REVIEW ARTICLE

INDONESIAN JOURNAL OF CANCER

The Association of Circumcision and Genitourinary Cancer, Especially Penile Cancer and Prostate Cancer: A 30-Year Systematic Review and Meta-Analysis

Prima Ardiansah Surya*, Alfin Putratama, Radika Naufal Hadi Surya, I Gede Yogi Prema Ananda

Medical Faculty, Universitas Airlangga, Surabaya, Indonesia

ARTICLE INFO

Received : 21 September 2023
Reviewed : 25 October 2023
Accepted : 12 December 2023

Keywords:
cancer, genitourinary cancer, penile cancer, prostate cancer

*Corresponding Author:
Prima Ardiansah Surya
Medical Faculty, Universitas Airlangga, Surabaya, Indonesia
prima.ardiansah1922@gmail.com

ABSTRACT

Background: The relationship between genitourinary cancer and circumcision has been debated for a long time. Two types of genitourinary cancer that are often discussed in relation to circumcision are penile cancer and prostate cancer.

Methods: A systematic review was conducted on the Science Direct database and Perish with the following databases: Pubmed, Google Scholar, and Crossref. Case-control studies were assessed with the Newcastle-Ottawa Scale. Meta-analysis was performed on penile cancer in situ, invasive penile cancer, and prostate cancer. Meta-analysis of proportions was carried out on penile cancer.

Results: 10 studies were analyzed for penile cancer and prostate cancer, and 9 studies were analyzed for penile cancer proportion. Total OR in circumcision and penile cancer in situ (OR = 0.90; 95% CI 0.48–1.69; p = 0.74). Total OR in circumcision and invasive penile cancer (OR = 1.04; 95% CI 0.27–3.94; p = 0.95). Total OR in circumcision and prostate cancer (OR = 0.97; 95% CI 0.79–1.19; p = 0.78). The uncircumcised proportion among penile cancer cases (0.82; 95% CI 0.60–0.97).

Conclusions: There was no significant relationship between circumcision and genitourinary cancer. Malignant cells in penile cancer and prostate cancer occur due to a chronic inflammatory process.

INTRODUCTION

The association between circumcision and urogenital cancer has been debated for a long time. The mystery of the emergence of penile cancer and prostate cancer is still being investigated, starting from simple factors to complex factors such as biochemical molecule problems, enzymatic problems, and chromosomal problems. In this study, we discuss circumcision as a preventive factor for prostate cancer and penile cancer. The incidence of penile cancer is estimated at 1 new case per 100,000 population in Europe and North America, in other parts of the world, the incidence is even greater in South America, Africa, and Asia. Meanwhile, prostate cancer is the most common cancer that occurs in men in America, it is estimated that by 2023, there will be 280 thousand new cases per year and 34 thousand deaths [1]. According to WHO cancer data, the incidence of penile cancer reaches 0.26% of new cases compared to other types of cancer, while prostate cancer reaches 3.4% of new cases compared to other types of cancer [2].

Several risk factors for penile cancer include phimosis, lack of penile circumcision, balanitis, obesity, lichen sclerosus, smoking, low socioeconomic status, Human Papilloma Virus (HPV) infection, and Psoralen Plus Ultraviolet A (PUVA) [3,4]. Simultaneously, risk factors for prostate cancer include excess consumption of meat and dietary fats, smoking, obesity, elevated lipid levels, and high calcium intake [5,6]. Circumcision is not mentioned as a risk factor for prostate cancer in general but occurs indirectly through a chronic inflammatory process.

Circumcision has been known since the heliolithic civilization around 15,000 years ago and is estimated to have existed in ancient Egyptian civilization since 2300 BC [7,8]. Circumcision is also performed for religious reasons, particularly for Jews and Muslims, and is a common practice among many ethnic groups around the world. It is estimated that 30% of men worldwide have undergone circumcision, and 2 out of 3 of them are Muslims [8]. We investigated the effect of circumcision on the occurrence of genitourinary cancers, especially penile and prostate cancers.

METHODS

Protocol and registration of the study

This study followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 flow chart [9]. This study protocol was recorded in the PROSPERO International Prospective Register of Systematic Reviews (CRD42023458495).

Literature search and study selection

A systematic search was conducted in several databases through Science Direct and Harzing's Publish and Perish application with the following databases: Pubmed, Google Scholar, and Crossref up to May 2023. Relevant studies were searched using a Boolean operator with the following search strategy: (Circumcision) AND (Cancer OR Prostate Cancer OR Penile Cancer).

Eligibility criteria

The search of this study was prioritized for studies that assessed the comparison of circumcised and not on genitourinary cancer subjects. If a study met the following inclusion criteria, it was considered eligible: (1) English and Bahasa Indonesia articles; (2) Randomized Controlled Trial (RCT), cohort, and case-control study design; (3) the data comparing circumcised and not circumcised were available. We excluded the studies of reviews, commentaries, letters, experimental animal studies, abstracts, and single-arm case series.

Data extraction and quality assessment

Three reviewers performed the article selection and data extraction (AP, RNHS, and YPA). Any disagreements between the reviewers were settled through discussions with senior authors (PAS). Case-control studies were assessed with the Newcastle-Ottawa Scale (NOS) [10]. NOS score was considered good quality if they met the score equal to or more than six, while a score of five or less was considered poor quality.

Outcomes

The primary outcome of this study was genitourinary cancer, especially prostate cancer and penile cancer, and its relationship to circumcision.

Statistical analysis

The fixed-effects model was selected if low heterogeneity was detected in between studies (I^2 < 50%; p-value ≥ 0.05). However, if the pooled analysis reveals high heterogeneity, the random-effects model was selected (I ≥ 50%; p-value < 0.05). Because the extracted data is dichotomous, we presented the pooling analysis of our result in Odds Ratio (OR) with a 95% confidence interval (CI). If p-value < 0.05, the result was regarded as significant. Statistical Software Review Manager 5.4 and R-Studio were used to analyze the study. The descriptive study articles for meta-analysis of proportion were analyzed using RStudio using tidyverse, meta, and metaphor packages [11].

RESULTS

Search results and baseline characteristics of the study

The initial search turned up a total of 2771 articles with 220 duplications and 315 records marked as ineligible by automated tools, as displayed in **Figure 1**. After identification, we performed an initial screening for 2237 articles by excluding 352 opinion and editorial letter articles, 688 review articles, and 126 non-relevant design articles. From the 1071 sought-retrieval articles, we found 497 not relevant population articles, 198 not relevant intervention articles, and 320 not relevant outcome articles. Then, 56 eligible studies were found, and we excluded 37 reports that did not meet the inclusion criteria. Finally, 10 studies were analyzed for meta-analysis of odds ratios on penile cancer and prostate cancer, and 9 studies were analyzed for meta-analysis of the proportion of penile cancer. We did not find articles discussing kidney cancer, bladder cancer, and testicular cancer in this study. Baseline characteristics of each included study were provided.

Risk of bias assessment in the study

The quality assessment of non-randomized studies among inclusion demonstrated a high and moderate risk of bias. A study which was conducted by Mallon et al. [12] had a low score due to the lack of comparison clarity. The results showed a relatively moderate risk of bias, as shown in **Table 3**.

Outcome

Table 1 summarizes the meta-analysis of odds ratio studies, 3 case controls discuss penile cancer with circumcision, and 7 case controls discuss prostate cancer with circumcision. The age groups included in this meta-analysis ranged from 4 years to 93 years. The countries of origin of the subjects included were also diverse, ranging from Europe, Latin America, and Asia (China), as well as the races included in this study, ranging from Asian, Caucasian, and African.

Further, **Table 2** summarizes the meta-analysis of proportion studies, 9 studies discuss penile cancer and uncircumcised subjects. We also tried to look for descriptive studies on prostate cancer, but we couldn't find any. The age range included in this proportion analysis is quite diverse, from 21 years to 92 years. The countries included varied from Latin America, Africa, and Indonesia.

P-ISSN: 1978-3744 E-ISSN: 2355-6811

Association of circumcision and penile cancer in situ

We found one study that separated the population into two groups above 1 year and under 1 year. Insignificant heterogeneity was found between the included studies (I2= 0%, p = 0.74), as illustrated in **Figure 2**. The fixed-effects model was chosen. Pooled analysis suggested that patients who were circumcised had an insignificant risk of penile cancer in situ (OR = 0.90; 95% CI 0.48–1.69; p = 0.74).

Association of circumcision and invasive penile cancer

In our analysis, we found three studies that reported the association of circumcision with invasive penile cancer. Significant heterogeneity was found between the included studies (I2 = 67%, p = 0.03), as illustrated in **Figure 3**. Then, the random-effects model was chosen. Pooled analysis suggested that circumcision had an insignificant risk of invasive penile cancer (OR = 1.04; 95% CI 0.27–3.94; p = 0.95).

Association of circumcision and prostate cancer

Seven studies were found that reported an association of circumcision with prostate cancer. There was significant heterogeneity among the included studies (I2 = 68%, p = 0.004), as illustrated in **Figure 4**. Therefore, the random-effects model was selected. According to the pooled data analysis, patients who underwent circumcision had an insignificant risk of prostate cancer than those who had not been circumcised (OR = 0.97; 95% CI 0.79–1.19; p = 0.78).

The uncircumcised proportion of penile cancer case

Nine studies were found that reported a proportion of circumcision in penile cancer subjects. There was significant heterogeneity among the included studies (I2 = 99%, p = < 0.01), as illustrated in **Figure 5**. Therefore, the random-effects model was selected. Pooled data analysis showed the proportion of uncircumcised subjects among penile cancer cases (0.82; 95% CI 0.60–0.97).

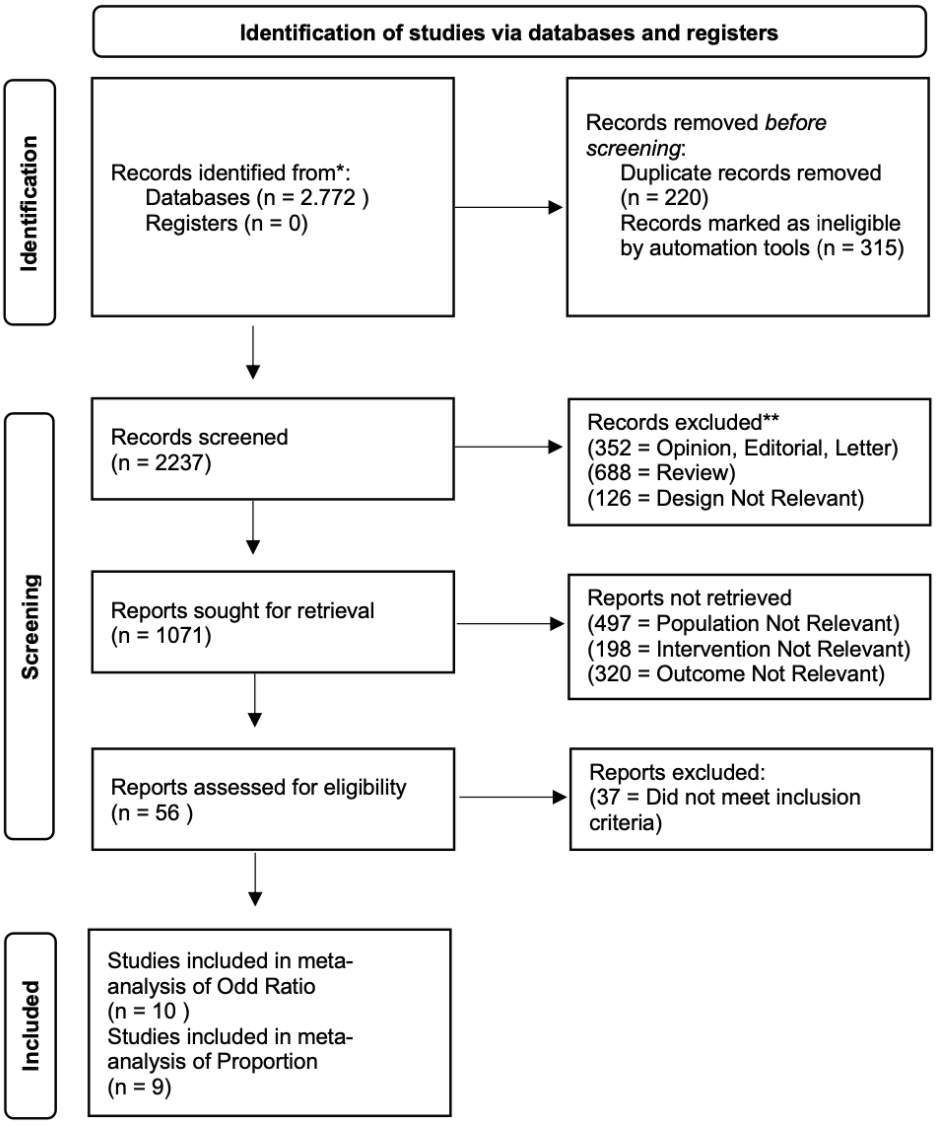

Figure 1. PRISMA 2020 diagram of association of circumcision and genitourinary cancer especially prostate cancer and penile cancer

P-ISSN: 1978-3744 E-ISSN: 2355-6811

Table 1. Study summary for meta-analysis of odd ratio between circumcision with penile cancer and prostate cancer

Study (Year)	Case (n)	Control (n)	Age Range	Study Design	Country	Data Retrieval	Race
Penile Cancer							
Mallon (2000)[12]	357	305	4–97	Case-Control	England	Interview	Unknown
Brinton (1991)[13]	141	150	20–74	Case-Control	China	Interview	Asian
Tseng (2001)[14]	100	100	≤ 45–> 65	Case-Control	United States	Interview	African American, Latin, White
Prostate Cancer							
Newell (1989)[15]	103	211	41–86	Case-Control	United States	Interview	White
Ewings (1996)[16]	40	106	≤ 70–> 80	Case-Control	England	Interview	Unknown
Rosenblatt (2001)[17]	753	703	40–64	Case-Control	United States	Interview	Black and White
Madsen (2008)[18]	86	103	≤ 40–> 60	Case-Control	Denmark	Interview	Unknown
Wright (2012)[19]	1754	1654	35–74	Case-Control	United States	Interview	Caucasian, African, American
Spence (2014)[20]	1555	1586	40–79	Case-Control	Canada	Interview	White, Black, Asian, Other
Chang (2023)[21]	140	135	55–86	Case-Control	Taiwan	Interview	Asian

Table 2. Study summary for proportion meta-analysis of uncircumcised among penile cancer cases

Study (Year)	Uncircum-cised	Total	Age Range	Study Design	Country	Data Retrieval	Race
Hubbel (1988)[22]	175	175	27–101	Descriptive Study	United States	Medical Report	Black
Schoen Invasive (2000)[23]	87	89	Median 65	Descriptive Study	United States	Medical Records	Unknown
Schoen In Situ (2000)[23]	102	118	Median 58	Descriptive Study	United States	Medical Records	Unknown
Ritchie (2004)[24]	23	193	21–92	Descriptive Study	United Kingdom	Interview	Unknown
Favorito (2008)[25]	246	283	≤ 26–> 66	Descriptive Study	Brazil	Interview	Unknown
Koifman (2011)[26]	184	230	25–98	Descriptive Study	Brazil	Interview	Unknown
Ngendahayo (2018)[27]	30	30	33–83	Descriptive Study	Rwanda	Interview	Black
Zamzami (2019)[28]	15	20	Unknown	Descriptive Study	Indonesia	Medical Records	Asian
Vieira (2020)[29]	84	110	23–93	Descriptive Study	Brazil	Interview	Unknown
Kusumajaya (2021)[30]	7	13	28–67	Descriptive Study	Indonesia	Medical Records	Asian

Table 3. NOS score of penile cancer and prostate cancer studies

Author (Year)	Quality Score			Total
	Selection	Comparison	Exposure	
Tseng (2001)[14]	**	*	**	5
Brinton (1991)[13]	***	*	**	6
Mallon (2000)[12]	*		*	2
Newell (1989)[15]	**	*	***	6
Ewings (1996)[16]	**	*	***	5
Rosenblatt (2001)[17]	**	*	***	7
Madsen (2008)[18]	**	*	**	5
Wright (2012)[19]	***	*	***	7
Spence (2014)[20]	***	*	***	7
Chang (2023)[21]	**	*	***	6

P-ISSN: 1978-3744 E-ISSN: 2355-6811

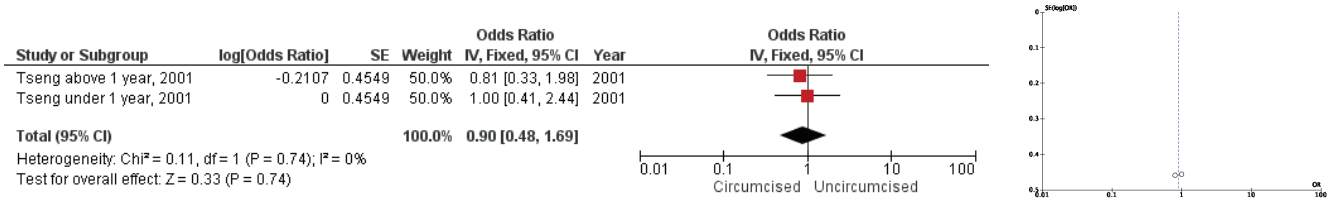

Figure 2. Forest plot and funnel plot of penile cancer in situ between circumcised and uncircumcised groups.

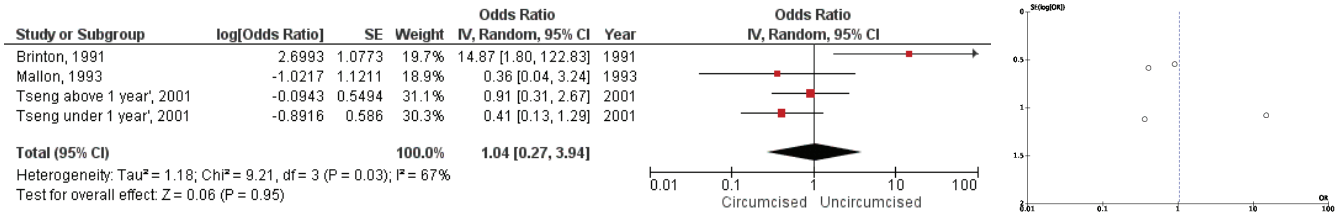

Figure 3. Forest plot and funnei plot of invasive penile cancer between circumcised and uncircumcised groups.

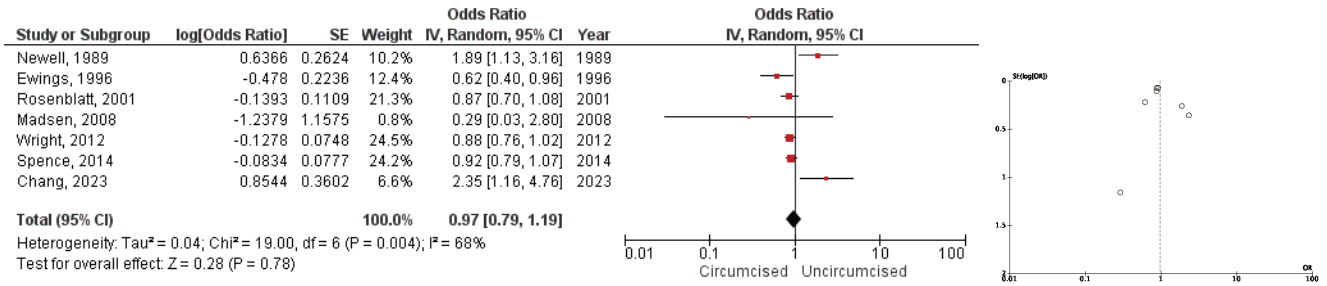

Figure 4. Forest plot and funnel plot of prostate cancer between circumcised and uncircumcised groups.

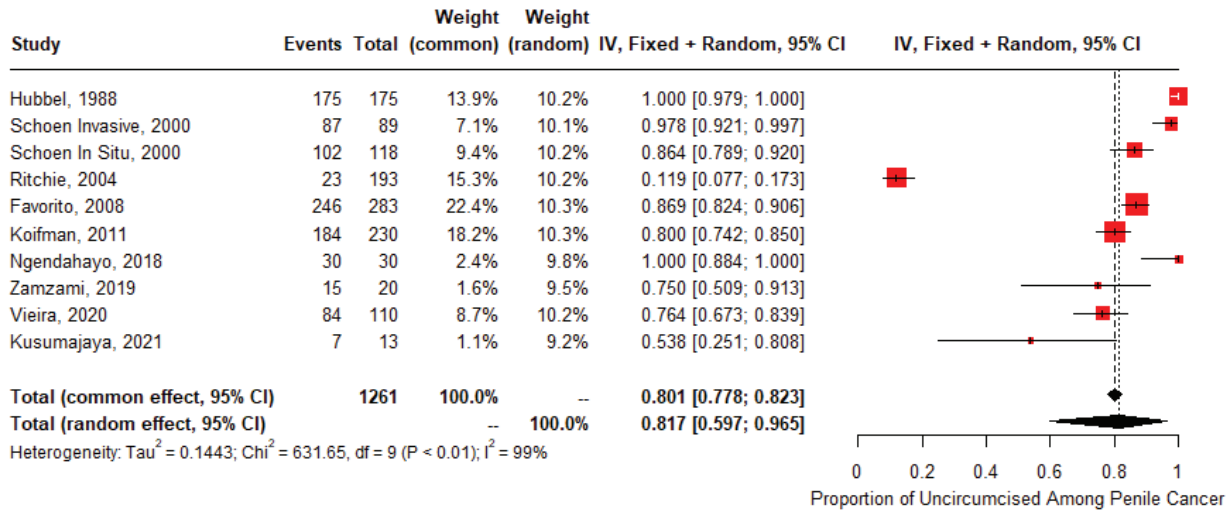

Figure 5. Forest plot of uncircumcised proportion among penile cancer case

DISCUSSION

The role of circumcision in the incidence of penile cancer and prostate cancer is still under debate. We have not found case-control investigating the role of circumcision in relation to other types of genitourinary cancer such as kidney cancer, bladder cancer, and testicular cancer.

Penile cancer is rare but has severe consequences, especially in developing countries with limited treatment options. Investing in infant male circumcision programs is considered a valuable long-term strategy to prevent not only penile cancer but also cervical cancer, HIV, and other sexually transmitted infections [31]. Some of the mechanisms that support circumcision as a protective factor against penile cancer are: Circumcision helps detect malignant cells early through visual examination, penile cancer usually appears first in the foreskin that is removed during the circumcision procedure, and circumcision prevents the accumulation of smegma which is considered carcinogenic and prevents chronic inflammation due to infection [4]. Childhood or adolescent circumcision is associated with a reduced risk of invasive penile cancer. Interestingly, there were no significant association is observed between circumcision at any age and precancerous conditions (PIN) or in situ penile cancer [32].

In the case-control studies included in this research, phimosis occurring only in subjects who had not undergone circumcision was a strong predictor of penile cancer, especially in invasive cases [14]. Phimosis is a condition that causes the inability to retract the foreskin over the glans penis. A study found that 35.2% of penile cancer cases occurred in phimosis, compared to controls which accounted for 7.6% of penile cancer cases found in circumcised subjects [33]. Another study found that in subjects who were not circumcision at birth, the relative risk of developing penile cancer increased 3.2-fold compared with controls [34]. Therefore, circumcision needs to be done in infancy to prevent excess prepuce and phimosis [13,14]. Due to chronic inflammation, inflammatory dermatosis is more common in men who have not undergone circumcision [12]. The condition of phimosis which is the background for circumcision, in one study it was stated that 27% of penile SCC sufferers experienced phimosis, compared to 10% of controls with penile SCC [18]. The uncircumcised environment also makes preputial dermatoses vulnerable to carcinogenic exposure from smegma and chronic inflammation [35].

Circumcision is not mentioned as a risk factor for prostate cancer in general, however, studies with large numbers of subjects show a protective effect of circumcision [17,19,20], answered previous research that questioned the effect of circumcision on the occurrence of prostate cancer [15,16]. The occurrence of infection and inflammation in the prostate which triggers prostate cancer, causes sexually transmitted disease to be suspected as the etiology of prostate cancer, with a 15% reduction in the relative risk of prostate cancer in men who were circumcised before first sexual intercourse [19,20]. Even men who are circumcised at the age of over 36 years also have a protective effect against prostate cancer [20]. Although some case controls showed protective factors, these results still need to be studied further. On the contrary, a geographical study stated that higher life expectancy is associated with increased prostate cancer incidence and higher circumcision prevalence is linked to shorter male life expectancy. The study also stated that the association between circumcision status and the likelihood of developing prostate cancer is still uncertain [36].

Although the meta-analysis of the odds ratio for penile cancer is not significant, this study shows that the proportion of patients with penile cancer who have not undergone circumcision is much greater than those who have not undergone circumcision. Meta-analysis of proportion studies themselves is still not popular. However, in discussions that cannot present information regarding the impact of an intervention due to the lack of comparative studies, a meta-analysis of proportions is quite useful to provide an overview of an intervention on a particular outcome [11].

This study has several limitations. Most of the studies included in this meta-analysis used data obtained through interviews, so it was subjective. This study only examined the association between circumcision and penile and prostate cancer. There was still not enough data on research about circumcision and its association with kidney, bladder, and testicular cancer. Also, there were no studies about the association between uncircumcised and the proportion of prostate cancer. Future research needs to be conducted to explore the association between circumcision and the proportion of prostate cancer.

CONCLUSIONS

This study concluded that there was no significant difference between circumcision and genitourinary cancer, especially penile cancer and prostate cancer compared to controls. The proportion of uncircumcised penile cancer cases is quite large in various studies. Case-control research on circumcision and genitourinary cancer needs to be increased in number with more subjects and controls.

P-ISSN: 1978-3744 E-ISSN: 2355-6811

DECLARATIONS

Ethics approval and consent to participate
Not applicable.

Competing interest
The authors declare no competing interest in this study.

Funding source
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgment
The authors would like to thank the anonymous reviewers of this journal for their insightful suggestions and careful reading of the manuscript.

REFERENCES

1. American Cancer Society. About Penile Cancer [Internet]. 2018 [cited 2023 Jul 27]. Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/8783.00.pdf
2. World Health Organization. Global Cancer Observatory [Internet]. 2020 [cited 2023 Jul 27]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf
3. Douglawi A, Masterson TA. Penile cancer epidemiology and risk factors: A contemporary review. Curr Opin Urol. 2019 Mar 1;29(2):145–9.
4. Thomas A, Necchi A, Muneer A, et al. Penile cancer. Nat Rev Dis Primers. 2021 Dec 1;7(1).
5. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: Age, location, and behavioral correlates. Clin Epidemiol. 2012;4(1):1–11.
6. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med. 2018;8(12).
7. Dunsmuir WD, Gordon EM. The history of circumcision. BJU Int. 1999;83(1):1–12.
8. Weiss H, Polonsky J, Bailey R, et al. Male circumcision: Global trends and determinants of prevalence, safety, and acceptability. London School of Hygiene and Tropical Medicine: World Health Organization; 2008. p. 7–9.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. International Journal of Surgery. 2021 Apr 1;88.
10. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis [Internet]. Oxford; 2000 [cited 2023 Aug 29]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
11. Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. Vol. 21, BMC Medical Research Methodology. BioMed Central Ltd; 2021.
12. Mallon E, Hawkins D, Dinneen M, et al. Circumcision and Genital Dermatoses. Arch Dermatol. 2000;136:350–4.
13. Brinton LA, Jun-Yao L, Shou-De R, et al. Risk Factors for Penile Cancer: Results from A Case-Control Study in China. International Journal Cancer. 1991;47:504–9.
14. Tseng HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: Results of a population-based case-control study in Los Angeles County (United States). Cancer Cause and Control. 2001;12:267–77.
15. Newell GR, Fueger JJ, Spitz MR, Joseph Babaian AR. A Case-Control Study of Prostate Cancer. Am J Epidemiol. 1989;130(2).
16. Ewings P, Bowie C. A case-control study of cancer of the prostate in Somerset and East Devon the study took the form of a hospital-based case-control study of patients diagnosed at Taunton, Yeovil and Exeter Hospitals. Cases of prostatic cancer. British Journal of Cancer. 1996;74:661–6.
17. Rosenblatt KA, Wicklund KG, Stanford JL. Sexual Factors and the Risk of Prostate Cancer. Am J Epidemiol. 2001;153(12).
18. Madsen BS, Van Den Brule AJC, Jensen HL, et al. Risk factors for squamous cell carcinoma of the penis - Population-based case-control study in Denmark. Cancer Epidemiology Biomarkers and Prevention. 2008 Oct;17(10):2683–91.
19. Wright JL, Lin DW, Stanford JL. Circumcision and the risk of prostate cancer. Cancer. 2012 Sep 15;118(18):4437–43.
20. Spence AR, Rousseau MC, Karakiewicz PI, Parent MÉ. Circumcision and prostate cancer: A population-based case-control study in Montréal, Canada. BJU Int. 2014 Dec 1;114(6):E90–8.
21. Chang HJ, Pong YH, Chiang CY, et al. A matched case-control study in Taiwan to evaluate potential risk factors for prostate cancer. Sci Rep. 2023 Mar 16;13(1).
22. Hubbell CR, Rabin VR, Mora RG. Cancer of the skin in blacks. V. A review of 175 black patients with squamous cell carcinoma of the penis. Journal American Academic Dermatology. 1988;18(2):292–8.
23. Schoen EJ, Oehrli M, Colby CJ, Machin G. The Highly Protective Effect of Newborn Circumcision Against Invasive Penile Cancer. Pediatrics. 2000;105(e36).
24. Ritchie AWS, Foster PW, Fowler S. Penile cancer in the UK: Clinical presentation and outcome in 1998/99. BJU Int. 2004 Dec;94(9):1248–52.
25. Favorito LA, Nardi AC, Ronalsa M, et al. Epidemiologic Study on Penile Cancer in Brazil. International Braz J Urol. 2008;34(5):587–93.

26. Koifman L, Vides AJ, Koifman N, et al. Epidemiological aspects of penile cancer in Rio de Janeiro: Evaluation of 230 cases. International Braz J Urol. 2011 Mar;37(2):231–40.
27. Ngendahayo E, Nzayirambaho M, Bonane A, et al. Pattern and clinical management of penile cancer in Rwanda. African Journal of Urology. 2018 Dec 1;24(4):274–81.
28. Zamzami Z. The Risk Factors of Penile Cancer Patients in Arifin Achmad Regional General Hospital, Riau Province, Indonesia. South East Asia j med sci. 2019;3(1):01–3.
29. Vieira CB, Feitoza L, Pinho J, et al. Profile of patients with penile cancer in the region with the highest worldwide incidence. Sci Rep. 2020 Dec 1;10(1).
30. Kusumajaya C, Safriadi F. Characteristics of Penile Cancer at Tertiary Centre Hospital: A Nine Years Study from 2010-2019. Indonesian Journal of Cancer. 2022 Apr 1;16(1):28.
31. Morris BJ, Gray RH, Castellsague X, et al. The strong protective effect of circumcision against cancer of the penis. Adv Urol. 2011
32. Larke NL, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and penile cancer: A systematic review and meta-analysis. Cancer Causes Control. 2011;22(8):1097–110.
33. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: Importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer. 2005 Sep 10;116(4):606–16.
34. Maden C, Sherman KJ, Beckmann AM, et al. History of Circumcision, Medical Conditions, and Sexual Activity and Risk of Penile Cancer. J Natl Cancer Inst. 1993;85(1):19–24.
35. Porter WM, Francis N, Hawkins D, et al. Clinical and Laboratory Investigations Penile intraepithelial neoplasia: clinical spectrum and treatment of 35 cases. British Journal of Dermatology. 2002;147:1159–65.
36. Van Howe RS. Male circumcision and prostate cancer: A geographical analysis, meta-analysis, and cost Analysis. Can Urol Assoc J. 2020;14(7).