

Glioma Risk in Relation to Serum Levels of Insulin-Like Growth Factors

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Abstract

Several studies have suggested that insulin-like growth factors (IGF) are related to cancer risk. We investigated the associations between serum levels of IGF-I and IGF-binding protein-3 and glioma risk. A nested case-control study was conducted within a cancer prevention study, including 29,133 men (ages 50-69 years). In total, 22 glioma cases and 400 randomly selected controls were included. Serum samples were collected a minimum of 5 years before cancer diagnosis. Serum concentrations were measured using ELISA and divided into tertiles

based on measurements among controls. Odds ratios and 95% confidence intervals were calculated using the lowest tertile as the reference category. No statistical association was detected between glioma and IGF-binding protein-3. IGF-I was inversely associated with glioma when comparing the lowest tertile with the other tertiles combined (odds ratio, 0.3; 95% confidence interval, 0.1-0.7). The results encourage future research on IGFs in relation to brain tumors in larger studies.

Introduction

Insulin-like growth factors (IGF) regulate cell growth and are, in concert with their receptors and binding proteins (IGFBP), involved in controlling key processes in brain development (1). The IGF system also has an important role in the brain in adults, and any disruptions may have serious consequences for differentiation, proliferation, and apoptosis of brain cells (1). Altered expression in the IGF system has been reported to influence cellular transformation and tumor cell proliferation (1-4), and epidemiologic studies have suggested that circulating levels of IGF-I and IGFBP-3 may be related to various types of cancer (5-9), although the results are not consistent (10-12). For central nervous system tumors, such as glioma, IGFs have been reported to be overexpressed to varying degrees (13, 14), and *in vitro* studies have shown that IGF-I promotes mitogenesis and differentiation in glial cells (15-17). Observations in the literature suggest that the IGF pathways show similar expression and functional features during central nervous system development and tumorigenesis (18-20). In this study, we investigated the association of IGF-I and IGFBP-3 serum levels and risk of glioma.

Materials and Methods

The study population was all individuals in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Details of the original intervention study have been published

previously (21, 22). In brief, 29,133 men between the ages of 50 and 69 years who smoked at least five cigarettes per day were recruited from southwestern Finland between 1985 and 1988. Individuals with prior cancer were ineligible. Participants received α -tocopherol, β -carotene, both supplements, or placebo capsules for 5 to 8 years until death or trial closure in April 1993. The study was approved by the institutional review boards of the U.S. National Cancer Institute and the National Public Health Institute of Finland, and written informed consent was obtained from each participant before randomization.

For this nested case-control study, we identified incident primary intracerebral tumor cases that occurred between their 5th follow-up year following baseline blood draw through December 1997 from the Finnish Cancer Registry. Medical records were reviewed by one study physician to confirm the diagnoses. Only cases confirmed as incident primary intracerebral tumors ($n = 22$) were included in the study; 16 cases were histopathologically confirmed gliomas, and 12 of these cases were classified as glioblastomas. Six cases were defined as malignant intracerebral tumors of unspecified type. In this study, we assumed these six cases to be gliomas. We randomly selected 400 controls from the study population (11, 12). To reduce the potential influence of subclinical cancer on IGF concentrations, all participants were alive and without clinical evidence of cancer during the first 5 years after blood collection.

Fasting serum samples were collected at the study baseline and stored at -70°C until assayed. Laboratory personnel was blinded to case, control, and quality control sample status. Concentrations of IGF-I and IGFBP-3 were measured using ELISA with reagents from Diagnostic Systems Laboratories (Webster, TX). The quality control intrabatch and interbatch coefficients of variation were 5.23% and 4.57% for IGF-I and 4.18% and 6.17% for IGFBP-3, respectively. IGF-I to IGFBP-3 molar ratio was calculated as an indicator of the bioactive IGF-I using $1\text{ ng/mL IGF-I} = 0.130\text{ nmol/L}$ and $1\text{ ng/mL IGFBP-3} = 0.036\text{ nmol/L}$. Serum concentrations were categorized as tertiles based on the distributions among controls. The lowest

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tertile was used as reference category. Odds ratios and 95% confidence intervals were calculated to estimate the relative risk using unconditional logistic regression models. In the multivariate analyses, age, body mass index, smoking, self-reported history of allergy, education, intervention group assignment, and time period of diagnosis were included as covariates, but none of these factors markedly influenced the odds ratios; therefore, crude odds ratios are reported here.

Results

Selected characteristics of cases and controls were generally similar, except for age, IGF-I serum level, and molar ratio (Table 1). The average IGF-I level was borderline significantly lower ($P = 0.07$), and the molar ratio was significantly lower ($P = 0.03$) in cases than in controls.

IGF-I serum level was inversely associated with glioma when comparing the lowest tertile with the top two tertiles combined (odds ratio, 0.3; 95% confidence interval, 0.1-0.7), and the risk estimates were similar for the second and third tertile separately (Fig. 1A). No significant association was detected between glioma and IGFBP-3 serum level when comparing the lowest tertile with the top two tertiles combined (odds ratio, 0.6; 95% confidence interval, 0.3-1.4) or for the second and third tertiles separately (Fig. 1B). The risk estimates were similar when restricting the analysis for histopathologically confirmed gliomas and in restricted analyses for glioblastoma cases (data not shown).

Discussion

Results in the present study indicate a possible association between serum concentrations of IGFs and glioma risk. The results suggest that low levels of serum IGF-I are associated with higher risk of developing glioma, which is at odds with several previously published studies indicating increasing cancer (i.e., breast and prostate) risk associated with high circulating levels of IGF-I (5-9). To our knowledge, no previous study has investigated serum IGF-I and brain tumor risk. A study on acromegaly (a syndrome resulting from excessive growth hormone) and cancer risk reported a positive association with brain tumors based on small numbers (nine cases; ref. 23).

The observed number of cases in the study population is approximately the number we expected based on reported incidence in the Nordic countries (24). Blood samples were taken a minimum of 5 years before cancer diagnosis, lessening but not precluding the likelihood that IGF levels were influenced by the tumor. Serum IGF concentrations among controls were comparable with those observed in another published study (25) with a similar study population (smokers, similar age distribution, and >75% males).

The results in this study should be interpreted with caution because of the small number of cases. This is especially of concern because our finding indicates that cancer risk is

Table 1. Mean values for selected baseline characteristics of cases and controls

	Cases ($n = 22$)	Controls ($n = 400$)	P
Age at baseline (y)	59	56	0.01
Age at diagnosis (y)	66	N/A	
Years of cigarette smoking	37	35	0.16
BMI*	25.6	26.6	0.24
Energy intake (kcal/d)	2,611	2,834	0.24
Alcohol intake (g/d)	16.8	19.6	0.61
IGF-I (ng/mL)	127	147	0.07
IGFBP-3 (ng/mL)	2,391	2,399	0.96
IGF-I/IGFBP-3 molar ratio	0.20	0.22	0.03

*Body mass index [weight (in kilograms)/height (in meters)²].

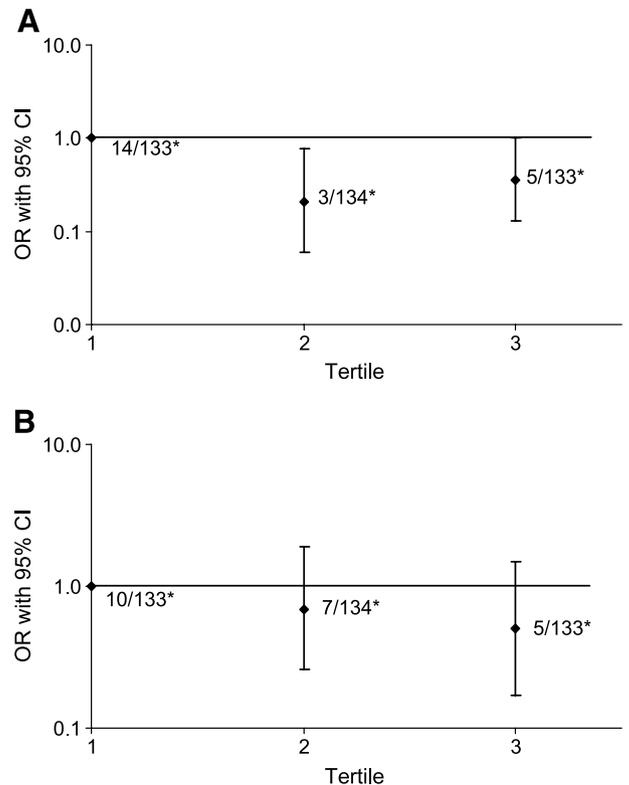


Figure 1. Glioma risk in relation to IGF-I (A) and IGFBP-3 (B) serum concentration (in tertiles). Results for 22 cases and 400 controls. The lowest tertile is set as the reference category. **A.** Asterisks, number of cases/controls. Tertile 1, <122.0 ng/mL; tertile 2, 122.0 to 159.1 ng/mL; tertile 3, >159.1 ng/mL. **B.** Asterisks, number of cases/controls. Tertile 1, <2,073 ng/mL; tertile 2, 2,073 to 2,638 ng/mL; tertile 3, >2,638 ng/mL. OR, odds ratio; 95% CI, 95% confidence interval.

associated with low circulating levels of IGF-I, which is an unexpected observation. However, one study has suggested that individuals with a specific IGF-I receptor allele have lower plasma levels of IGF-I and an increased risk of prostate cancer (26). Lastly, the study is restricted to smokers and older men, which limit potential generalizability of the results.

Experimental data support the possibility that IGFs are related to brain tumor development and progression (1). Perturbation of IGF signaling functions may result in changes in cell proliferation, differentiation, and apoptosis (1-3). Although IGFs are basically regarded as being synthesized in the liver, IGFs are also synthesized in the brain. The actions of IGFs on the brain are caused by a combination of peripheral IGFs that enter the central nervous system and local IGFs synthesized in the brain (19). The observed low circulating levels of IGF-I could perhaps be explained by a compensatory relation between peripheral IGF-I and central nervous system IGF-I levels.

Our results suggest that low IGF-I serum concentration may be related to the pathogenesis of glioma. The interpretation of the results is, however, limited by the small number of cases. The results encourage future research on IGF in relation to brain cancers in large populations.

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