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Older age at the completion of linear growth is associated with an increased risk of adult glioma

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Abstract

Purpose—To examine the association of age when adult height was attained with glioma risk.

Methods—We analyzed data from a US-based case-control study of glioma risk factors. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) associated between age at attainment of adult height and glioma risk. Multivariate models were adjusted for age, race, sex, education, and state of residence. We examined associations overall, and according to glioma grade, sex, and final adult height.

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

Results—The study set included $n=951$ controls and $n=776$ cases, with a median age of 56 [18-92], the majority was male (53.8%) and identified as Caucasian. Older age at height completion was associated with an increased risk of glioma. A significant positive trend was observed both for glioblastoma (OR 1.10; 95% CI 1.04-1.17 per 1 year increase in age) and lower-grade non-glioblastoma subtypes combined (OR 1.18; 95% CI 1.10-1.28 per year increase in age). The association was observed in men and women, and in all categories of final adult height.

Conclusions—We observed for the first time a positive association between glioma risk and a prolonged adolescent growth phase. Our results suggest a role for factors governing the timing and intensity of growth in adolescence as risk-promoting exposures in adult glioma.

Keywords

case-control studies; glioma; glioblastoma; adolescence; height; menarche

Introduction

Brain tumors represent a small, but lethal fraction of all primary cancers diagnosed each year in the US and Europe. The disproportionate mortality and morbidity burden associated with brain tumors merits a greater understanding of their cause. The incidence rate of glioma increases in the fifth decade of life, is higher in males, and is elevated in Caucasians when compared to other racial groups in the US [1]. The risk of glioma is higher in some rare inherited syndromes [2] and genetic susceptibility has been documented with the identification of single nucleotide variants associated with increased or decreased risk of glioma in genome-wide association studies [3]. Of the many environmental exposures studied, only ionizing radiation is a confirmed cause of primary human brain tumors [4]. However, the immune system response to the environment may also impact glioma in that a history of chicken pox [5] and respiratory allergies [6] are protective against glioma.

Taller stature is associated with an increased risk of several malignancies [7], though an association in glioma remains equivocal [8-12]. Posited mechanisms relating greater height to cancer risk include metabolic and molecular interactions during human development [13,14]. We and others have reported that glioma risk varies with other developmental milestones including increased risk with an elevated body mass index (BMI) in early adulthood, but not later in life [9,11], and with an increased age at menarche in women [15,16]. These findings taken together suggest that growth and maturation during adolescence may be important factors in adult glioma risk.

To shed further light on this hypothesis, we examined the association of age when height is attained with the risk of glioma in the context of a large US-based case-control study geographically confined to the southeastern United States. To the best of our knowledge, ours is the first study to consider the association of the timing of attainment of adult height during the lifespan with onset of glioma.

Materials and Methods

Study Population

Subjects in the analysis were enrolled in a clinic-based case-control study examining risk factors for adult glioma. All individuals were aged 18 or older. Glioma cases had a recent (within 3 months) primary diagnosis of glioma and were identified in neurosurgery and neuro-oncology clinics in the Southeastern US including Vanderbilt University Medical Center (Nashville, TN); Moffitt Cancer Center (Tampa, FL) and affiliated hospitals; University of Alabama at Birmingham (Birmingham, AL); Emory University (Atlanta, GA); and Norton Cancer Institute (Louisville, KY). 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 or non-blood related family members ($n = 257$) of cases or were identified through telephone listings frequency matched to individual cases on age, gender, race, and neighborhood via postal zip code ($n = 1,127$). An estimated 50% of contacted eligible households yielded a participating control. Enrollment occurred between December 2004 and July 2014. Institutional Review Boards of each participating institution approved the study. Written informed consent was obtained from all participants.

Data Collection

Demographic data and information on known and suspected glioma risk factors were collected in structured interviews [17,18]. For purposes of the current study, participants were asked to report the age at which they reached their maximum height. Portions of the questionnaire were previously validated [17] based on a second interview of 148 control subjects interviewed 2 to 4 months following the initial interview, which yielded strong correlation between first and second responses for adult height (Spearman $r = 0.99$). [Age at height attainment was not included in the second interview.]

Statistical Analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) associated with the exposure of age at attainment of maximum adult height. After excluding individuals who did not report age when height was attained, the analysis included 951 controls and 776 glioma cases. Multivariate models included a priori confounder terms for age at interview, race (Caucasian, non-Caucasian), sex, level of education (high school or less, some college, college degree, graduate degree), and US state of residence (AL, FL, GA, KY, TN, other). As height [8,9,12] and age at menarche [15] were previously found to be associated with glioma risk, final adult stature and, in models restricted to women, age at menarche were also considered as potential confounders. We examined associations of age at height attainment with glioma risk, overall, and according to glioma grade (glioblastoma and non-glioblastoma) and gender, for 5 levels of age at height attainment (15 years [referent], 16, 17, 18 and 19). We also considered associations according to tertile of final adult height (short, average, tall) with tertile cut-points established separately in males and females based on sex-specific distributions of reported height at age 21; 4 levels of exposure (16 years [referent group], 17, 18 and 19) were considered given sparse data per cell.

Spearman's rank correlations were calculated to test for potential relationships between adult height, age at maximum height, and age at menarche.

Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC). A p -value <0.05 was considered statistically significant and all statistical tests were two-sided.

Results

Demographics

Descriptive characteristics of study participants are summarized in Table 1. Median age for cases and controls was 56 and 57 years old, respectively. Men comprised over half of cases (57.0%) and controls (51.2%), and the majority of participants were Caucasian. Controls were more likely than cases to be college graduates (28.5% vs. 22.4%). Overall, controls were well matched to cases by age, gender, and race. Glioblastoma was the largest subgroup of gliomas ($n = 501$; 64.6%).

Self-reported mean adult height was 64.9 inches ($SD = 2.6$) for women and 70.7 inches ($SD = 2.8$) for men. The median age when maximum height was reached was 16 years in women (interdecile range: 13-19 years) and 18 years in men (interdecile range: 15-20 years) (results not shown).

Age at height attainment and risk of glioma

Increasing age at height attainment was significantly associated with an overall increased risk of glioma (Table 2) in crude and multivariate models. Compared to persons that reached adult height at age 15 years, a statistically significant increased adjusted odds of glioma was observed for an age at height attainment of 17 years (multivariate OR 1.53, 95% CI 1.12-2.10), 18 years (multivariate OR 1.61, 95% CI 1.18-2.21) and 19 years (multivariate OR 1.91, 95% CI 1.36-2.70). For each 1-year increase in age at height attainment, the multivariate odds of glioma increased by a factor of 1.12 (95% CI 1.07-1.18). Odds of glioma among persons attaining final height at age 19 or older were approximately twice that of persons aged 15 or younger at final height (multivariate OR 1.91, 95% CI 1.36-2.70). Significant positive associations were slightly more prominent for lower grade tumors (multivariate OR 1.18, 95% CI 1.10-1.28, per year increase in age) than for glioblastoma (multivariate OR 1.10, 95% CI 1.04-1.17, per year increase in age).

Correlations between developmental milestones and adult height

Among 798 women in the analysis, 768 (96.2%) women reported age at menarche. Three percent of women reported their first menstrual cycle before the age of 10, 45.4% ages 10-12, 38.8% ages 13-14, and 12.8% were over the age of 14 years. Women's final height and age at menarche were not highly correlated (Spearman $r = 0.07$; $p = 0.01$) whereas age at height attainment was positively correlated with age at menarche (Spearman $r = 0.20$; $p < 0.0001$), consistent with declining rate and cessation of growth around the time of puberty [19]. Age when maximum height was achieved and final height were uncorrelated in women (Spearman $r = -0.01$; $p = 0.68$) and men (Spearman $r = -0.1$; $p = 0.78$).

Associations according to gender

A positive association with increased age at final height and glioma risk was observed in men (multivariate OR 1.15, 95% CI 1.07-1.24, per year increase in age) and in women (multivariate OR 1.11, 95% CI 1.04-1.18, per year increase in age) (Table 3). Results were similar regardless of the choice of referent group; an increased risk with older age attained height was observed for 20 vs. 16 (referent) in men (multivariate OR 2.65, 95% CI 1.65-4.27, p for trend <0.0001) and 18 vs. 14 (referent) in women (multivariate OR 1.77, 95% CI 1.15-2.71, p for trend <0.01) (results not shown). Adjusting for final height and age at menarche did not change these results (results not shown).

Associations according to final adult height

A significant positive association of glioma with age at height attainment was observed regardless of final adult height (Table 4), with a significant positive trend found in the shortest (multivariate OR 1.17, 95% CI 1.07-1.28), average (multivariate OR 1.14, 95% CI 1.03-1.27), and tallest (multivariate OR 1.09, 95% CI 1.01-1.17) tertile of final height.

Discussion

In this study of 951 controls and 776 glioma cases, older age at height attainment was associated with an increased risk of glioma. The association was observed in men and women, and found for both glioblastoma and non-glioblastoma tumors. Moreover, when data were stratified according to final height, a positive association with older age at final height was observed regardless of final height attained. To our knowledge, this is the first study to examine the timing of height attainment in relation to adult glioma risk, with results suggesting that adolescent growth and development may contribute to the risk of glioma onset in later life.

In line with these results, previous studies support a link between growth in early life and glioma risk. In the Swedish Birth Registry cohort, Crump et al [20] reported that high fetal growth (determined by standardized intrauterine growth curves) was associated with an increased risk of glioma in childhood and early adulthood. Suggestive results were also noted for a higher birth weight and length, though tests for trend did not reach significance [20]. Using the Copenhagen School Health Records Register (CSHRR), Kitahara and colleagues [21] found that individuals who were larger babies and men who were taller boys between the ages of 7-13 had a higher risk of adult glioma [21]. Risk associations with growth in early life have also been seen in other cancers. The aforementioned CSHRR cohort demonstrated positive associations between height in childhood with the risk of prostate [22] and thyroid cancers [21]. Similar associations have been observed in breast, colorectal, hematopoietic, and endometrium cancers [23]. The current results thus add further evidence linking early life body size and growth velocity with the risk of adult cancer across a spectrum of tumors including glioma.

The relationship of glioma risk with age at height attainment in the present study was observed regardless of glioma grade, though data were consistent with a more prominent association in lower grade gliomas. Lower grade tumors develop in younger persons than do

glioblastomas and have a more indolent course [24]. We are unaware of any mechanism to explain the observed stronger association in non-glioblastomas and these findings may be due to chance.

The present findings suggest the timing of, or prolonged exposure to growth factors such as growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in childhood may contribute to adult glioma risk. Normal linear growth during adolescence is dependent on GH and IGF-1. GH stimulates growth plates in the vertebrae and long bones, notably in the leg, in addition to regulating the production and circulation of IGF-1 [25], which possesses strong anti-apoptotic properties [14]. The ability of IGF-1 to prevent programmed cell death and increase the rate of mitosis are crucial during development, but are also hallmark characteristics of cancer [14]. Some studies link longer leg length attributing to total stature to greater risk of cancer [14]. Serum levels of IGF-I have been linked to cancer risk [26] and are positively associated with growth rate in children [27]. The present results could indicate that elevated or prolonged exposure to IGF-I or other growth factors during the adolescent growth phase may contribute to glioma risk in later life.

Linear growth ends around the time of menarche [19], and we [15] and others [16] have reported that delayed menarche is associated with an increased risk of glioma in women. However, all associations persisted after multivariate adjustment for age at menarche in women, and final height, so that present findings are unlikely to reflect confounding by these factors. Puberty also marks the beginning of cyclic estrogen exposure in women and a later menarche is associated with reduced lifetime exposure to estrogen (accounting for the negative association between age at menarche and breast cancer risk [28]). Therefore, estrogen could be protective for glioma, as observed for several neurodegenerative diseases and brain injury [29], and may explain the lower incidence of glioma in women [30]. In support of this hypothesis, some studies indicated a protective association of exogenous estrogens (e.g. hormone replacement after menopause) with glioma risk [16]. However, a mechanism related to estrogen for the current findings (via cessation of growth with an earlier puberty) would not explain findings observed also in men. Finally, the present results could indicate relationships with prenatal and childhood nutrition as calorie restriction and lower socioeconomic status have been linked to slower development in childhood and shorter adult stature [31-33]. Although only speculation, the present observations support the possibility that early-life nutrition drives growth velocity and also the timing of puberty, and in turn exposure to hormones and growth factors that influence organ size and glial tissue at risk for tumor development decades later.

Strengths and limitations

Strengths of this study include its large size in a histologically-confirmed rare disease. Furthermore, a large majority of eligible glioma cases were enrolled in the study. Lower than optimal response rates in controls is a limitation although we can posit no reason that selective enrollment of controls on the primary exposure could explain reported associations with age at attained height. Furthermore, findings were robust, with similar associations demonstrated in all examined subgroups of participants. As with any case-control study, the reliance on lucid memories of participants presents a possible limitation. Middle-aged

individuals were able to recall their adolescent height relative to their peers [34], and elderly men and women were able to recall their height in the last year of high school [35] offering assurance that age at height attainment was recalled with reasonable accuracy. Furthermore, the age when one completes growth surrounds memorable life events, such as procuring a driver's license and matriculation, and timing of menarche in women that would aid in recall [34]. Given height, age at adult height, and age at menarche are not publicized risk factors of glioma, we would expect reporting error to be random and results, if anything, to be biased toward the null.

Summary

To our knowledge, this is the first report linking age of actualization of maximum height with subsequent risk of glioma. We observed a positive association between a prolonged adolescent growth phase and glioma risk, regardless of sex, glioma grade, and final stature. A postulated mechanism is that a prolonged growth phase may increase exposure to as-yet unknown growth factors that enhance glioma risk. These findings suggest complex interactions with the timing and intensity of risk-promoting exposures, and warrant further study.

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References

1. Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Ehemann C, Jemal A, Anderson RN, Ajani UA, Edwards BK. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *Journal of the National Cancer Institute*. 2011; 103(9):714–736. DOI: 10.1093/jnci/djr077 [PubMed: 21454908]
2. Farrell CJ, Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. *Neurologic clinics*. 2007; 25(4):925–946. viii. DOI: 10.1016/j.ncl.2007.07.008 [PubMed: 17964021]
3. Rice T, Lachance DH, Molinaro AM, Eckel-Passow JE, Walsh KM, Barnholtz-Sloan J, Ostrom QT, Francis SS, Wiemels J, Jenkins RB, Wiencke JK, Wrensch MR. Understanding inherited genetic risk of adult glioma - a review. *Neuro-oncology practice*. 2016; 3(1):10–16. DOI: 10.1093/nop/npv026 [PubMed: 26941959]
4. Braganza MZ, Kitahara CM, Berrington de Gonzalez A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro-oncology*. 2012; 14(11):1316–1324. DOI: 10.1093/neuonc/nos208 [PubMed: 22952197]
5. Amirian ES, Scheurer ME, Zhou R, Wrensch MR, Armstrong GN, Lachance D, Olson SH, Lau CC, Claus EB, Barnholtz-Sloan JS, Il'yasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Jenkins RB, Bernstein JL, Merrell RT, Davis FG, Lai R, Shete S, Amos CI, Melin BS, Bondy ML. History of

chickenpox in glioma risk: a report from the glioma international case-control study (GICC). *Cancer medicine*. 2016; 5(6):1352–1358. DOI: 10.1002/cam4.682 [PubMed: 26972449]

6. Amirian ES, Zhou R, Wrensch MR, Olson SH, Scheurer ME, Il'yasova D, Lachance D, Armstrong GN, McCoy LS, Lau CC, Claus EB, Barnholtz-Sloan JS, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Bernstein JL, Merrell RT, Davis FG, Lai R, Shete S, Amos CI, Melin BS, Bondy ML. Approaching a Scientific Consensus on the Association between Allergies and Glioma Risk: A Report from the Glioma International Case-Control Study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2016; 25(2):282–290. DOI: 10.1158/1055-9965.epi-15-0847
7. Wren S, Haggstrom C, Ulmer H, Manjer J, Borge T, Nagel G, Johansen D, Hallmans G, Engeland A, Concin H, Jonsson H, Selmer R, Tretli S, Stocks T, Stattin P. Pooled cohort study on height and risk of cancer and cancer death. *Cancer causes & control : CCC*. 2014; 25(2):151–159. DOI: 10.1007/s10552-013-0317-7 [PubMed: 24173535]
8. Benson VS, Pirie K, Green J, Casabonne D, Beral V, Million Women Study C. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *British journal of cancer*. 2008; 99(1):185–190. DOI: 10.1038/sj.bjc.6604445 [PubMed: 18560401]
9. Moore SC, Rajaraman P, Dubrow R, Daresky AS, Koebnick C, Hollenbeck A, Schatzkin A, Leitzmann MF. Height, body mass index, and physical activity in relation to glioma risk. *Cancer research*. 2009; 69(21):8349–8355. DOI: 10.1158/0008-5472.CAN-09-1669 [PubMed: 19808953]
10. Michaud DS, Bove G, Gallo V, Schlehofer B, Tjonneland A, Olsen A, Overvad K, Dahm CC, Teucher B, Boeing H, Steffen A, Trichopoulou A, Bamia C, Kyrozi A, Sacerdote C, Agnoli C, Palli D, Tumino R, Mattiello A, Bueno-de-Mesquita HB, Peeters PH, May AM, Barricarte A, Chirlaque MD, Dorronsoro M, Jose Sanchez M, Rodriguez L, Duell EJ, Hallmans G, Melin BS, Manjer J, Borgquist S, Khaw KT, Wareham N, Allen NE, Travis RC, Romieu I, Vineis P, Riboli E. Anthropometric measures, physical activity, and risk of glioma and meningioma in a large prospective cohort study. *Cancer prevention research*. 2011; 4(9):1385–1392. DOI: 10.1158/1940-6207.CAPR-11-0014 [PubMed: 21685234]
11. Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, Browning JE, Egan KM, Nabors LB. Anthropometric factors in relation to risk of glioma. *Cancer causes & control : CCC*. 2013; 24(5):1025–1031. DOI: 10.1007/s10552-013-0178-0 [PubMed: 23456313]
12. Kitahara CM, Wang SS, Melin BS, Wang Z, Braganza M, Inskip PD, Albanes D, Andersson U, Beane Freeman LE, Buring JE, Carreon T, Feychting M, Gapstur SM, Gaziano JM, Giles GG, Hallmans G, Hankinson SE, Henriksson R, Hsing AW, Johansen C, Linet MS, McKean-Cowdin R, Michaud DS, Peters U, Purdue MP, Rothman N, Ruder AM, Sesso HD, Severi G, Shu XO, Stevens VL, Viswanathan K, Waters MA, White E, Wolk A, Zeleniuch-Jacquotte A, Zheng W, Hoover R, Fraumeni JF Jr, Chatterjee N, Yeager M, Chanock SJ, Hartge P, Rajaraman P. Association between adult height, genetic susceptibility and risk of glioma. *International journal of epidemiology*. 2012; 41(4):1075–1085. DOI: 10.1093/ije/dys114 [PubMed: 22933650]
13. Gunnell D, Oliver SE, Donovan JL, Peters TJ, Gillatt D, Persad R, Hamdy FC, Neal DE, Holly JM. Do height-related variations in insulin-like growth factors underlie the associations of stature with adult chronic disease? *The Journal of clinical endocrinology and metabolism*. 2004; 89(1):213–218. DOI: 10.1210/jc.2003-030507 [PubMed: 14715852]
14. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. *Epidemiologic reviews*. 2001; 23(2):313–342. [PubMed: 12192740]
15. Anic GM, Madden MH, Nabors LB, Olson JJ, LaRocca RV, Thompson ZJ, Pamnani SJ, Forsyth PA, Thompson RC, Egan KM. Reproductive factors and risk of primary brain tumors in women. *Journal of neuro-oncology*. 2014; 118(2):297–304. DOI: 10.1007/s11060-014-1427-0 [PubMed: 24700240]
16. Krishnamachari B, Il'yasova D, Scheurer ME, Bondy ML, Wrensch M, Davis FG. A pooled multisite analysis of the effects of female reproductive hormones on glioma risk. *Cancer causes & control : CCC*. 2014; 25(8):1007–1013. DOI: 10.1007/s10552-014-0400-8 [PubMed: 24890803]
17. Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, Browning JE, Egan KM, Nabors LB. Anthropometric factors in relation to risk of glioma. *Cancer causes & control : CCC*. 2013; 24(5):1025–1031. DOI: 10.1007/s10552-013-0178-0 [PubMed: 23456313]

18. Egan KM, Nabors LB, Thompson ZJ, Rozmeski CM, Anic GA, Olson JJ, LaRocca RV, Chowdhary SA, Forsyth PA, Thompson RC. Analgesic use and the risk of primary adult brain tumor. *European journal of epidemiology*. 2016; 31(9):917–925. DOI: 10.1007/s10654-016-0129-7 [PubMed: 26894804]
19. Biro FM, McMahon RP, Striegel-Moore R, Crawford PB, Obarzanek E, Morrison JA, Barton BA, Falkner F. Impact of timing of pubertal maturation on growth in black and white female adolescents: The National Heart, Lung, and Blood Institute Growth and Health Study. *The Journal of pediatrics*. 2001; 138(5):636–643. DOI: 10.1067/mpd.2001.114476 [PubMed: 11343036]
20. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Perinatal and familial risk factors for brain tumors in childhood through young adulthood. *Cancer research*. 2015; 75(3):576–583. DOI: 10.1158/0008-5472.CAN-14-2285 [PubMed: 25511376]
21. Kitahara CM, Gamborg M, Berrington de GA, Sorensen TI, Baker JL. Childhood height and body mass index were associated with risk of adult thyroid cancer in a large cohort study. *Cancer Res*. 2014; 74(1):235–242. [PubMed: 24247722]
22. Cook MB, Gamborg M, Aarestrup J, Sorensen TI, Baker JL. Childhood height and birth weight in relation to future prostate cancer risk: a cohort study based on the copenhagen school health records register. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2013; 22(12):2232–2240. DOI: 10.1158/1055-9965.EPI-13-0712
23. Okasha M, Gunnell D, Holly J, Davey Smith G. Childhood growth and adult cancer. *Best practice & research Clinical endocrinology & metabolism*. 2002; 16(2):225–241. DOI: 10.1053/beem.2002.0204 [PubMed: 12064890]
24. Omay SB, Piepmeyer JM, Knisely JP. Low-grade gliomas: when and how to treat. *Hematology/oncology clinics of North America*. 2012; 26(4):797–809. DOI: 10.1016/j.hoc.2012.05.001 [PubMed: 22794284]
25. Baron J, Savendahl L, De Luca F, Dauber A, Phillip M, Wit JM, Nilsson O. Short and tall stature: a new paradigm emerges. *Nature reviews Endocrinology*. 2015; 11(12):735–746. DOI: 10.1038/nrendo.2015.165
26. Grimberg A. Mechanisms by which IGF-I may promote cancer. *Cancer biology & therapy*. 2003; 2(6):630–635. [PubMed: 14688466]
27. Rogers I, Metcalfe C, Gunnell D, Emmett P, Dunger D, Holly J, Avon Longitudinal Study of Parents Children Study T. Insulin-like growth factor-I and growth in height, leg length, and trunk length between ages 5 and 10 years. *The Journal of clinical endocrinology and metabolism*. 2006; 91(7):2514–2519. DOI: 10.1210/jc.2006-0388 [PubMed: 16670160]
28. Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. *Annual review of public health*. 1996; 17:47–67. DOI: 10.1146/annurev.pu.17.050196.000403
29. Engler-Chiurazzi EB, Brown CM, Povroznik JM, Simpkins JW. Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive aging and brain injury. *Progress in neurobiology*. 2016; doi: 10.1016/j.pneurobio.2015.12.008
30. CBTRUS. 2012 Statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004-2008. 2012. http://www.cbtrus.org/2012-NPCR-SEER/CBTRUS_Report_2004-2008_3-23-2012.pdf
31. Ong KK, Ahmed ML, Dunger DB. Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. *Molecular and cellular endocrinology*. 2006; 254-255:8–12. DOI: 10.1016/j.mce.2006.04.018 [PubMed: 16757103]
32. Grasgruber P, Cacek J, Kalina T, Sebera M. The role of nutrition and genetics as key determinants of the positive height trend. *Economics and human biology*. 2014; 15:81–100. DOI: 10.1016/j.ehb.2014.07.002 [PubMed: 25190282]
33. van Noord PA. Breast cancer and the brain: a neurodevelopmental hypothesis to explain the opposing effects of caloric deprivation during the Dutch famine of 1944-1945 on breast cancer and its risk factors. *The Journal of nutrition*. 2004; 134(12 Suppl):3399S–3406S. [PubMed: 15570045]
34. Casey VA, Dwyer JT, Coleman KA, Krall EA, Gardner J, Valadian I. Accuracy of recall by middle-aged participants in a longitudinal study of their body size and indices of maturation earlier in life. *Annals of human biology*. 1991; 18(2):155–166. [PubMed: 2024949]

35. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. *American journal of epidemiology*. 1993; 138(1):56–64. [PubMed: 8333427]

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Table 1
Descriptive characteristics of glioma cases and controls

Variable	Controls (N=951)	Glioma cases (N=776)
Age		
Mean (SD)	56 (14.9)	54 (15.3)
Median (range)	57 (18-90)	56 (18-92)
Gender, N (%)		
Female	464 (48.8)	334 (43.0)
Male	487 (51.2)	442 (57.0)
Race, N (%)		
Caucasian	913 (96.0)	723 (93.2)
Non-Caucasian	38 (4.0)	53 (6.8)
Education, N (%)		
High School or Less	238 (25.0)	260 (33.5)
Some College	268 (28.2)	222 (28.6)
College Degree	271 (28.5)	174 (22.4)
Graduate Degree	174 (18.3)	120 (15.5)
State, N (%)		
FL	351 (36.9)	392 (50.5)
TN	233 (24.5)	104 (13.4)
AL	132 (13.9)	155 (20.0)
GA	109 (11.5)	68 (8.8)
KY	75 (7.9)	23 (3.0)
Other	51 (5.4)	34 (4.4)
Glioma histology, N (%)		
Glioblastoma		501 (64.6)
Lower grade astrocytoma		147 (19.0)
Oligodendroglial tumors		77 (9.9)
Other gliomas		51 (6.6)

Table 2
Age at final height and risk of glioma, overall, and according to glioma subtype

Age attained adult height	Controls n (%)	Glioma cases n (%)	All Gliomas			Glioblastoma		Other Gliomas		
			Crude OR (95% CI)	p-value	Multivariable OR (95% CI)*	p-value	Multivariable OR (95% CI)*	p-value		
15	211 (22.2)	116 (15.0)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
16	206 (21.7)	127 (16.4)	1.12 (0.82, 1.54)	0.48	1.01 (0.73, 1.41)	0.94	0.91 (0.62, 1.34)	0.64	1.34 (0.82, 2.19)	0.25
17	167 (17.6)	140 (18.0)	1.53 (1.12, 2.10)	<0.01	1.41 (1.00, 2.00)	<0.05	1.44 (0.98, 2.10)	0.06	1.49 (0.88, 2.51)	0.14
18	219 (23.0)	224 (28.9)	1.86 (1.39, 2.50)	<0.0001	1.61 (1.18, 2.21)	<0.01	1.53 (1.07, 2.18)	0.02	1.99 (1.24, 3.21)	<0.01
19	148 (15.6)	169 (21.8)	2.08 (1.51, 2.85)	<0.0001	1.91 (1.36, 2.70)	<0.001	1.73 (1.17, 2.54)	<0.01	2.73 (1.62, 4.60)	<0.001
P _{trend}				<0.0001		<0.001		<0.01		<0.01
<hr/>										
Per 1 year increase					1.12 (1.07, 1.18)	<0.001	1.10 (1.04, 1.17)	<0.001	1.18 (1.10, 1.28)	<0.001

* Multivariable models adjusted for age at diagnosis, sex, race (Caucasian, non-Caucasian), education (high school or less, some college, college degree, graduate degree), and state of residence.

Table 3

Age at final height and risk of glioma stratified by gender

		Controls n (%)	Glioma Cases n (%)	Crude OR (95% CI)	p-value	Multivariable OR (95% CI)*	p-value
Men	Age attained max height						
	15	61 (12.5)	32 (7.6)	1.00 (Ref)		1.00 (Ref)	
	16	93 (19.1)	63 (14.3)	1.29 (0.76, 2.20)	0.35	1.18 (0.68, 2.06)	0.55
	17	97 (19.9)	84 (19.0)	1.65 (0.98, 2.77)	0.06	1.52 (0.89, 2.60)	0.13
	18	133 (27.3)	138 (31.2)	1.98 (1.21, 3.23)	<0.01	1.71 (1.03, 2.84)	0.04
	19	103 (21.2)	125 (28.3)	2.31 (1.40, 3.82)	<0.01	2.16 (1.28, 3.63)	<0.01
	<i>P</i> _{trend}				<0.01		0.02
Per 1 year increase						1.15 (1.07, 1.24)	<0.001
Women	Age attained max height						
	15	150 (32.5)	84 (25.2)	1.00 (Ref)		1.00 (Ref)	
	16	113 (24.4)	64 (19.2)	1.01 (0.67, 1.52)	0.96	0.96 (0.63, 1.46)	0.83
	17	70 (15.1)	56 (16.8)	1.43 (0.92, 2.22)	0.11	1.46 (0.92, 2.32)	0.11
	18	86 (18.5)	86 (25.8)	1.79 (1.20, 2.67)	<0.01	1.65 (1.08, 2.51)	0.02
	19	45 (9.7)	44 (13.2)	1.75 (1.07, 2.86)	0.03	1.76 (1.04, 2.97)	0.03
	<i>P</i> _{trend}				0.01		0.03
Per 1 year increase						1.11 (1.04, 1.18)	<0.01

* Multivariable models adjusted for age at diagnosis, race (Caucasian, non-Caucasian), education (high school or less, some college, college degree, graduate degree), and state of residence.

Table 4

Age at final height and risk of glioma by tertile of adult stature

	Tertile 1*			Tertile 2*			Tertile 3*		
	Women n (%)	Men n (%)		Women n (%)	Men n (%)		Women n (%)	Men n (%)	
Age attained adult height									
16	130 (23.9)	75 (13.8)	1.00 (Ref)	124 (25.7)	62 (12.9)	1.00 (Ref)	163 (23.3)	106 (151)	1.00 (Ref)
17	50 (9.2)	41 (7.5)	1.37 (0.81, 2.33)	49 (10.2)	35 (7.3)	1.33 (0.76, 2.33)	68 (9.7)	64 (91)	1.41 (0.90, 2.19)
18	72 (13.2)	84 (15.4)	1.69 (1.07, 2.66)	64 (13.3)	58 (12.0)	16.0 (0.97, 2.64)	83 (11.9)	82 (117)	1.51 (1.00, 2.30)
19	43 (7.9)	50 (9.2)	1.74 (1.01, 3.00)	41 (8.)	49 (10.2)	2.27 (1.29, 3.99)	64 (9.1)	70 (100)	1.85 (1.17, 2.93)
P _{trend}			0.09						<0.05
Per 1 year increase			1.17 (1.07, 1.28)			1.14 (1.03, 1.27)			1.09 (1.01, 1.17)
			<0.001			0.01			0.04

* Tertile distributions established separately in males and females based on reported height at age 21 (see text).

** Model adjusted for age at diagnosis, sex, race (Caucasian, non-Caucasian), education (high school or less, some college, college degree, graduate degree), and state of residence.
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