

Original Article

Incidence of penile intraepithelial neoplasia and treatment strategies in Sweden 2000–2019

Sinja Kristiansen¹ , Christian Torbrand^{2,3}, Åke Svensson¹, Ola Forslund⁴ and Carina Bjartling⁵

¹Department of Dermatology and Venereology, Skane University Hospital, Lund University, Malmö, Sweden,

²Department of Urology, Helsingborg Hospital, Helsingborg, Sweden, ³Institution of Translational Medicine, Lund

University, Malmö, Sweden, ⁴Laboratory Medicine, Department of Medical Microbiology, Lund University, Lund,

Sweden, and ⁵Department of Obstetrics and Gynaecology, Skane University Hospital, Lund University, Malmö, Sweden

Objectives

To analyse the incidence, treatment strategies and complications associated with penile intraepithelial neoplasia (PeIN) in Sweden over a period of 20 years.

Materials and methods

Data on PeIN from the Swedish National Penile Cancer Register were analysed regarding treatment in relation to age, size of the PeIN lesion, localization of the PeIN lesion and complications using chi-squared tests and logistic regression. The incidence of PeIN was calculated and age-standardized according to the European Standard population.

Results

Between 2000 and 2019 a total of 1113 PeIN cases were reported. The age-standardized incidence of PeIN was 1.40 per 100 000 men (95% confidence interval [CI] 1.32–1.49). An increase in incidence over time was seen, with a standardized incidence rate of 2.37 (95% CI 1.56–3.70) in 2019 compared to the baseline year, 2000. Surgical or topical treatments were given in 75.0% and 14.6% of cases, respectively. The complication rate was higher in laser surgery (12.1%, 7/58) compared to local surgery (4.6%, 16/348; $P = 0.03$) with an age-adjusted odds ratio (OR) of 2.82 (95% CI 1.10–7.19; $P = 0.03$). Local surgery was more common than laser surgery in the last 5 years compared to the first 5 years of the study period: OR 5.75 (95% CI 2.94–11.27). Treatments with imiquimod and topical 5-fluorouracil (5-FU) were more common than destructive methods such as photodynamic therapy, cryotherapy, curettage and electrocautery in the last 5 years compared to the first 5 years: OR 9.48 (95% CI 2.29–39.24).

Conclusions

A twofold increase in the age-standardized incidence of PeIN was seen in Sweden over 20 years. Complications were three times more common in laser surgery compared to local surgery. Changes in treatment showed an increase of treatment strategies such as local surgery and treatment with imiquimod and topical 5-FU over time.

Keywords

penile intraepithelial neoplasia, penile cancer, incidence, treatment, #uroonc, #PenileCancer

Introduction

Penile cancer is a malignancy with a reported incidence in 2007 of 0.45–1.7/100 000 men in Europe [1]. In Sweden the age-adjusted incidence was similar to that of Europe, at 2.1/100 000 men between 2000 and 2012 [2]. Penile cancer is histologically diagnosed as squamous cell carcinoma (SCC) in 94%–99% of cases [2,3]. Penile intraepithelial neoplasia (PeIN) is penile SCC *in situ*, constituting approximately 34%

of the penile cancer cases in Sweden [2]. The newly updated classification of PeIN divides it into *undifferentiated* PeIN, caused by human papillomavirus, and *differentiated* PeIN, originating from inflammatory skin diseases such as lichen sclerosus and lichen planus [4]. Further risk factors for PeIN, reported in 2019 by this group, and in 2005 by Daling et al. comprise immunosuppression, diseases of the prepuce such as phimosis, balanitis, former penile surgery (circumcision in newborns excluded) and smoking [5,6].

Treatment guidelines for PeIN are based on data from small studies and case series because data from randomized controlled trials are lacking [7,8]. Organ-preserving procedures are recommended for PeIN lesions, Ta, T1 and select cases of T2 tumours, and studies in invasive penile cancer show that centralized treatment in larger centres favours penile-preserving treatments and these reduce mortality [8–10]. Recurrence rates in invasive penile cancer have been demonstrated to be higher with penile-preserving treatments, but do not seem to influence the overall survival rates [8,11–13]. Studies in invasive penile cancer have shown organ-sparing techniques to improve patients' quality of life and sexual function [14]. Surgical treatment of PeIN has been shown to be the most common treatment (49%–85% of cases), with circumcision being the mainstay and minimal margins of a few millimetres considered sufficient [12,15,16]. Chipollini et al. reported a risk of recurrence with surgical treatment of PeIN in 15%–20% of cases in 2018 [17].

A relatively new organ-sparing technique recommended for PeIN is total glans resurfacing, whereby the skin of the glans is excised and replaced by a split skin graft [8,18]. Another surgical and organ-sparing option for PeIN is laser excision and/or vaporization with ablative carbon dioxide (CO₂) laser or neodymium:yttrium-aluminium-garnet (Nd:YAG). Laser treatment in PeIN has shown complete clearance in up to 96% of cases, with recurrence rates of between 10% and 48% [17,19–21]. Topical treatment options for PeIN are photodynamic therapy (PDT), treatments with imiquimod or topical 5-fluorouracil (5-FU), cryotherapy with liquid nitrogen, curettage and diathermy or electrocautery. In a study of 23 patients, treatment with PDT showed an 83% complete clearance rate [22] but a review from 2016 with a total of 67 patients showed complete clearance in only 67% of cases [19]. Topical treatment with imiquimod or 5-FU in patients with PeIN showed complete clearance in 57%–73% of cases [15,23,24]. Cryotherapy has been shown to be effective in one randomized controlled trial of extragenital SCC *in situ*, but no corresponding study for PeIN exists [25]. Curettage and diathermy/electrocautery are common treatments for extragenital SCC *in situ*, but only small studies exist on complete clearance in PeIN [7,26].

Knowledge on changes in the incidence of PeIN over time is limited, and apart from PeIN in the penile foreskin, for which circumcision is the preferred treatment, data on localization, size of PeIN lesion and age of the patient in relation to treatment chosen are scarce [8]. There are only limited data on complication rates related to different treatment methods. To the best of our knowledge, data on how treatment for PeIN has changed over time do not exist.

The aim of this study was to describe and analyse changes in treatment strategies and related complications in PeIN over a

period of 20 years in Sweden. We also investigated changes in incidence of PeIN over time.

Materials and Methods

The Swedish National Penile Cancer Register (NPECR) was launched in 2000. The coverage of the NPECR is assessed by cross-linkage to the Swedish Cancer Register, a nationwide register established in 1958 into which reporting is mandatory by law. The coverage in the NPECR compared to the Swedish Cancer Register was 99%–100% up to the year 2017, 96% in the year 2018 and 91% in the year 2019. Inferior numbers in 2018 and 2019 were due to a lag in registration to the NPECR. The register undergoes improvements regularly, resulting in new data being added over time. In 2009, complications and information on whether the diagnosis was based on histological or clinical examination were added to the register. Data describing laser surgery cover both vaporization and laser excision and include both the CO₂ laser and Nd:YAG laser, although the CO₂ laser is more widely used. The NPECR does not contain information on recurrence rates of PeIN.

Incidence was calculated with numbers of PeIN per year derived from the NPECR, divided by the numbers of men in Sweden for every year, in turn, derived from the National Population Register [27].

Wide local excision (WLE) and circumcision are often performed at the same time when the PeIN lesions are localized both on the glans and on the prepuce, hence they were included in the same variable, named 'local surgery'. The mode of treatment was divided into two groups, with the first group being 'surgical treatments', consisting of local surgery, laser surgery, total glans resurfacing, glansectomy, urethrectomy, partial and total penectomy, and the second group being 'topical treatments', consisting of treatments such as imiquimod, topical 5-FU, PDT, cryotherapy and curettage and diathermy/electrocautery. When more than one treatment method was used, the case was grouped under the least organ-preserving treatment (Table 3). Cases are registered under the most advanced tumour stage after pathological examination in the register. Statistical analysis was performed both with the two groups and with each treatment separately.

The sizes of the PeIN lesions are reported in centimetres in the register. The lesions are measured macroscopically by the clinicians in the clinic or in the operation theatre. PeIN lesions were divided into two groups along the median, with small lesions defined as ≤1 cm and large lesions as >1 cm in size.

Regarding localization of the PeIN lesion, two groups were created, consisting of the glans and/or prepuce in one and the penile shaft in the other. Reported localization of the PeIN lesion as penis unspecified was not used in the calculations.

Data extraction from the NPECR was performed on 7 December 2020. The study was approved by the ethics board in Lund, with diary number 2015/907.

Statistics

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0. (IBM Corp., Armonk, NY, USA). The chi-squared test was used to calculate differences between groups. Fisher's exact test was used in the case of small numbers. When differences were found, logistic regression was used to calculate CIs and multivariable logistic regression was used to adjust for possible confounding variables such as age. Age-standardized incidence and 95% CIs are presented with the statistical analysis performed in Stata SE 16.1. We also standardized the population at risk according to the latest European Standard population from 2013.

Results

Cohort Characteristics

From 2000 to 2019, 1113 men, diagnosed with PeIN, were registered in the NPECR. The median (interquartile range) age at diagnosis was 66 (53–75) years (Table 1). The age-standardized incidence of PeIN between 2000 and 2019 was 1.40 per 100 000 men (95% CI 1.32–1.49; Fig. 1). An increase in incidence over time was seen, with a standardized incidence rate of 2.37 (95% CI 1.56–3.70) in 2019 compared to the baseline incidence in 2000 (Table 2).

The median size of the PeIN lesion was 1.0 cm, with a lower quartile of 0.6 cm and an upper quartile of 2.0 cm. Diagnosis of PeIN was histologically verified in 98.2% of cases (726/739; Table 1). All the topically treated PeIN cases were histologically confirmed by biopsy.

In 31.7% of cases (353/1113), localization of PeIN was on the foreskin and in 27% (301/1113) on the glans penis. In 6.8% of cases (76/1113), PeIN was localized both on the glans and foreskin, and in 13.8% of cases (154/1113) it was localized on the penile shaft.

Overall, complications were reported in 6.9% of cases (51/739), with infection being the most common complication, seen in 2.4% (18/739), followed by unspecified complications in 1.6% (12/739). Complications for the different treatment methods are shown in Table S2.

Treatment of PeIN

Surgical treatment was given in 75.0% of cases (835/1113) and topical treatment in 14.6% (163/1113) of PeIN cases (Table 3). The most common treatment was local surgery, performed in 49.6% of cases (552/1113). The second most

Table 1 Cohort characteristics.

	Median (Mean)	Interquartile range
Age, years	66 (62.4)	53–75
PeIN size, cm	1.0 (1.57)	0.6–2.0
PeIN localization	Cases (N = 1113)	Percentage
Glans*	301	27.0
Prepuce	353	31.7
Glans + prepuce [†]	76	6.8
Penile shaft	154	13.8
Penis UNS <i>n</i> = 49 [‡]	49	4.4
Missing	180	16.2
Total	1113	100.0
Diagnosis 2009–2019	Cases (N = 739)	Percentage
Histology	726	98.2
Clinical	12	1.6
Missing	1	0.1
Total	739	100.0
Complications from 2009–2019	Cases (N = 739)	Percentage
Infection	18	2.4
Lymphocele	6	0.8
Reoperation	6	0.8
Bleeding	3	0.4
Lymphedema	3	0.4
Meatus stenosis	2	0.3
Skin necrosis	1	0.1
UNS	12	1.6
No reported complication	499	67.5
Missing	189	25.6
Total	739	100.0

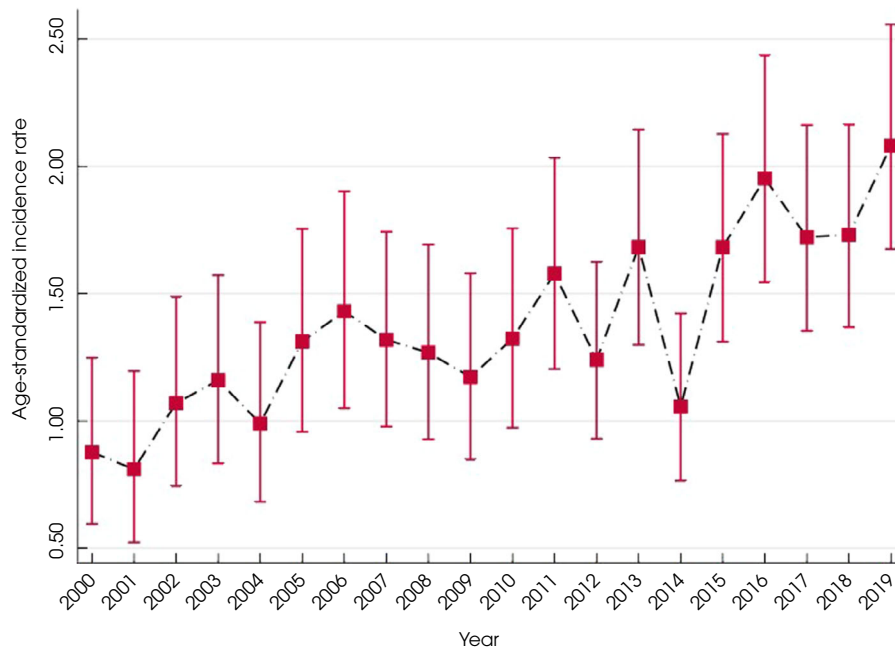
*PeIN, penile intraepithelial neoplasia; UNS, unspecified. *Including two PeIN lesions on glans + distal urethra and three PeIN cases in distal urethra. †Including one PeIN lesion on glans + prepuce + distal urethra. ‡Including six PeIN lesions located on glans + penile shaft.*

common treatment was laser surgery, performed in 11.5% of cases (128/1113).

Among topical treatments, treatment with imiquimod was given to 3.5% of patients (39/1113) and PDT to 3.2% (36/1113). The remaining treatment methods were used in <3% of the PeIN cases. In 15% of cases (167/1113), more than one treatment method was used (Table 3).

3.3.3.3. Surgical Treatments vs Topical Treatments

The surgical and topical treatment groups were compared regarding age at diagnosis, with the older patient group (those older than the median age of 66 years) compared to younger patients (those younger than or with the median age of 66 years). An increased odds ratio (OR) of 1.90 (95% CI 1.34–2.69; *P* < 0.001) for surgical treatment was observed in older patients (Table S1). There were no differences when comparing surgically and topically treated groups considering histological vs clinical diagnosis, localization of the PeIN

Fig. 1 Age-standardized incidence rate of penile intraepithelial neoplasia per 100 000 men and year.**Table 2** Incidence of penile intraepithelial neoplasia per 100 000, in the years 2000–2019, by year.

Year	PeIN cases, <i>n</i>	Age-standardized* rate (95% CI)	SIR (95% CI)
2000	32	0.88 (0.60–1.25)	1.0 (Reference)
2001	27	0.81 (0.52–1.20)	0.92 (0.52–1.62)
2002	37	1.07 (0.74–1.49)	1.22 (0.73–1.62)
2003	43	1.16 (0.83–1.57)	1.32 (0.81–2.18)
2004	36	0.99 (0.68–1.39)	1.13 (0.67–1.90)
2005	48	1.31 (0.96–1.75)	1.50 (0.92–2.45)
2006	50	1.43 (1.05–1.90)	1.63 (1.01–2.66)
2007	52	1.32 (0.98–1.74)	1.50 (0.94–2.44)
2008	49	1.27 (0.93–1.69)	1.45 (0.89–2.36)
2009	46	1.17 (0.85–1.58)	1.34 (0.82–2.20)
2010	51	1.36 (0.97–1.76)	1.51 (0.94–2.46)
2011	64	1.58 (1.20–2.03)	1.80 (1.14–2.88)
2012	55	1.24 (0.93–1.62)	1.41 (0.89–2.29)
2013	69	1.68 (1.30–2.14)	1.92 (1.23–3.05)
2014	45	1.06 (0.77–1.42)	1.20 (0.74–1.98)
2015	73	1.68 (1.31–2.13)	1.92 (1.24–3.03)
2016	83	1.95 (1.54–2.44)	2.23 (1.45–3.50)
2017	78	1.72 (1.35–2.16)	1.96 (1.27–3.09)
2018	80	1.73 (1.37–2.16)	1.97 (1.28–3.10)
2019	95	2.08 (1.67–2.56)	2.37 (1.56–3.70)

CI, confidence interval; PeIN, penile intraepithelial neoplasia; SIR, standardized incidence rate. *Standardized to the European Standard population 2013.

lesion, size of the PeIN lesion or complication rate (data not shown).

Comparison of Different Surgical Treatments

The two most common surgical treatment methods, local surgery and laser surgery (patients treated with both WLE and/or circumcision and laser surgery were excluded) were

compared. Regarding PeIN localization and complications, significant differences were seen. PeIN lesions localized at the glans and/or prepuce were more often treated with local surgery compared to laser surgery, age-adjusted OR 8.77 (95% CI 2.71–28.32; $P < 0.001$ [Table S1]). Laser surgery showed complications in 12.1% of patients (7/58) and local surgery in 4.6% (16/348; $P = 0.03$, Fisher's exact test) and, when adjusting for age, logistic regression showed an increased OR for complications with laser surgery compared to local surgery of 2.82 (95% CI 1.10–7.19; $P = 0.03$). When including age at diagnosis, diagnosis made clinically or by histopathology and size of the PeIN lesion, no statistically significant differences were found (Table S1).

Comparison of Different Topical Treatments

When different topical treatments were compared as single treatments and as grouped treatments, no statistically significant differences were found (data not shown).

Changes in Treatments over Time

Analysis of proportions of patients treated with local surgery and laser surgery in the first 5 years compared to the last 5 years of the study period, showed an increased age-adjusted OR of 5.75 (95% CI 2.94–11.27; $P < 0.001$) for local surgery for the last 5 years.

When comparing changes in topical treatments for the first 5 years vs the last 5 years, two groups were studied, one group having treatments including imiquimod and 5-FU, and another group having PDT/cryotherapy/diathermy/

Table 3 Treatment methods for penile intraepithelial neoplasia.

	<i>n</i> (%)	More than one treatment method, <i>n</i> (%)
Surgical treatment	835 (75.0)	160 (14.4)
Topical treatment	163 (14.6)	7 (0.6)
Missing	115 (10.3)	–
Total	1113 (100.0)	167 (15.0)
Surgical treatments, <i>n</i> = 835		
WLE	539 (48.4)	103 (9.3)
WLE alone	436	
WLE + circumcision	27	
WLE + laser surgery	55	
WLE + topical treatments	21	
Circumcision	72 (6.5)	12 (1.1)
Circumcision alone	60	
Circumcision + laser surgery	4	
Circumcision + topical treatments	8	
Laser surgery	128 (11.5)	8 (0.7)
Laser surgery alone	120	
Laser surgery + topical treatments	8	
TGR	24 (2.2)	9 (0.8)
Glansectomy	27 (2.4)	8 (0.7)
Partial penectomy	27 (2.4)	5 (0.4)
Urethrectomy	10 (0.9)	7 (0.6)
Total penectomy	7 (0.6)	3 (0.3)
Chemotherapy	3 (0.3)	3 (0.3)
Radiotherapy	2 (0.2)	2 (0.2)
Total	835 (75)	160 (14.4)
Topical treatments, <i>n</i> = 163		
Imiquimod	39 (3.5)	0 (0)
5-FU	28 (2.5)	0 (0)
PDT	36 (3.2)	1 (0.09)
Cryotherapy	20 (1.8)	5 (0.4)
Diathermy	24 (2.2)	1 (0.09)
Other topical treatments	7 (0.6)	0 (0)
Missing	9 (0.8)	–
Total	163 (14.6)	7 (0.6)

5-FU, 5-fluorouracil; PDT, photodynamic therapy; TGR, total glans resurfacing; WLE, wide local excision.

electrocautery. Multivariable logistic regression showed an age-adjusted OR of 9.48 (95% CI 2.29–39.24; $P = 0.002$) for receiving treatment with imiquimod and 5-FU compared to PDT/cryotherapy or diathermy/electrocautery for the last 5 years compared to the first 5 years. Regarding the age of the patients, an increased OR of 1.52 (95% CI 1.07–2.17; $P = 0.02$) was seen for being over 66 years of age when diagnosed with PeIN in the last time period compared to the first time period (Table S1).

Discussion

This study analyses the incidence and different treatments in 1113 cases of PeIN in Sweden over 20 years. It is, to our knowledge, the most extensive study so far. The study shows a twofold age-standardized increase in the incidence of PeIN in Sweden over the last 20 years. This is in alignment with data from the Netherlands and Denmark, which also report

an increase in incidence [3,28,29], although the age-standardized PeIN incidence in Sweden is markedly higher (mean incidence 1.40/100 000 men) than in the Netherlands (mean incidence 0.47/100 000 men) [28]. The increased age-standardized incidence in this study, from 0.88/100 000 men in 2000 to 2.08/100 000 men 2019, is also considerably higher than the age-standardized incidence rate of PeIN in Denmark, increasing from 0.5 per 100 000 men-years to 0.9 per 100 000 men-years over 11 years [29]. An explanation for the more marked increase in incidence of PeIN in Sweden could be that our study spans 20 years, including up to the end of 2019, whereas the study from the Netherlands investigated the incidence between 1998 and 2007 and the Danish study between 1978 and 2008 [28,29]. In a study from Norway, Hansen *et al.* observed increased incidence of invasive penile cancer between 1956 and 2015 [30], contrary to the stable incidence of invasive penile cancer between 2000 and 2012 in Sweden as shown by Kirrander *et al.* [2]. Since data from Sweden includes only years 2000 until 2012, it is conceivable that the incidence of invasive penile cancer could have increased during the following 7 years up to 2019. Human papillomavirus (HPV) is frequently present (93%) in PeIN [26], and we tentatively speculate that our observation of an increased incidence of PeIN is attributable to changes in sexual behaviours through the sexual revolution around 1968. Such speculation is supported by studies of the HPV-associated disease oropharyngeal cancer, for which an increased incidence over time has also been reported [31]. For oropharyngeal cancer, increased HPV exposure is thought to lead to an increased number of cancers after 20–30 years. Increased incidence of PeIN could possibly also be attributable to earlier presentation by the patients, before the PeIN progresses to invasive cancer, to earlier recognition or to better documentation by the clinicians.

In this study the most common location for PeIN was on the prepuce (31.7%) and the second most common location was on the glans (27%). PeIN located on the penile shaft was only seen in 13.8% of cases. This is similar to the study by Hoekstra *et al.*, who showed that most PeIN cases were located on the prepuce (45%), followed by the glans (38%) and penile shaft (3%) [28]. Chipollini *et al.* also reported that PeIN localized on the penile shaft was less common but, contrary to our study, they reported a location on the glans to be more common than on the prepuce: 44.9% compared to 21.5% [17]. The advantage of our study was a low risk of bias in treated cases resulting from a high coverage of PeIN cases regardless of where the patient received healthcare.

In the majority of the PeIN patients in this study, the treatment method was surgical, with local surgery performed in almost half of the patients. In a minority (14%) of the patients, the treatment was chosen within the topical field. This is in agreement with a large study published in 2020 on the treatment of PeIN by Kravvas *et al.*, who

retrospectively evaluated treatments given to 263 PeIN patients and showed that PeIN was treated with circumcision in 65.8% of cases while 14.4% were treated only with topical agents, cryotherapy or a combination of both [16]. In 15% of the PeIN cases in Sweden, more than one treatment method was used, and in only a few cases were three different treatment methods reported. Kravvas et al. showed that 46.4% of patients underwent two treatment methods and 16.7% required treatment with three or more methods [16]. Our finding that laser surgery was the second most common treatment method after local surgery is consistent with that of Chipollini et al., who studied 205 PeIN cases and showed that 28.3% were treated with laser surgery only [17]. In our study approximately 11% of PeIN cases the registered treatment was glansectomy, partial or total penectomy, treatments not recommended for PeIN in any guidelines. The explanation for that could be that PeIN in the meatus and urethra sometimes results in glansectomy or a partial penectomy to obtain free margins. Another explanation could be errors made by the doctors filling in the register data.

The most common topical treatment in our study was imiquimod, followed by PDT, in contrast to the study by Alnajjar et al., who studied 86 PeIN patients, of whom 44 received topical chemotherapy with 5-FU as the first-line treatment, while nine patients received imiquimod as the second-line treatment [15].

Comparison between local surgery and laser surgery showed that local surgery was almost nine times more common in PeIN localized on the glans or the prepuce compared to PeIN on the penile shaft. The rate of complications was almost three times higher after laser surgery compared to local surgery in this study. This is in contrast to the results from a review of laser treatment for PeIN by Maranda et al., including 27 patients treated with CO₂ laser and seven with Nd:YAG laser showing the administered CO₂ laser therapy was well tolerated except in two case studies describing one patient each, reporting some pain or slight burning sensation during the treatment. However, in this review, no post-treatment complications were reported [19]; therefore, it is possible that our result is a closer reflection of the rate of complications, with the reservation that the number of registered complications was low.

The ratio of PeIN cases in men aged over 66 years to PeIN cases in men aged under 66 years changed over the study period, with a greater number of older cases in the last 5 years. This is similar to data from Denmark, showing an increasing and particularly higher incidence of PeIN in 50–69-year-old men and no change in the average annual number of men aged below 50 years [29].

Analysis of changes over time in surgical treatment methods showed an increased OR for treatment with local surgery

compared to laser surgery in the later time period, when comparing the first 5 years with the last 5 years. The higher recurrence rate after laser surgery of 48.3% compared to 25% in WLE ($P < 0.001$) shown by Chipollini et al., could be one explanation for the increase in local surgery in favour of laser surgery [17]. In 2013, multidisciplinary team conferences were introduced in Sweden, consisting of urologists, dermatologists, pathologists, oncologists and radiologists, where all cases of PeIN and invasive penile cancer are discussed, and that could partly explain changes in treatment given.

The topical treatments showed an increased OR for treatments with imiquimod and topical 5-FU compared to PDT, cryotherapy and diathermy/electrocautery in the last 5 years compared to the first 5 years. This was probably due to recent publications showing a complete response in up to 74% of those given topical 5-FU and a 63% complete response rate for those given imiquimod, and a similar recurrence rate to that of WLE (up to 25%) [23,24].

A major strength of this study is the large number of PeIN cases included (1113) and the study period of 20 years. In addition, data were derived from a national register with more than 90% coverage of all PeIN cases in Sweden. A further strength is that the incidence was age-standardized, allowing comparisons among countries with different population age distributions. Another strength is that the register contains data allowing analysis of treatments in relation to different characteristics of PeIN lesions and changes over time. A major limitation is that the NPECR does not contain information on rates of recurrences in patients with PeIN, resulting in data lacking treatment outcome, risk of recurrence, quality of life after different treatment methods, and risk of PeIN progression to malignancy. Another limitation was some missing data resulting from incomplete forms (Table 1).

In conclusion, this study shows a more than twofold increase in the standardized incidence rate of PeIN in Sweden between 2000 and 2019. Although PeIN is a rare disease, the increase highlights the importance of awareness of the condition among medical doctors, as well as the importance of taking biopsies from suspicious lesions and treating confirmed PeIN cases in order to prevent development into invasive penile cancer. Data indicate that treatment with laser surgery resulted in a three times higher complication rate compared to local surgery. Earlier studies have shown a high recurrence rate as well, calling for more research on treatment outcomes and risk of recurrence in laser treatment. This study also shows that local surgery and treatment with imiquimod and topical 5-FU were offered to patients with PeIN more often in recent years. Further research is needed to explore treatment strategies that result in the highest complete

clearance of PeIN, the least risk of recurrence and the highest prevention of development of invasive cancer. Future studies also need to address treatment outcomes and risk of recurrence with respect to classification of the PeIN as undifferentiated or differentiated.

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Conflict of Interests

None declared.

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Correspondence: Sinja Kristiansen, Jan Waldenströmsgata 16, 214 28 Malmö, Sweden.

e-mail: sinja.kristiansen@med.lu.se

Abbreviations: 5-FU, 5-fluorouracil; HPV, human papillomavirus; Nd:YAG, neodymium:yttrium-aluminium-garnet; NPECR, Swedish National Penile Cancer Register; OR, odds ratio; PDT, photodynamic therapy; PeIN, penile intraepithelial neoplasia; SCC, squamous cell carcinoma; WLE, wide local excision.

Table S1 Multivariable logistic regression analysis.

Table S2 Complications in relation to treatment method for PeIN cases.

Supporting Information

Additional Supporting Information may be found in the online version of this article: