*Short Communication*

# Risk of Cancer among Relatives of Patients with Glioma[1]

**Brian P. O'Neill,[2] Hannes Blondal, Ping Yang, Gurri H. Olafsdottir, H. Sigvaldason, Robert B. Jenkins, David W. Kimmel, Bernd W. Scheithauer, Walter A. Rocca, Johannes Bjornsson, and Hfran Tulinius**

Departments of Neurology [B. P. O., D. W. K., W. A. R.], Health Sciences Research [P. Y., W. A. R.], and Laboratory Medicine, Mayo Clinic and Foundation [R. B. J., B. W. S.], and the Mayo Clinic Cancer Center, Rochester Minnesota 55905 [B. P. O., P. Y., R. B. J., D. W. K., B. W. S.]; Department of Anatomy and Pathology, University of Iceland, Reykjavik, Iceland [H. B., J. B.]; and the Icelandic Cancer Registry, Reykjavik, Iceland [G. H. O., H. S., H. T.]

## Abstract

**We report a population-based, retrospective study of 396 Icelandic people diagnosed with glioma in the years 1940–1995. The purpose of this study was to test whether astrocytomas, other glial tumors, other central nervous system tumors, or other cancers aggregate in families identified through glioma probands who were of Icelandic origin. Pedigrees of the 396 cases were traced by the Genetical Committee of the University of Iceland and linked to the Icelandic Cancer Registry. A total of 25,546 relatives, including 2,080 individuals with cancer were identified within these pedigrees. There was no statistically significant increase of glioma in relatives of glioma patients, nor was there any statistically significant increase in risk for other central nervous system tumors. There was no overall increase in incidence of all cancer combined, nor of specific common cancers (lung, prostate, breast, stomach, and colorectal) and uncommon cancers (melanoma and pancreas) in the relatives of glioma patients. Our results do not support the hypothesis of a familial aggregation of glioma indicative of a glioma susceptibility gene.**

## Introduction

The majority of gliomas occur sporadically, and familial clusters appear in <5% of cases (1–4). Notable families are those with an inherited germ-line mutation that confers a unique genetic susceptibility to glial tumors and other malignancies (5). Investigation now has turned toward determining whether genetic factors play a significant etiologic role in the more common sporadic glioma (6–10). The unique epidemiological resources in Iceland provide the optimal setting for testing whether astrocytomas, other gliomas, other central nervous system tumors, or other cancers aggregate in glioma families (11). We herein report a population-based, retrospective study of 396 extended pedigrees identified by probands with glioma diagnosed in Iceland.

## Materials and Methods

ICR[3], founded in 1954 by the Icelandic Cancer Society, has published population-based cancer incidence annually since January 1, 1955 (11). To identify families with an increased incidence of brain tumors and other cancer, pedigrees generated by the Genetical Committee of the University of Iceland were cross-referenced against the files of the ICR to yield the cancer diagnosis for each member of the pedigree with a malignancy.

A memorandum of understanding was signed by representatives of Mayo Foundation, the University of Iceland, and the ICR. Permission to register personal data was submitted to the Icelandic Data Commission. The name, social security number, and gender of each Icelandic patient with glioma were submitted to the Genetics Committee of the University of Iceland. Each subject was assigned a running number so that the actual patient identity was not contained in the database for analysis. Similar to previous publications, a patient is kept as a proband, although he or she is a relative in another family (12, 13). The resulting genealogy was additionally linked to the ICR to identify families with brain tumors and families with other cancers.

There were 402 gliomas identified by one of the authors (H. B.) from departmental databases (Department of Pathology, University Hospital, Reykjavik, Iceland, and Department of Neuropathology, Rigshospitalet, Copenhagen, Denmark) maintained since 1940. Before 1971, all Icelandic patients were surgically diagnosed at one of three affiliated hospitals of the University of Copenhagen. Since 1971, virtually all Icelandic glioma patients had their surgery at University Hospital, Reykjavik. Two neuropathologists (H. B., B. W. S.) reviewed the diagnostic tissues of all cases. In all but two of the cases, sections were recut from the paraffin blocks and restained, including immunohistochemistry staining (when necessary), and classified according to the most recent WHO classification (15).

Each member of the pedigrees was classified by type of relative, *i.e.,* first-, second-, or third-degree relative of the proband. For each relative, the years lived from January 1, 1955 to December 31, 1995 were grouped by (*a*) sex of the individual, (*b*) 5 years in age, and (*c*) 5 calendar years. The expected rate of each tumor at each site was computed by multiplying the age and time-specific incidence rates of the Icelandic population by the sum of the number of years spent in each sex-, age-, and calendar year-specific category. RRs were computed as the ratio between observed and expected numbers.

Received 11/2/00; revised 4/23/02; accepted 5/13/02.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported in part by the Linse Bock Foundation and the Mayo Clinic Cancer Center, Rochester MN. This work was presented in part at the 90th annual meeting of the American Association for Cancer Research, Philadelphia, April 1999.
[2] To whom requests for reprints should be addressed, at Department of Neurology, Mayo Clinic and Foundation, 200 Southwest First Street, Rochester MN 55905. E-mail: boneill@mayo.edu.

[3] The abbreviations used are: ICR, Icelandic Cancer Registry; RR, relative risk.

*Table 1* RR of glioma in relatives of glioma cancer patients

| Relatedness | Number | | Ratio observed/ expected | 95% confidence interval |
|---|---|---|---|---|
| | Observed | Expected | | |
| 1st degree | 8 | 5.47 | 1.46 | 0.63–2.88 |
| 2nd degree | 12 | 10.06 | 1.19 | 0.62–2.08 |
| 3rd degree | 24 | 19.34 | 1.24 | 0.79–1.85 |

*Table 2* RR of other central nervous tumors in relatives of glioma cancer patients

| Relatedness | Number | | Ratio observed/ expected | 95% confidence interval |
|---|---|---|---|---|
| | Observed | Expected | | |
| 1st degree | 11 | 6.50 | 1.69 | 0.84–3.03 |
| 2nd degree | 12 | 12.15 | 0.96 | 0.50–1.68 |
| 3rd degree | 25 | 21.86 | 1.14 | 0.74–1.69 |

## Results

Between the years 1940 and 1995, 402 Icelandic residents were diagnosed with glioma. Six of the 402 were foreign-born, leaving 396 persons with glioma eligible for this study. Of these, 45 were children and adolescents (≤18 years of age) and 351 were adults. There were 328 astrocytomas, including 208 cases of glioblastoma multiforme, 36 pilocytic astrocytomas, 34 mixed oligoastrocytomas, and 5 other less common forms of astrocytic tumors. In addition, there were 31 oligodendrogliomas, 16 ependymomas, and 21 other primary tumors. All but 15 were intracranial. There were 4 patients with known familial syndromes: a father and son with neurofibromatosis each had astrocytoma and two unrelated patients had subependymal giant cell astrocytoma and tuberous sclerosis.

Within these 396 pedigrees, a total of 25,546 relatives was identified, including 2,080 individuals with cancer. Table 1 displays the members of the pedigrees with glioma and categorizes them by their relationship with the proband, *i.e.*, first-, second-, and third-degree relatives. There was not a statistically significant increase of glioma in relatives of glioma patients; overall, a total of 44 relatives had glioma, 35 were expected. The co-occurrence of glioma and other central nervous system tumors in relatives of glioma probands is displayed in Table 2. The term "other central nervous system tumors" includes neoplasms such as meningiomas, pituitary adenomas, craniopharyngiomas, and acoustic and spinal schwannomas. There was not an overall statistically significant increase in risk for "other central nervous system tumors"; a total of 48 relatives had other central nervous system tumors, 41 were expected. Furthermore, there was not an overall statistically significant increase in risk for any tumors (*i.e.*, glioma plus "other central nervous system tumors"); 92 relatives had any central nervous system tumors, 76 were expected.

International Classification of Diseases-7 codes were used to evaluate the association of glioma and specific systemic cancers as well as all systemic cancer combined. Cancers were arbitrarily grouped as common (lung, prostate, breast, stomach, and colorectal) or uncommon (melanoma and pancreas) based on the latest ICR analysis of cancer incidence rates for the Republic of Iceland (11). Table 3 displays the RR for all cancers combined and for each common and uncommon systemic cancer. There was not an overall increase in incidence of all cancers combined, nor of specific common and uncommon cancers represented in the relatives of glioma patients. For all sites combined, 2,080 were observed and 2,130 were expected. As examples of specific cancers, 219 relatives with prostate cancer were observed and 173 were expected, and 64 relatives with endometrial cancer were observed and 55 were expected.

## Discussion

In this study, the most important finding is that there was no statistically significant increase of glioma in relatives of glioma patients, and there was not an overall significant increase in risk for all other central nervous system tumors. Furthermore, there was no overall increase in incidence of all cancer combined, nor of specific common cancers (lung, prostate, breast, and colorectal) and uncommon ones (melanoma and pancreas) in the relatives of glioma patients.

Until recently, there has been a paucity of reports on the familial aggregation of primary brain tumors in general and gliomas in particular. Those reports usually lumped all primary brain tumors within reports of systemic cancers (8, 9, 16), lacked neuropathological confirmation of diagnoses (17), or focused on those tumor predisposition syndromes known to be associated with uncommon brain tumors.

The Utah Population Database has supported extensive investigations on the familial aggregation of many cancer sites (8). Specific to glioma families, these studies have not subtyped gliomas and have not differentiated among tumor types [some tumors such as meningioma and acoustic schwannoma have specific genetic implications] (18). deAndrade *et al.* (19) and Malmer *et al.* (4) both studied sizable populations of brain tumor patients and concluded that familial glioma occurs in ≤5% of all glioma cases and that a multifactorial Mendelian model was favored with perhaps as many as 1% having an autosomal dominant inheritance.

The 396 patients accurately reflect the number of Icelandic patients diagnosed with glial tumors during the 55-year period under investigation. Immigration and emigration from the Republic of Iceland is rare (immigration or emigration is currently estimated to be <3%/year). Thus all patients who developed their tumor in Iceland sought diagnosis there and had their surgery there or at the collaborating hospitals in Copenhagen (before 1971). Lastly, the neuropathological diagnoses are secure.

There were several inherent limitations of this study. One might expect any familial increase in risk to be strongest when restricted to those tumors diagnosed at a young age. The literature provides guidelines as to the definition of younger and older patients (17). Because pediatric glioma may be genotypically (20, 21) and phenotypically distinct from adult glioma, we separately analyzed those patients whose gliomas were diagnosed at or below the age of 50. Unfortunately there were insufficient numbers of patients to do this subgroup analysis. In addition, one might expect any familial increase in risk to be strongest when restricted to those subtypes with the largest number of cases. A separate analysis was attempted for patients with astrocytoma only. Again there were insufficient numbers of patients to do this subgroup analysis. Lastly, if there was a recessive component, then the sibling RR would be higher than the parent-child RR. Thus, data from siblings were analyzed separately from other first-degree relatives. We were unable to do this subgroup analysis because of insufficient data on siblings.

An ascertainment bias cannot be excluded. Analysis of the numbers of brain tumors, including glioma per year and as a percentage of the total Icelandic population, showed an increase in incidence over time. Although there could be a real increase in brain tumors in Iceland, it is more likely because of increas-

*Table 3* RR of systemic cancer in relatives of glioma cancer patients

| Cancer | First degree | | | Second degree | | | Third degree | | |
|---|---|---|---|---|---|---|---|---|---|
| | Obs | RR | 95% CI | Obs | RR | 95% CI | Obs | RR | 95% CD[a] |
| All sites | 373 | 0.98 | 0.88–1.09 | 624 | 0.94 | 0.86–1.03 | 1083 | 0.99 | 0.93–1.05 |
| Breast (female) | 40 | 0.88 | 0.63–1.20 | 80 | 1.01 | 0.81–1.26 | 159 | 1.16 | 0.99–1.36 |
| Ovary | 15 | 1.31 | 0.73–2.16 | 15 | 0.75 | 0.42–1.24 | 37 | 1.06 | 0.75–1.46 |
| Endometrium | 15 | 1.51 | 0.85–2.49 | 21 | 1.29 | 0.80–1.97 | 28 | 0.97 | 0.65–1.41 |
| Cervix | 3 | 0.32 | 0.07–0.93 | 18 | 1.05 | 0.62–1.66 | 28 | 0.91 | 0.61–1.32 |
| Prostate | 32 | 0.81 | 0.55–1.14 | 59 | 0.95 | 0.73–1.24 | 128 | 1.18 | 0.99–1.41 |
| Stomach | 47 | 1.04 | 0.76–1.38 | 84 | 1.01 | 0.81–1.26 | 123 | 1.09 | 0.91–1.31 |
| Pancreas | 7 | 0.53 | 0.21–1.09 | 30 | 1.34 | 0.90–1.92 | 31 | 0.88 | 0.60–1.25 |
| Lung | 47 | 1.29 | 0.95–1.72 | 50 | 0.89 | 0.66–1.17 | 96 | 0.86 | 0.70–1.06 |
| Colon/rectum | 38 | 0.98 | 0.68–1.34 | 43 | 0.65 | 0.47–0.88 | 87 | 0.82 | 0.66–1.02 |
| Kidney | 24 | 1.36 | 0.87–2.03 | 32 | 1.09 | 0.75–1.54 | 61 | 1.20 | 0.93–1.56 |
| Bladder | 23 | 1.27 | 0.81–1.90 | 31 | 1.07 | 0.73–1.52 | 52 | 0.98 | 0.73–1.31 |
| Brain | 19 | 1.59 | 0.96–2.50 | 24 | 1.08 | 0.65–1.51 | 49 | 1.19 | 0.86–1.52 |
| Thyroid | 19 | 1.60 | 0.96–2.50 | 15 | 0.69 | 0.39–1.14 | 38 | 1.05 | 0.73–1.44 |
| Leukemia | 5 | 0.54 | 0.17–1.25 | 21 | 1.17 | 0.72–1.79 | 31 | 1.03 | 0.70–1.46 |
| Melanoma | 8 | 1.50 | 0.65–2.96 | 7 | 0.70 | 0.28–1.44 | 15 | 0.87 | 0.49–1.44 |

[a] CI, confidence interval; Obs, observed.

ing availability of diagnostic services (neurosurgery in Iceland only since 1971 and modern neuroimaging since 1982), increasing age of the population (there was a substantial gain in life expectancy over the 55-year period of this study), and an increasing medical sophistication of the community at large. If there was a higher incidence of primary brain tumors, one might see associations appear per decade over the length of the study. Secondly, this is a case ascertainment series and most brain tumor epidemiological studies have relied on registry data such as Surveillance, Epidemiology, and End Results (upon which the aforementioned two studies were based) in the United States and other such registries internationally. The autopsy rate has not been constant in Iceland over the study period 1940–1995. In 1951, the autopsy rate was 13.9%, reaching 42.0% in 1978 but falling to 19.9% in 1995.[4] Thus, patients with primary brain tumors, glioma, and others may have been missed because we relied only on histologically reviewed material. One might expect that this would influence associations in the earlier part of the study. The low numbers prevented an analysis restricted to the past two decades when more patients were clinically diagnosed rather than diagnosed by surgery or autopsy. This will be thoroughly examined when the data are more mature.

Familial clustering of two or more cancer sites is usually attributed to specific, rare, dominantly inherited, susceptibility genes. Examples of germ-line syndromes, which have an increased risk for both central nervous system and systemic malignancies, include the Li-Fraumeni syndrome and neurofibromatosis, both of which have abnormalities on chromosome 17 (5, 7, 18). Addressing this point, Thomas *et al.* (16) suggested a possible familial association between brain tumors and stomach cancer or myeloma. The lack of any association in our study may simply be a matter of numbers, and we may have exhausted the usefulness of a retrospective study using surgically acquired tissue. Thus, trends may simply not have achieved significance because of small numbers.

Our next step is to focus on those families where there was more than one member affected (so-called multiplex families). It is tempting to speculate that brain tumor susceptibility genes are responsible. Thus, we will proceed in two directions. Firstly, because there are 45 multiplex families, we will screen candidate pedigrees for glioma markers already known to be important for the pathogenesis of sporadic gliomas (22). Paunu *et al.* (23) used comparative genomic hybridization on 21 patients from 17 families with two or more gliomas. They found that loss of 6q was the most frequent loss in these familial gliomas and also represented the most common intrafamilial aberration. No study previous to ours has such a rich resource of population-based data. Secondly, we will begin to construct a data resource that prospectively acquires clinical and imaging data and biological specimens so that we can leverage research efforts to test hypotheses on central nervous system tumor susceptibility genes and their interaction with other genes and environmental exposures.

[4] H. Blondal, unpublished data.

## Acknowledgments

We thank Leslie Ottjes (Translational Research Program in Neuro-Oncology, Mayo Clinic Cancer Center, Rochester MN) for excellent administrative support. We also thank Dr. Henning Laursen (Institute of Neuropathology, University of Copenhagen, Copenhagen, Denmark) for providing us access to histological material from Icelanders who underwent surgery. We also thank the Genetical Committee of University of Iceland for tracing the families.

## References

1. Landis, S. H., Murray, T., Bolden, S., and Wingo, P. A. Cancer statistics, 1998. CA - Cancer J. Clin., *48:* 6–29, 1998.

2. Radhakrishnan, K., Mokri, B., Parisi, J. E., O'Fallon, W. M., Sunku, J., and Kurland, L. T. The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. Ann. Neurol., *37:* 67–73, 1995.

3. Bohnen, N. J., O'Neill, B. P., and Kurland, L. T. Epidemiology of brain tumors. *In:* J. Loeffler and P. M. Black (eds.), Cancer of the Nervous System, pp. 3–24, Cambridge, MA. Blackwell Scientific Publications, 1997.

4. Malmer, B., Iselius, L., Holmberg, E., Collins, A., Henriksson, R., and Gronberg, H. Genetic epidemiology of glioma. Br. J. Cancer, *8:* 429–434, 2001.

5. Li, F. P., Fraumeni, J. F., Jr., Mulvihill, J. J., Blattner, W. A., Dreyfus, M. G., Tucker, M. A., and Miller, R. W. A cancer family syndrome in twenty-four kindreds. Cancer Res., *48:* 5358–5362, 1988.

6. Ganju, V., Jenkins, R. B., O'Fallon, J. R., Scheithauer, B. W., Ransom, D. T., Katzman, J. A., and Kimmel, D. W. Prognostic factors in gliomas: a multivariate analysis of clinical, pathologic, flow cytometry, cytogenetic, and molecular markers. Cancer (Phila.), *74:* 920–927, 1994.

7. Trent, J. M., Kaneko, Y., and Mitelman, F. Report of the committee on structural chromosome changes in neoplasia. Cytogenet. Cell Genet., *51:* 533–562, 1989.

8. Cannon-Albright, L. A., Thomas, A. Goldgar, D. E., Gholami, K., Rowe, K., Jacobsen, M., McWhorter, W. P., and Skolnick, M. H. Familiality of cancer in Utah. Cancer Res., *54:* 2378–2385, 1994.

9. Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A., and Skolnick, M. H. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J. Cell. Biochem. Suppl., *86:* 1600–1608, 1994.

10. Kerber, R. A. Method for calculating risk associated with family history of a disease. Genet. Epidemiol., *12:* 291–301, 1995.

11. Tulinius, H., Storm, H. H., Pukkala, E., Andersen, A., and Ericsson, J. Cancer in the Nordic countries, 1981–1986. Acta Pathol. Microbiol. Immunol. Scand., *100* (Suppl. 31)*:* 1–194, 1992.

12. Bai, Y., Sherman, S., Khoury, M. J., and Flanders, W. D. Bias associated with study protocols using epidemiologic studies of disease familial aggregation. Am. J. Epidemiol., *151:* 927–937, 2000.

13. Tulinius, H., Olafsdottir, G. H., Sigvaldason, H., Tryggvadottir, L., and Bjarnadottir, K. Neoplastic diseases in families of breast cancer patients. J. Med. Genet., *31:* 618–621, 1994.

14. Kernohan, J. W., and Sayre, G. P. Tumors of the Central Nervous System: Fasicle 35, Atlas of Tumor Pathology. Washington DC: Armed Forces Institute of Pathology, 1952.

15. Kleihues, P., Burger, P. C., and Scheithauer, B. W. The new WHO classification of brain tumors. Brain Pathol., *3:* 255–268, 1993.

16. Thomas, A., Cannon-Albright, L. A., Bansal, A., and Skolnick, M. H. Familial associations between cancer sites. Comput. Biomed. Res., *32:* 517–529, 1999.

17. Legler, J. M., Ries, L. A., Smith, M. A., Warren, J. L., Heineman, E. F., Kaplan, R. S., and Linet, M. S. Cancer surveillance series: brain and other central nervous system cancers: recent trends in incidence and mortality. J. Cell. Biochem. Suppl., *91:* 1382–1390, 1999.

18. Seizinger, B. R., Rouleau, G. A., Lane, A. H., Farmer, G., Ozelius, L. J., Haines, J. L., Parry, D. N., Korf, B. R., Pericak-Vance, M. A., Faryniarzag, A. G., *et al*. Linkage analysis in von Recklinghausen neurofibromatosis (NF1) with DNA markers for chromosome 17. Genomics, *1:* 346–348, 1987.

19. de Andrade, M., Barnholtz, J. S., Amos, C. I., Adatto, P., Spencer, C., and Bondy, M. L. Segregation analysis of cancer in families of glioma patients. Genet. Epidemiol., *20:* 258–270, 2001.

20. Pollack, I. F., Finkelstein, S. D., Woods, J., Burnham, J., Holmes, E. J., Hamilton, R. L., Yates, A. J., Boyett, J. M., Finlay, J. L., and Sposto, R. Expression of p53 and prognosis in children with malignant gliomas. N. Engl. J. Med., *346:* 420–427, 2002.

21. Bredel, M., Pollack, I. F., Hamilton, R. L., and James, C. D. Epidermal growth factor receptor expression and gene amplification in high-grade non-brainstem gliomas of childhood. Clin. Cancer Res., *7:* 1786–1792, 1999.

22. Louis, D. L. A molecular genetic model of astrocytoma histopathology. Brain Pathol., *7:* 755–764, 1997.

23. Paunu, N., Sallinen, S. L., Karhu, R., Miettinen, H., Sallinen, P., Kononen, J., Laippala, P., Simola, K. O., Helen, P., and Haapasalo, H. Chromosome imbalances in familial gliomas detected by comparative genomic hybridization. Genes Chromosomes Cancer, *29:* 339–346, 2000.