Low-dose ionizing radiation increases the mortality risk of solid cancers in nuclear industry workers: A meta-analysis

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Received November 27, 2017; Accepted February 28, 2018

DOI: 10.3892/mco.2018.1590

Abstract. Low-dose ionizing radiation (LDIR) may increase the mortality of solid cancers in nuclear industry workers, but only few individual cohort studies exist, and the available reports have low statistical power. The aim of the present study was to focus on solid cancer mortality risk from LDIR in the nuclear industry using standard mortality ratios (SMRs) and 95% confidence intervals. A systematic literature search through the PubMed and Embase databases identified 27 studies relevant to this meta-analysis. There was statistical significance for total, solid and lung cancers, with meta-SMR values of 0.88, 0.80, and 0.89, respectively. There was evidence of stochastic effects by IR, but more definitive conclusions require additional analyses using standardized protocols to determine whether LDIR increases the risk of solid cancer-related mortality.

Introduction

Adverse health effects due to exposure to ionizing radiation (IR) have been reported since the first application of X-rays. Stochastic effects, primarily the carcinogenic effects of IR exposure, first became known from the Life Span Study of atomic bomb survivors in Japan (1). In contrast to the high-dose or high-dose-rate IR only seen in Japanese atomic bomb survivors (2) and nuclear accidents, such as Chernobyl (3), nuclear industry and medical workers are nominally only exposed to low-dose or low-dose-rate IR. A large, international cohort study strongly supported that long-term exposure to low-dose IR (LDIR) increases the risk of leukemia, although the increase is only minuscule (4-6). However, recent epidemiological studies highlighted the detrimental effect of persistent exposure to LDIR, and research on nuclear industry workers has demonstrated increased cancer mortality risks following a cumulative dose of <100 mSv and dose rates of <10 mSv per year (7), particularly in solid cancers, by the linear non-threshold model (8). As the extensive use of IR in the medical industry, including radiodiagnosis and radiotherapy, is justified and has been well-studied, the aim of the present study was to focus on the health effects of occupational and environmental IR exposure in the nuclear industry.

Mining, historically the primary source of occupational and environmental health risk exposure, was the only means of obtaining natural radionuclides of uranium. As is well known, U-238 comprises >99% of uranium ore, and radioactive U-235 comprises only 0.71% in nature. Uranium mining constituted an internal radiation exposure risk in nuclear industrial workers when they inhaled massive amounts of radon gas and its decay species in mines (9). While there is little information on the association between health risks and internal exposure after inhaling uranium dust (10), the physicochemical properties of uranium are known to present a hazard (11). An international retrospective cohort study demonstrated that uranium workers exhibited a higher solid cancer mortality risk compared with control populations living near nuclear facilities (12-14). In fact, uranium workers were put at significant risk, not only by the α-particles of radioactive uranium decay, but also by γ-ray exposure in the mines.

Radioepidemiology studies in nuclear industry workers confirmed that external exposure to γ-rays and X-rays in medical care settings increased the health risks of partial solid cancers (15,16). The effect on health care workers was a source of bias in occupational epidemiological studies and was recorded (17-19). The risk was not statistically significant in terms of excess relative risk (ERR) and/or standard mortality ratio (SMR), but there was evidence of increasing cancer mortality risk from exposure to IR (20,21). A number

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Key words: solid cancer, mortality, low-dose ionizing radiation, nuclear industry, meta-analysis

of complex factors affect the health of nuclear industry workers, their external exposure to radiation and death of the residents (20,22). There are important statistical limitations in recent epidemiological studies, including the number of subjects in those cohorts, the follow-up period, the mode of adjustment and the differences in statistical methods. Therefore, the challenge was to increase the number of international cohort studies in order to improve the ability to assess health risk and to monitor the long-term follow-up evaluations of nuclear industry workers.

The present study utilized a systematic review of the literature related to the mortality risk of solid cancers, including cancers of the lung, brain and central nervous system (CNS), liver, stomach, colorectum, kidney, bladder and prostate, affecting nuclear industry workers in uranium mining, refining, enrichment and gaseous diffusion plants. The primary aims of this meta-analysis were to determine whether LDIR increases the mortality risk of solid cancers in nuclear industry workers, to determine whether there is a standard mortality risk value among any of the solid cancers from LDIR, and whether the cancer mortality risks exhibited a trend for variation from the classical epidemiological studies.

Data collection methods

Search strategy. Two electronic search strategies were performed through the PubMed and Embase databases using key words for all fields of 'solid cancer' OR 'lung cancer' OR 'brain cancer' OR 'central nervous system cancer' OR 'liver cancer' OR 'stomach cancer' OR 'colorectal cancer' OR 'colon cancer' OR 'intestinal cancer' OR 'rectum cancer' OR 'kidney cancer' OR 'bladder cancer' OR 'prostate cancer' AND 'mortality' AND 'nuclear industry' OR 'nuclear facility'. The search was limited to journal articles published between January 1, 2000 and December 31, 2016, and there were no language restrictions. The bibliographies of all articles included for data extraction were searched independently for further eligible articles by two authors (S-GQ and JG).

Data selection. The present meta-analysis included original research evaluating subjects working in the nuclear industry with a main occupation in mining, refining, enrichment, non-destructive testing and nuclear weapon research, but not in nuclear power plants, medical facilities, education or nuclear accidents. Atomic bomb survivors were also excluded. LDIR was limited to whole-body IR exposure, with a cumulative mean dose of <0.5 Sv per year, or at a low dose rate (<10 mSv/day) (23). Only studies published in English were considered for inclusion.

The quality of this systematic review was assessed by detailed selection of participants and by comparison of the results. The data in this study included cohort workers, follow-up period, number of deaths caused by cancers of particular interest to the present study, SMR and 95% confidence interval (CI). Data were excluded for all reviews, books and reports where workers were engaged in their activities for <1 year, and from all articles containing insufficient/incomplete data. Three articles were excluded, although they involved uranium workers and nuclear power (20,24) and uranium gaseous diffusion plants (25), as the radiation doses were closely controlled and were within the range considered as safe. Three articles on the Oak Ridge National Laboratory staff (26,27) and nuclear test participants (28) were also excluded. The data selection was confirmed by carefully reading the full text and supplementary information for each article. In the identified studies, disease was observed and graded according to the International Classification of Diseases, revisions 9/10, and the disease categories were carefully examined. Small intestinal, colon and rectum cancer cases were combined under 'colorectal cancer' in this meta-analysis, as the number of those cancers was small (29).

Statistical analysis. The SMR and 95% CI were used to evaluate the outcome of the cohort and as measures of solid cancer mortality. If the SMR and 95% CI were not available for meta-analysis, cohort outcome and mortality were calculated by comparing the number of reported deaths against the expected number of deaths in each group. If the results were published for a single type of cancer, a combined value was computed via analysis of the single sample value. The SMR and 95% CI were unified in analysis, although reports using 90% CI were also common for meta-analyses of disease outcomes for the cancers of interest.

Forest plots were used to visually assess the pooled estimates and corresponding 95% CIs. Homogeneity across studies was tested using Cochran's Q test at $P<0.1$, and quantified using the I^2 statistics, which represents the percentage of heterogeneity that may be attributed to the variation across studies. In the presence of significant heterogeneity, a random-effects model was applied. We further performed a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each iteration. The presence of publication bias was assessed using the Begg's and Egger's tests and by examining funnel plots. Two-tailed $P<0.05$ was considered statistically significant. All the data were analyzed using STATA software, version 11.0 (Stata Corp LP, College Station, TX, USA).

Results

Selected articles. In the initial search, 547 relevant articles were identified. Of these, 66 were excluded as duplicates, 368 were excluded after reviewing their titles and abstracts, 24 were excluded as reviews, and 62 were excluded as they fell outside the dates of interest of the present study. Following the review, 27 articles (15,17,26-50) were finally selected for the present meta-analysis. The study selection process is summarized in Fig. 1.

Description of studies. The characteristics of the 27 articles included in the present meta-analysis are detailed in Table I. The articles were all retrospective cohorts and the majority were published after 2010. Of the articles included in this study, 1 was performed in Asia, 2 in Australia, 10 in North America and 14 in Europe. Not all the studies included data on all eight types of solid cancers of interest in the present analysis plus the total cancers. Such was the case for the article published by Drubay *et al* (30), which only included information on kidney cancer and its SMR and 95% CI.

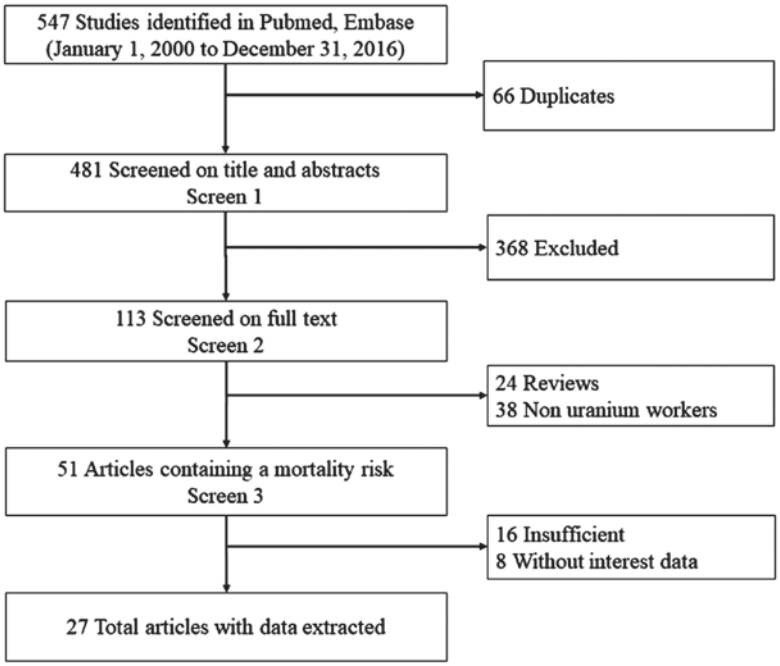

Figure 1. Flow chart of literature search and study selection.

Solid cancer analysis. Only 6 of the 27 studies reported SMR for the solid cancers of interest. The meta-SMR (95% CI) of solid cancers in nuclear industry workers was 0.80 (0.71-0.90) after a meta-analysis using the random-effects model (Fig. 2). The fixed-effects model yielded a meta-SMR (95% CI) of 0.85 (0.84-0.87), as shown in Table II. There was significant heterogeneity across the 6 studies (I^2=94.6%, P=0.00). These results indicated that LDIR did not significantly increase solid cancer mortality risk.

Analysis of other tumors. The meta-analysis results of the SMR and 95% CI for the 8 solid cancers of interest in this study are shown in Table II. The combined SMR was lower compared with that for total cancer (0.87), solid cancer (0.85), lung (0.89), liver (0.73) and stomach cancer (0.85) compared with the general population, and the homogeneity for colorectal cancer, bladder cancer and prostate cancer was unsatisfactory using the random-effects model after the meta-analysis. The heterogeneity analysis revealed significance of the SMR of total cancer, solid cancer, lung, stomach, colorectal cancer, bladder and prostate cancer (P<0.1), and the I^2 value was <50% for stomach and prostate cancers. However, the SMRs of the brain and CNS, liver and kidney cancers displayed little heterogeneity in nuclear industry workers (P>0.1). Furthermore, the I^2 value for kidney cancer was 0.00%, with the same results for SMR obtained using the fixed-effects and random-effects models. The forest plots for the SMR of the 8 solid cancers of interest are not shown.

Sensitivity analysis. Sensitivity analysis was conducted to explore potential sources of heterogeneity in the association between solid cancer mortality risk and LDIR, and to determine the influence of various exclusion criteria on the overall risk estimates. No sensitivity analysis was performed for total cancer, solid cancer, or lung cancer as the heterogeneity (I^2) was >90% for these cases. The analysis of brain and CNS cancer produced a meta-SMR (95% CI) of 1.16 (1.02-1.31), with the exclusion of the Muirhead *et al* study, using the fixed-effects model (I^2=0.00%, P=0.02) (17). Exclusion of the study by Gun *et al* (28) decreased the SMR for heterogeneity in colorectal cancer (I^2) to 14.6% (P=0.00) and the combined SMR was 0.88 (95% CI: 0.82-0.94) using the random-effects model. However, in kidney cancer, exclusion of the Rage *et al* study decreased the P-value to 0.03 with the I^2 remaining at 0.00% (29), and the difference was statistically significant.

Subgroup analysis of the observed SMR was not performed in the present study, as the reviewed studies did not all include grouping in their reports.

Publication bias. No sign of publication bias was observed when the funnel plots were examined, although the heterogeneity of total cancer, solid cancer and lung cancer was relatively high (Table III). The result of Begg's test (continuity corrected) and Egger's test did not indicate evidence of publication bias (P>0.1).

Discussion

There has been a rapidly growing interest in the association between LDIR and stochastic effects in nuclear industry workers. It has been demonstrated that LDIR may increase the mortality and morbidity risk of solid cancers, particularly in the lung, brain and CNS, liver and kidney. However, there have been no published pooled studies investigating point-estimate risk of radiation-induced health effects in workers involved in uranium mining, milling, machining and reprocessing. The present study reviewed the available relevant literature to investigate whether exposure to LDIR affects the mortality of solid cancers, and focused on uranium-processing workers, excluding exposure in the medical setting, radiation research,

Table I. Description of reviewed studies on the mortality risk of solid cancer following exposure to uranium.

Study (year of publication)	Country	Follow-up period	Average follow-up period (years)	Work type	Cohort workers	No. of cancer deaths										(Refs.)
						Total	Solid	Lung	Brain and CNS	Liver	Stomach	Colorectal	Kidney	Bladder	Prostate	
Zhivin *et al* (2016)	France	1968-2008	30.0	B	4,688	429	406	100	17	17	12	39	13	12	30	(46)
Samson *et al* (2016)	France	1968-2008	27.9	All	12,649	912	NA	217	32	31	29	86	24	26	71	(44)
Rage *et al* (2015)	France	1946-2007	35.4	A	5,086	721	NA	211	28	31	33	63	24	25	51	(29)
Schubauer-Berigan *et al* (2015)	USA	1944-2005	33.7	All	119,195	11,332	9,979	3,228	NA	535	NA	NA	NA	NA	NA	(27)
Sokolnikov *et al* (2015)	Russia	1948-2008	NA	O	25,757	2,980	NA	841	66	91	452	302	NA	NA	NA	(31)
Kreuzer *et al* (2015)	Germany	1946-2008	39.0	A	4,054	457	434	159	13	NA	49	48	12	20	30	(38)
Zablotska *et al* (2014)	Canada	1956-1993	13.4	O	15,937	NA	208	NA	NA	NA	NA	NA	NA	NA	NA	(32)
Drubay *et al* (2014)	Germany	1968-2003	34.8	O	58,985	NA	NA	NA	NA	NA	NA	NA	165	NA	NA	(30)
Silver *et al* (2013)	USA	1951-2004	37.0	O	5,551	786	NA	285	23	20	30	77	15	21	71	(42)
Richardson *et al* (2013)	USA	1943-2008	39.0	O	5,919	467	NA	110	6	7	7	46	6	14	NA	(26)
Zablotska et al (2013)	Canada	1950-1999	6.4	A	2,645	266	225	99	5	NA	14	37	6	10	21	(39)
Gilbert *et al* (2013)	Russia	1953-2008	NA	O	14,621	NA	NA	486	NA	NA	NA	NA	NA	NA	NA	(33)
Dufey *et al* (2013)	Germany	1946-2003	34.0	A	58,987	NA	NA	NA	NA	159	NA	NA	NA	NA	NA	(50)
Metz-Flamant *et al* (2011)	France	1968-2004	27.6	All	36,769	NA	2,035	508	102	72	88	206	58	51	137	(47)
Chan *et al* (2010)	USA	1952-2003	NA	O	6,759	461	NA	146	16	NA	11	NA	5	4	18	(48)

Table I. Continued.

Study (year of publication)	Country	Follow-up period	Average follow-up period (years)	Work type	Cohort workers	No. of cancer deaths										(Refs.)
						Total	Solid	Lung	Brain and CNS	Liver	Stomach	Colorectal	Kidney	Bladder	Prostate	
Guseva *et al*(2010)	France	1968-2005	28.0	B	2,709	193	NA	48	7	5	6	19	14	NA	NA	(45)
Muirhead *et al* (2009)	UK	1976-2001	NA	All	174,541	7,136	NA	2,130	261	83	498	823	170	261	605	(17)
Boice *et al*(2008)	USA	1979-2005	36.4	A	2,745	246	NA	117	5	9	5	12	6	4	13	(40)
Ahn *et al* (2008)	Korea	1992-2004	NA	O	30,147	72	NA	7	NA	NA	NA	NA	NA	NA	NA	(49)
Gun *et al* (2008)	Australia	1982-2001	NA	O	10,983	1,465	NA	433	NA	19	77	209	NA	9	136	(28)
Telle-Lamberton *et al* (2007)	France	1968-1994	17.8	All	29,204	745	NA	159	25	26	30	NA	24	16	32	(34)
Engels *et al* (2005)	Belgium	1969-1994	22.0	O	7,229	79	NA	25	5	6	5	10	NA	7	NA	(37)
Habib *et al* (2005)	Australia	1970-1998	17.4	O	4,717	135	NA	26	6	1	6	18	6	6	12	(36)
Pinkerton *et al* (2004)	USA	1979-1998	37.0	A	1,484	184	NA	78	NA	4	NA	14	4	NA	15	(41)
Shilnikova *et al* (2003)	Russia	1948-1997	NA	All	21,557	1,854	1,730	569	NA	67	308	142	NA	39	NA	(35)
Dupree-Ellis *et al* (2000)	USA	1942-1993	34.6	O	2,514	283	257	98	12	2	4	36	8	8	23	(43)
Ritz *et al* (2008)	USA	1959-1994	25.4	O	2,297	133	NA	46	6	NA	6	15	5	3	7	(51)

NA, not available; A, uranium mining and milling; B, uranium refining and enrichment; O, other nuclear work; All, uranium mining, refining, enrichment and others; CNS, central nervous system.

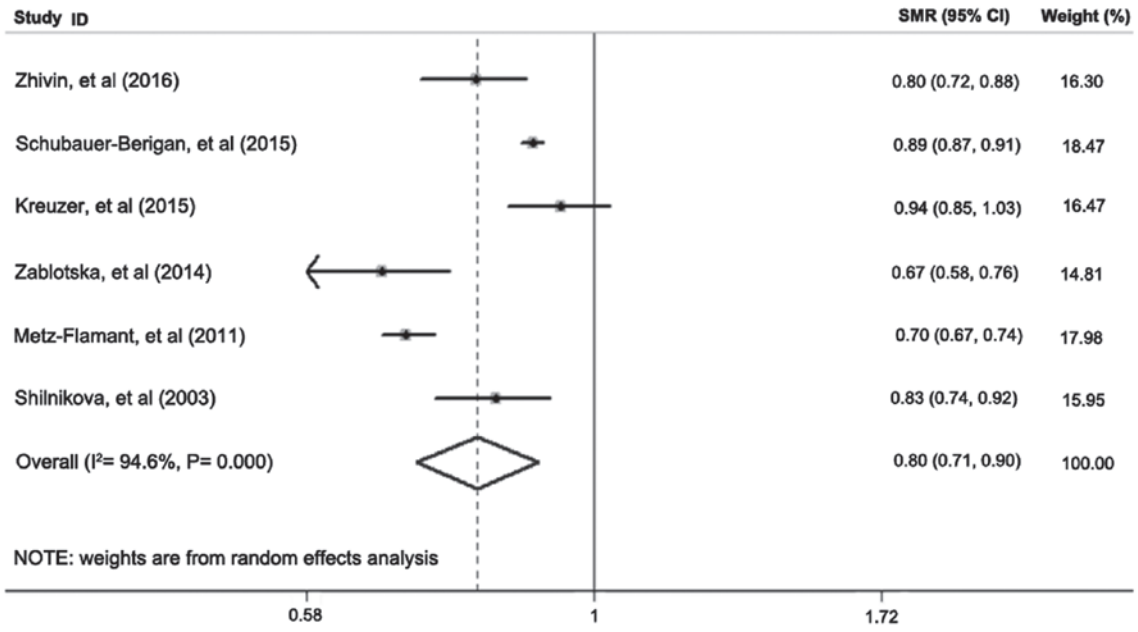

Figure 2. Standard mortality ratio (SMR) and 95% confidence interval (CI) for solid cancers in reviewed studies on uranium workers.

nuclear weapons manufacturing and nuclear power plant industries.

There are several complicating factors of solid cancer mortality risk in the nuclear industry, such as age at first exposure, mean length of occupational exposure, follow-up period, race, type of occupation, socioeconomic status and lifestyle. Meta-analyses combine multiple articles to highlight the advantages of SMR, while avoiding the limitations inherent in sporadic, single reports. Thus, our meta-analysis of the 27 independent observational studies provided strong evidence that LDIR increases solid cancer mortality risk, compared with control populations, despite the SMR being <1. Unfortunately, the large international cohort studies assessed the excess mortality risk of cancer using excess relative risk (ERR) rather than SMR (15,31-33). We found that the high heterogeneity (I^2=94.6%, P=0.00) in solid cancer mortality risk was attributed to the 6 complete studies, but there was enough evidence to conclude that LDIR could significantly increase brain and CNS cancer mortality risk (combined SMR=1.16; 95% CI: 1.02-1.31), regardless of whether the fixed-effects or random-effects model was used. Subgroup analysis was not performed, as its over stratification would substantially reduce the subject-pool size, but the result of sensitivity analysis of brain and CNS, colorectal and kidney cancers, it was statistically significant with little heterogeneity (17,28,29). The 90% CI of SMR was applied in 2 studies (34,35); this value was difficult to convert to 95% CI for the present meta-analysis, and the calculation of skewed distribution may have reduced the precision. Another source of bias was the combined colorectal SMR in three individual parts of the colon, small intestines and rectum in several studies (17,26,36-47), which could increase heterogeneity. Unfortunately, while the type of work-related exposure may be similar, a large-scale study also has significant differences in sensitivity and may have skewed the results of the meta-analysis.

As the observed populations were not limited only to uranium workers, but included subjects whose primary duties were not mining, such as office administrators, it was quite difficult to determine the effect outcomes of solid cancer mortality resulting from LDIR in the nuclear industry based only on the current studies using non-standard protocols (48). An epidemiological study (11) published in 2014 reported that exposure to the physicochemical properties of uranium could increase the lung cancer mortality risk of nuclear industrial workers, compared with the general population. Similarly, our results demonstrated the relative SMR of lung cancer in uranium-processing workers. There was no statistical significance of SMR for increasing total and solid cancer mortality risk in uranium facility workers when combined with nuclear power plant and medicinal research (49), and the health worker effect was observed. This effect consists of three components, namely the health worker survival (17-19), health worker exposure (52-55) and health worker selection (55,56) effects in occupational exposure epidemiology, and leads to the selection of a working population that is healthier compared with the general population. As a result, the observed SMR of the cancers of interest in this study was lower compared with the control population. Therefore, it is necessary to control the deviation observed in healthcare workers and adjust the sensitivity indicators when comparing the health effects of LDIR exposure of these subjects to uranium-processing workers.

While the absorbed dose of uranium is widely considered as benchmark data to analyze the dose-response association between LDIR and cancer mortality risk, we did not address LDIR dosimetry with ERR in analyzing the influence on uranium workers in this meta-analysis. During the initial study design, it was intended to collect and compare the ERR among the target tumors. In the final study design, however, acquisition and expression of these data and the effect on tumor outcomes was exceedingly difficult and unsatisfactory, as it was also reported by Zhivin *et al* (11). Dose level,

Table II. Meta-analysis results on SMR and heterogeneity analysis for solid cancers of interest in nuclear industry workers.

	SMR (95% CI)		Heterogeneity analysis			
Category	Fixed-effects model	Random-effects model	Q-value	P-value	df	I^2 (%)
Total cancer	0.87 (0.860.88)	0.88 (0.830.94)	376.35	0.00	19	95.0
Solid cancer	0.85 (0.840.87)	0.80 (0.710.90)	92.45	0.00	5	94.6
Lung cancer	0.89 (0.800.98)	0.89 (0.800.98)	267.25	0.00	20	92.5
Brain and CNS	1.05 (0.961.14)	1.09 (0.981.21)	18.16	0.31	16	11.9
Liver cancer	0.73 (0.680.78)	0.75 (0.670.84)	20.18	0.17	15	25.7
Stomach cancer	0.85 (0.800.91)	0.51 (0.750.97)	33.18	0.01	17	48.8
Colorectal cancer	0.91 (0.870.95)	0.93 (0.841.04)	45.72	0.00	16	65.0
Kidney	0.93 (0.851.01)	0.93 (0.851.01)	13.86	0.68	17	0.0
Bladder	0.87 (0.790.95)	0.96 (0.801.17)	40.48	0.00	16	60.5
Prostate	1.00 (0.941.06)	0.99 (0.911.08)	23.69	0.07	15	36.7

SMR, standard mortality ratio; CI, confidence interval; df, degree of freedom; CNS, central nervous system.

Table III. Begg's and Egger's tests of the reviewed studies in the metaanalysis of solid cancers of interest from LDIR in the nuclear industry.

Cancer category	Begg's test	Egger's test
Total cancer	0.974	0.563
Solid	0.452	0.340
Lung	0.651	0.413
Brain and CNS	0.127	0.332
Liver	0.685	0.562
Stomach	0.820	0.657
Colorectal	0.837	0.607
Kidney	0.596	0.446
Bladder	0.650	0.197
Prostate	0.558	0.494

LDIR, lowdose ionizing radiation; CNS, central nervous system.

radiation category, dose monitor standard and particle size associated with LDIR all affect cancer mortality risk, but these factors are often overlooked in basic epidemiological studies. Additionally, classical epidemiological methods rely on risk stratification rather than adjustment for complex factors, and may lead to errors in the analysis of cancer mortality risk.

In the present study, we evaluated the health outcomes due to tumor-related mortality due to LDIR exposure in the uranium industry, despite the fact that the results were complex. As most of the occupational environmental epidemiological findings combined SMR, we did not obtain a positive result. This should be attributed to the collection and analysis of raw data from multiple studies using multiple collection and reporting methodologies. In summary, the results of analytical epidemiological studies lacking statistical efficacy are unsubstantiated. Similarly, the significance of the results gained from a hybrid study that increases statistical performance, but lacks a unified theoretical basis, is also limited.

In summary, the present epidemiological study cannot report definitive findings on the association between LDIR and cancer mortality risk. Based on the available data, a preliminary conclusion could be proffered, using meta-analysis with SMR, that exposure to uranium IR may increase cancer mortality risk, particularly from solid cancers, lung cancer, brain and CNS cancer, colorectal cancer, kidney cancer, bladder cancer and prostate cancer. A convincing and exact outcome could be reached if a more complete study was performed and results that are more precise could be calculated using commonly accepted statistical methods with standardized protocols.

Acknowledgements

Not applicable.

Funding

The present study was supported by Chinese Science and Technology Plan Project (no. 2014GB112006), National Natural Science Foundation of China (no. 81372921), The Nuclaer Eneragy Devolopemnt Project (no. 2016-1295) and Postgraduate Research and Practice Innovation Program of Jiangsu Province (KYCX17-2017).

Author contributions

SGQ and JG performed the meta-analysis and BY performed the data analysis. SGQ, JG and BT participated in writing this paper, YPS and YT designed the study and participated in writing the paper. All authors have read and approved this manuscript.

Availability of data and materials

The analysed data sets generated during the study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that that they have no competing interests.

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