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Meta-analysis of Incidence of Brain Cancer Among Aircrew

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Abstract

Introduction: Previous studies on brain and other nervous system cancers (BNSC) and aircrew have shown inconsistent results, possibly due to their relatively small sample sizes; therefore, the current study aimed to increase the precision of risk estimates.

Methods: Systematic searches of PubMed and Embase for pertinent studies up to August 2016 were performed and supplemented by manual reviews of bibliographies. The pooled standard incidence ratio (SIR) and corresponding 95% CIs were estimated with random effects models.

Results: Among the 903 studies retrieved, 7 studies (5 cohort studies and 2 pooled analyses) were included in the current meta-analysis. The pooled SIR (95% CI) of BNSC incidence in aircrew was 1.01 (0.77, 1.31) with no significant heterogeneity (I^2=36.1%, P=.199). The null association persisted when the analysis was stratified by geographic area (Europe or America), publication year (before or after 2001), air population (pilots or cabin crew), cancer site (brain, nervous system, or brain/nervous system), and gender (male or female).

Conclusion: The current evidence is not sufficient to support a significant positive association between aircrew employment and BNSC risk. However, the interpretation and extrapolation of this meta-analysis are restricted by the possible impact exerted by health worker effect and potential clinical heterogeneity. More studies based on other populations, including Asian aircrews, are warranted.

Keywords: Brain neoplasms, Nervous system neoplasms, Aircrew, Meta-analysis

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Introduction

Brain and other nervous system cancer (BNSC) have been reported as the second reason of death from neurological illness.[1] There is considerable interest in the correlation between cancer and employment as aircrew. Flight-based employees are deemed to have a higher risk of cancer owing to occupational exposures, mainly including cosmic ionizing radiation, circadian disruption, and extremely low frequency electromagnetic fields (EMFs). However, epidemiological studies on the association between employment as aircrew and BNSC risk have reported inconsistent results.[2-12] A possible explanation for these conflicting results could be that individual study, which had relatively small sample size, did not have sufficient statistical power to demonstrate any significant effect, therefore leading to broad confidence intervals.

A previous meta-analysis of observational studies on cancer incidence published in 2005 focused only on male aircrew and examined all types of cancer as a whole, including BNSC.[13] After that, several cohort studies regarding similar topics were conducted.[12,14,15] The current meta-analysis was carried out to quantitatively evaluate BNSC incidence among aircrew of both genders on a larger sample size by combining the findings of all available studies. The study also aimed to increase the precision of risk estimates of BNSC incidence among aircrew.

Methods

This meta-analysis was conducted and reported based on the meta-analysis of observational studies in epidemiology criteria (MOOSE).[16]

Data Sources and Search Strategy

Two researchers (L. T. B. and Z. C. Y.) systematically and independently searched PubMed and Embase for epidemiological studies from the date of database inception to August 2016, and any inconsistency was resolved by a third researcher (W. S. S.). There was no language restriction. Two groups of terms were included in the literature search strategy: (1) pilots, cockpit crew, cabin crew, flight crew, aircrew, flight personnel, cabin attendants, flight attendants; and (2) cancer, tumor, neoplasia, neoplasm. The reference lists of pertinent publications were also reviewed, including reports, reviews, and meta-analyses, to identify additional relevant studies. The authors of relevant publications were contacted when more data was wanted.

Selection Criteria

Two researchers (L. T. B. and Z. C. Y.) independently evaluated the eligibility of each study, and any inconsistency was resolved by a third researcher (Z. J.). Studies included in this meta-analysis followed the inclusion criteria: (1) the incidence of BNSC among aircrew was evaluated; and (2) standardized incidence ratio (SIR) with CIs or standard errors (SE) were reported. There was no language restriction. SIR is a measure of the incidence in a study population (in this study, aircrew) in comparison with the general population. SIR is normally standardized by age, sex, and calendar year. Figures for SIR higher than 1 indicate an increased incidence among the study population when compared with the general population (a national or state reference population). If more than one paper analyzed data from one single study, the most recent and complete one were included.

Data Extraction and Quality Assessment

The following data was collected from the included studies: first author, publication year, country, number of participants, new cases, follow-up person-years, study period, effect estimates, and comparison categories. For studies that reported several multivariable adjusted SIRs, we selected the effect estimate, which were adjusted for the greatest number of potential confounding factors.

The Newcastle–Ottawa Scale (NOS),[17] a validated scale designed for the evaluation of non-randomized studies in meta-analysis, was applied to assess the quality of each study. There are three subscales: selection (4 items), comparability (1 item), and outcome (3 items). In addition, quality assessment was conducted using a 'star system' (range 0–9).

Statistical Analyses

For the primary analyses, the pooled SIRs and corresponding 95% CI were calculated based on adjusted SIRs which were extracted from each study. Whether or not heterogeneity existed between studies, a random-effect model was performed to evaluate the pooled SIR with 95% CI due to the relatively small number of included studies. Later, subgroup analyses stratified by geographic area (Europe or America), publication year (before or after 2001), air population (pilots or cabin crew), cancer site (brain, brain/nervous system, or nervous system), and gender (male or female) were performed. Heterogeneity across the included studies was assessed using the Q test and the I^2 statistic test. A *P* value ≤ .10 was deemed statistically significant for the Q test. The I^2 statistic was used to represent the extent of the total estimated variation accounted for by heterogeneity; I^2 values of 25%, 50%, and 75% were deemed as cut-off values to represent, moderate, and high magnitude of heterogeneity, respectively. The possibility of potential publication bias was assessed with the Egger test[18] and Begg test[19] and represented visually with funnel plots. For sensitivity analysis, a leave-one-out analysis was conducted to investigate the degrees of the influence of each study on combined risk estimates. All the statistical analyses were conducted using STATA software, version 12.0 (Stata Corporation, USA). All Statistical tests were 2-sided, with *P* <.05 of statistically significance.

Results

Literature Search

The detailed information regarding the literature searching strategy for this meta-analysis is shown in Figure 1. Initially, 903 studies were identified, including 892 from PubMed and Embase and 11 from reference lists. After duplicates were removed, there were 532 unique studies, and those studies were then screened by title and abstract. After exclusions, 36 studies were assessed in full text for eligibility. Finally, totally 7 studies met the inclusion criteria and were included in the meta-analysis.

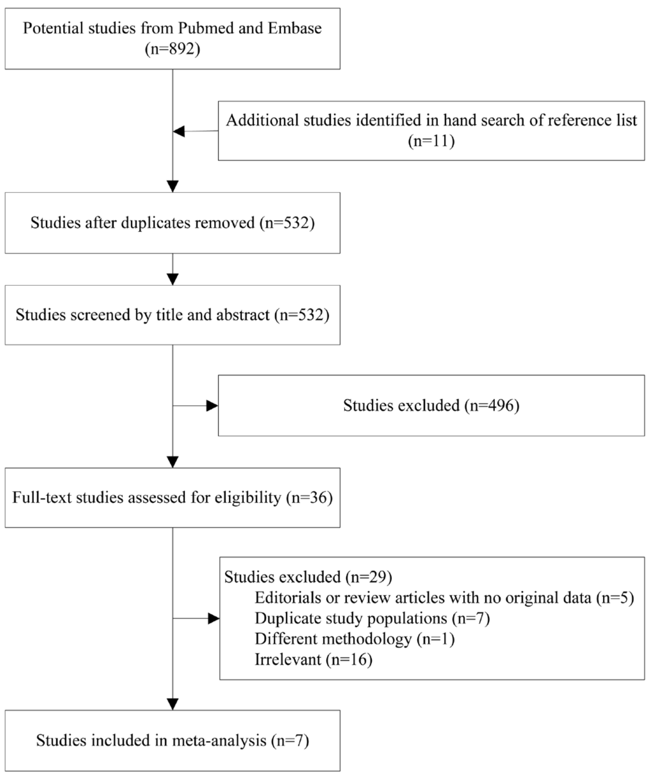

Figure 1. Flowchart of Study Identification and Inclusion.

Table 1. Main Characteristics of the Studies Included in This Meta-analysis

Study	Publication Year	Country	Air Population	Study Period	New Cases	No. of Participants	Person-Years	Cancer Site	NOS
Band et al[20]	1990	Canada	Pilots	1950-1988	4	913	18060	Brain	5
Band et al[4]	1996	Canada	Pilots	1950-1992	7	2680	61856	Brain	5
Mllanov et al[6]	1999	Bulgaria	Pilots	1964-1994	3	Not present	Not present	Brain/nervous system	4
Reynolds et al[11]	2002	USA	Cabin crew	1988-1995	1	58848	Not present	Brain/nervous system	6
Silva et al[12]	2013	UK	Pilots	1989-2008	28	16329	285259	Nervous system	7
Pukkala et al[15]	2012	Denmark, Iceland, Finland, Sweden, Norway	Cabin crew	1947-1997[a]	26	10066	237627	Brain/nervous system	7
Pukkala et al[14]	2003	Denmark, Iceland, Finland, Sweden, Norway	Pilots	1937-1996[a]	18	10211	177243	Brain/nervous system	5

[a]Variable per country.

Study Characteristics

Characteristics of the 7 studies included in this meta-analysis are shown in Table 1. These studies, published between 1900 and 2013, reported data on flight pilots and cabin crew from nine countries and included more than 99 047 participants with 87 new cases and around 780 045 follow-up person-years. The duration of follow-up ranged from 7 to 50 years. The estimated quality of the included 7 studies ranged from 4 to 7 scores. Among the 7 studies included in this meta-analysis, 2 were pooled analyses. One was published in 2003 and included data regarding pilots from 5 European countries (Denmark, Iceland, Finland, Sweden, and Norway).[14] The other one published in 2012 investigated cabin crew and involved information from Denmark, Iceland (both of which were not published), and an additional follow-up for Finland, Sweden, and Norway.[15]

Summary Standard Incidence Ratio

The results from the included studies were summarized to provide data for BNSC incidence among aircrew. Compared with the general population, the pooled SIR (95% CI) for BNSC among aircrew was 1.01 (0.77, 1.31), and the heterogeneity across the studies was not significant ($I^2 = 36.1\%$, $P = .199$) (Figure 2). The funnel plot did not reveal asymmetry (Figure 3), and neither the Egger test ($t = 1.27$, $P = .259$) nor the Begg test ($z = 1.50$, $P = .133$) were significant, all indicating there was no significant publication bias among the studies included in the meta-analysis.

Subgroup Analysis

Based on gender (male or female), air population (pilots or cabin crew), cancer site (brain, nervous system or brain/nervous system), geographic area (America or Europe), and publication year (before or after 2001), subgroup analyses were conducted with random effects models to identify the stability of the primary results and examine the source of potential heterogeneity.

When the analysis was stratified by gender, the pooled SIR was 1.19 (95% CI, 0.80-1.78; $I^2 = 36.1\%$; p for heterogeneity $= 0.166$; 6 records) for male aircrew and 0.85 (95% CI, 0.46-1.25; 1 record) for their female counterparts. When the analysis was stratified by air population, the pooled SIR was 1.11 (95% CI, 0.75-1.62; $I^2 = 51.3\%$; P for heterogeneity $= .084$; 5 records) for pilots and 0.90 (95% CI, 0.63-1.31; $I^2 = 0.0\%$; P for heterogeneity $= .678$; 2 records) for cabin crew. When the analysis was stratified by cancer site,

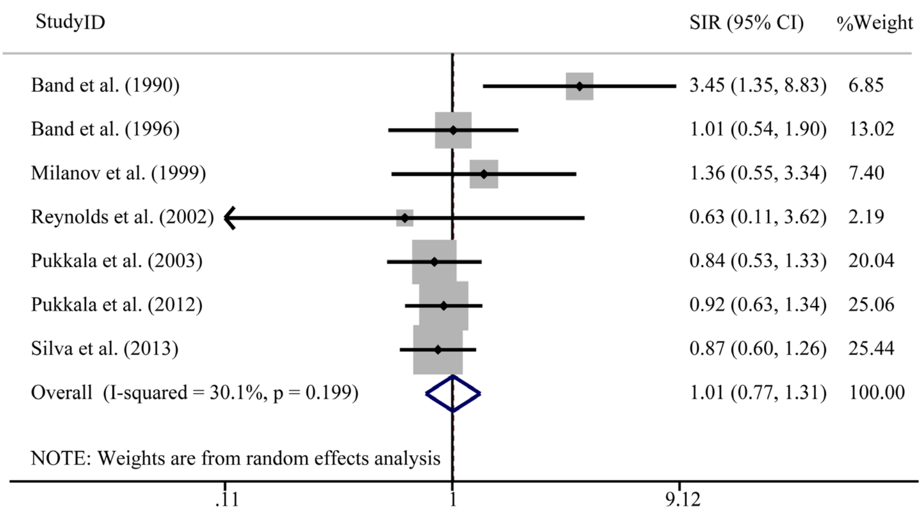

Figure 2. Meta-analysis of Observational Studies on BNSC Incidence Among Aircrew Based on Random-Effect Models.

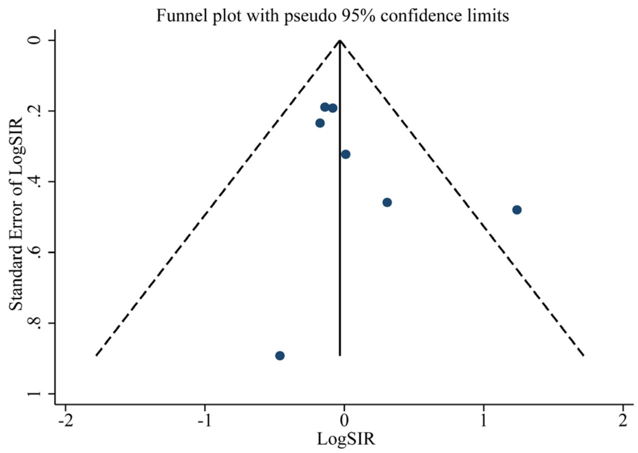

Figure 3. Funnel Plot for Publication Bias.

the pooled SIR was 1.77 (95% CI, 0.53-5.89; $I^2 = 77.9\%$; *P* for heterogeneity = .033; 2 records) for brain cancer, 0.87 (95% CI, 0.53-1.21; 1 record) for nervous system cancer, and 0.92 (95% CI, 0.70-1.20; $I^2 = 0.0\%$; *P* for heterogeneity = .788; 4 records) for BNSC. When the analysis was stratified by geographic area, the pooled SIR was 0.90 (95% CI, 0.72-1.13; $I^2 = 0.0\%$; *P* for heterogeneity = .815; 4 records) for Europe and 1.43 (95% CI, 0.55-3.73; $I^2 = 62.7\%$; *P* for heterogeneity = .068; 3 records) for America. When the analysis was stratified by publication year, the pooled SIR was 1.58 (95% CI, 0.78-3.21; $I^2 = 56.0\%$; *P* for heterogeneity = .103; 3 records) among studies conducted before 2001 and 0.88 (95% CI, 0.70-1.10; $I^2 = 0.0\%$; *P* for heterogeneity = .972; 4 records) among studies after 2001. The null association persisted among all the subgroup analyses; therefore, the combined SIR of BNSC was not significantly modified by gender, air population, cancer site, geographic area, or publication year. Table 2 showed the results of subgroup analyses.

Sensitivity Analysis

The leave-one-out analysis was conducted to assess the sensitivity of the results regarding the combined effects of BNSC incidence among aircrew compared with the general population. The leave-one-out analysis was conducted by eliminating one single study in turn. The non-significant link was not significantly altered among the leave-one-out analyses, with pooled SIRs (95% CI) ranging from 0.91 (0.74-1.12) to 1.08 (0.77-1.53).

Discussion

This meta-analysis included 7 studies (5 cohort studies and 2 pooled analyses) and more than 99 047 participants with 87 new cases and 780 045 follow-up person-years and provided quantitative estimates of the association between employment as aircrew and BNSC risk.

Air travel has been becoming increasingly widespread for decades, and the health of aircrew has concerned researchers of civil aviation health and administrators of civil aviation globally. It has been hypothesized that aircrew may have a higher risk of cancer, mainly because of the occupational exposure to circadian rhythm disruption and cosmic radiation.[21] However, most studies on the association between BNSC risk and employment as aircrew reported a null link.[3,4,6,12,22] Similarly, the current meta-analysis observed that the combined SIR for aircrew (compared with the general population) was 1.01 (95% CI: 0.77-1.31), with no evidence of substantial heterogeneity or obvious publication bias, indicating no association between employment as aircrew and the risk of BNSC. In addition, the null association persisted when the analysis was stratified by gender, air population, cancer site, geographic area, or publication year. These findings were similar to previous meta-analyses[13] on this topic.

Although the current study did not observe a statistically

Table 2. Subgroup Analysis of the SIR of BNSC in Aircrew Compared With the General Population

Study Group	No. of Study	SIR (95% CI)	*P* for Heterogeneity	I^2
All	7	1.01 (0.77-1.31)	0.199	30.1%
Geographic area				
Europe	4	0.90 (0.72-1.13)	0.815	0.0%
America	3	1.43 (0.55-3.73)	0.068	62.7%
Publication year				
Before 2001	3	1.58 (0.78-3.21)	0.103	56.0%
After 2001	4	0.88 (0.70-1.10)	0.972	0.0%
Air population				
Pilots	5	1.11 (0.75-1.62)	0.084	51.3%
Cabin crew	2	0.90 (0.63-1.31)	0.678	0.0%
Cancer site				
Brain	2	1.77 (0.53-5.89)	0.033	77.9%
Brain/nervous system	4	0.92 (0.70-1.20)	0.788	0.0%
Nervous system	1	0.87 (0.53-1.21)	-	-
Gender				
Male	6	1.19 (0.80-1.78)	0.166	36.1%
Female	1	0.85 (0.46-1.25)	-	-

significant association between aircrew employment and BNSC risk, the possibility that the healthy worker effect (HWE) might influence this association should be considered. Epidemiological studies on worker cohorts are usually influenced by a selection bias known as HWE,[23] which presumptively derives from a screening process, allowing relatively healthy people to become or remain workers. When workers are compared with the general public, the bias from HWE arises and is likely to result in underestimation of the risk. This may explain, at least in part, the reason why there is no link between employment as an aircrew and BNSC risk.

This meta-analysis of 7 studies (5 cohort studies and 2 pooled analyses) involving more than 99 047 participants with 87 new cases improved the statistical power and therefore observed a more reliable risk estimate of BNSC among aircrew. All studies included in this meta-analysis had a cohort design, which could reduce the recall and selection bias. In addition, neither the heterogeneity nor the publication bias were significant across the included studies. Moreover, incidence is a better risk indicator, because mortality is reduced for several cancers, including BNSC, with a higher chance of recovery in case of early diagnosis.

There were several limitations in this meta-analysis. First, regarding the general public as a reference was likely to result in underestimation of the cancer risk among workers due to HWE. Moreover, the possibility of publication bias and potential clinical heterogeneity remained an intractable issue for this meta-analysis due to the limited number of qualified studies.

Conclusion

In conclusion, the currently available evidence is not sufficient to support a significant positive association between employment as aircrew and BNSC risk. However, the interpretation and extrapolation of this meta-analysis are restricted by the possible impact exerted by health worker effect and potential clinical heterogeneity; therefore, rash conclusions that employment as aircrew is not associated with BNSC risk simply cannot be drawn based on current evidence. More rigorous prospective studies with larger sample sizes and more ethnic groups, including an Asian population, are required.

Authors' Contributions

TL, CZ, SW, and JZ designed and conducted the research, analyzed the data, and wrote the draft. All authors read, reviewed, and approved the final manuscript. TL had primary responsibility for the final content.

Conflict of Interest Disclosures

No conflicts of interest.

Ethical Approval

Not applicable.

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Research Highlights

What Is Already Known?

Flight-based employees have been deemed to have a higher risk of cancer owing to occupational exposures, mainly cosmic ionizing radiation, circadian disruption, and extremely low frequency electromagnetic fields.

What This Study Adds?

The current evidence is not sufficient to support a significant positive association between employment as aircrew and BNSC risk. More studies based on other populations, including an Asian aircrew, are warranted.

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