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SYSTEMATIC REVIEW OF THE EPIDEMIOLOGY OF A SINGLE PHYSICAL TRAUMA AND CANCER

Damien M McElvenny[a.b]*, Alice Davis[a], Ken Dixon[a], Carla Alexander[a], Girish Gupta[c], Ioanna Nixon[d,e], Joanne O Crawford[a]

[a]Research Division, Institute of Occupational Medicine, Edinburgh, UK

[b]Centre for Occupational and Environmental Health, University of Manchester, Manchester, UK

[c]University Department of Dermatology, NHS Lothian, Edinburgh, UK

[d]NHS Greater Glasgow & Clyde, Glasgow, UK

[e]School of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK

*Address for correspondence:

Prof. D. M. McElvenny PhD

Institute of Occupational Medicine

Research Avenue North

Riccarton

Edinburgh EH14 4AP

Damien.McElvenny@iom-world.org

Tel: +44 (0) 131 449 8085

Fax: +44 (0) 131 449 8084

Twitter: @DamienMcElvenny

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ADDITIONAL INFORMATION

As this was a systematic review of published data, no ethical approval or consent were required.

Consent to publication is not required as the manuscript contains no personal information.

All the data used in this report are publicly available or can be derived from such.

None of the authors have a conflict of interest.

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Authors' contributions: Damien McElvenny and Joanne Crawford co-led the project. Ken Dixon was responsible for designing and implementing the literature search strategy. Alice Davis and Carla Alexander extracted the data from the included studies, under supervision of Damien McElvenny and Joanne Crawford. Girish Gupta and Ioanna Nixon were responsible for medical input into the interpretation of the findings. All authors were involved in the writing of the final manuscript.

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BACKGROUND

Physical trauma is defined as a body wound produced by sudden physical injury from impact, violence or accident. The two main types of trauma are blunt force trauma (when an object or force strikes the body, often causing concussions, lacerations or broken bones) and penetrating trauma (when an object pierces the skin or body, creating an open wound). In their landmark review for the US Congress of the causes of cancer, Doll and Peto's only mention of trauma or injury was in relation to cancer of the cervix uteri arising from the trauma of childbirth[1]. A fairly recent editorial that updated their work did not mention either trauma or injury as a cause of cancer[2]. An overview by the International Agency for Research on Cancer (IARC) on preventable exposures associated with human cancers also made no mention of trauma or injury as a cause of cancer[3].

At the outset of our review, concern was expressed by the funders of this research mostly in relation to skin cancer at the site of burns and bone cancer at the site of bony injuries or fractures. The expectation was that, were the epidemiological evidence to be sufficient to determine causality, and the traumatic exposures occurred as a consequence of work, then these cancers might be compensable as work-related.

Thus, the aim of this review was to carry out a systematic review of the available literature on trauma or injury and cancer, carrying out meta-analyses where possible, in order to determine whether physical trauma at any age was a cause of cancer.

MATERIALS AND METHODS

Literature search terms were first trialled by running the searches in online databases. The databases searched and the search terms used for the wider literature search are set out in Table 1. The searches were carried out in June 2016. As well as single physical trauma, the search terms also searched for the traumatic consequences of an assault on the body, such as surgery, but these are not included in this paper. Titles and abstracts were initially screened independently by two reviewers to eliminate those papers not relevant. Those seemingly meeting the inclusion criteria were carried forward for full paper review.

The inclusion criteria were epidemiological cohort and case-control studies of primary malignant tumours, where a physical trauma was of interest. There were no age restrictions on the populations studied or language restrictions on the papers identified. Where pooled studies were included, their constituent studies were included, but not included in any meta-analyses to avoid duplication. Ecological and cross-sectional studies were included in the qualitative assessment of the evidence, but case series and case reports were excluded.

A data-extraction sheet was developed to include sections on: screening for relevance (include/exclude), including reasons for exclusion; research question(s) being addressed; study specifics (study population, exposure period, case ascertainment, exposure data, factors adjusted for, outcome, results); quality criteria for cohort and case control studies (applied Newcastle-Ottawa scale)[4]; relevant papers identified in the bibliography; and additional notes and comments.

Four reviewers from the project team undertook a pilot of the data-extraction sheet with a sample of papers, firstly to test the application of the inclusion/exclusion criteria and secondly to establish if there was consistency in data extraction. The initial testing of the inclusion/exclusion criteria identified only one paper where there was some confusion over inclusion. From this, via discussion, it was identified where the data-extraction

sheet needed slight adaptations. The subsequent testing of the data extraction found no discrepancies and so no further changes were made.

The data extraction for each paper was undertaken independently by two reviewers. Through this process the papers identified through initial screening were either included, as they informed the findings of the current review and therefore had their data extracted, or excluded. Where there were inconsistencies in the decision to include or exclude, a third reviewer was consulted and, if this did not lead to consensus, this reviewer's view, which now was also the majority view, was adopted. Figure 1 presents the PRISMA diagram of the study selection process.

The Newcastle-Ottawa criteria for cohort and case-control studies[4], were used to assess study quality, and both scales scored studies on a scale of zero to nine.

Where there were a sufficient number of risk estimates, a meta-analysis[5] was carried out and reporting was according to the MOOSE guidelines[6]. Where relative risks adjusted for confounders were presented, these were preferred to unadjusted risk estimates, as were lagged relative risks that attempted to account for cancer latency. A fixed-effect analysis was carried out in the presence of a lack of statistically significant heterogeneity and, if significant heterogeneity was present, a random-effects analysis was carried out[7]. The variation attributable to heterogeneity was assessed using the Cochran chi-squared statistic, although it is acknowledged as having limited statistical power[8].

If the outcomes under study are rare in all populations and subgroups under review, one can generally ignore the distinctions among the various measures of relative risk (e.g. odds ratio, rate ratio and risk ratios)[9]. Thus, all effect measures were combined into a single meta-analysis, but as this approach remains controversial they were also analysed separately. An assessment of the robustness of any findings was made by examining important subgroups of the data, for example, cohort and case-control studies examined separately; and the exclusion of lower quality studies (as determined by assessment

using the Newcastle-Ottawa Scale[4]). Publication bias was assessed using funnel plots[10] and Egger's test[11]. All analyses were carried out using the statistical package Stata[12].

RESULTS

Brain cancer following traumatic brain injury

The cohort studies are summarised in Table 2 and the case-control studies in Table 3. A total of 5 cohort studies[13-17] and 16 case-control studies[18-33] were identified for potential inclusion in the review. Several case-control studies were excluded[18, 19, 29, 31, 32] because they appear in the international case-control studies co-ordinated by the International Agency for Research on Cancer[30], and one[22] because of overlapping coverage with an earlier study[13] that was deemed to have a larger case coverage, leaving 5 cohort studies and 8 case-control studies that were included in a meta-analysis. The earliest study was published in 1979[13] and the most recent in 2015[16]. There was a range of definitions of head trauma. Some studies described a head injury involving loss of consciousness, amnesia or a skull fracture, others relied on a self-reported head injury requiring medical treatment and some simply a traumatic brain injury. Most studies included all brain tumours in the follow-up period whereas some excluded brain cancers occurring less than 12 months since the traumatic brain injury, and other studies seemed to ignore the potential for reverse causality and included all brain cancers occurring after the exposure incident. Other studies used longer latencies to examine the effect. The earlier studies in particular presented analyses unadjusted for potential confounders, although given the lack of knowledge of risk factors for brain cancer, this may not be too problematic. Some presented results for all brain cancers combined and other by diagnostic subgroup, chiefly glioma and meningioma. The relative risks ranged from a potential protective effect with a relative risk of 0.32 for glioma[16] to a highly statistically significant excess for a relative risk of over 16 for meningioma[26]. Newcastle-Ottawa Scale scores ranged from 2 to 7.

For the meta-analysis of all brain cancers combined, a fixed effect analysis gave a meta-relative risk (meta-RR) for all risk estimates combined of 1.15 (95% confidence interval (CI): 1.06 to 1.25). However, this was in the presence of significant heterogeneity among

all studies ($p<0.001$) and between cohort and case control studies ($p = 0.014$). The random effects meta-analysis gave a meta-RR for cohort studies of 1.19 (95%CI: 0.88 to 1.61) and for case-control studies of 1.58 (95%CI: 1.09 to 2.29). The forest plot for this analysis is shown in Figure 2 and a funnel plot to examine the potential for publication bias is shown in Figure 3. The funnel plot and the Eggar' test p-value of 0.47 suggest no strong evidence of publication bias. To examine the robustness of the finding for the case-control studies, each was excluded in turn and the meta-RR re-calculated. Only for the exclusion of one study which had the highest relative risk[25] did the statistical significance of the meta-RR disappear.

In order to further explore the excess found in particular from the case-control studies, separate analyses were carried out for the two main histological subtypes of brain cancer, namely glioma and meningioma. For glioma there was significant heterogeneity between the studies and the random effects analysis gave meta-RRs of 0.96 (95%CI: 0.49 to 1.88) and 1.53 (95% CI: 1.02 to 2.27) for cohort and case-control studies respectively. Given marginal statistical significance for the case-control studies, it is not surprising that the statistical significance disappears when many of the studies with raised odds ratios are removed in turn from the analysis. For meningioma, there was also statistically significant heterogeneity between studies, with the random effects analysis producing meta-RRs of 1.22 (95% CI 0.95 to 1.76) and 1.88 (0.84 to 4.19) respectively, suggesting that if there exists an excess relative risk, it may not necessarily be restricted to glioma. Thus there is suggestive human epidemiological evidence that traumatic brain injury increases the subsequent risk of developing brain cancer, whether glioma or meningioma.

Malignancies in scars of burns and burns in general

Three population-based cohort studies have examined skin cancer at the site of burns. The Hospital Discharge Register in Denmark was used to identify 18,008 patients with thermal or chemical burns during 1978 to 1993[34]. The cohort was linked to the Danish

Cancer Registry, with follow-up to the end of 2002. The standardised incidence ratio (SIR) for malignant melanoma was 0.7 (95%CI: 0.4 to 1.1). For squamous cell carcinoma, the SIR was 0.9 (95% CI: 0.6 to 1.5) and for basal cell carcinoma it was 0.7 (95% CI: 0.6 to 0.9). None of these differed materially by sex or age at time of injury. The authors also conducted an analysis of skin cancers confined to the burned area of the body. SIRs were 0.7 for malignant melanoma in men and women, 0.8 and 1.2 respectively for squamous cell carcinoma, and 0.7 and 0.8 for basal cell carcinoma, respectively, for all burned sites combined. These risks did not differ materially by the severity of the lesion, or between persons with and without skin transplants.

A historical cohort study was conducted in Swedish patients with burn injuries[35]. Using the national Inpatient Registry, 37,095 patients were identified who had been hospitalised for burn injuries. The cohort was linked to the Swedish Cancer Registry for virtually complete follow-up. The SIRs for squamous cell carcinoma and malignant melanoma were not elevated with values of 0.88 (95% CI: 0.70 to 1.09) and 0.88 (95%CI: 0.69 to 1.12) respectively.

A population-based retrospective cohort study was carried out using record-linkage systems in Scotland and Australia to investigate the risk of cancer in persons hospitalised with burn injury during 1983 to 2008[36]. The cohort consisted of 61,340 persons. This study did not focus on skin cancers at the sites of the burns, but on overall cancer incidence in the cohort. The SIR for malignant melanoma in Western Australia for males and females combined was 0.7 (95% CI: 0.6 to 0.8) and for Scotland the SIR was 0.8 (95% CI: 0.6 to 1.1).

Thus overall, there is no epidemiological evidence that burns victims are at increased risk of any type of skin cancer, either in general or specifically at the site of the burn.

Osteosarcoma arising from bone injuries

A case-control study of 64 cases aged under 25, and 124 friend and neighbour controls individually-matched on sex, race and birth year was carried out[37]. Questionnaire data

were obtained through telephone interviews with mothers and family physician and school records. Only injuries, and bone conditions requiring attention at least one year before diagnosis were considered. The relative risk for fractures or other bone injuries (presumably such as dislocations, crush Injuries, and bone wounds) at any site was 1.0 (95% CI: 0.5 to 1.8). For fracture or other bone injury at the tumour sites, the relative risk was 5.5 (95% CI: 1.1 to 28.1), based on six cases and three controls. However, none of the injuries among the cases were fractures and there was little data to evaluate the severity of the injury. Thus, there is little epidemiological evidence that bony fractures increase the subsequent risk of bone cancer.

Sinonasal and nasopharyngeal cancers as a result of nose injuries

A population-based case-control study was carried out in the USA[38]. Cases in California were diagnosed with nose, sinus or nasopharyngeal cancer between 1979 and 1985 and were obtained from local tumour registries. Controls were individual matches to cases on age, sex, race and area of residence. The final study included 178 case-control pairs (54 nose, 44 sinus, 82 nasopharynx). Analyses were carried out using conditional logistic regression. The relative risk for nasopharyngeal cancer for a single injury was 2.2 (95% CI: 0.8 to 5.7). For nose cancer the odds ratio was 0.8 (95% CI: 0.3 to 2.0) and for sinus cancer was 0.8 (95% CI: 0.2 to 3.4). Thus, there is no epidemiological evidence that nose injuries increase the risk of subsequent airway tract cancers.

Testicular Cancer following testicular trauma

A case-control study of 271 men with testicular cancer and 259 controls was conducted in the USA[39]. Cases were newly diagnosed between 1976 and 1981. Controls were patients in the same hospital as the cases, diagnosed with a malignancy other than cancer of the genital tract. It is not clear if they were individually- or frequency-matched. Face-to-face interviews were conducted at the hospital, using a standardised questionnaire. Odds ratios were calculated using the Mantel-Haenszel method, adjusting for the stratification variables and age at diagnosis. The relative risk for study

subjects reporting a history of trauma to the testis was significantly elevated with odds ratio 2.3 (95% CI: 1.3 to 4.1) and remained elevated when traumas in the two years before cancer diagnosis were removed from the analysis.

A descriptive epidemiological study of 1,116 cases of testicular cancer among Australian residents has been carried out[40]. The frequency of recorded history of trauma was 219/782 (28%) with a higher proportion among non-seminomatous germ cell histologies (32%) than among seminoma (25%) patients. The median interval between trauma and date of diagnosis was 1 year or less, with a range of 0 to 61 years.

A population-based case-control study was carried out in Germany including 269 cases and 797 controls[41]. Excluding reports of trauma within 12 months of the index date, the odds ratio for trauma was 2.1 (95% CI: 1.24 to 3.61). Restricting the analysis to testicular trauma yielded an odds ratio of 3.49 (95% CI: 1.78 to 6.81). Restricting attention to those episodes where medical attention was sought yields an odds ratio of 0.70 (0.19 to 2.63). Thus, there is very limited epidemiological evidence that testicular trauma increases the subsequent risk of testicular cancer.

Breast Cancer following breast trauma

A UK case-control study of female breast cancer was carried out during 1996 to 1998[42]. Cases were 67 women aged 50-65 with invasive breast carcinoma confirmed by biopsy. Two controls per case were individually matched on age, age of menarche and age of first birth, and were recruited at routine mammography. A short questionnaire was completed giving details of date of birth, age at menarche and menopause, parity and family history of breast cancer. Additional data were collected on life-course events, residential, occupational and reproductive histories, along with lifestyle factors such as smoking, alcohol consumption and stress. The cases reported significantly more physical trauma to the breast in the five years before screening than did the controls. The odds ratio for physical trauma to the breast was 3.3 (95% CI: 1.3 to 10.8).

A retrospective case-control study was carried out in Jordanian women[43]. Cases were obtained from the Jordanian Cancer Registry for 1996. Of the total sample of 451, 156 were dead, 170 could not be traced, 17 were diagnosed before 1996, and 8 refused to participate in the study, leaving 100 cases. A convenience sample of 100 controls matched on age, parity, level of education and place of residence was recruited. A culturally sensitive questionnaire was administered to the cases and controls. Analysis was via logistic regression. Twenty five per cent of the 100 case participants reported trauma to the breast: 21% more than once. Seventy three per cent reported that the trauma was to the affected breast. Only 6% of the 100 control participants reported breast trauma. The univariable odds ratio was 5.01 (95% CI: 1.97 to 12.96). However, a multivariable model fitted to the data did not include trauma of the breast as a significant risk factor. Thus, there is limited epidemiological evidence that breast trauma is a risk factor for the subsequent development of breast cancer in women.

DISCUSSION

We believe this is the first wide-ranging review of the epidemiology of single physical trauma and cancer. We found little epidemiological evidence for skin cancer at the site of burns or bone cancer at the site of fractures. We also found little or no evidence for sinonasal and nasopharyngeal cancers as a result of nasal injury, testicular cancer following testicular trauma, and breast cancer following breast trauma. The association for which the evidence was strongest, was for brain cancer, in particular glioma following traumatic brain injury.

Overall, there appears to be a lack of aetiological epidemiological studies examining physical trauma and resulting cancer. We updated our search to cover the years following our original search until November 2020 and found no additionally relevant publications. This is in spite of there being interest in trauma as a potential cause of cancer for many decades. For example an editorial in the 1960s states that the issue had been a concern for the medical profession for many years[44]. More recently, a 1980s editorial suggested that trauma had been regularly proposed as an aetiological factor for malignant melanoma for several decades, but made no specific mention of burns[45].

Some of the studies considered in this review did not explicitly exclude the occurrence of multiple trauma episodes to the same site. Also, where relevant, most studies adjust did not adjust for the potential confounding effects of the trauma of undergoing surgery.Glioma is the most common primary intracranial cancer accounting for around 80% of all malignant brain cancers[46], but few established risk factors have been robustly identified[47]. Aside from demographic risk factors such as age and sex, ionising radiation is the only established cause for glioma, although recent evidence suggests that the risk may be higher for meningioma[48]. Few studies adjusted for the potential carcinogenic effects of diagnostic or therapeutic X-ray or CT scans of the brain.

There is some evidence that viruses such as cytomegalovirus increase the risk of brain cancer[49] and allergic conditions may be associated with a reduced risk[50]. Recent

evidence is against obesity and related traits as being significant risk factors for glioma[51]. Mobile phones have not been found to increase the risk of glioma or meningioma[52] and nor has tobacco smoking[53].

Inflammation plays critical and complex roles after injury. It is needed for healing, but can also lead to complications. Studies of gene activity show that severe injury alters a large number of genes and the extent of the genetic damage varies considerably between individuals[54]. Chronic inflammation, along with the resulting genetic polymorphisms, may thus be associated with an increased cancer risk. Genetic polymorphisms also occur after damage to bones with the potential for an increased cancer risk[55].

There was no formal assessment of risk of bias carried out as part of this study, and the Newcastle-Ottawa scale has received some criticism[56]. Many of the studies included in this review, considered physical trauma as one of a number of potential risk factors considered in their analyses. It is notable, that the meta-RR for case-control studies was slightly higher than that for cohort studies, suggesting a possible role for recall bias in elevating the odds ratios for those studies where the participants knew or suspected the hypothesis being investigated. Even if registry data were available, such as those in Trauma Audit and Research Network (TARN) [57], it would be difficult to isolate a single trauma to relate to a subsequent cancer diagnosis. The variation in the definition of head trauma and a small number of studies dealing with latency further undermines the finding.

CONCLUSIONS

In conclusion, we found suggestive evidence of an increased risk of brain cancer, mainly in relation to glioma rather than meningioma and recommend that further epidemiological studies, perhaps utilising trauma registries should be carried out.

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Table 1 – Databases searched and search terms

NIOSHTIC-2, OLDMEDLINE and ProQuest Dialog Healthcare databases were searched including Current Contents; BIOSIS; ProQuest Dissertations and Theses Professional; EMBASE; MEDLINE; Scisearch; and Psychinfo. The search string used for the above bibliographic databases was: (trauma OR injury OR hurt OR wound OR wounding OR sore OR bruise OR cut OR laceration OR lesion OR abrasion OR contusion OR “heat trauma” OR “cold trauma” OR “UV trauma” OR “noise trauma” OR “multiple trauma exposures” OR “chemical trauma” OR “heat strokes” OR (exposure AND wind) OR (exposure AND solar) OR burn OR fracture) AND (cancer OR neoplasm OR neoplasms OR tumour OR tumours OR tumour AND (“systematic review” OR review OR “cohort study” OR “case-control study” OR “case-referent study” OR meta-analysis OR “cross-sectional-study” OR “ecological study”) The Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts on Reviews of Effects (DARE) were searched using the search string: trauma AND cancer. Grey literature searches were carried out in Google; Google Scholar; New York Academy of Medicine’s Grey Literature Report; and Open Grey.

Web site Searches were undertaken using the following web sites: IARC; Cancer Research UK; NCI; CDC; IOSH; WHO; CCSRI; Canadian Cancer Society; BC Cancer Agency; and Australian Cancer Research. The search string used was (trauma OR injury OR wound) AND cancer AND epidemiology.

Table 2 – Cohort studies of brain cancer following traumatic brain injury

Reference	Study Type	Study Population	Traumatic event	Exposure Period	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Annegers *et al*, 1979[13]	Retrospective cohort study of patients	2,953 survivors of significant head trauma	Head injury with brain involvement manifested by loss of consciousness, amnesia or skull fracture	1935 to 1974	Age, sex, calendar year	All brain 1.0 (0.3 to 2.6, 4) Glioma 0.7 (0.0 to 5.6, 1) Meningioma 1.6 (0.3 to 4.7, 3)	6

Reference	Study Type	Study Population	Traumatic event	Exposure Period	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Inskip *et al*, 1998[15]	Retrospective cohort study of patients	228,055 patients in Denmark hospitalised because of concussion, fractured skull or other head injury	Fractured skull, concussion or cerebral laceration or contusion	1977 to 1992	Age, sex, calendar year	>1 year since discharge Intracranial tumours 1.1 (1.0 to 1.3, 199) Glioma 1.0 (0.8 to 1.2, 79) Meningioma 1.2 (0.8 to 1.7, 30)	6

Reference	Study Type	Study Population	Traumatic event	Exposure Period	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Nygren *et al*, 2001[17]	Retrospective cohort study of patients	311,006 patients hospitalised for traumatic brain injury	Skull trauma	1965 to 1994	Age, sex, calendar year	>1 year since discharge Primary brain cancer 1.0 (0.8 to 1.1, 161)	6

Reference	Study Type	Study Population	Traumatic event	Exposure Period	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Chen *et al*, 2012[14]	Retrospective cohort study of patients and a comparison cohort matched on age, sex and index year	5,007 patients who had visited ambulatory care centres or had been hospitalised with a diagnosis of TBI and 25,035 controls randomly selected from a national health insurance	Traumatic brain injury	2001 to 2002	Geographic location, urbanisation, monthly income	The RR of brain cancer within 3 years of follow-up was 4.67 (1.84 to 11.83, 9) for the TBI versus non-TBI cohort.	7

Reference	Study Type	Study Population	Traumatic event	Exposure Period	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		research database					
Munch *et al*, 2015[16]	Retrospective cohort study of patients with TBI and the general population	48,194 patients with a traumatic brain injury	TBI	1978 to 2001	Age, sex, calendar year	Glioma 1-4 years after TBI 1.99 (1.00 to 3.50, 10) Glioma 5+ years after TBI 0.32 (0.10 to 0.75, 4)	6

Table 3 – Case-control studies of brain cancer following traumatic brain injury

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Choi *et al*, 1970[21]	Retrospective hospital-based case-control study	157 central nervous system cancer cases; 157 hospital-matched controls with condition other than cancer, neurologic, ophthalmic or lymphatic condition. Matching	Brain injury such as fractured skull unconsciousness, or bleeding from the head requiring hospitalisation and/or operation	1963 to 1964	None	All brain 0.84 (0.32 to 2.20, 8) All glioma 1.34 (0.35 to 5.21, 5) Meningioma 0.52 (0.04 to 6.22, 1) [Not provided in the paper, so calculated using	3

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		variables included hospital, sex, age, race, area of residence and urban status.				unmatched method]	
Preston-Martin *et al*, 1980[29]	Population-based case-control study	185 women with intracranial meningioma and 185 neighbourhood controls matched on sex, age and race	Medically treated head trauma	1972 to 1975	Results unadjusted, but an additional analysis adjusting for head X-rays didn't alter findings	RR 2.0 (1.2 to 3.5, not stated)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Preston-Martin *et al*, 1983[31]	Population-based case-control study	105 men with intracranial meningioma and 105 neighbourhood controls matched on sex, age and race	Serious head injury and/or boxing	1972 to 1979	Results unadjusted	RR 1.9 (1.1 to 3.2, 40)	4
Hochberg *et al*, 1984[24]	Retrospective population-based case-control study.	160 cases of glioblastoma and 125 population controls, known but not related to the cases,	Severe head injuries were those resulting in skull fracture or concussion followed by a	1977 to 1981	None.	RR all trauma 2.1 (1.1 to 4.0, 35)	5

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		matched on sex, age and area of residence	complication; Mild head trauma included concussion or brief loss of consciousness with no complications.				
Ahlbom *et al*, 1986[18]	Hospital- and population-based case-control study	79 astrocytoma cases with 197 unmatched clinical controls having a diagnosis of meningioma,	Head injuries not within 5 years of tumour	1980 to 1981	None	Astrocytoma 1.6 (0.7 to 3.9, 12) (population controls) 1.2 (0.6 to 2.5, 12) (clinical controls)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		pituitary adenoma or cerebral aneurysm and 92 population controls matched on age, sex and location of residence.					
Carpenter *et al*, 1987[20]	Nested case-control study of brain cancer in two nuclear facilities	82 cases and 328 controls matched on race, sex, facility, year of birth and year of hire	Head injury (from occupational health records)	1943 to 1979	Socioeconomic status	0.9 (0.2 to 4.2, 2)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Burch *et al*, 1987[19]	Hospital-based case-control study	215 cases of glioma ad 215 non-cancer hospital controls matched on age, sex area of residence, year of birth, year of diagnosis/death	Brain injury or accident	1977 to 1981	None	RR 2.51 (2.09, 3.02) RR restricted to accidents requiring medical attention 1.20 (0.88 to 1.64)	4
Preston-Martin *et al*, 1989[28]	Population-based case-control study	272 males with primary brain cancer and 272 controls matched on age, sex, race	Head injury 20 years or more before diagnosis resulting in a medical visit, loss	1998-1984	None	Glioma 0.8 (0.5 to 1.3, 202) Meningioma 2.3 (1.1 to 5.4, 70)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		and area of residence	of consciousness or dizziness			A significant increasing exposure response was seen for number of serious injuries for meningioma	
Codd *et al*, 1990[22]	Population-based case-control study	100 cases of glioma and 200 population controls matched on age and sex	Head trauma	1950 to 1977	None	1.7 (0.5 to 6.9, 4)	6

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Schlehofer *et al*, 1992[32]	Population-based case-control study	226 cases of primary brain cancer with 418 controls frequency matched on age and sex from same area	Head injury involving consultation with a doctor at least 5 years prior to interview	1987 to 1988	None, although multivariable regression gave same resultss	All brain cancer 0.71 (0.5 to 1.1, 39) Glioma 0.70 (0.4 to 1.2, 27) Meningioma 0.52 (0.3 to 1.0)	5
Zampieri *et al*, 1994[33]	Hospital-based case-control study	195 cases glioma and 195 controls, matched on age, sex, date of hospitalisation and residence.	Mild (brief loss of consciousness) and sever (loss of consciousness of > 1 hour, neurological	1986 to 1988	None	Glioma 0.7 (0.3 to 1.4, 31)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		Controls had a variety of non-malignant diagnoses	deficits, epilepsy, cranial fracture or any neurosurgical procedure)				
Preston-Martin *et al*, 1998[30]	Multi-centre international population-based case-control study	1178 cases of glioma; 330 meningioma cases and 2236 population controls, mixture of individual and frequency matched on age, and sex, with	Medically treated head injury	1984 to 1992	None (multivariable adjusted latency analysis presented in Table 4 of paper)	Male, meningioma 1.49 (0.86 to 2.57, 26) Female meningioma 0.83 (0.54 to 1.28, 33)	2

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		some additionally matched on race and residence				Male glioma 1.18 (0.94 to 1.48, 210) Female glioma 1.03 (0.42 to 2.55, 87)	
Hu *et al*, 1998[25]	Hospital-based case-control study	218 cases of glioma and 436 individually-matched controls with non-neoplastic or non-neurological disease, matched	Head trauma requiring medical attention	1989 to 1995	Income, education, number of years drinking liquor, occupational exposure, fruit and vegetable consumption.	5.90 (.251 to 10.31, 34)	5

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		on age, sex and area of residence					
Hu *et al*, 1999[26]	Hospital-based case-control study	218 cases of glioma and 436 individually-matched controls with non-neoplastic or non-neurological disease, matched on age, sex and area of residence	Head trauma requiring medical attention	1989 to 1996	Income, education, occupational exposure, fruit and vegetable consumption	16.36 (5.45 to 49.12, 33)	5

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
Monteiro *et al*, 2006[27]	Hospital-based case-control study	231 adults with primary brain tumour and 261 hospital controls matched for gender, age and hospital diagnosed with a condition unrelated to brain tumours	Head injury at least 1 year prior to diagnosis (cases) or hospitalisation (controls)	1999 to 2002	Age, gender, schooling, epilepsy, alcohol consumption	All brain cancer 1.49 (1.03 to 2.15, 107) Glioma 1.30 (0.71 to 2.35, 31) Meningioma 1.63 (0.96 to 2.75, 38)	6
Gousias *et al*, 2009[23]	Population-based case-control study	56 cases of glioma; 112 controls matched	Cranial trauma	Not defined	Alcohol, smoking, mobile phone use	3.74 (0.30 to 47.29, 41)	4

Reference	Study Type	Study Population	Traumatic event	Case ascertainment	Factors accounted for in analysis	RR (95% CI, number of (exposed) cases)	Quality Score (NOS)
		on age, sex and area of residence					

Figure 1 - PRISMA Diagram

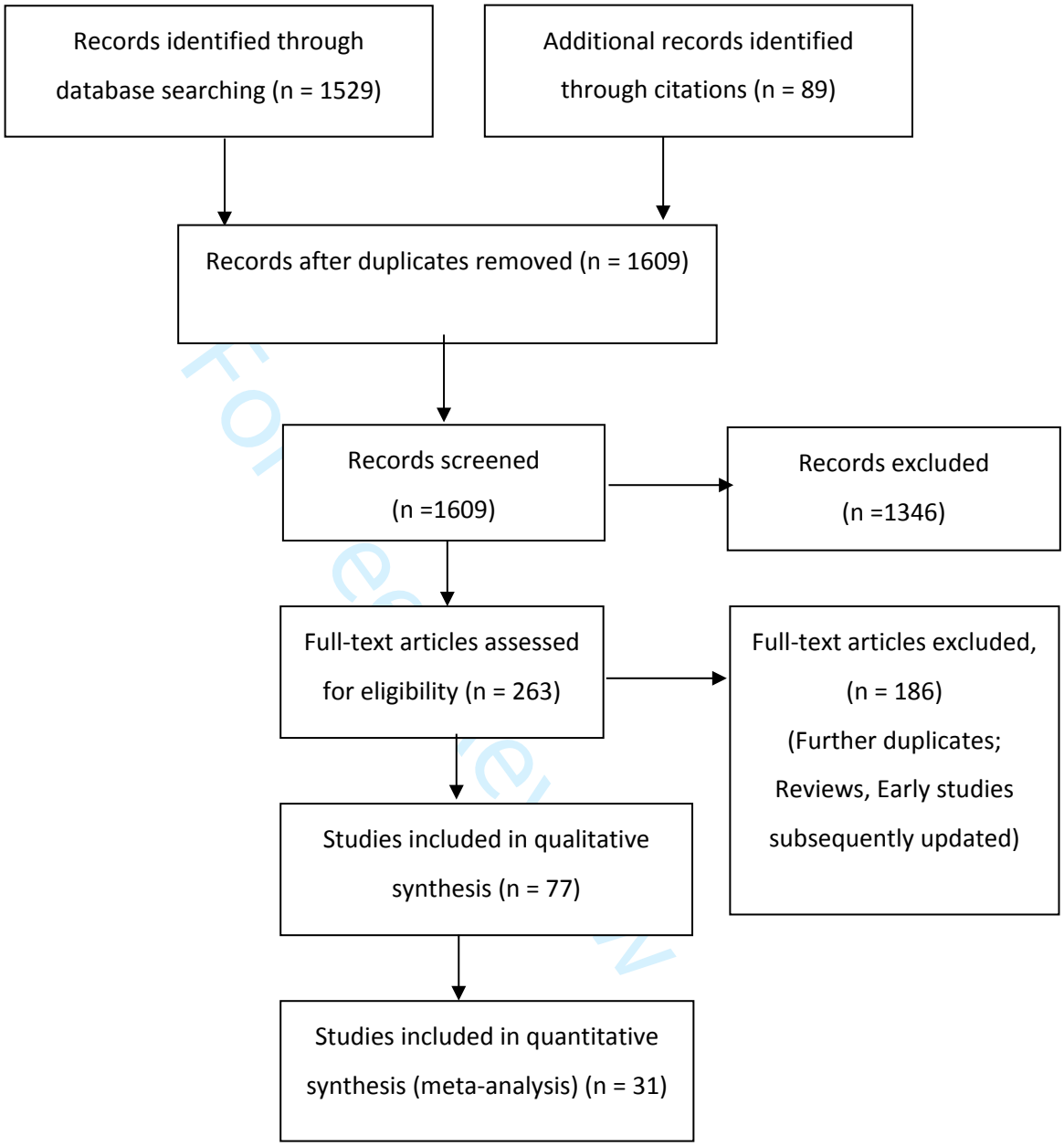

Figure 2 – Random effects meta-analysis for traumatic brain injury and brain cancer

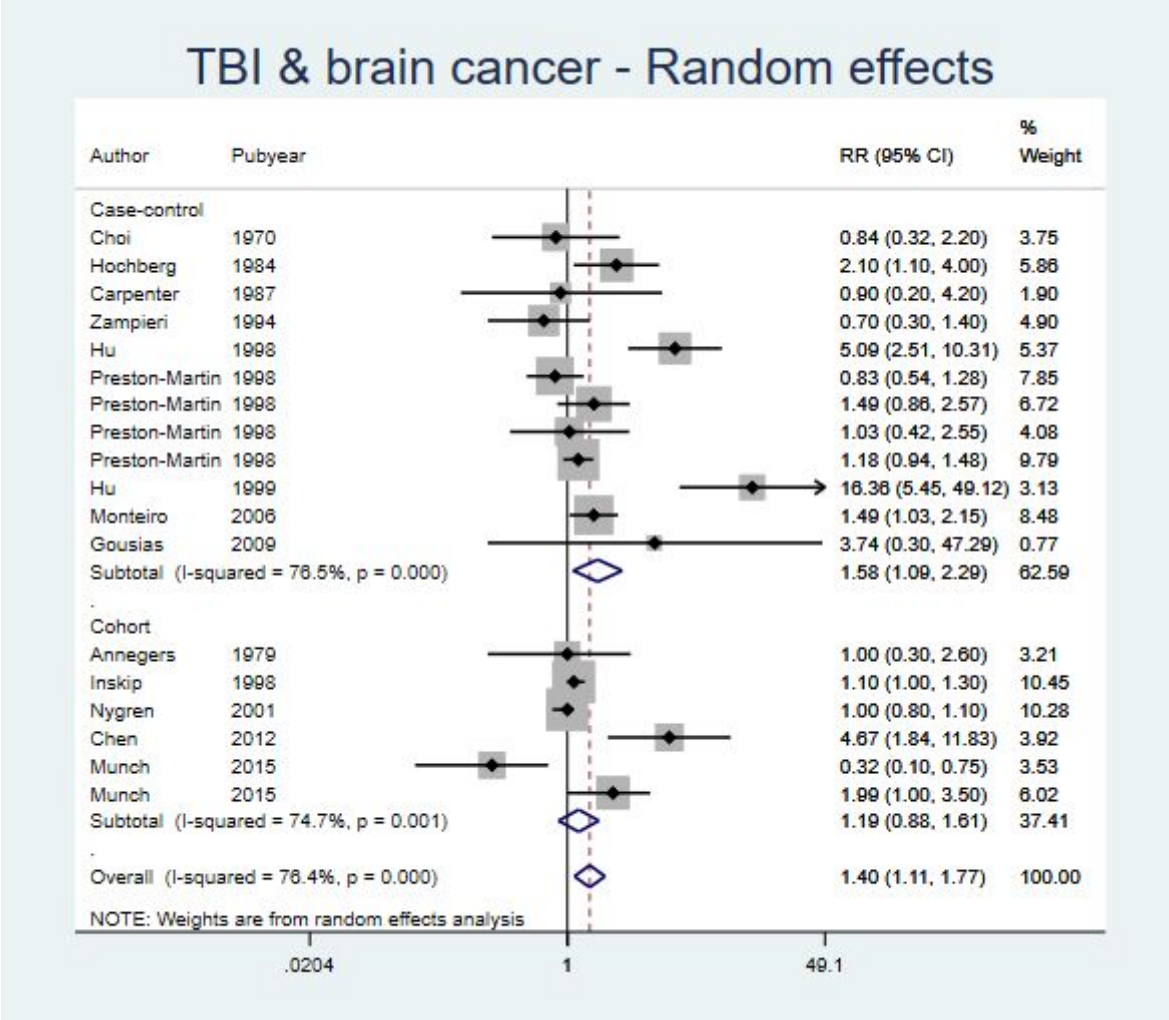

Figure 3 – Funnel plot for brain cancer meta-analysis