patient-years in that period. Age-adjusted prevalence rates of (pre)malignancies in the studied cohort were calculated per 100 000 individuals using the European Standard Population (as defined by the WHO) for comparative purposes. Data on prevalence of (pre)malignancies in the general population were obtained from national and international literature and from the Netherlands Cancer Registry.

Statistical analysis

Descriptive statistics were used to reproduce study results as percentages, means, medians and standard deviations. To test the correlation between the occurrence of skin cancer and lower genital tract malignancies in female RTRs, a Spearman Rho correlation coefficient was determined. Different ratios of smears per patient-year were compared using Student's *t*-tests. Calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA). *P*-values of <0.05 were considered statistically significant.

Results

The baseline characteristics of the 224 female RTRs are shown in Table 1. The number of transplantations was almost equally divided over the years, and predominantly carried out between the age of 41 and 60 years: the median age of patients at transplantation in our cohort was 44.6 years (range: 5.1–74.6 years).

Table 1. Baseline characteristics of renal transplant recipients.

	No. patients
	N (%)
Age at transplantation (years)	
0–18	19 (8.5)
19–40	79 (35.3)
41–60	104 (46.4)
>60	22 (9.8)
Year of transplantation	
1991	47 (21.0)
1992	38 (17.0)
1993	37 (16.5)
1994	51 (22.8)
1995	51 (22.8)
Total renal transplantations	
1	175 (78.1)
2	43 (19.2)
>2	6 (2.7)

A minority of patients ($n = 49$, 21.9%) went through more than one RT. Ten patients were lost to follow-up because of transplantation in another transplantation centre ($n = 5$), emigration ($n = 1$) or unknown reasons ($n = 4$). Median duration of follow-up was 12.8 years (range: 0–17.6 years) and the median duration of immunosuppression was 11.0 years (range: 0–29.6 years). At the end of the follow-up period, 123 patients (55%) were still alive. One hundred and one patients (45%) were deceased, particularly because of fulminant infections and cardiovascular diseases. Median time between transplantation and death was 6.0 years (range: 0–14.9 years).

Our cohort consisted of 21 RTRs with less than 1 year follow-up after their 18th year of life. One patient died before the age of 18. Consequently, 202 RTRs remained available for further analysis. Of these patients, 128 women (63.4%) underwent at least one cervical smear while 74 patients (36.6%) never had a cervical smear after their transplantation. There was only one patient who had a mean screening ratio of 1.0, which implies that the cervical smears were performed at least once a year. Seventy-four patients were screened in accordance with the recommended screening in the general population (once in 5 years). A mean screening ratio lower than 0.2 was seen in 53 patients, which means that these patients were screened with an interval greater than the recommended population screening interval. Taking all cervical smears (449) and patient-years after transplantation (2198) into account, the overall cervical smear/patient-year ratio after transplantation was 0.2. This ratio is significantly less than the recommended screening ratio of 1.0 for female

RTRs ($P < 0.001$), but comparable with the national guidelines for women aged 30–60 years. The mean screening ratio in all RTRs ($n = 202$) before the detection of any low- or high-grade SIL was 0.13.

We counted 17 histopathological examinations of the cervix performed after an abnormal cervical smear in 11 patients. See Figure 1 for an overview. CIN after renal transplantation was detected in eight patients (3.6%). One patient developed CIN 3 and subsequently CIN 1, a year later. One patient of our cohort developed cervical carcinoma (0.4%). Two patients developed meta- or hyperplasia of the uterine cervix and were excluded from further analysis on cervical pathology. The median interval between first transplantation and the development of CIN was 12.3 years (range: 3.5–13.7 years). In the eight RTRs with CIN, the median interval between the first transplantation and the first smear performed was 1.2 years (range: 0.2–12.5 years).

The cervical carcinoma developed 5 years after transplantation at the age of 38 years. The first cervical smear in this patient was performed because of irregular blood loss. Histopathology of a biopsy after colposcopy showed a cervical cancer. The screening ratio before the detection of any low- or high-grade SIL was 0.08 in the RTRs with cervical pathology ($n = 9$), which did not differ significantly from the ratio in RTRs without cervical pathology (0.13; $n = 193$) ($P = 0.60$). The mean number of cervical smears per patient-year after RT was 0.53 (SD ± 0.31, range: 0.1–1.0), which is significantly higher when compared with RTRs without cervical pathology ($P < 0.001$). No information is available about possible complaints that may have led to cervical cytology.

Eight VIN lesions were detected in four of our RTRs during the study period. All of these lesions were HPV-related VIN types (*usual* VIN). The mean age at presentation of the first VIN lesion was 40.3 years (SD ± 4.6 years). The median interval between first RT and first VIN lesion was 13.3 years (range: 5.1–14.4 years). SCC of the vulva developed in two patients of our cohort: 10.2 and 13.8 years after transplantation. No cases of vaginal carcinoma occurred in the female RTRs. There was only one patient with vaginal intraepithelial neoplasia (VAIN), which occurred simultaneously with SCC of the vulva. Table 2 compares the standardized, age-adjusted prevalence rates of CIN, cervical carcinoma and vulvar carcinoma between transplant recipients and the general population. We were not able to present this comparison for VIN, as no publications concerning prevalence rates of VIN in the general population exist.

Table 2. Comparison of different prevalence rates between renal transplant recipients and the general population.

	Comparison of prevalence rates			
	Transplant recipients		General population	Increased risk
	N (%)	Prevalence*	Prevalence*	Rate ratio†
CIN	8 (3.6)	3454.8	600–2000‡	1.7–5.8
Cervical carcinoma	1 (0.4)	280.0	88.9§	3.2
Vulvar carcinoma	2 (0.9)	717.5	14.4§	49.8

CIN, cervical intraepithelial neoplasia.
*European Standardized Rate, per 100 000.
†Rate ratio is the age-adjusted rate in RTRs divided by the rate in the general population.
‡Obtained from literature references [25,30,31].
§Obtained from the Netherlands Cancer Registry.

Table 3 shows an evaluation of the cervical smears and histology of cervix and vulva after transplantation. The majority of the lower genital tract (pre)malignancies occur after a median interval of 11.5 years (range: 5–13.5 years). At least seven RTRs hardly received screening smears before the development of serious cervical/vulvar pathology. In three patients, a relatively short period of time (approximately 2 years) elapsed between the transformation of benign cervical smears to low-grade SIL, leading to CIN in two patients. In the third patient, a vulvar carcinoma and VAIN were diagnosed after the low-grade SIL was detected.

Forty-two out of 224 RTRs (18.8%) developed at least one cutaneous malignancy. Twenty-nine RTRs developed 63 SCCs on nongenital skin. The remaining part of the skin tumours were mostly BCCs. The median interval

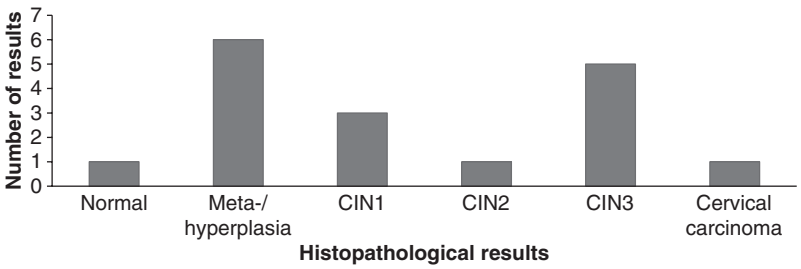

Figure 1 Cervical histopathological examinations in 11 patients after renal transplantation. CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3.

Table 3. Cervical smears and histology of cervix and vulva after transplantation.

	Years after Tx																									
	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16
Pt																											
1																			L		L-CIN3						
2					N				N											L-CIN0	N	L-CIN3		N	N	N	
3																	L-CIN3	N			N	N		N	N		
4	AU		N				AU		AU-CIN3			N	N	N-VIN3	VIN3				N				N				
5	AU				N			L		AU-CIN1		L	L			L				L-CINnVIN3-N				L-VIN3-L		L	
6		N							N						L	L					H-CIN3	AU		AU-CIN1VIN2	AU	L	
7	L-CIN0-L	L-CIN1	N																								
8																		AU	AU	L-CIN2							
9				L H	CxCa																						
10					VIN1			N					VIN3		L VCa												
11							N										N								L Vca+VAIN		

N, normal smear result; AU, cytologically determined atypical squamous cells of undetermined significance; L, cytologically determined low-grade squamous intraepithelial lesion of the cervix; H, cytologically determined high-grade squamous intraepithelial lesion of the cervix; CINn, histologically determined normal cervix; CIN0, histologically determined meta- or hyperplasia of the cervix; CIN1, histologically determined cervical intraepithelial neoplasia grade 1; CIN2, histologically determined cervical intraepithelial neoplasia grade 2; CIN3, histologically determined cervical intraepithelial neoplasia grade 3; VIN1, vulvar intraepithelial neoplasia grade 1; VIN2, vulvar intraepithelial neoplasia grade 2; VIN3, vulvar intraepithelial neoplasia grade 3; VCa, vulvar carcinoma; CxCa, cervical carcinoma; |, Deceased; ||, End of follow up.

Table 4. Correlation between lower genital tract (pre)malignancies and skin cancer in renal transplant recipients (absolute count).

Type	Patients (*n*)	VIN	CIN	VAIN	CxCa	VulvaCa	SkinCa
VIN	4		3	0	0	1	0
CIN	8	3		0	0	0	0
VAIN	1	0	0		0	1	1
CxCa	1	0	0	0		0	0
VulvaCa	2	1	0	1	0		1
SkinCa	42	0	0	1	0	1	

VIN, vulvar intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; CxCa, cervical carcinoma; VulvaCa, vulvar carcinoma; SkinCa, skin cancer.

between transplantation and the first skin malignancy was 6.2 years (range: 0.3–16.5 years).

There was only one patient with skin cancer who also had vulvar pathology in combination with a VAIN lesion. No significant correlation between skin cancer and lower genital tract (pre)malignancies was found in our RTR population (Spearman Rho = −0.044, SD ± 0.058; $P = 0.508$). The absolute numbers of (pre)malignancies can be found in Table 4.

Discussion

Our study shows that cervical screening smears in RTRs are not being performed in accordance with the recommended interval of once a year. We confirmed the elevated risk for RTRs to develop vulvar and cervical (pre)malignancies, which developed 5–13 years after transplantation. It appears that skin malignancies and gynaecological (pre)malignancies, which are both considered to be related to HPV and more frequent after RT, are not related with each other; of all women who developed skin malignancies (19%), only one vulvar carcinoma combined with vaginal dysplasia was diagnosed.

We investigated the performance of cervical smears in RTRs. The recommended screening interval for RTRs as suggested in previous publications varies between 6 and 12 months (1–2 smears per patient per year) [25–27], although there is no evidence that cervical screening with a short interval (when compared with the national screening programme in the Netherlands: between age of 30–60; once in 5 years) will either decrease the incidence of lower genital tract (pre)malignancies or improve the prognosis.

The interval of the smears performed in our cohort was comparable with the national screening programme in the Netherlands, with a mean number of 0.2 smears per patient per year (one smear once in 5 years for each patient). This low number of smears (when compared with the guideline of yearly smears) might be explained

by several factors. First, the coverage rate of the national screening programme only reaches 77% [29], which might be explained by lack of motivation or fear for screening. Therefore, we could not expect a 100% coverage rate in our RTR population. Furthermore, it might be possible that the advise for yearly cervical smears is not well implemented in the daily practice of the nephrologist or the general practitioner, because of lack of evidence for this policy or because of plain inattention. Moreover, patients may avoid cervical screening either because they underestimate the importance of screening or because they find the investigation aggravating.

The ratio of the smears that were performed before the first low- or high-grade SIL was lower (0.13) than the overall screening ratio (0.2). In the years after an abnormal smear, the ratio of smears was higher attributable to the follow-up smears that are required to be performed with more regular intervals according to national guidelines.

We detected CIN lesions in eight patients (3.6%). Previous publications reported the occurrence of cervical dysplasia in 1.28%, 2.0% and 0.6% of the general population in the Netherlands, USA and Canada respectively [25,30,31]. On the basis of these percentages, it seems that our RTRs have at least a twofold to sixfold increased risk of developing CIN, when compared with the general population. This result supports the findings of earlier investigations that showed that the prevalence of CIN is increased in RTRs [27,32].

Only four patients with dysplasia of the vulva were found. All of the lesions were HPV-related VIN types. Likely, VIN is underreported, because there is no screening instrument for VIN resulting from its low incidence with limited malignant potential. Moreover, RTRs are not routinely asked for vulvar complaints and no standard gynaecological examination is performed. Although pruritus is the most common symptom of VIN, this symptom is frequently misclassified, as RTRs are prone to develop candidiasis, which is the most frequently made diagnosis in case of pruritus. Finally, it might be possible that suspicious lesions are not always histopathologically examined.

Cervical carcinoma was diagnosed in only one patient. Comparing this number with the rates of cervical carcinomas in the age-adjusted standardized general population, the RTRs in the studied cohort have at least a threefold higher risk for developing cervical carcinomas than the general population. A limited number of earlier studies report comparable standardized incidence rates between 3.3 and 8.5 [5,6,33]. The cervical carcinoma in our study developed 60 months after transplantation, which agrees with the data reflected in other studies (38–102 months) [5,34].

Carcinomas of the vagina are rare, with a prevalence of 1.7 per 100 000 in the Dutch general population. Based on recently published standardized incidence rates for RTRs for developing vaginal carcinomas (15.8 and 36.0) [5,6], we could have expected 0.06 to 0.14 cases of vaginal carcinoma in our cohort. It is therefore not surprising that we did not diagnose any patients with a vaginal malignancy.

Two patients were diagnosed with SCCs of the vulva, which is an extremely rare disease. This is a 50-fold increased risk compared with the European Standardized Rate of vulvar carcinomas in the general population. Both vulvar carcinomas had usual VIN (related to HPV infection) in the adjacent tissue, which proves a causal relationship between HPV and vulvar carcinoma just like in cervical cancer. Two studies concerning solely vulvar carcinomas demonstrated a 25- to 40-fold increased risk for RTRs to develop vulvar carcinomas [5,6]. An epidemiological study from Sweden published in 1986 documented a 100-fold increased risk of developing carcinomas of the vulva and anus compared with the general population [8].

We observed a median interval of 12.3 years (range: 3.5–13.7 years) between the first transplantation and the development of CIN. Three earlier studies found an average interval between the beginning of immunosuppressive medication and CIN to be between 38 and 47 months [25,27,34]. The longer interval in our study might be partly explained by demographic differences of the patients in the cohorts studied and use of other immunosuppressive medication. The vulvar SCCs of our cohort developed after an average interval of 144 months (SD ± 30.5 months), which seems to correspond with data reported in the literature [5,8].

In the nine patients with CIN and cervical carcinoma significantly more cervical smears were performed (0.53 per patient per year; $P < 0.001$) compared with the RTRs without cervical (pre)malignancies. Two explanations for this result can be given. First, a considerable number of low- and high-grade SILs originated in these patients before the CIN lesions were diagnosed; all patients with abnormal cytology or histology will undergo more frequent follow-up smears. Second, patients with cervical dysplasia might have had more gynaecological complaints when compared with the general population. Unfortunately, no information is available on possible gynaecological complaints in this cohort. The screening ratio before the detection of any low- or high-grade SIL in this group of RTRs did not differ significantly from the ratio in RTRs without cervical pathology. Nevertheless, at least five RTRs were screened only barely before the diagnosis of serious cervical pathology. Through more frequent follow-up with more smears some of

these cervical (pre)malignancies could have been detected earlier.

Immunosuppression has direct carcinogenic effects, it predisposes patients to develop infections and potentiates oncogenic viruses like HPV. Based on the results of earlier publications, it is very likely that HPV infections play a prominent role in the higher incidence of lower genital tract (pre)malignancies in RTRs [8,25,32,35,36]. Halpert *et al.* [25] presented higher rates of HPV infections in transplant patients (8.5–17.1%) compared to the general population (1.85%). This finding was confirmed by Brown *et al.*, who reported a significant difference in the presence of HPV-positive lower genital tract neoplasms between female RTRs and an immunocompetent group. For example, 100% of the vulvar lesions in RTRs were HPV-positive compared to 21–57% in immunocompetent individuals [35]. Furthermore, several studies showed a significantly higher rate of infections with hrHPV subtypes 16 and 18 in lower genital tract malignancies of RTRs when compared with the general population [32,35]. Paternoster *et al.* [36] noted a constant association between those hrHPV types and lower genital tract intraepithelial lesions.

Screening for cervical/vulvar pathology and hrHPV infections just before transplantation is not a common procedure, because the exact timing of transplantation is not planned ahead. As more and more elective kidney transplantations with a kidney from a living donor are performed, it might be possible to introduce a screening just before the date of transplantation for cervical/vulvar pathology and presence of hrHPV infections.

The exact mechanism underlying the high prevalence of HPV infections in RTRs remains unclear. Normally, the majority of HPV infections are transient resulting from clearance from the HPV-infected epithelium. It might be possible that RTRs have a diminished ability to clear new HPV infections because of the impairment of immunological surveillance. This, in combination with high prevalence of HPV subtypes 16 and 18, might additionally lead to more aggressive growth of malignancies. However, it is not likely that RTRs acquire new HPV infections as, based on the average age at transplantation, the majority of the RTRs already had their sexarche long before transplantation. Besides, transplant recipients may be sexually less active than the average population as a result of the burden of their disease. Another, more plausible explanation might be that the beginning of immunosuppressive medication may activate a latent HPV infection, resulting in a rise of the viral load [37].

The development of cutaneous malignancies, and the interval after which they develop, does not seem to be associated with the development of lower genital tract malignancies and *vice versa*. It might be possible that different HPV types are responsible for the occurrence of malignancies in the genital area and for neoplasms of other skin areas, although the role of HPV in skin cancer remains unclear [38]. Furthermore, other factors (like UV radiation) might play a more important role in the development of nongenital skin malignancies.

Our investigation was conducted as a single-centre study, which implicates a relatively small number of patients. On the other hand, the relatively long follow-up after transplantation is an important strength of our study, as malignancies such as lower genital tract (pre)malignancies hardly occur in the first 5 years after transplantation. A limitation of the retrospective design of our study is the lack of data about lifestyle risk factors (e.g. smoking, riskful sexual behaviour and skin cancer-related risks) and the exact medication schedules (many different schedules with multiple conversions during follow-up). Further prospective investigations and the use of a standardized questionnaire might eliminate this possible bias.

Annual screening for cervical cancer in RTRs using conventional cytology recently proved to be cost-effective [39]. Yearly cervical smears might be combined with a thorough vulvar inspection. Our data suggest that the majority of patients with cervical pathology is diagnosed 9 years after RT. Therefore, it is justified, in our opinion, to postpone the recommended yearly screening to approximately 3 years after RT. This is allowed under the condition that

Table 5. Suggested gynaecological standard screening procedure of cervix and vulva for female renal transplant recipients.

		Post-transplantation	
	Pretransplantation	Normal*	Abnormal†
Start	0–6 months before RT	Approximately 3 years after RT	Immediate after RT
Frequency	Once	Once a year	Once a year
Screening	Routine‡	Routine‡	According to current gynaecological guidelines; thereafter routine‡

RT, renal transplantation.

*In case of normal pretransplant screening result.

†In case of abnormal pretransplant screening result.

‡Routine screening comprises anamnesis, inspection and cytology (smear).

patients are screened on cervical and vulvar pathology and HPV infections before their RT, as pre-RT cervical/vulvar pathology might worsen when immunosuppression is started. This way the 'doctor-density' can be limited in the first years after transplantation when patients and doctors are focussed on preservation of kidney function. If RTRs have abnormal screening results before transplantation, a more intense follow-up schedule should be carried out immediately after RT. Table 5 recapitulates the suggested gynaecological standard screening procedure for female RTRs. It is important to keep in mind that there is no evidence yet that this schedule will decrease the incidence of female genital malignancies.

To conclude, this study emphasizes the need for more regular screening for potentially lethal malignancies of the lower genital tract in RTRs, as close and careful monitoring and treatment of suspected lesions may prevent more serious pathology. Additionally, RTRs have to be advised properly about the importance of regular screening and self-examination of the vulvar region.

Authorship

KAPM, JAH and MMR: research design, performance of the research, collection of data, data analysis and the writing of the paper. PCMK and LFAGM: writing of the paper. AJH: research design and the writing of the paper.

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