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Handedness and the Risk of Glioma

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Abstract

Gliomas are the most common type of malignant primary brain tumor and few risk factors have been linked to their development. Handedness has been associated with several pathologic neurological conditions such as schizophrenia, autism, and epilepsy, but few studies have evaluated a connection between handedness and risk of glioma. In this study, we examined the relationship between handedness and glioma risk in a large case-control study (1,849 glioma cases and 1,354 healthy controls) and a prospective cohort study (326,475 subjects with 375 incident gliomas). In the case-control study, we found a significant inverse association between left handedness and glioma risk, with left-handed persons exhibiting a 35% reduction in the risk of developing glioma (Odds Ratio (OR)=0.65, 95% Confidence Interval (CI): 0.51, 0.83) after adjustment for age, gender, race, education, and state of residence; similar inverse associations

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Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability: Contact the corresponding author to request data or analyses from the case-control study. Contact the UKBiobank to request data from the cohort study.

were observed for GBM (OR=0.69, 95% CI: 0.52, 0.91), and non-GBM (OR=0.59, 95% CI: 0.42, 0.82) subgroups. The association was consistent in both males and females, and across age strata, and was observed in both glioblastoma and in lower grade tumors. In the prospective cohort study, we found no association between handedness and glioma risk (Hazards Ratio=0.92, 95% CI: 0.67, 1.28) adjusting for age, gender, and race. Further studies on this association may help to elucidate mechanisms of pathogenesis in glioma.

Keywords

case-control study; cohort study; glioma; glioblastoma; handedness; UK Biobank

Introduction

Gliomas have an annual incidence rate of 6 per 100,000, and account for about 27.5% of all primary brain tumors and 80% of all malignant primary brain tumors [1]. This highly aggressive form of cancer is more common among males and Caucasians [2]. Although glioma is a relatively rare type of cancer, the high mortality rate and poorly understood pathogenesis of the condition prompts further efforts to identify contributors to glioma risk. Several developmental factors have been linked to increased risk of glioma, including a longer adolescent growth phase, taller attained height, obesity during adolescence, and later age at menarche [3–6].

Over the past 30 years, a decrease in low-grade gliomas but an increased incidence of high-grade glioma has been reported [7]. Gliomas occur most often in the frontal and temporal lobes, and the incidence of tumors diagnosed in these locations has increased annually [8]. Both low- and high-grade gliomas have experienced a laterality shift over the last 30 years toward left-sided tumors, especially in patients diagnosed at a younger age (20-49 years of age) [7]. Explanations for these shifts of laterality and tumor incidence are unclear.

The majority of persons are right-handed, with approximately 11% of the United States population overall being left-handed or mixed-handed [9]. The proportion of left-handed people also decreases after age 50, possibly due to a social stigma against left-handed activities (such as eating and writing) seen earlier in the twentieth century as well as a higher mortality among sinistrals [9]. A meta-analysis found a higher prevalence of left-handedness in males, with a combined male to female sinistrality ratio of 1.23 [10]. Determination of handedness begins at least in part prenatally as early as the first trimester, and is thought to be the result of a complex combination of developmental and genetic forces involving brain asymmetry and language lateralization [11–13]. Several genes and chromosomal regions have been identified as associated with handedness, and twin studies indicate that the genetic effect accounts for about 25% of variance in the population [14, 15]. The role of prenatal intrauterine exposure to testosterone is controversial, with some studies reporting increased levels of testosterone associated with left handedness and others reporting decreased testosterone in left-handed persons [16, 17]. In recent years, the latter theory appears to be better supported, as a lower prevalence of left handedness has been found in female twins with a male co-twin compared with same-sex twins [18]. Sinistrality is increased in female

infants exposed to diethylstilbestrol (DES), an estrogen-like compound, early in gestation [19]. Left-handedness has been linked to a number of traits and pathological conditions including schizophrenia, autism, temporal lobe epilepsy, and breast cancer [20–23] though the mechanism is unclear.

A relationship between handedness and glioma risk has been examined in only one previous epidemiologic study [24] with findings suggesting lower incidence of glioma in left-handed persons. Here, we re-examine the relationship between handedness and glioma risk in a large case-control study and a prospective cohort study.

Subjects and methods

Study Population

Case-control study—The case-control study for this analysis has been described in previous reports [4, 5]. In brief, persons aged 18 or older with a recent diagnosis of a first primary glioma (ICD9/10: 191 and C71) including glioblastoma multiforme (GBM) (9440-9441) and nonglioblastoma subtypes (non-GBM) (9382, 9400-01, 9410-11, 9420, 9424-25, 9450-9451) were recruited at neuro-oncology and neuro-surgery clinics affiliated with academic medical centers in the southeastern US. Eighty-seven percent of eligible glioma patients were enrolled in the study and completed the study interview a median of 1.0 month following the glioma diagnosis (interquartile range: 2 weeks – 1.7 months). Controls were friends and acquaintances of the cases, or were identified from white page listings with frequency matching to cases on age, gender, and neighborhood via postal zip code. An estimated 50% of contacted eligible households yielded a participating control. Enrollment occurred between December 2004 and July 2014. In structured interviews, information was collected on demographic information, personal and family medical history, as well as known and suspected glioma risk factors. For the present analysis, subjects were asked “are you right or left-handed” with responses recorded as “right”, “left” or “use both hands equally”. Clinical reports were also obtained to determine tumor subtype. The study was approved by the institutional review boards at each participating medical center. Written informed consent was obtained from all participants.

Cohort study—Subjects included in the cohort analysis were selected from participants in an established population-based cohort, the UKBiobank [25, 26]. This cohort follows approximately 500,000 individuals from the UK who were 40-69 years old at the time of recruitment in 2006-2010. Prospective subjects for this cohort were identified from National Health Service patient registries and invited to participate by attending one of the 22 assessment centers. As part of the baseline intake survey, subjects were asked to report their dominant hand as ‘left’, ‘right’ or ‘both’. Participants were followed via record linkage to the National Health Service (NHS) Central Registers which provide information on cancer diagnoses coded according to the WHO International Classification of Diseases for tumors of the central nervous system [27, 28], with the last linkage date of November 30, 2014 for residents of England and Wales and December 31, 2014 for the residents of Scotland. Of 502,619 participants in UKBiobank, we excluded those with a history of any cancer (other than non-melanoma skin) at recruitment and all genetically related controls, leaving 326,475

subjects remaining for the present analysis. All participants of UKBiobank provided written consent at recruitment. Data were downloaded from UKB as part of an approved protocol.

Statistical Analysis

For the case-control study analyses, we estimated odds ratios (OR) and 95% confidence intervals (CI) for handedness (or dominant hand) and risk of glioma using logistic regression. Terms for age, gender, state of residence, and education were included in regression models. We considered associations overall and according to gender and glioma subtype, ie. glioblastoma multiforme (GBM) or lower-grade (non-GBM) subtypes. All tests were two-sided and statistical significance of associations was assessed at the 0.05 significance level. These analyses were performed using SAS (SAS Institute Inc. version 9.4).

For the cohort study analysis, we estimated hazard ratios (HR) and 95% CIs for newly diagnosed incident glioma according to handedness using Cox proportional hazards regression. Follow-up time for persons diagnosed with glioma began at study entry and ended at glioma diagnosis. Follow up for unaffected persons began at baseline and ended at the time of death or the last linkage with Cancer Registry data (November 30, 2014 for England and Wales or December 31, 2014 for Scotland), whichever came first. The models were adjusted for age, gender, and race. All the tests were two-sided and significance of the effects was assessed at the 0.05 significance level. These analyses were performed using R (version 3.3.3).

Results

Case-control Study Analysis

Case-control study analyses were based on 1,849 glioma cases and 1,354 healthy controls. The median age at enrollment was 54 years for glioma cases (54 and 55 years in men and women, respectively) and 56 years for controls (57 and 55 years in men and women, respectively). The majority of cases and controls were Caucasian (~90%). A descriptive summary of cases and controls on age, gender, race, education and state of residence is found in the supplemental table.

Table 1 shows the association between handedness and risk of glioma overall and by glioma subtype. Left-handedness was reported by 8.9% of glioma cases, including 8.8% of GBM and 9.0% of non-GBM cases, and 12.4% of controls. Use of both hands equally was reported by 1.2% of cases and 1.6% of controls. In multivariate regression, a protective association with glioma overall was observed for left handedness (OR=0.65, 95% CI: 0.51, 0.83) after adjustment for age, gender, race, education, and residence; similar inverse associations were observed for GBM (OR= 0.69, 95% CI: 0.52, 0.91), and non-GBM (OR= 0.59, 95% CI: 0.42, 0.82) subgroups. No meaningful differences in ORs were evident when considering associations by age (OR (95% CI): 0.61 (0.42, 0.88) for age < 50 years; 0.65 (0.50, 0.89) for age 50 -60 years; and 0.67 (0.44, 1.02) for age greater than 60 years, respectively). Inverse associations for ambidexterity were nonsignificant though data were sparse.

Table 2 presents associations according to gender. Significant inverse associations with glioma for left-handedness were found both in males (OR=0.73, 95% CI: 0.54, 0.99) and females (OR=0.50, 95% CI: 0.35, 0.72), adjusting for age, race, education, and residence. Data were too sparse for regression analyses on ambidexterity; however, this was reported by fewer cases than controls both in men and women.

Cohort Study Analysis—Cohort study analyses were based on 326,475 participants with no history of cancer at baseline. A descriptive summary of cases and controls on age, gender, race and education is found in the supplemental table. Left-handedness was reported by 10.4% of men and 8.6% of women. When also including subjects reporting use of both hands equally, the proportion rose to 12.5% of men and 10.0% of women. Figure 1 shows the proportion of left-handed subjects in the UKBiobank according to age and gender. As reported previously, left-handedness was more common in men, regardless of age. The proportion of left-handed persons declined with age, regardless of gender, with some narrowing of the male left-handed excess among the oldest participants.

Associations with glioma risk are shown in Table 3. A total of 375 gliomas were documented in follow up among whom 40 (10.7%) reported being left-handed or using both hands equally. We observed no significant association for all gliomas combined, or when restricting to glioblastoma. (Lower grade gliomas were identified in only 96 participants.) Furthermore, no significant associations with risk were observed in either gender (not shown) though the numbers of incident glioma cases that were left-handed or ambidextrous was limited in gender-stratified analyses (27 males and 13 females).

Discussion

In a large case-control study, glioma patients were less likely to be left-handed when compared to the controls, with left-handed persons having a 35% reduced risk for glioma. Results were adjusted for potentially confounding variables including age, race, gender, and state of residence. The inverse association for left-handedness was consistent across age strata and in both males and females, with a potentially stronger association in women. In contrast, we observed no significant association between handedness and glioma incidence in a large prospective cohort of subjects initially free of glioma.

Similar findings as in the present case-control study were reported in the only previous study of this association [24]. In a hospital-based case-control study of 489 glioma cases and 799 hospital controls, persons who described themselves as left-handed or ambidextrous had a significantly 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 whereas no association was observed for meningioma or acoustic neuroma.

The protective association for left-hand dominance in the case-control study analysis was not validated in the cohort study analysis. The reason for these discordant results is unclear. Cohort analyses were based on relatively few incident cases (n=375 of whom 40 were left-handed or ambidextrous) and power was limited to detect associations. However, of note, in the same cohort, expected positive associations are observed for older age at menarche [5]

and increasing height [6] (unpublished data). Competing risk due to higher mortality from causes other than glioma in sinistrals [9] may potentially have contributed to null results in the cohort analyses. However, we note that left-handedness is only modestly and nonsignificantly related to all-cause mortality in the cohort of 326,475 UKBiobank participants including 7,868 deaths (HR: 1.05; 95% CI: 0.98, 1.12; p=0.20) when adjusting for age, gender and race, suggesting that competing risk is unlikely to have played a major role in the findings. Case-control study results may have been influenced by recall or selection bias. Recall bias would have led to observed associations if cases systematically underreported left dominance (or controls overreported left dominance), though such bias seems unlikely. Selection bias was also possible given the relatively low participation rate among contacted households (~50%); higher participation rates in left-handed persons would have given rise to the observed protective association for left-dominance. The data suggest some evidence for selective participation of left-handed persons among controls. The prevalence of left-handedness in controls in the study was higher than that of the UKBiobank cohort as a whole (12.4% versus 9.4%) that encompassed persons of similar age (40-70) and a comparable proportion of men (47% in UKBiobank and 49% in the current study). Furthermore, the well-established 20% higher prevalence of left-handedness among men as observed in the large Gilbert survey from the early 1990s (~11% in men versus ~9% in women among respondents aged 50-60) [9] and in the UKBiobank cohort (10.4% and 8.5%, respectively), while observed amongst cases in the present study (10.2% and 8.6%, respectively) was not found in the controls (12.7% and 12.2%, respectively). We have no explanation as to why left-handed persons contacted for the study, especially women, were more likely than right-handed persons to agree to participate in the case-control study.

In summary, in a large case-control study, we observed reduced risk of glioma in person reporting left-handedness consistent with results from the only previous study of the association. However, findings were not validated in a prospective cohort study. Further research on handedness and other developmental risk factors based on large prospective cohort studies will be useful to gain further insights on pathogenic mechanisms in glioma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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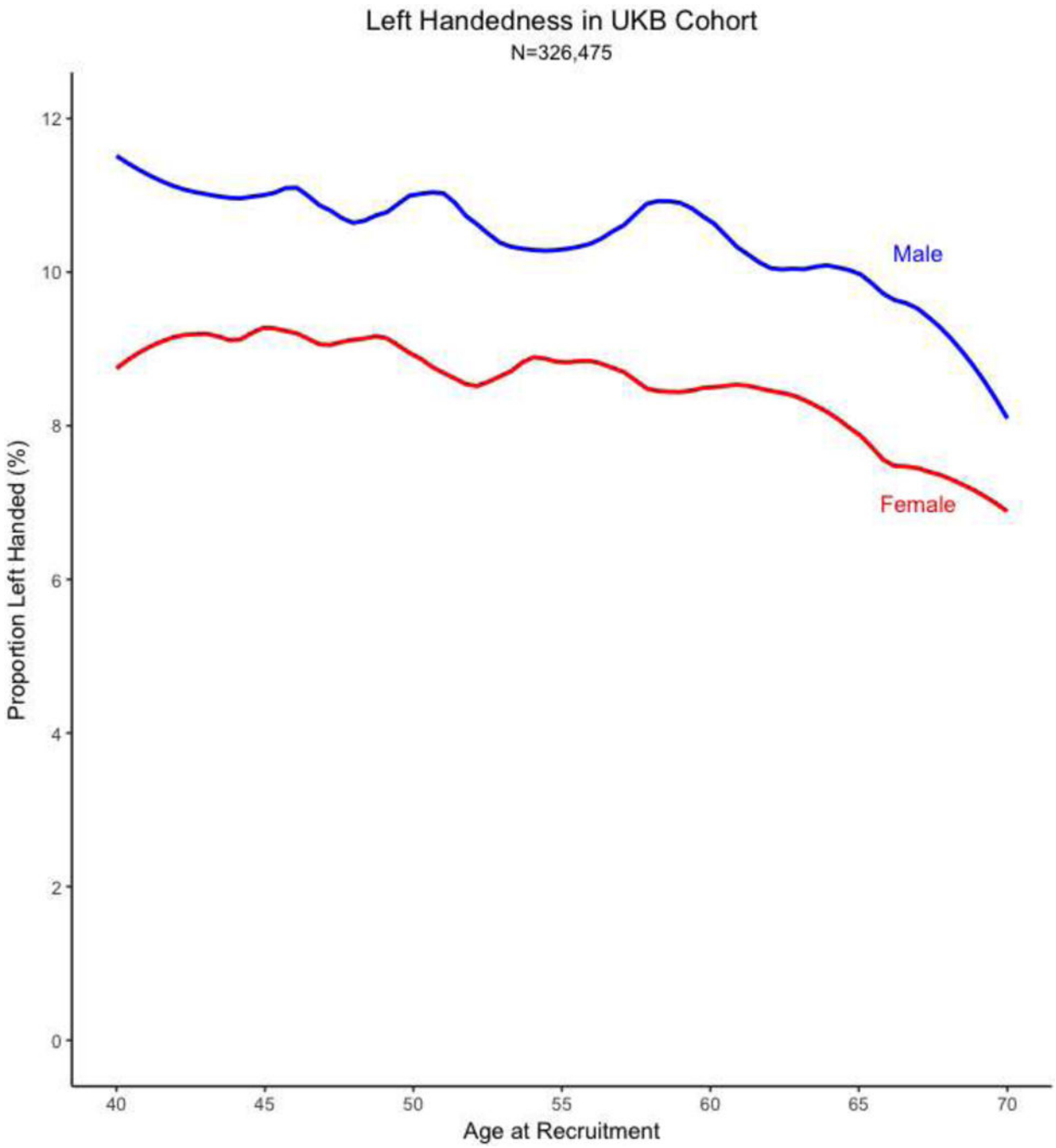

Fig. 1.
Left-handedness in UKB Cohort by age and gender

Table 1

Case-control associations between handedness and risk of glioma

					Glioma		Glioblastoma		Non-GBM	
Dominant Hand	**Glioma Cases n (%)**	**Glioblastoma Cases n (%)**	**nonGBM Cases n (%)**	**Controls n (%)**	**OR (95% CI)***	**p-value**	**OR (95% CI)***	**p-value**	**OR (95% CI)***	**p-value**
right	1662 (89.8)	1023 (89.8)	639 (90.0)	1164 (85.6)	*ref*	----	*ref*	----	*ref*	----
left	164 (8.9)	100 (8.8)	64 (9.0)	168 (12.4)	0.65 (0.51,0.83)	<0.01	0.69 (0.52, 0.91)	<0.01	0.59 (0.42, 0.82)	<0.01
both	23 (1.2)	16 (1.4)	7 (1.0)	22 (1.6)	0.70 (0.36, 1.30)	0.26	0.80 (0.41, 1.57)	0.51	0.46 (0.18, 1.19)	0.11

*Odds ratios (OR) and 95% Confidence Intervals (CI) adjusted for age (3 year age groups), gender, race, education, and state of residence.

Table 2

Case-control associations between handedness and risk of glioma by gender

	Males		Females		Males		Females	
Dominant Hand	**Cases (n, %)**	**Controls (n, %)**	**Cases (n, %)**	**Controls (n, %)**	**OR (95% CI)***	**p-value**	**OR (95% CI)***	**p-value**
right	955 (88.4)	566 (85.3)	707 (91.9)	598 (86.5)	*ref*		*ref*	
left	108 (10.0)	84 (12.7)	56 (7.28)	84 (12.2)	0.73 (0.54, 0.99)	0.04	0.50 (0.35, 0.72)	<0.01
both	17 (1.6)	13 (2.0)	6 (0.78)	9 (1.3)				

*Odds ratios (OR) and 95% Confidence Intervals (CI) adjusted for age (3-year age groups), race, education, and state of residence. Left handedness and left-right co-dominance are combined in logistic regression models.

Table 3

Handedness and risk of incident glioma in the UK Biobank cohort

	All Gliomas			Glioblastoma		
Dominant Hand	**Count**	**HR (95% CI)**	**p-value**	**Count**	**HR (95% CI)**	**p-value**
Right	335	*ref*		245	*ref*	
Left/ Both	40	0.92 (0.67–1.28)	0.64	34	1.07 (0.75–1.54)	0.70

Multivariate hazard ratio (mHR) adjusted hazard ratios and 95% Confidence Intervals (CIs) derived from Cox regression models. Multivariate models included terms for age (continuous), gender, and race.