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Original Article

Incidence, risk factors, and temporal trends of penile cancer: a global population-based study

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Objectives

To examine the global disease burden and country-specific trends of penile cancer incidence by age group and investigate its associations with several factors.

Materials and Methods

The Global Cancer Observatory database was interrogated for penile cancer incidence. The 10-year cancer incidence rates were collected from the Cancer Incidence in Five Continents Plus. The country-specific data were extracted from the World Health Organization Global Health Observatory and Global Burden of Disease databases for conducting risk factors analysis. The penile cancer incidence was presented using age-standardised rates. Its associations with various factors were examined by linear regression, while the incidence trend was estimated using joinpoint regression and presented as average annual percentage change with 95% confidence intervals in different age groups.

Results

There were an estimated 36 068 new cases of penile cancer in 2020. There was a considerable geographical disparity in the disease burden of penile cancer, with South America reporting the highest incidence. Overall, alcohol drinking, human immunodeficiency virus (HIV) infection, and unsafe sex were positively associated with a higher penile cancer incidence, while circumcision was found to be a protective factor. There has been a mixed trend in penile cancer incidence overall, but an increasing trend was found among younger males.

Conclusions

There was a global variation in the penile cancer burden associated with prevalence of alcohol drinking, HIV infection, unsafe sex, and circumcision. The increasing penile cancer incidence in the younger population is worrying and calls for early detection and preventive interventions.

Keywords

epidemiology, incidence, Penile cancer, risk factor, trend

Introduction

Penile cancer is a malignancy rarely found in Western countries [1], accounting for <1% of cancers in men [2]. However, it has been an alarming public health problem in less developed countries, constituting up to 10% of malignant diseases in some African and South American countries, partially due to poor hygiene, phimosis, and ethnic variations [3,4]. Penile cancer bears remarkable physical and psychological ramifications [5] and survival depends largely on its stage with a 5-year overall survival of ~90% in localised penile cancer [6], and <10% in patients with metastatic disease [7]. Therefore, it is speculated that early diagnosis can improve the overall survival rate of the cancer.

Some potential risk factors for penile cancer include smoking [8], lack of circumcision [9], phimosis [9], and HIV infection [8]. Meanwhile, its association with other factors such as alcohol drinking and ultraviolet (UV) light exposure remains inconclusive. In this study, the risk factors of penile cancer were analysed by population subgroups to examine the difference in the interaction between those factors and the incidence of penile cancer.

Previous studies have evaluated the epidemiology of penile cancer but were often restricted to the evaluation of trends in specific countries [10], for all age groups without subgroup analysis [8], or with relatively old data [11]. Also, few studies have evaluated the associations between lifestyle factors and penile cancer at a population level. This study aimed to provide a more comprehensive analysis of the global disease burden, associated risk factors, and temporal incidence trends of penile cancer in population subgroups using data from global cancer registries and risk factor databases. We aimed to facilitate early diagnosis and inform policy-making on primary prevention of the cancer.

Materials and Methods

Data Sources

Among 185 countries, the incidence of penile cancer in 2020 was obtained from the Global Cancer Observatory (GLOBOCAN) database [12]. The GLOBOCAN is an on-line database that provides data on 26 types of cancer worldwide by age group to support cancer prevention and research. This database was created by the International Association of Cancer Registries (IACR) through partnerships with population-based cancer registries and the WHO, or based on on-line accessible data. The estimated incidence-to-mortality ratios, trend prediction, and approximation from nearby countries were calculated by information from the international or national cancer registries [13]. The 10-year cancer incidence (from 2003 to 2012) in 108 countries were collected from the Cancer Incidence in Five Continents Plus (CI5 Plus) database in order to generate the proportions of penile cancer incidence by geographical location [14]. The database involves yearly cancer incidence from >100 cancer registries by various population groups, the most recent and older data available were used for time trend analyses and interpretation of their changes. The country-specific data were extracted from the WHO Global Health Observatory (GHO) [15] and Global Burden of Disease (GBD) databases [16] for conducting risk factors analysis, including the prevalence of cigarette smoking, alcohol consumption, unsafe sex (the risk of disease due to sexual transmission), circumcision, HIV infection, and UV light exposure. The health burden of diseases, injuries, and risk factors were measured by the GBD database, enhancing healthcare systems, and eliminating disparities. Data on early mortality and disability for >350 illnesses and injuries were collected and analysed by >7000 researchers in 156 countries and regions. The United Nations (UN) and the World Bank Open Data were used to extract the Human Development Index (HDI) of and gross domestic product (GDP) per capita of each country, respectively [17,18].

Statistical Analysis

Multi- and univariate linear regression was adopted to analyse the relationships between penile cancer incidence and potential associated factors, such as HDI, GDP per capita, lifestyle, and metabolic risk factors according to age for each country. The beta coefficients (β) and the 95% CIs were generated accordingly from the regression analysis. β estimates are the unit of change in the outcome variable (age-standardised rates [ASRs] of incidence) for the unit of increase in a predictor variable (risk factor). All CIs were presented at the 95% level, and statistical significance was determined at a $P < 0.05$.

For the trend analysis, the joinpoint regression analysis program, which was developed under the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute of the United States, was applied to conduct the analysis. The average annual percentage change (AAPC) by regions and countries was calculated to examine the temporal trend of penile cancer incidence [19]. Following the standard practice for its computation, the most recent 10-year data were selected for calculation in cancer epidemiology research. The transformation of incidence data was made logarithmically, and the associated standard errors were evaluated. The AAPC illustrated the temporal trends of penis cancer incidence, where a positive AAPC indicated an upward trend and vice versa. The accuracy of trend estimations was evaluated using the 95% CI; e.g., an interval that overlaps with 0 shows a stable trend without a significant change. Also, changes in the penile cancer incidence were examined in relation to age (all population: 0 to ≥85, young population: 15–49, elderly population: 50–74 years) and geographic regions (Asia, Oceania, America, Europe, and Africa).

Results

Penile Cancer Incidence in 2020

There were an estimated 36 068 newly reported cases in 2020, with an ASR of 0.80 per 100 000 persons (Fig. 1). The region with the highest ASR was South America (1.5), followed by the Caribbean (1.4), Melanesia (1.4), South-Central Asia (1.3), and Eastern Africa (1.2). Meanwhile, Northern Africa (0.05), Western Asia (0.08), Western Africa (0.10), Eastern Asia (0.4), and Northern America (0.5) had the lowest ASRs. In terms of countries, Eswatini (7.0), Uganda (4.6), Botswana (4.4), Saint Lucia (3.9), and Paraguay (3.4) had the highest ASRs; while lower ASRs were found in Iraq (0.00), Algeria (0.02), Sierra Leone (0.02), Egypt (0.03), and Saudi Arabia (0.03). Overall, populations with a medium HDI had the highest ASR (1.3), followed by those with a very high HDI (0.66), high HDI (0.63), and low HDI (0.56). Assessing the ASRs of populations of different income levels, populations with low middle income (1.2) had almost twice the incidence of other populations (0.64–0.66).

Penile Cancer Incidence by Subgroup in 2020

Among the younger cohort aged 15–49 years, there were 6114 estimated new cases globally (ASR = 0.29) (Fig. 1). Southern Africa had the highest incidence (0.82), followed by Southern America (0.65), and the Caribbean (0.62); whereas Western Asia had the lowest incidence (0.01), followed by Western Africa (0.03), and Northern Africa (0.03). The countries with the highest ASRs were Eswatini (4.7), Botswana (3.4), and Malawi (2.5). In terms of the HDI, populations with a medium HDI had the highest ASR (0.41), followed by high HDI (0.27), low HDI (0.26), and very high HDI (0.19). Low-middle (0.36) and low (0.32) income level countries had the highest ASRs, followed by upper-middle (0.28) and high (0.18) income countries.

Among the older cohort aged 50–74 years, the incidence was higher with an estimated total of 21 700 cases reported (2.8) (Fig. 1). The highest ASRs were observed in South-Central Asia (5.1), Melanesia (5.0), and the Caribbean (4.9). Conversely, lower ASRs were observed in Northern Africa (0.16), Western Africa (0.26), and Western Asia (0.31). Countries with higher ASRs included Eswatini (20.2), Uganda (13.5), and Botswana (12.3). Similar to their younger counterparts, populations with a medium HDI had the highest ASR of 5.1, followed by very high HDI (2.4), high HDI (2.0), and low HDI (1.7). In terms of income level, low-middle income populations had the highest ASR (4.3), followed by high (2.4) and upper-middle (2.1) income populations, whereas low income countries had the lowest ASR (1.9).

The overall old-to-young incidence ratio was 9.7:1, and the ratio was the highest in Western Asia (31:1), followed by Melanesia (21.7:1), Western Europe (17.1:1), Southern Europe (13.9:1), and South-Central Asia (13.4:1). In contrast, Southern Africa (4.1:1), Middle Africa (4.4:1), and Northern Africa (5.3:1) had the lowest ratio. In terms of the HDI, the highest ratios were found among very high (12.6:1) and medium (12.4:1) HDI populations, while low ratios were found in low (6.5:1) and high (7.4:1) HDI regions. Likewise, for income level, populations with high (13.3:1) and lower-middle income (11.9:1) were observed with the greatest ratios, while those with low (5.9:1) and upper-middle income levels had smaller ratios (7.5:1).

Associations of Risk Factors with Penile Cancer Incidence

Overall, a higher incidence of penile cancer was associated with a higher prevalence of alcohol drinking ($\beta = 0.026$, 95% CI 0.005–0.047; $P = 0.017$), HIV infection ($\beta = 0.025$, 95% CI 0.020–0.030; $P < 0.001$), and unsafe sex ($\beta = 0.009$, 95% CI 0.007–0.012; $P < 0.001$), and a lower prevalence of smoking ($\beta = -0.027$, 95% CI -0.046 to -0.007; $P = 0.007$), and circumcision ($\beta = -0.012$, 95% CI -0.015 to -0.008; $P < 0.001$; Fig. 2, Table S1). However, no significant linear association was found between penile cancer incidence and the prevalence of HDI, GDP per capita, and UV light exposure. The multivariable analysis showed similar results (Table S2).

Associations of Risk Factors with Penile Cancer Incidence by Subgroup

Among the younger cohort, a higher incidence of penile cancer was associated with a higher prevalence of HIV infection ($\beta = 0.015$, 95% CI 0.013–0.017; $P < 0.001$) and unsafe sex ($\beta = 0.006$, 95% CI 0.005–0.007; $P < 0.001$; Fig. 3, Table S1). On the contrary, it was negatively associated with the HDI ($\beta = -0.122$, 95% CI -0.202 to -0.041; $P = 0.003$), GDP per capita ($\beta = -0.085$, 95% CI -0.147 to -0.023; $P = 0.008$), and the prevalence of smoking ($\beta = -0.039$, 95% CI -0.057 to -0.021; $P < 0.001$), and circumcision ($\beta = -0.005$, 95% CI -0.008 to -0.002; $P = 0.004$). There was no significant linear association between the incidence of penile cancer and UV light exposure at a population level. Among the older cohort, a higher incidence of penile cancer was associated with a higher prevalence of alcohol drinking ($\beta = 0.140$, 95% CI 0.071–0.208; $P < 0.001$), HIV infection ($\beta = 0.033$, 95% CI 0.026–0.041; $P < 0.001$), and unsafe sex ($\beta = 0.011$, 95% CI 0.008–0.014; $P < 0.001$). In contrast, a negative association was found

Fig. 1 Global age-standardised incidence of penile cancer in 2020, males.

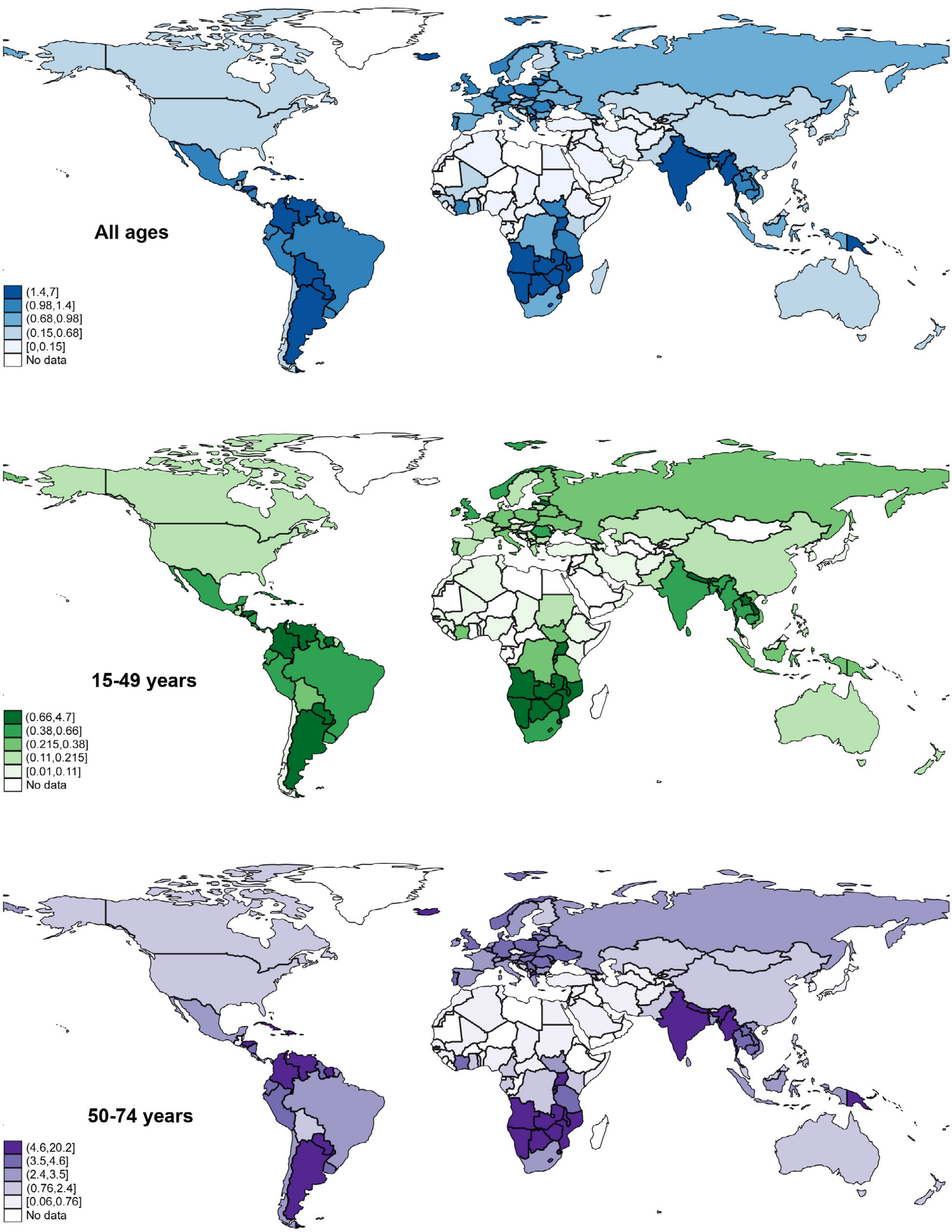
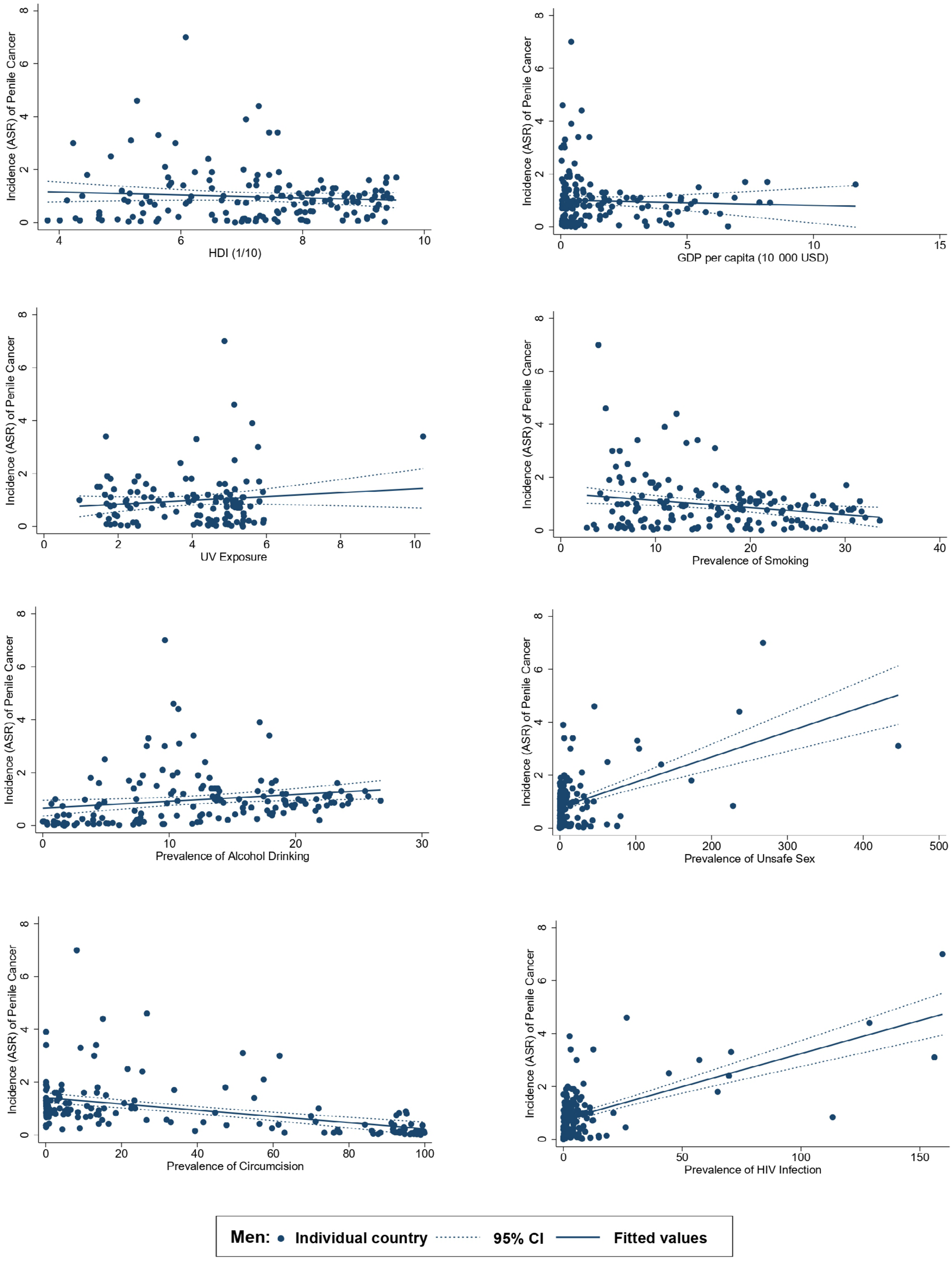


Fig. 2 Associations between risk factors and penile cancer incidence.



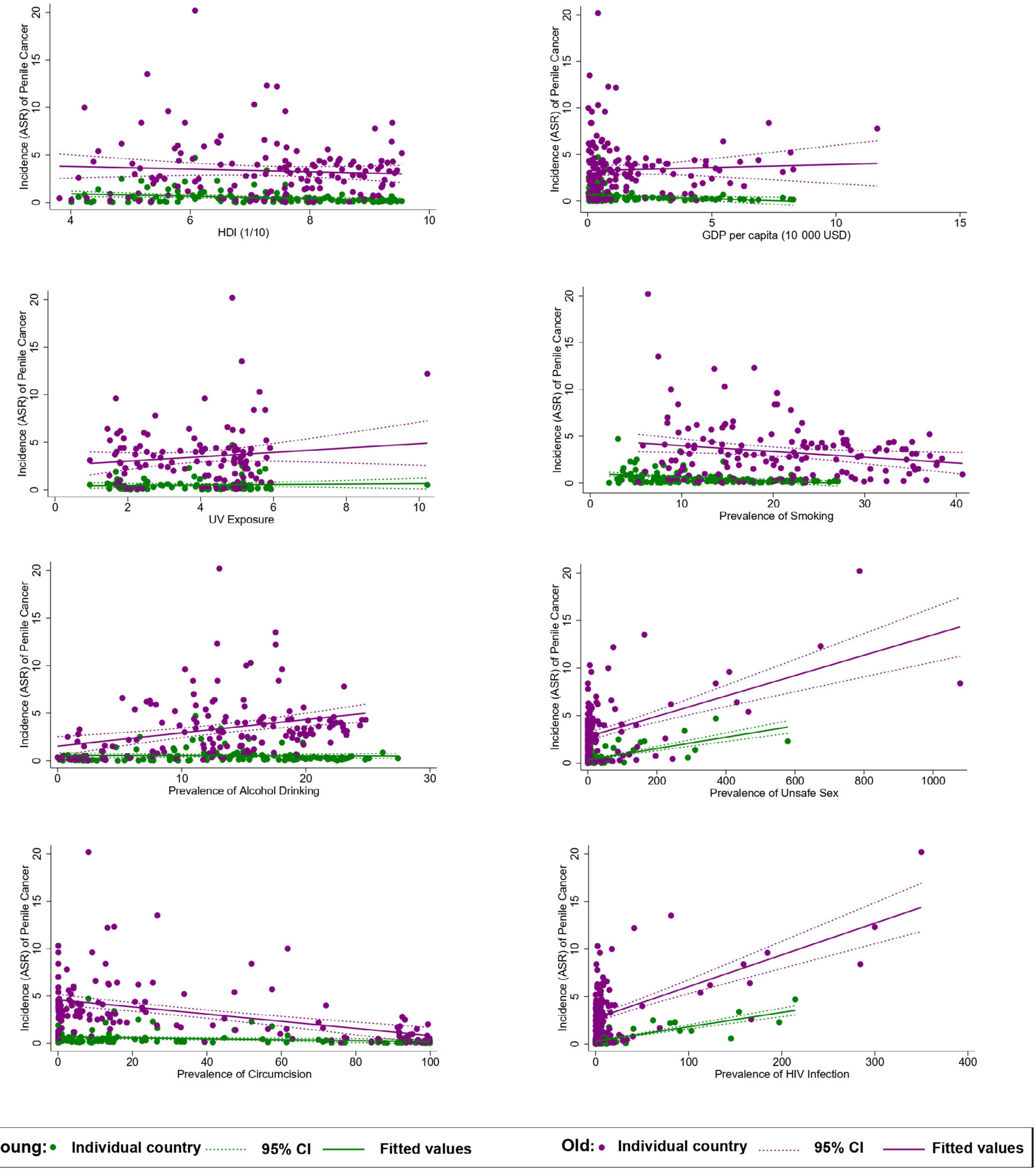


Fig. 3 Associations between risk factors and penile cancer by ages.

between higher penile cancer incidence and smoking ($\beta = -0.061$, 95% CI -0.114 to -0.009; $P < 0.001$), and circumcision ($\beta = -0.038$, 95% CI -0.049 to -0.027; $P < 0.001$). Meanwhile, there was not a significant linear association between the incidence of penile cancer and the HDI, GDP per capita, and UV exposure.

Temporal Trends of Penile Cancer Incidence

Overall, there was a mixed trend in the temporal incidence trend of penile cancer (Table S3, Figs. S1-S3). Significant increasing trends were reported in Ecuador (AAPC = 17.76, 95% CI 0.37–38.16; P = 0.046) and the UK (AAPC = 2.58, 95% CI 0.79–4.41; P = 0.010). Meanwhile, a significant reduction was observed in three countries, all located in Asia. The greatest decrease was found in Turkey (AAPC = −11.85, 95% CI −20.72 to −1.98; P = 0.025), followed by India (AAPC = −5.70, 95% CI −9.36 to −1.89; P = 0.009) and China (AAPC = −2.69, 95% CI −5.18 to −0.14; P = 0.041). There were no significant trends among the remaining countries.

Temporal Trends of Penile Cancer Incidence by Subgroup

Among the younger cohort aged 15–49 years, there was an overall increasing trend in the incidence of penile cancer (Fig. S4). Five countries, including Martinique (AAPC = 29.84, 95% CI 25.74–34.06; P < 0.001), Turkey (AAPC = 27.14, 95% CI 20.90–33.71; P < 0.001), Korea (AAPC = 12.94, 95% CI 0.69–26.68; P = 0.040), Japan (AAPC = 12.84, 95% CI 6.09–20.02; P = 0.002), and Poland (AAPC = 5.04, 95% CI 2.00–8.17; P = 0.005) reported significant increasing trends, while only Switzerland (AAPC = −22.39, 95% CI −35.82 to −6.15; P = 0.009) and Malta (AAPC = −10.34, 95% CI −10.97 to −9.71; P < 0.001) showed significant decreases.

For the older cohort aged 50–74 years, there was a mixed trend in penile cancer incidence (Fig. S5). Three countries showed significant increasing trends, all of them were in Europe. Iceland was found with the most remarkable increase in incidence (AAPC = 12.14, 95% CI 1.44–23.97, P = 0.030), followed by the UK (AAPC = 2.80, 95% CI 0.24–5.42; P = 0.035), and the Netherlands (AAPC = 2.47, 95% CI 0.38–4.60; P = 0.026). In contrast, evident decreasing trends were found in Turkey (AAPC = −12.02, 95% CI −17.64 to −6.00; P = 0.002) and India (AAPC = −7.66, 95% CI −12.46 to −2.61; P = 0.009).

Discussion

Summary of Major Findings

This study investigated extensively the disease burden, risk factors, and temporal trends of penile cancer by subgroups. The major findings include: (i) a considerable geographical disparity in the disease burden of penile cancer, with South America having the highest ASR, 30 times higher than that of Northern Africa, which had the lowest ASR; yet, regional variation differed by age groups, as the highest ASRs among younger and older males were found in Southern Africa and South-Central Asia, respectively; (ii) the old-to-young incidence ratio was smaller in the African region and countries with a low HDI, and larger in regions with a very high and medium HDI, indicating a difference in the age pattern of the disease burden of various regions; (iii) higher prevalence of alcohol drinking, HIV infection and unsafe sex was associated with a higher incidence of penile cancer, while the HDI, GDP per capita, and circumcision were negatively associated with penile cancer incidence among younger males; (iv) there was an overall mixed trend in the temporal incidence trends; nevertheless, an overall increase in incidence was found among younger males, and significant decreases were found in some Asian countries overall and among older males.

Variation in the Disease Burden

An alarmingly high disease burden was observed in South America, but the reasons underlying this trend remains uncertain because of the lack of epidemiological studies in this geographical region [20]. Nonetheless, previous studies had suggested race and lower socioeconomic status might be potential factors. In a registry-based study in the USA, Hispanics were found to have an ASR 72% higher than non-Hispanics [21]. A Paraguayan study indicated that the majority of the patients lived in rural or suburban regions with only primary education [22]. Similarly, a study showed that Maranhão, the most rural state in Brazil marked by extreme poverty, had an estimated minimum ASR of 6.1, more than seven times higher than the global ASR [23]. Conversely, the lower, negligible incidence found in Northern Africa and Western Asia could probably be attributed to a remarkably higher estimated prevalence of circumcised males, as almost every male in those regions such as Morocco (99.9%), Afghanistan (99.8%), Iran (99.7%), and Iraq (98.9%) were estimated to be circumcised due to religious and cultural reasons, as compared to the global estimate at 37.4% in 2011 [24].

As penile cancer typically affects older men aged between 50 and 70 years [21,25], the incidence among the older males was noticeably higher than the younger males. We found that the old-to-young incidence ratio varied substantially among geographical regions, HDI, and GDP per capita, indicating potential disparity in the median onset age (62 years in Black vs 68 years in White, 58 years in Hispanic vs 69 years in non-Hispanic) [21]. Furthermore, African regions had the smallest difference in the ASRs between the two age groups, which was likely because of the lack of improvement in the knowledge of the disease, access to healthcare, sanitation and hygiene, and reduced availability of physical contraceptive methods [2,26]. The latter contributed to the spread of both HIV and human papillomavirus (HPV) infections, which subsequently increased the incidence of penile cancer [7].

Risk Factors Associated with Penile Cancer Incidence

Our study identified alcohol consumption, unsafe sex, and HIV infection as risk factors increasing the risk of penile cancer. The link between HIV infection and penile cancer has been well established, with HIV-positive men having a two- to three-times higher risk than that of HIV-negative individuals [27]. The association between unsafe sex and penile cancer may be explained by HPV infection. HPV transmission through unprotected sex has been demonstrated [28,29], and a serological case–control study involving 905 subjects also verified the association between HPV and penile cancer [30]. Therefore, unsafe sex behaviour may lead to penile cancer through HPV transmission. Also, no significant association (odds ratio [OR] 1.5, 95% CI 0.9–2.6) was found between alcohol consumption and penile cancer in previous studies [26]. It is suspected that the three factors interacted and formed an extension to the causal link between drinking, unsafe sex, and HIV [31] in the way that alcohol use indirectly increased the risk of penile cancer by increasing the intentions to engage in unprotected sex (5.0% per 0.1 mg/mL increase in blood alcohol content, 95% CI 2.8–7.1%), thus increasing the chance of HIV transmission [32]. Therefore, it is possible that the implementation of alcohol reduction interventions could diminish the chance of developing penile cancer.

Circumcision has been identified as a protective factor in our risk factor analysis, which supported the lower incidence found in regions with a high proportion of circumcised males. A meta-analysis has found a strong protective effect of childhood/adolescent circumcision on penile cancer (OR 0.33, 95% CI 0.13–0.83) [33], probably because it reduced the risk of phimosis, one of the most important risk factors associated with penile cancer [34,35]. In contrast, adulthood circumcision might not be encouraged as a means of penile cancer prevention, as its association with the risk of penile cancer (OR 2.71, 95% CI 0.93–7.94) was not found to be statistically significantly different.

The HDI and GDP per capita was negatively associated with penile cancer incidence, but only among younger males, which may be suggestive of an inconsistency in the improvement in hygiene, healthcare provision, and knowledge in the disease [36]. The findings also supported the disparity in the old-to-young incidence ratio among regions. Unlike Psoralen and UVA radiation (PUVA) used in treatment, which increased the risk of penile cancer [37], UV light exposure in the environment was not identified as a risk factor for penile cancer incidence at a population level—avoidance of UV light exposure might not be an appropriate method to prevent penile cancer. In our study, smoking was negatively associated with penile cancer incidence, which contradicted with previous studies [38,39]. The variation in findings could be ascribed to the difference in study design, as an ecological design was used in this study to evaluate risk factors at a population level.

Temporal Incidence Trends of Penile Cancer

We have found an overall mixed trend in penile cancer incidence, which was inconsistent with the increasing trends identified in previous studies [8]. One of the possible explanations might be the difference in the time period selected for analysis. Nevertheless, increases have been found in some European countries, particularly the UK, the Netherlands, and some Scandinavian countries, were likely due to centralisation of services with strict or mandatory recording within National registries [40,41]. Meanwhile, an increase in the penile cancer incidence for younger males has been observed, reflecting the increasing prevalence of its associated lifestyle factors and possible improvement of disease detection. Education on the knowledge regarding penile cancer prevention should be provided to the general public, particularly on points relevant to the danger of unprotected sex, as some parts of the population may not have a high level of knowledge in that regard [42].

Strength and Limitations

This study used high-quality cancer data from 186 countries to produce a comprehensive result of the global incidence, risk factors, and temporal trends of penile cancer. Despite that, there are several limitations on the data source, study design, and statistical analysis. First, one should be cautious about cancers being unreported or misclassified in some countries due to suboptimal quality of cancer data, registry coverage, and analytical capability, which are more likely to happen in low- and low-middle-income countries (LMICS) with poorer cancer reporting infrastructure. Similarly, it is likely that the data for risk factors were significantly under reported, as risk factors were not recorded prospectively in all patients. Second, direct comparisons between different countries may not be applicable as the state cancer registries may change over time. However, the comparisons of country- and site-specific results at the same time period are relatively reliable. Meanwhile, caution should be exercised when extrapolating the trends as the most recent temporal data was from 2012.

Implications

There was a significant geographical disparity in the disease burden of penile cancer, mainly attributed to race and poor socioeconomic status. The high disease burden will likely persist until remarkable improvement has been made to the hygiene and healthcare in the regions. Circumcision, despite being the main protective factor as supported by the low incidence in Western Asia and Northern Africa, should not be encouraged as a means to prevent penile cancer at any age, due to the lack of supporting evidence. On the other hand, this study discovered a potential link between penile cancer and alcohol consumption, unsafe sex, and HIV infection, which likely contributed to the increasing trend in some populations. Sex education should be provided, and the danger of unprotected sex should be highlighted. Further studies should be performed to capture the subsequent incidence and mortality trends of penile cancer.

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Disclosure of Interests

The authors declare that they have no competing interest.

Ethics Committee Approval

This study was approved by the Survey and Behavioural Research Ethics Committee, The Chinese University of Hong Kong (No. SBRE-20-332).

Consent to Participate

Given that no patients were recruited for the study, there are no plans to disseminate the results to study participants.

Author Contributions

Junjie Huang contributed conceptualisation and supervision, data curation and formal analysis, and manuscript drafting. Sze Chai Chan contributed data curation, formal analysis, and manuscript drafting. Wing Sze Pang contributed manuscript drafting. Xianjing Liu, Lin Zhang, Don Eliseo Lucero-Prisno III, Wanghong Xu, Zhi-Jie Zheng, Anthony Chi-Fai Ng, Andrea Necchi, Philippe E. Spiess, Jeremy Yuen-Chun Teoh, and Martin C.S. Wong contributed manuscript review and editing. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Statement

The data that supports findings of this study are available from the corresponding author, upon reasonable request.

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Abbreviations: AAPC, average annual percentage change; ASR, age-standardised rate; GBD, Global Burden of Disease; GDP, gross domestic product; GLOBOCAN, Global Cancer Observatory; HDI, Human Development Index; HPV, human papillomavirus; OR, odds ratio; UV, ultraviolet.

Supporting Information

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

Table S1. Results for risk factors analysis of penile cancer.

Table S2. Results of multivariate analysis of risk factors for penile cancer.

Table S3. The AAPC results for trend analysis of penile cancer.

Fig. S1. Incidence and mortality trends of penile cancer.

Fig. S2. Joinpoint regression analysis of penile cancer.

Fig. S3. The AAPC of penile cancer incidence, males, all ages.

Fig. S4. The AAPC of penile cancer incidence, males, aged 15–49 years.

Fig. S5. The AAPC of penile cancer incidence, males, aged 50–74 years.