

### Short Communication

## Handedness and Risk of Brain Tumors in Adults

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### Abstract

The objective of this study was to evaluate the relation between handedness, and the risk of malignant and benign brain tumors. Handedness has been hypothesized to serve as a behavioral marker of prenatal hormonal exposures or other factors that influence subsequent cancer risk. A case-control study was conducted at hospitals in three United States cities between 1994 and 1998. The cases were adult patients newly diagnosed with glioma ( $n = 489$ ), meningioma ( $n = 197$ ), or acoustic neuroma ( $n = 96$ ), and the 799 frequency-matched controls were patients admitted to the same hospitals for a variety of nonmalignant conditions. Handedness was determined by interview. Unconditional logistic regression was used to estimate odds ratios (ORs) and calculate 95% confidence intervals (CIs). Persons who described themselves as left-handed or ambidextrous appeared to be at reduced risk of glioma relative to those who described themselves as right-handed (OR, 0.7; 95% CI, 0.5–0.9). The association was similar for men and women, and for left-sided and right-sided tumors. Neither meningioma (OR, 0.9; CI, 0.6–1.5) nor acoustic neuroma (OR, 0.9; CI, 0.5–1.7) showed significant associations with handedness. These findings require confirmation but raise the possibility that early neurodevelopmental events or genetic factors related to handedness also influence the risk of glioma among adults.

### Introduction

A longstanding, albeit controversial, hypothesis put forth by Geschwind, Behan and Galaburda (1, 2) in the 1980s proposes that levels of testosterone (or a related factor) in the brain of the developing fetus influence cerebral hemispheric dominance, with high concentrations delaying development in the left hemisphere relative to the right hemisphere, thereby allowing the right hemisphere to gain an advantage (1–4). The hypothesis additionally holds that such “anomalous” hemispheric

dominance is associated not only with left-handedness, but with a variety of health effects as well, including developmental disorders of language and speech, and immune dysfunction. Others have hypothesized that handedness is a marker of prenatal hormonal exposures or other factors that influence subsequent breast cancer risk (5); however, to our knowledge, there is no literature concerning handedness and brain tumors. Here, we describe the relationship between handedness and risk of glioma, meningioma, and acoustic neuroma. We reported previously evidence of a reduced risk of glioma associated with a history of immune disorders (6).

### Materials and Methods

This case-control study was conducted among adults at hospitals in Phoenix, Arizona; Boston, Massachusetts; and Pittsburgh, Pennsylvania between 1994 and 1998 (6). Cases were patients newly diagnosed with glioma ( $n = 489$ ), meningioma ( $n = 197$ ), or acoustic neuroma ( $n = 96$ ). Controls were persons admitted to the same hospitals as the cases for a variety of conditions, the most common of which were trauma ( $n = 197$ ), and diseases of the circulatory ( $n = 179$ ), musculoskeletal ( $n = 172$ ), digestive ( $n = 92$ ), and nervous systems ( $n = 58$ ). Handedness was classified based on the answer of each participant to the question, “Are you left-handed or right-handed?” If a respondent hesitated or said “It depends,” the interviewer asked “What hand do you write with?” Unconditional logistic regression was used to evaluate associations between handedness, and risk of tumors of the brain and nervous system, using SAS software versions 6.12 and 8.2 (SAS Institute Inc., Cary, NC).

### Results

Overall, 10.6% of controls described themselves as left-handed and 5.3% as mixed-handed (Table 1). Left-handedness was more common among controls <60 years of age than among older persons, among college-educated men and women compared with those with lesser schooling, and among never-married than ever-married persons (data not shown). For glioma, the OR<sup>2</sup> for left-handedness relative to right-handedness was 0.7 (95% CI, 0.5–1.1), and the OR for mixed-handedness was 0.6 (95% CI, 0.3–1.0). For left- or mixed-handedness combined, the association was significant (OR, 0.7; 95% CI, 0.5–0.9;  $P = 0.02$ ). No significant associations with handedness were seen for meningioma or acoustic neuroma (Table 1).

For glioma, patterns were similar for men and women, and for left- and right-sided tumors (data not shown). The OR for left- or mixed-handedness did not show a clear trend with age at tumor diagnosis but was lowest for ages >60 years (OR, 0.5; 95% CI, 0.2–0.9). The OR varied little, depending on whether any of the other major categories of control diagnoses were

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<sup>2</sup> The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Risk of tumors of the brain and acoustic nerve according to handedness

Handedness	Controls		Glioma		Meningioma			Acoustic neuroma		
	n (%)	n (%)	OR <sup>a</sup>	95% CI	n (%)	OR <sup>a</sup>	95% CI	n (%)	OR <sup>a</sup>	95% CI
Right <sup>b</sup>	672 (84.1)	432 (88.3)	1.0		171 (86.8)	1.0		81 (8.4)	1.0	
Left	85 (10.6)	40 (8.2)	0.7	0.5–1.1	11 (5.6)	0.6	0.3–1.2	12 (12.5)	1.2	0.6–2.2
Mixed	42 (5.3)	17 (3.5)	0.6	0.3–1.0	15 (7.6)	1.5	0.7–2.8	3 (3.1)	0.5	0.1–1.5
Left + mixed	127 (15.9)	57 (11.7)	0.7	0.5–0.9	26 (13.2)	0.9	0.6–1.5	15 (15.6)	0.9	0.5–1.7

<sup>a</sup> Adjusted for matching variables, level of education, and marital history (ever/never).

<sup>b</sup> Reference category.

Table 2 Risk of glioma with respect to handedness and self-reported history of allergies or autoimmune diseases

	Handedness						<i>P</i> (heterogeneity) <sup>b</sup>
	Right			Left or mixed			
	Cases	Controls	OR (95% CI) <sup>a</sup>	Cases	Controls	OR (95% CI) <sup>a</sup>	
Allergies							
No	303	402	1.0 <sup>c</sup>	31	74	0.5 (0.3–0.8)	0.08
Yes	113	251	0.6 (0.5–0.8)	23	50	0.6 (0.4–1.0)	
Autoimmune diseases							
No	358	514	1.0 <sup>c</sup>	49	100	0.7 (0.5–1.0)	0.51
Yes	53	137	0.6 (0.4–0.8)	5	26	0.3 (0.1–0.6)	

<sup>a</sup> Adjusted for matching variables, level of education, and marital history.

<sup>b</sup> Test of null hypothesis that the OR for left- or mixed-handedness is the same for persons with and without a history of allergies or autoimmune disorders.

<sup>c</sup> Reference category.

included or excluded. In particular, the OR was essentially unchanged when trauma patients were excluded.

No association between handedness and risk of glioma was observed among persons who reported a history of allergies (Table 2). Results indicate an approximately 40–50% reduced risk associated with being either left-handed or having a history of allergies, but no additional lowering of risk was associated with having both characteristics [*P* (heterogeneity) = 0.08]. Results for autoimmune diseases and handedness were more compatible with a multiplicative relationship.

## Discussion

In one of the first studies to evaluate handedness and brain tumor occurrence, the risk of glioma, but not meningioma or acoustic neuroma, appeared to be lower among adults who reported using their left hand with equal or greater dexterity than their right hand. We are unaware of other published data with which to compare or contrast our findings.

A possible biological basis of an association between handedness and glioma is through effects on the developing nervous system, which may bear on cancer risk later in life. Recent evidence suggests that early developmental processes that give rise to cerebral asymmetry also influence susceptibility to dementias or other neurodegenerative diseases associated with old age (7–9). However, the mechanism by which such processes might influence cancer development many years later is unclear.

The absence of an association with handedness among persons with a history of allergies is noteworthy, although the test for heterogeneity fell short of statistical significance. An inverse association between the risk of glioma and history of allergies has been observed repeatedly in case-control studies (6, 10, 11). Pleiotropy of the sort inherent in the hypothesis of Geschwind, Behan and Galaburda (1, 2) offers a possible link among neurodevelopment, handedness, immune disorders, and

brain cancer, even if the mechanism is not exactly as they describe, and the mediators are factors other than hormones. Recent reports have noted that certain genes thought previously to have effects specific to the immune system, such as those of the class I MHC and some cytokines, also influence brain development (12–15). One might speculate that both handedness and allergies (or susceptibility to allergies) are related to the risk of glioma, but only indirectly and through their shared association with the true causal factor, as yet unknown. It is possible that left-handedness is a marker for pre- or perinatal stress, although it is not clear that such stress is associated with decreased risk of glioma (16).

Our results should be interpreted cautiously, insofar as the association with handedness was modest and might be due to chance, or to an unusually high frequency of left- and mixed-handedness among controls, rather than an unusually low frequency among the glioma cases. If the association was due to chance, it is curious that it was only seen among persons who did not have a history of allergies. Among controls, the prevalence of left-handedness was 10.6%, and the prevalence of mixed-handedness was 5.3%. Comparisons with the literature are complicated by variable definitions of left-handedness, including how mixed-handedness is classified, and demographic or cultural differences between populations. Reported prevalences range from 6 to 14% (2, 17–19). It has been suggested that left-handers have a higher accident rate than right-handers (20), but, for glioma, the OR associated with left- or mixed-handedness varied little, depending on whether trauma or any of the other major categories of control diagnoses were included or excluded. Furthermore, the same controls were used for meningioma and acoustic neuroma as for glioma, but neither of these tumor types showed a notable association with handedness. The associations that we observed among handedness and age, sex, and marital status among controls were in the same direction as has been reported previously (21).

Handedness was classified based on self-reported responses to a single question inquiring about which hand was used for writing. Writing hand is the most important factor in determining self-reported handedness, but laterality scores based on a battery of questions concerning the major hand used for different activities provide a basis for classifying persons on a continuous scale (22, 23). Whether mixed-handedness represents an intermediate category on such a scale is unclear. In the present study, the ORs for left-handedness and mixed-handedness were nearly equal; there was no indication of a gradient in risk.

Current handedness may not reflect original handedness for persons born before 1950, as those born left-handed in older generations often were forced or encouraged to switch hand used for writing (22, 24). In the present study, the OR for nonright-handedness did not show a significant trend with age, but the lowest OR was observed for the oldest age group. Older persons who persisted in using their left hand, despite familial or societal pressure to change, might represent a subgroup with a stronger predisposition to left-handedness (5).

The association between handedness and glioma is intriguing, notwithstanding the absence of an *a priori*, biologically based, directional hypothesis and the possibility that the association is due to chance. If the association with handedness is confirmed, it could provide important clues to developmental or genetic risk factors for glioma, a highly fatal disease for which our understanding of etiology is woefully lacking (25).

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