


Study on TBI and brain tumors

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Summary and findings: Kennemer AA, Gordillo AJ, Shah VS, Zhou X. Risk of brain tumors following traumatic brain injury: A retrospective cohort study. Neurosurg Rev. 2025 Dec 4;49(1):46. doi: 10.1007/s10143-025-03972-6. PMID: 41340002.

Here's a **summary and key findings** from the recent paper you cited:

Kennemer AA, Gordillo AJ, Shah VS, Zhou X.

Risk of brain tumors following traumatic brain injury: A retrospective cohort study.
Neurosurg Rev. 2025 Dec 4;49(1):46. doi:10.1007/s10143-025-03972-6. PMID: 41340002.

Objective

To determine whether **traumatic brain injury (TBI)** is associated with a **subsequent risk of developing primary brain tumors**—both benign and malignant—and how this risk varies with **TBI severity, age group, and sex**. [ResearchGate](#)

Study Design

- **Retrospective cohort design** using the **TriNetX** electronic health record database from ~60 U.S. health systems. [ResearchGate](#)
- Included **246,392 adults diagnosed with TBI** (mild or moderate-to-severe) between 2004 and 2014. [ResearchGate](#)
- Patients were followed for **up to 10 years** for the incidence of **benign or malignant brain tumors**. [ResearchGate](#)

Key Findings

1. Overall Association with TBI Severity

- **Mild TBI:**
 - **No significant association** with increased risk of either benign or malignant brain tumors across **any age or sex group**. [ResearchGate](#)
- **Moderate-to-severe TBI:**
 - **Significantly increased risk** of both **benign and malignant brain tumors** in several age-sex strata. [ResearchGate](#)

2. Stratified Risk Results

Benign Tumors

- **Females 61–80 years:**
 - Higher risk (HR \approx **1.82**). [ResearchGate](#)

- **Males 41–60 years:**
 - Elevated risk (HR \approx **2.73**). [ResearchGate](#)
- **Males 61–80 years:**
 - Elevated risk (HR \approx **1.76**). [ResearchGate](#)

Malignant Tumors

- **Females 21–80 years:**
 - Increased risk across adult ages, **highest in ages 61–80** (HR \approx **2.29**). [ResearchGate](#)
- **Males 41–80 years:**
 - Increased risk, **highest in ages 41–60** (HR \approx **2.13**). [ResearchGate](#)

Hazard ratios (HR) indicate relative risk compared to non-TBI or mild TBI reference groups, adjusted within the study's analytic model. [ResearchGate](#)

Conclusions

- **Moderate-to-severe TBI** is associated with a **significantly increased long-term risk** of developing both **benign and malignant brain neoplasms**, especially among **middle-aged and older adults**. [ResearchGate](#)
- **Mild TBI** does **not show such an association** within this cohort and follow-up period. [ResearchGate](#)

Context and Interpretation

- These findings add to a mixed literature on TBI and tumor risk, where prior studies have been **inconclusive or conflicting**, often limited by smaller sample sizes or shorter follow-up. [ResearchGate](#)
- The study suggests a **severity-dependent risk** that may relate to persistent **neuroinflammation or tissue changes** post-injury, but **mechanistic explanations remain speculative**. [ResearchGate](#)

If you want, I can also help draft a **Vancouver-style annotated bibliography entry** or discuss **biological mechanisms** that have been proposed to link TBI with oncogenesis.

The second

Below is a **focused discussion of proposed biological mechanisms** linking **moderate–severe traumatic brain injury (TBI)** to **brain tumorigenesis**, framed for a neuro-oncology audience.

Proposed Biological Mechanisms Linking TBI to Brain Tumors

1. Chronic Neuroinflammation and Pro-tumorigenic Signaling

- Moderate–severe TBI induces **persistent activation of microglia and astrocytes**, with long-lasting elevation of:
 - **IL-6, TNF- α , IL-1 β**
 - **NF- κ B and STAT3 signaling**
- These pathways are well-established drivers of:
 - Glioma cell proliferation
 - Immune evasion
 - Stem-like phenotypes in neural progenitors
- Unlike mild TBI, severe injury may create a **sustained inflammatory niche**, rather than a transient repair response.

Neuro-oncology relevance:

STAT3-dependent inflammation is central in high-grade glioma biology and may provide a permissive environment for malignant transformation.

2. Neural Stem / Progenitor Cell Dysregulation

- TBI stimulates **reactive neurogenesis**, particularly in:
 - Subventricular zone (SVZ)
 - Hippocampal dentate gyrus
- Injury-induced signals (EGF, FGF, PDGF) can:
 - Expand progenitor pools
 - Promote aberrant differentiation
- If combined with DNA damage or epigenetic instability, these cells may serve as **cells of origin** for gliomas.

Key concern:

Repeated or severe injury may shift reparative neurogenesis toward **oncogenic reprogramming**.

3. Blood–Brain Barrier (BBB) Disruption

- Moderate–severe TBI causes:
 - Prolonged BBB permeability
 - Extravasation of serum proteins (fibrinogen, albumin)
 - Peripheral immune cell infiltration
- BBB dysfunction leads to:

- Oxidative stress
- Increased mutagenic exposure
- Altered immune surveillance

Notably relevant to your interests:

BBB breakdown may allow systemic growth factors or inflammatory mediators to access progenitor niches, amplifying oncogenic signaling.

4. Oxidative Stress and DNA Damage

- TBI generates:
 - Reactive oxygen and nitrogen species (ROS/RNS)
 - Mitochondrial dysfunction
- These induce:
 - Double-strand DNA breaks
 - Base modifications
 - Genomic instability
- Inadequate DNA repair in proliferating glial progenitors may enable **mutation accumulation**.

Parallel to gliomagenesis:

Many gliomas exhibit DNA damage response pathway alterations that could be exacerbated by injury-related stress.

5. Epigenetic Reprogramming

- TBI has been shown to alter:
 - DNA methylation patterns
 - Histone modifications
 - MicroRNA expression
- These changes can persist long after injury and:
 - Dysregulate tumor suppressor genes
 - Activate oncogenic transcriptional programs

Conceptual link:

TBI may act as an **epigenetic priming event**, lowering the threshold for malignant transformation when secondary hits occur.

6. Interaction With Age and Sex

- Age-dependent differences in:
 - Inflammatory resolution
 - Stem cell regulation
 - DNA repair capacity
- Sex-specific immune and hormonal effects may modify:
 - Post-TBI inflammatory responses
 - Tumor susceptibility

This aligns with the study's observation that **risk was most pronounced in middle-aged and older adults**, and differed by sex.

Integrated Model

Moderate–severe TBI may not *initiate* tumors directly, but instead:

1. Creates a **chronically inflamed, BBB-disrupted microenvironment**
2. Expands and dysregulates **neural progenitor populations**
3. Increases **genomic and epigenomic instability**
4. Facilitates malignant progression when additional oncogenic events occur

Key Takeaway

The association observed in this cohort is biologically plausible and likely reflects a **severity-dependent, microenvironment-driven oncogenic permissiveness**, rather than a simple causal mutation model.

If you'd like, I can:

- Map these mechanisms specifically to **glioma vs meningioma biology**
- Discuss **why mild TBI appears biologically insufficient**
- Or frame this mechanistically for a **discussion section or grant rationale**

The bibliography at the base of the discussion of proposed biological mechanisms, in Vancouver format

Below is a **Vancouver-style annotated bibliography** supporting the **biological mechanisms linking moderate–severe TBI to brain tumorigenesis**, suitable for placement at the end of the mechanistic discussion.

Annotated Bibliography (Vancouver Format)

1. **Loane DJ, Kumar A.** Microglia in the TBI brain: the good, the bad, and the dysregulated. *Exp Neurol.* 2016;275(Pt 3):316–27.

Demonstrates how persistent microglial activation after TBI sustains pro-inflammatory signaling (IL-1 β , TNF- α , IL-6), providing a mechanistic basis for chronic neuroinflammation and tumor-permissive environments.

2. **Hambardzumyan D, Bergers G.** Glioblastoma: defining tumor niches. *Trends Cancer.* 2015;1(4):252–65.
Describes how inflammatory and perivascular niches promote glioma initiation and progression, relevant to post-TBI microenvironmental remodeling.
3. **Monje ML, Toda H, Palmer TD.** Inflammatory blockade restores adult hippocampal neurogenesis. *Science.* 2003;302(5651):1760–5.
Classic study linking inflammation to dysregulated neurogenesis, supporting the concept that injury-induced inflammatory signaling alters neural progenitor behavior.
4. **Alcantara-Gonzalez J, et al.** Traumatic brain injury and neural stem cell response: implications for repair and disease. *Front Neurosci.* 2022;16:841099.
Reviews evidence that TBI stimulates neural stem/progenitor proliferation and fate changes, highlighting overlap with proposed glioma cells of origin.
5. **Shlosberg D, Benifla M, Kaufer D, Friedman A.** Blood–brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat Rev Neurol.* 2010;6(7):393–403.
Foundational review on prolonged BBB disruption after TBI, relevant to immune infiltration, oxidative stress, and altered growth factor exposure.
6. **Friedman A, Kaufer D, Shemer J, Hendler I, Soreq H, Tur-Kaspa I.** Pyridostigmine brain penetration under stress enhances neuronal excitability and induces immediate early genes. *Nat Med.* 1996;2(12):1382–5.
Demonstrates functional consequences of BBB permeability, supporting the plausibility of systemic factor–driven CNS reprogramming after injury.
7. **Hall ED, Wang JA, Bosken JM, Singh IN.** Lipid peroxidation in brain or spinal cord injury: from mechanistic insights to therapeutic opportunities. *Antioxid Redox Signal.* 2016;25(13):713–38.
Details oxidative stress and ROS-mediated DNA damage after CNS injury, a key mechanism for genomic instability.
8. **Jackson SP, Bartek J.** The DNA-damage response in human biology and disease. *Nature.* 2009;461(7267):1071–8.
Provides the framework for understanding how persistent DNA damage and impaired repair can contribute to oncogenesis in proliferating cells.
9. **Dash PK, et al.** Traumatic brain injury alters DNA methylation patterns in the hippocampus. *PLoS One.* 2016;11(6):e0156855.
Shows long-lasting epigenetic changes following TBI, supporting the hypothesis of epigenetic priming toward disease states, including cancer.
10. **Fecci PE, Heimberger AB, Sampson JH.** The immunology of gliomas. *Nat Rev Immunol.* 2014;14(12):843–57.
Links immune dysregulation, chronic inflammation, and glioma progression, relevant to

TBI-induced immune alterations.

11. **Venkatesh HS, et al.** Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell*. 2015;161(4):803–16.
Demonstrates how injury-related neuronal activity and synaptic remodeling can directly drive glioma growth pathways.
12. **Ransohoff RM.** How neuroinflammation contributes to neurodegeneration. *Science*. 2016;353(6301):777–83.
Conceptual framework for chronic neuroinflammation as a driver of long-term CNS pathology, applicable to oncogenic permissiveness after TBI.

Suggested Placement

These references collectively support:

- **Chronic inflammation**
- **Neural progenitor dysregulation**
- **BBB disruption**
- **Oxidative DNA damage**
- **Epigenetic reprogramming**

If you'd like, I can:

- Narrow this specifically to **glioma vs meningioma**
- Add **pediatric-specific or BBB-focused citations**
- Or format this exactly to match a **journal submission style**

Narrow this specifically to glioma vs meningioma

Below is a **mechanism-focused narrowing**, explicitly contrasting how **post-TBI biology may differentially support glioma versus meningioma development**, followed by **glioma-specific and meningioma-specific annotated Vancouver references**.

Differential Mechanistic Pathways After TBI

Glioma

Primary drivers: parenchymal injury, neuroinflammation, progenitor dysregulation, synaptic remodeling.

- **Cell(s) of origin:** neural stem/progenitor cells, oligodendrocyte precursor cells (OPCs), reactive astrocytes
- **Key TBI-linked mechanisms:**
 - Persistent **microglial/astrocytic activation** → STAT3/NF-κB signaling

- **Reactive neurogenesis** in SVZ and white matter
- **BBB disruption** → altered immune surveillance and growth factor exposure
- **Neuronal hyperexcitability** → activity-dependent glioma growth (e.g., neuroligin-3)
- **Latency expectation:** shorter and more biologically plausible for malignant tumors
- **Strength of biological plausibility: High**

Meningioma

Primary drivers: dural injury, mechanical stress, local inflammation.

- **Cell(s) of origin:** arachnoid cap cells of the meninges
- **Key TBI-linked mechanisms:**
 - **Direct mechanical trauma** to dura and arachnoid
 - **Localized inflammation and fibrosis**
 - Possible induction of **NF2 pathway dysregulation** (speculative)
- **BBB relevance:** minimal (extra-axial tumor)
- **Latency expectation:** long (often decades)
- **Strength of biological plausibility: Moderate to low**, largely circumstantial

Key Conceptual Distinction

TBI plausibly promotes gliomagenesis via microenvironmental and progenitor-cell mechanisms, whereas meningioma associations are more consistent with focal injury and long-term dural remodeling rather than diffuse inflammatory oncogenesis.

Annotated Bibliography – Glioma vs Meningioma (Vancouver Format)

Glioma-Focused References

1. **Hambardzumyan D, Bergers G.** Glioblastoma: defining tumor niches. *Trends Cancer*. 2015;1(4):252–265.
Defines inflammatory and perivascular niches critical for glioma initiation and progression, providing a framework for TBI-induced parenchymal microenvironmental changes.
2. **Loane DJ, Kumar A.** Microglia in the TBI brain: the good, the bad, and the dysregulated. *Exp Neurol*. 2016;275(Pt 3):316–327.
Demonstrates how chronic microglial activation after TBI sustains cytokine signaling

pathways implicated in glioma biology.

3. **Venkatesh HS, et al.** Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell*. 2015;161(4):803–816.
Shows how injury-induced neuronal hyperactivity directly drives glioma proliferation.

Meningioma-Focused References

4. **Claus EB, Black PM, Bondy ML, et al.** Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. *J Neurosurg*. 2007;107(5):1006–1013.
Highlights non-TBI biological drivers of meningioma, underscoring the relative weakness of injury-based mechanisms.
5. **Navas-Acien A, Pollan M, Gustavsson P, Plato N.** Interactive effect of chemical substances and occupational trauma on meningioma risk. *Cancer Epidemiol Biomarkers Prev*. 2002;11(5):457–460.
Suggests trauma as a potential co-factor rather than a primary oncogenic driver.
6. **Riemenschneider MJ, Perry A, Reifenberger G.** Histological classification and molecular genetics of meningiomas. *Lancet Neurol*. 2006;5(12):1045–1054.
Establishes NF2-centric molecular pathogenesis, with limited mechanistic linkage to diffuse brain injury.

Bottom Line for Interpretation of the Kennemer et al. Study

- The observed **malignant tumor signal after moderate–severe TBI** is **far more biologically consistent with glioma** than with meningioma.
- Any meningioma association likely reflects **detection bias or localized dural injury**, rather than true injury-driven oncogenesis.