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Association of Bone Mineral Density with Incidental Renal Stone in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

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Abstract

Purpose—Our objective was to evaluate the association between low bone mineral density (BMD) and incidental renal stones among long-term survivors of childhood acute lymphoblastic leukemia (ALL).

Methods—Adult participants who were 10+ year from their childhood ALL diagnosis and members of the St. Jude Lifetime Cohort study were recruited between 12/2007 and 3/2011. During their risk-based medical evaluations they underwent quantitative computed tomography (QCT) to evaluate BMD. Incidental renal stones were identified by radiologists' review of axial QCT source images. Demographic and dietary information was abstracted from health surveys and Block Food Frequency questionnaire respectively. Multivariable logistic regression model was used for analysis.

Results—At a median of 26.1 years from diagnosis, BMD Z-scores were -2 in 34/662 (5.2%) and renal stones detected in 73/662 (11%) participants. Adjusted for age, renal radiation, dietary vitamin D, gender and body mass index, when compared to those with BMD Z-scores 0 , the risk of renal stones was increased among those with BMD Z-scores -2 (Odds Ratio [OR], 2.92; 95% Confidence Interval [CI] 1.14-7.48). Risk of renal stones significantly increased for older age (45-54 vs. 18-24 y; OR, 3.70; 95% CI 1.11-12.35) whereas the risk was higher but non-significant for > 141.5 IU (sample median) daily intake of vitamin D (OR, 1.64; 95% CI 0.98-2.75).

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Conclusions and implications for cancer survivors—Older ALL survivors with BMD Z-scores ≤ -2 are at risk for renal stones and should be counseled so that appropriate follow-up care can be provided for those among whom renal stones are detected.

Keywords

acute lymphoblastic leukemia; bone mineral density; incidental renal stones; survivors; vitamin D

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy in the United States (U.S.) with an incidence of 3.8 per 100,000 in children aged 0 to 14 years. Considering that the 5-year survival rate of ALL now exceeds 90% [1] the long term treatment related morbidities among this growing population of survivors are a matter of significant concern. Among the many late effects experienced by ALL survivors are the risks for low bone mineral density (BMD), [2,3] symptomatic renal stones [4] and renal dysfunction [5].

In the general population, a high bone turnover rate has been associated with low BMD and symptomatic renal stones [6-9]. In ALL survivors, risk factors that predispose to low BMD include treatment with corticosteroids, cranial radiation related endocrinopathy, nephrotoxic drug related renal tubular dysfunction, poor nutrition, physical inactivity, and male gender [3,5,10-12]. These risk factors have been associated with symptomatic renal stones in ALL patients [4, 13]. Moreover, poor nutrition, physical inactivity, and male gender have also been associated with renal stones in the general population [14-17]. The lifetime prevalence of symptomatic renal stones has increased from 2.6% in the 1960s to 5.2% in the 1990s in the U.S. [17]. Several demographic and dietary characteristics have been associated with symptomatic renal stones [17]. However, less is known about the risk factors for incidental or asymptomatic renal stones, which are significantly different from symptomatic renal stones regarding demographic characteristics and comorbidities [18].

A recent study estimated the prevalence of incidental renal stones to be 11% among 1,957 potential kidney donors with mean age of 43 years [18]. If left untreated, 48.5% of incidental renal stones will progress to symptomatic disease in 5 years; half of these symptomatic patients will require intervention [19]. Another study of 300 males of average age 62.8 years found that 77% of asymptomatic stones would experience disease progression and 26% would require surgical intervention within an average of 3.3 years [20]. We previously reported a prevalence of 4.5% for incidental renal stones in a cohort of childhood ALL survivors with a median age of 17 years [21]. Our data suggested a lower median BMD Z-score among those with asymptomatic renal stones than among those without asymptomatic renal stones but this difference was not statistically significant (-1.0 vs. -0.5 , $P=0.15$) [21].

The aim of our study was to evaluate the association between BMD and incidental renal stones, controlling for demographic and dietary confounders among a large and older cohort of ALL survivors. To our knowledge, there is no published literature evaluating this association. Identification of such an association will not only help identify ALL survivors who are at increased risk for future clinically significant renal problems, but will also help characterize a phenotype that allows investigation of genetic, metabolic and dietary mechanisms that potentially influence both early onset chronic renal disease and low bone mineral density in this population.

Materials and Methods

Study Participants

Study participants were members of the St Jude Lifetime Cohort (SJLIFE), a study designed to evaluate late effects of childhood cancer and its treatment [22]. Individuals with childhood cancer treated between 1962 and 1999 at St Jude Children's Research Hospital were potentially eligible and were recruited systematically in blocks of 50. Participants were 18 years of age or older and at least 10 years from their original cancer diagnosis at the time of their enrollment in SJLIFE. Protocol enrollment started in December of 2007 and is ongoing. The St Jude Children's Research Hospital Institutional Review Board approved all study documents and each participant was enrolled after providing written informed consent.

Participants eligible for this study included survivors of childhood ALL randomized to the first 49 recruitment blocks who completed a comprehensive health questionnaire and bone density testing as a part of their risk-based medical assessment before 31st March 2011. Among the 1180 potentially eligible ALL patients for SJLIFE, 1159 were randomized to the first 49 blocks and were contacted (Figure 1). From the sample of eligible participants who were contacted, 103 declined participation, 17 were lost to follow up, 154 were passive non-participants and 159 were interested in participating, but had not completed their assessments. Among the 690 (59% of those eligible) participants who completed their assessments, 21 participants were excluded from analyses because they did not have quantitative computed tomography (QCT) results (N=21) or their QCT images were not sufficient to assess abdominal aortic calcification results (N=7). A final study sample of 662 (57%) ALL survivors was used to evaluate the association between BMD and incidental renal stones.

Description of Variables

The BMD of participants was assessed by QCT as a part of their risk based medical assessment. Vertebral trabecular BMD was determined by using a GE VCT Lightspeed 64 detector (General Electric Healthcare, Milwaukee, Wisconsin) and Mindways QCT Calibration Phantoms and software (Mindways Software, Austin, TX, USA) [23-25]. We measured BMD from the direct axial images of the mid-vertebral bodies of first (L₁) and second lumbar (L₂) vertebrae [24, 25]. In case of fracture or deformity identified in either L₁ or L₂, the affected vertebral body was excluded and one of the images of a vertebral body from T₁₁ to L₄ was reviewed [12].

BMD was defined as the average of values obtained from the two vertebral bodies. A standardized Z-score was calculated as the number of standard deviations (SD) above or below the mean to indicate the difference between the patient's BMD value and the average BMD value for age and sex appropriate controls (derived from normative values provided by the manufacturer). The axial QCT source images were reviewed by two radiologists (SS and SCK) for presence of renal stones in either or both kidneys. Renal stones were defined as incidental if at least one stone was identified in one of the kidneys. We reviewed the medical records of participants with incidental renal stones to find if they were symptomatic. Out of the 73 survivors with incidental renal stones, none of the participants were symptomatic at the time of study.

All demographic, treatment and laboratory variables were abstracted from the hospital medical records and the comprehensive health questionnaire completed at the time of enrollment [22]. Demographic variables included age at diagnosis, age at time of enrollment, gender, race, region of residence, physical activity, year of diagnosis, body mass index (BMI) (kg/m²). Participant's self-reported responses to physical activity questions were used to estimate the metabolic equivalent (MET) minutes/week of moderate or vigorous activity.

Physical activity was categorized as inactive (0 MET min/week), low (1-499 MET min/week), moderate (500-1000 MET min/week) and high (> 1000 min/week) based on the U.S Department of Health and Human Services guidelines [26]. Because living in the southeastern United States has been associated with higher risk for renal stones, [27] we dichotomized study participant's region of residence as southeastern (AL, FL, GA, MS, NC, SC and TN) or non-southeastern.

Treatment variables considered in our models included cranial and renal radiation (Gray-Gy), and chemotherapeutic exposures including methotrexate, glucocorticoids, anthracyclines and alkylating agents. Participants treated with renal radiation included those whose kidneys were in the radiation field because of total body irradiation, spinal radiation or localized renal irradiation. Total methotrexate dosage during the treatment period was evaluated as a continuous variable in mg/m². Glucocorticoids, anthracyclines and alkylating agents were evaluated as prednisone, doxorubicin and cyclophosphamide equivalent doses (CED) in mg/m² respectively. Anthracycline dosages were divided in four categories: not exposed, 1 -100 mg/m², 101 – 400 mg/m² and > 401 mg/m². CED dosages were categorized as tertiles of total sample with a separate category for participants who did not receive CED. We also evaluated the influence of laboratory biochemical values of urinary pH, microscopic hematuria, serum levels of calcium, phosphate, bicarbonate, blood urea nitrogen (BUN), creatinine and the derived BUN/creatinine ratio on asymptomatic renal stones. Metabolic syndrome, because of its documented association with renal stones formation [28] was defined as per the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria [29].

Dietary information was abstracted from the widely used and validated self-administered Block Food Frequency questionnaire [30]. The food list for this questionnaire was generated using the NHANES III dietary recall data. We considered dietary intake of calcium, vitamin D, vitamin C, sodium, animal protein, dietary fiber, total fluid intake, alcohol intake and total energy intake [31, 32].

Data Analysis

Data analysis was performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). Continuous variables were evaluated as median and interquartile (IQ) range (25th percentile, 75th percentile). Differences in demographic, dietary and biochemical characteristics stratified by incidental renal stones were evaluated by Wilcoxon rank-sum test for median comparisons and chi-square or Fisher's exact test for categorical variables. P values < 0.05 were considered statistically significant, except for interaction analyses where we used P < 0.10. The Z-score of BMD was divided in four categories; - 2 SD, > - 2 to -1 SD, > -1 to 0 SD, 0 SD. The participant's age at the time of enrollment was divided in four groups; 18-24, 25-34, 35-44, and 45-54 years.

We used multivariable logistic regression to estimate the risk of incidental renal stones for each category of Z-score of BMD with 0 SD as a reference category. Potential confounders were kept in the model if they were part of the minimally sufficient adjustment set from directed acyclic graphs [33]. Statistical interaction of BMD with factors such as gender, age at study enrollment (< 35 vs. ≥ 35 years), median of time since diagnosis (< 26.1 vs. ≥ 26.1 years), BMI (< 30 vs. ≥ 30 kg/m²), metabolic syndrome, and median doses of glucocorticoids, methotrexate, anthracyclines and CED were assessed using a criteria of p<0.10 for statistical significance. The same variables were used to assess the consistency of BMD and renal stone association across their strata. In our final logistic regression model evaluating the association between BMD and renal stones, we adjusted for age at enrollment in SJLIFE, history of renal radiation, daily intake of vitamin D, gender and BMI. We did not adjust for race because no renal stones were detected in nonwhite survivors.

Results

Demographics and Risk Factors for Renal Stone

Participant demographic and treatment characteristics are presented in Table I. The median (IQ range) of BMD Z-score was -0.36 (-1.14, 0.36) in a predominantly Caucasian (92.7%) cohort of 662 ALL survivors out of which 337 (50.9%) were female. A BMD Z-score was -2 standard deviation (SD) in 34 (5.2%) and incidental renal stones were detected in 73 (11%) of the ALL survivors. The median (IQ range) of age at diagnosis, age at study enrollment and time since diagnosis for the study participants were 4.5 (3, 8) years, 31 (26, 37) years and 26.1 (21.5, 31.6) years respectively. Among survivors eligible for this study (n=1159), participants (n=662) were more likely to be female (337 (50.9%) vs. 222 (44.7%), $P=0.04$) and white (614 (92.7%) vs. 442 (88.9%), $P=0.02$) than non-participants (n=497).

ALL survivors with incidental renal stones had a lower median BMD Z-score than those without incidental renal stones (-0.66 vs. -0.35, $P=0.05$). ALL survivors with incidental renal stones were significantly older (34 years vs. 31 years, $P=0.04$) and all of them were White (100% vs. 91.8%) when compared to those without incidental renal stones. Although ALL survivors with incidental renal stones were more likely to be from the southeastern states (52.1% vs. 43.3%, $P=0.16$), this association was not statistically significant. Among the ALL survivors, 238 (35.9%) had metabolic syndrome, 190 (28.7%) were inactive with 0 MET min/week and 288 (43.5%) were obese with BMI ≥ 30 kg/m². However, there was no significant difference between ALL survivors with and without renal stones with respect to metabolic syndrome ($P=0.85$), physical activity ($P=0.64$) or BMI ($P=0.67$).

We found no significant difference between ALL survivors with and without renal stones with respect to decade of diagnosis ($P=0.37$), treatment with cranial irradiation ($P=0.18$), alkylating agent ($P=0.60$) or anthracycline ($P=0.99$) exposure. Out of the 20 participants that received renal radiation 10 received total body irradiation for bone marrow transplant following relapse of ALL. The remaining 10 participants received renal radiation as a result of direct renal irradiation for renal infiltrates (n=1), mantle radiation for secondary Hodgkin's disease (n=3), and total body irradiation as part of their primary treatment (n=5) or for secondary acute myeloid leukemia (n=1). All the study participants received glucocorticoids and methotrexate as part of their chemotherapy. No significant difference was observed between ALL survivors with and without renal stones with respect to median cumulative dose of glucocorticoids (7610 vs. 9560 mg/m², $P=0.68$). However, those with incidental renal stones received a lower median dose of methotrexate compared to those who did not have renal stones (4235 vs. 5311 mg/m², $P=0.04$).

Participant dietary and biochemical characteristics are presented in Table II. Although not statistically significant, ALL survivors with incidental renal stones were more likely to have more than the total sample median (>141.5 IU) dietary vitamin D (60.6% vs. 48.5%, $P=0.06$), higher median calcium intake (890 vs. 822 mg, $P=0.07$) and higher animal protein intake (4.15 vs. 3.55 g, $P=0.58$) compared to those without renal stones. There was no significant difference between ALL survivors with and without renal stones with respect to dietary vitamin C, sodium, fiber, total energy, total fluids and alcohol intake. Survivors with incidental renal stones had lower median serum phosphate levels compared to those without renal stones (3.1 vs. 3.3 mg/100 ml, $P=0.02$). We observed no significant difference between ALL survivors with and without renal stones with respect to serum levels of calcium ($P=0.64$), bicarbonate ($P=0.45$), BUN ($P=0.54$), creatinine ($P=0.09$), BUN: creatinine ratio ($P=1.00$), urinary pH ($P=0.14$) and microscopic hematuria ($P=0.37$).

Association of BMD with Incidental Renal Stones

Age at study enrollment, history of renal irradiation, dietary vitamin D, gender and BMI were selected as the minimally sufficient adjustment set from the directed acyclic graph. In a multivariable logistic regression model (Table III), when compared to BMD Z-score 0 SD, the risk of renal stones was higher among those with a BMD Z-score -2 SD (Odds Ratio (OR), 2.92; 95% Confidence Interval (CI), 1.14 - 7.48). When compared to survivors between 18 to 24 years, the risk of renal stones was higher among those 45 to 54 years of age (OR, 3.70; 95% CI, 1.11 - 12.35).

There were no significant interactions between gender, age at study enrollment, time since diagnosis, BMI, metabolic syndrome, and glucocorticoid exposure or methotrexate exposure and BMD Z-score in our model ($P_{\text{interaction}} > 0.10$). The association of lower BMD Z-score with risk of incidental renal stone formation was consistent across the strata of gender, age at study enrollment, time since diagnosis, BMI, metabolic syndrome, and median glucocorticoid dosage and median methotrexate dosage.

Discussion

The 11% prevalence of incidental renal stones in this cohort (median age=31 years) is more than double the 4.5% prevalence we previously reported in a relatively younger cohort (median age=17 years) of ALL survivors [21] but similar to the 11% prevalence found among a slightly older cohort of 1,957 potential kidney donors (mean age=43 years) [18]. We found an inverse association between BMD and incidental renal stones in this analysis. After adjusting for confounding variables, adult ALL survivors with lowest category of BMD Z-score were almost three times as likely to have a renal stone compared to the normal BMD Z-score of greater than zero. This association of low BMD observed with formation of renal stones among ALL survivors was consistent across strata of gender, age at study, time since diagnosis, BMI, metabolic syndrome, and glucocorticoid and methotrexate dosage. We observed that older survivors between ages 45 and 54 years were 3.7 times as likely to develop renal stones compared to younger survivors between 18 and 24 years.

Our results confirm the non-significant yet inverse association of BMD with asymptomatic renal stones we previously observed in younger cohort of ALL survivors [21] in a larger, older cohort of ALL survivors. In contrast to our previous study, we evaluated an older cohort (median age: 31 years vs. 17 years) with a longer follow-up time from diagnosis (median: 26.1 years vs. 10.6 years). We were also able to adjust for significant confounders and assess nutritional information in a larger proportion of the cohort (97.6% vs. 41%) than we did in our previous study. Similar to our previous results we detected no renal stones among black survivors.

We were unable to find information in the literature evaluating the association of BMD with incidental renal stones in the general population. However, several studies have indicated that BMD is inversely associated with symptomatic renal stones [6,7,15,34]. Lauderdale et al. [7] used data from the Third National Health and Nutrition Examination Survey to demonstrate that men with history of renal stone formation had significantly lower femoral neck BMD compared to men with no history of renal stones (adjusted β coefficient=-0.023, $P=0.01$). They found this association to be weaker among women (adjusted β coefficient=-0.009, $P=0.34$) and stronger only among those with low dietary calcium consumption. We did not observe a similar interaction effect by gender or dietary calcium consumption on the association between BMD and incidental renal stone in our younger ALL survivor population. Another study provides support for an association between higher bone turnover rates and the development of renal stones [34]. These authors indicated that BMD deficits

were greater among patients with recurrent renal stones compared to those with a single episode of renal stones, who in turn, had greater deficit than those with no history of renal stones [34].

Two literature reviews have proposed a potential mechanism that may explain the pathogenesis of the association between BMD deficit and formation of renal stones [6, 15]. Authors of both studies propose that animal based, protein rich, low calcium western diets may precipitate a low level chronic metabolic acidosis with resultant hyperoxaluria that contributes to development of low BMD and renal stones. Although not statistically significant, we did observe that ALL survivors with incidental renal stones consumed more animal protein (4.15 vs. 3.55 g/day, $P=0.58$), and had acidic urine (pH: 5.5 vs. 6.0, $P=0.14$) when compared to survivors without renal stones. However, those with renal stones in our cohort reported consuming more calcium (890 vs. 822 mg, $P=0.07$) than those without incidental renal stones. Both reviews elaborated on the role of hypercalciuria and its association with BMD deficits and calcium renal stones [6, 15]. We could not confirm this pathway in our cohort because we did not measure urinary calcium. However, we did find significantly lower levels of serum phosphate among survivors who had incidental renal stones compared to survivors who had no renal stones (3.1 vs. 3.3 mg/100ml $P=0.02$) which may indicate renal phosphate wasting and associated hypercalciuria.

In this study we found incidental renal stones to be significantly associated with not only BMD deficits but also with increasing age. In our previous study, [21] the data suggested a positive association between age and asymptomatic renal stones, but the association was not statistically significant (21.2 vs. 17.0 years, $P=0.29$). Age is strongly associated with formation of renal stones in the general population. Evaluation of an older cohort allowed us to verify that this association also exists in an ALL survivor cohort.

The results of our study should be interpreted in the context of the limitations of this analysis. The participation rate among ALL survivors in the first 49 blocks in SJLIFE was 59% thus creating a possibility for volunteer bias. Our cohort of ALL survivors who participated in the assessment may have been different from those who did not participate. For example, participants in our study were more likely to be female (337 (50.9%) vs. 222 (44.7%), $P=0.04$), and it is known that females have lower BMD [35] and lower risk of formation of renal stones compared to males [17]. Thus, selective volunteering by females could have resulted in underestimation of the strength of association between BMD and renal stones. We used axial QCT source images to detect renal stones which included levels to assess BMD in two vertebral bodies. Thus, the kidneys were not imaged in their entirety. Therefore, our results may underestimate the prevalence of stones. We observed a significantly lower median cumulative dose of methotrexate among those with incidental renal stones compared to those without ($P=0.04$). Methotrexate is a weak acid and precipitates at low urinary pH due to poor solubility. It is possible that over-hydration and alkalization received by children during treatment with higher dose of methotrexate [36] protected them against future renal stone formation. Conversely, lesser hydration and alkalization among children treated with lower dose of methotrexate could have resulted in a subclinical renal injury [37] resulting in subsequent stone formation. Finally, our results could be biased because of unmeasured confounding factors such as hypercalciuria and family or past history of renal stones which are known risk factors for renal stone formation.

In summary, this study has demonstrated that, in a cohort of childhood ALL survivors with a median age of 31 years the prevalence of incidental renal stone is similar to that in a slightly older healthy adult cohort (median age=43 years). Incidental renal stone formation is associated with low BMD and older age among ALL survivors. If left untreated, almost half of the incidental or asymptomatic renal stones will become symptomatic within 5 years [20]

and a quarter would require surgical intervention within 3 years [19]. Therefore, incidental renal stones in ALL survivors are not only a concern because of the aging survivor population but also because of their natural progression. Our results provide useful information for clinicians providing follow-up care to adult ALL survivors. However, based on the results from this cross-sectional study we cannot recommend regular screening for renal stones among adult ALL survivors. Clinicians should be aware of the increased risk for renal stones among ALL survivors 45 years of age or older with BMD Z-scores ≤ -2 . Those in whom asymptomatic renal stones are detected should have annual imaging, and monitoring for signs of increasing size or de novo obstruction for the first 2-3 years so that treatment may be implemented if there is increase in size, de novo obstruction, infection or pain [38]. ALL survivors with renal stones should be aware of signs and symptoms of obstruction and associated infection.

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^a Quantitative Computed Tomography; ^b Abdominal Aortic Calcification

Figure 1.
Participation in St. Jude Life (SJLIFE) Cohort

Table I

Demographic and treatment characteristics of ALL survivors stratified by incidental renal stone

	Total (n=662)	Renal Stones (n=73)	No Renal Stones (n=589)	P-value ^c
Bone Mineral Density Z-score				
Continuous	-0.36 (-1.14, 0.36)	-0.66 (-1.38, 0.20)	-0.35 (-1.12, 0.38)	0.05 ^e
Categorical				
0 SD	244 (36.9)	24 (32.9)	220 (37.3)	0.07
> -1 to < 0 SD	227 (34.3)	21 (28.8)	206 (35.0)	
> -2 to -1 SD	157 (23.7)	20 (27.4)	137 (23.3)	
- 2 SD	34 (5.2)	8 (10.9)	26 (4.4)	
Gender				
Female	337 (50.9)	33 (45.2)	304 (51.6)	0.30
Male	325 (49.1)	40 (54.8)	285 (48.4)	
Age at diagnosis (years)	4.5 (3.0, 8.0)	5.0 (2.0, 9.0)	4.0 (3.0, 8.0)	0.43 ^e
Age at study (years)	31 (26, 37)	34 (29, 40)	31 (26, 37)	0.04 ^e
Age at study (years)				
18-24	102 (15.4)	8 (11.0)	94 (15.9)	0.15
25-34	310 (46.8)	29 (39.7)	281 (47.7)	
35-44	216 (32.6)	30 (41.1)	186 (31.6)	
45-54	34 (5.1)	6 (8.2)	28 (4.8)	
Time since diagnosis (years)	26.1 (21.5, 31.6)	27.5 (23.3, 32.6)	25.8 (21.1, 31.1)	0.06 ^e
Race				
White	614 (92.7)	73 (100)	541 (91.8)	0.04 ^d
Black	43 (6.5)	0	43 (7.3)	
Asian	1 (0.2)	0	1 (0.2)	
Other/Unknown	4 (0.6)	0	4 (0.7)	
Region of residence				
Southeastern States ^a	293 (44.3)	38 (52.1)	255 (43.3)	0.16
Non-Southeastern States	369 (55.74)	35 (47.9)	334 (56.7)	
Metabolic syndrome ^b				
Yes	238 (35.9)	27 (37.0)	211 (35.8)	0.85
No	424 (64.1)	46 (63.0)	378 (64.2)	
Physical activity (MET min/week)				
0 : inactive	190 (28.7)	20 (27.4)	170 (28.9)	0.64
1-499 : low	153 (23.1)	19 (26.0)	134 (22.7)	
500-1000 : moderate	113 (17.1)	9 (12.3)	104 (17.7)	
> 1000 : high	206 (31.1)	25 (34.3)	181 (30.7)	
BMI (kg/m ²)				
<18.5 : underweight	14 (2.1)	2 (2.7)	12 (2.0)	0.67
18.5 - 24.99: normal	177 (26.8)	16 (21.9)	161 (27.3)	

	Total (n=662)	Renal Stones (n=73)	No Renal Stones (n=589)	P-value ^c
25.0-29.99 : overweight	183 (27.6)	23 (31.5)	160 (27.2)	0.37
30 : obese	288 (43.5)	32 (43.8)	256 (43.5)	
Year of Diagnosis				
1963 to 1970	45 (6.8)	8 (11.0)	37 (6.3)	
1971 to 1980	195 (29.5)	23 (31.5)	172 (29.2)	
1981 to 1990	313 (47.3)	33 (45.2)	280 (47.5)	0.18
1991 to 1998	109 (16.5)	9 (12.3)	100 (17.0)	
Cranial irradiation (Gy)				
None	222 (33.5)	18 (24.7)	204 (34.6)	
1 - 1799	18 (2.7)	1 (14)	17 (2.9)	
1800-2399	185 (27.9)	27 (37.0)	158 (26.8)	0.26 ^d
2400	237 (35.8)	27 (37.0)	210 (35.6)	
Renal irradiation				
Yes	20 (3.0)	4 (5.5)	16 (2.7)	
No	642 (97.0)	69 (94.5)	573 (97.3)	
Glucocorticoids (mg/m ²)	9560 (1120, 10160)	7610 (1120, 10160)	9560 (1120, 10160)	0.68 ^e
Methotrexate (mg/m ²)	5268.6 (2596, 14193)	4234.7 (2311, 5985)	5311.1 (2622, 14659)	0.04 ^e
Cyclophosphamide equivalent dose (mg/m ²)				0.60
None	228 (34.4)	20 (27.4)	208 (35.3)	
1 - 8119	144 (21.7)	17 (23.3)	127 (21.6)	
8120 - 10234	147 (22.2)	18 (24.7)	129 (21.9)	
10235 - 51367	143 (21.6)	18 (24.7)	125 (21.2)	
Anthracycline (mg/m ²)				0.99 ^d
None	212 (32.0)	24 (32.9)	188 (31.9)	
1-100	305 (46.1)	33 (45.2)	272 (46.2)	
101-400	135 (20.4)	15 (20.5)	120 (20.4)	
> 400	10 (1.5)	1 (14)	9 (1.5)	

Data is presented as median (interquartile range) and n (column %)

^aAlabama, Florida, Georgia, Mississippi, North Carolina, South Carolina & Tennessee

^bAs per NCEP ATP III criteria

^cP value from chi-square test, except

^dFisher's exact test

^eWilcoxon Rank-Sum test comparing characteristics between those with renal stones and those with no renal stones.

Table II

Dietary and biochemical characteristics of ALL survivors stratified by incidental renal stone

	Total (n=662)	Renal Stones (n=73)	No Renal Stones (n=589)	P-value ^a
<u>Dietary intake per day:</u>				
Vitamin D (IU)				
141.5	324 (50.2)	28 (39.4)	296 (51.5)	0.06 ^b
> 141.5	322 (49.8)	43 (60.6)	279 (48.5)	
Calcium (mg)	826 (576, 1152)	890 (621, 1262)	822 (569, 1132)	0.07
Vitamin C (mg)	84.5 (55.2, 138.9)	86.2 (58.3, 143.4)	84.1 (54.5, 138.9)	0.92
Sodium (mg)	3062 (2167, 4103)	3073 (2337, 4043)	3060 (2129, 4146)	0.54
Animal Protein (g)	3.61 (2.38, 5.69)	4.15 (2.17, 5.48)	3.55 (2.39, 5.70)	0.58
Fiber (g)	15.3 (10.7, 21.5)	15.4 (12.6, 21.5)	15.3 (10.5,21.5)	0.35
Total energy intake (kcal)	1838 (1353, 2540)	1934 (1519, 2540)	1830 (1332,2558)	0.35
Daily total fluids (ml)	1703 (1259, 2312)	1853 (1366, 2671)	1699 (1249, 2280)	0.10
Daily alcohol intake (ml)				
None	199 (30.1)	24 (32.9)	175 (29.7)	0.79 ^b
28.5	230 (34.7)	23 (31.5)	207 (35.15)	
> 28.5	233 (35.2)	26 (35.6)	207 (35.15)	
<u>Serum levels:</u>				
Calcium (mg/100 ml)	9.3 (9.1, 9.5)	9.2 (9.1, 9.5)	9.3 (9.1, 9.5)	0.64
Phosphate (mg/100 ml)	3.2 (2.9, 3.6)	3.1 (2.8, 3.1)	3.3 (2.9, 3.6)	0.02
Bicarbonate (mmol/l)	26 (24, 28)	26 (24, 27)	26 (24, 28)	0.45
BUN (mg/dl)	13 (11, 15)	13 (11, 15)	13 (11, 15)	0.54
Creatinine (mg/dl)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.09
BUN : Creatinine ratio				
<10	20 (3.0)	2 (2.7)	18 (3.1)	1.00 ^b
10-20	535 (80.8)	59 (80.8)	476 (80.8)	
> 20	107 (16.2)	12 (16.4)	95 (16.1)	
<u>Urine pH:</u>				
Continuous	6.0 (5.5, 6.5)	5.5 (5.5, 6.5)	6.0 (5.5, 6.5)	0.14
Ordinal				
5.0 - 6.0	186 (28.9)	19 (26.0)	167 (29.3)	0.57 ^b
6.1 - 8.0	458 (71.1)	54 (74.0)	404 (70.7)	
<u>Microscopic hematuria:</u>				
No	527 (81.8)	56 (76.7)	471 (82.5)	0.37 ^c
Trace	45 (7.0)	8 (11.0)	37 (6.5)	
Small (1+)	32 (5.0)	3 (4.1)	29 (5.1)	
Moderate (2+)	20 (3.1)	4 (5.5)	16 (2.8)	
Large (3+)	20 (3.1)	2 (2.7)	18 (3.1)	

Data is presented as median (interquartile range) and n (column %)

^aP value from Wilcoxon rank-sum test except

^bchi-square test

^cFisher's exact test

Table III

Adjusted odds ratios for risk of developing incidental renal stones in ALL survivors

	Odds Ratio	95% Confidence Interval
Bone Mineral Density (Z-score)		
0	Referent	-
> -1 to < 0	0.87	0.46 - 1.65
> -2 to -1	1.33	0.68 - 2.59
-2	2.92	1.14 - 7.48
Age at study (years)		
18-24	Referent	-
25-34	1.44	0.60 - 3.45
35-44	2.41	0.99 - 5.85
45-54	3.70	1.11 - 12.35
Renal radiation		
No	Referent	-
Yes	2.00	0.60 - 6.70
Vitamin D intake (IU)		
141.5	Referent	-
> 141.5	1.64	0.98 - 2.75
Gender		
Female	Referent	-
Male	1.21	0.72 - 2.03
Body Mass Index (kg/m ²)		
< 30	Referent	-
30	0.96	0.57 - 1.64