Congenital Anomalies of the Kidney and Urinary Tract and Adulthood risk of Urinary Tract Cancer

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Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common kidney diseases in childhood. Alterations in genes governing nephrogenesis may cause CAKUT, and in some cases may contribute to development of urinary tract (UT) tumors later in life. We aimed to assess the association between CAKUT and UT cancer in adulthood.

Methods: We conducted a population-based historical cohort study encompassing 1,510,042 recruits to the Israeli army between 1967 and 1997. CAKUT exposure was determined by army medical coding of CAKUT in childhood. Incidence of UT cancer (kidney, ureter, or bladder) was available through record linkage with the Israeli Cancer Registry. Recruits were followed from the prerecruitment assessment until cancer diagnosis, death, or study termination, in 2012. Cox proportional hazards models were constructed to estimate the hazard ratios (HRs) for UT cancer in participants with vs. without CAKUT.

Results: During a mean follow-up of 30.4 years, 2959 participants (2573 men and 386 women) developed UT cancer. Men with CAKUT exhibited an increased risk of UT cancer compared with men without CAKUT, yielding an adjusted HR of 1.98 (95% confidence interval [CI] 1.03-3.82). Among women CAKUT was associated with a HR of 5.88 (95% CI 2.19-15.76). Notably, upon stratification according to age of cancer diagnosis, the association between CAKUT and UT cancer was statistically significant only before 45 years of age in women and only after 45 years of age in men.

Conclusion: CAKUT is associated with a significantly increased risk of UT cancer, although the incidence and absolute risk remained quite low.

Kidney Int Rep (2021) 6, 946–952; https://doi.org/10.1016/j.ekir.2021.01.003

KEYWORDS: congenital anomalies of the kidney and urinary tract (CAKUT); kidney cancer; renal cell carcinoma (RCC)

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CAKUT account for approximately 50% of cases of chronic kidney disease in children.1 CAKUT occur

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Received 27 July 2020; revised 21 December 2020; accepted 4 January 2021; published online 10 January 2021

in about 3 to 6 per 1000 live births and constitute 20% to 30% of all anomalies identified in the neonatal period. It may appear with familial aggregation in ≤15% of cases and can be isolated or part of a multiorgan syndrome. Single-gene mutations account for 12% to 20% of CAKUT cases that often exhibit genetic and phenotypic heterogeneity.2–4

It has been suggested that aberrant nephrogenesis might not only lead to CAKUT but also predispose to tumorigenesis. For instance, horseshoe kidney, a relatively common (1:400 births) subtype of CAKUT, has been suggested to be associated with increased risk of Wilms’ tumor,5 transitional cell carcinoma, and
neuroendocrine tumors.\textsuperscript{6,7} However, these associations have only been shown in small retrospective case series. Taken together, these associations indicate that abnormal renal development might result not only in congenital anomalies but may also potentially confer an increased risk for cancer. To further test this hypothesis, we carried out a nationwide, population-based historical cohort study among Israeli adolescents evaluated for military service who were followed for 30 years in order to investigate the risk of developing UT cancer (i.e., involving the kidney, ureter, or bladder) after a history of CAKUT.

**METHODS**

**Study Participants**

We conducted a historical cohort study of Israeli adolescents that included potential army recruits. Israeli adolescents are called up to recruitment centers, predominantly at 17 years of age, for an obligatory medical board examination to assess their suitability for military service. All future conscripts are asked to provide copies of all available medical records, and their family physicians are requested to provide a comprehensive health history summary on a structured form. The summary is reviewed by the physicians who perform the primary medical board examination. In addition, at the time of that medical examination, each future conscript undergoes a physical examination that includes anthropometric measurements, measurement of blood pressure and heart rate, and a dipstick urinalysis test.\textsuperscript{8,9} All future conscripts for whom a kidney-related diagnosis cannot be ruled out on the basis of the medical record or examination at the time of the medical board assessment are sent for additional tests and referred to a board-certified nephrologist. All future conscripts with a history of childhood kidney disease, including CAKUT, are referred to a board-certified nephrologist for confirmation of the diagnosis.\textsuperscript{8} The accuracy and completeness of the medical information with respect to each diagnosis of childhood kidney disease, including a diagnosis established by the nephrologist during subsequent medical evaluation, are additionally assessed and verified by a committee of 2 trained military service physicians. Each diagnosis is assigned a numerical code and recorded in a central database.\textsuperscript{8,9} The current study cohort includes Israeli men and women who were 16 to 19 years of age at the time of examination between 1967 and 1997 (Figure 1). Excluded from the study were all participants who were diagnosed with any type of childhood cancer before the army’s medical assessment, including those who were diagnosed with Wilms’ tumor during childhood (Figure 1). The exposed group was defined as those receiving codes of CAKUT. Overall, we included in this population-based historical cohort study 1,508,941 potential recruits to the Israel Defense Forces between 1967 and 1997 (Figure 1). Excluded from the study were all participants who were diagnosed with any type of childhood cancer before the army’s medical assessment, including those who were diagnosed with Wilms’ tumor during childhood (Figure 1). The exposed group was defined as those receiving codes of CAKUT. Overall, we included in this population-based historical cohort study 1,508,941 potential recruits to the Israel Defense Forces between 1967 and 1997. This database has been linked with the Israel National Cancer Registry (INCR), updated to December 31, 2012.

**Diagnosis of CAKUT**

A medical history of congenital anomalies of the kidney and urinary tract included the following phenotypes: congenital single kidney, unilateral/bilateral renal hypoplasia, renal ectopia, horseshoe kidney, hydronephrosis, hydroureter, ureteropelvic junction stenosis, ureterovesical junction stenosis, and other congenital kidney and urinary malformations not
otherwise specified. According to the army database coding system, these were divided into the following categories: horseshoe kidney, “parenchymatic” CAKUT (renal hypoplasia, cystic dysplasia, and multicystic dysplastic kidney), double collecting system, hydronephrosis not requiring surgery, obstructive uropathy requiring corrective surgery, unspecified CAKUT requiring nephrectomy, and CAKUT NOS.

All CAKUT were confirmed by renal imaging studies performed before enrollment. In addition, as noted above, participants with CAKUT at enrollment were referred to a board-certified nephrologist for final diagnosis confirmation. The diagnosis of CAKUT was available to us as a coded, grouped diagnosis.

The INCR
We linked the cohort to the INCR by way of the personal identification number given to all Israeli citizens at the time of birth or immigration. Reporting to the INCR began in 1960 and became mandatory in 1982, with a coverage for solid tumors exceeding 95%. The INCR data include dates of diagnosis, site affected, histologic type, and stage. Coding is based on the third edition of the International Classification of Diseases for Oncology.

Outcome Variables and Follow-Up
The primary outcome was any UT cancer diagnosis (defined as cancer of the kidney, ureter, or bladder) between January 1, 1967, and December 31, 2012, as recorded in the INCR. The follow-up period was measured from the initial medical board assessment until UT cancer diagnosis, death, or to December 31, 2012, whichever came first.

Statistical Analysis
The demographic and clinical characteristics at baseline of the study population are described by exposure group (having CAKUT or not).

Cox proportional hazards models were constructed to compare survival between the groups controlling for potential confounders, yielding HRs and 95% CIs. All analyses were conducted using SPSS software (version 21; IBM Corp., Chicago, Illinois, USA).

The institutional review board of the Israel Defense Forces approved the study and waived the requirement for informed consent based on preserving participants’ anonymity.

RESULTS
Study Population
Figure 1 shows the study design with stratification according to history of CAKUT. Of the 1,510,042 participants examined between January 1, 1967, and December 31, 1997, we excluded 2974 participants because of a history of childhood cancer or missing data (Figure 1). The study population included 3165 participants with CAKUT and 1,503,903 participants without CAKUT (Figure 1). The characteristics of the study population by history of CAKUT and sex are shown in Table 1. Participants with and without CAKUT had similar baseline characteristics, except for a slightly higher rate of hypertension in the CAKUT group, particularly among males.

CAKUT and Risk for UT Cancer
During the follow-up period, 2959 participants (2573 men and 386 women) developed UT cancer, 2944 participants without CAKUT and 15 participants with CAKUT. Among the latter, we identified 10 cases of bladder cancer, 4 cases of kidney cancer, and 1 case of cancer of the ureter. One hundred twenty-nine additional cases of cancer were found among the CAKUT group in non-UT locations (Supplementary Table S1).

Table 2 shows the crude and adjusted associations between CAKUT and the future risk of UT cancer during the follow-up period. Among males, the cumulative incidence rates of UT cancer were 0.6% and 0.3% for those with and without CAKUT, respectively, yielding an unadjusted HR of 2.27 (95% CI 1.26-4.11). Controlling for body mass index, year of recruitment, origin, and blood pressure at baseline yielded a HR of 1.98 (95% CI 1.03-3.82). Among women with and without CAKUT, the incidence rates of UT cancer were 0.3% and 0.1%, respectively, yielding a crude HR of 6.61 (95% CI 2.25-16.10) and an adjusted HR of 5.88 (95% CI 2.19-15.76).

Next, to assess the effect of age on the risk of UT cancer we stratified the cohort to those who developed UT cancer before and after 45 years of age (often referred to as the cutoff for “early onset” UT cancer11,12; Supplementary Table S2). Interestingly, among those diagnosed after 45 years of age, the association between CAKUT and UT cancer remained statistically significant only in males, with an adjusted HR of 2.46 (95% CI 1.23-4.92). Notably, although the association in females did not reach statistical significance, this might result from the relatively low number of cases, as indicated by the HR point estimate of 3.08 (95% CI 0.43-22.00). In contrast, among those with UT diagnosed before 45 years of age, the association was nonsignificant among males (HR 1.84 [95% CI 0.59-5.73]), but strong among females, with an HR of 8.90 (95% CI 2.84-27.87). Taken together, these results indicate that while CAKUT is associated with UT cancer in both males and females, the latter have a
significantly higher risk of cancer before 45 years of age, while the former are at risk after 45 years of age.

**DISCUSSION**

In this population-based cohort study, history of CAKUT was found to be associated with a significantly increased risk of UT cancer in adulthood. The current study is the first, to the best of our knowledge, to investigate the association between CAKUT—as a phenotype of abnormal nephrogenesis and development of the UT—and UT cancer, encompassing the kidney, ureters, and urinary bladder.

The annual incidence of renal cell carcinoma (RCC), which accounts for 90% to 95% of kidney malignancies, is increasing with male to female ratio of 2:1 and a peak incidence between 50 and 70 years of age.\textsuperscript{13} Many potential environmental risk factors have been investigated, with smoking, hypertension, and elevated body mass index demonstrating the strongest association with RCC.\textsuperscript{14} Cancer of the urinary bladder is slightly more common than RCC, and similarly demonstrates a male predominance and association with smoking and an average age of diagnosis of 67 years.\textsuperscript{13}

Notably, we show that among women with CAKUT, the increased risk of UT cancer results from women <45 years of age, which show almost 9 times the risk of UT cancer compared with their counterparts without CAKUT. The opposite is true for men with CAKUT, whose increased risk for UT cancer was evident among those >45 years of age. While the numbers of both CAKUT cases at enrollment and UT cancer cases during adulthood were small, indicating that the absolute risk is not high, these gender- and age-dependent associations merit further study. In particular, it would be interesting to test whether the younger age at UT cancer diagnosis among women

**Table 1.** Baseline characteristics of 1,510,042 participants examined between 1967 and 1997 according to the presence of CAKUT and sex

| Characteristic | Men | Without CAKUT (n = 938,467) | With CAKUT (n = 1999) | Women | Without CAKUT (n = 565,436) | With CAKUT (n = 1166) |
|---------------|-----|-----------------------------|-----------------------|-------|-----------------------------|-----------------------|
| Father’s place of birth, n (%)\textsuperscript{a} | | | | | | |
| Europe/Americas | 280,149 (30.3) | 550 (28.2) | 206,238 (36.6) | 421 (36.3) |
| Asia | 244,257 (26.4) | 524 (26.9) | 142,018 (25.3) | 276 (23.8) |
| Africa | 236,645 (25.6) | 554 (28.5) | 126,029 (22.5) | 296 (25.5) |
| USSR | 97,948 (10.6) | 20 (10.3) | 57,372 (10.3) | 107 (9.2) |
| Israel | 59,632 (6.5) | 117 (6) | 28,886 (5.1) | 58 (5) |
| Ethiopia | 5013 (0.5) | 2 (0.1) | 1133 (0.2) | 1 (0.1) |
| Israel born, n (%)\textsuperscript{b} | | | | | | |
| Yes | 770,743 (82.2) | 1,649 (82.5) | 498,376 (88.2) | 1,046 (89.6) |
| No | 166,777 (17.8) | 349 (17.5) | 66,908 (11.8) | 119 (10.4) |
| Year of birth, n (%) | | | | | | |
| 1947-1956 | 194,383 (20.7) | 360 (18.0) | 75,818 (13.4) | 96 (8.2) |
| 1957-1966 | 260,359 (27.7) | 651 (32.6) | 151,059 (26.7) | 379 (32.6) |
| 1967-1976 | 338,691 (36.1) | 732 (36.6) | 234,095 (41.4) | 525 (45) |
| 1977-1981 | 145,034 (15.5) | 256 (12.8) | 104,464 (18.5) | 166 (14.2) |
| BMI, kg/m\textsuperscript{2}, n (%)\textsuperscript{c} | | | | | | |
| <18.5 | 126,952 (13.8) | 299 (15.3) | 74,134 (13.3) | 172 (15) |
| 18.5-25.5 | 694,430 (75.7) | 1456 (74.7) | 417,022 (74.8) | 818 (71.4) |
| 25.5-30 | 79,620 (8.7) | 164 (8.4) | 55,854 (10.0) | 127 (11.1) |
| >30 | 16,264 (1.8) | 29 (1.5) | 10,824 (1.9) | 29 (2.5) |
| HTN, n (%) | | | | | | |
| 0.6 | 5996 (0.6) | 45 (2.3) | 638 (0.1) | 3 (0.3) |
| DM2, n (%) | | | | | | |
| 5996 (0.6) | 2 (0.1) | 537 (0.1) | 1 (0.1) |

BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; DM2, diabetes mellitus type 2; HTN, hypertension; USSR, Union of Soviet Socialist Republics.
\textsuperscript{a}Data available for 98.7% of the study population.
\textsuperscript{b}Data available for 99.9% of the study population.
\textsuperscript{c}Data available for 98.1% of the study population.

**Table 2.** Association between presence of CAKUT and sex and kidney cancer, according to the Cox proportional hazards model

| Characteristic | Men | Without CAKUT | With CAKUT | Women | Without CAKUT | With CAKUT |
|---------------|-----|---------------|------------|-------|---------------|------------|
| Incidence of urinary tract cancer, n (%) | 2562 (0.3) | 11 (0.6) | 382 (0.1) | 4 (0.3) |
| Mean age of diagnosis, n (SD) | 48.6 (9.3) | 49.0 (8.2) | 44.9 (10.4) | 36.7 (12.0) |
| Mean years of follow-up, n (SD) | 31.0 (9.2) | 31.0 (8.2) | 27.2 (10.2) | 18.7 (11.8) |
| Hazard ratio (95% CI) for kidney cancer | | | | |
| Unadjusted | 2.27 (1.26–4.11) | 6.01 (2.25–16.10) |
| Adjusted for BMI and recruitment year | 2.27 (1.25–4.10) | 5.94 (2.22–15.92) |
| Adjusted for BMI and recruitment year and origin and HTN | 1.98 (1.03–3.82) | 5.88 (2.19–15.76) |

BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; HTN, hypertension; SD, standard deviation.
with CAKUT indicates a genetic predisposition stemming from the same genotype that resulted in developmental anomaly, although other explanations (e.g., hormonal effects) cannot be ruled out. It should also be noted that although the HR was higher among women, the larger CI reflects the smaller number of UT cancer cases compared with men (4 vs. 11, respectively).

Importantly, because of the nature of the military database, which did include information regarding the specific type of CAKUT in each participant, we were unable to assess the association between particular anomalies and the risk of UT cancer. It is important to remember that while we referred to CAKUT as a single entity, this group of conditions is extremely heterogeneous, encompassing a wide range of anomalies. Moreover, CAKUT are characterized by considerable genetic heterogeneity, even in patients with the same anomaly, and even within the same family. One specific type of CAKUT we were able to identify was horseshoe kidney, found in 18 participants during the study period. Interestingly, although this type of CAKUT has previously been linked to cancer,\textsuperscript{5–7} none of the participants in our cohort that demonstrated this anomaly was found to develop cancer of any kind. In addition, aside from the 15 cases of UT cancer that developed in the CAKUT group during the study period, we detected 129 additional cases of non-UT cancer. The full list of diagnosed malignancies is shown in Supplementary Table S2. In addition, there were also 6 individuals in the cohort with CAKUT and a history of cancer before their enrollment. While we did not have exact information on the type of cancer, these were all solid tumors.

Embryonic nephrogenesis is a highly complex process that involves reciprocal interactions between 2 precursor tissues, the metanephric mesenchyme and ureteric bud,\textsuperscript{16–18} which results in reiterative differentiative events into mature nephrons. Failure of this differentiation process might result in the persistence of undifferentiated renal tissue, and consequently in tumorigenic transformation, as often seen in Wilms’ tumor. Although RCC emerges decades later, it is certainly possible, considering the relatively slow cycling nature of the kidney, that embryonic remnants persist into adulthood, at which time environmental tumorigenic events lead to their transformation and expansion into a tumor. In addition, many cases of CAKUT result from mutations in key developmental genes.\textsuperscript{4} It is plausible that dysfunction of these genes, many of which are key transcription factors, could result in abnormal cellular behavior and carcinogenesis. Therefore, the same molecular events that result in abnormal kidney development during fetal life might confer an increased risk of cancer later in life, potentially after additional, somatic mutations take place. For instance, PAX2, the causative gene in renal coloboma syndrome, which involves abnormal renal development, has also been implicated in the pathogenesis of RCC.\textsuperscript{19–21}

The association between allegedly benign developmental anomalies and cancer has been previously suggested for other organs as well. For example, congenital pulmonary airway malformation has been reported to result in a slightly increased risk of lung tumor after several decades,\textsuperscript{22} although conclusive proof is still lacking for this association. Similarly, individuals with congenital malformations in the nervous system were found to have an increased risk of developing cancer in the brain/nervous system.\textsuperscript{23} It is currently unclear, however, whether the increased incidence of cancer in these cases stems directly from the anomalies, or whether both cancer and anomaly reflect a general tendency for abnormal differentiative processes.

While it should be noted that the numeric codes used by the army to denote CAKUT during the study period did not provide complete details on the exact type of anomaly, all CAKUT cases were grouped into 7 types of anomalies (except for horseshoe kidney, which had a unique code). These included: horseshoe kidney, parenchymatic CAKUT (e.g., renal hypodysplasia, cystic dysplasia, and multicystic dysplastic kidney), double collecting system, hydroureret/hydronephrosis not requiring surgery, obstructive uropathy requiring corrective surgery, unspecified CAKUT requiring nephrectomy, and CAKUT NOS. Accordingly, during the study period (1967–1997) there were 18 cases of horseshoe kidney, 1083 cases of parenchymatic CAKUT, 130 cases of double collecting system, 428 cases of hydroureret/hydronephrosis not requiring surgery, 899 cases of obstructive uropathy requiring corrective surgery, 517 unspecified CAKUT requiring nephrectomy, and 90 cases of CAKUT NOS.

Several limitations should be considered when interpreting the results of this study. First, the absolute numbers of cancer cases are relatively low, in particular in the CAKUT group ($n = 15$); second, we did not have data on smoking history of the study participants, which is a well-established risk factor for cancer of the kidney and urinary bladder. Nonetheless, it is reasonable to assume that a similar proportion of participants with and without CAKUT were smokers, and this should not have materially affected our results. Third, no data about clinical events during the follow-up period, which might affect the risk for cancer, were available. However, this is true for both the study and control populations. Fourth, as discussed above, the exact subtype of CAKUT, which encompasses a wide spectrum of disorders, was unavailable to us. Similarly,
we did not have any information about genetic testing that was potentially carried out in participants with CAKUT. In this context, it would be interesting to explore the association between specific anomalies/phenotypes and the risk of cancer. Fifth, our study was restricted to Jewish recruits, thereby limiting its generalizability. In addition, our cohort included a nationally representative group of Jewish men but not of Jewish women, because Orthodox women are exempt from military service. Sixth, UT cancers usually arise at a later age than that covered in our study. To address this issue, we stratified the cohort according to age at diagnosis (before and after 45 years), which demonstrated that CAKUT is still associated with UT cancer, albeit only among men. Future studies with longer follow-up periods are needed to test whether the association still exists into the older ages. Lastly, although the INCR cancer database has been in use since 1960, it has become mandatory only in 1982 (15 years after the beginning of the study period); therefore, we cannot exclude the possibility that some cases of UT cancer were not reported between 1967 and 1982, but it is likely that there were similar rates of unreported cancer cases among the study and control groups (CAKUT and non-CAKUT).

The main strengths of this study are the reliance on large cohorts with detailed clinical assessment parameters, along with a long follow-up period and comprehensive documentation of cancer diagnosis. These allowed us to determine the risk for UT cancer, which is a relatively uncommon outcome in this age group.

CONCLUSION

In conclusion, we report that the presence of CAKUT during childhood is associated with a significantly increased risk of UT cancer. The association between CAKUT and UT cancer among women is evident before 45 years of age, while among men it is seen after 45 years of age.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF).

Table S1. Cancer cases among participants with CAKUT.

Table S2. Association between CAKUT and urinary tract cancer according to age at end of follow-up.

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