

# **Does risk of brain cancer increase with intracranial volume? A population-based case-control study**

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## **Running title**

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## **Conflict of interest**

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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## Abstract

**Background:** Glioma is the most common primary brain tumor and is believed to arise from glial stem cells. Despite large efforts there are limited established risk factors. It has been suggested that tissue with more stem cells may exhibit higher risk of cancer due to chance alone. Assuming a positive correlation between the number of stem cell divisions in an organ and size of the same organ, we hypothesized that variation in intracranial volume, as a proxy for brain size may be linked to risk of high-grade glioma.

**Methods:** Intracranial volume was calculated from pre-treatment 3D T1-weighted MRI brain scans from 124 patients with high-grade glioma and 995 general population based controls. Binomial logistic regression analyses were performed to ascertain the effect of intracranial volume and sex on the likelihood that participants have high-grade glioma.

**Results:** An increase in intracranial volume of 100 mL was associated with an odds ratio (OR) of high-grade glioma of 1.69 (95 % CI 1.44 to 1.98;  $P < 0.001$ ). After adjusting for intracranial volume, female sex emerged as a risk factor for high-grade glioma (OR for male sex = 0.56, 95 % CI 0.33 to 0.93;  $P = 0.026$ ).

**Conclusions:** Intracranial volume is strongly associated with risk of high-grade glioma. After correcting for intracranial volume, risk of high-grade glioma was higher in women. The development of glioma is correlated to brain size and may to a large extent be a stochastic event related to the number of cells at risk.

## **Keywords**

Glioma

HUNT study

Intracranial volume

MRI

Risk factors

## **Importance of study**

Gliomas are more common in men than women, but the etiology is largely unknown. Recent studies have found associations between height/organ size and risk of several types of cancer, and it has been shown that risk of cancer in an organ is positively correlated with the estimated number of stem cell divisions in the organ. No previous study has explored brain size as a risk factor for high-grade glioma, and the results from the present study indicates a strong correlation. The difference in intracranial volume between men and women explain the previously reported higher risk in men. Assuming that the number of cell divisions is related to organ size, our findings is a clinical example supportive of the controversial “bad luck”-theory which claims that development of cancer often results from a lottery of random mutations in normal stem cells, with important implications in our understanding of cancer etiology.

## Background

Gliomas are believed to arise from glial stem cells and represent the most common type of primary brain tumor. For most patients with glioma, the etiology is unknown. Despite large epidemiological studies on gliomas only age, male sex, ionizing radiation, Caucasian ethnicity and few rare hereditary syndromes are established risk factors, while there is an inverse relationship between risk of glioma and atopic disease/allergies.<sup>1</sup>

A much debated recent study suggests that risk of cancer in general correlates with the total number of divisions of the organ stem cells.<sup>2</sup> Hence, tissue with more stem cells may exhibit higher risks of cancer due to chance alone. Assuming a positive correlation between the number of stem cell divisions in an organ and size of the same organ, the inter-individual variation in organ size may be linked to cancer risk at the individual level. In general, the size of human organs increases with height, as does also the risk of several types of cancers.<sup>3</sup> Furthermore, evidence of a positive association between breast size and risk of breast cancer has been documented.<sup>4</sup> On average, men are taller and have larger brains compared to women, with men having a reported increased risk of glioma of 1.4.<sup>5,6</sup> We therefore hypothesized that the higher glioma risk in men is associated with their larger brain size.

In the present study, the association between brain size, measured as intracranial volume and risk of high-grade glioma was assessed using a population-based case-control design. The effect of sex on risk of glioma after adjusting for ICV was also investigated.

## Methods

### Study population

Consecutive patients diagnosed with glioma from January 2007 through November 2015 were identified from the surgery database at the Department of Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. The Department of Neurosurgery exclusively serves a defined geographical catchment region with approximately 715 000 inhabitants. A tissue diagnosis is advocated in patients with suspected malignant intracranial tumors, ensuring a population-based case selection of patients with histopathologically confirmed tumors. Only patients with verified diffuse glioma grade III or grade IV were included. Preoperative contrast-enhanced 3D T1-weighted cerebral MRI scans are routinely acquired in patients with glioma. Patients without contrast-enhanced 3D T1-weighted cerebral MRI scans prior to surgery, patients who had undergone previous intracranial surgery, patients with infratentorial tumor localization, and patients with Chiari malformations were excluded. Patients with Chiari malformations were excluded as they have cerebellar parenchyma protruding below the foramen magnum, resulting in a potential mismatch between brain volume and intracranial volume. Likewise, patients with infratentorial tumor localization were excluded as they could theoretically also have a Chiari malformation before developing a glioma. The control group was recruited from the entire HUNT-MRI cohort of 1006 participants, which consists of subjects aged 50-66 from the general population.<sup>7</sup> The HUNT-MRI cohort geographical catchment region is part of the same catchment region as the study population. To match the control population, only patients between 50 and 66 years of age at diagnosis were included. Although intracranial volume does not change in adulthood,<sup>8</sup> the age balance between cases and controls ensured that the known association between age and glioma risk and differences in lifetime exposures (e.g. to radiation) would not confound results. The study was approved by the Regional Committee for Medical Research Ethics

(REK), Health Region IV in Norway (ID 2017/34), and the HUNT board. For the patient population, the study was approved with a waiver of informed consent for retrospective review of MRI images obtained as part of clinical routine due to the majority of patients being deceased or critically ill. All participants in the control population provided written, informed consent as part of the HUNT study.

### **Volumetric analyses**

Intracranial volume has been shown to be highly correlated to maximum brain volume and does not change significantly after the age of 16.<sup>8</sup> Intracranial volume in mL was therefore used as the best proxy for lifetime maximum brain size. Intracranial volume was estimated with an automated reverse brain mask method (ARBM) using the “new segment” approach of the SPM8 toolbox (rel. 5236) ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)), which has a very high correlation ( $ICC_{(2,1)} = 0.97$ ) with manual measurements.<sup>9</sup> In short, the method depicts the intracranial volume inside the dura (brain and cerebrospinal fluid), excluding the pituitary gland by a straight line through the upper pituitary stalk in the axial plane. The lowest point of the cerebellum defines the intracranial volume’s caudal border. 3D T1 MRI images acquired at 1.5 or 3 Tesla were the input to the segmentation algorithm. A high-grade glioma is highly unlikely to affect the estimated intracranial volume in adults based on this method, as it would require significant osseous remodeling of the cranium or direct bone invasion, which is exceedingly rare in gliomas.<sup>10</sup> All intracranial volume segmentations of patients were quality assessed visually by two investigators independently (EHF and TIH), but no manual adjustments were made.

### **Statistical analysis**

Given an approximate average intracranial volume of  $1350 \text{ cm}^3 \pm 150 \text{ cm}^3$  in an adult population,<sup>11</sup> a sample size of 140 patients and 1000 controls will have 80 % power to detect a difference between the groups of 0.25 SD or  $37.5 \text{ cm}^3$ . Since patient data were collected from multiple MRI scanners and control data from one 1.5 T scanner, the effect of the MRI scanner (scanner id) on the intracranial volume estimate was examined using a linear mixed model with sex and group as fixed effects and scanner id as random effect. The variance of the scanner id effect was estimated at zero and scanner id was therefore not included in subsequent analyses. Binomial logistic regression was then performed to ascertain the effect of intracranial volume and sex on the likelihood that participants have high-grade glioma. Linearity of the continuous intracranial volume variable with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure. Statistical level of significance was set to  $P \leq 0.05$ . Data is presented as arithmetic mean  $\pm$  SD if not otherwise stated. The linear mixed model analysis was run in R v3.2.3 using the lme4 package. IBM SPSS Statistics version 23.0.0.2 64-bit for OS X was used for all other analyses. Analyses were performed by authors TIH and ØS.



## Results

A total of 296 patients with high-grade glioma and 1006 controls were screened, and 124 patients and 995 controls were included in the analyses. A flow chart of the inclusion process is presented in Figure 1.

*Please insert Figure 1 approximately here.*

Descriptive statistics are presented in Table 1. There was no difference in age between cases and controls. The mean intracranial volume of female patients with high-grade glioma was 55 mL larger than in female controls ( $P = 0.001$ , 95% CI 21 to 89 mL). Also, the mean intracranial volume of male patients with high-grade glioma was 92 mL larger than in male controls ( $P < 0.001$ , 95% CI 62 to 122 mL).

*Please insert Table 1 approximately here.*

The binomial logistical regression analyses demonstrated that intracranial volume and sex was statistically significantly associated with risk of glioma (Table 2). For each 100 mL increase in intracranial volume a person had 1.69 times higher OR (95 % CI 1.44 to 1.98,  $P < 0.001$ ) of having a high-grade glioma. After adjusting for intracranial volume, male sex was associated with lower risk (OR 0.56, 95 % CI 0.33 to 0.93) compared to female sex. The interaction between intracranial volume and sex did not significantly contribute to the model and was omitted in the final model.

*Please insert Table 2 approximately here.*

## Discussion

In this population-based case-control study we found a strong positive correlation between intracranial volume and risk of high-grade glioma. This association was present for both men and women. After adjusting for intracranial volume, male sex was associated with lower risk of high-grade glioma, suggesting that the known higher incidence in men is explained by the sex difference in brain volumes. Our results are in line with the recent and controversial “bad luck”-theory which posits that development of cancer to a large part results from a lottery of random mutations that occur during DNA replication in normal stem cells, and hence number of cell divisions and indirectly organ size is a major risk factor for cancer.<sup>2,12</sup>

The association between sex, brain volume and number of glial stem cells (susceptible to neoplastic formation) is not known. In a small morphological study of neocortical cell numbers, the human male brain was found to be approximately 10% larger than the female brain, and contain about 40% more glial cells.<sup>6</sup> Interestingly, the risk of glioblastoma in men has been reported to be 1.58 compared to women.<sup>13</sup> The male to female ratio in patients screened for inclusion in our study was 1.72 (95 % CI 1.35 to 2.19), which is comparable to data from the Norwegian Cancer registry.<sup>14</sup> A recent study based on the same HUNT-MRI dataset used in the present study found that relative white matter volume increases with intracranial volume.<sup>15</sup> Further, absolute white matter volumes for men were higher. However, adjusted for intracranial volume there was no difference in white matter volumes between men and women. Our results suggest that the higher incidence of high-grade glioma among men is explained by the sex differences in brain volumes. Further, the reported effect of height on glioma risk<sup>16</sup> may be an effect of brain volume and not height per se since physical height is associated with increased brain size.<sup>17</sup> A recent study reported that high socioeconomic status is associated with increased risk of glioma.<sup>18</sup> Socioeconomic status is

linked to height<sup>19</sup> and brain volume,<sup>20</sup> and the increased risk of glioma with higher socioeconomic status might therefore reflect an effect of brain volume. Thus, brain volume may be an important underlying factor for many previously reported risk factors, changing our understanding of the disease. This has implications for future research on the etiology of glioma, and the presented organ volume approach may be of interest for studying other cancers as well.

Several studies have reported differences in glioma incidence in different ethnic groups.<sup>18,21</sup> The sample in our population-based study is mainly Caucasian, thus not permitting analyses exploring any possible correlation between intracranial volume and risk of glioma in other ethnicities. Our findings may also shed light on the recent report that risk of glioma is reduced in the years following an acute brain injury.<sup>22</sup> It is possible that the cell death and atrophy following traumatic brain injury<sup>23</sup> reduces the risk of glioma by a reduction of cells at risk. The age-adjusted risk of glioblastoma increases until it peaks at 75-79 years, after which it declines.<sup>24</sup> One could speculate that the declining risk in the oldest age groups might in part be explained by the age-dependent atrophy that reduces the number of cells at risk, but there is also a risk of underdiagnosing high-grade glioma in the highest age group due to increased comorbidity.

From the demonstrated large effect of intracranial volume on risk of high-grade glioma, one could hypothesize a link between glioma and genes related to intracranial volume. Indeed, genetic loci/single nucleotide polymorphisms (SNPs) involved in the insulin-like growth factor and PI3K-AKT pathways, which promote cell proliferation, inhibits apoptosis, and mediates whole-body growth are associated with both increased intracranial volume<sup>25</sup> and growth of glioma.<sup>26</sup> A recent, large meta-analysis of SNPs in patients with glioma found

increased risk of glioma with SNPs in a total of 27 loci.<sup>27</sup> The SNPs accounted for approximately 27% and 37% of familial risk in glioblastoma and non-glioblastoma patients, respectively. Differences in associated SNPs were observed for glioblastomas and other gliomas, suggesting differences in etiology between glioma subtypes. The possible effects of hormonal pathways and genetic variation on risk of high-grade glioma through effects on intracranial volume are currently undetermined, and their roles as possible confounding factors for the results presented here are not known. However, in a recent large publication of the etiology of different types of cancer including brain cancer, the clear majority of mutations were attributed to replicative (i.e. random) mutations and not hereditary or environmental mutations,<sup>12</sup> suggesting an important effect of chance.

The lower risk of high-grade glioma in men compared to women when adjusting for intracranial volume was a surprising finding. The proportion of neural stem cells in the brain, from which glial stem cells are likely to be derived, has been estimated to 0.16%.<sup>28</sup> Glioblastomas are associated with the periventricular white matter regions,<sup>29</sup> and the ventricular-subventricular zone contains a high number of mitotically active neural stem cells.<sup>30</sup> Increased risk of glioma in these regions is coherent with the theory of number of cells at risk. However, the relationship between intracranial volume, sex, and number of stem cell divisions is still unknown. Intracranial volume is a surrogate for white matter volume, which again is a surrogate for number of glial cells and stem cell divisions. We cannot exclude that simple adjustment for intracranial volume is an over- or underadjustment for the actual sex differences in the brain. Also, age dependent white matter changes may affect some white matter regions more than others with a possible gender difference,<sup>31</sup> perhaps further effecting the risk of glioma risk. However, no overall difference in white matter volume or age-related white matter atrophy between men and women when adjusting for intracranial volume has

been established.<sup>15,32</sup> One may also speculate whether hormonal effects might play a role. Sex-dependent differences including p53-mutations, cAMP levels, immune function and vascular function have been reported, but the summated effects in humans are not established.<sup>33</sup> Testosterone may have a protective cardiovascular effect, and endothelial crosstalk has been found to have a role in the etiology of glioblastoma.<sup>33</sup> Still, a direct effect of sex hormones is perhaps less likely since sex hormones change with age while the male to female incidence ratio of GBM is not age dependent.<sup>21</sup> Our findings of higher risk in women after adjustment for intracranial volume needs to be confirmed in later studies.

The strengths of our study include the population-based patient recruitment, eliminating the risk of referral bias, the large representative, population-based control group, and refined method of automatic segmentation of intracranial volume,<sup>9</sup> eliminating the possibility of observer dependent assessment bias. In the presented study intracranial volume was measured instead of brain volume or white matter volume, but intracranial volume and premorbid brain volume correlate closely.<sup>8</sup> Accurate assessment of brain volume or white matter volume is impossible in patients with a glioma due to the infiltrative nature of the disease, and thus intracranial volume was used as a proxy for premorbid brain volume. Assessing premorbid brain or white matter volume in unselected patients with expansive intracranial neoplasms is not feasible due to the rarity of the disease. Although age has limited or no impact on intracranial volume in adults, we sought to avoid any potential bias by including the same age groups as had been done in the MRI control group, since lifetime exposure to different environmental factors increases with age, as does cancer risk. As the control population consisted of a population-based sample in the ages of 50-66 years, we age-matched the patient population to reduce risk of bias. A previous study has found comparable male to female ratios in the incidence rates of glioblastoma for different age groups, reducing the risk of a

skewed male to female ratio in our age-matched population.<sup>21</sup> With few low-grade gliomas in this age group, only patients with high-grade glioma were included in the present study.

Although results may not necessarily be extrapolated to other types of gliomas, a completely different effect of intracranial volume in low-grade gliomas seems unlikely in light of the same male predominance.

In conclusion, brain volume, here measured indirectly as intracranial volume, is strongly associated to risk of high-grade glioma. This explains the male predominance and possibly also several associated epidemiological risk factors. For many patients, the development of brain cancer may be a stochastic event related to the number of cells at risk.

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## Tables

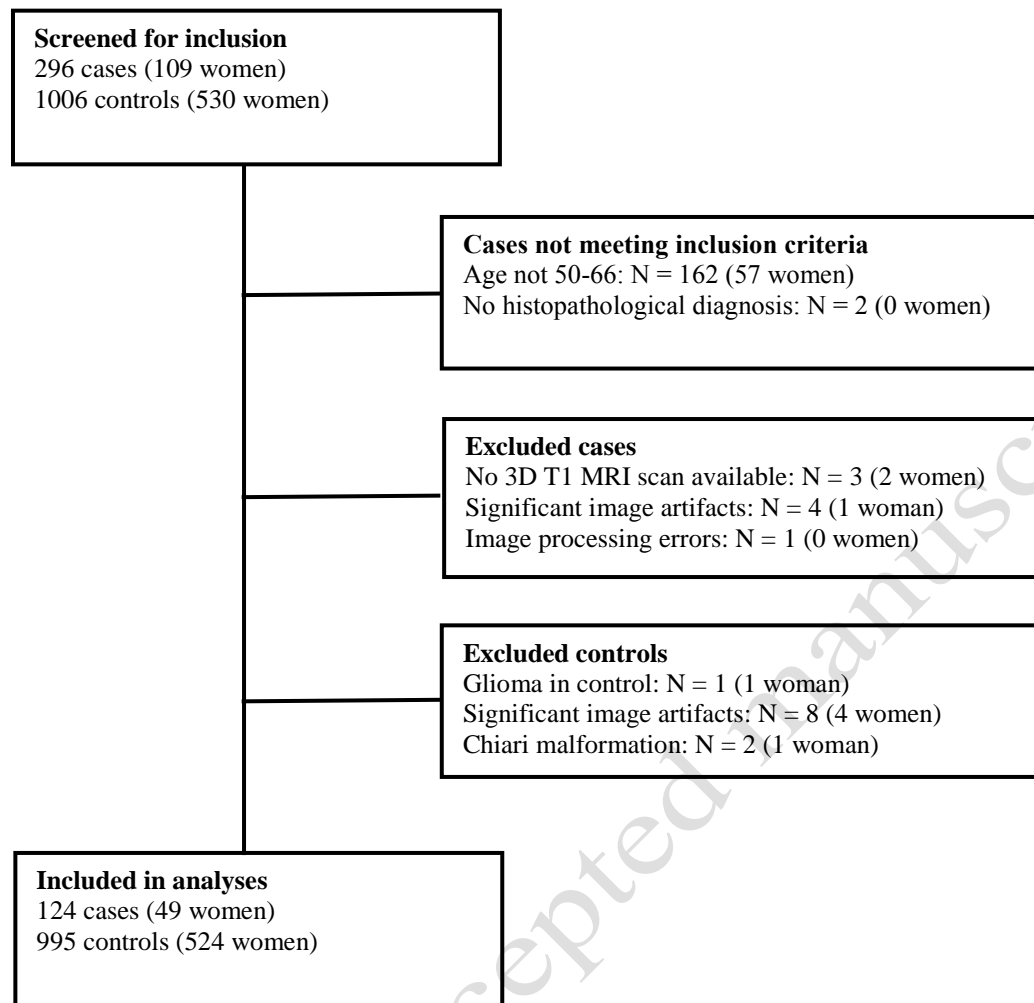
**Table 1.** Intracranial volume (ICV) and age given as mean  $\pm$  standard deviation by sex in patients with high-grade glioma (HGG) and controls.

	Patients with HGG		Controls	
	Female (n = 49: 39.5 %)	Male (n = 75: 60.5 %)	Female (n = 524: 52.3 %)	Male (n = 471: 47.7 %)
ICV (mL)	1537 $\pm$ 130	1781 $\pm$ 129	1482 $\pm$ 114	1689 $\pm$ 122
Age (years)	59.7 $\pm$ 5.1	59.2 $\pm$ 4.5	58.7 $\pm$ 4.3	59.2 $\pm$ 4.2

**Table 2.** Logistic regression predicting likelihood of glioma based on intracranial volume (ICV) and sex.

	Odds ratio (95 % CI)	P-value of OR
ICV (per 100 mL)	1.69 (1.44 to 1.98)	< 0.001
Male sex	0.56 (0.33 to 0.93)	0.026

## Figures



### Legend to figure 1

**Figure 1.** Flow chart of the inclusion process