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## Potential risk factors for incident glioblastoma multiforme: the Honolulu Heart Program and Honolulu-Asia Aging Study

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### Abstract

Glioblastoma multiforme (GBM) is the most common adult primary malignant brain tumor. Ninety percent of adult GBM patients die within 24 months after diagnosis. The etiology of GBM is unknown. The Honolulu Heart Program (HHP) and Honolulu-Asia Aging Study (HAAS) are prospective, cohort studies of cardiovascular and neurodegenerative disease based on 8,006 Japanese–American men followed since 1965. The Japan Hawaii Cancer Study provides data on incident cancer cases in the HHP/HAAS cohort. We used data from these studies to obtain epidemiologic information about GBM. GBM cases were identified by searching the 1965–1998 databases using International Classification of Diseases (ICD-9) codes. Nine histologically confirmed GBM cases, 58–80 years old, were identified. The incidence rate was 6.2/100,000 person–years. Records of each case were reviewed. Selected variables from the first three examinations (1965–1968; 1968–1970; 1971–1974) were used to identify potential candidate GBM risk factors. A multivariate Cox proportional hazards model showed sugar intake and occupational exposure to carbon tetrachloride were independently and significantly associated with development of GBM.

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## Keywords

Keywords Brain tumor; Cancer; Epidemiology; Glioma; Risk factors

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## Introduction

Glioblastoma multiforme (GBM) is the most common adult primary malignant brain tumor with a peak incidence between 55 and 84 years of age [1]. Fifty percent of adult GBM patients die within 10–12 months after diagnosis. Approximately 10 % of adult patients survive 24 months after diagnosis [2]. The causes of most glioblastomas are unknown. Established risk factors include inherited genetic syndromes and therapeutic ionizing radiation but account for only a small fraction of cases [3].

Analytic epidemiologic studies of glioblastoma compare the risk of developing GBM in persons with and without certain characteristics (cohort studies) or compare the histories of persons with and without GBM (case–control studies) to identify possible risk factors including lifestyle habits, environmental and occupational exposures to toxic agents, genetic factors and infections. Cohort studies are preferred because they ensure exposure occurs before disease develops and permit risk estimates based on exposure status. Accrual of statistically robust numbers of cases for a cohort study of GBM risk factors, however, is time consuming and difficult because the tumor is relatively rare. Most epidemiologic studies of GBM are case–control studies. Accrual of adequate numbers of cases is quicker in these studies. Interpretation of data from case control studies is more difficult because of potential problems such as recall bias, difficulty in selecting an unbiased control group, and lack of adequate exposure information.

The Honolulu Heart Program (HHP) is a prospective cohort study of cardiovascular disease based on the island of Oahu, Hawaii that began in 1965 with enrollment of 8,006 men of Japanese ancestry living on the island of Oahu, Hawaii. Research on neurodegenerative diseases of aging began in 1991 with establishment of the Honolulu- Asia Aging Study (HAAS). Data on incident cancer cases in the cohort is provided by the Japan Hawaii Cancer Study. We used the HHP/HAAS database to investigate the incidence of GBM in this population and identify potential GBM risk factors.

## Materials and methods

### Study population

The HHP/HAAS is a cohort study of cardiovascular disease and aging among 8,006 men of Japanese ancestry who were born between 1900 and 1919 and were 45–68 years of age at the time of their initial examination between 1965 and 1968. The cohort was identified through selective service records from World War II, and men were located through searches of telephone, business, and state agency records. Of the estimated 14,426 men born in 1900–1919 and believed to be residents of Oahu, 11,148 were located; 8,006 completed the baseline examination [4]. Thus the study population represents over 70 % of the target population.

## Glioblastoma multiforme

Since the initial examination (1965–1968), the cohort has been followed through a series of six follow-up examinations performed in 1968–1970; 1971–1974; 1991–1993; 1994–1996; 1997–1999; and 1999–2000. In addition to the periodic examinations the cohort is followed through rigorous surveillance of hospital admissions and records, obituaries in local newspapers, and death certificates. Deaths are ascertained by daily review of newspaper obituaries, telephone calls to relatives, mortuaries, hospitals, and the medical examiner's office and searches of the National Death Index (NDI). The Japan-Hawaii Cancer Study provides information on incident cancer cases in the cohort through surveillance of hospital discharge records on Oahu and through links with the Hawaii Tumor Registry for cases in other parts of the state. Information on participants living on the mainland is obtained from local relatives, interviews during island visits of participants, and the NDI. Out-migration from Oahu has been less than one per 1,000 per year and only five participants have been lost to follow-up. The final cause of death is determined by an expert panel of three physicians based on all available information obtained from follow-up examinations, surveillance of hospital discharge records, autopsy reports, and death certificates. Protocol autopsies are obtained on approximately 25 % of cohort deaths.

All primary and secondary CNS tumors were identified through searching the entire cohort database for the years 1965–1998 using International Classification of Diseases (ICD 9) codes for oncology. The original records of each of these cases were reviewed by one of the authors (JSN) to identify cases of GBM.

## Risk factors

Selected variables from the first three examinations (1965–1968; 1968–1970; and 1971–1974) were used to identify potential candidate GBM risk factors. These examinations included questionnaires that provided basic demographic, occupational and socioeconomic data, medical history, and lifestyle factors including usual physical activity, smoking habits, alcohol intake, and dietary habits [5]. Specific questions that were available included whether they ever had chest surgery, any blood transfusion and recurrent herpes. Other procedures included an electrocardiogram, grip strength assessment, pulmonary function testing, blood measurements including hematocrit, glucose (1-h post 50-gram load), cholesterol, and triglycerides, seated blood pressure determination, and various anthropometric measures such as height, weight, and subscapular and triceps skinfold thickness. Self-reported weight gain from age 25 was also ascertained. Separate evaluation of each man's diet was carried out by a dietician, using the 24-hour recall method [6]. A common food grouping system was used to estimate nutrient composition. Dietary data were also validated by repeat 24 h recall interviews and 7-day dietary records in a subset of 329 men examined 2 years later [7].

Occupational exposure data were available from the entire cohort based on information collected at the first and third examinations. Participants were asked what their present and usual jobs were and how many years they worked in these jobs at both examinations. Their jobs were assigned two three-digit occupation and industry codes according to the U.S. Bureau of the Census [8]. All unique occupation/industry combinations were identified and

independently assessed by three industrial hygienists for the likelihood of exposure to pesticides (insecticides, herbicides and fungicides), metals (manganese, mercury and iron) and solvents (carbon tetrachloride and carbon disulfide) [9, 10]. Likelihood of exposure was assigned by consensus as none, low, medium, and high. An intensity score was calculated by multiplying the likelihood of exposure by the number of years worked. Usual occupation was used in these analyses.

### Statistical analysis

Follow-up for incident GBM among the 8,006 men occurred over the approximate 30-year period from the time of study initiation through the end of 1998. Incidence of GBM was calculated using person-years of follow-up. Participants were considered at risk of developing GBM from the date of their initial examination until onset of this disease for cases and date of death, date lost to follow-up or the end of the follow-up period for non-cases. Corresponding 95 % confidence interval (CI) for incidence of GBM was computed assuming the number of cases (events) follows a Poisson distribution. Data analysis included comparing mean values of selected continuous variables for GBM cases and non-cases; comparing percentages of participants with a specified variable in GBM cases and non-cases by levels of selected categorical variables; and computing GBM incidence rates and associated 95 % CIs by categories of selected variables. The Wilcoxon rank sum test was used to compare the distribution of continuous variables between GBM cases and non-cases, while the Fisher's exact test was used to compare categorical variables. Due to small sample size (GBM cases) exact *P* values were preferred. Instead the Monte Carlo method was used to obtain an empirical *P* value that approximates the exact *P* value without relying on asymptotic distributional theory or exhaustive enumeration. The GENMOD procedure in SAS was used to estimate incidence rates of glioblastoma and associated 95 % CI by assuming a Poisson distribution and specifying person-years at risk as the offset. Exact logistic regression analysis relating GBM to each potential risk factor was performed to obtain exact *p*-values which were later used to assess the linear trend in incidence rates of GBM across categories of the predictor variables [11]. A multivariate analysis to estimate hazard ratio (HR) associated with each risk factor was performed using the Cox proportional hazards regression model.

## Results

### GBM incidence

Nine participants, 58–80 years of age at diagnosis (mean age = 66.8 years), developed GBM during the follow-up period between 1974 and 1995. All cases were confirmed by histological examination. Average age at death was 67.6 years for GBM cases and 77.6 years for non-GBM cases. All tumors were supratentorial. The incident GBM cases occurred during 144,405 person-years of follow-up, yielding an overall incidence rate of 6.2 per 100,000 person-years (95 % CI = 2.8–11.8).

### Risk factors

Comparisons of participants who developed GBM and did not develop GBM revealed several characteristics that differed significantly or were of borderline significance (Table

1). Participants developing GBM were significantly more educated and more likely to have a usual job that involved high carbon tetrachloride exposure. Although differences were of borderline statistical significance, compared with participants who did not develop GBM, those who developed GBM gained twice as much weight since age 25 (10.6 vs. 20.9 lbs), had larger triceps skinfold thickness (8.0 vs. 10.0 mm), consumed a greater percentage of calories from carbohydrate (46.4 vs. 53.3 %) and a 1.5-fold greater amount of sugar in the diet (45.2 vs. 70.0 g), and reported more frequent chest surgery (0.9 vs. 11.1 %) and blood transfusion (13.7 vs. 37.5 %), respectively. No significant differences were observed for age, body mass index, physical activity index, recurrent herpes labialis, smoking, total calories, coffee and tea consumption, and level of solvent exposure at one's usual job. In addition, no differences were found for pesticide or metal exposure at work (data not shown).

Incidence rates of GBM are presented in Table 2 across levels of categorical variables and across tertiles of continuous variables that reached significant or borderline significant levels. Although tests for trend tended not to be significant for most of the continuous variables, incidence rates increased with increasing tertiles of triceps skinfold and percentage of calories from carbohydrate, decreased with increasing coffee consumption, or were highest in the highest tertile of weight gain from age 25 and dietary intake of sugar. Incidence rates tended to be higher in those who had a technical or university education. Although the number of participants was limited, incidence rates were significantly elevated in those who had chest surgery, a blood transfusion and a usual job that involved exposure to medium or high levels of carbon tetrachloride. Results using the composite intensity score based on level and duration of usual job exposure to carbon tetrachloride were similar (data not shown).

Results from a multivariate Cox proportional hazards model are shown in Table 3. Age, education, triceps skinfold thickness, coffee and tea consumption, chest surgery, and having a blood transfusion were not independently associated with development of GBM. Dietary sugar intake and a usual job that involving high carbon tetrachloride exposure were independently associated with risk of GBM. A 10 g increase in dietary intake of sugar was associated with a 15 % increase in the risk of GBM (HR = 1.15, 95 % CI = 1.00–1.32) after adjusting for other variables in the model. Having a job with high carbon tetrachloride exposure was also independently associated with a significantly elevated risk of developing GBM. For the latter potential risk factor, wide confidence intervals reflect some instability.

## Discussion

Based on US Central Brain Tumor Registry data, glioblastomas account for 18.5 % of reported brain tumors. They represent approximately 1.42 % of all primary malignant cancers expected to be diagnosed in the United States in 2007. The US age-adjusted incidence rate for all reported glioblastomas is 3.09 cases per 100,000 person–years [1]. GBM incidence is higher in males than in females, 3.94 versus 2.38 [1, 3]. The incidence rate for GBM in this study of 6.2 per 100,000 person–years is lower than that reported for US men and women in the 65–74 year age group (12.47 per 100,000 person–years) [1, 12, 13]. Comparable data from Japan are limited. One study reports an age-adjusted incidence rate of 2.8/100,000 person–years for Japanese men over the age of 70 years [14]. The mean

age at diagnosis was 67 years in this study which was similar but slightly older than the average of 64 years reported for men and women combined in the US [1].

The only established risk factors for glioblastoma are ionizing radiation and certain inherited genetic disorders [3]. A number of other possibilities have been explored including, but not limited to, occupational exposures, infectious agents, medications, head trauma, blood transfusion, surgery, anesthesia, and lifestyle factors such as diet, however, the evidence for their role as GBM risk factors is inconclusive [3, 12, 13, 15, 16, 17].

Although this study has a relatively small number of incident GBM cases and resultant statistical power is low, results indicate that at least two variables are worthy of further investigation, intensity of carbon tetrachloride exposure and dietary levels of glucose. A usual job with medium or high exposure to carbon tetrachloride was independently associated with development of GBM; examples of such occupations included dry cleaners, firemen, chemists, machinists, and radio/TV repairmen. The association of carbon tetrachloride and other chlorinated aliphatic hydrocarbons has been reported previously [18]. An epidemiologic investigation showed elevated brain cancer mortality was associated with cumulative exposure to chlorinated hydrocarbons [19]. Dietary factors have been associated with cured meat consumption and low intake of foods high in vitamin C [20, 21]. Consumption of caffeinated beverages, especially coffee and tea, has been associated with a reduced risk of glioma [22, 23]. Although we observed a slight inverse trend of decreasing incidence with increasing coffee intake, neither coffee nor tea consumption was independently associated with GBM incidence. The biological basis for a possible association of high levels of dietary glucose with GBM risk is uncertain. Glucose and other reducing sugars in foods react with asparagine and other amino acids also in foods during cooking especially at temperatures above 120 °C to form acrylamide [24, 25]. Female rats given acrylamide in the drinking water have an increased incidence of tumors including CNS tumors [26]. On the basis of animal studies acrylamide is considered by the WHO as a probable human carcinogen. The link between acrylamide and human cancer, however, is unproven and the oncogenic risk of dietary acrylamide is controversial [27].

Although some studies have reported associations between infectious agents and GBM [28, 29], we did not observe an association with self-reported recurrent herpes infection. We observed an elevated incidence of GBM in those who reported a blood transfusion which could be linked with an increased likelihood of exposure to infectious agents, diagnostic radiation or exposure to anesthesia in a hospital setting. However, this association with blood transfusion was not independent of other potential risk factors. Although chest surgery was associated with borderline statistical significance in the current study and others have suggested this could be related to halogenated hydrocarbons found in anesthesia [12, 30, 31] chest surgery was relatively rare in this population (0.8 %) and associated GBM confidence intervals for the incidence rates were therefore imprecise.

Limitations of this study include the small number of participants who developed GBM and the resultant instability of hazard ratio estimates for some risk factors. Adjustment for multiple comparisons was not made given that the objective was to generate hypotheses. Some misclassification of occupational exposure is possible due to changes in a job over

time; however, there was a high degree of concordance (89–99 %) between job related exposure estimates available at the first and third examinations. If exposure misclassification were present, it is likely this would have been non-differential and thus would have minimized the associations observed. Competing risks for mortality may have made it more difficult to identify potential risk factors. In addition, since this study was not initially designed to identify risk factors for this cancer, risk factors that could be important may not have been ascertained.

Strengths of this study include its prospective design, the large sample size of at risk individuals, histologic confirmation of all GBM cases, and population-based investigation of a relatively homogeneous sample. Ascertainment of all cases of GBM was enhanced because of the comprehensive surveillance, review of detailed hospital records, tumor registry reports, and autopsy reports, and assessment of underlying cause of death. Baseline risk factors were measured before onset of clinical disease providing estimates of risk based on exposure status that would not be influenced by recall bias.

## Conclusion

In this long-term prospective epidemiologic study of Japanese–American men the incidence rate of glioblastoma multiforme was 6.2 per 100,000 person–years. Dietary intake of sugar and having a usual job with medium or high carbon tetrachloride exposure were identified as factors independently associated with its development.

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**Table 1**

Characteristics of incident glioblastoma multiforme cases and non-cases, 1965–1974

Characteristics <sup>a</sup>	GBM cases ( <i>n</i> = 9)	Non-cases ( <i>n</i> = 7997)	<i>P</i> value <sup>b</sup>
Age, years	52.8 (2.9)	54.5 (5.6)	0.584
Education, %			0.038
<High school	33.3	51.0	
High school	22.2	34.7	
Technical	22.2	4.0	
University	22.2	10.4	
Weight gain from age 25, lbs	20.9 (20.6)	10.6 (17.8)	0.096
Body mass index, kg/m <sup>2</sup>	24.7 (2.9)	23.8 (3.1)	0.341
Triceps skinfold, mm	10.0 (3.8)	8.0 (3.4)	0.084
Physical activity index	311.4 (31.1)	328.1 (45.4)	0.286
Current smoking, %	22.2	43.8	0.315
Total calories	2301.1 (736.1)	2273.6 (738.9)	0.934
Calories from carbohydrate, %	53.3 (13.8)	46.4 (11.0)	0.081
Sugar, g	70.0 (47.5)	45.2 (36.8)	0.097
Coffee-4 oz	3.0 (3.0)	3.4 (3.2)	0.770
Tea-4 oz	2.4 (3.4)	1.8 (2.3)	0.895
Chest surgery, %	11.1	0.9	0.080
Blood transfusion, %	37.5	13.7	0.085
Recurrent herpes, %	12.5	16.0	1.000
Usual job included solvents, %			0.300
None	55.6	48.6	
Low	11.1	30.6	
Medium	0.0	6.4	
High	33.3	14.5	
Usual job included carbon tetrachloride, %			0.008
None	77.8	74.5	
Low	0.0	22.9	
Medium	11.1	1.9	
High	11.1	0.8	

Note Values are means (SD) or percentages

<sup>a</sup> Assessed at Exam I (1965–1968) except for the following: chest surgery and blood transfusion (Exam II, 1968–1970), recurrent herpes (Exam III, 1971–1974), and occupational exposure (Exam I, 1965–1968 and Exam III, 1971–1974)

<sup>b</sup> Based on Monte Carlo estimates for the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables

**Table 2**  
Incidence rates of glioblastoma by levels of selected characteristics, 1965–1998

Characteristic <sup>d</sup>	Level	No. of cases/ no. of subjects at risk	Person-years at risk	Rate per 100,000 person-years	95 % CI	P value <sup>b</sup>
Education	<High school	3/4,077	97,172	3.1	0.6–9.0	0.137
	High school	2/2,773	70,526	2.8	0.3–10.2	
Wt gain from age 25, lbs	Tech or Univ	4/1,153	29,414	13.6	3.7–34.8	
	–81–2	2/2,613	60,859	3.3	0.4–11.9	0.192
Triceps, mm	3–18	2/2,737	69,166	2.9	0.4–10.5	
	19–98	5/2,565	65,099	7.7	2.5–17.9	
Calories from CHO, %	1–6	1/2,896	70,789	1.4	0.04–7.9	0.073
	7–8	3/2,240	55,907	5.4	1.1–15.7	
Sugar, g	9–32	5/2,865	70,454	7.1	2.3–16.5	
	0–41.8	1/2,662	65,686	1.5	0.04–8.5	0.055
Coffee-4 oz	41.9–51.0	3/2,683	66,772	4.5	0.9–13.1	
	51.1–96.9	5/2,656	64,595	7.7	2.5–18.0	
Tea-4 oz	0–23.9	2/2,645	61,882	3.2	0.4–11.7	0.043
	24.0–53.2	2/2,693	67,167	3.0	0.4–10.8	
Chest Surgery	53.3–337.1	5/2,668	68,151	7.3	2.4–17.1	
	0	2/1,287	31,936	6.3	1.57–25.04	0.721
Blood transfusion	1–3	5/3,733	90,926	5.5	0.27–113.3	
	4	2/2,986	74,337	2.7	0.09–76.37	
Usual job included medium or high CCL <sub>4</sub> exposure	0	5/3,770	92,081	5.4	2.3–13.0	0.430
	1–3	2/2,502	61,459	3.3	0.26–40.29	
CCI <sub>4</sub> exposure	4	2/1,734	43,659	4.6	0.37–56.73	
	No	8/7,385	185,555	4.3	1.9–8.5	0.042
Usual job included medium or high CCL <sub>4</sub> exposure	Yes	1/68	1,536	65.1	1.7–362.6	
	No	5/5,837	153,109	3.3	1.1–7.6	0.050
Usual job included medium or high CCL <sub>4</sub> exposure	Yes	3/929	22,996	13.0	2.7–38.1	
	No	7/7,782	191,469	3.7	1.5–7.5	0.012
Usual job included medium or high CCL <sub>4</sub> exposure	Yes	2/212	5,421	36.9	4.5–133.2	
	No					

Assessed at Exam I (1965–1968) except for the following: chest surgery and blood transfusion (Exam II, 1968–1970), and occupational exposure (Exam I, 1965–1968 and Exam III, 1971–1974)

<sup>g</sup>Tests for linear trend in incidence rates for continuous variables and differences in incidence rates for dichotomous variables using exact logistic regression

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**Table 3**

Hazard ratios for risk of glioblastoma, 1965–1998

Potential risk factor	Hazard ratio <sup>a</sup>	95 % CI	P value
Age, years	0.55	0.11–2.69	0.459
Education, %			
<High school	1.00		
High school	0.78	0.13–4.76	0.786
Tech or university	2.62	0.49–13.90	0.258
Triceps skinfold, mm	2.26	0.36–14.11	0.384
Sugar, g	1.15	1.00–1.32	0.046
Coffee-4 oz			
0	1.00		
1–3	1.83	0.21–16.25	0.589
4	0.89	0.08–10.02	0.924
Tea-4 oz			
0	1.00		
1–3	0.79	0.14–4.47	0.789
4	1.21	0.22–6.76	0.827
Chest surgery, %	8.60	0.86–85.92	0.067
Blood transfusion, %	3.79	0.80–18.06	0.094
Usual job included carbon tetrachloride, %			
None	1.00		
Low or medium	0.62	0.07–5.44	0.669
High	26.59	2.90–243.50	0.004

<sup>a</sup>Hazard ratios and 95 % CIs are determined from a multivariate Cox proportional hazards model and are based on a 10-unit change in the continuous independent variables