Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection

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Summary
Background A decrease in risk of urinary-tract infection is one of the most commonly given reasons for circumcision of newborn boys. Previous studies have reported rates of UTI to be 10–20 times higher in uncircumcised than in circumcised boys. This population-based cohort study followed neonates in Ontario, Canada, prospectively to study the relation between circumcision and subsequent UTI risk.

Methods Eligible boys were born to residents of Ontario between April 1, 1993, and March 31, 1994. We used hospital discharge data to follow up boys until March 31, 1996.

Findings Of 69 100 eligible boys, 30 105 (43·6%) were circumcised and 38 995 (56·4%) uncircumcised. 888 boys circumcised after the first month of life were excluded. 29 217 uncircumcised boys were matched to the remaining circumcised boys by date of birth. The 1-year probabilities of hospital admission for UTI were 1·88 per 1000 person-years of observation (83 cases up to end of follow-up) in the circumcised cohort and 7·02 per 1000 person-years (247 cases up to end of follow-up) in the uncircumcised cohort (p<0·0001). The estimated relative risk of admission for UTI by first-year follow-up indicated a significantly higher risk for uncircumcised boys than for circumcised boys (3·7 [2·8–4·9]). 195 circumcisions would be needed to prevent one hospital admission for UTI in the first year of life.

Interpretation Although our findings support the notion that circumcision may protect boys from UTI, the magnitude of this effect may be less than previously estimated.

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Introduction
Circumcision for infant boys remains controversial, but it is still a common procedure. About one in six boys and men in the world has been circumcised, in most cases for religious reasons. The medical reasons most commonly given for circumcision of infant boys are: to prevent phimosis, paraphimosis, and balanitis; to decrease the risk of cancer of the penis; and to decrease the risk of urinary-tract infection (UTI) among infants.

According to the US National Center for Health Statistics, 61% of the 1·95 million boys born during 1987 in the USA were circumcised; thus, circumcision was the commonest surgical procedure done in boys in the USA. A declining trend has been observed by Wiswell, who reported that the proportion of infants circumcised in US military hospitals, involving a large, widely dispersed population, had substantially decreased, from about 85% in 1975 to about 70% 9 years later. During the late 1980s, there was an increase in the rate of circumcision. The rate of circumcision in 1970 was 48% in Canada, 24% in the UK, and 70% in Australia. Based on in-hospital circumcision of infants younger than 28 days old in Ontario during 1985–95, the rate in the province remained almost constant at 35%. After a sharp increase in the rate of circumcision in 1991 (from 35% to 42%) there was a slow decline to 30% by 1995.

Most previous studies, with case-control designs, compared the rate of UTI in the first year of life among circumcised and uncircumcised boys. Although these studies suggested a protective effect of circumcision on the risk of UTI in boys, they did not follow up children prospectively to observe the risk of subsequent UTI. Questions remain about both short-term and long-term benefits of circumcision. We used population-based data to follow up circumcised and uncircumcised boys for up to 3 years from birth. Their risk of UTI was calculated and compared by life-table and cohort analyses.

Methods
Study population
Computerised data from the Canadian Institute for Health Information on hospital discharges in Ontario were used for fiscal years 1993–94 to 1995–96 (April 1 to March 31 of the following year). Collection of hospital discharge data for submission to the Institute is mandatory for all hospitals in Canada. Data are collected on all patients discharged from public, private, and federal hospitals in Ontario, including acute-care and chronic-care hospitals and acute psychiatric hospitals. Therefore, all UTIs that necessitated hospital admission were included in this study. The database includes, for each patient on each hospital stay, demographic (birth date, sex, and place of residence) and clinical data (admission date, discharge date, length of stay, codes from the International Classification of Diseases, 9th revision for discharge diagnoses [ICD9; up to 16 fields], and procedures undertaken). Studies by researchers in Canada suggest that the data held by the Canadian Institute for Health Information contain complete demographic information on patients (eg, age, sex, and residence codes) and good quality information on surgical procedures.
Evaluation Sciences in Ontario).

Reasons for exclusion from the study were lack of a valid health-care number, multiple birth, and stillbirth. So that the cohort consisted of initially healthy infants, those with any major complications at birth were also excluded (4% of single male livebirths). Compared with singleton liveborn babies, offspring of multiple pregnancies have a higher frequency of complications at birth (eg, low birthweight, prematurity, death). Since multiple births constituted only 2% of the total population of male infants, they were excluded from this study. Children who were circumcised after the first month of life were also excluded (2.9%).

None of these children developed subsequent UTI during the 2–3 years of observation.

All boys with a Canadian Institute for Health Information entry code of NB (newborn) born to residents of Ontario in fiscal year 1993 were included. Two cohorts of male infants were identified—circumcised (defined by the Canadian Classification Procedure Code during the first month of life 76-0) and uncircumcised (no circumcision during the 2–3 years of observation). From April 1, 1993, the health-care number was used to follow up the infants from birth to March 31, 1996.

Follow-up

Personal identifiers were available from April 1, 1993, until March 31, 1996, and are essential in tracing individuals for their readmissions. Identifiers used in linking the initial birth record to the subsequent hospital admissions were date of birth and health-care number/Ontario Health Insurance Plan (OHIP) number. The OHIP fee-for-service payments fund diagnostic tests and physicians’ services in Ontario. Each child was followed up from birth to the first occurrence of UTI or to the end of March, 1996.

The main outcome measure was hospital admission for UTI. We used the following ICD-9 codes to define UTI—infecions of the kidneys (990), cystitis (995), urethritis (997), and other unspecified UTI (990). Cases of UTI necessitating hospital admission generally represent the most severe of the broad range of UTIs, and are, thus most relevant with respect to the balance of harm and benefit in terms of both cost and morbidity.

Analyses

We used the life-table method to calculate the cumulative probability of hospital admission for UTI, the log-rank statistic to compare the cumulative probabilities between the two cohorts, and Cox proportional-hazards regression to model the risks of hospital admission for UTI. Cases of UTI not resulting in hospital admission were not captured in this study. Hospital admission rates were expressed as rates per 1000 Ontario male population, with population figures based on the Canada Census 1991 data. All data analyses were done with SAS software (version 6.11).

Results

69 100 eligible infant boys were included in the study. 30 105 (43.6%) were circumcised and 38 995 uncircumcised. Of the circumcised boys, almost all (29 217 [97.1%]) underwent the procedure during the first month of life. The 888 boys who were circumcised after the first month of life were excluded. No infant had UTI before his circumcision. Of the 38 995 uncircumcised boys, 29 217 were matched to boys in the circumcised cohort by date of birth. Since the birth cohort includes babies who were born between April, 1993, and March, 1994, the aim of age-matching procedure was to ensure that the circumcised and uncircumcised babies had equal length of follow-up.

During the 2–3 years of follow-up, 7960 (27.2%) circumcised boys and 7270 (24.9%) uncircumcised boys were readmitted to hospital. The median number of admissions was one for both groups. Thus, the two cohorts did not differ significantly in median number of admissions.

**Table 1:** Cumulative probabilities of hospital admission for UTI or proportions of readmissions. The median lengths of stay in hospital for UTI or other disorders were identical in the two study cohorts (9–0 days for UTI admissions and 3–0 days for non-UTI admissions).

63 549 admissions to hospital during the 2–3 years of follow-up were not captured in this study. There were some differences between cohorts in proxy measures of socioeconomic status. A higher proportion of families of uncircumcised infants than of circumcised infants came from low-income (less than C$35 000) postal-code areas (63.0 % vs 58.5 %), p<0.001. The proportion of individuals with low educational attainment (individuals 15 years and older with less than 10 years of education) was also higher in the uncircumcised than in the circumcised cohort (47.3 % vs 52.6 %, p<0.001).

Of the 25 549 admissions to hospital during the 2–3 years of follow-up among the two study cohorts, 330 (5.6 % per 1000 person-years) were for UTI. Both cohorts showed low probabilities of hospital admission for UTI (life-table method), though the probability was higher in the uncircumcised cohort than in the circumcised cohort. The 1-month probability of admission for UTI was 1.54 per 1000 in the uncircumcised cohort p=0.34 at 1000 in the circumcised cohort (p<0.0001, table 1). The corresponding 1-year probabilities were 7.02 and 8.75 per 1000 (p=0.001).

The relative risk of admission for UTI in the first month of life for uncircumcised compared with circumcised boys was 4.5 times (95% CI 2.4–8.4). The relative risk decreased steadily during the follow-up period to 3.7
(2.8–4.9) at 1 year. Because of the difference in indicators of socioeconomic status (low-income postal-code area and low educational attainment) between the cohorts, these variables were included in the regression model to control for potential confounding effects. Circumcision status (uncircumcised) remained as the only factor significantly associated with UTI admission rates (estimated relative risk 3.7 [2.8–5.0], p<0.0001). Cox proportional-hazards regression (which accounts for both the matched cohort design and time to UTI) also estimated an increased risk of UTI for the uncircumcised cohort (relative risk 3.0 [2.4–3.9]).

The attributable risk (also called risk difference) of UTI at 1 year was 5.14 per 1000 (7.02 minus 1.88 per 1000, table 1). From this risk measure, we estimated that 195 circumcisions were needed to prevent one admission for UTI in the first year of life.

### Discussion

A substantially lower incidence of UTI among circumcised boys has been cited as one of the major benefits of circumcision. In 1982, Ginsburg and McCracken reported an inverse association between UTI and circumcision in infant boys based on 109 UTI cases, of which 95% were in uncircumcised boys. Subsequent studies have confirmed a higher rate of UTI in uncircumcised than in circumcised boys (table 2).

Since rate of admission for UTI is low, a large number of participants is required to show any significant effect of circumcision. Our study used a cohort based on population data (including almost 60 000 infants) to estimate subsequent UTI risk in relation to circumcision. The advantages of this population-based cohort design are the inclusion of babies from the complete sociodemographic range from a universal health-care coverage system. Several previous studies were based on subsamples of the general population (infants born in US army hospitals). Whether this sample is representative of a general population is not clear.

One of the limitations of our study is that we cannot say for certain that no uncircumcised child included had a circumcision outside the hospital setting, since we had information only on hospital circuncisions. The OHIP data (physicians’ billings) showed that about 3% of circumcisions were done by clinicians outside the hospital setting. No existing systematic database captures all circumcisions on children. Previous studies shared the same limitation, since they were also based on hospital data.

The lack of accurate information on outpatient reports of UTI among children is another limitation of the study. We were unable to study directly the rate of UTIs that did not necessitate admission to hospital. There are no comprehensive population-based data in North America that could be used to account accurately for the rate of UTI treated without hospital admission. Previous studies had no estimates of outpatient rates.

We could not directly study the incidence of outpatient UTIs in Ontario, but we have estimated the rates of these infections in our study population from physicians’ billings. The results suggest that we have not underestimated the risk ratio—for every circumcised infant admitted for UTI, there were 11 outpatient billings for UTI compared with five for the uncircumcised infants. Therefore, there is no evidence to suggest that the incidence of outpatient UTIs could have been significantly differently underestimated in the circumcised population. In fact, if the billings accurately estimate the incidence of outpatient UTIs, the relative risk for all UTIs in uncircumcised compared with circumcised boys would be decreased to 1.73. These observations support our findings that the previously reported relative risks of UTI in uncircumcised infants overstate the current risks.

The range of presentations and complications from UTIs may differ between circumcised and uncircumcised boys. No study has directly addressed this issue. The impact of this differential misclassification on the estimated size of clinical benefit is likely to be negligible because UTIs necessitating admission represent the more severe cases. The morbidity associated with outpatient infection may be of more questionable clinical and financial significance; thus the relative risk for UTIs necessitating admission may reflect the most important difference in disease burden between the groups.

In Ontario each year, 23 000 infant boys are circumcised. A 10-year trend analysis reflected declining circumcision rates in Ontario since 1991–92 but with large geographical variations. The uncertainty about the medical indications for and benefits of circumcision continues to raise important questions about this procedure as a medical intervention. Our population-based cohort study estimated that 195 circumcisions were needed to prevent one hospital admission for UTI in the first year of life. Our estimated relative risk for admission for UTI of 3.07 was similar to that reported by Craig and colleagues (4.8, table 2) but lower than estimates reported by others. Studies published since the early 1980s showed a consistent protective effect of circumcision against UTI.

We conclude that although our study findings support the notion that circumcision may protect infant boys from UTI, the magnitude of this effect is significantly less than previously estimated.

### Contributors

Teresa To designed the study, did statistical analyses and interpretation, and wrote the paper. Paul Dick and William Feldman formulated the research question, interpreted the results, and wrote the paper. Mohammed Agha was responsible for SAS programming, data linkage, and statistical analyses.
Organochlorine exposure and risk of breast cancer

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Summary
Background Some organochlorine compounds may have weak oestrogenic effects and are, therefore, suspected of increasing the risk of breast cancer. We assessed prospectively the risk of breast cancer in relation to serum concentrations of several organochlorine compounds.

Methods In 1976, serum samples from 7712 women were obtained from participants in the Copenhagen City Heart Study as part of physical examinations and interviews about lifestyle factors. During 17 years of follow-up, 268 women developed invasive breast cancer. Each woman with breast cancer was matched with two breast-cancer-free women from the remaining cohort. We analysed in 1996–97 the serum samples from 240 women with breast cancer and 477 controls.

Findings Dieldrin was associated with a significantly increased dose-related risk of breast cancer (adjusted odds ratio 2.05 [95% CI 1.17–3.57], p for trend 0.01). β-hexachlorocyclohexane increased risk slightly but not significantly (p for trend 0.24). There was no overall association between risk of breast cancer and p,p’-dichlorodiphenyltrichloroethane or metabolites or for polychlorinated biphenyls. Exclusion of women with breast cancer diagnosed within 5 years of blood sampling strengthened the result for dieldrin, but did not affect the other results.

Interpretation These findings support the hypothesis that exposure to xeno-oestrogens may increase the risk of breast cancer.


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Introduction
Breast cancer is the most common cancer among women in many western countries. In Denmark, about 14% of all women develop breast cancer, and the incidence has more than doubled in the past 30 years. This trend is seen also in some developing countries with lower incidences. Recognised risk factors for breast cancer and improved diagnostic methods such as mammography can account for only a small part of this trend. Most of the risk factors for breast cancer, such as early menarche, late menopause, nulliparity, late conception of the firstborn, and hormone-replacement treatment after menopause suggest that oestrogen has a prominent role in the pathogenesis of breast cancer. The substantial international differences and changes in incidence of breast cancer seen among migrants highlight environmental factors. Certain organochlorine compounds, including agricultural pesticides, such as p,p’-dichlorodiphenyltrichloroethane (DDT), chlordane, lindane, dieldrin, and industrial chemicals such as polychlorinated biphenyls, may disrupt the endocrine system. More than 15 000 organic chlorinated compounds have been or are currently used. Biological half-lives of several years have been reported in human beings for some substances, which leads to accumulation in lipid-rich tissue. The xeno-oestrogens known so far have a much lower oestrogenic potency than oestradiol. Human beings can, however, be exposed to several compounds at the same time, and there is evidence of synergistic effects.

We investigated whether women with high serum concentrations of potentially oestrogenic compounds (kepone, dieldrin, o,p’-DDT, p,p’-DDT, and low chlorinated PCB congeners) are at increased risk of breast cancer.

Methods
Participants We used information on women enrolled in the Copenhagen City Heart Study (CCHS). The study population was selected randomly through the Civil Registration System in ten electoral constituencies around Rigshospitalet, Copenhagen,

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