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Original Article

Positive association between low-dose ionizing radiation and cataract risk: results from a meta-analysis

Furu Wang[1*], Qiaoqiao Fang[2*], Jin Wan[1], Xiaoyong Yang[1], Baoli Zhu[1]

[1]*Jiangsu Provincial Center for Disease Prevention and Control, 172 Jiangsu Road, Nanjing 210029, China;* [2]*Department of Respiratory Medicine, Children's Hospital of Nanjing Medical University, Nanjing, China.* [*]*Equal contributors.*

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Abstract: Aims: To comprehensively estimate the association of low-dose ionizing radiation (IR) exposure with cataract risk among radiation-associated staff and patients, a meta-analysis was conducted. Methods: A predefined search was conducted on 61,496 subjects (exposed group = 21,465) from 15 published studies by searching electronic databases and reference lists of relevant articles. Random-effects or fixed-effects model was used to access the overall and stratification effect on Low-dose IR exposure to the risk of cataract as appropriate. Results: We found a significant association between the low-dose IR exposure and the risk of cataract (RR = 1.52, 95% CI: 1.22-1.88). Stratified analysis further detected that both Asian and Caucasian population showed significant associations between low-dose IR exposure and cataract risk (RR = 1.74, 95% CI: 1.18-2.57 for Asian group, RR = 1.38, 95% CI: 1.03-1.84 for Caucasian group, respectively). Different exposed subject group also found significant association (RR = 1.91, 95% CI: 1.22-3.00 for interventional cardiologists, RR = 2.52, 95% CI: 1.71-3.71 for supporting staff and RR = 1.66, 95% CI: 1.22-2.25 for industrial radiographers and patients who had undergone radiation therapy, respectively). In addition, low-dose IR exposure might contribute high risk to posterior subcapsular cataract (RR = 2.41, 95% CI: 1.72-3.38). Conclusion: Our study suggested that the low-dose IR exposure may contribute to cataract development among radiation-associated population, especially to high risk for posterior subcapsular cataract. Further well-designed studies are needed to clarify how relatively low dose of IR exposure promotes progression of cataracts and understanding the requirements of radiation-protection professionals.

Keywords: Ionizing radiation, exposure, cataract, association, RR

Introduction

The lens of the eye is one of the most radiosensitive tissues and has long been recognized as being highly responsive to ionizing radiation (IR) [1, 2], and the International Commission on Radiological Protection (ICRP) report 103 [3] even suggested that the lens of the eye may be more radiosensitive than previously thought. Some epidemiological studies [4] have demonstrated that acute dose of IR exposure on the order of 1 Gy can lead to development of cataracts, which is clinically defined as progressive opaqueness of the lens leading to loss of vision [5]. The Lens Opacities Classification System (LOCS) anatomically classified the cataract into three main forms: posterior subcapsular cataract (PSC), cortical, and nuclear cataract [6]. Although cataractogenesis is a lengthy and complex process, the IR is traditionally associated with the formation of PSC [7]. However, PSC is not a unique signature of IR exposure, reports demonstrated that cortical cataract and PSC were present in Chernobyl clean-up workers [8] and nuclear cataract were present in airline pilots [9].

However, the lowest cataractogenic dose and the dose-response relation in humans are not well established. For radiation protection purpose, the ICRP suggested an assumed absorbed dose threshold of 0.5 Gy for the lens of eye and conclude with the recommendation to reduce the occupational equivalent dose limit for the lens from 150 mSv per year to 20 mSv per year, averaged over defined period of 5 years, with no single year exceeding 50 mSv [10]. Unfortunately, medical radiation proce-

Table 1. Baseline characteristics of qualified studies included in the meta-analysis

Author	Year	Country	Study design	Cataract type	Exposed group: Sample size	Population	Age (yr)	Working time (yr)	Cumulative lens dose during work life (Sv)	Control: Sample size	Population	Age (yr)	Working time (yr)	Matched
Ciraj-Bjelac O	2010	Malaysia	CH	PSC	67	ICs + Nurses	ICs: 42±7 Nurses: 38±11	ICs: 9.2±6.9 Nurses: 6.0±4.6	ICs: 3.7±7.5 Nurses: 1.8±3.1	22	Health care professionals not working in interventional medicine	44±9	NA	Sex, age
Vano E	2010	Uruguay	CH	PSC	116	ICs + Nurses + Technicians	ICs: 46±8 Nurses + Technicians: 38±7	ICs: 14±8 Nurses + Technicians: 7±5	ICs: 6.0±6.6 Nurses + Technicians: 1.5±1.4	93	Non-medical professionals unexposed to IR in the head and neck region	41±10	NA	Age
Yuan MK	2010	China	CS	Cataract	733	Cardiologists performing cc	NR	NR	NR	988	Doctors not performing cc	NR	NR	Age
Ciraj-Bjelac O*	2012	Malaysia	CH	PSC	52	ICs + Nurses + Radiographers	ICs: 43±9 Nurses + Radiographers: 34±9	ICs: 8±6 Nurses + Radiographers: 5±4	ICs: 1.1±1.7 Nurses + Radiographers: 1.8±4.5	34	Physicians and paramedics not working in interventional medicine	40±16	NA	Sex, age
Jacob S	2013	France	CC	Lens opacities	106	ICs	51.1±7.3	NR	NR	99	Unexposed nonmedical workers	49.6±6.7	NR	Sex, age
Vano E*	2013	Uruguay	CS	Lens opacities	123	ICs + Nurses + Technicians	ICs: 47.7±8.8 with opacity/41.5±9.5 without opacity Nurses + Technicians: 43.3±11.2 with opacity/35.4±8.8 without opacity	ICs:16.6±9.3 with opacity/10.4±8.9 without opacity Nurses + Technicians: 12.1±8.5 with opacity/8.4±6.7 without opacity	ICs: 8.3±5.4 with opacity/3.0±2.9 without opacity Nurses + Technicians: 2.7±2.0 with opacity/1.8±1.9 without opacity	93	Non-medical professionals unexposed to IR in the head and neck region	41±10	NA	Age
Yuan MK*	2013	China	CH	Cataract	2776	Patients who had undergone CT	40.27±8.38	NR	NR	27761	Subjects who were never exposed to CT	40.00±8.98	NR	Time of enrollment, age, sex, etc
Auvinen A	2015	Finland	CH	Lens opacities	21	Interventional radiologists + cardiologists + surgeons	54	NR	0.22	16	Physicians excluding radiologists and cardiologists	63	NR	Sex, age

Bitarafan Rajabi A	2015	Iran	CH	Lens opacity	83	ICs + Technicians	Adult intervention laboratory: 42.9±8.7 Pediatric intervention laboratory: 44.3±10.7 Electrophysiology laboratory: 39.1±8.2 Adult and pediatric intervention laboratory: 37.6±3.2 Adult and electrophysiology laboratory: 38.4±12.5	Adult intervention laboratory: 10±8.5 Pediatric intervention laboratory: 10.6±9.9 Electrophysiology laboratory: 9.8±7.7 Adult and pediatric intervention laboratory: 5.6±2.3 Adult and electrophysiology laboratory: 10.6±12	Adult intervention laboratory: $4.8*10^{-3}$±4.5 Pediatric intervention laboratory: $4.3*10^{-3}$±4.5 Electrophysiology laboratory: $17.2*10^{-3}$±11.9 Adult and pediatric intervention laboratory: $4.3*10^{-3}$±2.9 Adult and electrophysiology laboratory: $5.9*10^{-3}$±6.6	14	Professional nurses with no history of ionizing radiation exposure to the head or neck	41.8±6.9	NR	Nr
Lian Y	2015	China	CH	Cataract	1401	Industrial radiographers	NA	NA	NA	1878	Participants without radiation	NA	NA	Random sampling
Andreassi MG	2016	Italy	CS	Cataract	466	ICs/ eletrophysiologists + Nurses + Technicians	ICs/ eletrophysiologists: 46±9 Nurses: 42±7 Technicians: 40±12	10	ICs/ eletrophysiologists: $2.1*10^{-2}$ Nurses: $7*10^{-2}$	289	Physicians never experience occupational exposure to IR	43±7	NR	Randomly selected
Azizova TV	2016	Russia	CH	Cataract	15131	Workers occupationally exposed to IR more than 20 years	NR	≥20	NA	5929	Workers occupationally exposed to IR less than 20 years	NR	< 20	Nr
Domienik J	2016	Poland	CS	Lens opacity	69	ICs	41±7.73	9±6.46	NR	23	A group of non-exposed physicians	44±9.43	NR	Sex, age
Thrapsanioti Z	2016	Greece	CS	Lens opacity	44	ICs	48.9±6.7	15.3±9.7	NA	22	Unexposed non-cardiologists workers	48.6±5.4	NR	Nr
Liang CL	2017	China	CH	Cataract	277	Patients who had undergone GKRS	46.3±15.3	NR	NR	2770	Patients who had never undergone GKRS	46.3±15.3	NR	Time of enrollment, age, sex, etc

*The later research with different exposed group. NR, not reported; NA, not available. IR, ionizing radiation; PSC, posterior subcapsular cataract; ICs, interventional cardiologists; GKRS, gamma knife radiosurgery. CC, case-control study; CS, cross-sectional study; CH cohort study.

Table 2. The frequency of cataract prevalence among exposed group and control group

Author (ref)	Exposed group			Control		
	Events (%)	Non-events (%)	Sum (%)	Events (%)	Non-events (%)	Sum (%)
Ciraj-Bjelac O	34 (0.88)	33 (0.19)	67 (0.31)	2 (0.14)	20 (0.05)	22 (0.05)
Vano E	34 (0.88)	82 (0.47)	116 (0.54)	11 (0.78)	82 (0.21)	93 (0.23)
Yuan MK	9 (0.23)	724 (4.11)	733 (3.41)	8 (0.56)	980 (2.54)	988 (2.47)
Ciraj-Bjelac O*	26 (0.67)	26 (0.15)	52 (0.24)	7 (0.49)	27 (0.07)	34 (0.08)
Jacob S	71 (1.84)	35 (0.20)	106 (0.49)	74 (5.22)	25 (0.06)	99 (0.25)
Vano E*	55 (1.43)	68 (0.39)	123 (0.57)	11 (0.78)	82 (0.21)	93 (0.23)
Yuan MK*	27 (0.70)	2749 (15.61)	2776 (12.93)	201 (14.17)	27560 (71.37)	27761 (69.35)
Auvinen A	14 (0.36)	7 (0.04)	21 (0.10)	13 (0.92)	3 (0.01)	16 (0.04)
Bitarafan Rajabi A	64 (1.66)	19 (0.11)	83 (0.39)	10 (0.71)	4 (0.01)	14 (0.03)
Lian Y	81 (2.10)	1320 (7.70)	1401 (6.53)	30 (2.12)	1848 (4.79)	1878 (4.69)
Andreassi MG	22 (0.57)	444 (2.52)	466 (2.17)	2 (0.14)	287 (0.74)	289 (0.72)
Azizova TV	3335 (86.53)	11796 (66.98)	15131 (70.49)	824 (58.11)	5105 (13.22)	5929 (14.81)
Domienik J	15 (0.39)	54 (0.31)	69 (0.32)	6 (0.42)	17 (0.04)	23 (0.06)
Thrapsanioti Z	39 (1.01)	5 (0.03)	44 (0.20)	18 (1.27)	4 (0.01)	22 (0.05)
Liang CL	28 (0.73)	249 (1.41)	277 (1.29)	201 (14.17)	2569 (6.65)	2770 (6.92)

*The later research with different exposed group.

Table 3. Summary RRs and heterogeneity results for associations between the radiation exposure and cataract risk

Comparison (N$)		Exposed group		Control		RR	95% CI	*P**	I^2 (%)
		Events	Total	Events	Total				
Overall (15)		3854	21465	1418	40031	1.52	1.22-1.88	0.00	73.2
Ethnicity	Asian (7)	269	5389	33008	33467	1.74	1.18-2.57	0.00	70.3
	Caucasian (8)	3585	16076	959	6564	1.38	1.03-1.84	0.00	76.6
Cataract type	PSC (7)	148	1789	39	2163	2.41	1.72-3.38	0.80	0.0
	Cortical cataract (4)	107	1572	67	2001	1.21	0.53-2.77	0.00	87.5
	Nuclear cataract (4)	154	1572	126	1989	1.11	0.77-1.61	0.02	68.2
Staff type	ICs (10)	289	1423	140	1668	1.91	1.22-3.00	0.00	76.0
	Supporting staff& (6)	80	434	34	536	2.52	1.71-3.71	0.66	0.0
	Others# (4)	3486	16809	1082	10577	1.66	1.22-2.25	0.00	80.6

$N refers to the number of studies in each meta-analysis. *Test for heterogeneity: Random-effects model was used when *P* value for heterogeneity test < 0.05 and I^2 > 50%; otherwise, fixed-effects model was used. &Supporting staff refers to physicians and nurse working in interventional cardiology. #Others refers to industrial radiographers and patients who undergone radiation theraphy.

dures now are dramatically becoming frequent and popular in treatments, which led to increased complexity in both medical staff and patient exposure profiles [11]. It is undeniable that occupational IR account for a considerable portion of artificial radiation exposure, where individuals receive readily measurable exposures [12].

In recent decades, numbers of epidemiological studies have been performed to evaluate the risk of radiation-induced cataract among occupational radiation-associated population, such as medical staff, industrial radiographer or patients who had undergone radiation therapy [13-28], but due to the difference between researchers, regions, staff type and sample size, there are still some unresolved questions about cataract developing factors under the effects of radiation and hard to reach the consistent conclusion. To better shed light on these conflicting findings and provide a more thorough perspective, we conducted a comprehensive meta-analysis on 15 published studies from

Table 4. Methodological quality assessment of included studies by NOS

Author (ref)	Selection				Comparability		Exposure/Outcome			NOS (stars*)
	Representativeness of exposed cohort	Selection of non exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start	Controls matched for important factor	Controls matched for additional factor	Ascertainment of outcome	Long enough follow up time	Loss follow up rate	
Ciraj-Bjelac O	0	1	1	1	1	0	1	0	1	6
Vano E	0	1	1	1	1	0	1	0	1	6
Yuan MK	0	1	0	1	1	0	1	0	0	4
Ciraj-Bjelac O*	0	1	1	1	1	0	1	0	0	5
Jacob S	0	1	0	1	1	0	1	0	1	5
Vano E*	0	1	1	1	1	0	1	0	0	5
Yuan MK*	0	1	1	1	1	1	1	1	0	7
Auvinen A	0	1	1	1	1	0	1	1	1	7
Bitarafan Rajabi A	0	1	1	1	0	0	1	1	1	6
Lian Y	0	1	1	1	0	0	1	1	1	6
Andreassi MG	0	1	1	1	0	0	0	0	1	4
Azizova TV	0	1	1	1	0	0	1	1	1	6
Domienik J	0	1	0	1	1	0	1	0	0	4
Thrapsanioti Z	0	1	0	1	0	0	1	0	1	4
Liang CL	0	1	0	1	1	1	1	1	1	7

*The later research with different exposed group.

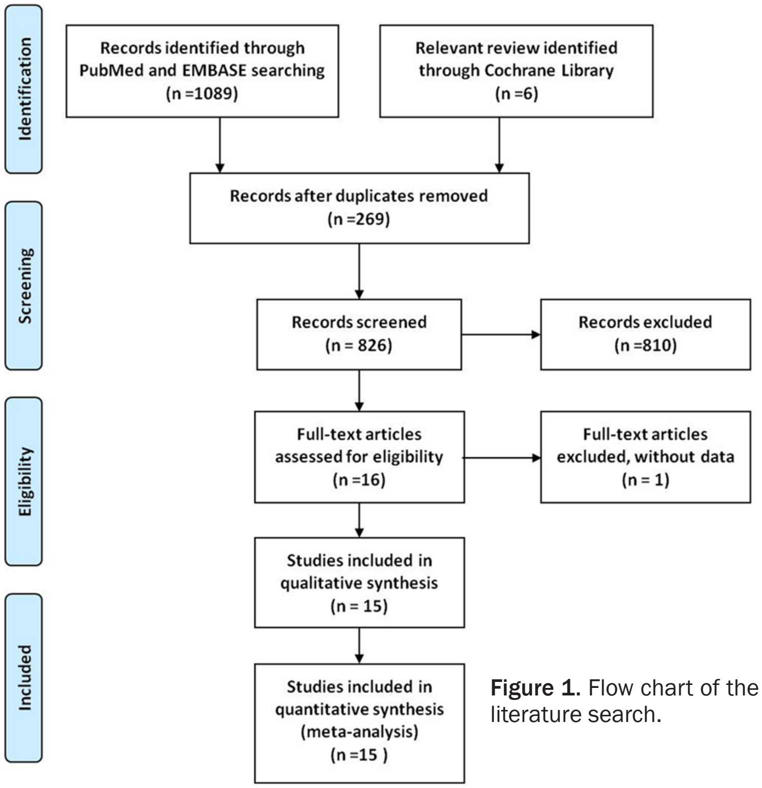

Figure 1. Flow chart of the literature search.

2010 to 2017, with 61,496 subjects (exposed group = 21,465) relating Low-dose IR exposure to the risk of developing cataract.

Methods

This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting systematic reviews and meta-analysis. Study selection, data extraction, and quality assessment were completed independently by two investigators. Disagreement was resolved through discussion. If the discussion did not lead to a consensus, Professor Wang made the final decision.

Identification and eligibility of relevant studies

We attempted to include all related studies that reported the association between cataract risk and IR in exposure group and control group in the meta-analysis. Exposed group were categorized into (i) interventional cardiologists (ICs), (ii) supporting staff (physicians and nurse working in interventional cardiology), (iii) industrial radiographers, (iv) patients who had undergone radiation therapy. The control group consisted of subjects not working in interventional medicine or unexposed to IR in the head and neck region or never exposed to radiation therapy.

We first identified studies by searching the electronic literature PubMed and Embase for relevant reports and Cochrane Library for relevant reviews in English (from January 1996 to April 2017, using the search terms "(lens opacity) and (cataract) and (ionizing radiation)". We chose articles which conducted among human subjects. We restricted attention to the studies that satisfied all of the following criteria: Studies related to the relationship between IR and cataract were determined regardless of sample size, occupational type and study design (case-control, cross-sectional or cohort studies); cataract frequency in each group was reported, and there was sufficient information for extraction of data; If studies had partly overlapped subjects, only the one with a larger and/or latest sample size was selected for the analysis. Additional studies were identified by hands-on searches from references of original studies or review articles on this topic. According to these criteria, we finally included 15 papers in our meta-analysis.

Data extraction and conversion

Two investigators extracted data independently and reached a consensus on all items. Data extracted from these articles included the first author's name, publication year, country, assessment of lens changes, cataract type, population characteristics and the number of exposed group and controls. The frequencies of the cataract events were extracted or calculated for both experimental group and controls. For some studies without sufficient information for extraction of data, we tried to contact with the studies' authors by sending emails from their articles to request missing data.

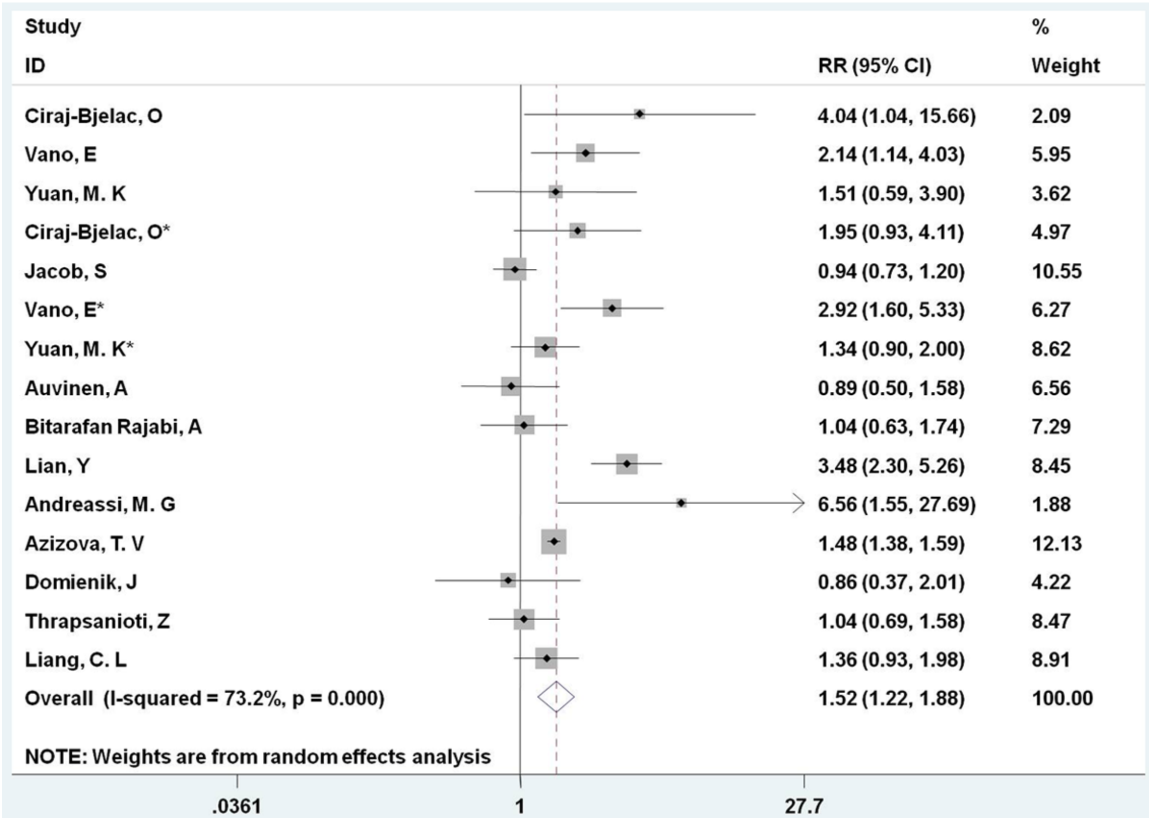

Figure 2. RR of Cataract risk associated with low-dose ionizing radiation exposure. The graph shows individual and pooled estimates.

Quality assessment and study stratification

The Newcastle-Ottawa scale (NOS) method was used to assess the observational included studies. The NOS is composed of three parts (8 entries): selection, comparability and outcome. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars can be given for comparability. It is a semi-quantitative scale, and a score of 0-9 stars is assigned to each study. The scores of included studies were shown in **Table 4**.

Meta-analysis

Our meta-analysis evaluated the relationship between the Low-dose IR exposure and the risk of cataract for each study by risk ratio (RR) with 95% confidence intervals (95% CI). In addition, we conducted stratification analysis by ethnicity, cataract type and exposed subject type. A sensitivity analysis, which examines the effect of excluding specific studies, was also performed [29].

The χ^2-based Q statistic test was used to estimate the heterogeneity, and it was considered significant for $P < 0.05$. Heterogeneity was quantified with the I^2 metric, which is independent of the number of studies in the meta-analysis. I^2 takes values between 0 and 100%, with higher values indicating greater degree of heterogeneity ($I^2 > 50\%$ was considered significant) [30]. The fixed-effects model and the random-effects model were used based on the Mantel-Haenszel method and the DerSimonian and Laird method, respectively, to combine values from each of the studies. When the effects were assumed to be heterogeneous, the random-effects model was then used; otherwise, the fix-effects model was more appropriate [31]. In addition, meta-regression analyses were further conducted to access the source of heterogeneity. Publication bias was assessed according to the Begg adjusted rank correlation test and the Egger regression asymmetry test [32, 33]. All analysis was done by using the Stata soft (v.12.0). All the P values were two-sided.

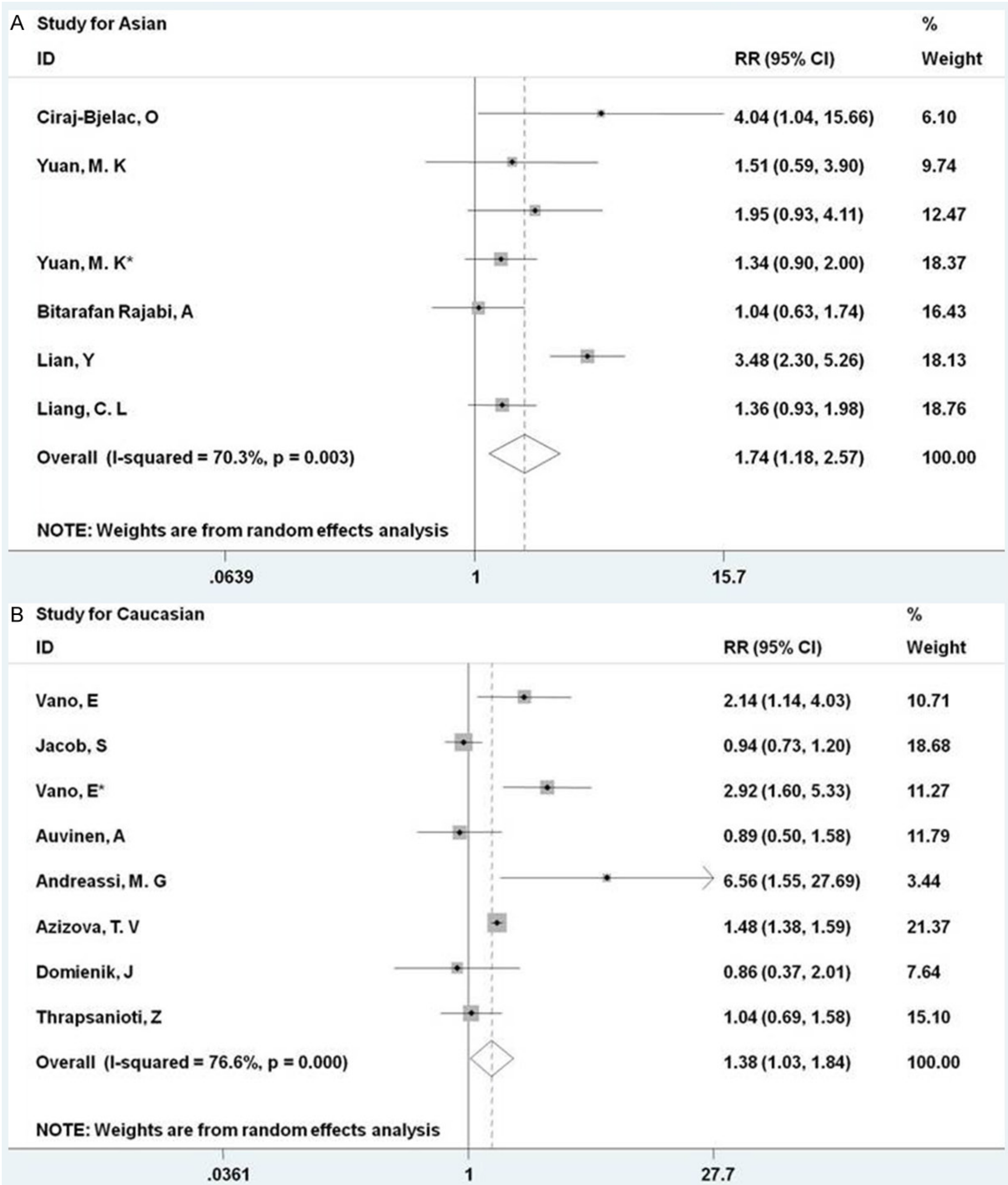

Figure 3. RR of Cataract risk associated with low-dose ionizing radiation exposure from stratified analysis by ethnicity. A. For Asian group; B. For Caucasian group.

Results

Literature search

The study selection process is shown in **Figure 1**. A total of 1089 articles (PubMed 1089, Embase 269 and Cochrane Library 6) were identified from the databases, and 269 duplicates were excluded through EndNote (X7). In addition, 810 articles were excluded based on a review of the titles and abstracts, and 16 full-text articles were assessed for eligibility; 1 articles were excluded due to could not provide sufficient information for extraction of data. Finally, a total of 15 [13-27] articles with a total

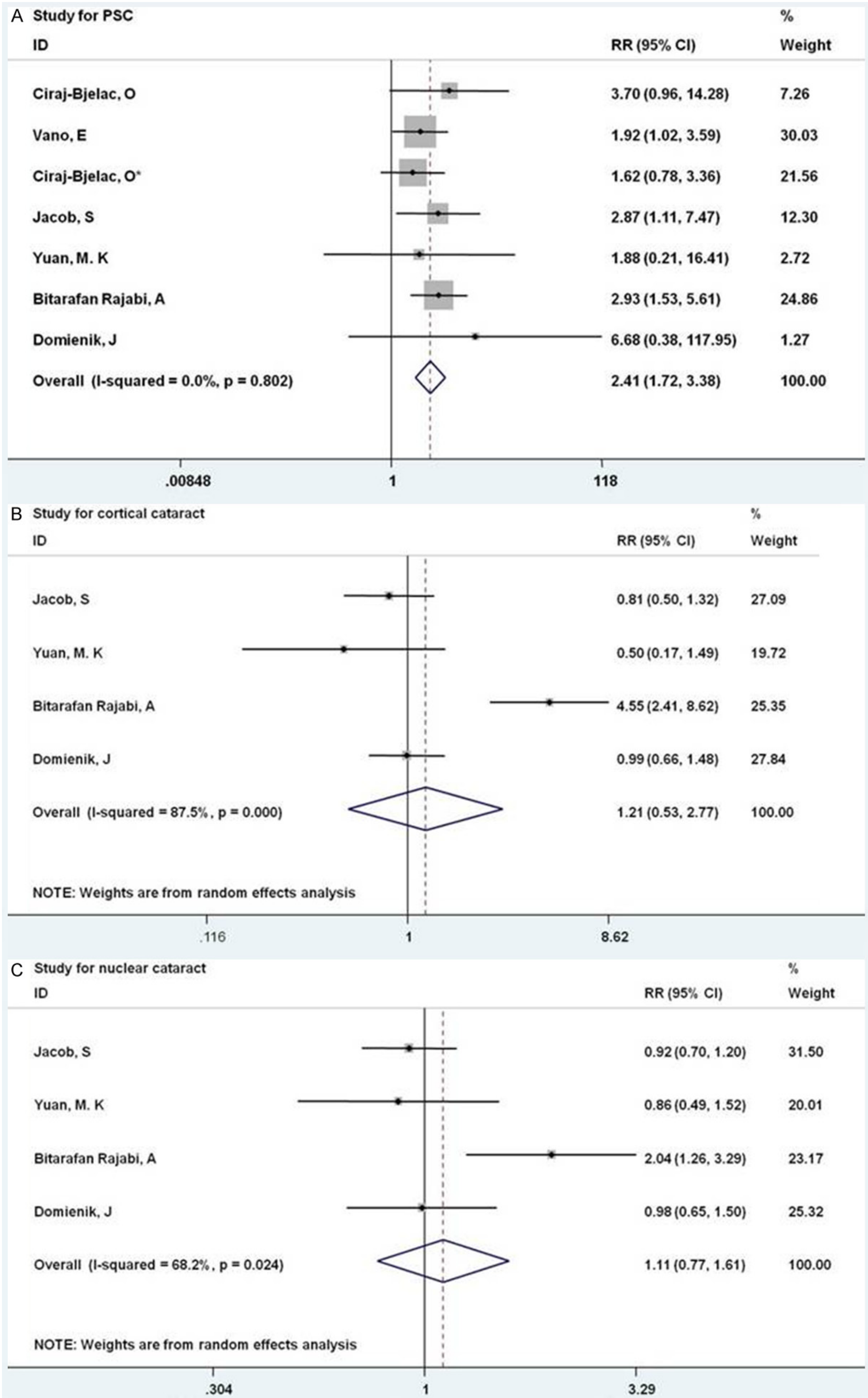
A Study for PSC
ID
RR (95% CI)
% Weight
Ciraj-Bjelac, O 3.70 (0.96, 14.28) 7.26
Vano, E 1.92 (1.02, 3.59) 30.03
Ciraj-Bjelac, O* 1.62 (0.78, 3.36) 21.56
Jacob, S 2.87 (1.11, 7.47) 12.30
Yuan, M. K 1.88 (0.21, 16.41) 2.72
Bitarafan Rajabi, A 2.93 (1.53, 5.61) 24.86
Domienik, J 6.68 (0.38, 117.95) 1.27
Overall (I-squared = 0.0%, p = 0.802) 2.41 (1.72, 3.38) 100.00
.00848
1
118
B Study for cortical cataract
ID
RR (95% CI)
% Weight
Jacob, S 0.81 (0.50, 1.32) 27.09
Yuan, M. K 0.50 (0.17, 1.49) 19.72
Bitarafan Rajabi, A 4.55 (2.41, 8.62) 25.35
Domienik, J 0.99 (0.66, 1.48) 27.84
Overall (I-squared = 87.5%, p = 0.000) 1.21 (0.53, 2.77) 100.00
NOTE: Weights are from random effects analysis
.116
1
8.62
C Study for nuclear cataract
ID
RR (95% CI)
% Weight
Jacob, S 0.92 (0.70, 1.20) 31.50
Yuan, M. K 0.86 (0.49, 1.52) 20.01
Bitarafan Rajabi, A 2.04 (1.26, 3.29) 23.17
Domienik, J 0.98 (0.65, 1.50) 25.32
Overall (I-squared = 68.2%, p = 0.024) 1.11 (0.77, 1.61) 100.00
NOTE: Weights are from random effects analysis
.304
1
3.29

Figure 4. RR of Cataract risk associated with low-dose ionizing radiation exposure from stratified analysis by cataract type. A. For PSC; B. For cortical cataract; C. For nuclear cataract.

of 62,316 participants were included in this meta-analysis.

Eligible studies and study characteristics

The selected study baseline characteristics of the qualified studies are provided in **Table 1** and the frequency of cataract prevalence among exposed group and control group are shown in **Table 2**. For 15 studies, 7 studies [13, 15, 16, 19, 21, 22, 27] were performed among Asian population, and 8 studies [14, 17, 18, 20, 23-26] were among Caucasian population, 10 studies [13-18, 21, 23, 25, 26] selected interventional cardiologists as the exposed group, and 6 studies [13, 14, 16, 18, 20, 21, 23] selected supporting staff (physicians and nurse working in interventional cardiology) as the exposed group. 2 studies [22, 24] selected industrial radiographers, and 2 studies [19, 27] selected patients who had undergone radiation therapy as the exposed group. In addition, 7 studies [13, 14, 16, 17, 19, 21, 25] conducted stratified research on PSC and 4 studies [17, 19, 21, 25] on cortical and nuclear cataract, respectively. On the assessment of lens changes, for 15 studies, each participant was evaluated separately by at least two independent examiners trained in the recognition and evaluation of characteristic radiation-induced lens morphology, except 1 study [23] based on self-report.

Main results, stratification, and sensitivity analyses

The estimation results of the relationship of the low-dose IR exposure with cataract are presented in **Table 3**. **Figures 2**-**5** show the overall results and stratified analysis results for the association between the radiation exposure and the risk of cataract.

As it shown in **Table 3**, the overall analysis found a significant association between the Low-dose IR exposure and the risk of cataract compared to non-exposed controls (RR = 1.52, 95% CI: 1.22-1.88), which suggested that Low-dose IR exposure might increase the risk of cataract.

Stratified analysis was further conducted by ethnicity (Asian or Caucasian), cataract type (PSC or cortical cataract or nuclear cataract) and exposed subject type (ICs or supporting staff or others). For ethnicity factor, we detected that both the Asian and Caucasian population showed positive significant associations between Low-dose IR exposure and cataract risk (RR = 1.74, 95% CI: 1.18-2.57 for Asian group, RR = 1.38, 95% CI: 1.03-1.84 for Caucasian group, respectively). In addition, all three different exposed subject group found positive significant association compared to controls (RR = 1.91, 95% CI: 1.22-3.00 for ICs group, RR = 2.52, 95% CI: 1.71-3.71 for supporting staff group and RR = 1.66, 95% CI: 1.22-2.25 for industrial radiographers and patients who had undergone radiation therapy, respectively).

It is worth emphasizing that the results from stratified analysis by cataract type indicated that Low-dose IR exposure might contribute high risk to PSC compared to controls (RR = 2.41, 95% CI: 1.72-3.38). However, we failed to find any significant relationship to cortical and nuclear cataract risk and Low-dose IR exposure.

Further sensitivity analysis was conducted by excluding three studies [17, 18, 22] for the effect of individual studies on the summary effect size from funnel plots, which almost did not alter the pattern of results in overall analysis (RR = 1.48, 95% CI: 1.38-1.58).

Source of heterogeneity and publication bias

From **Table 3**, we found that the heterogeneity between studies was observed in overall comparisons as well as subgroup analyses. We estimated the source of heterogeneity by ethnicity, cataract type, exposed subject type and study design by meta-regression analyses and the results were shown in **Table 5**. It revealed that all factors could not influent significantly between-study heterogeneity: ethnicity ($P = 0.46$), cataract type ($P = 0.51$), and study design ($P = 0.64$), except for exposed subject type ($P = 0.04$). Thus, exposed subject type factor might be the source of heterogeneity between studies ($P = 0.04$ and contributed 39.6% source of heterogeneity).

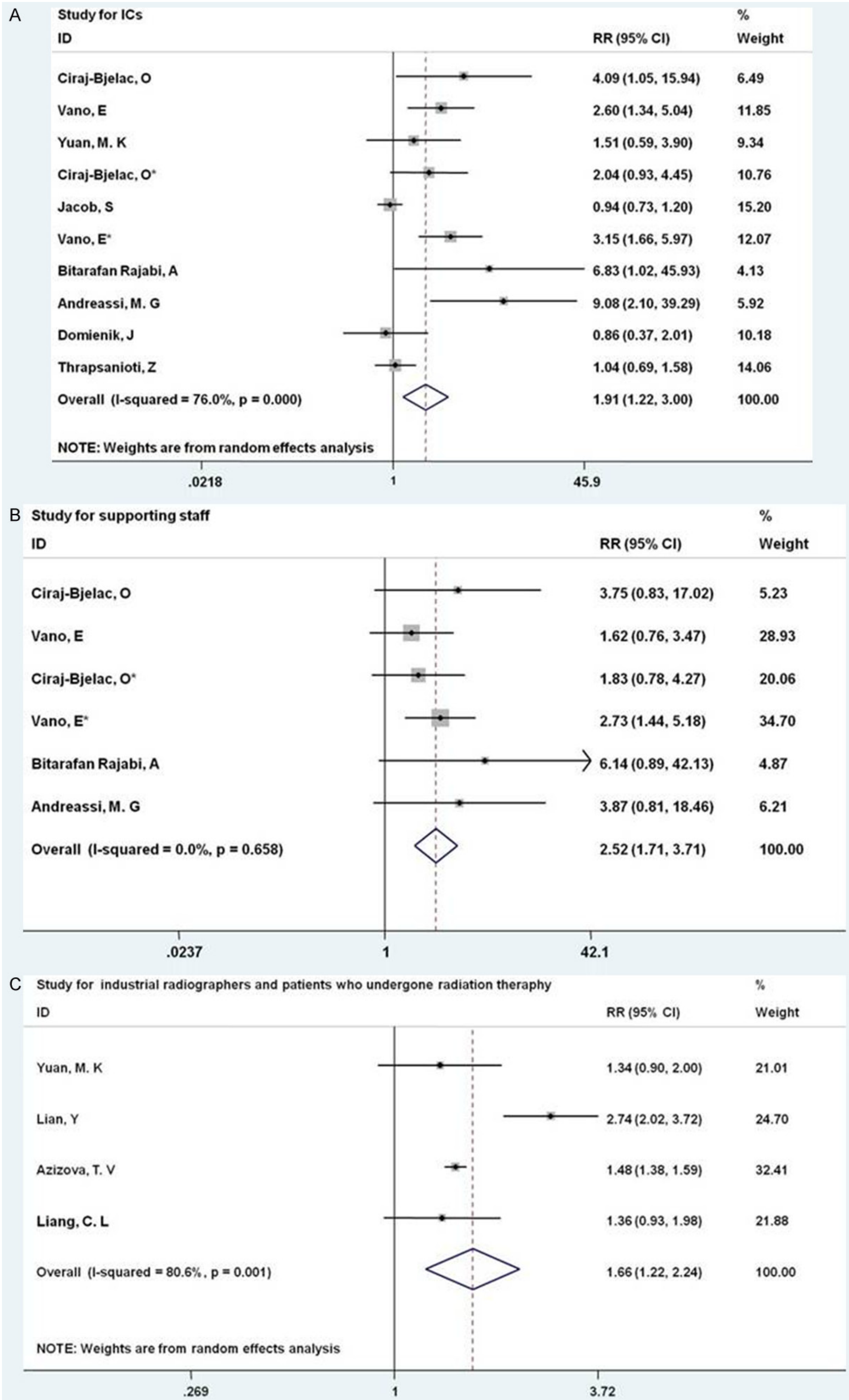
A
Study for ICs
ID
RR (95% CI)
%
Weight
Ciraj-Bjelac, O
4.09 (1.05, 15.94)
6.49
Vano, E
2.60 (1.34, 5.04)
11.85
Yuan, M. K
1.51 (0.59, 3.90)
9.34
Ciraj-Bjelac, O*
2.04 (0.93, 4.45)
10.76
Jacob, S
0.94 (0.73, 1.20)
15.20
Vano, E*
3.15 (1.66, 5.97)
12.07
Bitarafan Rajabi, A
6.83 (1.02, 45.93)
4.13
Andreassi, M. G
9.08 (2.10, 39.29)
5.92
Domienik, J
0.86 (0.37, 2.01)
10.18
Thrapsanioti, Z
1.04 (0.69, 1.58)
14.06
Overall (I-squared = 76.0%, p = 0.000)
1.91 (1.22, 3.00)
100.00
NOTE: Weights are from random effects analysis
.0218
1
45.9
B
Study for supporting staff
ID
RR (95% CI)
%
Weight
Ciraj-Bjelac, O
3.75 (0.83, 17.02)
5.23
Vano, E
1.62 (0.76, 3.47)
28.93
Ciraj-Bjelac, O*
1.83 (0.78, 4.27)
20.06
Vano, E*
2.73 (1.44, 5.18)
34.70
Bitarafan Rajabi, A
6.14 (0.89, 42.13)
4.87
Andreassi, M. G
3.87 (0.81, 18.46)
6.21
Overall (I-squared = 0.0%, p = 0.658)
2.52 (1.71, 3.71)
100.00
.0237
1
42.1
C
Study for industrial radiographers and patients who undergone radiation theraphy
ID
RR (95% CI)
%
Weight
Yuan, M. K
1.34 (0.90, 2.00)
21.01
Lian, Y
2.74 (2.02, 3.72)
24.70
Azizova, T. V
1.48 (1.38, 1.59)
32.41
Liang, C. L
1.36 (0.93, 1.98)
21.88
Overall (I-squared = 80.6%, p = 0.001)
1.66 (1.22, 2.24)
100.00
NOTE: Weights are from random effects analysis
.269
1
3.72

Figure 5. RR of Cataract risk associated with low-dose ionizing radiation exposure from stratified analysis by exposed subject type. A. For ICs; B. For supporting staff; C. For industrial radiographers and patients who undergone radiation theraphy.

Table 5. Meta-regression analysis on the source of heterogeneity

Sources	*P**
Ethnicity	0.46
Cataract type	0.51
Study design	0.64
Staff type	0.04

**P* value from meta-regression analysis and it was considered significant for $P < 0.05$.

The potential presence of publication bias was estimated by using a funnel plot by evaluating log-risk ratio for the cataract prevalence against the reciprocal of its standard error (**Figure 6**). As it shown, we failed to observe any significant funnel asymmetry which could indicate publication bias. We further conducted the Egger regression asymmetry test and the Begg adjusted rank correlation tests to estimate the publication bias of included literatures in the meta-analysis. Finally, no publication bias was found for the radiation expose and risk of cataract ($P = 0.60$ for Egger test and $P = 0.96$ for Begg test).

Discussion

ICRP considers IR induced cataracts as a deterministic effect with a threshold of 0.5 Gy for vision impairing cataracts irrespective of the rate of dose delivery [10], so the radiation-associated exposed population are likely to develop IR induced cataracts with exposure doses < 0.5 Gy [5]. One research considered genomic damage of lens epithelial cells (LECs) to be one of the critical mechanisms for initiation of IR induced cataractogenesis [34]. In vitro studies have reported research on both genotoxic stress induced by IR and the associated oxidative stress, which may result in aberrant LECs cell division, cell migration, differentiation [35, 36] and new point mutations (insertion, deletion or substitutions) and DNA strand breaks (DNA base damage) [37]. These aberrant consequences potentially allow LECs to transmit the unstable phenotype, possibly deregulating the tightly controlled lens differentiation process and leading to cataract [38-40]. In addition, it is necessary to quantify the IR exposure for understanding the cataract risk associated with IR exposure. Although it is hard to obtain high quality dosimetry at low doses, with frequent use of questionnaires relying on recall, or generic calculations [4], several epidemiological evidences suggested that protracted low-dose IR exposure do lead to significant elevation of cataract incidence [7, 10, 41, 42]. Indeed, numerous epidemiological investigations into the potential role of IR exposure as a risk factor for cataract have been conducted over the past decades, but with controversial results.

Although Elmaraezy et al [43] had reported a meta-analysis on risk of radiation-induced cataract, our meta-analysis performed more comprehensive and powerful review and analysis on IR exposure to risk of cataract and obtained several critical different conclusions from it. Firstly, in Elmaraezy et al's report, they only included 8 studies from 2010 to 2015 with 2,559 subjects (exposed group = 1224), which relatively provides poor power to detect smaller effect sizes and estimates real effect of IR exposure to cataract risk appropriately; Secondly, they just assessed the risk of cataract among interventional cardiologists and ignored the different effects by ethnicity factor, which might restrict the extension of conclusion, to a certain extent; Thirdly, they did not perform meta-regression analysis to access the sources of between-study heterogeneity and found the publication bias for comparison.

In contrast, we conducted a comprehensive meta-analysis on 15 published studies from 2010-2017 with 61,496 subjects (exposed group = 21,465) among occupational radiation-associated population, such as medical staff, industrial radiographer or patients who had undergone radiation therapy, which can provide better power to detect smaller effect sizes. Its strength was based on the accumulation of published data giving greater information to detect significant differences. As a result, we found the significant effects for low-dose IR exposure on cataract risk with all studies, without any publication bias. Sensitivity analysis for the effect of individual studies on the summary

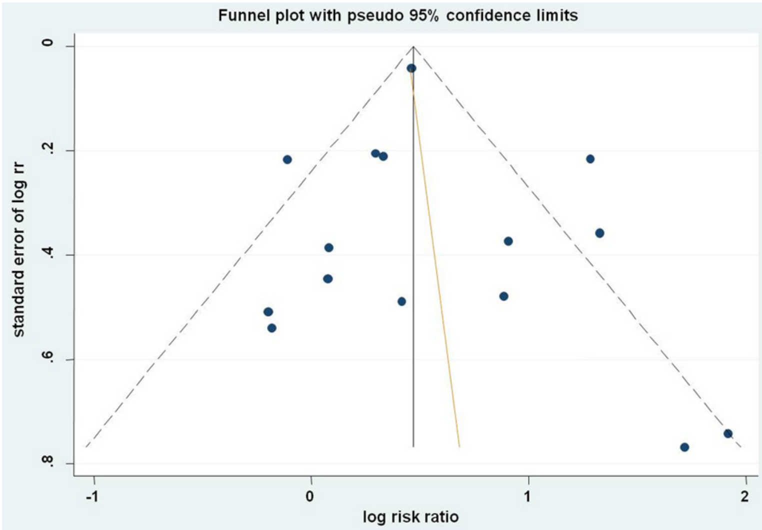

Figure 6. Evaluation of publication bias for all studies using funnel plots. No significant funnel asymmetry was observed which could indicate publication bias.

effect size from funnel plots were also performed, which almost did not alter the pattern of results in overall analysis. From subgroup analysis by ethnicity, cataract type and exposed subject type, we also detected that low-dose IR exposure may highly increase cataract risk in both Asian and Caucasian population among all three different exposed subject group. In addition, we also found that low-dose IR exposure might contribute higher risk to PSC than cortical and nuclear cataract.

It is interesting that we found higher risk of Low-dose IR exposure to cataract among supporting staff (RR = 2.52), compared to ICs group (RR = 1.91). This might be explained by different protection measures and self-protection awareness between them. Although supporting staff such as nurses and technicians may absorb relative lower dose during working time than ICs, several epidemiological studies [16, 18] showed that less support staff used the ceiling-suspended screens and regularly wore the lead eye glass during interventional cardiology operation, compared to ICs.

We further evaluated the source of heterogeneity and the publication bias of included literatures. It is worth mentioning that we found exposed subject type factor might be the source of heterogeneity between studies. To provide better power to detect smaller effect sizes, studies related to the IR exposure on cataract risk were determined according to the predefined included standard of exposed group. However, different occupational type may generate potential effect to meta-analysis. For example, the ICs may receive much more radiation dose during their work time, compared to supporting staff, and patients who undergone the radiation therapy may obtain different exposure way, compared to other occupational workers research conclusion. Therefore, the overall effect of all studies with different exposed subject type might be deviated from the real effect, to some extent.

Despite the clear strengths of our study, some limitations merit consideration. First, non-English, non-indexed, and non-published studies were not reviewed in our meta-analysis, which might introduce some bias [44]; In addition, since individual data for possible confounding factors (e.g. age, sex, UV exposure, myopia) were not provided, only the unadjusted pooled RRs were calculated. Furthermore, the risk effect may depend on the interaction with other risk factors: age, diabetes, years of work, cumulative lens dose, radiation protection measures and so on, all of which modulate the development of cataract [45]. Therefore, further well-designed epidemiological studies, particularly interact with dose-response and protection measures are needed to confirm the real contribution of low-dose IR exposure to cataract development.

In conclusion, our present meta-analysis finds that the Low-dose IR exposure may contribute to cataract development among occupational radiation-associated population, such as medical staff, industrial radiographer or patients who had undergone radiation therapy, especially to posterior subcapsular cataract. Further well-designed studies are needed to clarify how relatively low dose of IR exposure promotes progression of cataracts and understanding the requirements of radiation-protection professionals.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Baoli Zhu, Jiangsu Provincial Center for Disease Prevention and Control, 172 Jiangsu Road, Nanjing 210029, China. Tel: 86-025-83759544; Fax: 86-025-83759544; E-mail: zhubl@jscdc.cn

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