Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

Cancer Epidemiology, Biomarkers & Prevention

Personal History of Diabetes, Genetic Susceptibility to Diabetes, and Risk of Brain Glioma: A Pooled Analysis of Observational Studies

Cari M. Kitahara, Martha S. Linet, Alina V. Brenner, et al.

Cancer Epidemiol Biomarkers Prev 2014;23:47-54. Published OnlineFirst November 12, 2013.

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Personal History of Diabetes, Genetic Susceptibility to Diabetes, and Risk of Brain Glioma: A Pooled Analysis of Observational Studies

Cari M. Kitahara[1], Martha S. Linet[1], Alina V. Brenner[1], Sophia S. Wang[3], Beatrice S. Melin[11], Zhaoming Wang[1,2], Peter D. Inskip[1], Laura E. Beane Freeman[1], Melissa Z. Braganza[1], Tania Carreón[4], Maria Feychting[12], J. Michael Gaziano[5,6,7], Ulrike Peters[8,9], Mark P. Purdue[1], Avima M. Ruder[4], Howard D. Sesso[5,6], Xiao-Ou Shu[10], Martha A. Waters[4], Emily White[9], Wei Zheng[10], Robert N. Hoover[1], Joseph F. Fraumeni Jr[1], Nilanjan Chatterjee[1], Meredith Yeager[1,2], Stephen J. Chanock[1,2], Patricia Hartge[1], and Preetha Rajaraman[1]

Abstract

Background: Brain glioma is a relatively rare and fatal malignancy in adulthood with few known risk factors. Some observational studies have reported inverse associations between diabetes and subsequent glioma risk, but possible mechanisms are unclear.

Methods: We conducted a pooled analysis of original data from five nested case–control studies and two case–control studies from the United States and China that included 962 glioma cases and 2,195 controls. We examined self-reported diabetes history in relation to glioma risk, as well as effect modification by seven glioma risk-associated single-nucleotide polymorphisms (SNP). We also examined the associations between 13 diabetes risk-associated SNPs, identified from genome-wide association studies, and glioma risk. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable-adjusted logistic regression models.

Results: We observed a 42% reduced risk of glioma for individuals with a history of diabetes (OR = 0.58; 95% CI, 0.40–0.84). The association did not differ by sex, study design, or after restricting to glioblastoma, the most common histological subtype. We did not observe any significant per-allele trends among the 13 diabetes-related SNPs examined in relation to glioma risk.

Conclusion: These results support an inverse association between diabetes history and glioma risk. The role of genetic susceptibility to diabetes cannot be excluded, and should be pursued in future studies together with other factors that might be responsible for the diabetes–glioma association.

Impact: These data suggest the need for studies that can evaluate, separately, the association between type 1 and type 2 diabetes and subsequent risk of adult glioma. *Cancer Epidemiol Biomarkers Prev; 23(1); 47–54. ©2013 AACR.*

Introduction

Glioma, the most common type of malignant brain tumor in adulthood, is a relatively uncommon and highly fatal malignancy, with a 5-year survival rate of only 34% (1). The most common and aggressive subtype of glioma, glioblastoma, has a 5-year survival of less than 5% (1). Currently, there are no effective means of glioma prevention apart from avoiding unnecessary exposure to ionizing radiation, particularly during childhood (2).

Several studies (3–9), although not all (10–13), have suggested that elevated blood glucose levels or a previous history of diabetes are inversely associated with risk of glioma or other brain tumors. Diabetes, particularly type 2, has been associated with an increased risk of several other types of malignancies, possibly mediated by inflammatory markers or elevated levels of glucose, insulin, or insulin-like growth factor-1 (14). The potential biological mechanisms that could explain an inverse association between diabetes and risk of glioma remain unclear, although immune response may play a role (15). Similar

Authors' Affiliations: [1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda; [2]Core Genotyping Facility, National Cancer Institute, SAIC-Frederick, Inc., Gaithersburg, Maryland; [3]Division of Cancer Etiology, Department of Population Sciences, City of Hope and the Beckman Research Institute, Duarte, California; [4]Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, Ohio; [5]Division of Preventive Medicine; [6]Division of Aging, Brigham and Women's Hospital, Harvard Medical School; [7]Massachusetts Veterans Epidemiology, Research and Information Center, Geriatric Research Education and Clinical Center, VA Boston Healthcare System, Boston, Massachusetts; [8]Fred Hutchinson Cancer Research Center; [9]Department of Epidemiology, University of Washington, Seattle, Washington; [10]Vanderbilt University Medical Center, Nashville, Tennessee; [11]Department of Radiation Sciences, Oncology, Umeå University, Umeå; and [12]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Cari M. Kitahara, Division of Cancer Epidemiology and Genetics, 9609 Medical Center Drive, Room 7E-566, Bethesda, MD 20892. Phone: 240-276-7406; Fax: 240-276-7874. E-mail: meinholdc@mail.nih.gov

doi: 10.1158/1055-9965.EPI-13-0913

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

to diabetes, a personal history of allergies has consistently been associated with an approximately 40% reduced risk of glioma (16).

To further our understanding of the relationship between diabetes and glioma and possible underlying biological mechanisms, we combined questionnaire-based and genotyping data from 5 cohort and 2 case–control studies to examine the association between self-reported history of diabetes and subsequent risk of glioma and possible effect modification by 7 glioma-related single nucleotide polymorphisms (SNP). We additionally examined whether an association between diabetes and glioma risk might be explained by genetic mechanisms using genotyping data from 13 diabetes risk-associated SNPs.

Materials and Methods

Study population

The study population included glioma cases and controls from the previously conducted genome-wide association study (GWAS) in the GliomaScan Consortium (17). This collaborative project included 1,856 incident cases and 4,955 controls from 3 case–control studies, 1 population-based case–only study, and 14 case–control studies nested within cohort studies. For the current analysis, we restricted the study population to the 5 nested case–control studies [Agricultural Health Study (AHS), Physicians' Health Study I and II (PHS), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), Shanghai Men's and Women's Health Study (SMWHS), Vitamins and Lifestyle Study (VITAL)] and 2 case–control studies [Multicenter Study of Environment and Health-National Cancer Institute- Adult Brain Tumor Study (NCI-BTS) and National Institute for Occupational Safety and Health-Upper Midwest Health Study (NIOSH-UMHS)] in which one or more glioma cases and controls reported a history of diabetes (18–26). Six of these studies were conducted in the United States, and one in China (SMWHS). Four studies collected information on age at diabetes diagnosis (NCI-BTS, AHS, PHS, and SMWHS). We excluded 1 case and 2 controls under the age of 18, 13 cases and 31 controls with missing questionnaire data on history of diabetes, and 1 case and 1 control from SMWHS whose self-reported ages at diagnosis of diabetes occurred after the age or referent age at glioma diagnosis. The final study population consisted of 962 glioma cases (557 males and 405 females) and 2,195 controls (1,196 males and 999 females). Brief descriptions of studies and participant characteristics are shown in Table 1.

Outcome definition

Glioma cases were defined as primary malignant brain tumors with ICD-O-3 histology codes 9380–9480 (or equivalent). We further classified the following mutually exclusive subgroups of glioma according to histology: glioblastoma including gliosarcoma (ICD-O-3 codes 9440–9442), astrocytoma (ICD-O-3 codes 9384, 9400–9401, 9410–9411, 9420–9421, 9424), and oligodendroglioma/oligoastrocytoma/oligodendroblastoma (ICD-O-3 codes 9382, 9450, 9451, and 9460). Cases with histology codes outside of these ranges were classified as "other and unspecified gliomas." Controls from cohort studies were originally chosen from a subset of the full cohort for the purposes of previous GWAS, or were matched to cases on age or year of birth, sex, race, and/or other factors (Table 1), and were glioma-free at the time of glioma diagnosis. Controls from case–control studies were frequency-matched by age, sex, and other factors, and were glioma-free at the time of interview.

Questionnaire data

All variables included in this analysis were combined across studies using standardized definitions and categories. Demographic characteristics, including dates of birth, sex, race/ethnicity (White, Black, American Indian/Alaskan Native, Asian/Pacific Islander, other), education (less than high school graduate, high school graduate or equivalent, some college or vocational school post-high school, college graduate or post-graduate), personal history of allergies including asthma, hay fever, eczema, other allergy, or allergic skin condition (yes, no), hormone replacement therapy (ever, never), and smoking status (never, former, current) were self-reported in study-specific questionnaires and provided by all 7 studies. Height and weight were measured by study personnel in the SMWHS study and self-reported in all other studies. Questionnaire data on personal history of diabetes (yes, no) and other factors were ascertained at study enrollment in most of the cohort studies (AHS, PHS, PLCO, VITAL), apart from one (SMWHS) that assigned diabetes status using questionnaire information from both baseline and follow-up. Case–control studies (NCI-BTS, NIOSH-UMHS) ascertained this information soon after diagnosis among cases and at the corresponding referent age among controls (i.e., the age at time of interview). Missing data for any of the covariates (<1% for race, education, smoking, and body mass index; 14% for history of allergies; 34% for hormone replacement therapy use in women) were handled by including missing indicator variables in the models.

Genotyping

Blood, saliva, or buccal samples were provided by each of the studies (apart from SMWHS, which did not contribute to the genetic analyses) to use for the extraction of DNA for genotyping. Genotyping was performed using the Illumina 660-W Human BeadChip for all glioma cases. Genotyping for controls was conducted using various platforms (Table 1). To account for differences in the assays used, SNP data for the control samples were imputed if necessary, as described by Marchini and colleagues (27). A total of 13 SNPs that have been associated with diabetes and 7 SNPs that have been associated with glioma, based on statistical significance after correction for multiple testing in previous GWAS (17, 28–35), were selected to evaluate the association for diabetes-related genetic polymorphisms on risk of glioma and the potential for effect

Table 1. Descriptive characteristics of the 7 studies included in the GliomaScan Consortium Study

Study	Study acronym	Study type	Control SELECTION	Platform used for genotyping (controls)	Study period (recruitment)	Location	Study sample		Mean age at diagnosis, y	Mean age at interview/ study entry, y	
							Cases	Controls	Cases	Cases	Controls
Agricultural Health Study (18)	AHS	Nested case-control	Frequency-matched 2:1 by year of birth, sex, race	Illumina 660W	1993–1997	USA (IA, NC)	20	41	59	53	52
Multicenter Study of Environment and Health -National Cancer Institute Adult Brain Tumor Study (19)	NCI-BTS	Case-control	Hospital controls frequency-matched 2:1 by hospital, age, sex, race, residential distance from hospital	Illumina 660W	1994–1998	USA (AZ, MA, PA)	364	478	51	51	49
Upper Midwest Health Study - National Institute for Occupational Safety and Health (20)	NIOSH-UMHS	Case–control	Population-based controls frequency-matched 1.5:1 by age, sex, state	Illumina 660W	1995–1997	USA (IA, MI, MN, WI)	326	581	48	49	60
Physician's Health Study I and II (21, 22)	PHS	Nested case–control	Glioma-free controls with previous GWAS data	Illumina 550K	1982–1984, 1997–2001	USA (several states)	39	54	73	57	55
Prostate, Lung, Colorectal and Ovarian Screening Trial (23)	PLCO	Nested case–control	Glioma-free controls with previous GWAS data	Illumina 550K	1992–2001	USA (several states)	115	843	70	63	64
Shanghai Men's and Women's Health Study (24, 25)	SMWHS	Nested case–control	Glioma-free controls with previous GWAS data	Illumina 550K[a]	1996–2000 (women), 2001–2006 (men)	China (urban communities in Shanghai)	38	78	59	56	63
Vitamins and Lifestyle (26)	VITAL	Nested case–control	Matched on age, sex, race, time to diagnosis	Illumina 660W	2000–2002	USA (WA)	60	120	69	65	65
Total							962	2,195			

[a]Excluded from genetic analyses because of <80% European ancestry.

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

modification of the diabetes–glioma association by genetic susceptibility to glioma, respectively. We computed a genetic risk score for the diabetes and glioma SNPs by assigning 0, 1, or 2 for homozygous for the nonsusceptible allele, heterozygous, or homozygous for the susceptible allele, respectively, and summing these values.

Statistical analysis

We calculated pooled odds ratios (OR) and 95% confidence intervals (CI) for glioma using unconditional logistic regression models adjusted for study, age (at baseline for cohort studies or at time of diagnosis/pseudodiagnosis for case–control studies), and birth year (<1930, 1930–1939, 1940–1949, 1950–1959, ≥1960). Models that combined male and female subjects were further adjusted for sex. Adjustment for other potential confounders, including race, education, body mass index (weight in kg divided by height in meters squared), smoking status, menopausal hormone replacement therapy, and history of allergies did not meaningfully change the β coefficients for diabetes (<10% change), so these covariates were not retained in the final models.

We also examined the possible effect modification by sex, current and early-adulthood BMI, history of allergies, and 7 recently identified glioma risk-associated variants by comparing the magnitude of the associations for diabetes and glioma risk across categories of these potential effect modifiers. Tests for interaction were conducted by comparing the fit of a model with an additional cross-product term for diabetes and the potential effect modifier to a model without this term using the likelihood ratio test. Between-study heterogeneity was evaluated using the Mantel–Haenszel χ^2 test.

Pooled ORs were additionally estimated for 13 diabetes-associated SNPs using the most common genotype among controls as the referent genotype. Trend tests were conducted by modeling the genotypes (categorized as 0, 1, and 2, corresponding to the number of variant alleles) as continuous variables, and statistical significance was evaluated by comparing the fit of a model with the continuous term to one without using the likelihood ratio test.

All statistical analyses were conducted using Stata/SE 11.0 (StataCorp).

Results

Of the 962 total glioma cases, 517 (311 male and 206 female) were classified as glioblastoma, 200 (119 male and 81 female) as astrocytoma, and 152 (74 male and 78 female) as oligodendroglioma/oligoastrocytoma/oligodendroblastoma. The median age at glioma diagnosis was 57 years (interquartile range: 42–69; range: 18–91).

We observed a 42% reduced risk of glioma (OR = 0.58; 95% CI, 0.40–0.84) for individuals with a history of diabetes versus those without (Table 2). Similar ORs were observed in men and women ($P_{interaction} = 0.91$) and by case–control and nested case–control design ($P_{heterogeneity} = 0.87$). Results were similar after excluding each individual study. The association between diabetes history and glioma risk was more strongly inverse among participants with current BMI values of 18.5 to 24.9 (OR = 0.48; 95% CI, 0.24–0.96) and 25.0 to 29.9 (OR = 0.43; 95% CI, 0.22–0.85) compared with those with BMI ≥30 (OR = 1.16; 95% CI, 0.61–2.20), but these differences were not statistically significant ($P_{interaction} = 0.12$). Among 210 glioma cases and 1,027 controls with data on BMI in early-adulthood (age 18–21), there was no clear variation in ORs for diabetes history within strata of early-adult BMI ($P_{interaction} = 0.72$). We found no evidence of a multiplicative interaction by history of allergies ($P_{interaction} = 0.21$). The inverse association was statistically significant for diabetes diagnosed before age 50 but not for diabetes diagnosed at older ages (Table 2). After additionally excluding 2 cases and 7 controls diagnosed with diabetes within 2 years of glioma diagnosis, the ORs for history of diabetes versus no history (OR = 0.59; 95% CI, 0.40–0.86) and for history of diabetes by age at diagnosis (OR = 0.34, 0.55, and 0.52 for diabetes diagnosis at <50, 50–59, and ≥60 years old, respectively; $P_{trend} = 0.24$) did not change materially. Similar results were observed when we restricted the analysis to glioblastoma while keeping the same controls (based on 25 cases with diabetes and 492 without; OR = 0.58; 95% CI, 0.37–0.92). Although the number of cases was small, we also observed reduced risks associated with a diabetes history for astrocytoma (based on 6 cases with diabetes and 194 without; OR = 0.56; 95% CI, 0.24–1.31) and oligodendroglioma (based on 2 cases with diabetes and 157 without; OR = 0.28; 95% CI, 0.07–1.18).

Within the population subset with genetic data, we did not observe any significant per-allele trends among the 13 diabetes-related SNPs examined in relation to glioma risk (Table 3). Nonetheless, the TT genotype for rs2237892 on the *KCNQ1* gene (OR = 4.46; 95% CI, 1.19–16.70) was associated with significantly increased risk of glioma compared with the CC genotype. Among controls, however, only rs7480010 and rs1113132 were significantly associated with self-reported history of diabetes. The diabetes genetic risk score was not significantly associated with risk of glioma [ORs (95% CI) for risk scores of ≥11–<13, ≥13–<15, and ≥15 vs. <11 = 1.00 (0.72–1.38), 1.13 (0.83–1.55), and 1.18 (0.86–1.62), respectively; $P_{trend} = 0.22$], nor with self-reported diabetes among controls [OR (95% CI) = 0.95 (0.41–2.20), 0.79 (0.35–1.80), and 1.60 (0.75–3.42); $P_{trend} = 0.27$]. Additional adjustment for the diabetes genetic risk score had little influence on the OR for history of diabetes (OR = 0.57 and 0.55 before and after adjustment, respectively). None of the 7 glioma risk-associated SNPs individually modified the association between history of diabetes and glioma risk (Supplementary Table S1); however, the inverse association for diabetes was nonsignificantly greater among individuals with a lower versus higher glioma genetic risk score [OR (95% CI) for risk scores of 0–<7, 7–<9, and ≥9–14 were 0.39 (0.18–0.86), 0.59 (0.30–1.18), and 0.96 (0.38–2.42), respectively; $P_{interaction} = 0.11$].

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

Table 2. ORs and 95% CIs for the association between diabetes history and risk of glioma

	Men		Women		Total	
	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[b]
Diabetes history						
No	536/1,115	1.00 (Reference)	387/923	1.00 (Reference)	923/2,038	1.00 (Reference)
Yes	21/81	0.59 (0.35–0.99)	18/76	0.57 (0.33–0.99)	39/157	0.58 (0.40–0.84)
Case–control studies						
Diabetes history						
No	372/499	1.00 (Reference)	290/481	1.00 (Reference)	662/980	1.00 (Reference)
Yes	14/40	0.56 (0.29–1.07)	14/39	0.65 (0.35–1.24)	28/79	0.60 (0.38–0.94)
Nested case–control studies						
Diabetes history						
No	164/616	1.00 (Reference)	97/442	1.00 (Reference)	261/1,058	1.00 (Reference)
Yes	7/41	0.68 (0.29–1.60)	4/37	0.41 (0.14–1.21)	11/78	0.54 (0.28–1.05)
Age at diabetes diagnosis[c]						
No diagnosis					437/588	1.00 (Reference)
4–49					6/21	0.38 (0.15–0.95)
50–59					8/19	0.52 (0.22–1.22)
60–77					8/23	0.45 (0.19–1.04)
P_{trend}[d]						0.43

[a]Adjusted for age at enrollment (cohort studies) or diagnosis/pseudodiagnosis (case–control studies), birth year, and study.
[b]Additionally adjusted for sex.
[c]Restricted to studies that collected this information; results not shown for men and women separately due to a small number of glioma cases in each category of age at diabetes diagnosis ($\leq$5).
[d]Calculated by modeling the age at diabetes diagnosis categories as continuous and excluding the "no diagnosis" group.

Discussion

We observed a 42% reduced risk of glioma for individuals with a history of diabetes versus those without (OR = 0.58; 95% CI, 0.40–0.84). Results were similar by sex, study design (case–control vs. nested case–control), and after restricting the outcome to glioblastoma, the most common histological subtype. The risks for other glioma subtypes were also reduced for those with versus without diabetes, albeit nonsignificantly. Diabetes-associated SNPs identified from GWAS were generally not associated with glioma risk, nor did these SNPs explain the inverse association we observed between glioma risk and diabetes history.

A lower risk of glioma associated with diabetes was first reported in a 1965 study, reporting a lower frequency of intracranial gliomas among diabetics versus nondiabetics but no difference in the frequency of meningiomas and pituitary neoplasms (36). Our finding of an inverse association between diabetes and glioma risk is consistent with results from previous case–control studies on glioma, all reporting relative risks below 1.0 for individuals with before diagnosis versus those without (range: 0.3–0.82; refs. 3–7). Like our study, these studies did not distinguish between type 1 versus type 2 diabetes. One case–control study showed a stronger inverse association for diabetes diagnosed at younger versus older ages (6), which could act as a proxy for type 1 versus type 2 diabetes, but this study was among those included in the current pooled analysis. Results from prospective cohort studies, which have lower potential for biases because of the reliance on proxy respondents or differential recall or selection of cases and controls, have been lacking. The California Seven-Day Adventists cohort, which included only 21 incident cases of glioma, did not show a clear association between self-reported history of diabetes and glioma risk (relative risk = 1.84; 95% CI, 0.28–7.38; ref. 10). A larger record-linkage study in Denmark found no association between hospital discharge records for diabetes and subsequent brain and central nervous system cancers in either men [standardized incidence ratio (SIR) = 1.1; 95% CI, 0.9–1.4] or women (SIR = 1.1; 95% CI, 0.8–1.3), based on 80 and 79 cases, respectively (11).

An inverse association between history of diabetes and risk of adult glioma may reflect a protective effect of heightened immune response, as has been hypothesized to underlie the relationship between allergies and glioma risk (16). History of allergies was also inversely associated with risk of glioma in this population (data not shown), but this association was independent of diabetes. Studies with more specific information on diabetes history, including type 1 versus type 2, and specific biomarkers of immune function and insulin resistance could provide additional insight on biological

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

Table 3. The association of diabetes-related SNPs and glioma risk

SNP	Gene	Diabetes risk allele	Genotype	Controls	Cases	OR (95% CI)[a]
rs13266634	*SLC30A8*	C	CC	915	364	1.00 (Reference)
			CT	834	337	1.04 (0.86–1.25)
			TT	160	71	1.23 (0.89–1.70)
						$P_{trend} = 0.29$
rs7754840	*CDKAL1*	C	GG	449	286	1.00 (Reference)
			GC	401	277	1.12 (0.90–1.39)
			CC	104	58	0.89 (0.62–1.27)
						$P_{trend} = 0.99$
rs7903146	*TCF7L2*	T	CC	968	403	1.00 (Reference)
			CT	770	299	0.97 (0.80–1.17)
			TT	172	70	1.05 (0.76–1.46)
						$P_{trend} = 0.98$
rs1111875	*HHEX*	G	GG	633	256	1.00 (Reference)
			GA	944	402	1.03 (0.84–1.25)
			AA	332	114	0.80 (0.61–1.05)
						$P_{trend} = 0.20$
rs7923837	*HHEX*	G	GG	702	300	1.00 (Reference)
			GA	943	365	0.90 (0.74–1.09)
			AA	263	107	0.89 (0.67–1.18)
						$P_{trend} = 0.29$
rs7480010	*LOC387761*	G	AA	991	399	1.00 (Reference)
			AG	744	298	0.97 (0.80–1.17)
			GG	174	74	1.07 (0.78–1.47)
						$P_{trend} = 0.89$
rs1113132	*EXT2*	C	CC	507	315	1.00 (Reference)
			CG	359	249	1.10 (0.89–1.37)
			GG	85	51	0.98 (0.67–1.44)
						$P_{trend} = 0.67$
rs8050136	*FTO*	A	CC	668	254	1.00 (Reference)
			CA	947	385	1.04 (0.86–1.27)
			AA	294	132	1.10 (0.85–1.44)
						$P_{trend} = 0.47$
rs4402960	*IGF2BP2*	T	GG	906	362	1.00 (Reference)
			GT	795	310	1.00 (0.83–1.21)
			TT	201	97	1.23 (0.92–1.64)
						$P_{trend} = 0.29$
rs1470579	*IGF2BP2*	C	AA	907	363	1.00 (Reference)
			AC	798	309	0.99 (0.82–1.20)
			CC	203	98	1.23 (0.93–1.65)
						$P_{trend} = 0.29$
rs5219	*KCNJ11/ABCC8*	T	CC	395	246	1.00 (Reference)
			CT	426	283	1.06 (0.85–1.32)
			TT	133	92	1.13 (0.82–1.54)
						$P_{trend} = 0.43$
rs2237892	*KCNQ1*	C	CC	1,662	676	1.00 (Reference)
			CT	242	90	0.88 (0.67–1.16)
			TT	5	6	4.46 (1.19–16.70)
						$P_{trend} = 0.92$
rs2943641	*IRS1*	C	CC	774	335	1.00 (Reference)
			CT	897	347	0.89 (0.73–1.07)
			TT	237	90	0.91 (0.68–1.22)
						$P_{trend} = 0.31$

[a]Adjusted for age at diagnosis/pseudodiagnosis, sex, and study.

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

mechanisms that may underlie the inverse association between diabetes and glioma risk. Alternatively, our results could be explained by long-term suppression of diabetes-related symptoms, particularly those related to immune response, during glioma development (37). However, assuming that glioma (and, particularly, glioblastoma) has a relatively short natural history because of its relatively aggressive nature, reverse causation is unlikely to explain the significant inverse association we observed for diabetes diagnosed at younger ages.

Our pooled analysis combined original data across a diverse set of studies, which allowed an examination of the consistency of the association between men and women and case–control and case–control studies nested within prospective cohort studies. We applied a standard format for the categorization of variables and standard methods for statistical analysis, which reduced the potential for methodological heterogeneity across studies. We also had information on potential confounding factors, including race/ethnicity, education, and history of allergies, as well as data to assess potential effect modification by genetic susceptibility to glioma. Nevertheless, our results were based on a relatively small number of cases reporting a previous diagnosis of diabetes. Self-reported diabetes diagnoses were not validated in any of the studies included in the current analysis, and the number of individuals with a history of diabetes may have been underestimated. Assuming random misclassification of this exposure, our results may have been biased toward the null. Furthermore, apart from age at diabetes diagnosis, we lacked sufficient data to more accurately distinguish between type 1 and type 2 diabetes. Participants from nested case–control studies were originally selected from the full cohorts for the purposes of genetic analyses. This could have biased our results if the controls had been selected on factors associated with diabetes history; however, the pooled ORs did not differ after individually excluding each nested case–control study. Thus, our findings should be confirmed in larger studies, preferably full prospective cohort studies, with medically validated data on diabetes history. Although we found no significant interactions between diabetes and 7 glioma risk-associated SNPs on glioma risk, statistical power to detect such interactions was limited. Of the 13 SNPs previously strongly associated with diabetes, we found that the TT genotype for rs2237892 on the *KCNQ1* gene was associated with a more than 4-fold increased risk of glioma compared with the CC genotype, an association opposite to those observed for risk of type 2 diabetes, higher fasting glucose levels, and reduced β-cell function (31). This finding, should it replicate in other studies, may provide some clues about the role of insulin resistance in the etiology of glioma. Although we did not observe significant associations with glioma in log-additive models for this SNP or 12 other diabetes-associated SNPs, it is possible that as yet undetermined genetic loci may contribute to the protective effect on glioma.

In summary, our international pooled study revealed an inverse association between diabetes and glioma risk, which is consistent with previous case–control studies. The role of genetic susceptibility cannot be excluded and should be pursued in future studies together with other factors that might be responsible for the diabetes–glioma association. Identification of these factors may help to improve our understanding of glioma pathogenesis and identify possible avenues for prevention of this highly fatal disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.M. Kitahara, A.V. Brenner, B. Melin, M. Waters, N. Chatterjee, S.J. Chanock, P. Hartge, P. Rajaraman
Development of methodology: C.M. Kitahara, A.V. Brenner, J.M. Gaziano, M. Waters, P. Hartge, P. Rajaraman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Melin, P.D. Inskip, L.B. Freeman, T. Carreon, J.M. Gaziano, U. Peters, M.P. Purdue, A. Ruder, H.D. Sesso, X.-O. Shu, M. Waters, E. White, W. Zheng, R.N. Hoover, M. Yeager, S.J. Chanock, P. Rajaraman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. Kitahara, A.V. Brenner, Z. Wang, P.D. Inskip, M. Feychting, H.D. Sesso, N. Chatterjee, S.J. Chanock, P. Rajaraman
Writing, review, and/or revision of the manuscript: C.M. Kitahara, M. Linet, A.V. Brenner, S.S. Wang, B. Melin, Z. Wang, Peter D. Inskip, L.B. Freeman, M.Z. Braganza, T. Carreon, M. Feychting, J.M. Gaziano, U. Peters, M.P. Purdue, A. Ruder, H.D. Sesso, X.-O. Shu, M. Waters, E. White, R.N. Hoover, J.F. Fraumeni Jr, P. Hartge, P. Rajaraman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.D. Sesso, X.-O. Shu, M. Yeager, P. Rajaraman
Study supervision: X.-O. Shu, R.N. Hoover, M. Yeager, P. Rajaraman

Acknowledgments

The authors thank all investigators who contributed data for the GliomaScan study.

For PHS: The PHS is supported by grants CA 97193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health.

For PLCO: This research was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS.

For NIOSH: This research was supported by NIOSH operating funds. The contributions of former laboratory director Mary Ann Butler are gratefully acknowledged. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

For VITAL: Grant K05CA154337 is funded by the National Cancer Institute (NCI) and the NIH Office of Dietary Supplements (ODS).

Grant Support

This work was supported in part by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

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.

Received September 3, 2013; revised November 1, 2013; accepted November 4, 2013; published OnlineFirst November 12, 2013.

Published OnlineFirst November 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0913

References

1. CBTRUS. Statistical Report: Primary brain and central nervous system tumors diagnosed in the United States in 2004–2008. Hinsdale, IL: Central Brain Tumor Registry of the United States; 2012.
2. Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro Oncol 2012;14:1316–24.
3. Cicuttini FM, Hurley SF, Forbes A, Donnan GA, Salzberg M, Giles GG, et al. Association of adult glioma with medical conditions, family and reproductive history. Int J Cancer 1997;71:203–7.
4. Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer 1999;82:155–60.
5. Schlehofer B, Blettner M, Becker N, Martinsohn C, Wahrendorf J. Medical risk factors and the development of brain tumors. Cancer 1992;69:2541–7.
6. Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG, Black PM. History of allergies and autoimmune diseases and risk of brain tumors in adults. Int J Cancer 2002;99:252–9.
7. Schwartzbaum J, Jonsson F, Ahlbom A, Preston-Martin S, Malmer B, Lönn S, et al. Prior hospitalization for epilepsy, diabetes, and stroke and subsequent glioma and meningioma risk. Cancer Epidemiol Biomarkers Prev 2005;14:643–50.
8. Stocks T, Rapp K, Bjørge T, Manjer J, Ulmer H, Selmer R, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. PLoS Med 2009;6:e1000201.
9. Swerdlow AJ, Laing SP, Qiao Z, Slater SD, Burden AC, Botha JL, et al. Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. Br J Cancer 2005;92:2070–5.
10. Mills PK, Preston-Martin S, Annegers JF, Beeson L, Phillips RL, Fraser GE. Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. Neuroepidemiology 1989;8:266–75.
11. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360–5.
12. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
13. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 2012;35:1835–44.
14. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–85.
15. Nokoff NJ, Rewers M, Cree Green M. The interplay of autoimmunity and insulin resistance in type 1 diabetes. Discov Med 2012;13:115–22.
16. Chen C, Xu T, Chen J, Zhou J, Yan Y, Lu Y, et al. Allergy and risk of glioma: a meta-analysis. Eur J Neurol 2011;18:387–95.
17. Rajaraman P, Melin BS, Wang Z, McKean-Cowdin R, Michaud DS, Wang SS, et al. Genome-wide association study of glioma and meta-analysis. Hum Genet 2012;131:1877–88.
18. Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. The Agricultural Health Study. Environ Health Perspect 1996;104:362–9.
19. Hatch EE, Linet MS, Zhang J, Fine HA, Shapiro WR, Selker RG, et al. Reproductive and hormonal factors and risk of brain tumors in adult females. Int J Cancer 2005;114:797–805.
20. Ruder AM, Waters MA, Carreon T, Butler MA, Davis-King KE, Calvert GM, et al. The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents. J Agric Saf Health 2006;12:255–74.
21. Steering Committee of the Physicians' Health Study Research Group. Final report of the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129–135.
22. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, et al. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA 2012;308:1751–60.
23. Hayes RB, Reding D, Kopp W, Subar AF, Bhat N, Rothman N, et al. Etiologic and early marker studies in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21:349S–55S.
24. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 2005;162:1123–31.
25. Cai H, Zheng W, Xiang YB, Xu WH, Yang G, Li H, et al. Dietary patterns and their correlates among middle-aged and elderly Chinese men: a report from the Shanghai Men's Health Study. Br J Nutr 2007;98:1006–13.
26. White E, Patterson RE, Kristal AR, Thornquist M, King I, Shattuck AL, et al. VITamins and Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol 2004;159:83–93.
27. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet 2007;39:906–13.
28. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881–5.
29. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341–5.
30. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331–6.
31. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, et al. Varients in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 2008;40:1092–7.
32. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proenca C, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat Genet 2009;41:1110–5.
33. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet 2009;41:899–904.
34. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet 2009;41:905–8.
35. Sanson M, Hosking FJ, Shete S, Zelenika D, Dobbins SE, Ma Y, et al. Chromosome 7p11.2 (EGFR) variation influences glioma risk. Hum Mol Genet 2011;20:2897–904.
36. Aronson SM, Aronson BE. Central nervous system in diabetes mellitus: lowered frequency of certain intracranial neoplasms. Arch Neurol 1965;12:390–8.
37. Turner MC, Krewski D, Armstrong BK, Chetrit A, Giles GG, Hours M, et al. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. Cancer Causes Control 2013;24:949–60.