# Penile Cancer

**Chapter** · January 2018

DOI: 10.1093/oso/9780190238667.003.0055



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**Note: This is the accepted manuscript version of a book chapter, which may be cited as follows:**
**Frisch M. 2018. Penile Cancer. In: Thun M J, Linet M S, Cerhan J S, Schottenfeld D (Eds.), Cancer Epidemiology and Prevention (4th ed., pp. 1029-1038). Oxford University Press, New York.**

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# CANCER Epidemiology and Prevention

FOURTH EDITION

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# Chapter 55
# Penile Cancer

## Overview

Penile cancers are rare primary malignancies located on the glans, foreskin, or shaft of the penis, excluding the urethra. The vast majority of penile cancers are epithelial tumors representing histological subtypes of squamous cell carcinoma (SCC). Most penile SCCs are believed to develop through preinvasive lesions known as penile intraepithelial neoplasia and penile carcinoma *in situ*.

Penile cancers account for 0.1%–0.3% of all incident cancers (excluding non-melanoma skin cancers) in the United States and other developed countries and up to 1% of all cancers in some countries in sub-Saharan Africa. Annual incidence rates per 100,000 men (world standardized) are typically between 0.3 and 1.0 in developed countries, being 0.5 in the United States. During 2002–2011, SEER data showed rather stable penile cancer rates with no statistically significant changes in incidence or mortality.

Being rare in men younger than 40 years, penile cancers are typically diagnosed among men above age 60. The 5-year relative survival rate after penile cancer was 67% for all stages combined in US patients recorded in SEER registries during 2004–2010, with foreskin cancers having a more favorable prognosis than cancers at other penile sites.

The two most important risk factors for penile cancer are pathological phimosis and infection with high-risk types of human papillomaviruses (HPV), which are both preventable conditions. Non-surgical strategies to reduce the frequency of pathological phimosis need consideration, particularly because rates of newborn circumcision are declining in the United States and elsewhere. Increased awareness among doctors and parents about the importance of non-

interference with the physiological foreskin separation process in young boys, and the promotion of safe-sex practices, possibly combined with preadolescent gender-neutral HPV vaccination programs, will likely reduce the frequencies of pathological phimosis and sexually acquired HPV infections and, eventually, reduce the burden of penile cancer at the population level.

## Introduction

Penile cancer is one of the rarest malignancies for which site-specific data are available in cancer registries. In 2003–2007, penile cancers accounted for 0.15% of all incident cancers in the United States, thus ranking 43rd in incidence among all site-specific cancers in US males. Penile cancer is not among the 10 most common malignancies in males in any national cancer registry; even in high-incidence regions of South America, Africa, and Asia, the risk of developing penile cancer before age 75 years is below 0.4% (Forman et al., 2013).

## Tumor Classification

In studies reporting on the exact penile site of origin, usually between one-quarter and one-half of penile cancers cannot be accurately categorized. Generally, however, whether in circumcising or non-circumcising cultures, more than half of assessable penile cancers originate in the glans, followed by cancers of the foreskin. Penile shaft cancers are rare and may comprise cutaneous malignancies that are indistinguishable from non-genital skin cancers (Barnholtz-Sloan et al., 2007; Chaux et al., 2013; Daling et al., 2005; Krustrup et al., 2009; Maiche and Pyrhönen, 1990).

By far, most penile cancers are variants of SCC. Of 6539 invasive penile cancers in the United States diagnosed in 1995–2003, 93% were penile SCC (Goodman et al., 2007). In an

international study of 1266 invasive penile cancers from four continents, 99.8% of tumors were invasive SCC (Backes et al., 2009).

As with cancers at other anogenital sites, including the anus, vulva, vagina and cervix, a considerable proportion of penile SCCs are believed to emerge through consecutive grades of premalignant squamous intraepithelial lesions. Such penile SCCs and their precursor lesions are often found to contain DNA from high-risk HPV types known to be causally involved in the majority of cervical cancers (see Chapter 24). Other penile SCCs develop without the involvement of HPV (Rubin et al., 2001).

## Descriptive Epidemiology

Rates of penile cancer incidence and mortality vary substantially among populations around the world, and there is considerable variation by age, race/ethnicity, and socioeconomic patterns within populations. In the following, unless otherwise specified, age-standardization to the world standard population is used to present summary measures of penile cancer incidence, as well as for geographical comparisons between rates.

### International Variation in Incidence

In most developed parts of the world, penile cancers occur at annual incidence rates of 0.3–1.0 per 100,000 men. However, there is major geographic variation (Forman et al., 2013). Based on 2003–2007 data from national cancer registries and regional registries with at least 10 recorded cases in the 5-year period, the range in annual penile cancer incidence per 100,000 (all racial/ethnic groups combined) was 0.1–2.2 in Asia, 0.2–1.0 in North America, 0.3–0.6 in Oceania, 0.4–1.9 in Europe, 0.6–3.3 in Central and South America, and 0.8–2.6 in Africa. In the United States, rates per 100,000

were between 0.3 and 0.8 in all states, except in Delaware (0.2) and Puerto Rico (1.8) (Figure 55.1). Internationally, incidence rates per 100,000 men were low in Israel (0.1), Japan (0.2), South Korea (0.2), and China (0.3), intermediate in New Zealand (0.4), Australia (0.5), the United States (0.5), Canada (0.5), and most countries of Europe (0.5–1.0), and higher in some regions of Thailand (Chiang Mai: 1.5), Spain (Cuenca: 1.9), India (Barshi: 2.2), Uganda (Kampala: 2.2), Malawi (Blantyre: 2.6) and Brazil (Goiania: 3.3) (Figure 55.2).

## Incidence and Mortality in the United States

Based on SEER data for the period 2008–2012, the overall annual penile cancer incidence (all races combined) was 0.9 per 100,000, and mortality was 0.2 per 100,000 (US 2000 standardized) (SEER, 2015b).

## Age-Specific Patterns

Based on SEER data 2007–2011, the median age at penile cancer diagnosis in US males was 68 years, being 68 years in whites and 62 years in blacks. For all races combined, age-specific incidence rates per 100,000 person-years increased steadily with age, from 0.5 in men aged 40–44 years to between 4.0 and 7.5 in men aged 70 years or older (SEER, 2015a). Correspondingly, only 2.9% of 1530 invasive penile SCCs diagnosed in The Netherlands in 1989–2006 were in men below 40 years of age (Graafland et al., 2011).

## Temporal Trends in Incidence

In the United States and several countries in Europe (Frisch et al., 1995; Pukkala and Weiderpass, 2002) and Africa (Wabinga et al., 2014), the incidence of penile cancer has declined over the past

several decades. Based on SEER data, there has been a continuous downward trend in penile cancer incidence of approximately 1.7% per year during 1973–2002, declining from 0.84 per 100,000 (US 2000 standardized) in 1973–1982 to 0.58 per 100,000 in 1993–2002 (Barnholtz-Sloan et al., 2007). However, the decline appears to have stopped; an insignificant increase in incidence of 0.4% per year took place during 2002–2011 (SEER, 2015a). In Denmark, penile cancer incidence declined from 1.15 per 100,000 (world standardized) in 1943–1947 to 0.82 per 100,000 in 1988–1990 (Frisch et al., 1995), but this decline has been followed by an insignificant increase in recent years (Ulff-Møller et al., 2013). Other observations in Europe corroborate the impression that the decline in penile cancer incidence has stopped. A study in the Netherlands showed a stable incidence of invasive penile SCC between 1989 and 2006 (Graafland et al., 2011). In England, a study of 9,690 men diagnosed with penile cancer between 1979 and 2009 showed an annual increase in age-standardized incidence of 0.007 per 100,000 person-years, amounting to an overall increase of 21% during the 31-year observation period (Arya et al., 2013).

## Racial/Ethnic Patterns of Incidence in the United States

Using SEER data from 2003–2007, the overall age-standardized incidence of penile cancer in the United States was 0.5 per 100,000 (world standardized), but there is considerable variation among racial/ethnic groups. Lowest rates were for Asian/Pacific Islanders (0.3), followed by non-Hispanic whites (0.4), African Americans (0.5), and Hispanic whites (0.9) (Forman et al., 2013). In one study based on 1993–2002 SEER data, American Indians/Alaskan Natives had the second highest incidence (0.8) after non-Hispanic whites (Barnholtz-Sloan et al., 2007).

## Socioeconomic Patterns

Some studies suggest an inverse relationship between socioeconomic status and penile cancer risk. In 1998–2003, rates of penile SCC were 43% higher in areas of the United States with 20% or more of the population at the poverty level compared with areas with less than 10% poverty (Hernandez et al., 2008a). High educational level was associated with reduced risk in a US/Canadian case-control study (Maden et al., 1993), but studies in Scandinavia have failed to confirm an independent influence of socioeconomic status. Compared with population controls, penile cancer patients in Sweden more often belonged to the two lowest socioeconomic classes, but after adjustment for tobacco smoking, the association with social group disappeared (Hellberg et al., 1987). Danish men with penile cancer did not differ from control subjects with respect to years at school or level of education (Madsen et al., 2008), and in Finland, there was no significant difference in penile cancer incidence among men in five different social class categories (Pukkala and Weiderpass, 2002). The univariate association observed in some studies with indicators of low socioeconomic status, which disappears after adjustment for other covariates, likely reflects a higher prevalence of penile cancer risk factors in socially underprivileged groups.

## Marriage and Partner Status

Studies rather consistently find that risk of penile cancer is low in married men compared with men in other marital status categories. In a study from California based on 1972–1981 data, researchers reported that penile SCC patients above age 45 years were significantly more likely to be separated or divorced than male residents in the underlying study area (Peters et al., 1984). In western Washington in 1979–1998, men with invasive or *in situ* penile cancer were considerably more likely to have remained unmarried than age-matched population controls (Daling et al., 2005). Men diagnosed in 1943–1990 with invasive penile cancer in Denmark were more likely to have remained

unmarried than patients with colon or stomach cancer, and unmarried penile cancer patients were younger at diagnosis than patients in other marital status categories (Frisch et al., 1995). Danish patients diagnosed in 1982–2010 with invasive or *in situ* penile SCC were more likely to be unmarried, divorced, or widowed than other Danish men (Ulff-Møller et al., 2013).

## Risk Factors

Due to the rareness of penile SCC, case-control studies addressing its risk factors often include non-SCC penile cancers and cases of penile carcinoma *in situ* to gain statistical power. This should be kept in mind, because risk factors, or their strength of association, may differ considerably between histological types and between preinvasive and invasive penile SCC (Daling et al., 2005; Madsen et al., 2008; Tseng et al., 2001).

## High-Risk Human Papillomavirus Infection

Similar to SCCs of the vulva (Ueda et al., 2011) (see Chapter 49) and anus (Frisch et al., 1999) (see Chapter 37), penile SCCs appear to develop through at least two etiologically distinct pathways, one of which depends on sexually acquired infections with high-risk HPV types, and one (or more) that is unrelated to HPV infection (Krustrup et al., 2009; Mannweiler et al., 2013; Rubin et al., 2001). A detailed description of the molecular mechanisms involved in HPV-associated cancers is provided elsewhere (see Chapter 24).

Two large reviews have evaluated the worldwide prevalence of HPV in invasive penile cancers, showing an overall prevalence of HPV in 47%–48% of these tumors (Backes et al., 2009; Miralles-Guri et al., 2009). In a review of 30 studies with a total of 1266 invasive penile SCCs from Europe, North America, South America, and Asia, the overall HPV prevalence in tumor tissue was

48%, ranging from 40% of cancers from South America to 59% in Asia (Backes et al., 2009). The proportion of HPV-associated penile SCCs increased over time, from 43% in studies from 1989–1995 to 54% in studies from 2003–2007, and even higher proportions of HPV-positive invasive penile SCCs were reported in recent studies from Belgium (61%), Denmark (68%), the United States (70%), Spain (78%), Thailand (82%), and South Africa (88%) (D'Hauwers et al., 2012; Daling et al., 2005; Lebelo et al., 2014; Madsen et al., 2008; Pascual et al., 2007; Senba et al., 2006). In contrast, a small study from Japan, a low-incidence country for penile cancer, found only 12% of invasive penile SCCs to be HPV-positive as determined by the polymerase chain reaction (PCR) technique (Yanagawa et al., 2008). By histological subtype, penile SCCs of the warty/basaloid type have been found consistently more often to be positive for high-risk HPV types than penile SCCs of the keratinizing or verrucous types (Backes et al., 2009; Bezerra et al., 2001a; Krustrup et al., 2009; Miralles-Guri et al., 2009; Pascual et al., 2007). As seen for premalignant and invasive cancers at other anogenital sites, proportions of HPV-positive *in situ* penile SCCs are generally higher than invasive penile SCCs (D'Hauwers et al., 2012; Ferrandiz-Pulido et al., 2013; Krustrup et al., 2009; Rubin et al., 2001).

As for other HPV-associated anogenital malignancies, the predominant HPV type involved in penile cancer has been HPV 16 in a vast majority of studies. In a review of 31 studies with a total of 1466 penile cancers, the overall HPV prevalence in tumor tissue was 47%. Across histological types, HPV 16 was by far the most common HPV type detected, accounting for 60% of HPV-positive penile cancers, followed by HPV 18 (13%) and HPV 6/11 (8%) (Miralles-Guri et al., 2009). However, there are geographic exceptions. In northern Thailand, PCR-determined HPV-positivity was established in 82% of 65 invasive penile cancers, and the predominant HPV type, present in 55% of cases, was HPV 18; HPV 16 was detected in only one case of invasive penile cancer in that study (Senba et al., 2006).

Despite the low proportion of HPV-associated penile SCCs in some low-incidence countries (Yanagawa et al., 2008), the international variation in overall penile cancer incidence appears not simply to be explained by a higher incidence of HPV-positive tumors in high-incidence geographic areas. In one study comparing tumor tissues from two countries with intermediate (United States) and high (Paraguay) overall penile cancer incidence, the proportion of warty/basaloid SCCs, the histological subtypes most strongly associated with HPV infection, were not higher in Paraguay than in the United States (Rubin et al., 2001). Also, overall proportions of HPV-positive invasive penile cancers, as determined by either PCR or immunohistochemical analysis, have been found to be comparatively low in high-incidence countries like Brazil (31%) and Paraguay (36%) (Bezerra et al., 2001b; Chaux et al., 2013).

## Other Sexually Transmitted Diseases

In some studies carried out before HPV was established as a risk factor, a history of sexually transmitted infections other than HPV was noted to be more common among penile SCC patients than controls (Brinton et al., 1991). However, while there is no evidence to support a genuine causal role for any specific sexually transmitted infections other than HPV, presumably any type of penile ulceration, including lesions caused by syphilis, chancroid, or genital herpes simplex virus infection, might provide easy access for cancer-associated HPV types to basal layers of the penile epithelium and thus may facilitate HPV infection. Additionally, repeated episodes of penile inflammation from sexually transmitted infections might be associated with an increased risk of pathological phimosis, an established risk factor for penile cancer (Brinton et al., 1991; Daling et al., 2005; Madsen et al., 2008).

## Heterosexual Behavior

Various indicators of a non-monogamous heterosexual lifestyle have been linked to an increased risk of penile cancer. Married men are at lower risk of penile SCC than unmarried and divorced men (Daling et al., 2005; Peters et al., 1984), which plausibly reflects less stable partner relations in unmarried men and thus a higher risk of infection with high-risk HPV types. A national study of 1139 invasive penile SCCs in Denmark in 1982–2010 showed a significant 13% increase in penile cancer risk with each additional prior female cohabiting partner (Ulff-Møller et al., 2013).

Several studies (Chaux et al., 2013; Daling et al., 2005; Maden et al., 1993; Madsen et al., 2008; Tseng et al., 2001), though not all (Brinton et al., 1991; Hellberg et al., 1987), have found a higher risk of penile cancer, notably HPV-positive penile cancers, in men with many partners. A case-control study in western Washington of 137 patients with invasive or *in situ* penile cancers diagnosed in 1979–1998 and 671 population controls showed a statistically significant association between the lifetime number of female partners and penile cancer risk in men who had been circumcised before age 10 years, but not in men with a foreskin (Daling et al., 2005). In Denmark, men diagnosed in 1993–1998 with invasive or *in situ* penile SCC were more likely than controls to report sexual debut before age 17 and to have a high lifetime number of female partners, particularly before age 20 years (Madsen et al., 2008). Additionally, Danish penile SCC patients reported receiving oral sex considerably more often than controls, a sexual practice that was not associated with penile cancer risk in a US study (Maden et al., 1993). In a study from rural areas of Brazil, a larger proportion of penile cancer patients than controls had visited a prostitute (74% vs. 64%) (Zequi et al., 2012).

## Homosexual Behavior

Whereas indicators of unstable heterosexual partner relations have been linked to an increased risk of penile cancer in several studies, there is no compelling evidence to suggest a link between same-sex sexual activity and penile cancer risk. Among the penile cancer patients in the study from western Washington, 4% reported a bisexual/homosexual orientation, which was indistinguishable from the 3% bisexual/homosexual men among the population controls (Daling et al., 2005). Of 69 Danish men with penile cancer, 3% reported ever having had homosexual activity versus 2% of 179 controls (Madsen et al., 2008). In the Netherlands, only 1% of a series of 316 patients with invasive penile cancer reported having a male partner (de Bruijn et al., 2013).

Compared with heterosexual men, the lack of an apparent excess of *in situ* and invasive penile cancers among immunocompetent men who have sex with men (MSM) is interesting, because the average number of sexual partners, and thus the risk of HPV exposure, may be considerably higher in MSM than in heterosexual men (Laumann et al., 1994). HPV-associated precancerous lesions and invasive SCCs of the anus and anal canal occur at markedly elevated rates in MSM (Frisch et al., 1997; Palefsky et al., 2011). Consequently, men who engage in unprotected anal sex with unstable same-sex partners would expectedly also be at elevated risk of penile high-risk HPV infections, which, over time, should translate into elevated rates of precancerous and invasive penile SCCs among MSM. However, even among men with AIDS, the relative risk for invasive penile cancer is only around one-sixth of that for invasive anal cancer (Grulich et al., 2007), and standardized incidence ratios of *in situ* and invasive penile cancer are considerably lower in MSM than in heterosexual men with AIDS (Chaturvedi et al., 2009; Frisch et al., 2000).

It is unclear why sexually active MSM at high risk of penile HPV infections do not experience markedly higher rates of *in situ* and invasive penile SCC than heterosexual men. One possible explanation might be that the *per act* risk of HPV transmission is greater during opposite-

sex than same-sex sexual activities; among heterosexual couples, the rate of HPV transmission has been found to be substantially higher from women to men than from men to women (Hernandez et al., 2008b). This might reflect a lower viral load transmitted to the penis during oral or anal sex with an infected male partner than during vaginal intercourse with an infected female partner, or that the keratinized epithelium of the penis is less susceptible to HPV infection than the mucosal linings of the anal canal (Kreuter and Wieland, 2009). Alternatively, if MSM on average exhibit greater awareness and receive appropriate treatment more promptly than heterosexual men when detecting early signs of HPV-related penile morbidity, this might contribute to the rather inconspicuous risk of HPV-associated penile malignancies among MSM.

## Other Sexual Behavior

A multicenter case-control study with 118 penile cancer patients and 374 controls in rural areas of Brazil reported positive associations of penile cancer risk with several indicators of sexual promiscuity. In multivariate analysis, however, the only sexual behavior that remained significantly associated with elevated penile cancer risk was a history of ever having had sex with domestic animals (OR = 2.1), a common habit during adolescence and young adulthood reported by 45% of penile cancer patients and 32% of control subjects (Zequi et al., 2012).

## Phimosis and Foreskin Status

### Distinction Between Foreskin Non-Retractability and Pathological Phimosis

Pathological phimosis, a chronic state of foreskin non-retractability, has been recognized as a major risk factor for penile cancer for more than a century (Barney, 1907), and recent case-control studies have confirmed this. However, terms used for foreskin non-retractability in boys and men often fail

to distinguish between age-appropriate foreskin immaturity in childhood and adolescence, which is unrelated to penile cancer risk, and cases of chronic, pathological phimosis. This is unfortunate, because traumatic handling of physiological foreskin non-retractability in infancy and childhood is a likely cause of pathological phimosis in boys and men (Kaplan and McAleer, 2005; Smey and Travis, 1987).

The foreskin is fused to the glans in almost all newborn males, and the timing of the normal physiological process of foreskin separation is highly variable (Gairdner, 1949). Most boys gradually develop full foreskin retractability during preschool and school years, and only a few boys will have a foreskin that cannot be freely retracted by the end of puberty (Hsieh et al., 2006; Øster, 1968). Unfortunately, the inability to retract the foreskin over the glans in infants and toddlers is often mistaken for pathological phimosis. Studies in the United Kingdom have shown that boys referred to a pediatric surgery unit for evaluation of foreskin non-retractability rarely have true pathological phimosis with circumferential scarring of the preputial tip (Huntley et al., 2003; Rickwood and Walker, 1989). Specifically, among 420 boys aged 0–14 years, pathological phimosis was nonexistent in boys under the age of 5 years; in boys referred with a non-retractile foreskin at age 5–6 and 13–14 years, however, pathological phimosis was present in 15% and 73%, respectively (Rickwood and Walker, 1989).

## Pathological Phimosis and Risk of Penile Cancer

In Paraguay, clinical evaluation of 215 men without cancer showed that the foreskin covered the penile glans entirely in 77%. Among penile cancer patients, the corresponding proportion was 78%, implying that a glans-covering foreskin *per se* is an unlikely risk factor for penile cancer. However, while 7% of the healthy men with long foreskins could not retract their foreskin over the glans, the corresponding proportion among penile cancer patients was 52% (Velazquez et al., 2003). Several

early studies reported very high proportions (74%–92%) of penile cancer patients with a history of pathological phimosis (Barney, 1907; Barringer and Dean, 1924; Dean, 1929; Marcial et al., 1962). Lower proportions (34%–52%) of pathological phimosis in penile cancer patients in more recent studies likely reflect the impact of improved sanitary conditions over time, possibly combined with an increased frequency of phimosis-independent HPV-associated penile cancers (Brinton et al., 1991; Daling et al., 2005; Madsen et al., 2008; Tseng et al., 2001).

Several case-control studies have found a strong positive association between pathological phimosis and risk of invasive penile cancer, with relative risk estimates between 5 and 65 (Brinton et al., 1991; Daling et al., 2005; Harish and Ravi, 1995; Hellberg et al., 1987; Madsen et al., 2008; Tseng et al., 2001). Two of these showed that the repeatedly noted inverse association of infant male circumcision with invasive penile cancer risk was explained entirely by the reduced risk of pathological phimosis in circumcised men (Daling et al., 2005; Tseng et al., 2001).

## Penile Inflammatory Conditions

Inflammation of the glans (balanitis), the prepuce (posthitis) or both (balanoposthitis) have been linked to an increased risk of penile cancer (Daling et al., 2005; Hellberg et al., 1987; Madsen et al., 2008; Tseng et al., 2001). However, because penile inflammation is sometimes accompanied by pathological phimosis or sexually transmitted diseases, it is not clear whether penile inflammatory conditions are independent risk factors or are part of the same processes that link pathological phimosis and HPV infections to penile cancer risk.

Penile inflammatory lesions may occur on an infectious basis, resulting from bacterial, viral, or yeast infections. For more than a century, inflammation and ulceration associated with syphilis were believed to be etiologically involved (Dean, 1929). Indeed, second only to phimosis, syphilis

was considered the most important risk factor for penile cancer (Barney, 1907), an idea that has now been abandoned (Frisch et al., 1996).

Between 33% and 49% of male patients with psoriasis have penile involvement (Meeuwis et al., 2011). Some studies have reported an increased incidence of penile cancers in patients with psoriasis and a strong dose–response relationship between oral psoralen drugs in combination with ultraviolet A radiation (PUVA) and penile cancer risk in these patients (Boffetta et al., 2001; Perkins et al., 1990; Stern, 1990).

Lichen sclerosus, or balanitis xerotica obliterans, is a chronic, progressive inflammatory dermatosis of unknown etiology that predominantly afflicts genital skin, with a prevalence among prepubertal boys around 0.1%–0.4% (Becker, 2011). It is not clear if pediatric onset lichen sclerosus is associated with increased penile cancer risk (Poindexter and Morrell, 2007). However, a recent review suggested that 4%–8% of adult men with lichen sclerosus will eventually develop penile SCC (Clouston et al., 2011). In a British study of 26 patients with penile SCC, 50% of tumors also showed histological evidence of lichen sclerosus (Prowse et al., 2008). However, while lichen sclerosus of the vulva is considered an established precursor lesion for vulvar SCC, it remains debated whether penile lichen sclerosus is a genuine penile SCC precursor (Clouston et al., 2011).

## Hygiene

Undue manipulation and forceful retraction of the immature foreskin of infants and toddlers is likely to explain some proportion of seemingly idiopathic cases of pathological phimosis. Attempts to cleanse the subpreputial space with soap in boys whose foreskins have not completely detached from the glans may result in chemical irritation, balanitis, or balanoposthitis, leading to ulceration

and, eventually, scarring and shrinking of the foreskin, a condition that may ultimately give rise to pathological phimosis (Kaplan and McAleer, 2005; Smey and Travis, 1987).

Smegma, a physiological lubricant composed of immunologically active compounds, desquamated cells, and commensal bacteria, may accumulate under the prepuce of both males and females, particularly in association with foreskin non-retractability and low standards of personal hygiene. Early studies suggested a strong positive association of smegma with the risk of invasive penile cancer (Pratt-Thomas et al., 1956). However, current beliefs are that, after taking phimosis and HPV infections into account, smegma is not an independent risk factor for penile SCC (Van Howe and Hodges, 2006).

## Circumcision

It was long believed that boys circumcised soon after birth were almost 100% protected against penile cancer development (Schoen, 1996; Schrek and Lenowitz, 1947; Wolbarst, 1932). In recent years, however, studies have shown that a non-trivial proportion of penile cancers occur in neonatally circumcised men.

A case-control study in California with 100 patients with penile cancer (50 *in situ*, 50 invasive) and 100 matched neighborhood controls found no evidence of a link between childhood circumcision and *in situ* penile cancer. Risk of invasive penile cancer was non-significantly reduced in men circumcised in childhood but, upon restriction to men without a history of phimosis, there remained no indication of a protective effect of childhood circumcision (Tseng et al., 2001).

A subsequent case-control study in western Washington confirmed these findings, reporting that 37% of 75 patients with *in situ* penile cancer and 56% of 62 patients with invasive penile cancer had been circumcised before age 10 years; of a total of 64 patients with *in situ* or invasive penile cancer who had been circumcised in childhood, 92% had been circumcised at birth (Daling et

al., 2005). Overall, no association was seen between childhood circumcision and risk of *in situ* penile cancer, but men who were not circumcised in childhood were at elevated risk of invasive penile cancer (OR = 2.3; 95% CI: 1.3–4.1). As in the study by Tseng et al., however, stratification on history of phimosis revealed that childhood circumcision was not protective against invasive penile cancer in men without a history of phimosis. Indeed, genitally intact men without a history of phimosis were at non-significantly reduced risk of invasive penile cancer compared with men circumcised in childhood (OR = 0.5; 95% CI: 0.1–1.7) (Daling et al., 2005). Based on a review of the existing literature, there is no evidence to suggest that circumcision in adulthood protects against penile cancer (Larke et al., 2011).

Internationally, there is no clear link between rates of infant male circumcision and penile cancer incidence. Israel, with its extremely high rate of infant male circumcision, has a very low annual incidence of penile cancer (0.1 per 100,000, world standardized). However, the corresponding rate of penile cancer in the United States (0.5), where neonatal circumcision is a widespread cultural norm, is higher than in New Zealand (0.4), where circumcision is rare, and in China (0.3) and Japan (0.2), where this childhood surgery is almost unheard of (Figure 55.2). While many cultural and behavioral differences may contribute to the international variation in incidence, the proportion of men without a foreskin in a given population appears not to be a determining factor.

## Circumcision in Childhood and Risk of HPV Infection

While the often reported inverse association of childhood circumcision with invasive penile cancer risk seems to be explained to a large extent by the low risk of pathological phimosis in circumcised men (Daling et al., 2005; Tseng et al., 2001), theoretically, childhood circumcision might also modify the individual's risk of acquiring high-risk HPV infections in adulthood. This, however,

does not appear to be the case. In a meta-analysis of 21 studies with a total of 8046 circumcised and 6336 genitally intact men, HPV prevalence was lower in circumcised men, but there was no significant evidence of a lower risk of HPV acquisition (RR = 1.01; 95% CI: 0.66–1.53) or of greater HPV clearance (RR = 1.57; 95% CI: 0.51–4.89) in circumcised men (Albero et al., 2012).

A cohort study of 4033 healthy men age 18–70 years in the United States, Brazil, and Mexico showed that a man's foreskin status has no impact on his risk of penile HPV acquisition, whether considering all oncogenic, all non-oncogenic, or all HPV types combined (Albero et al., 2014; Giuliano et al., 2011). Specifically, the incidence rate of infection with oncogenic HPV types per 100 person-years was 28.7 in circumcised men versus 28.4 in genitally intact men, and the corresponding cumulative 12-month incidences were 23.3% and 23.7%, respectively. When considering HPV 16 alone, the high-risk HPV type most strongly associated with penile cancer risk, the cumulative 12-month incidence was marginally higher in circumcised men (6.6% vs. 5.1%). The median time used to clear an incident HPV 16 infection was significantly longer in circumcised than genitally intact men (11.1 vs. 7.1 months), with an associated hazard ratio for HPV 16 clearance of 0.56 (95% CI: 0.42–0.75) (Albero et al., 2014). Circumcision before age 18 years thus appears not to provide protection against penile HPV infections, and may even be associated with a decreased ability to clear penile cancer–associated HPV infections.

In Uganda, the incidence of multiple, but not single infections with high-risk HPV types was reduced in the first 2 years after surgery among men who underwent circumcision in adulthood (Gray et al., 2010). However, as there is no evidence to suggest a protective effect of adult circumcision against invasive penile cancer development (Larke et al., 2011), such findings are of limited relevance to penile cancer etiology and prevention.

It has been estimated that between 909 and over 322,000 boys will have to be circumcised to prevent one case of penile cancer (Learman, 1999; Swafford, 1985). Considering the rareness of

this malignancy and the modest reduction in both relative and absolute risk associated with childhood circumcision (Larke et al., 2011), international medical consensus is lacking regarding the medical and ethical justifiability of early life circumcision for the prevention of penile cancer and other rare diseases.

## Tobacco

Cigarette smoking has been linked to increased penile cancer risk in several case-control studies (Daling et al., 2005; Harish and Ravi, 1995; Hellberg et al., 1987; Maden et al., 1993; Tseng et al., 2001; Zequi et al., 2012). In one study, researchers found a strong, positive association of current tobacco smoking with risk of invasive (OR = 4.5), but not *in situ* (OR = 1.5) penile cancer, suggestive of a late-stage, promotional role of smoking (Daling et al., 2005). This theory, however, found little support in another US study showing a stronger association of current heavy tobacco smoking with risk of *in situ* penile SCC (OR = 7.1) than with invasive penile SCC (OR = 4.2) (Tseng et al., 2001). A study in Denmark found no difference in proportions of current smokers between penile SCC patients and controls, thus failing to support tobacco smoking as an etiological factor (Madsen et al., 2008).

## Immunosuppression

Large-register studies have shown a markedly increased risk of both *in situ* and invasive penile cancers in patients with AIDS (Chaturvedi et al., 2009; Frisch et al., 2000). Overall, standardized incidence ratios were 19.7 and 5.3 for *in situ* and invasive penile cancer, respectively, in the interval 4–60 months after AIDS onset; calculations spanning the period from 5 years before to 5 years after AIDS onset showed that the risk of *in situ* penile cancer increased significantly with increasing

duration of immunosuppression, but the same was not seen for invasive penile cancers (Chaturvedi et al., 2009). Theoretically, this might reflect a role of poor immunological control in the acquisition of genital HPV infections, the establishment of HPV persistence, and subsequent early steps of malignant transformation, whereas progression to invasive penile cancer might not be equally influenced by immunosuppression. However, long-term follow-up of 263,254 AIDS patients showed a relative risk of penile cancer that increased from 3.2 in the interval 3–5 years after AIDS diagnosis to 8.5 in the interval 6–10 years after (Simard et al., 2010).

Register linkage studies in Australia and the United States have documented a marked excess of anogenital HPV-associated *in situ* and invasive cancers among organ transplant patients (Madeleine et al., 2013; Vajdic et al., 2006). Among 187,649 US organ transplant recipients, standardized incidence ratios of *in situ* and invasive penile cancers were 18.6 and 3.9, respectively (Madeleine et al., 2013).

Other immunosuppressed states have been linked anecdotally to penile cancer risk. Case reports suggest that biological treatment of autoimmune rheumatic or dermatologic diseases with anti-TNFa medications such as adalimumab and etanercept may be associated with both HPV-positive and HPV-negative penile malignancies (Fryrear et al., 2004; Kreuter et al., 2011).

## Pathogenesis

At least two distinct pathogenetic pathways may lead to penile SCC; one that depends on infection with certain high-risk HPV types, and one (or more) that is independent of HPV. High-risk HPV types are involved in around half of invasive penile SCCs, with HPV 16 as the predominant type (Backes et al., 2009; Miralles-Guri et al., 2009).

Papilloma virions transmitted through sexual contact with an infected partner may infect basal layers of penile epithelia and give rise to a cascade of molecular events that may eventually

transform normal cells to the malignant phenotype. Following initial HPV infection, which is thought to depend on viral access through epithelial lesions, a complex series of host–virus interactions take place. The crucial features responsible for HPV neoplastic effects are the interactions of viral proteins E6 and E7 with pRb and p53-related cellular pathways, respectively, thus interfering with normal cell-cycle regulation. A detailed description of the molecular mechanisms underlying the development of penile and other HPV-associated cancers is provided elsewhere (see Chapter 24).

Genital manifestations of dermatological diseases, including psoriasis, lichen planus, and lichen sclerosus, have been implicated in the etiology of some cases of penile SCC, notably subtypes where HPV DNA is not systematically detected in the tumor tissue. However, the exact role of inflammatory skin lesions in the pathogenesis of penile SCCs is not well understood. Histopathological evaluation of 67 penile SCCs in Paraguay revealed lichen sclerosus in 67% of cases, particularly in HPV-negative penile SCCs (Chaux et al., 2013). The frequent coexistence of lichen sclerosus and differentiated penile intraepithelial neoplasia in HPV-negative keratinizing penile SCC and the finding of lichen sclerosus in two-thirds of adult patients with phimosis have led researchers to suggest a common phimosis–lichen sclerosus pathway to HPV-independent penile SCC (Oertell et al., 2011).

## Survival

In a large international study, the overall 5-year relative survival rate after invasive penile cancer was 70% in Europe and 63% in the United States for the years 2002–2007 (Verhoeven et al., 2013). In England, 5-year relative survival increased from 61% to 70% between 1971 and 2010 (Arya et al., 2013).

## Socio-demographic Factors

In the United States, racial and ethnic differences in survival may reflect a higher proportion with regional or distal stage at diagnosis among African Americans and Hispanics than among non-Hispanic whites (Hernandez et al., 2008a). Five-year relative survival based on SEER data in 2004–2010 was 67% among whites and 61% among African Americans. Advanced age is associated with poorer survival, even after controlling for tumor characteristics at diagnosis (Graafland et al., 2011). In England, 5-year relative survival was 77% among patients under 60 years versus 53% among patients aged 80 years or more at diagnosis (Arya et al., 2013). Poor socioeconomic conditions and unmarried status may be associated with reduced survival, presumably due to more advanced disease at diagnosis among less privileged groups (Arya et al., 2013; Thuret et al., 2013).

## Tumor Characteristics

Penile subsite, tumor stage, histological grade, and overall clinical stage at diagnosis bear importantly on both tumor management and survival (Graafland et al., 2011; Moses et al., 2014; Solsona et al., 2001). Cancers located in the penile foreskin tend to have a more favorable prognosis than those involving other parts of the penis (Shabbir et al., 2014); in one large US study, patients with foreskin SCC had significantly higher disease-specific 10-year survival (89%) than patients with cancers at other penile subsites (79%), after controlling for age, stage, and tumor grade (Tyson et al., 2012). Among 1530 Dutch penile cancer patients diagnosed in 1989–2006, only 15% were clinical disease stage III or IV tumors. Ten-year relative survival was 93%, 89%, and 81% for patients with clinical stage 0, I, and II tumors, respectively, and less than 50% for patients with stage III tumors. Among patients with stage IV tumors, 2-year relative survival was only 21% (Graafland et al., 2011).

Immunohistochemical examination for the tumor suppressor protein p16ink4a, a surrogate marker of high-risk HPV infection, is increasingly used in clinical practice (Ferrandiz-Pulido et al., 2013; Mannweiler et al., 2013). Penile cancers that exhibit strong nuclear and cytoplasmic staining for p16ink4a throughout the dysplastic epithelium are associated with reduced risk of lymph node metastases and a more favorable prognosis (Bethune et al., 2012; Ferrandiz-Pulido et al., 2013; Gunia et al., 2012a; Poetsch et al., 2011). Conversely, penile tumors expressing p53 immunoreactivity are associated with increased rates of local spread to pelvic lymph nodes and poorer survival (Gunia et al., 2012b; Liu et al., 2013; Zhu et al., 2007).

# Opportunities for Prevention

## Safe Sexual Practices

Promoting safe sexual practices is an important step toward improving sexual health in the population (Wittenberg and Gerber, 2009). The future burden of HPV-associated morbidities, including penile cancer, depends on the success of teaching current and future generations to consistently use condoms with new sexual partners, so as to reduce their risk of acquiring cancer-associated HPV infections (Baldwin et al., 2004; Hernandez et al., 2008b; Nielson et al., 2007).

## Phimosis Prevention

The two most well-established risk factors for penile cancer, pathological phimosis and infection with high-risk HPV types, are preventable conditions. Appropriate strategies to reduce their frequency in boys and men carry the potential for long-term reduction in penile cancer incidence (Verhoeven et al., 2013). Over the past several decades, the popularity of infant male circumcision

has declined in the United States and elsewhere around the world. While 64%–65% of boys were circumcised during their birth hospitalization in 1979–1981, the corresponding proportion had dropped to 56%–58% in 2008–2010 (Owings et al., 2013). Accordingly, increased focus should be on the prevention of phimosis by non-surgical means, a strategy that will also apply to that majority of countries around the world where routine infant male circumcision is not practiced.

The foreskin is fused to the glans at birth. However, there is a widespread misconception among doctors and parents that the foreskin should be forcibly manipulated back over the glans already in newborn boys (Steadman and Ellsworth, 2006). Such myths are rooted in outdated beliefs that a freely retractile foreskin is essential for proper penile hygiene in young boys, and that foreskin separation should be completed shortly after birth (Deibert, 1933). However, it is now widely recognized that the natural separation process usually takes several years, and that some boys only obtain full foreskin retractability in their mid-teens (Hsieh et al., 2006; Øster, 1968). Textbooks in pediatrics and neonatology warn against forced foreskin retraction, because the repeated sequence of laceration, bleeding, and inflammation with subsequent scarring may ultimately produce pathological phimosis (Kaplan and McAleer, 2005; Smey and Travis, 1987). In a small fraction of boys older than 5 years, the resulting pathological phimosis may be associated with lichen sclerosus (Chalmers et al., 1984; Clemmensen et al., 1988; Rickwood and Walker, 1989), a chronic inflammatory condition that has also been observed in some patients with HPV-negative penile cancers (Oertell et al., 2011). Counseling parents about their newborn son's normal penile anatomy and the natural separation process of the foreskin, and emphasizing that the boy should be the first to retract his foreskin over the glans (Metcalf et al., 1983; Wright, 1994), will likely reduce the number of boys and men with pathological phimosis and thereby provide primary prevention against a non-trivial fraction of penile cancers in the future.

## HPV Vaccination

HPV vaccination of boys to prevent condylomata acuminata and penile, anal, and oropharyngeal cancer precursors and invasive SCCs will hopefully become a cost-effective public health measure in the near future. This is not only relevant from a gender equality viewpoint; there is growing recognition that some boys and men will not be protected effectively against HPV infections through high vaccination coverage in girls, including men with unvaccinated female partners and MSM (Kirby, 2015; Stanley, 2014). In the Netherlands, one study suggested that gender-neutral HPV vaccination of 12-year old children compared favorably in terms of quality-adjusted life-years saved with already introduced vaccination programs against hepatitis B infection in infants (Bogaards et al., 2015). Future developments in vaccine pricing and uptake of HPV vaccination in girls will determine the cost-effectiveness of also offering HPV vaccination to boys (Bogaards et al., 2015; Bresse et al., 2014; Marty et al., 2013).

A nonavalent HPV vaccine has recently been approved for the prevention of HPV-associated anogenital lesions in the United States, Canada, and the European Union; in the United States it was approved for use in both females and males aged 9–26 years (Petrosky et al., 2015). Since HPV is involved in most cases of *in situ* penile SCC and in around half of invasive penile SCCs, gender-neutral HPV vaccination may contribute importantly to reducing the incidence of penile cancer, as well as of HPV-associated anal and oropharyngeal cancers in males. However, since 2011, when HPV vaccination was recommended for all boys aged 11–12 years in the United States, vaccine uptake has been slow. According to one survey, only around 35% of 13–17 year-old US boys had received at least one dose of HPV vaccine in 2013 (Stokley et al., 2014). Other countries have recently implemented gender-neutral HPV vaccination programs, including Canada, Australia, and Austria, which will likely speed up herd immunity, with a resulting rapid decline in viral load among both males and females in these populations (Stanley, 2014).

## Tobacco Prevention

While some studies suggest an increased risk of penile cancer in smokers, there is no consensus about its possible etiological role. If causally involved, quitting the habit, or never starting to smoke in the first place, will eliminate a cofactor and thereby potentially contribute to reducing the future burden of penile cancer.

# Future Research Directions

When numerically possible, future studies should analyze data for *in situ* and invasive penile SCCs separately, and the likely dual etiology of penile SCC should be kept in mind, with HPV being involved in internationally varying proportions of penile SCC. New epidemiological insights will likely come from powerful, collaborative studies large enough to distinguish between *in situ* and invasive penile SCCs, as well as between HPV-associated and HPV-unassociated cancers.

With favorable developments in vaccine pricing, gender-neutral HPV vaccination programs will likely be implemented in successively more countries in the years to come. Concomitantly, studies should be conducted to monitor their effectiveness in reducing the burden of HPV-related penile and other anogenital morbidities in the population.

During adulthood, around one in 10 men will develop pathological phimosis, and others will develop lichen sclerosus. Studies of childhood and adult life risk factors for these conditions, which are both associated with risk of penile SCC, may provide useful insights for primary prevention and thereby potentially contribute to a long-term reduction in penile cancer incidence.

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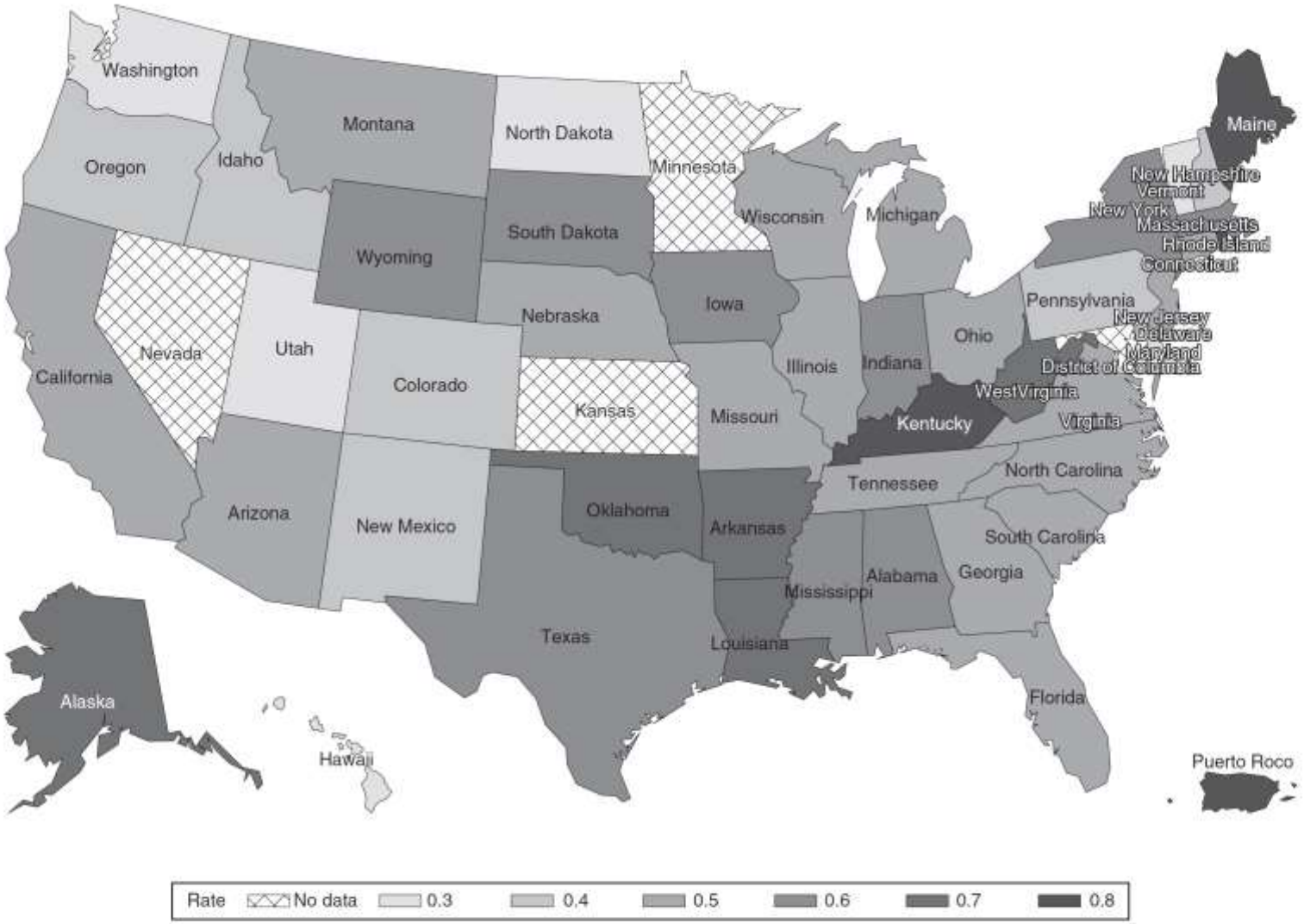


Figure 55.1. Penile cancer incidence, United States, 2003–2007. Annual age-standardized incidence rates of invasive penile cancer per 100,000 male population (world standardized) in the United States. In all states for which data were available, actual incidence rates were between 0.3 and 0.8 per 100,000 male population, except in Delaware (0.2) and Puerto Rico (1.8). Data from Forman et al. (2013).


Figure 55.2. Penile cancer incidence, international data, 2003–2007. Annual age-standardized incidence rates of invasive penile cancer per 100,000 male population (world standardized) in selected countries and regions around the world, 2003–2007. Data from Forman et al. (2013).