BJD
British Journal of Dermatology

Stop routine screening for associated malignancies in cutaneous noninvasive vulvar Paget disease?*

M. van der Linden,[1] M.S. Schuurman,[2] J. Bulten,[3] L.F.A.G. Massuger,[1] J. IntHout,[4] M.A. van der Aa[2] and J.A. de Hullu[1]

[1]Department of Obstetrics and Gynaecology (791), [3]Department of Pathology (812) and [4]Department for Health Evidence (133), Radboud Institute for Health Sciences; Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands
[2]Department of Research, Comprehensive Cancer Organisation the Netherlands (IKNL), Utrecht, the Netherlands

Linked Comment: Cooper and Matin. *Br J Dermatol* 2018; **179**:1242.

Correspondence
Michelle van der Linden.
E-mail: Michelle.vanderLinden@radboudumc.nl

Accepted for publication
11 June 2018

Funding sources
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of interest
None to declare.

Parts of these data have been presented previously, at the 11th Congress of the European College for the Study of Vulval Disease, 15–17 September 2016, Turin, Italy and the 16th Biennial Meeting of the International Gynecologic Cancer Society, 29–31 October 2016, Lisbon, Portugal.

*Plain language summary available online

DOI 10.1111/bjd.16894

Summary

Background Vulvar Paget disease (VPD) is extremely rare and thought to be associated with other malignancies.
Objectives To evaluate the risk of developing breast, intestinal and urological malignancies in patients with VPD compared with the general population, and in particular to focus on the risk of malignancy in patients with cutaneous noninvasive VPD.
Methods Data on the oncological history of patients with any type of VPD between 2000 and 2015 were obtained from PALGA, a nationwide archive containing all pathology reports in the Netherlands. Follow-up data and a control group from the general population were obtained from the Netherlands Cancer Registry. After correction for age and calendar year at time of diagnosis, standardized incidence ratios (SIRs) for the first 3 years after VPD diagnosis were estimated with 95% confidence intervals (CIs).
Results We identified 199 patients with a first diagnosis of VPD [164 noninvasive, 35 (micro)invasive] between 2000 and 2015. The SIR of developing an associated malignancy in the first 3 years after diagnosis was 4·67 (95% CI 2·66–7·64). This was due mainly to the high incidence of intestinal malignancies among patients with secondary VPD. Subgroup analysis for cutaneous noninvasive VPD did not reveal a significantly increased risk for associated malignancies: SIR 2·08 (95% CI 0·76–4·62).
Conclusions Of our patients with VPD, 76·9% were diagnosed with cutaneous noninvasive VPD, and this group has no increased risk for developing malignancies of the breast, intestine or urological tract. Our study suggests that routine screening for these malignancies in patients diagnosed with cutaneous noninvasive VPD may not be necessary.

What's already known about this topic?

- In the past, all types of vulvar Paget disease (VPD) were associated with breast, intestinal and urological malignancies.

What does this study add?

- This study challenges the long-held assumption that primary cutaneous noninvasive VPD is associated with these malignancies.
- This population-based study showed no increased risk of malignancies of the breast, intestine or urological tract in patients with cutaneous noninvasive VPD.
- There is no evidence to support routine screening for underlying malignancies in patients with cutaneous noninvasive VPD.

Vulvar Paget disease (VPD) is a rare skin disorder, most commonly seen in postmenopausal white women.[1] VPD causes itching or burning erythematosquamous plaques and is diagnosed when typical Paget cells are seen in the epidermis. VPD can be classified according to origin and invasion: it can be primary and of cutaneous origin (type 1) or secondary to an intestinal (type 2) or urological (type 3) malignancy.[2] Most cases of primary disease (i.e. cutaneous) are noninvasive (type 1a). Cutaneous VPD can invade through the basal membrane (type 1b) or be seen in conjunction with a vulvar adenocarcinoma (type 1c). The difference between primary and secondary VPD cannot be made on histopathological assessment alone.[3] The aetiology and origin of Paget cells remain unknown.[1]

VPD has been considered to be associated with malignancies of the breast, intestinal tract and urological tract.[4,5] Some consider VPD secondary to intestinal or urological malignancies a pagetoid spread rather than a separate entity. Therefore, some consider primary noninvasive VPD to be the only 'true' VPD, and secondary VPD a 'pagetoid phenomenon'.[6–9]

In the late 19th century, skin lesions like the nipple ulceration associated with breast cancer became known as extramammary Paget disease (EMPD).[10–12] The histological characteristics of EMPD resemble those of mammary Paget disease, raising the suspicion of a comparable pathogenesis.[13] The term VPD is used for EMPD specifically localized on female genital skin. In 1975, Friedrich *et al.* analysed 11 published articles, including 78 patients with VPD, of whom 14 (18%) were diagnosed with breast cancer around VPD diagnosis.[4] The authors concluded that screening for breast cancer should be standard care in patients with VPD.

In 1985, Chanda summarized 197 cases of EMPD in a literature review.[5] Of these patients, 128 had VPD. Simultaneous occurrence of a malignancy and VPD was reported in 12% of cases, and overall 29% of the patients were reported to have had a malignancy of either the breast or gynaecological, intestinal or urological tracts. The true association between these so-called 'associated' malignancies and EMPD was questioned, as most malignancies were not diagnosed at the same time as EMPD, and the two diseases were not shown to have a parallel course. However, Chanda concluded that clinicians should consider a search for malignancies of the gastrointestinal tract in cases of perianal EMPD, or for genitourinary malignancies in genital EMPD. Ever since, the assumed association between VPD and malignancies has been generally accepted. Nowadays, international guidelines advise that women with VPD should be screened for associated malignancies.[14,15] However, the extent and timing of screening and the preferred diagnostics are not exemplified.

Our recent analysis of publications describing 10 or more patients with VPD suggests that breast, intestinal and urological malignancies in patients with VPD are rare: 3·2% had a history of breast cancer, 2·2% of intestinal cancer and 3·9% of urological cancer.[1]

The aim of this study was to estimate the risk of developing breast, intestinal or urological malignancies in all patients with (non)invasive VPD in comparison with the general population, and moreover to evaluate whether all patients with VPD should be routinely screened for malignancies.

Patients and methods

Patient selection

The PALGA database, a nationwide network and registry of histo-and cytopathology in the Netherlands with national coverage since 1991, was searched for all cases of VPD and vulvar adenocarcinomas. All cases with a first diagnosis of VPD, noninvasive and invasive, between 1 January 2000 and 31 December 2014 were included. We excluded cases of adnexal gland tumours, mammary-like gland tumours or vulvar adenocarcinomas without evidence of VPD. Patients with vulvar localization of an intestinal or urological malignancy were also excluded.

We recorded the type of VPD as reported in the pathology report: primary VPD (of cutaneous origin), which can be distinguished with the following immunohistochemical (IHC) profile: $CK7^{+}$ $CK20^{-}$; secondary VPD of intestinal origin, which can be distinguished with the IHC profile $CK7^{-}$ $CK20^{+}$ $CDx2^{+}$; and secondary VPD of urological origin with the IHC profile $CK7^{\pm}$ $CK20^{+}$ and uroplakin-III^{+}. Pathology reports that concluded with 'vulvar Paget disease' but in which IHC results were not available were reported as VPD not otherwise specified (NOS); these were assumed to be primary VPD, as this is the most common type.[1] Follow-up data were retrieved via the Netherlands Cancer Registry (NCR), which has national coverage since 1989 and registers all malignancies in the Netherlands. If follow-up data were not available from the NCR, we used the date of the last pathology report as the last date of follow-up.

Associated malignancies

Patients with VPD diagnosed with associated malignancies were identified from the pathology reports, as were the age at diagnosis of the associated malignancy and the date of diagnosis.

All invasive breast, intestinal or urological tumours were defined as being potentially associated with VPD. Besides invasive tumours, ductal carcinoma *in situ* of the breast was also included, because it is considered to be a malignancy. Intestinal malignancies included tumours of the colon, rectum, rectosigmoid junction and anus. Urological malignancies included tumours of the kidney, ureter, bladder and urethra.

All women with histological confirmation of one or more of the aforementioned tumours between 2000 and 2015 were selected from the NCR. The total number of women living in the Netherlands by age category and calendar year was obtained from Statistics Netherlands.

Statistical analysis

The incidence of associated malignancies in women with VPD was compared with the incidence of these malignancies in women from the general population. The expected incidence was extracted from data from the NCR and population data from Statistics Netherlands. Risks were stratified by age and calendar-year diagnosis of malignancy. The standardized incidence ratio (SIR) was estimated as the observed incidence of an associated malignancy in women with VPD divided by the expected incidence in women from the general population. SIRs were estimated until 36 months after VPD diagnosis, as we assumed that malignancies diagnosed within 36 months after VPD diagnosis might have already been present, possibly as a premalignancy, at the time of VPD diagnosis. Furthermore, this time frame ensured a reasonable sample size for the study cohort. We performed subgroup analyses for cases reported as primary noninvasive VPD only. Statistical models were based on a Poisson distribution using person-time at risk as an offset.

Person-time at risk was calculated as the time from the date of first VPD diagnosis to the date of first histological confirmation of the associated malignancy of interest, date of death or date of last follow-up, whichever came first. Follow-up data were available up to 1 January 2015. Analyses were performed using Stata/SE 13.0 (StataCorp, College Station, TX, U.S.A.). SIRs and their 95% confidence intervals (CIs) were based on the Mid-P exact test[16] and were calculated using the OpenEpi Standardized Mortality Ratio Calculator (OpenEpi version 3.01).[17] The figures were designed using Microsoft Office Excel 2007 and Visio 2007.

Results

Population

In total, 199 women with a first diagnosis of VPD in the Netherlands (around 17 million inhabitants) between 2000 and 2015 were identified from the pathology reports. Noninvasive VPD was diagnosed in 164 patients (82·4%), microinvasive VPD in 12 (6·0%) and invasive VPD in 23 (11·6%). An overview of the types of VPD per diagnosis is presented in Table 1. We considered NOS as primary cutaneous VPD in further analyses. The median age at diagnosis was 74 years (range 40–97), and did not differ between patients with noninvasive and (micro)invasive disease ($P = 0·84$). The median follow-up time of all patients was 36 months (range 0–182) after VPD diagnosis.

Table 1 Overview of types of vulvar Paget disease (VPD) per diagnosis

	Noninvasive VPD	(Micro)invasive VPD	Total
NOS	133 (66·8)	25 (12·5)	158 (79·4)
Type 1, cutaneous	20 (10·1)	8 (4·0)	28 (14·1)
Type 2, intestinal	8 (4·0)	2 (1·0)	10 (5·0)
Type 3, urological	3 (1·5)	0	3 (1·5)
Total	164 (82·4)	35 (17·6)	199 (100)

Values are n (%). NOS, not otherwise specified.

Associated malignancies

Of all patients, 27 (13·6%) were diagnosed with breast cancer, 17 (8·5%) with an intestinal malignancy and nine (4·5%) with a urological malignancy before, simultaneously with or after the diagnosis of VPD (Table S1; see Supporting Information). Three patients (1·5%) had a history of two associated malignancies.

Eighteen of the 27 patients (67%) with breast cancer received this diagnosis before they were diagnosed with VPD; the median time difference was 102 months (range 3–213). Three of these 18 patients were diagnosed with breast cancer within 3–6 months prior to the VPD diagnosis, which was primary noninvasive in all three. Eight of the 27 patients (30%) were diagnosed with breast cancer after their VPD diagnosis, and the median time difference between diagnoses was 46 months (range 1–116). Two of these eight patients were diagnosed with breast cancer within 2 months after the VPD diagnosis, which was primary noninvasive in both. It is uncertain whether these malignancies were detected with the VPD screening protocol. The time of breast cancer diagnosis in relation to VPD diagnosis was unknown for one patient.

In six (35%) of the 17 patients with intestinal malignancies and VPD, the intestinal malignancy was diagnosed before they were diagnosed with VPD, with a median time difference of 201 months (range 96–272). Two of the 17 patients (12%) were diagnosed with the intestinal malignancy and VPD simultaneously, both having type 2 VPD. Nine patients (53%) were diagnosed with an intestinal malignancy at a median time difference of 16 months (range 1–90) after VPD diagnosis. Four of these nine patients (44%) had a urological malignancy before the VPD diagnosis, with a median time difference of 152 months (range 103–249). Urological malignancies were diagnosed after VPD in the other five patients (56%), after a median of 50 months (range 11–147).

Figure 1(a) shows the time differences between diagnoses of VPD and the associated malignancies for all patients, and Figure 1(b) shows the time differences between VPD diagnosis and the associated malignancies for the subgroup of primary noninvasive VPD. The time difference between VPD diagnosis and urological malignancies, for example, was between 250 months prior to and 150 months after VPD diagnosis.

Risk of developing an associated malignancy after any type of vulvar Paget disease diagnosis

The cumulative risk of developing any of the associated malignancies within 36 months after diagnosis of any type of VPD was increased, with an SIR of 4·67 (95% CI 2·66–7·64). This increased risk was based mainly on the statistically significantly increased risks of developing an intestinal malignancy, SIR 8·18 (95% CI 3·99–15·0), and a urological malignancy, SIR 6·67 (95% CI 1·19–22·0). The SIR for developing a breast

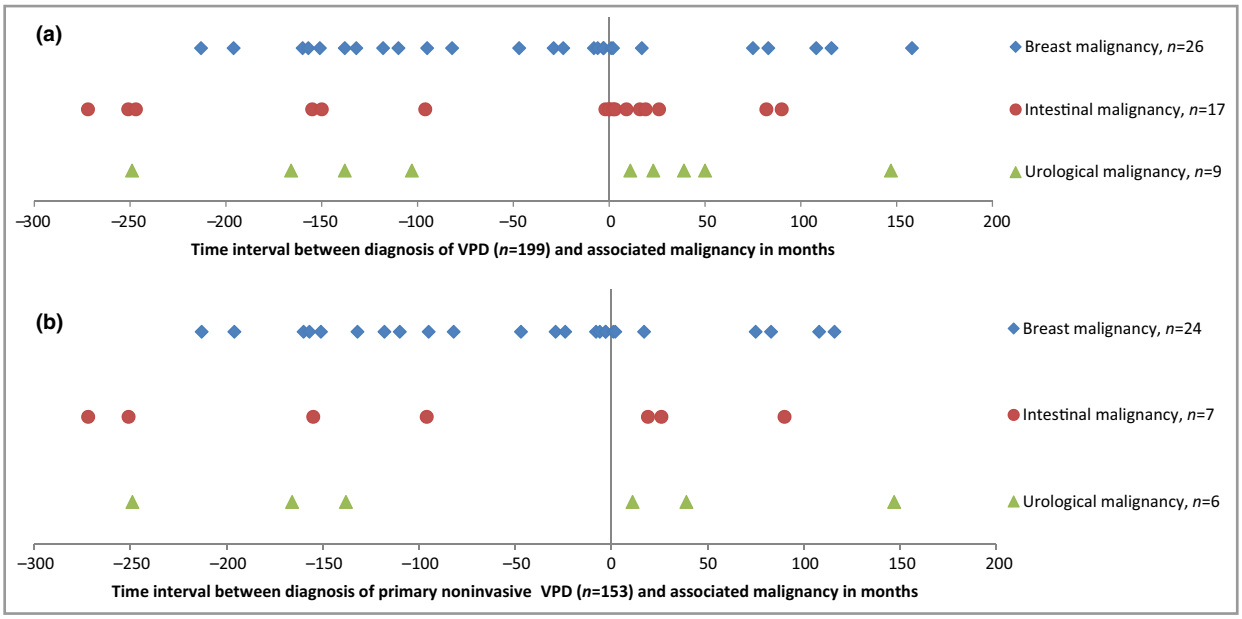

Fig 1. (a) Time interval between diagnosis of vulvar Paget disease (VPD) (all types) and associated malignancy. (b) Time interval between diagnosis of noninvasive primary VPD and associated malignancy.

malignancy was not statistically significant: SIR 2·00 (95% CI 0·51–5·44) (Table 2).

Risk of developing an associated malignancy after diagnosis of primary noninvasive vulvar Paget disease

Table 3 shows the analysis restricted to patients with primary noninvasive VPD. The SIR for developing any of the associated malignancies was 2·08 (95% CI 0·76–4·62). The SIR for breast cancer was 2·50 (95% CI 0·64–6·80), the SIR for intestinal malignancies was 1·11 (95% CI 0·06–5·48) and the

Table 2 Risk of developing an associated malignancy within 3 years after diagnosis, all types of vulvar Paget disease (VPD)

	Year after VPD	Observed	Expected	SIR	95% CI
Cumulative risk	1	9	1·2		
	2	4	1·0		
	3	1	0·8		
		14	3·0	4·67*	2·66–7·64
Breast cancer	1	2	0·6		
	2	1	0·5		
	3	0	0·4		
		3	1·5	2·00	0·51–5·44
Intestinal malignancy	1	6	0·4		
	2	2	0·4		
	3	1	0·3		
		9	1·1	8·18*	3·99–15·0
Urological malignancy	1	1	0·1		
	2	1	0·1		
	3	0	0·1		
		2	0·3	6·67*	1·12–22·0

SIR, standardized incidence ratio; CI, confidence interval. *Statistically significant SIR.

Table 3 Risk of developing an associated malignancy, non-invasive primary VPD

	Year after VPD	Obs	Exp	SIR	95% CI
	1	3	1·0		
	2	2	0·8		
	3	0	0·6		
Cumulative risk		**5**	**2·4**	**2·08**	**0·76–4·62**
	1	2	0·5		
	2	1	0·4		
	3	0	0·3		
Breast cancer		**3**	**1·2**	**2·50**	**0·64–6·80**
	1	0	0·4		
	2	1	0·3		
	3	0	0·2		
Intestinal malignancy		**1**	**0·9**	**1·11**	**0·06–5·48**
	1	1	0·1		
	2	0	0·1		
	3	0	0·1		
Urological malignancy		**1**	**0·3**	**3·33**	**0·17–16·44**

Risk of developing an associated malignancy within 3 years after diagnosis with non-invasive primary VPD. VPD: vulvar Paget disease. Obs: observed cases per year and in total. Exp: expected cases per year and in total. SIR: standardized incidence ratio. 95%CI: 95% confidence interval. Statistically significant SIRs are marked with an asterisk (*).

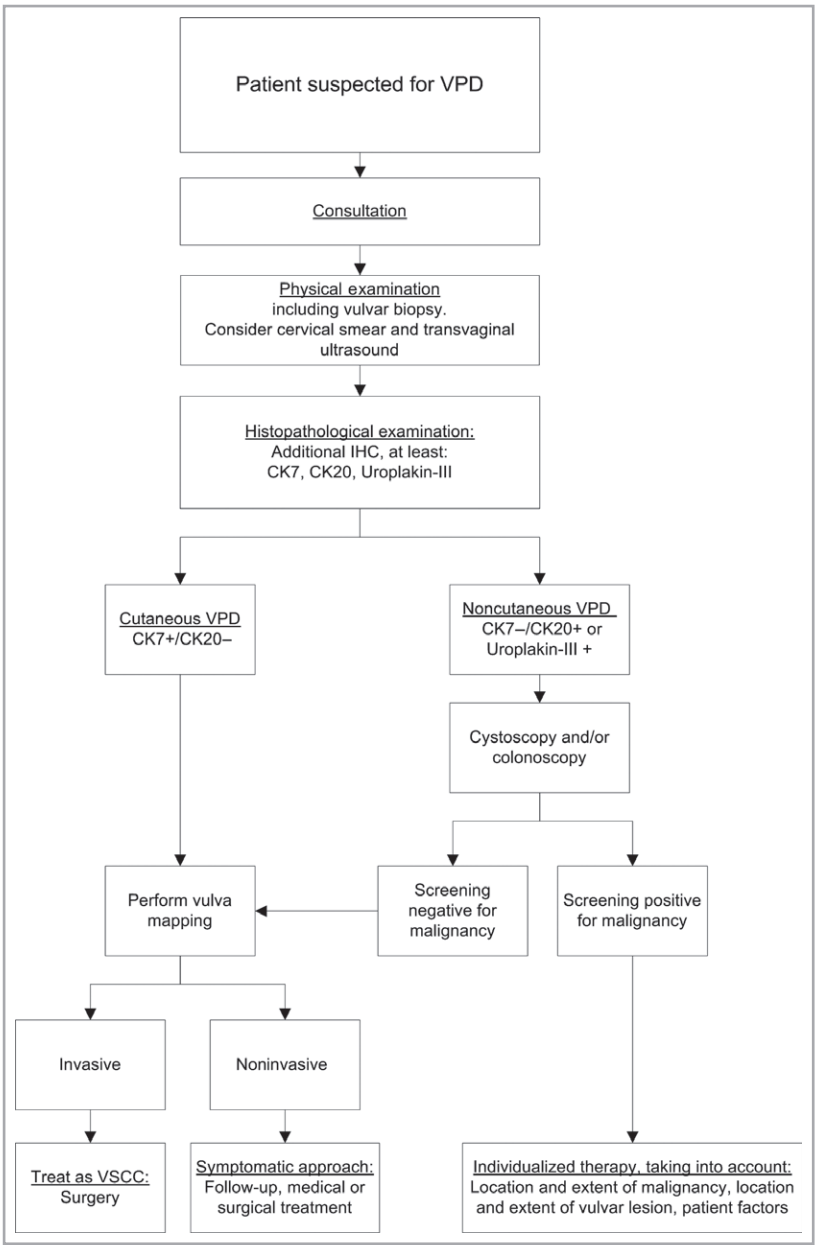

Fig 2. Flowchart for the work-up of newly diagnosed patients with vulvar Paget disease (VPD). Vulvar mapping ideally consists of several punch biopsies taken from all suspicious lesions; histological slides are reviewed under the microscope and additional immunohistochemistry (IHC) is performed on all of the slides. VSCC, vulvar squamous cell carcinoma.

SIR for urological malignancies was 3·33 (95% CI 0·17–16·4). None of these SIRs was statistically significant.

Discussion

This is the first population-based study investigating the incidence of possibly associated malignancies in patients with VPD. The risk of developing an associated malignancy within 3 years after VPD diagnosis of any subtype is significantly increased compared with the general Dutch female population. However, subgroup analysis of the patients with primary noninvasive VPD showed no significantly increased risk of developing one of the associated malignancies. Therefore, there is no evidence for a routine screening programme for these malignancies in patients diagnosed with primary noninvasive VPD.

All patients who were diagnosed with an intestinal or urological malignancy around the time of VPD diagnosis were diagnosed with secondary VPD (type 2 or 3). In patients with primary (i.e. cutaneous), noninvasive VPD the time interval between VPD diagnosis and the diagnosis of the associated malignancy varied greatly. We were therefore unable to identify a clear parallel course between primary noninvasive VPD

and the so-called associated malignancies. This raises the question of a consistent or comparable aetiology.

The main limitation of our study is the large group of cases labelled NOS. Our data were collected from two nationwide databases. This means it was not viable to review the histopathological samples and perform additional IHC studies to define the origin. We relied on the assessment of multiple pathologists throughout the country, which reflects daily practice. We assumed patients with VPD NOS to have noninvasive cutaneous VPD. The distribution of the different types of VPD in our study cohort resembles the distribution reported in the literature.[1] It is possible that this assumption caused us to overestimate the incidence of associated malignancies in this subgroup, as we might have included patients with VPD secondary to another malignancy.

Several studies have reported that perianal localization of EMPD is a risk factor for intestinal or anal malignancies, and recent literature indicates that the location of the skin lesion influences the disease-specific survival.[18,19] Nonetheless, it is uncertain how the skin lesion and the intestinal malignancy are related to each other in cases of secondary VPD. A recent epidemiological study by Karam and Dorigo reported a higher risk of intestinal malignancies in EMPD.[20] They reported an SIR for any malignancy of 1·47 (95% CI 1·17–1·84), but did not find a statistically significantly increased risk for breast cancer (SIR 1·41, 95% CI 0·85–2·20), anorectal and colorectal malignancies (SIR 1·64, 95% CI 0·90–2·76), bladder malignancies (SIR 2·39, 95% CI 0·65–6·13) or kidney/pelvic malignancies (SIR 0·93, 95% CI 0·02–5·21). However, this study included male and female patients with invasive disease. If the intestinal malignancy grows continuously to the epidermis, the question may be raised whether the EMPD lesion should be considered an expansion of the tumour rather than a separate entity. This holds true especially in cases with invasive disease, as it is impossible to determine which lesion came first.

As suggested above, differentiation between the subtypes of VPD (primary cutaneous, or secondary to an intestinal or urological malignancy) may be of great importance for the risk of developing other malignancies. However, currently there are no clear guidelines for this differentiation. It is generally accepted that the IHC profile of Paget cells can help to characterize different subtypes. As stated above, the cutaneous phenotype is determined by a $CK7^{+}$ $CK20^{-}$ profile, the intestinal phenotype by $CK7^{-}$ $CK20^{+}$ $CDx2^{+}$ and the urological phenotype by $CK7^{\pm}$ $CK20^{+}$ and uroplakin-III^{+}. These are the main markers that have been used to distinguish primary from secondary VPD for almost two decades.[3,21–23] There are no studies assessing the sensitivity and specificity of IHC analysis in differentiating the different subtypes of VPD, and the reliability of several other IHC stains can be discussed. An example is GATA3, which is reported to be sensitive, and also a potential pitfall, in recognizing VPD secondary to urothelial malignancies.[24,25]

Acknowledging this limitation, we assessed the risk of not screening for malignancy in those patients with a cutaneous IHC profile. Based on our data, refraining from additional screening for malignancies where IHC analysis shows a cutaneous profile would have missed five patients over 15 years in the Netherlands, a country of around 17 million inhabitants. However, there are national screening programmes for both breast and intestinal malignancies in which most patients would be screened anyway. In case IHC analysis shows an intestinal or urological origin for the VPD lesion, a directed surveillance for the specific malignancies can be performed. To assist clinicians in the work-up of newly diagnosed patients with VPD, we suggest a work-up according to the flowchart in Figure 2. Even though our results indicate that there may be no association between cutaneous VPD and underlying malignancy, screening may still be warranted depending on the clinical context.

Our study population contains 15 years of national data and is the first to focus on primary noninvasive VPD. We were not able to match all cases reported in the PALGA database to patients registered in the NCR to obtain follow-up data. We therefore used the date of the last pathology report as the last date of follow-up. This may shorten follow-up times and therefore reduce the sample size: at 36 months after VPD diagnosis the cohort consisted of 101 patients. With a small cohort the number of expected events (i.e. the development of one of the associated malignancies), based on the incidence in the general age- and calendar-year-corrected population, would be smaller than 1 patient per year. This causes the SIR to be disproportionately high for those years in which an associated malignancy was diagnosed.

For inclusion in the study we required that associated malignancies had to be histologically confirmed. It is possible that we missed cases of associated malignancies that were diagnosed via clinical examination or imaging, without histology. However, this is corrected by including only histologically confirmed malignancies in our background file of the general population.

The main goal of this study was to estimate the risk of developing associated malignancies in patients with VPD and to evaluate the need for screening for these malignancies. Looking at all patients with any type of VPD, we find that the risk of developing an associated malignancy is increased. VPD can be a sign of an internal malignancy, and may be a valuable cutaneous sign prompting earlier diagnosis. A diagnosis of secondary VPD, with an IHC phenotype favouring noncutaneous origin, should prompt a search for internal malignancy above and beyond physical examination.

The data in this study suggest promisingly that there is no statistically significant increase in cancer diagnosed in the first 3 years after primary noninvasive VPD compared with the general population. This may assist clinicians in reassuring and allaying the concerns of patients with noninvasive VPD. Reassuringly, most of these patients are often at an age where they are offered screening for bowel, breast and cervical cancer. Therefore, our main conclusion is that there is no evidence for the need for routine screening in patients diagnosed with primary noninvasive VPD.

References

1 van der Linden M, Meeuwis KA, Bulten J *et al.* Paget disease of the vulva. *Crit Rev Oncol Hematol* 2016; **101**:60–74.
2 Wilkinson E, Brown H. Vulvar Paget disease of urothelial origin: a report of three cases and a proposed classification of vulvar Paget disease. *Hum Pathol* 2002; **33**:549–54.
3 Brown HM, Wilkinson EJ. Uroplakin-III to distinguish primary vulvar Paget disease from Paget disease secondary to urothelial carcinoma. *Hum Pathol* 2002; **33**:545–8.
4 Friedrich EG Jr, Wilkinson EJ, Steingraeber PH, Lewis JD. Paget's disease of the vulva and carcinoma of the breast. *Obstet Gynecol* 1975; **46**:130–4.
5 Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol* 1985; **13**:1009–14.
6 Haga R, Suzuki H. Rectal carcinoma associated with pagetoid phenomenon. *Eur J Dermatol* 2003; **13**:93–4.
7 Lau J, Kohler S. Keratin profile of intraepidermal cells in Paget's disease, extramammary Paget's disease, and pagetoid squamous cell carcinoma *in situ*. *J Cutan Pathol* 2003; **30**:449–54.
8 Suenaga M, Oya M, Ueno M *et al.* Anal canal carcinoma with Pagetoid spread: report of a case. *Surg Today* 2006; **36**:666–9.
9 Lu B, Liang Y. Pagetoid spread of bladder urothelial carcinoma to the vagina and vulva. *J Low Gen Tract Dis* 2015; **19**:e13–16.
10 Paget J. On disease of the mammary areola preceding cancer of the mammary gland. *St Bartholemew Hosp Res Lond* 1874; **10**:87–9.
11 Crocker H. Paget's disease affecting the scrotum and penis. *Trans Pathol Soc Lond* 1889; **40**:187.
12 Dubreuilh W. Paget's disease of the vulva. *Br J Dermatol* 1901; **13**:407–13.
13 Fetissoff F, Arbeille-Brassart B, Lansac J *et al.* [Associated Paget disease of the vulva and of the nipple in the same patient: pathology with ultrastructural study]. *Ann Dermatol Venereol* 1982; **109**:43–50 (in French).
14 Royal College of Obstetricians and Gynaecologists. Guidelines for the diagnosis and management of vulval carcinoma. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/vulvalcancerguideline.pdf (last accessed 19 June 2018).
15 Royal College of Obstetricians and Gynaecologists. Vulval skin disorders, management (Green-top Guideline No. 58). Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg58 (last accessed 19 June 2018).
16 Miettinen. Mid-P exact test. In: *Epidemiologic Analysis With a Programmable Calculator (NIH Publication, no. 79-1649)* (Rothman KJ, Boice JD, eds). Washington, DC: National Institutes of Health, 1979.
17 Dean A, Sullivan K, Soe M. OpenEpi: open source epidemiological statistics for public health. www.OpenEpi.com (last accessed 19 June 2018).
18 Cohen JM, Granter SR, Werchniak AE. Risk stratification in extramammary Paget disease. *Clin Exp Dermatol* 2015; **40**:473–8.
19 Karam A, Dorigo O. Treatment outcomes in a large cohort of patients with invasive extramammary Paget's disease. *Gynecol Oncol* 2012; **125**:346–51.
20 Karam A, Dorigo O. Increased risk and pattern of secondary malignancies in patients with invasive extramammary Paget disease. *Br J Dermatol* 2014; **170**:661–71.
21 Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget's disease. *Br J Dermatol* 2000; **142**:243–7.
22 Wilkinson E. Premalignant and malignant tumors of the vulva. In: *Blaustein's Pathology of the Female Genital Tract* (Kurman R, ed.), 5th edn. New York: Springer-Verlag, 2002; 123–8.
23 Crum CP, Herrington CS, McCluggage WG *et al.* Tumours of the Vulva. In: *WHO Classification of Tumours of Female Reproductive Organs* (Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds.), 4th edn. Lyon: WHO, 2014; 236–7.
24 Zhao M, Zhou L, Sun L *et al.* GATA3 is a sensitive marker for primary genital extramammary Paget disease: an immunohistochemical study of 72 cases with comparison to gross cystic disease fluid protein 15. *Diagn Pathol* 2017; **12**:51.
25 Morbeck D, Tregnago AC, Netto GB *et al.* GATA3 expression in primary vulvar Paget disease: a potential pitfall leading to misdiagnosis of pagetoid urothelial intraepithelial neoplasia. *Histopathology* 2017; **70**:435–41.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Overview of patients with associated malignancies.