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Penile Cancers Attributed to Human Papillomavirus Are Associated with Improved Survival for Node-positive Patients. Findings from a Norwegian Cohort Study Spanning 50 Years

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Abstract

Background: Human papillomavirus (HPV) infection is a risk factor for the development of penile squamous cell carcinoma (PSCC). It remains inconclusive whether HPV-related PSCC has a different prognosis from non–HPV-related PSCC.

Objective: To investigate the relationship between HPV status and survival as well as temporal changes in the proportion of HPV-related PSCC.

Design, setting, and participants: A retrospective cohort of 277 patients treated in Norway between 1973 and 2022 was investigated for HPV DNA in tumor tissue. Clinicopathological variables and disease course were registered.

Outcome measurements and statistical analysis: Kaplan-Meier curves and Cox regression were used to investigate the determinants of cancer-specific survival (CSS). The chi-square test for trend in proportions enabled investigation of temporal changes in the HPV-related proportion of PSCC patients treated in Western Norway (n = 211).

Results and limitations: HPV DNA was detected in tumor tissue from 131 (47%) patients. Stratified by HPV status, 5-yr CSS did not differ between groups (p = 0.37). When investigating only node-positive patients, however, presence of HPV DNA was an independent predictor of better survival in multivariable Cox regression after adjustment for age, nodal stage, and adjuvant therapy (hazard ratio 0.54, 95% confidence interval: [0.30–0.99], p = 0.04). In cases from Western Norway, an increasing proportion of HPV-related cases over time was found (p = 0.01). The main limitation is the retrospective study design.

Conclusions: HPV DNA in tumor tissue was associated with significantly better CSS for node-positive patients. The proportion of HPV DNA–positive PSCC has increased significantly in Western Norway over the past 50 yr.

Patient summary: We investigated the impact of human papillomavirus (HPV) on the survival of penile cancer patients treated over a 50-yr period in Norway. We found that

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for patients with lymph node metastasis, survival was better for HPV-related cases. We also found that the proportion of cases due to HPV has increased in Western Norway.

1. Introduction

Penile squamous cell carcinomas (PSCCs) are known to arise through two main pathways of carcinogenesis, one related to human papillomavirus (HPV) infection and the other related to chronic inflammation [1]. Accordingly, the World Health Organization (WHO) classifies PSCCs into HPV-related and non–HPV-related carcinomas [2]. Each of these carcinomas represents a distinct biological variant of PSCC. Detection of HPV in tumor tissue could therefore serve as a versatile biomarker, having a prognostic value in predicting clinical outcome and survival, as well as influencing decisions on treatment and follow-up strategy. Currently, however, the published results on HPV status as a prognostic marker for survival are conflicting [3,4]. European and American guidelines on PSCC therefore emphasize that more data are needed regarding the prognostic value of HPV status [5].

In recent decades, the incidence of PSCC has increased in Norway [6]. Moreover, similar trends have been reported globally [7–9]. While the underlying cause remains not fully known, one possible explanation could be an increase in the HPV-related proportion of PSCCs. While some studies have reported a temporal trend of more HPV-related PSCCs in recent years [10,11], other studies have not identified such a shift [12,13]. As such, more studies regarding the temporal changes in the proportion of PSCCs attributed to HPV are needed.

This study includes a large cohort of patients treated for PSCC over a 50-yr period in Norway. The primary aim of this study was to investigate whether the presence of HPV DNA in penile carcinomas (HPVpos) was associated with a different prognosis from that for carcinomas without HPV DNA (HPVneg). The secondary aim of this study was to investigate whether the proportion of PSCCs attributable to HPV in Western Norway has changed over the study period.

2. Patients and methods

2.1. Patient selection and cohort characteristics

After obtaining ethical approval (REK vest project no. 291376), patients from two Norwegian PSCC cohorts were included and combined in this study.

The first cohort consisted of patients treated at Haukeland University Hospital, a tertiary referral center in Western Norway. All patients who underwent operative surgery for PSCC between 1973 and 2022 were identified, and all but one accepted inclusion. The local diagnostic biobank was then screened for stored formalin-fixed paraffin-embedded (FFPE) blocks containing tumor tissue eligible for an HPV analysis. Representative tissue was retrieved for 211 out of 213 patients. For each tissue sample, a uropathologist confirmed the presence of tumor tissue. HPV DNA status was then determined by polymerase chain reaction amplification of virus DNA, detection of virus DNA in agarose gel, and Sanger sequencing of HPV-positive samples to identify specific HPV subtypes. The GP5+/GP6+ primer system (Applied Biosystems, Waltham, Massachusetts, USA) for the detection of the HPV *L1* gene was used [14]. Hospital records were analyzed for clinical variables and disease course. All histopathological examinations were restaged by an experienced uropathologist according to the current 2016 UICC TNM classification [15].

The second cohort was provided by the Cancer Registry of Norway (CRN), which, in accordance with Norwegian law, receives detailed clinical and histopathological information, including the pathological specimen descriptions, of all patients with PSCC in Norway [6]. HPV status, however, is not reported routinely. The included patients have thus been recruited from a research project where the CRN screened the Janus Serum Bank cohort in Norway [16] and identified 71 participants who were treated for PSCC between 1977 and 2015. FFPE tissue blocks from these patients were sent to the German Cancer Research Center (DKFZ) in Heidelberg, Germany, where type-specific HPV DNA and E6/E7 RNA status was determined in tumor tissue by multiplex HPV genotyping, a method developed by DKFZ and described in detail elsewhere [17–19]. For these patients, all registry data were re-evaluated and updated following the same criteria as for the first cohort.

Five patients were registered in both cohorts. HPV DNA status for these patients was used as an internal control on the agreement between the two HPV detection methods.

In total, 277 patients (211 and 66 distinct patients from the first and second cohorts, respectively) operated for PSCC between 1973 and 2022 were included. The detection of HPV DNA in tumor tissue was used to define the HPV status. For all the node-positive patients, pathological N stage (pN) was based on surgical dissections. During the early phase of the study period, patients without palpable lymph nodes were often followed by active surveillance. In accordance with previous studies, these patients were reclassified as having pN0 if there was no indication of metastasis after 2 yr of follow-up [20,21]. In recent years, bilateral dynamic sentinel node biopsy has been performed on all clinically node-negative patients. Thus, after reclassification, all patients had a definitive pathological N stage.

Survival time was calculated from the time of surgery until the end of the study period (December 31, 2022) or the time of death. The cause of death was obtained from the patient medical records and the Norwegian Cause of Death Registry. The temporal trend analysis for HPV-related PSCC was limited to cases from the first cohort, which contains virtually all cases treated in Western

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Norway, a geographically defined area containing approximately one-fourth of the Norwegian population.

2.2. Statistical analysis

Categorical variables were described with frequencies and percentages, and quantitative variables with median and interquartile range. Wilcoxon rank sum test, Fisher's exact test, and Pearson's chi-square test were used to evaluate the relationship between categorical variables stratified by HPV status. The chi-square test for trend in proportions was used to investigate temporal changes in the HPV-related proportion of PSCCs. Survival times and cause of death were used to create Kaplan-Meier curves to estimate cancer-specific survival (CSS) stratified by HPV status. The log rank test was used to evaluate potential differences in CSS between groups. Determinants of CSS were investigated using multivariable Cox regression. For this analysis, in addition to HPV status, other variables known to be associated with CSS (age, nodal stage, and adjuvant therapy) were included in the analysis.

A survival analysis with adjustment of population-based expected survival for each patient was also performed, enabling an independent assessment of survival in a relative survival setting (calculation of net survival) [22].

For all cases, a p value of <0.05 was considered statistically significant. Statistical analyses were performed using software R version 4.1.1.

3. Results

3.1. HPV types detected in tumor tissue

For the five patients registered in both cohorts, there was a complete match between the two HPV DNA tests. HPV was detected in tumor tissue from 131 (47%) patients. The types detected are shown in Table 1. Multiple types were detected in tumors from five patients, all belonging to the second cohort. Except for four cases with HPV types 6, 70, or 72, all cases had types classified as high risk according to the IARC classification [23].

Table 1 – Human papillomavirus (HPV) types detected in penile cancer tumor tissue

HPV types	Number of patients (N = 277)
Negative	146 (53%)
Positive	131 (47%)
6	2
16	96
16 + 31	1
16 + 44	1
16 + 81	1
18	9
31	3
33	8
35	1
45	1
45 + 52 + 56	1
51	2
59	1
61 + 62	1
62	1
70	1
72	1

Among the 71 patients from the second cohort, no HPV DNA–negative tumor was positive for HPV RNA. Six out of 32 HPV-16 DNA–positive tumors were negative for HPV-16 RNA. Detection of type-specific HPV DNA was also found for only one HPV-6 case as well as for the cases with HPV 61 + 62, 62, 72, and 81.

3.2. Proportion of HPV-attributable tumors over time

When dividing cases from the first cohort into the five 10-yr time periods (Fig. 1A), there was a significant linear trend with an increasing proportion of HPV-related cases over time (p = 0.01). When sorting cases by the time of operation, the cumulative proportion of HPV-related cases never stabilized and increased throughout the study period (Fig. 1B).

3.3. Cohort characteristics and histopathology

Stratified by HPV status, there was no difference in the median age at the time of surgery between the groups (p = 0.4; Table 2). Furthermore, there were no differences related to age group, type of penile or lymph node operation, or type of adjuvant treatment administered (all p > 0.1). The median observed survival time was similar for both groups (p = 0.8). Death due to PSCC was observed in 15% of the HPVpos patients versus 20% of the HPVneg patients (p = 0.3). Among the HPVpos patients, only those with HPV type 16 (18 patients), or type 18 or 33 (one patient each) died of PSCC.

Pathological T stage (pT) was not different between groups (p = 0.8; Table 3). There were significant differences in WHO grade, with more grade 1 for the HPVneg group and more grade 3 and 4 for the HPVpos group (p < 0.001). For ten patients from the second cohort, information of a definitive WHO grade was missing. Among the eight different histological subtypes registered, usual was most common, followed by mixed and basaloid subtypes. Nodal status was not different between groups (p = 0.2), nor was pN stage (p = 0.08).

3.4. Cancer-specific and net survival

Except for one HPVneg patient, all deaths caused by PSCC occurred within 5 yr of surgery. For all patients, the 5-yr CSS was 80%, while corresponding net survival was 77% (Supplementary Fig. 1A and 1B, respectively).

Stratified by HPV status, there was no difference in 5-yr CSS between the groups (p = 0.37; Fig. 2A). When investigating only node-negative patients, again no difference between groups was found (p = 0.83; Fig. 2B). However, for node-positive (pN+) patients, there was significantly better survival for the HPVpos group (p = 0.02; Fig. 2C). There was, however, no significant difference in CSS at any specific pN stage (Supplementary Fig. 2)

CSS for the node-positive patients who received adjuvant therapy was significantly better for the HPVpos group (p < 0.05; Supplementary Fig. 3A). CSS for the node-positive patients who did not receive adjuvant therapy did not differ between the groups (p = 0.2; Supplementary Fig. 3B).

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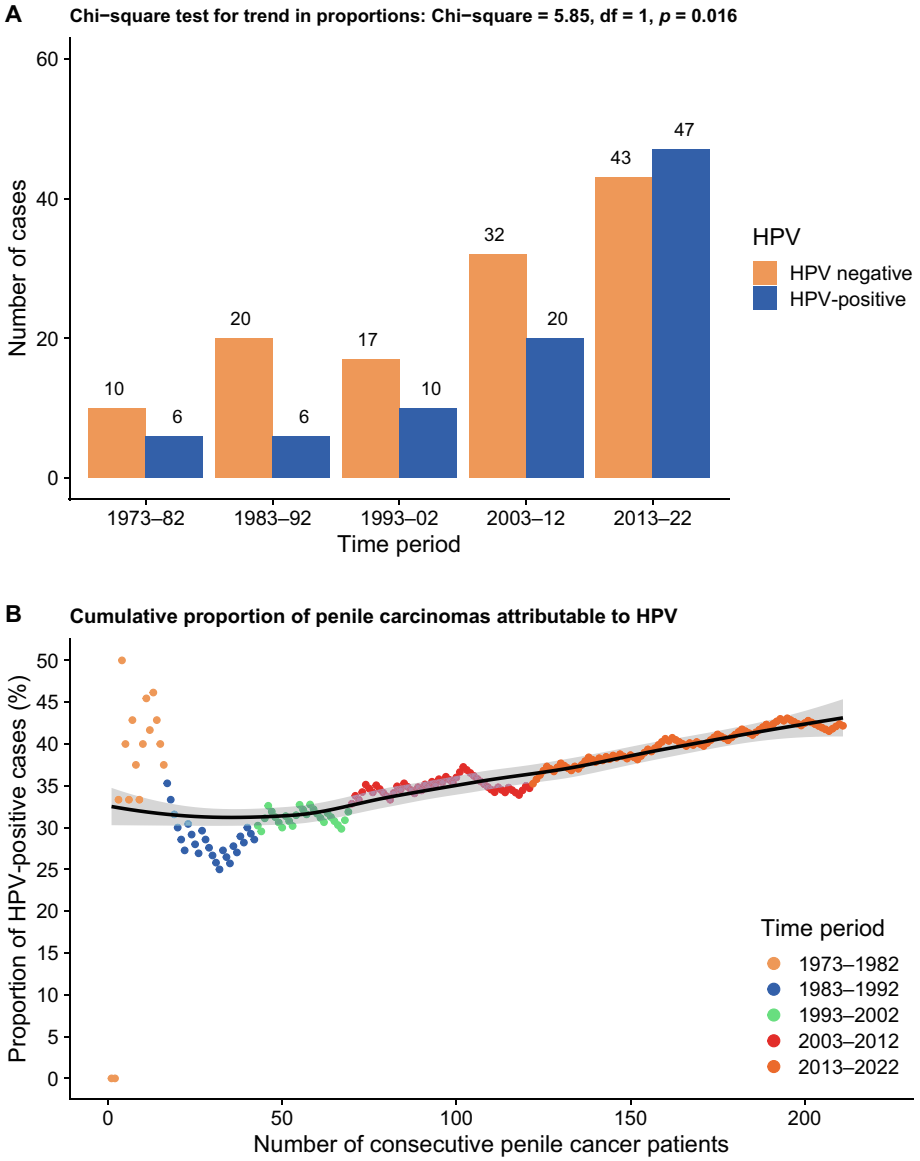

Fig. 1 – (A) Number of penile squamous cell carcinoma (PSCC) cases treated in Western Norway over the past 50 yr (1973–2022). The cases have been stratified by human papillomavirus (HPV) status and have been divided into five equal 10-yr time periods. (B) Cumulative proportion of HPV-positive cases over the same time period.

In a subgroup analysis on the node-positive patients (Table 4), HPV positivity remained an independent predictor of significantly better CSS after performing multivariable Cox regression with adjustment for age, nodal stage, and adjuvant therapy (hazard ratio 0.54, 95% confidence interval: [0.30–0.99], $p = 0.04$).

4. Discussion

The present study shows that the detection of HPV DNA in tumor tissue was associated with significantly better CSS for the node-positive PSCC patients. Moreover, the study also shows that the proportion of HPV-related PSCC has increased significantly in Western Norway over the past 50 yr.

Published results regarding the prognostic value of HPV status in PSCC are conflicting [3,4]. In a meta-analysis by Sand et al. [4], HPVpos patients had significantly better CSS than HPVneg patients. However, the survival analysis in that study included only HPV status and was not adjusted for by other important factors such as lymph node status. Patients who are node negative at the time of surgery rarely end up dying from their cancer [24]. For these patients, one would expect excellent CSS irrespective of HPV status. Significant differences in survival related to HPV status for the node-positive patients could therefore be concealed when including all patients in the analysis (Fig. 2). Different cohort compositions with varying proportions of node-positive patients could therefore be one possible explanation for the different results presented in the literature.

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Table 2 – Patient characteristics stratified by HPV status

Characteristic	Overall (*N* = 277)[a]	HPV negative (*N* = 146)[a]	HPV positive (*N* = 131)[a]	*p* value[b]
Age at surgery	67 (58, 76)	66 (57, 75)	67 (60, 76)	0.4
Age group				0.6
59 or younger	78 (28)	45 (31)	33 (25)	
60–69	91 (33)	47 (32)	44 (34)	
70–79	63 (23)	34 (23)	29 (22)	
80 or older	45 (16)	20 (14)	25 (19)	
Penile operation				0.6
Penile sparing surgery	138 (50)	71 (49)	67 (51)	
Partial amputation	113 (41)	59 (40)	54 (41)	
Total amputation	26 (9.4)	16 (11)	10 (7.6)	
ILND	107 (39)	50 (34)	57 (44)	0.11
PLND	39 (14)	23 (16)	16 (12)	0.4
Adjuvant treatment				0.3
No adjuvant treatment	217 (78)	116 (79)	101 (77)	
Chemotherapy	8 (2.9)	6 (4.1)	2 (1.5)	
Radiation	21 (7.6)	8 (5.5)	13 (9.9)	
Chemoradiotherapy	31 (11)	16 (11)	15 (11)	
Observed survival time	77 (20, 150)	80 (18, 150)	75 (20, 154)	0.8
Diseased	153 (55)	81 (55)	72 (55)	>0.9
CoD PSCC	49 (18)	29 (20)	20 (15)	0.3

CoD = cause of death; HPV = human papillomavirus; ILND = inguinal lymph node dissection; IQR = interquartile range; PLND = pelvic lymph node dissection; PSCC = penile squamous cell carcinoma.
[a] Median (IQR); *n* (%).
[b] Wilcoxon rank sum test; Pearson's chi-square test.

Table 3 – Histopathological characteristics stratified by HPV status

Characteristic	Overall (*N* = 277)[a]	HPV negative (*N* = 146)[a]	HPV positive (*N* = 131)[a]	*p* value[b]
pT stage				0.8
T1	137 (49)	75 (51)	62 (47)	
T2	97 (35)	51 (35)	46 (35)	
T3	40 (14)	19 (13)	21 (16)	
T4	3 (1.1)	1 (0.7)	2 (1.5)	
WHO grade				<0.001
1	70 (26)	56 (39)	14 (11)	
2	101 (38)	50 (35)	51 (41)	
3	96 (36)	37 (26)	59 (48)	
Unknown	10	3	7	
Histological subtype				
Usual	165 (60)	107 (73)	58 (44)	
Verrucous	10 (3.6)	9 (6.2)	1 (0.8)	
Papillary	6 (2.2)	4 (2.7)	2 (1.5)	
Sarcomatoid	1 (0.4)	1 (0.7)	0 (0)	
Mixed	41 (15)	9 (6.2)	32 (24)	
Basaloid	31 (11)	3 (2.1)	28 (21)	
Warty	22 (7.9)	13 (8.9)	9 (6.9)	
Adenosquamous	1 (0.4)	0 (0)	1 (0.8)	
Nodal status				0.2
Node negative	183 (66)	101 (69)	82 (63)	
Node positive	94 (34)	45 (31)	49 (37)	
pN stage				0.084
pN0	183 (66)	101 (69)	82 (63)	
pN1	24 (8.7)	8 (5.5)	16 (12)	
pN2	27 (9.7)	11 (7.5)	16 (12)	
pN3	43 (16)	26 (18)	17 (13)	

HPV = human papillomavirus; WHO = World Health Organization.
[a] *n* (%).
[b] Fisher's exact test; Pearson's chi-square test.

In a study by Bandini et al. [25], perioperative nodal radiotherapy, but not chemotherapy, was shown to be associated with superior overall survival for HPVpos patients. While the current study was too limited in cases and events to study these treatments separately, HPVpos patients who received adjuvant therapy with chemo- and/or radiotherapy had significantly better CSS than corresponding HPVneg patients. However, there were also relatively more pN1 and fewer pN3 cases in the HPVpos group. In the multivariable Cox regression, only HPV positivity and pN3, but not adjuvant therapy, were independent predictors of CSS for node-positive patients. Possibly, with a lower burden of

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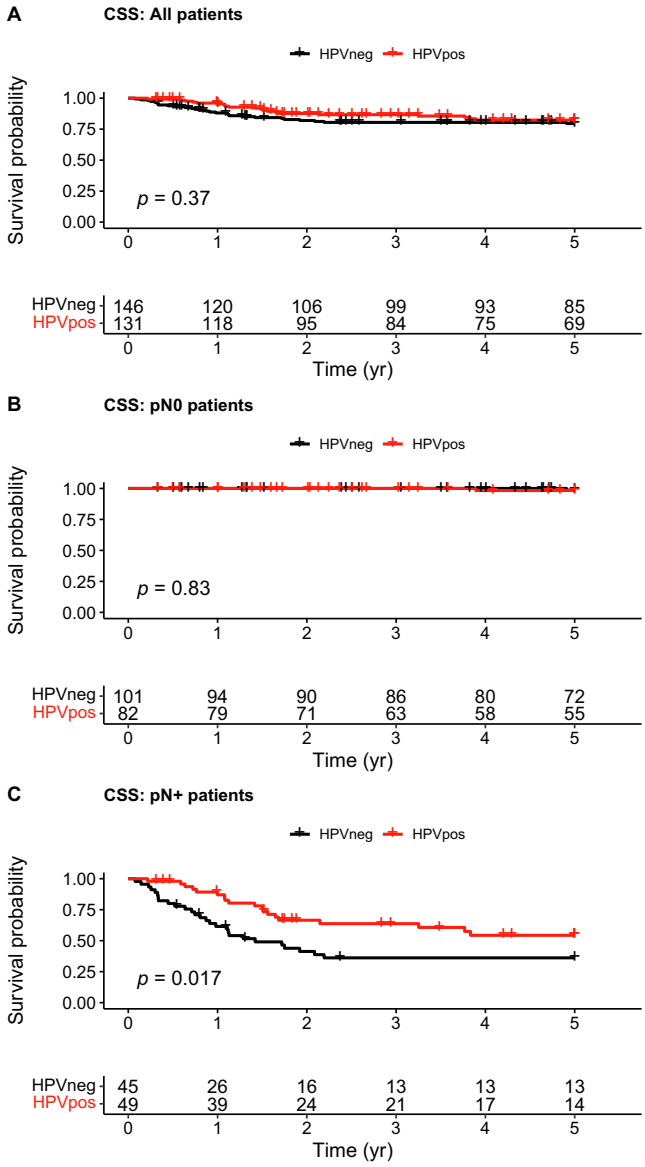

Fig. 2 – (A) Kaplan-Meier curves showing 5-yr cancer-specific survival (CSS) for all patients (total study population) stratified by human papillomavirus (HPV) status. (B) Corresponding Kaplan-Meier curves for the node-negative (pN0) patients. (C) Corresponding Kaplan-Meier curves for the node-positive (pN+) patients. HPVneg = absence of HPV DNA in penile carcinoma; HPVpos = presence of HPV DNA in penile carcinoma.

positive lymph nodes, the disease could more easily be treated radically with surgery, resulting in a better prognosis for the HPVpos group. Of note, also p16 positivity, a surrogate marker for HPV, has been shown to be an independent predictor of overall survival in PSCC after adjustment for nodal stage [26]. However, the current study did not find differences in survival related to HPV status for any given nodal stage, and this should be investigated further in larger cohorts.

The presence of HPV DNA does not automatically infer a causative effect of HPV infection on cancer development since the virus could be transcriptionally inactive. The correspondence between HPV DNA and HPV RNA found in this study were similar to previously published results [12]. Even if E6/E7 RNA is negative, one should exercise caution when deducing that the virus is transcriptionally inactive, as studies from head and neck and cervical cancers have shown the existence of an alternative carcinogenic pathway through HPV E2/E4/E5 [27]. Moreover, also testing for HPV DNA in circulating cell-free DNA in the blood has shown promise for the diagnosis and prognosis of other HPV-related cancers [28]. These findings should be investigated further also for PSCC.

The division of HPV types into high-risk and low-risk categories originates from studies investigating the association between HPV types and cervical cancer [23,29]. Similar information is currently unknown for PSCC. In this study, therefore, all HPV-positive tumors were grouped together, also including four cases with low-risk types. Death due to PSCC, however, occurred only for patients with the high-risk type 16, 18, or 33. Therefore, cases with low-risk types did not affect CSS.

One of the main findings of the present study was that the HPV-related proportion of PSCCs has increased in Western Norway over the 50-yr study period. Similar findings have been published for HPV-related head and neck cancers in Norway [30]. While the incidence of PSCC has increased in Norway [6], the underlying cause has remained unknown. Although only data for a geographically defined subset of the Norwegian population have been investigated, the results currently represent the strongest evidence that the observed increased incidence is in fact attributed to HPV infection.

The main weakness of this study is the retrospective study design. A major strength, however, is the large num-

Table 4 – Uni- and multivariable Cox regression analysis for predictors of cancer-specific survival for node-positive PSCC patients

Characteristic	Univariable				Multivariable		
	N	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at surgery	94	1.02	1.0, 1.04	0.13	1.02	1.00, 1.05	0.10
HPV status	94						
HPV negative		–	–		–	–	
HPV positive		0.48	0.27, 0.86	0.01	0.54	0.30, 0.99	0.04
Lymph node stage	94						
pN1		–	–		–	–	
pN2		0.80	0.32, 2.03	0.64	0.88	0.34, 2.27	0.8
pN3		2.49	1.20, 5.15	0.01	2.47	1.08, 5.62	0.03
Adjuvant treatment	94						
No		–	–		–	–	
Yes		1.22	0.65, 2.28	0.53	0.87	0.42, 1.80	0.7

CI = confidence interval; HPV = human papillomavirus; HR = hazard ratio; PSCC = penile squamous cell carcinoma.

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ber of cases supported by comprehensive clinicopathological and outcome data. Statistical corrections with *p*-value adjustment have not been performed. Results should therefore be interpreted in the context of multiple testing [31].

The HPV DNA analysis was performed by different methods in the two cohorts. However, identical results were found for the five patients registered in both cohorts. Moreover, currently a universal method for detecting HPV does not exist [32]. Multiple types were found only in the second cohort, most likely due to the hybridization method of multiplex HPV genotyping [17].

An increasing proportion of HPV-related tumors over time could potentially be caused by reduced tissue quality of the oldest FFPE blocks, resulting in more false negative HPV DNA examinations in the earlier period. However, HPV DNA was detected in tumors from all time periods (Fig. 1A), and an increasing proportion of HPV-positive examinations were also found for the three most recent decades, supporting the validity of the results.

With a limited number of mortalities due to PSCC, even a small number of incorrect causes of death classifications can lead to erroneous conclusions. In this study, however, similar results were obtained for both CSS and net survival. This serves as a strong indication of the correctness of CSS, since the net survival is independent of the cause of death [22].

5. Conclusions

This study demonstrates that the detection of HPV DNA in tumor tissue was associated with significantly better CSS for node-positive penile cancer patients. One possible explanation could be the reduced overall burden of node-positive disease for patients with HPV-positive tumors. Moreover, the proportion of HPV DNA–positive penile cancers has increased significantly in Western Norway over the past 50 yr. These findings may have clinical implications in guiding treatment and follow-up of penile cancer patients.

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***Author contributions*:** Christian A. Moen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Moen, Falkenthal, Beisland.
Acquisition of data: All authors.
Analysis and interpretation of data: Moen, Falkenthal, Nygård, Beisland.
Drafting of the manuscript: Moen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Moen, Falkenthal, Beisland.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.10.013.

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