

The Highly Protective Effect of Newborn Circumcision Against Invasive Penile Cancer

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ABSTRACT. *Objective.* We determined the relation between newborn circumcision and both invasive penile cancer (IPC) and carcinoma in situ (CIS) among adult male members of a large health maintenance organization.

Subjects and Methods. Circumcision status was ascertained by a combination of pathology reports, medical record review, and questionnaires for 213 adult male members of a large prepaid health plan who were diagnosed with IPC or CIS.

Results. Of 89 men with IPC whose circumcision status was known, 2 (2.3%) had been circumcised as newborns, and 87 were not circumcised. Of 118 men with CIS whose circumcision status was known, 16 (15.7%) had been circumcised as newborns.

Conclusions. Our results confirm the highly protective effect of newborn circumcision against IPC and the less protective effect against CIS. *Pediatrics* 2000;105(3). URL: <http://www.pediatrics.org/cgi/content/full/105/3/e36>; *circumcision, newborn, penile neoplasms, retrospective studies.*

ABBREVIATIONS. UTI, urinary tract infection; HIV, human immunodeficiency virus; STD, sexually transmitted disease; IPC, invasive penile cancer; CIS, carcinoma in situ; KP, Kaiser Permanente Medical Care Program of Northern California; SEER, Survival, Epidemiology, and End Results.

Pediatricians are understandably most concerned about preventive health benefits affecting infants and children. Disease-specific vaccines administered to infants are given primarily to protect against childhood diseases, although most can confer lifetime protection by use of later boosters. In contrast, newborn circumcision is a single procedure, performed most easily and safely in newborns, which protects against several diseases over a lifetime.¹⁻³ Compelling evidence has shown that newborn circumcision prevents urinary tract infection (UTI) in infancy⁴; balanoposthitis and phimosis in childhood and adolescence, human immunodeficiency virus (HIV) infection, and certain other sexually transmitted diseases (STDs) in young adults³;

and invasive penile cancer (IPC) in middle and old age.⁵ However, the American Academy of Pediatrics has issued varying and somewhat contradictory statements⁶⁻¹⁰; including the report of the 1999 Task Force on Circumcision.¹⁰ These statements may reflect jurisdictional issues: American Academy of Pediatrics subspecialty groups may be reluctant to consider benefits accruing in adulthood and old age. This reluctance could cause pediatricians to underestimate the benefits of newborn circumcision. Our study was designed to determine the relation between newborn circumcision and incidence of both IPC and carcinoma in situ (CIS) among adult male members of a large health maintenance organization in which population-based data are available.

METHODS

This retrospective case ascertainment study reviewed clinical information for patients diagnosed with IPC or CIS from 1954 through 1997 while these patients were members of the Kaiser Permanente Medical Care Program of Northern California (KP), a large health maintenance organization that serves 2.8 million members.

The State of California mandated cancer reporting in 1988. Because not all KP facilities reported their cancer cases from 1954 through 1987, cases from that period could not be used to determine incidence of IPC. Ascertainment of cases from the KP Northern California Region was complete for the 10-year period from 1988 through 1997. Diagnosis of IPC versus CIS was based on the original pathology reports. In questionable cases, the microscopic sections were reviewed by 1 of the authors (G.M.).

Clinical information was determined from pathology reports, review of individual medical charts, as well as from the KP computerized database, which uses *International Classification of Diseases, Ninth Revision* codes for hospitalizations and KP Outpatient Summary Clinic Record codes for outpatient visits.

All cases were identified through the population-based KP Cancer Registry, which receives data from 18 KP medical centers and 15 KP outpatient clinics in Northern California and is part of the California State Cancer Reporting System.¹¹ The KP Registry receives >14 000 new cases annually—approximately 30% of all cancer cases reported in the San Francisco Bay Area—and is part of the Survival, Epidemiology, and End Results (SEER) program of the National Cancer Institute.¹² Coupled with internal KP quality control mechanisms, periodic retrospective audits by both the SEER program, and the California Cancer Registry ensure that completeness of case reporting exceeds 97%. Moreover, the KP member population closely reflects the racial and ethnic diversity of the general California population¹³ and contains sufficient numbers of rarer cancers, such as penile cancer, for study.

Circumcision status was initially determined through review of individual medical charts and pathology reports. A patient questionnaire was sent in 3 mailings at 2-week intervals to further confirm circumcision status in these patients.

RESULTS

The 213 cases included 122 CIS and 91 IPC cases, a ratio of 1.3:1 for the period from 1954 through 1997

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Related material presented at the 39th annual meeting of the Ambulatory Pediatric Association; May 1-4, 1999; San Francisco, CA.

Received for publication Jul 16, 1999; accepted Oct 29, 1999.

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(Table 1). This ratio was the same for the 77 cases reported during the period when ascertainment was incomplete (1954–1987) and for the 136 cases reported during the period when ascertainment was complete (1988–1997). Anatomic site of IPC was specified in 60 (66%) of the 91 IPC cases but in only 34 (28%) of the CIS cases; this difference may reflect physicians' awareness of the importance of recording location of lesions considered more likely to be malignant. In cases of both IPC and CIS where anatomic location of lesion was specified, lesions on glans and prepuce predominated. Through review of surgical and pathology reports, patient charts, and responses to the patient questionnaire, circumcision status was determined in 207 (97%) of 213 cases (Table 2). Circumcision status was known for 89 of 91 patients with IPC; of these 89 patients, 2 (2.3%) had received newborn circumcision, whereas 16 (15.7%) of the 118 patients with CIS and known circumcision status had been circumcised as newborns. (Circumcision status was unknown for 4 of the 122 patients with CIS.) Median age at diagnosis of IPC was 65 years; median age at diagnosis of CIS was 58 years.

Most (85%) of the patients with IPC had squamous cell carcinoma. Combination of squamous cell and verrucous carcinoma accounted for 93% of IPC (Table 3). Histologic diagnosis of CIS was more varied: 97% of cases were diagnosed as Bowen's disease (44%), squamous cell CIS (36%), CIS not specified (10%), or Queyrat's erythroplasia (7%; Table 3). Treatment of CIS was local surgical excision or removal by laser or electric cautery.

Median age at diagnosis, 5-year relative survival rates, and incidence of IPC in our KP series were consistent with data reported by the State of California and SEER (Table 4).

The rarity of newborn circumcision among patients with IPC in our study (2 in 89 invasive cancer cases) warrants specific description of advanced age of onset and mild manifestations. In 1 patient, a large lesion (1.8 cm × 1.8 cm × .6 cm) located on the shaft of the penis was diagnosed in 1991, when the patient was 79 years old. The histologic report showed combined Bowen's disease and moderately differentiated, superficially infiltrating squamous cell carcinoma.

TABLE 2. Circumcision Status and Age at Diagnosis of IPC and CIS Among Adult Male Members of KP Health Plan as Reported From 1954 Through 1997

	No. (%) Patients With IPC (n = 91)*	No. (%) Patients With CIS (n = 122)†
Circumcision status known	89 (98)	118 (97)
Uncircumcised	87 (97.7)	102 (84.3)
Circumcised	2 (2.3)	16 (15.7)

* Median age at diagnosis: 65 years.

† Median age at diagnosis: 58 years.

The pathologic diagnosis was superficially infiltrating squamous cell carcinoma arising in the context of Bowen's disease. The lesion was locally excised without penectomy, and no chemotherapy or radiation treatment was given. The patient has had no readmissions or evidence of recurrence and was alive and well 7 years later (in 1998) at 87 years old. The second patient was diagnosed at 84 years old (in 1996); a small (4.0 cm × 3.0 cm × 3.0 mm) lesion on the glans was found and was locally excised. The histologic report indicated superficially invasive squamous cell carcinoma. Penectomy was not performed, and the patient did not have chemotherapy or radiation. In 1998 at 86 years old, the patient was alive and well and had not been admitted to the hospital since being diagnosed with penile cancer. These 2 rare cases of penile cancer in circumcised males were classified as stage I and showed no evidence of extension. Mean age at diagnosis was 82 years, which is 17 years older than mean age at diagnosis among the 87 uncircumcised patients. Neither man had penectomy, radiation, or chemotherapy, and they remained alive and well at 86 and 87 years old.

In contrast, 20 of the 87 uncircumcised men with invasive cancer showed evidence of stage II disease or higher, ie, regional extension, lymph node involvement, or more extensive disease. Partial or total penectomy was required in 44 (51%) of these 87 cases; 5 patients received radiation therapy alone, and 2 men had chemotherapy in addition to radiation therapy. The 5-year relative survival rate among the uncircumcised IPC patients (using 1989–1994 comparative data listed in Table 4) was 72%.

DISCUSSION

The protective effect of early circumcision against penile cancer has long been recognized and has been cited as a major medical rationale for recommending universal newborn circumcision.^{14,15} A 1991 review⁵ noted that 592 IPC cases reported from 5 major cancer centers in the United States included no men circumcised in infancy despite the >50% prevalence of newborn circumcision among US men by the mid-1930s and peak prevalence of >80% by the 1960s.¹⁶ Although >50 000 US men are estimated to have been diagnosed with IPC during a 55-year period, only 10 case reports have noted that affected men were circumcised as infants.⁵ However, no population-based studies associating circumcision and penile cancer have appeared, and IPC in circumcised men is probably underreported.

The overwhelming evidence of the role of the fore-

TABLE 1. Frequency and Anatomic Site of IPC and CIS Among 213 Adult Male KP Medical Care Program, Northern California Region Health Plan Members Is Reported From 1954 Through 1997

	No. (%) of Patients With IPC	No. (%) of Patients With CIS	Total No. (%) of Patients
Timespan			
1954–1987	32 (42)	45 (58)	77 (100)
1988–1997	59 (43)	77 (57)	136 (100)
Total cases			
1954–1997	91 (43)	122 (57)	213 (100)
Anatomic site			
Glans	41 (45)	16 (13)	
Prepuce	13 (14)	12 (10)	
Overlapping	2 (2)	0	
Body	4 (5)	6 (5)	
Not specified	31 (34)	88 (72)	

TABLE 3. Histologic Classification of IPC and CIS Among 213 Adult Male KP Health Plan Members as Reported From 1954 Through 1997

	No. (%) of Patients Affected		No. (%) of Patients Affected
Type of IPC (<i>n</i> = 91)		Type of CIS (<i>n</i> = 122)	
Squamous cell cancer	77 (85)	Bowen's disease	54 (44)
Verrucous cancer	7 (8)	Squamous cell CIS	44 (36)
Melanoma	3 (3)	CIS, not specified	12 (10)
Fibroblastic osteosarcoma	1 (1)	Queyrat's erythroplasia	9 (7)
Infiltrating duct cancer	1 (1)	Transitional cell CIS	1 (<1)
Malignant fibrous histiocytoma	1 (1)	Papillary CIS	1 (<1)
Carcinoma, not specified	1 (1)	Melanoma CIS	1 (<1)

TABLE 4. Comparative Data Reported by State of California, National Cancer Institute SEER and KP for IPC

	KP	SEER ¹²	State of California ¹¹
Median age at diagnosis (y), 1991–1995	64	68	65
5-y relative survival rates (%), 1989–1994	72	65	—
Incidence (no. of cases per 100 000 men), 1991–1995	.7	.7	.7

skin in penile cancer was questioned by a 1993 case-control report¹⁷ that found that although absence of neonatal circumcision was associated with increased risk of penile cancer, the association was much weaker than previously thought: the odds ratio reflected a 3.2-fold increased risk in uncircumcised men. However, an accompanying editorial¹⁸ criticized the study for combining IPC and CIS under the term penile cancer unlike the previous series,^{5,14,15} which included only IPC.

Our results confirm the highly protective effect of newborn circumcision against IPC. Considering the reported US circumcision rate of 50% in the 1930s¹⁶ (the median birth date of our IPC patients), relative risk of IPC for uncircumcised to circumcised men is 22:1. Reports of ~1400 cases of IPC annually in the United States¹² suggest the potential to reduce this number to <70 cases annually if all men were circumcised. In contrast, if all US men were uncircumcised, this number could increase to >2800 cases annually.

Combining CIS with IPC for analysis is not justifiable. IPC is a potentially lethal disease whose relative 5-year survival rate is 65% nationally and 72% in our patients; CIS is an easily treatable, nonlethal disease. Penile CIS is not included when calculating penile cancer incidence rates. In contrast to the rarity of IPC in circumcised men, CIS is not uncommon in circumcised men^{19–23} as was true in our series. Further, CIS is a heterogeneous disorder whose most benign form is bowenoid papulosis (penile intraepithelial neoplasia); this classification represents less aggressive disease than Bowen's disease or Queyrat's erythroplasia.^{21–24} In a review of bowenoid papulosis, Patterson et al²⁴ noted that CIS has never been found to progress to IPC and occurs in circumcised as well as uncircumcised men. Malek et al²¹ found that newborn circumcision was associated with minor-grade CIS lesions but not with major-grade CIS or IPC. These authors²¹ found that circumcision performed

during the neonatal period (but not later in life) gave almost total protection against invasive squamous cell penile carcinoma. The authors concluded²¹ that presence of the foreskin, particularly when phimotic, exposes the preputial cavity to many carcinogenic factors and that even high standards of hygiene do not fully protect uncircumcised men.

Our findings confirm the results of earlier studies that indicate the overwhelming predominance of IPC in uncircumcised men.^{5,14,15,18,19} Our study also calls into question the more recent claim of less protection afforded by circumcision against penile cancer¹⁷; that claim was made based on combining IPC and CIS and we believe that this combination is not valid.

The initial decision to perform newborn circumcision as a preventive health measure in US newborn boys began around the turn of the century. By the 1930s, the newborn circumcision rate exceeded 50% and increased evidence was developing of protection against penile cancer^{5,14,15} and promotion of improved genital cleanliness, ease of hygiene, prevention of foreskin infection (balanoposthitis), and phimosis.^{25–27} More recently, compelling evidence has shown that newborn circumcision prevents UTI, primarily in the first year of life,^{1,2,4,28–30} and also prevents certain STDs in men, particularly HIV^{3,31–33} and genital ulcer disease.^{31–34}

The incidence of penile cancer around the world is related to a combination of circumcision status and proper hygiene and varies from .1 case per 100 000 in Israel (where circumcision is almost universal) to 1 case per 100 000 in Denmark (where circumcision is not usually performed but hygiene is good) to 4.2 cases per 100 000 in countries such as Paraguay, where neither newborn circumcision nor adequate hygiene is common.³⁵ Thus, incidence can differ more than 40-fold between countries. Penile carcinoma is the most common cancer among Ugandan men³⁶ and constitutes 17% of all malignancies in some areas of Brazil.³⁷ Kochen and McCurdy³⁸ stated that the similar incidence of penile cancer in the United States and Denmark is misleading because in the United States, the rate of circumcision is high and penile cancer is essentially limited to uncircumcised US men, whose hygiene is apparently worse than in Danish men. Further, the authors pointed out that annual incidence rates do not address the lifetime risk of penile cancer. Based on life-table analysis, the authors³⁸ estimated that risk to be 1 in 600 for uncircumcised men in the United States. International cancer

TABLE 5. Comparison of Invasive Penile Cancer Incidence in Five Countries*

Country	No. Cases per 100 000 Males
Israel	.1
Denmark	1.0
Germany (GDR)	.9
Paraguay	4.2
United States (total)	.6
United States (Puerto Rican)	3.0
United States (Filipino)	.1

* Adapted and reproduced by permission of the publisher from Cancer incidence in 5 continents. Age-standardized incidence rates, 4-digit rubrics, and age-standardized and cumulative incidence rates, 3-digit rubrics.³⁵

incidence data for 1992³⁵ (Table 5) showed that in the Western European countries of Denmark and Germany, where newborn circumcision is rarely performed, penile cancer rates were 10-fold higher than in Israel, where virtually all newborn boys are circumcised. The overall penile cancer incidence in the United States (.6) represents a combination of uncircumcised and circumcised men and thus is between the incidence in Israel (.1) and the incidence in Denmark (1.0). Incidence in the United States varies 30-fold among ethnic groups and ranges from .1 in Filipino men, whose culture includes circumcision, to 3.00 in Puerto Rico, where men are not circumcised.³⁵

In counseling new parents who are contemplating circumcision for their newborn boys, physicians and other health care providers should be aware of the preventive health benefits occurring over a boy's lifetime: protection against UTI in the first year of life, decreased risk of phimosis and balanoposthitis in early childhood, and prevention of HIV and other STDs in early adulthood. Our study shows that the highly protective effect against IPC in middle and old age should also be part of this lifetime decision and should be pointed out during counseling.

ACKNOWLEDGMENTS

The research was supported by an innovation grant from The Permanente Medical Group.

The Medical Editing Department of Kaiser Foundation Research Institute provided editorial assistance.

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DOI: 10.1542/peds.105.3.e36

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