The impact of age and sex on the incidence of glial tumors in New York state from 1976 to 1995

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Object. In this study the authors describe secular trends in the incidence of three glial tumors—glioblastoma multiforme (GBM), astrocytoma not otherwise specified (ANOS), and anaplastic astrocytoma (AA)—in New York state from 1976 through 1995. They also describe the effect of age and sex on the relative risk (RR) for these tumors, specifically GBM.

Methods. Crude, age-, and sex-specific incidence rates were calculated for each tumor type from 1976 to 1995 by using data from the New York State Cancer Registry. Age-adjusted incidence rates were calculated by the direct standardization procedure, in which the 1970 United States Census Population Standard Million is used. The RR of GBM for the female population was calculated and plotted. Statistical comparisons were made using Pearson’s correlation coefficient and regression analysis with the coefficient of variation.

Conclusions. The age-adjusted incidence of these three glial tumors increased during the study period. Increases in age-specific incidence of GBM were primarily limited to patients 60 years of age or older. The reasons for these increases cannot be fully explained with the data. Those in the female population had a lower risk of developing these tumors than those in the male. For GBM, the protective effect of sex was first evident at the approximate age of menarche, was greatest at the approximate age of menopause, and decreased in postmenopausal age strata. The overall protective effect of female sex and the described trend in RR for GBM in the female population suggests that sex hormones and/or genetic differences between males and females may play a role in the pathogenesis of this tumor.

KEY WORDS • glioblastoma • astrocytoma • tumor incidence

Incidence rates for primary malignant tumors of the CNS have been slowly increasing over the last two decades. The rise in incidence rates has been seen primarily in elderly patients. Data from the Connecticut Tumor Registry, a part of the Surveillance, Epidemiology and End Results database, demonstrate considerable increases in brain tumor incidence between 1965 and 1988 in patients 65 to 84 years of age.13 Increased incidence of glial tumors of astrocytic origin—GBM, ANOS, and AA—as well as CNS lymphomas has been observed.13 Although the exact reasons for increased incidence in the elderly are not known, it is a fact that our ability to detect intracranial neoplasms has improved. The introduction of CT scanning in the early 1970s, followed by MR imaging in the early 1980s, has improved the sensitivity of brain imaging. Meanwhile, related advances in imaging-assisted stereotactic biopsy procedures have provided less morbidity-inducing and more accurate procedures to use for tissue diagnosis in primary brain tumors. These technological advances, coupled with a more aggressive diagnostic approach to elderly patients with neurological symptoms, have likely played a major role in the observed incidence trends.10,15

In addition to the increased incidence of primary intracranial tumors seen with advancing age, the female population appears to be at lower risk of developing GBM than the male. Evidence from animal models indicates that estrogen exposure confers a protective effect on both GBM incidence and survival.14,16,21 Studies of GBM incidence in human populations also indicate that the female subgroup is at lower risk for developing GBM compared with the male subgroup of similar age.5,10,12,22,23 In one case-control study it was observed that postmenopausal women were at a higher risk of GBM than were premenopausal females; however, none of the population-based studies considers the effect of age, as a proxy for menopausal status, on the RR of GBM in the female population. We examined the age-adjusted, age-, and gender-specific trends in GBM, ANOS, and AA incidence from 1976 to 1995 in New York state to determine secular trends in the incidence of these tumors. Given our interest in the putative protective effect of estrogen in GBM, we also described the effect of

Abbreviations used in this paper: AA = anaplastic astrocytoma; ANOS = astrocytoma not otherwise specified; CI = confidence interval; CNS = central nervous system; CT = computerized tomography; GBM = glioblastoma multiforme; ICD-9 = International Classification of Diseases, ninth revision; MR = magnetic resonance; NYSCR = New York State Cancer Registry; r2 = coefficient of variation; r = Pearson’s correlation coefficient; RR = relative risk.
Impact of age and sex on glial tumor incidence in New York state

TABLE 1
Number of cases and age-adjusted incidence rates of GBM from 1976 to 1995, calculated according to sex

<table>
<thead>
<tr>
<th>Year</th>
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<th>95% CI</th>
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TABLE 2
Number of cases and age-adjusted incidence rates of ANOS from 1976 to 1995, calculated according to sex

<table>
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<th>95% CI</th>
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* Dx = diagnosis; incid = incidence; LL = lower limit; UL = upper limit.
† Cases per 100,000 population.

Clinical Material and Methods

The NYSCR is a population-based registry encompassing all of New York state. Based on the results of hospital record audits, it has been estimated that more than 95% of all cancer cases in New York state outside New York City are reported to the registry. Using data from the NYSCR, all cases of GBM, ANOS, and AA (ICD-9 codes 191.0–191.9; morphology codes [GBM] M9380-1 and M9440-2; [ANOS] M9400, M9410-11, and M9420-21; and [AA] M9401) were identified for the period 1976 to 1995. The year 1976 was chosen as the starting point because before that year the data do not reliably account for cases from New York City.

The annual, age-specific incidence rates for each tumor type were calculated for the male and female populations. Next, the annual age-adjusted incidence rates were calculated for each sex by using direct standardization to the 1970 United States Census Population Standard Million. The 95% CI was calculated for these incidence rates by using the following formula: incidence rate/(number of cases) 1/2 .

The corresponding linear regression plots are presented in Figs. 1, 3, and 5, respectively. The plots were fitted using the following formula: incidence rate = (slope) × age + (intercept). The 95% CI was calculated for these incidence rates by using the formula: incidence rate/(number of cases) 1/2 .

The 20-year trends in age-adjusted incidence rates were calculated for each sex by using direct standardization to the 1970 United States Census Population Standard Million. The 95% CI was calculated for these incidence rates by using the formula: incidence rate/(number of cases) 1/2 .

The 95% CI for RR was calculated using the following formula: Exp[ln(RR) ± 1.96 × standard deviation ln(IRR)] .

Statistical and graphic analyses were performed using commercially available software (SPSS; SPSS, Inc., Chicago, IL, and Microsoft Excel; Microsoft Corp., Redmond, WA).

Results

Our review of NYSCR data identified 11,204 cases of GBM, 4613 cases of ANOS, and 878 cases of AA diagnosed from 1976 through 1995. The age-adjusted incidence rates with 95% CI for GBM, ANOS, and AA are presented in Table 1. The incidence rates were stratified by age and sex and compared using linear regression and r² analyses to test for significant changes over time. To determine the effect of age on incidence, the r between the age at diagnosis and crude incidence rates of each tumor was analyzed in a similar fashion. We then calculated the RR for GBM in the female population compared with their male counterparts by dividing the weighted average incidence in females by the weighted average incidence in males for each age stratum. The RR was then plotted against age strata. The 95% CI for RR was calculated using the following formula: Exp[ln(RR) ± 1.96 × standard deviation ln(IRR)].

The observed increases in GBM and AA were statistically significant, indicating that the increase observed over the full 20-year period was not due solely to the rarity of the diagnosis from 1976 to 1985. Furthermore, the increase in ANOS incidence was observed increases in GBM and AA were statistically significant, indicating that the increase observed over the full 20-year period was not due solely to the rarity of the diagnosis from 1976 to 1985. Further-
more, by this analysis we demonstrated that the age-adjusted incidence of AA continued to rise throughout the second half of the study period.

To examine incidence trends according to age strata, the correlations among the crude and age-specific incidence rates of each tumor type and the year of diagnosis were determined for each sex by using Pearson’s correlation coefficient. In the male population, GBM incidence increased significantly from 1976 to 1995 in the following age groups: 45 to 49, 60 to 64, 70 to 74, 75 to 79, 80 to 84, and older than 85 years of age. In the female population, GBM incidence rose significantly in all strata after 60 years of age (Table 5). No statistically significant increases in age-specific incidence were seen over the 20-year period for the female population 44 years of age or younger.

The RR for GBM in the female population in each age stratum was determined by dividing the age-specific, weighted-average incidence of GBM for the female by that for the male subgroup. We calculated the r and the $r^2$ to determine the correlation between age and RR for GBM in the female population, and a significant inverse correlation was found ($r = -0.71$; $r^2_{linear} = 0.50$; $r^2_{quadratic} = 0.78$; $p = 0.002$). That is, as members of the female population aged, their likelihood of developing GBM decreased relative to that of the male population. The RR reached its minimum in women aged 50 to 54 years, then increased in the remaining age strata. The line plot of RR for GBM in the female population appears in Fig. 7. The error bars represent the CI around the point estimate of RR for each age stratum. Regression plots of the relationship between age and RR for GBM in the female subgroup are presented in Fig. 8. In Fig. 8 upper a linear regression model yields an $r^2$ value of 0.50, whereas in Fig. 8 lower a quadratic regression model yields an $r^2$ value of 0.78.

The histological composition of the entire group of tumors diagnosed between 1976 and 1995 was determined and plotted (Fig. 9). In 1976, GBM accounted for approximately 75% of all tumors diagnosed, ANOS 25%, and AA less than 1%. In the early 1980s the incidence of AA began to rise dramatically, and by 1995 this histological subgroup accounted for approximately 10% of the total number of cases. Over the 20-year period, the proportion of GBMs decreased significantly ($r = -0.588$; $p = 0.006$), whereas AA accounted for a significantly higher percentage of tumors in 1995 than in 1976 ($r = 0.963$; $p < 0.0009$). The ANOS type comprised a slightly smaller proportion of tumors compared to GBM and AA.
fraction of the total number of tumors, but this decrease was not statistically significant ($r = -0.332; p = 0.152$).

**Discussion**

Several authors have addressed the apparent increase in the incidence of primary malignant CNS tumors. Although they generally agree that the incidence of primary malignant tumors has been rising, some rely on relatively small numbers of cases, lumping of tumor histological findings, or statistical sampling methods rather than a true population-based approach, to determine incidence rates. Some authors calculated disease-specific mortality rates to demonstrate similar findings.

In our study we used data from a population-based tumor registry and the New York State Census to determine genuine incidence rates. Although Fleury, et al., Kuratsu and Ushio, Polednak, and Preston-Martin, et al., used similar data sources, the combined number of cases from these studies is approximately 11,500 and includes at least 3270 nonastrocytic tumors. Our study alone includes more than 16,000 tumors, all of which are of astrocytic origin. This specificity is important because the age and sex distribution of primary CNS tumors differs according to histological subtypes. For example, meningioma is known to occur more commonly in the female population, whereas GBM, as our study demonstrates, occurs more commonly in the male. The trend we observed in RR for GBM in females could have been masked if our study had included all ICD-9 morphology codes for primary CNS tumors, especially because meningioma incidence is highest during roughly the same age range in which the RR for GBM is lowest in the female population. The inclusion of meningiomas would have tended to equalize the incidence rates in the female and male subgroups, thus obscuring the observed trend in RR. By limiting our analysis to astrocytic tumors, the described trends became evident. These trends are explained later in the discussion.

**Age-Adjusted Incidence**

From 1976 to 1995 the age-adjusted incidence of GBM increased for both sexes. In that time there had been an approximately 33% increase in incidence for the male and a 65% increase for the female subgroup. From 1984 to 1995 the age-adjusted incidence of AA in the male and female populations increased by approximately 150% and 160%, respectively. The increases in GBM and AA incidence were statistically significant. Although the incidence of ANOS appears to have increased by approximately 75% in the male and 50% in the female subgroup, these differences were not statistically significant.

**Age-Specific Incidence**

The increases in age-adjusted GBM incidence rates were the result of increases in the elderly population. Determination of age-specific incidence rates demonstrated that although there were significant increases in GBM incidence among men between the ages of 45 and 49 and 60 years and older and women 60 years of age and older, there were no significant changes in the population younger than 45 years of age from 1976 to 1995.
Although other investigators have also observed that increases in the incidence of glial tumors are limited to older populations, none has fully explained the reason for this phenomenon. Whether these increases have been the result of diagnostic advances during the last two decades is unclear. Two facts indicate that increased diagnostic sensitivity (provided by CT and MR studies) and capacity (provided by image-guided stereotactic biopsy procedures), as well as a more aggressive diagnostic approach to elderly patients may have played a major role in the increased incidence observed. First, improvements in the sensitivity of intracranial imaging have been closely followed by increases in CNS tumor incidence. Because CT scanning was introduced before the start of our study period, we cannot describe its effect on the incidence of these tumors in New York state. It is widely accepted, however, that the introduction of CT in the early 1970s increased the sensitivity of intracranial imaging. Consequently, case identification increased and, at least in part, led to increased astrocytic tumor incidence. In considering the effect of MR imaging on the increased incidence of astrocytic tumors, we noticed that AA incidence had increased markedly, beginning in 1982 and continuing through 1995. The emergence of AA coincided precisely with the introduction and increased utilization of MR imaging. Consequently, case identification increased and, at least in part, led to increased astrocytic tumor incidence. In considering the effect of CT and MR utilization rates over time would be interesting but difficult to perform, due to the lack of a single database containing imaging utilization data for patients of all ages. Another factor that potentially contributed to the increase in AA in the elderly was the increased utilization of stereotactic biopsy sampling in this population. Smaller tissue samples obtained during stereotactic biopsy procedures can lead to sampling error, which may result in undergrading of lesions that are not resected. The most common error is mistaking GBM for AA. Consequently, AA may be diagnosed more often at the expense of GBM in these patients.

A second factor that has probably played a role in the increases observed is the changing diagnostic approach to the elderly. Improvements in the health and life expectancy of the elderly have decreased medical nihilism toward this group. Neurological symptoms in an elderly person that in the past may have been attributed to a cerebrovascular event are now more likely to be worked up fully with CT or MR studies. If a lesion is detected, less invasive, image-guided stereotactic biopsy procedures are available that improve the risk-benefit ratio and make a tissue diagnosis more appealing. Although these scenarios are speculative, the fact that the increases in age-specific incidence have primarily been confined to patients 60 years of age and older lends credence to the argument that the increased incidence of astrocytic tumors has been due at least in part to increased case identification. However, we cannot assert on the basis of our data that this is so.

It is also interesting to note that AA incidence may have been leveling off in the last 5 years of our study, whereas GBM incidence has continued to rise. The explanation for this may be related to a differential penetration of MR imaging utilization into younger and older patient populations. Anaplastic astrocytoma tends to be found in younger patients, whereas GBM tends to affect older patients. If the penetration of MR imaging utilization occurred in younger patients first, we would expect the case composition in this group to be skewed toward AA and to level off after occult “prevalent” cases of AA are detected. Conse...
quently, the subsequent incorporation of MR imaging into the diagnostic work-up of older patients would be expected to skew the case composition in favor of GBM. Until the penetration of MR imaging into older patient populations levels off, we would expect to observe continued increases in GBM incidence as occult prevalent cases of this tumor type are detected. A systematic longitudinal study of age-specific MR imaging utilization rates and AA compared with GBM incidence rates would be required to test this hypothesis.

Some authors have attempted to demonstrate that the increased incidence of malignant glial tumors is not an artifact of increased case identification. By retrospective, blinded chart review, Desmeules, et al., determined that approximately 20% of CNS tumors remained undiagnosed without CT or MR imaging. Availability of CT or MR studies would therefore have resulted in a 20% increase in case identification. They argued that because the increased incidence of the aforementioned tumors among elderly patients in North America has been “at least two-fold . . . over the last two decades,” improved diagnosis with CT or MR imaging could not have been the sole reason for the observed increase. These authors may have underestimated the true incidence of missed tumors because they only considered patients who underwent CT or MR studies. Also, the potential constraints of the one-payer system in Canada (the site of the study) on the utilization of CT and MR studies was not addressed. This approach could also result in an overestimation of the increased incidence of gliomas in the study population, because Canadian national incidence data were used as the basis for comparison instead of the specific incidence in the study population. Thus, the twofold increase cited as the basis for comparison may not be accurate for the study population.

Age and Risk of GBM

We observed increased incidence of GBM, ANOS, and AA in the older age groups (data not included). The relationship between age and incidence is similar to that observed in the Surveillance, Epidemiology and End Results database and cited by Wrensch, et al., and is consistent with that reported in the literature for these tumors.

Sex and Risk of GBM

An effect of sex on GBM incidence rates was also demonstrated through the RR calculations. Overall, members of the male subgroup are approximately one and a half to two times more likely to develop GBM than are their female counterparts. The protective effect of female sex that we observed is consistent with data from other studies. Examination of the age-specific RR for GBM in the female population, however, reveals that the protection provided by being female does not emerge until the age stratum of 10 to 14 years. In this age group, we observed a decrease in RR for GBM in girls from approximately 1.02 to 0.78. This time frame roughly coincides with the onset of menstruation and cyclical ovarian estrogen production. The RR continues to decrease over the next several age strata, reaching a low of 0.51 for women.
investigations, the observation of Schlehofer, et al., 21 and
sent GBMs, logical types compared with the year of diagnosis.

the detrimental effects of exposure to male sex hormones.

sure to female sex hormones may actually be the result of

ble. For example, the proposed benefit derived from expo-

GBM, other explanations for our observations are plausi-

ry and epidemiological data presented indicates that fe-

babies are the first to demonstrate the effect of age within the

data from our large population-based analysis of GBM

the quadratic regression model appears to validate the pat-

menopause, followed by an increase in RR thereafter, is

corroborated by the regression analysis. Specifically, the

increase in $r^2$ observed when changing from the linear to

the quadratic regression model appears to validate the pat-

tern of changes in RR across age strata that we observed.

Although the overall protective effect of sex type on

GBM incidence can be inferred from other studies, our da-

ta are the first to demonstrate the effect of age within the

female subgroup on RR for GBM in a large population-

based study of GBM incidence. The overall protective

effect of female sex, coupled with the dissipation of pro-

tection after menopause, indicates that estrogen, proges-

terone, or their metabolites may be important inhibitors of

the pathogenesis of GBMs. Schlehofer, et al., 21 observed a

similar relationship between menopausal status and risk of

GBM. In a nested case-control study, they observed that

postmenopausal women were at an increased risk of GBM

compared with premenopausal women. The potential role

of female sex hormones is also supported by basic scient-

ific evidence. 1,14,16 The combination of these laboratory

investigations, the observation of Schlehofer, et al., 21 and

the data from our large population-based analysis of GBM

incidence should provide the impetus to investigate the

potheses involving sex and RR for GBM.

Conclusions

Analysis of GBM, ANOS, and AA cases from the

NYSCR confirms that, as a group, the incidence of these

CNS malignancies has increased over the last two decades

in New York state. Individually, the incidence of each of

these tumors rose, although the reasons for these increas-
es cannot be fully explained by our data. It appears that

some of these increases may be attributable to improved
diagnostic methods (CT scanning, MR imaging, stereo-
tactic biopsy procedures) and a more aggressive diagnos-
tic approach toward the elderly. Although we believe that

this is the dominant reason for the increasing incidence,

we cannot rule out the possibility that changes in environ-

mental exposures, tumorigenesis, or an inherent suscepti-

bility of elderly individuals are responsible for these ob-

servations.

The incidence of GBM grew in both men and women

in the period we studied. Men, however, have an overall

GBM incidence that is one and a half to two times that of

women. This trend toward lower risk for GBM in the fe-
male population appears to begin around the age of men-
arche and to be mitigated by menopause. An analysis of

the role of sex hormones and their metabolites or the con-
tribution of genetic differences between the sexes in the

pathogenesis and epidemiology of GBM should, there-
fore, be pursued aggressively.

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1984

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nervous system lymphoma be the most frequent brain tumor

role of computed tomography and other neuroradiologic pro-

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aged 50 to 54 years. This nadir in the RR for GBM in the
female population occurs approximately at menopause,
the time of cessation of ovarian estrogen production.
Women in subsequent age strata experience a rebound
increase in RR, although the RR never reaches 1. The RR
for GBM in women 55 to 79 years of age ranges from 0.64
to 0.71. This age range, in which there is subtle erosion of
the protective effect of sex, roughly coincides with the
postmenopausal years. This pattern of decreasing RR until
menopause, followed by an increase in RR thereafter, is

corroborated by the regression analysis. Specifically, the

increase in $r^2$ observed when changing from the linear to

the quadratic regression model appears to validate the pat-

tern of changes in RR across age strata that we observed.

Although the overall protective effect of sex type on

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effect of female sex, coupled with the dissipation of pro-

tection after menopause, indicates that estrogen, proges-

terone, or their metabolites may be important inhibitors of

the pathogenesis of GBMs. Schlehofer, et al.,21 observed a

similar relationship between menopausal status and risk of

GBM. In a nested case-control study, they observed that

postmenopausal women were at an increased risk of GBM

compared with premenopausal women. The potential role

of female sex hormones is also supported by basic scient-

ific evidence. 1,14,16 The combination of these laboratory

investigations, the observation of Schlehofer, et al.,21 and

the data from our large population-based analysis of GBM

incidence should provide the impetus to investigate the

potential roles that sex hormones may have in the origins

of GBM.

Although we argue that the combination of laboratory

and epidemiological data presented indicates that fe-
male sex hormones are protective against development of

GBM, other explanations for our observations are plausi-

ble. For example, the proposed benefit derived from expo-
sure to female sex hormones may actually be the result of

the detrimental effects of exposure to male sex hormones.

In this scenario, the female population, which has lower

exposure levels to male sex hormones, is thus at lower risk

for developing GBM than their male counterparts. An

alternative explanation for our observations may be root-
ed in genetic differences between the sexes. Innate dif-

ferences in the susceptibility of X and Y chromosomes
to tumorigenic stimuli may result in effect modification,

which would result in distinct risk profiles for each sex.

Finally, because our study is based on ecological compar-

isons, our observations may be the result of confounding

factors. Researchers must keep these possibilities in mind

when designing human and animal studies to test any hy-

potheses involving sex and RR for GBM.
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