EXTRA nephron

Nephron Extra 2016;6:1–11
DOI: 10.1159/000442827
Published online: February 11, 2016

Review Article

Renal Effects and Carcinogenicity of Occupational Exposure to Uranium: A Meta-Analysis

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Key Words

Uranium exposure · Kidney · Carcinogenicity · Meta-analysis · Standardized mortality ratio · Standardized incidence ratio · Biomarker

Abstract

Purpose: Uranium is a heavy metal with alpha radioactivity. We state the hypothesis that uranium exposure is harmful to human kidneys and carcinogenic to body tissues. Therefore, we review epidemiological studies from people with known long-lasting uranium exposure. ***Materials and Methods:*** Three meta-analyses are performed using clinical studies published in the PubMed database and applying RevMan 5.3 from the Cochrane Collaboration to calculate the outcome. The first two meta-analyses examine the standardized mortality ratio (SMR) and the standardized incidence ratio for any cancers of uranium workers who were operating in areas ranging from uranium processing to the assembly of final uranium products. The third meta-analysis evaluates the nephrotoxic risk in uranium workers as well as soldiers and of individuals with exposure to drinking water containing uranium. ***Results:*** Overall and contrasting to our hypothesis, the tumor risk is significantly lower for uranium workers than for control groups (SMR = 0.90 with a 95% confidence interval of 0.84 to 0.96). In addition and also contrasting to our hypothesis, the risk of nephrotoxicity is not increased either. This holds for both the incidence and the mortality due to renal cell carcinoma or due to acute kidney injury or chronic kidney disease. In contrast, a significantly better creatinine clearance is found for the uranium cohort as compared to the control groups (mean difference = 7.66 with a 95% confidence interval of 0.12 to 15.2). ***Conclusion:*** Our hypothesis that a chronic uranium exposure is associated with an increased risk of cancer mortality or of kidney failure is refuted by clinical data. The decreased risk may result from better medical surveillance of uranium workers.

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Introduction

In animal studies on the carcinogenicity of uranium, there are several analyses showing evidence of neoplasms [1]. Meta-analysis of animal studies on uranium nephrotoxicity yields controversial results: depending on the dose and the animal race, the major renal events are proteinuria, glycosuria and especially renal tubular degeneration and lesion [2]. Nevertheless, the kidney is a main target of uranium toxicity for various animal species [3].

Uranium is a naturally occurring element. Traces of it can be found in every animate being, ingesting it with their food and water. Three uranium isotopes are encountered in nature, all of them unstable and alpha emitters: 99.27% of the naturally occurring uranium is U-238 with a radioactive half-life time of 4.47 billion years, 0.72% U-235 with a half-life of 704 million years, and 0.0055% U-234 with a half-life of 247,000 years. Enriched uranium has an increased U-235 ratio of ~3% for nuclear power stations and ~90% for atomic bombs. Depleted uranium shows a decreased U-235 ratio down to 0.2% and is of interest due to its high specific weight and shielding capability. Alpha emitters can be shielded by any thin material layer. That is why uranium cannot harm the human body from outside.

It is known that workers in underground uranium mines have a higher lung cancer risk. This is due to the fact that lung cancer risk increases significantly with the radon and silica burden [4] in the air. Radon-222 is the decay product of radium and can be found in the decay series of uranium and thorium, with an alpha-emitting radioactive half-life of 3.8 days. In underground mines, radon-222 accounts for 54% of the effective dose for the lung. In contrast, long-lived radioactive dust, which contains radioactive elements with half-lives of more than 100 days, such as uranium, thorium and radium, accounts for just 10% of the effective dose [5].

Simply put, our purpose was to test the following two hypotheses: (1) chronically elevated uranium exposure is carcinogenic for humans, and (2) chronically elevated uranium exposure harms the human kidney.

Materials and Methods

To clearly avoid mixed exposure with radon and other radioactive elements rather than mainly uranium-involved exposure, we excluded studies of employees working in uranium mines, nuclear power stations or reprocessing plants. Instead, we focused on areas where uranium is the main pollutant, such as in the areas ranging from uranium ore processing sites to the assembly of the final products.

Uranium Exposure

The LD50 for acute chemical toxicity of highly soluble uranium compounds is suggested to be 5 g for oral intake and 1 g via inhalation [6]. The case outcome of 15 g orally ingested uranium acetate is acute renal failure with dialysis for 2 weeks, refractory anemia, rhabdomyolysis, myocarditis, liver dysfunction and a paralytic ileus. After 6 months, persistent incomplete Fanconi syndrome remained [7]. The uranium exposure we consider for this meta-analysis is below the acute toxicity but above the normal level. To assess internal uranium exposure, urinary uranium analyses are needed. Only one study performed urinary uranium analysis. At that uranium enrichment plant, 72% of the tested employees had urinary uranium levels above 10 μg/l, of which 15% were above 150 μg/l [8]. Other different US American uranium mills showed urinary uranium concentrations above 15 μg/l in 25.5% of tested workers [9]. For comparison, the 95th percentile of urinary uranium for the US population was 0.046 μg/l in the years 1999–2000 [10].

Table 1. Clinical studies used for the SMR meta-analysis

Ref.	Country	Work type	Working period	Mortality follow-up	Subgroup
[20]	France	Uranium metallurgic research	1950–1968	1968–1990	
[21]	Britain	Nuclear weapons research	1951–1982	Same	Internal uranium exposition
[22]	USA	Uranium milling and refining	1979–2001	1979–2005	Never worked in underground mines
[23]	USA	Nuclear fuel research (mainly uranium)	1948–1999	1948–2008	Any internal radiation
[24]	USA	Uranium enrichment	1952–2003	Same	
[25]	USA	Uranium milling, refining and research	1943–1949	1943–1979	Mortality rates are compared with surrounding districts if possible; if not, they are compared with home country rates
[26]	USA	Uranium milling, refining and metallurgy	1942–1966	1942–1993	
[27]	France	Uranium refining and enrichment	1960–2005	1968–2005	
[28]	USA	Uranium metallurgy	1956–1978	1956–1979	Industrial worker
[29]	Germany	Uranium milling and refining	1946–1989	1970–2008	
[30]	USA	Uranium enrichment and metallurgy	1947–1974	1947–1990	
[31]	Britain	Uranium enrichment	1946–1995	Same	Radiation workers
[32]	Britain	Uranium refining and nuclear fuel production	1946–1995	Same	Radiation worker
[33]	USA	Uranium enrichment	1955–1991	Same	Internal radiation exposure was preferred, missing cancer types are refilled with the uranium enrichment subgroup
[34]	USA	Uranium milling and refining	1940/ 1960–1998	Same	Mortality rates are compared with surrounding districts if possible; if not, they are compared with home country rates
[8]	USA	Uranium enrichment and metallurgy	1943–1947	1943–1973	Alpha and beta chemistry
[35]	USA	Uranium enrichment	1951–1985	1951–2004	Hourly paid male worker
[36]	USA	Uranium milling and phosphate fertilizer production	1953–1976	Same	
[37]	Canada	Uranium milling, refining and enrichment	1932–1980	1950–1999	

Table 2. Clinical studies used for the SIR meta-analysis

Ref.	Country	Work type	Working period	Follow-up	Subgroup
[28]	USA	Uranium metallurgy	1956–1978	1956–1979	Industrial worker
[31]	Britain	Uranium enrichment	1946–1995	1971–1991	Radiation workers
[37]	Canada	Uranium milling, refining and enrichment	1932–1980	1969–1999	

Clinical Study Selection

We searched for published clinical studies in the PubMed database. We also browsed the list of references for suitable studies. The articles had to be written in English or German and there is no annual cut used. The last query at PubMed was December 2014. Search terms for the PubMed database were: uranium kidney, uranium renal, depleted uranium, uranium carcinoma, cancer uranium miner, uranium drinking water, uranium SMR, uranium milling, uranium processing, uranium exposure mortality, uranium water cancer, uranium water risk and nuclear fuel cancer. In total, there were 2,890 hits. Of these hits, we selected cohort studies with information about standardized mortality ratio (SMR; table 1), standardized incidence ratio (SIR; table 2) and cross-sectional studies with information about renal biomarkers (table 3). For the SMR and SIR meta-analysis, we excluded studies of employees

Table 3. Studies used for the meta-analysis of biomarkers of kidney injury

Ref.	Country	Type of exposure	Uranium concentration of high-exposure cohort	Compared to	Cutoff high-exposure cohort
[11–17]	USA	Gulf War veterans shot with uranium ammunition in friendly fire attacks	0.1–78.125 µg/g creatinine urine	Other Gulf war veterans	0.1 µg uranium/g creatinine in urine
[38]	Sweden	Drinking water of private wells in uranium-rich bedrocks	0.2–470 µg/l drinking water	Local controls using municipal water	0.2 µg uranium/l drinking water
[39]	USA	Uranium milling and refining worker		Compared with equivalent local cement plant worker	
[40]	Canada	Drinking water of private wells in uranium-rich bedrocks	2–781 µg/l drinking water	Controls using municipal water	1 µg uranium/l drinking water
[41]	Canada	Aboriginal community with high uranium-containing drinking water of private wells	0–845 µg/l drinking water	High-excretion cohort compared to low-excretion cohort	0.1 µg uranium in urine excreted/day

working in uranium mines, nuclear power plants or reprocessing plants. We included only studies of workers operating from uranium processing sites down to the assembly of the final product. A study of workers operating at a phosphate fertilizer production facility is included because their ore has a high uranium content and they had uranium milling activities in the years 1953–1958. The renal biomarker meta-analysis consists of studies of the mentioned uranium workers, studies of soldiers having been targets of friendly fire with uranium projectiles and of individuals with uranium in their drinking water. If possible, mixed genders were used. Where the studies contained subgroups, the subgroup with the highest internal uranium exposure is favored. We selected the study with the longest follow-up if the same cohort was mentioned in different studies. Mortality and incidence rates of the uranium cohort are preferentially compared with mortality rates of surrounding districts.

Over the years 2000–2013, McDiarmid et al. [11–17] published seven different cross-sectional studies of a large cohort of approximately 70 US Gulf War veterans with retained uranium shrapnel fragments. We pooled the results of these seven publications and used it as one clinical study for the biomarker meta-analysis.

ICD Codes

The various clinical studies use different ICD codes for the same cancer topic. Not every cancer type can be inferred from the mentioned cancer topic. Therefore, we unified the ICD codes included for every cancer topic.

RevMan

We use RevMan 5.3 from the Cochrane Collaboration to calculate the outcome of the meta-analysis. If the heterogeneity test (I^2) is above 50%, we change fixed effects to random effects.

Table 4. SMR for uranium-exposed workers

Cause of death	Included trials	Participants	Statistical method	SMR (95% CI)	p value
All malignant neoplasms	19	71,114	M-H, random effects	0.90 (0.84 to 0.96)	0.0009
Lung cancer	17	68,056	M-H, random effects	0.95 (0.85 to 1.06)	0.35
Kidney cancer	14	63,989	M-H, fixed effect	0.85 (0.66 to 1.10)	0.22
Bladder cancer	13	58,359	M-H, fixed effect	0.87 (0.69 to 1.10)	0.24
All lymphatic and hematopoietic tissue neoplasms	9	42,578	M-H, fixed effect	0.87 (0.72 to 1.06)	0.16
Leukemia and aleukemia	14	59,416	M-H, fixed effect	0.85 (0.68 to 1.06)	0.16
Chronic lymphocytic leukemia	4	20,154	M-H, random effects	1.00 (0.48 to 2.06)	0.99
Non-Hodgkin's lymphoma	15	65,951	M-H, fixed effect	0.92 (0.73 to 1.15)	0.45
Hodgkin's lymphoma	11	51,449	M-H, fixed effect	1.22 (0.74 to 2.03)	0.44
Multiple myeloma	11	41,574	M-H, fixed effect	1.11 (0.77 to 1.60)	0.58
Uterine carcinoma	5	2,427	M-H, fixed effect	2.00 (0.50 to 7.99)	0.33
Ovary cancer	5	2,427	M-H, fixed effect	0.82 (0.24 to 2.84)	1
Breast cancer	7	14,631	M-H, fixed effect	1.04 (0.59 to 1.86)	0.88
Prostate cancer	10	45,610	M-H, fixed effect	0.88 (0.74 to 1.05)	0.14
Liver cancer	9	43,854	M-H, fixed effect	0.59 (0.42 to 0.81)	0.001
Central nervous system cancer	13	61,485	M-H, fixed effect	1.06 (0.82 to 1.36)	0.65
Bone cancer	10	49,034	M-H, fixed effect	0.77 (0.34 to 1.75)	0.51
Mesothelioma	5	22,863	M-H, fixed effect	1.60 (0.73 to 3.52)	0.24
Stomach cancer	14	61,450	M-H, fixed effect	0.85 (0.72 to 1.01)	0.07
Pancreas cancer	13	60,356	M-H, fixed effect	0.96 (0.80 to 1.16)	0.7
Esophagus cancer	12	53,597	M-H, fixed effect	0.67 (0.51 to 0.88)	0.004
Colon cancer	12	63,100	M-H, random effects	0.77 (0.65 to 0.92)	0.003
Rectum cancer	12	53,597	M-H, fixed effect	0.94 (0.74 to 1.19)	0.59
Connective tissue cancer	5	33,022	M-H, fixed effect	0.83 (0.36 to 1.93)	0.67
Acute and chronic renal failure	11	50,043	M-H, fixed effect	0.87 (0.63 to 1.19)	0.37
Acute renal failure	2	10,272	M-H, fixed effect	0.67 (0.11 to 3.99)	0.66
Chronic renal failure	7	41,739	M-H, fixed effect	0.84 (0.57 to 1.24)	0.38

M-H = Mantel-Haenszel statistics.

Biomarker

Beta-2 microglobulin (BMG) is part of the major histocompatibility complex. After being freely filtrated, over 99% is resorbed at the proximal tubule. That is why high urinary BMG values can be a marker of tubular damage. N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme found in many different tissues of the body. It cannot pass the glomerular filtration border because of its high molecular weight. Because of its high activity in proximal tubule cells, NAG is a marker of proximal tubular cell necrosis. We checked both markers for possible tubular cell damage.

Results

Mortality Results

The meta-analysis presents SMR results of 24 different cancer types and of 3 categories of renal toxicities resulting from a maximum of 71,114 uranium-exposed workers from 19 different clinical studies (table 4). The male proportion of these workers is 93.7% and therefore very high.

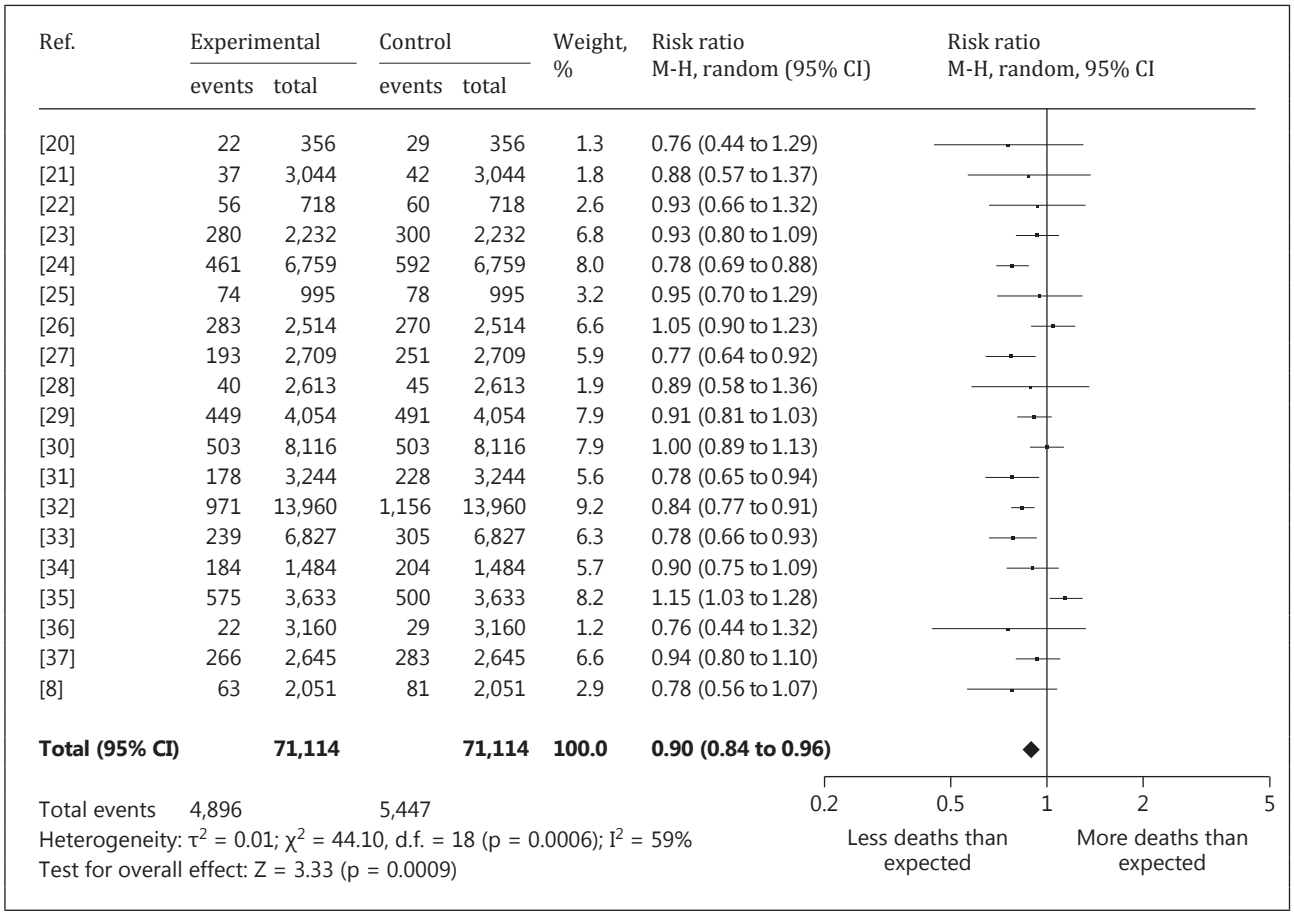

Fig. 1. Forest plot of the SMR of all malignant neoplasms.

Of the 24 different cancer types, 4 show a significantly decreased mortality rate in the uranium-exposed cohort. All malignant neoplasms [SMR = 0.90 with a 95% confidence interval (CI) of 0.84 to 0.96] (fig. 1), liver cancer (SMR = 0.59, 95% CI 0.42 to 0.81), esophageal cancer (SMR = 0.67, 95% CI 0.51 to 0.88) and colon cancer (SMR = 0.77, 95% CI 0.65 to 0.92) are included. There is no specific cancer type with a significantly increased mortality rate.

Though not being significant, all reviewed mortality rates of kidney (fig. 2) or bladder cancer, as well as acute or chronic renal failure, show decreased mortality rates in the uranium-exposed cohorts.

Cancer Incidence

Table 5 presents the SIR results of 14 different cancer types with a maximum of 8,858 uranium-exposed participants from 3 different clinical studies. The SIR of all malignant neoplasms reveals a significantly decreased rate (SIR = 0.89, 95% CI 0.80 to 0.98). There are no further significant rates.

Biomarker Results

With a maximum of 563 participants from 5 clinical studies, the renal biomarker meta-analysis has the smallest database (table 6). Nevertheless, there are two significant results.

Despite a significantly higher BMG (μg/l) value for uranium-exposed persons [mean difference (MD) = 11.38, 95% CI 1.09 to 21.68], it is not a reliable value because it is not age

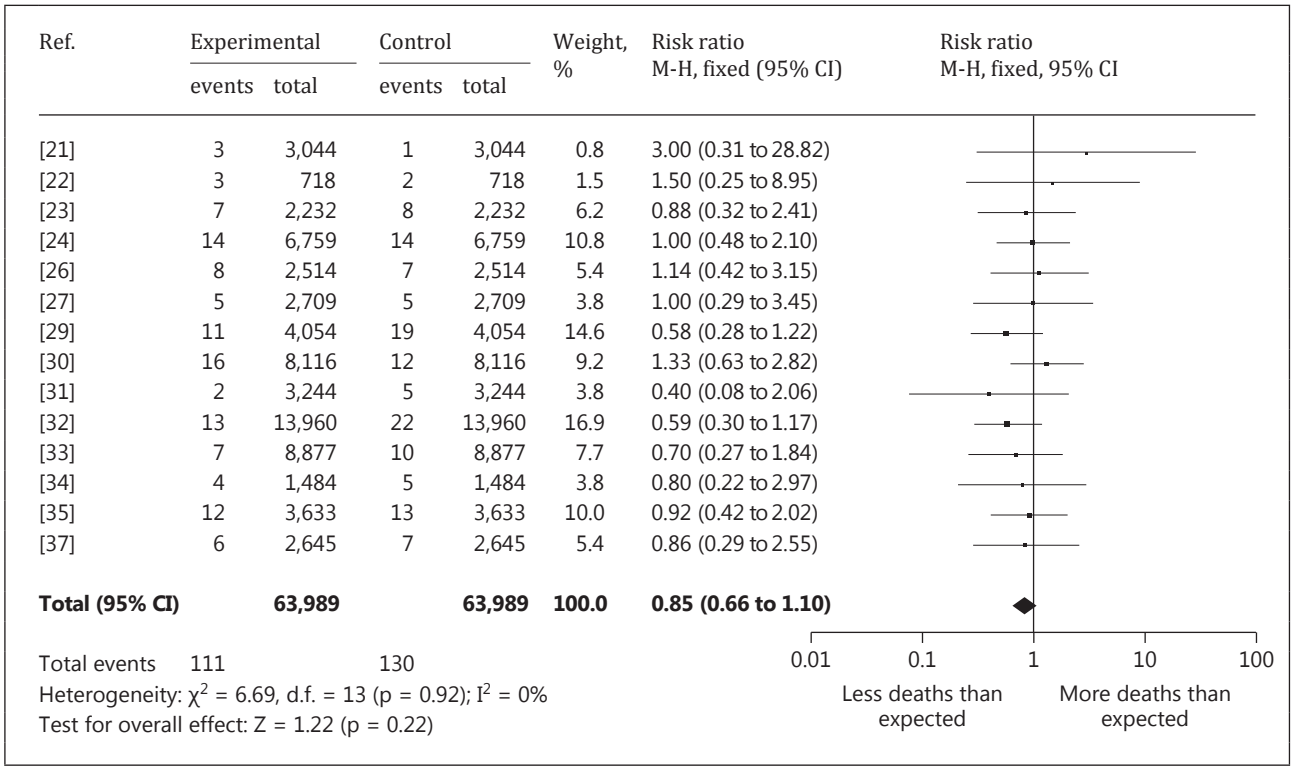

Fig. 2. Forest plot of kidney cancer SMR.

Table 5. SIR of uranium-exposed workers

Cancer type	Included trials	Participants	Statistical method	SIR (95% CI)	p value
All malignant neoplasms	3	8,858	M-H, fixed effect	0.89 (0.80 to 0.98)	0.01
Lung cancer	3	8,858	M-H, fixed effect	1.00 (0.81 to 1.23)	1
Kidney cancer	3	8,858	M-H, random effects	0.48 (0.22 to 1.01)	0.05
Bladder cancer	3	8,858	M-H, fixed effect	0.88 (0.59 to 1.32)	0.53
Leukemia and aleukemia	2	6,244	M-H, fixed effect	0.82 (0.41 to 1.67)	0.59
Non-Hodgkin's lymphoma	3	8,858	M-H, fixed effect	0.95 (0.52 to 1.75)	0.88
Prostate cancer	2	6,151	M-H, fixed effect	0.88 (0.68 to 1.15)	0.36
Central nervous system cancer	3	8,858	M-H, fixed effect	1.46 (0.72 to 2.96)	0.29
Bone cancer	2	5,858	M-H, random effects	1.00 (0.06 to 15.98)	1
Stomach cancer	2	6,244	M-H, fixed effect	0.84 (0.50 to 1.41)	0.51
Pancreas cancer	2	6,244	M-H, fixed effect	0.72 (0.35 to 1.47)	0.37
Esophagus cancer	2	6,244	M-H, fixed effect	0.73 (0.29 to 1.81)	0.49
Colon cancer	3	8,858	M-H, fixed effect	0.90 (0.63 to 1.29)	0.58
Rectum cancer	2	6,244	M-H, fixed effect	0.83 (0.51 to 1.35)	0.45

M-H = Mantel-Haenszel statistics.

standardized. The preferred value is urinary BMG measured in μg/g creatinine, which is not significantly elevated (MD = 8.76, 95% CI –12.32 to 29.84). Surprisingly, the uranium-exposed cohort has a significantly better creatinine clearance than the compared cohort (MD = 7.66, 95% CI 0.12 to 15.20).

Table 6. Renal biomarker differences of uranium-exposed persons

Biomarker	Included trials	Participants	Statistical method	MD (95% CI)	p value
NAG, U/g creatinine	4	439	IV, fixed effect	0.06 (–0.12 to 0.24)	0.52
BMG, µg/l urine	3	563	IV, fixed effect	11.38 (1.09 to 21.68)	0.03
BMG, µg/g creatinine	5	523	IV, random effects	8.76 (–12.32 to 29.84)	0.42
Urinary glucose, g/day	3	139	IV, random effects	0.03 (–0.02 to 0.08)	0.20
Creatinine clearance, ml/min	2	110	IV, fixed effect	7.66 (0.12 to 15.20)	0.05
Total urinary protein, mg/day	2	83	IV, fixed effect	6.70 (–4.61 to 18.02)	0.25
Total urinary protein, mg/g creatinine	3	393	IV, fixed effect	0.00 (–0.26 to 0.26)	0.98

IV = Inverse-variance weighting.

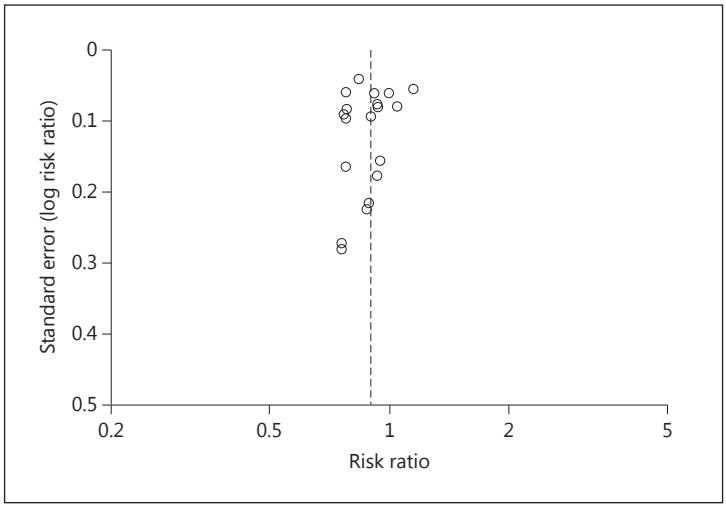

Fig. 3. Funnel plot for the cancer SMR of all malignant neoplasms.

Discussion

We found no significantly increased risk of cancer or nephrotoxicity in cohorts exposed to uranium. The nonsignificant results mainly reveal a reduced cancer risk. The SMR meta-analysis has the strongest explanatory power due to the large database. The question of bias has to be considered, though.

Causes of death are taken from national death certificates. To discuss the possibility of bias through incorrect death certificates, the SIR meta-analysis may help. With a maximum of only 3 clinical studies, the SIR analysis is not extensive enough to make insightful statements. But by comparing the SIR and SMR results, we can find no risk ratios varying in the opposite direction. This correlation speaks against a possible bias through incorrect death certificates.

Another bias could be resulting from conflicts of interest. Of the 19 studies, 6 are linked with the American Department of Energy and 5 with the Department of Defense or sponsored by uranium companies. If we remove these 11 possibly biased studies, we should observe an increase of the mortality rate in the case of a conflict of interest in national agencies. The SMR result of all malignant neoplasms, however, decreases from 0.90 (95% CI 0.84 to 0.96) to 0.88 (95% CI 0.81 to 0.96) without these studies. Therefore, we may exclude the bias of a conflict of interest.

There might remain bias that cannot be excluded. The first could be a possible publication bias. PubMed is a US American platform for citations. A look at the home countries of the studies found reveals only American-allied countries. There is for example no clinical study from China or Russia. Otherwise, there is an almost symmetrically distributed funnel plot for the cancer SMR of all malignant neoplasms (fig. 3).

Another bias may result from the integer number representation properties of RevMan 5.3, Cochrane's meta-analysis tool used for this article. We compared deaths of the uranium-exposed groups (integers) with standardized death rates of surrounding districts (point numbers) of the same group size. We had to round the point numbers for the meta-analysis tool. Especially in categories with a small amount of cancer deaths like in uterine, ovary or bone cancers, the rounding effect is noticeable. Another fact is that RevMan cannot estimate the risk ratio of studies with zero deaths in the uranium cohort and zero deaths (because of rounding) for the comparison group. Of the 5 uterine cancer studies introduced to the SMR meta-analysis, 3 are ignored for that reason.

To complete the bias analysis, we checked the 'healthy worker effect' mentioned e.g. for US American chemistry workers [18] and workers of the nuclear production complex of Hanford Site [19]. From 19 studies mentioned, we found 7 with SMR information for nonradiation workers. The average of the SMR of all malignant neoplasms of the nonradiation workers results in 0.99, which means there is no difference in cancer deaths compared to home country rates, and therefore no healthy worker effect. The average SMR of the uranium-exposed cohort in these seven studies results in 0.84.

The significantly decreased risk of the four mortality rates, one cancer incidence rate and the significantly better creatinine clearance for uranium-exposed workers, can be explained assuming that the health status might have been better protected by regular and detailed medical surveillance, especially for radiation workers.

These results can be used to help determining the risk and the toxicological profile of elemental uranium for humans. These findings are important for the uranium processing industry, showing that medical surveillance and the common safety standards are sufficient. But be aware that these results by no means change the hazardousness of the nuclear use of uranium and the fission products originating from it.

Conclusion

The SMR meta-analysis refutes the hypothesis that a chronically elevated uranium exposure is associated with an increased risk of cancer incidence or cancer mortality. Furthermore, if we stay below the acute toxicity limit of uranium, we can find no signs for acute or chronic kidney failure.

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