Male circumcision and prostate cancer: a meta-analysis revisited

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Introduction: *The relationship between circumcision and prostate cancer has been controversial. A recently published meta-analysis contradicted previous meta-analyses of male circumcision and prostate cancer risk. Our aim was to conduct a de novo meta-analysis and critically evaluate this recent paper published by Van Howe.*

Materials and methods: *We retrieved data from each of the 12 source studies Van Howe used, then performed a random effects meta-analysis of those data. We critically examined the data and other information in Van Howe's study.*

Results: *Using the same values as Van Howe, we confirmed his finding of a positive association of circumcision with prostate cancer (random effects summary OR = 1.14; 95% CI 0.99, 1.31). However, our independent meta-analysis found a negative association of circumcision with prostate cancer (random effects summary OR= 0.87; 95% CI 0.76, 1.00; p = 0.05). The reason for this critical discrepancy was Van Howe's erroneous transposition of values for circumcised and uncircumcised men in his Table columns, leading to inversion of the result. We further critically evaluated a geographical analysis and cost analysis of circumcision and prostate cancer, as well as claims denying a role for sexually transmitted infections in prostate cancer etiology, finding these too to be misleading.*

Conclusions: *Van Howe's 2020 meta-analysis was based on erroneous data transposition leading to an inverted outcome. The journal concerned recently corrected his Table. Van Howe's claim of a positive association of circumcision with country-level-age standardized prostate cancer prevalence and his cost analysis were found to be questionable. Our meta-analysis showed that circumcision is associated with lower prostate cancer risk.*

Key Words: male circumcision, prostate cancer, meta-analysis, geographical analysis, cost analysis

Introduction

A number of studies examined whether prostate cancer prevalence differs between circumcised and uncircumcised men.[1-12] A meta-analysis in 2015 by Pabalan et al of 7 case-control studies found a non-significantly lower risk of prostate cancer in circumcised men (odds ratio (OR) 0.88; 95% confidence interval (CI) 0.73, 1.07; p = 0.19).[13] After removal of 3 outlier studies risk reduction was significant (OR 0.90; 95% CI 0.82, 0.99; p = 0.04, I^2 = 0%). Risk was even lower in post-PSA testing populations (OR 0.88; p = 0.01), population-based studies (OR 0.84; p = 0.05), studies collecting data by personal interview (OR 0.83; p = 0.03), and studies of black race (OR 0.59; p = 0.02). A meta-analysis in 2016 by Li et al of 6 studies meeting the authors' inclusion criteria similarly found a lower incidence of prostate cancer in circumcised patients (OR 0.90; 95% CI 0.82, 0.98; p = 0.01).[14] The association was stronger for more aggressive prostate cancers (OR 0.84; 95% CI 0.72, 0.97; p = 0.02), but was not significant for less aggressive forms (OR 0.93; 95% CI 0.83-1.04; p = 0.19).

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In contrast to the literature, R.S. Van Howe's meta-analysis of 12 studies (published online on Feb 4, 2020 and in final form in July 2020) contained a Table showing higher risk of prostate cancer in circumcised men (OR 1.10; 95% CI 0.96, 1.26; I^2 82.8%).[15] Since the previous meta-analyses there had been only one additional study.[12] That study found prostate cancer was non-significantly lower in circumcised men (OR 0.96; 95% CI 0.77, 1.19). Because of the importance of knowing whether circumcision may be associated with an increased or decreased prostate cancer risk, we critically examined Van Howe's paper to determine reasons for the apparent discrepancy. A secondary aim was to determine whether other aspects of his article were accurate.

Materials and methods

Compilation of data

We examined relevant data in each publication used by Van Howe and compiled a Table showing number of prostate cancer cases and controls stratified by circumcision status. We compared these data with values shown in Van Howe's Table 3. We noted that rather than the conventional term, "uncircumcised," Van Howe used the non-medical term, "intact," which has emotive connotations implying that circumcised males are deficient. Since Van Howe excluded data for Jewish men, we did the same to maintain consistency in our dataset for the comparison undertaken. Similarly, when a study reported differences between strata, such as race, we showed these separately in the same way as Van Howe. Because the 2017 study by Nair-Shalliker et al did not include source data, we followed Van Howe by contacting Nair-Shalliker to obtain the relevant values.

Statistical analyses

We performed a meta-analysis using the "metafor" package[16] in R.[17] We used a random effects model with Inverse Variance method and DerSimonian-Laird to estimate between-study variance.[18]

Results

Data used for meta-analyses

Table 1 lists the studies and data Van Howe used in his original meta-analysis. Table 2 shows the actual

TABLE 1. **Values shown by Van Howe in his original Table 3 that were used in his meta-analysis of circumcision and prostate cancer**

	Circumcised (n)		Uncircumcised (n)	
	Prostate cancer	**Control**	**Prostate cancer**	**Control**
Kaplan 1966[1] – non-Jewish	34	19	90	61
Wynder 1971[2]	143	29	121	21
Rotkin 1977[3]	52	59	54	57
Mandel 1987[4]	124	102	137	103
Ross 1987[5] – White	81	61	57	85
Ross 1987[5] – Black	99	43	84	58
Newell 1989[6]	50	44	114	53
Ewings 1996[7]	123	36	221	104
Rosenblatt 2001[8]	253	500	215	488
Madsen 2008[9]	85	1	99	4
Wright 2012[10]	294	707	254	688
Spence 2014[11] – White	814	526	790	525
Spence 2014[11] – Black	81	22	44	31
Spence 2014[11] – Asian	19	6	50	20
Spence 2014[11] – Other	42	33	59	53
Nair-Shalliker 2017[12]	389	931	296	712

TABLE 2. **Actual values from each study. These were used in the present meta-analysis**

	Circumcised (n)		Uncircumcised (n)	
	Prostate cancer	**Control**	**Prostate cancer**	**Control**
Kaplan 1966[1] – non-Jewish	19	61	34	90
Wynder 1971[2]	29	21	143	121
Rotkin 1977[3]	52	54	59	57
Mandel 1987[4]	102	101	124	139
Ross 1987[5] – White	61	85	81	57
Ross 1987[5] – Black	43	58	99	84
Newell 1989[6] – non-Jewish	44	53	50	114
Ewings 1996[7]	36	104	123	221
Rosenblatt 2001[8]	500	488	253	215
Madsen 2008[9]	1	4	85	99
Wright 2012[10] *	707	688	294	254
Spence 2014[11] – White	526	525	814	790
Spence 2014[11] – Black	22	31	81	44
Spence 2014[11] – Asian	6	20	19	50
Spence 2014[11] – Other	33	53	42	59
Nair-Shalliker 2017[12]	931	712	389	296

*the values for Wright et al were 1207, 1176, 547 and 469, respectively, before deducting data from an earlier study of the Seattle cohort by Rosenblatt et al[8] from the totals, to avoid duplication

data reported in those studies. For most studies, numbers for circumcised and uncircumcised men were transposed in Van Howe's original Table 3. For Wright et al[10] the values in Van Howe's Table 3 bore no obvious relationship to the relevant values that appeared in Table 2 of the Wright et al. study.[10] Eventually we determined that those values were derived by deducting data from an earlier study, also in Seattle, by Rosenblatt et al[8] from the totals, to avoid duplication. Van Howe should have made this clear in his article. The values presented in our Table 2 were very similar, but not identical, to those used in the meta-analysis by Pabalan et al.[13] Furthermore, Pabalan et al did not include Kaplan et al,[1] Madsen et al,[9] or Rosenblatt et al,[8] nor did they subdivide the data in Spence et al[11] by race, but used only the totals (592, 637, 963 and 949 for circumcised cases and controls, and uncircumcised cases and controls, respectively).[11] In the meta-analysis by Li et al, studies with no control population, insufficient data, and data duplicated in separate articles were excluded.[14] Amongst the studies Li et al included, values for Ewings and Bowie,[7] and Newell et al[6] were the same as shown in Pabalan et al[13] and in our Table 2. For Rosenblatt et al,[8] values for circumcised men were the same as in our Table 2, whereas values for uncircumcised cases and controls were 488 and (703 minus 488 =) 215, respectively. For Mandel and Schuman,[4] the meta-analysis by Pabalan et al showed values of 102, 101, 124 and 139, respectively, whereas Li et al give values of 45, 205, 97 and 359.[14] Li et al appear, moreover, to have misinterpreted the values in Wright et al.[10]

Results of meta-analyses

In our meta-analysis of Van Howe's data, Table 1, we obtained a similar result (random effects summary OR = 1.14; 95% CI 0.99, 1.31; Figure 1), although curiously, Van Howe did not present a diagram depicting his results, as would be expected in any meta-analysis. Instead, he simply stated his overall result at the end of his Table 3 and in his text as, "random effects summary effect OR was 1.10 (95% CI 0.96, 1.26)." Our meta-analysis of the actual data from the 12 studies he used, Table 2, was quite different from that in Van Howe's Table 3 published in *Can Urol Assoc J* in 2020. We found a marginally lower risk of prostate cancer in

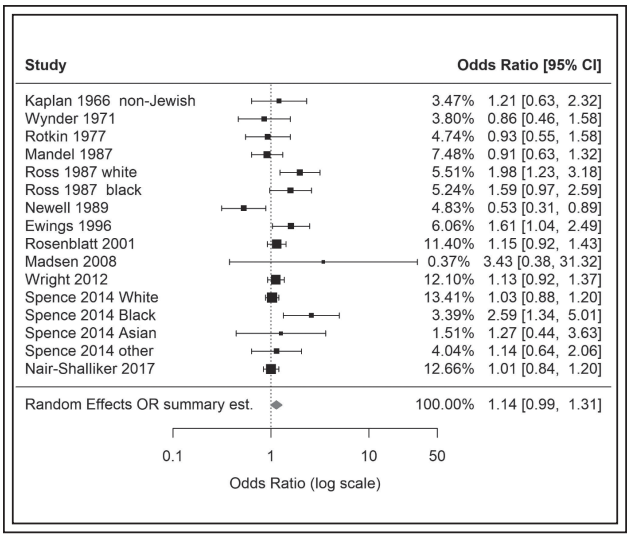

Figure 1. Results of random effects meta-analysis of circumcision and prostate cancer performed using the exact same values shown in Van Howe's original Table 3. Squares denote the odds ratio of each study, with square sizes directly proportional to the weight contribution (%) of the study. Horizontal lines on each side of the squares represent the 95% confidence intervals (CI). Diamond denotes the pooled odds ratio.

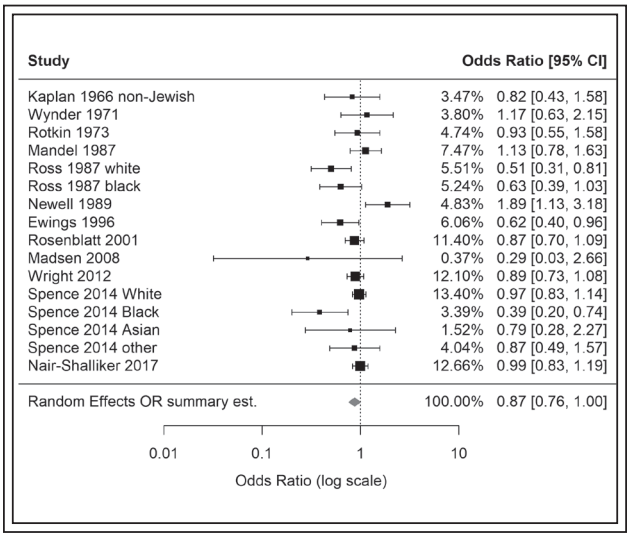

Figure 2. Results of random effects meta-analysis of circumcision and prostate cancer using the actual data shown in the publications listed. Squares denote the odds ratio of each study, with square sizes directly proportional to the weight contribution (%) of the study. Horizontal lines on each side of the squares represent the 95% confidence intervals (CI). Diamond denotes the pooled odds ratio.

circumcised men (random effects summary OR = 0.87; 95% CI 0.76, 1.00; p = 0.0517; Figure 2; heterogeneity: I^2 = 50.5%, $Q_{df\ 15}$ 30.3, p = 0.011). Our result was consistent with previous meta-analyses in 2015 (OR = 0.88)[13] and 2016 (OR = 0.90),[14] despite those involving 8 and 6 studies, respectively, and some discrepancies in the latter. In summary, rather than an error in Van Howe's statistical analyses, he made an error in placing data for circumcised men under column headings of uncircumcised men (or "intact" men, using Van Howe's parlance), and data for uncircumcised men under column headings for circumcised men, thus inverting the result.

Discussion

Meta-analyses

Contrary to meta-analyses that found circumcision reduced prostate cancer risk,[13,14] and a subsequent (neutral) study,[12] Van Howe's 2020 meta-analysis data showed that circumcision increases prostate cancer risk.[15] Crucially, values for circumcised and uncircumcised men in Van Howe's article were transposed. By swapping circumcised and uncircumcised values, the odds ratio Van Howe obtained was the reciprocal of the correct value, which would have been consistent with previous meta-analyses.[13,14] Van Howe's random-effects summary OR of 1.10 (95% CI 0.96, 1.26) for circumcised men actually applied to uncircumcised men. We concur with a reviewer that, "this is, perhaps, an unnatural way to define the OR."

Our meta-analysis of the actual data in the studies used by Van Howe resulted in an OR of 0.87, similar to the ORs of 0.88 and 0.90 in the meta-analyses preceding Van Howe's.[13,14] The Can Urol Assoc J published an erratum in March 2021[19] and a revised version that retained the original publication dates of Feb 4, 2020 for the online version and July 2020 for the final version, with the text of the PubMed citation being unchanged. Only when the PDF of the full article is now downloaded from the journal website does one see "(Revised)" at the end of the title, but the same dates of publication as above are retained (see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7337715/pdf/cuaj-7-e334.pdf). By not showing that this "revised" version was published in March 2021 readers who downloaded the original version might be unaware of the major changes.

Other issues include Van Howe's failure to (1) use raw data without adjustment in his calculation of the meta-analysis summary odds ratio, (2) reveal the importance of age of circumcision (where the large US[10]

and Canadian[11] studies found that circumcision prior to puberty was more protective), (3) provide a quality rating for each study, (4) point out racial differences noted in several studies, (5) give the correct source of participants in several studies (for example, the study by Ross et al was conducted in Los Angeles County, California, not Chicago[5]), (6) falsely stating an OR of 1.05 instead of 0.87 for the Seattle data of Wright et al,[10] and (7) describing the source of the cases in the Nair-Shalliker et al study[12] as, "population," whereas that study in fact identified patients from medical- or health-related databases as well as "volunteers" from promotional events.

Van Howe criticizes previous meta-analyses for missing studies. For example, Pabalan et al[13] did not include Madsen et al,[9] which was a study of squamous cell carcinoma of the penis and used 86 prostate cancer patients as one of two control groups. But only 1/86 patients and 4/103 population controls were circumcised, rendering those data uninformative. In contrast, Van Howe included the study in Seattle by Rosenblatt et al[8] in his meta-analysis. But those data were included within the Seattle study by Wright et al.[10] We eventually worked out that Van Howe had subtracted the Rosenblatt et al data from that in Wright et al.

Drawing on the findings in the 2015 meta-analysis,[13] of an overall 17% lower risk of prostate cancer associated with pre-pubertal circumcision, and the lifetime risk of prostate cancer in, for example, Canada of 1 in 8 (12.5%), we calculate that the percentage of men in the population who will be spared from prostate cancer by pre-pubertal circumcision can be calculated as 0.125 x 0.17 x 100 = 2.1%.

Geographical analysis

We find Van Howe's geographical analysis to be confused. Using age-standardized (world) incidence rates of prostate cancer, country-specific circumcision prevalence values,[20] and WHO life-expectancy estimates by country, Van Howe calculates the linear association of prostate cancer incidence with circumcision, life expectancy, and geographical region. Since prostate cancer prevalence increases with age, life-expectancy should be positively associated with prostate cancer incidence. If you don't live long, you won't get prostate cancer. Since race is associated with prostate cancer incidence, with blacks having a higher rate than whites, region should be associated with prostate cancer incidence. But Van Howe's Table 1 tells us nothing about how the regions are associated with circumcision, and it appears that he made no adjustment for proportion of blacks in each country. His Table 1 presents only ß estimates and p values, but not prevalence values, which would have been helpful, and there is no explanation to assist the reader. He adds, "An examination of the residuals found they were normally distributed with Mexico, the United States, China, and India as significant outliers ($r_{student}$ > 4)," but he does not explain what this might mean.

By selectively citing a single circumcision prevalence value of 2.7% for China, which comes from a 2008 study,[21] Van Howe criticizes the 14% figure used by Morris et al in their 2016 global circumcision prevalence study published in Population Health Metrics.[20] But he fails to appreciate that the Morris et al estimate came from that study and 8 other relevant Chinese studies available at the time,[21-29] including from the Western (Muslim) provinces, where circumcision prevalence is higher than the rest of China.

Countries with low circumcision prevalence are mostly developing nations with lower life expectancy and, thus, lower incidence of late-life diseases, such as prostate cancer. Therefore, Van Howe's unqualified statement, "circumcision prevalence is positively associated with the incidence of prostate cancer," is misleading.

Previous analyses found that higher circumcision prevalence was associated with lower prostate cancer incidence for 51 countries ($p = 0.02$)[30] and 181 countries ($p < 0.0001$).[31] Van Howe disputes findings showing that in countries globally in which circumcision prevalence is greater than 80%, prostate cancer-related mortality, corrected for potential confounding factors, is half that of countries with a low or intermediate circumcision prevalence.[32] His criticism of Wachtel et al because their, "specific methodology is not stated," is unfounded, as those authors enunciated their data sources and analytical approach (negative binomial regression). Van Howe refers to Kupferschmid's critique[33] of Wachtel et al, but not the Reply by Wachtel et al pointing out that Kupferschmid had failed to understand that the analysis was not about risk of developing prostate cancer, but the risk of death from prostate cancer (a "harder" endpoint when one considers that more men die with prostate cancer than from prostate cancer).[34] Wachtel et al further explained their use of WHO-designated circumcision prevalence categories, that the study had sourced its prostate cancer mortality estimates for a particular year, that circumcision data were from WHO estimates, as were gross national incomes per capita, male life expectancies at birth and gross national income per capita (each of which in part adjusted for covariates such as access to clean water and medical care raised by Kupferschmid), social factors, and proportions

of Muslims and Jews in countries. They stated that their use of WHO region as a covariate mitigated potential study bias arising from factors unrelated to circumcision. Wachtel et al further explained that "Americas" was not a term limited to the USA, where circumcision is common, but also included Central and South America, where circumcision prevalence is low. They pointed out their awareness of the role of lifestyle, dietary factors and obesity, which are relevant to high-income countries as well as Muslims and Jews. Wachtel et al concluded that the association they found between increased circumcision rates and decreased prostate cancer mortality rates could not be explained by chance.

Cost analysis

Van Howe's cost analysis suggests that circumcision reduces prostate cancer. He says, "Going from a circumcision rate of zero to 100% would theoretically prevent 6,876-15,608 cases of prostate cancer…". This is based on the summary OR estimate of 1.10 equating to 6,876 fewer cases per million, and the upper CI limit of 1.26 equating to 15,608 fewer cases per million. He ignores the lower CI limit of 0.96 which would equate to 3,152 more cases. In short, Van Howe's interpretation of his cost analysis is contradicted by proper interpretation of his summary OR estimate, and also does not properly examine the expected cases across the full OR confidence interval. These comments do not incorporate the separate issue of whether the incidence rate Van Howe uses is correct. Instead of lifetime (high) incidence, he uses annual incidence of prostate cancer of 96.6 per 100,000 (not disclosing the source of the latter value) and chooses, without explanation, to use the life-expectancy in Finland. For example, US National Cancer Institute lifetime prostate cancer risk is approximately 11.6%. Van Howe uses a cost of circumcision of $285 from a US study,[35] but does not cite a reference for his figure of $20,000 for treating prostate cancer. Since incidence rate, life expectancy, costs of circumcision and prostate cancer treatment all vary by country, it would have made more sense if his cost-analysis used comparable data for the same country. For example, a 2007 study of US data estimated that lack of circumcision would add $0.8-1.6 billion to the costs of treatment and terminal care for prostate cancer each year in that country.[36] These values, as well as circumcision prevalence and treatment costs, vary between countries, skewing his cost-analysis. A cost analysis by Johns Hopkins researchers of STIs and infant UTIs found that if circumcision prevalence in the US declined from 79% down to 10%, direct medical costs would increase by $4.4 billion over 10 annual birth cohorts.[37] Adding indirect costs, suggested as being 4 times higher,[37] would increase costs to approximately $22 billion, far exceeding Van Howe's "opportunity costs" for neonatal circumcisions. And would be even higher after adding treatment and other costs for various other adverse medical conditions that neonatal circumcision protects against. Van Howe's statement that medical practitioners do circumcisions merely for financial gain is questionable and derogatory.

Prostate cancer and history of sexually transmitted infections (STIs)

Contrary to Van Howe's long-standing claims,[38] there is considerable data, including from randomized controlled trials,[39-48] showing that circumcision reduces the risk of multiple STIs (namely, HIV, high-risk types of human papillomavirus [HPV], *Trichomonas vaginalis*, *Mycoplasma genitalium*, syphilis, chancroid, genital ulcer disease and hepatitis B),[49-52] but not sexually transmitted urethritis (i.e., *Neisseria gonorrhea*, *Chlamydia trachomatis* and non-specific urethritis).[53] We agree with Van Howe that data linking prostate cancer and history of STIs is mixed. A number of sexually transmitted organisms have been identified in the prostate (*M. genitalium*, *C. trachomatis*, *T. vaginalis*, HPV, human herpes virus-8 and HIV). Human herpes virus-8 seropositivity is associated with elevated PSA, a marker of prostate inflammation.[54] A 2005 meta-analysis found that men with a history of any STI had a 48% increased risk of prostate cancer.[55] For HPV, there was a 39% higher risk, and for gonorrhea increase in risk was 35%.[55] In a 2014 meta-analysis a history of any STI was associated with a 49% higher prostate cancer risk, for syphilis it was 27%, and for gonorrhea 20%.[56] A 2013 study found high nuclear HPV E7 oncoprotein in prostate cancer and its presence was associated with worse disease survival.[57] Moreover, when added to conventional therapy, circumcision of prostatitis patients improved their treatment outcomes.[58]

Van Howe points out that the, "studies on *Trichamonas* [sic] *vaginalis* are inconsistent". *Trichomonas vaginalis* is the most prevalent STI worldwide. This protozoan parasite has been found to be marginally more common in patients with benign prostatic hyperplasia,[59,60] and has been associated with prostate cancer in some studies,[61,62] but not all.[63] A 2018 study found an association of *T. vaginalis* with prostate cancer mortality.[64] Mechanistically, a role in prostate cancer is compelling. *T. vaginalis* secretes the macrophage migration inhibitory factor (MIF), TvMIF,

a proinflammatory cytokine that has tautomerase activity and inhibits macrophage migration.[65] By high-affinity binding to the CD74 MIF receptor, just as human MIF does, TvMIF triggers activation of ERK, Akt, and Bcl-2-associated death promoter phosphorylation, inflammation, and cell proliferation, triggering pathways contributing to growth and progression of prostate cancer.[65] As stated above, circumcision protects against trichomoniasis.

Van Howe tries to downplay the possibility of a link between STIs and prostate cancer by arguing that the cancer tends to arise in the posterior lobe of the prostate, which is furthest away from the urethra,[1] so is distal to the source of an infection such as a STI. This argument is not compelling, as the prostate is a complex organ consisting of several types of glands localized in various histologically distinct areas with differences in structural, molecular and functional features.[66] Inflammation is a characteristic feature of cancers.[67]

Penile microbiome

Van Howe does not mention the association of circumcision with a healthier penile microbiome.[68-75] Microbial dysbiosis has a potential role in the pathophysiology of various cancers,[76] including prostate cancer.[77,78] Inferior hygiene was reported in a study of uncircumcised compared with circumcised men in London, UK.[79]

Conclusions

Our review of Van Howe's study and subsequent meta-analysis demonstrated fundamental flaws as noted in our paper. In the Van Howe paper data for circumcised and uncircumcised men was classified incorrectly, contributing to an inverted result. Over a year after his article was published, the journal replaced the erroneous meta-analysis table with a corrected version. In our critical review of the Van Howe paper, we note flaws in the geographical analysis, cost analysis, and criticisms of studies by others. An updated review on STIs and a potential role for the microbiome in prostate cancer is provided in our paper as well.

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Disclosure

Brian J. Morris is a member of a not-for-profit professional, government-registered, medical association, the Circumcision Academy of Australia, which makes available on its website evidence-based educational material on male circumcision, together with contact information about medical practitioners who perform circumcision in Australia. He does not receive income from this organization. Stephen Moreton is an editor of, and contributor to, www.circfacts.org, a website that critically examines arguments opposing medical circumcision. John N. Krieger is co-inventor of a circumcision device patented by University of Washington. He has not received any income from this. □

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