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Legume and Nuts Consumption in Relation to Glioma: A Case- Control Study

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ABSTRACT

Data on the link between legume and nuts consumption and risk of glioma are controversial. The current study aimed to investigate the relation between legume and nuts consumption and glioma in a case-control study in Iranian adults. In this hospital-based case-control study, we enrolled 128 pathologically confirmed new cases of glioma and 256 age and sex-matched controls. Dietary intakes of study participants were assessed using the validated Block-format 123-item semi-quantitative FFQ. Data on potential confounders were also collected through the use of a pre-tested questionnaire. Mean age of cases and controls were 43.4 and 42.8 years, respectively. Individuals with the greatest legume and nuts consumption were less likely to have glioma compared with those with the lowest consumption (0.52; 95% CI: 0.30–0.88). This inverse association was not changed after controlling for age, sex and energy intake (0.46; 95% CI: 0.26–0.81). The association remained statistically significant even after taking other potential confounders, including dietary intakes into account (0.32; 95% CI: 0.14–0.72). Additional adjustments for BMI did not alter the association; such that individuals in the top category of legume and nuts consumption were 66% less likely to have glioma compared with those in the bottom category (0.34; 95% CI: 0.15–0.76). We found an inverse association between legume and nuts consumption and odds of glioma, even after controlling for a wide range of confounders.

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Introduction

Glioma is a general name for all primary brain tumors originated from the glial cells of the brain (1). Glioma constitute about 30% of all brain tumors and 80% of all brain malignant tumors (2). Global incidence rate of glioma is 3.7 per 100,000 for males and 2.6 per 100,000 for females (3). In US, the incidence is 19.89 per 100,000 (4). In Iran, incidence of glioma is 3.9 and 2.8 per 100,000 for men and women (5). It is associated with headaches, seizures, vision changes, memory problems, personality changes, increased intracranial pressure and vascular injury, based on growth rate and sites (6). Although the incidence of glioma is low, given the high mortality rate, it is important to identify factors involved in its occurence (7).

Several risk factors have been investigated in relation to glioma. The only known modifiable risk factor for glioma is exposure to high-dose ionizing radiation, which accounts for a small proportion of glioma cases (4). Among dietary factors, fresh fruits and vegetables consumption (8), high intake of antioxidants (9), fresh fish intake (8), as well as vitamin supplementation (10–12) have been linked to a lower risk of glioma. However, available data are still limited to have a dietary recommendation. Legume and nuts contain high amounts of vitamin C and E and fiber, the protective relation of these constituents with glioma have been reported (10, 12,13). Some studies have reported an inverse association between legume and nuts consumption and risk of glioma. Chen et al. indicated a 60% reduced risk of glioma by increased intake of

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legume (14). Lee and et al., have reported lower intake of nuts in glioma patients (15). However, such relations were not confirmed by others (8, 16,17).

It should be considered that most studies investigated the relation between legume and nuts intake and risk of glioma, have been limited to western countries and no information is available from Middle East, where legume are commonly consumed. High intake of legume in these countries might provide some reasons for a lower prevalence of glioma in these countries compared with western nations. In addition, due to different dietary cultures of Asian people, it seems that further studies are required to clarify the relation between legume and nuts consumption and risk of glioma. Furthermore, earlier studies on diet-glioma associations have not controlled for most confounders. The findings of these studies might be biased due to residual cofounding. This study aimed to investigate the relation between legume and nuts consumption and risk of glioma in a group of Iranian adults while controlling for a wide range of potential confounders.

Methods

Participants

This hospital-based case-control study was carried out in Tehran, Iran, between 2009 and 2011. Cases were individuals with pathologically confirmed glioma (ICD-O-2 morphology codes 9380–9481) during the previous month that had been referred to Neurosurgery department of the hospitals affiliated to Shahid Beheshti University of Medical Sciences (18). Controls were healthy individuals who were hospitalized in orthopedic and surgical departments, of the same hospitals or were outpatients referring to the same clinics. The participation rate was 100% among cases and 89% among controls. Cases and controls were selected by using convenience-sampling and individually matched in terms of age (±5) and sex. Individuals with a history of any type of pathologically confirmed cancer (except glioma), chemotherapy and radiotherapy (due to cancer) were not included in this study. All cases and controls provided written informed consent. The study was ethically approved by the Medical Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran.

Dietary Assessment

Usual dietary intakes of participants during the preceding year (a year before the diagnosis of glioma in the case group and a year before the interview in the control group) were examined using a validated Block-format 123-item semi-quantitative FFQ (19). The FFQ was consisted of 123 food items with standard portion sizes commonly consumed by Iranians. Out of these 123 food items, eight were about legume and nuts consumption. Participants were interviewed in the presence of individuals who were involved in the preparation and cooking of foods. All reported consumption frequencies were converted to grams per day using household measures (20). Daily intakes of energy and nutrients were computed for each person using the US Department of Agriculture food consumption database which was modified for Iranian foods (21). In the current study legumes were defined as the consumption of pea, beans, lentil, chickpea and soya and nuts by summing up the consumption of walnut, seeds and nuts.

Validation study of this FFQ on 132 apparently healthy people revealed good correlations between dietary intakes assessed by FFQ and those obtained from 12 dietary recalls (one 24-h recall per month). The reliability of the FFQ was assessed by comparing food group intakes obtained from two questionnaires that filled within a year. The energy-adjusted correlation coefficients for protein intake between the dietary intakes obtained from the FFQ and those from multiple 24-h dietary recalls were 0.60 in men and 0.77 in women. Overall these data indicated that the FFQ provides reasonably valid measures of the average long-time dietary intakes.

Assessment of Glioma

Glioma was diagnosed based on pathological test using International Classification of Diseases for Oncology second edition and morphology codes 9380–9481. Only patients with a maximally one month of the confirmation of glioma were included in the study.

Assessment of Other Variables

Data on other variables such as age, sex, marital status, place of residence, education, occupation, smoking status, use of supplements (Iron, Calcium and multivitamins), family history of cancers and glioma, history of allergy and trauma, history of hypertension, exposure to chemicals in the past 10 years (Formaldehyde, plastics, benzene, mercury, arsenic and lead), cooking methods, drug use (any type of medications), personal hair dye use, duration of cell phone use (years) and history of exposure to the radiographic X-ray were assessed using a pretested questionnaire. Physical activity was measured using International Physical Activity Questionnaire (IPAQ) through the face to face interview. All results of the IPAQ were expressed as Metabolic Equivalents per week (METs/week) (22). Body weight was quantified by digital scale to the nearest 500 g with the subjects wearing the light clothing and no shoes. Height was measured by a tape measure to the nearest 0.5 cm in standing status while the subjects' shoulders were in normal position. Body Mass Index (BMI) was calculated by dividing of weight in kilograms to height in meters squared. All measurements were completed by a trained dietitian.

On the basis of previous studies, we considered farmers as having a high risk occupation for glioma. Individuals who lived in places near the electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high risk areas. Individuals who consumed any kind of fried foods at least twice per week were considered frequent fried food users. This definition was also used for barbecue use, microwave use as well as consumption of canned foods (23).

Statistical Methods

Participants were categorized based on tertile cutoff points of control group's legume and nuts intake. General characteristics and dietary intakes of case and control groups across tertiles of legume and nuts intake were assessed using one-way ANOVA for continuous variables and chi-square for categorical variables. The relation between legume and nuts consumption and glioma was examined by using conditional logistic regression in different models. Energy intake (Kcal/d), sex and age was adjusted for in the first model. Additional controlling for physical activity (continuous), family history of cancers (yes/no), family history of glioma, marital status (yes/no), education (university graduated/non-university graduated), high-risk occupation (farmer/non-farmer), high risk residential area (yes/no), duration of cell phone use (continuous), supplement use (yes/no), history of exposure to the radiographic X-ray (yes/no), history of head trauma (yes/no), history of allergy (yes/no), history of hypertension (yes/no), smoking status (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye (yes/no), frequent fried food intake (yes/no), frequent use of barbecue (yes/no), canned foods and microwave use (yes/no) was done in the second model. Dietary intakes of red and processed meats, fruits, vegetables and dairy products were taken into account in the third model. Finally, we adjusted the analysis for BMI. All confounders were chosen based on previous publications and case and control differences. The statistical analyses were carried out by using SPSS version 18. P values were considered significant at <0.05.

Results

General characteristics and dietary intakes of cases and controls are compared in Table 1. Cases were more likely to have a high-risk job, high-risk residential area, and history of exposure to the radiographic X-ray, history of head trauma, family history of glioma and history of exposure to chemicals. Cases were also more likely to be frequent fried foods intake, had higher intakes of red meat, refined and whole grains and lower intakes of calcium, vitamin E, fruits, dairy products, legumes and nuts than controls and were less likely to be current smoker, hair dye user, supplement user, microwave user, and had a short duration of cell phone use.

General characteristics of study participants across tertiles of legume and nuts consumption are presented in Table 2. Participants with greater intake of legume and nuts were less likely to be current smoker and have a history of dental radiography. No significant difference was seen in terms of other variables across tertiles of legume and nuts consumption.

Dietary intakes of participants across tertiles of legume and nuts consumption are provided in Table 3. Participants with greater intakes of legume and nuts had higher intakes of energy, protein, fat, saturated fat, calcium, vitamin E and B_6, folate, and dietary fiber than those with lower intake. Legume and nuts consumption was also associated with greater intakes of white meats, red meats, fruit, vegetables and dairy products. No other significant differences were seen in other dietary intakes across tertiles of legume and nuts consumption.

Multivariable-adjusted odds ratios and 95% confidence intervals for glioma across tertiles of legume and nuts consumption are shown in Table 4. Individuals with the greatest legume and nuts consumption were less likely to have glioma compared with those with the lowest consumption (0.52; 0.30–0.88). This inverse association did not alter after controlling for energy intake, sex and age (0.46; 0.26–0.81). The association remained statistically significant even after taking other potential confounders,

Table 1. General characteristics and dietary intakes of cases and controls.

	Cases $n = 128$	Controls $n = 256$	P_{value}
Age(years)	43.4 ± 14.6	42.8 ± 13.3	0.65
Males (%)	58.6	58.2	0.94
Weight (Kg)	74.6 ± 13.7	72.1 ± 12.1	0.07
BMI(Kg/m^2)	26.3 ± 4.3	26.1 ± 3.8	0.76
Married (%)	78.9	80.1	0.66
University graduated (%)	11.7	16.8	0.19
High-risk jobs[1] (%)	10.2	2.7	0.01
High-risk residential area[2] (%)	30.5	21.5	0.05
Duration of cell phone use (years)	2.8 ± 2.9	3.7 ± 2.6	0.01
History of exposure to the radiographic X-ray (%)	15.6	7.4	0.01
History of head trauma (%)	43.8	28.9	0.01
History of allergy (%)	25.0	29.3	0.37
History of hypertension (%)	2.3	5.1	0.21
History of dental photography (%)	46.1	59.0	0.02
Current smoker	15.6	25.0	0.01
Frequent fried food intakes[3] (%)	90.6	78.1	0.01
Frequent use of barbecue[4] (%)	15.6	12.1	0.34
Frequent microwave use[4] (%)	7.8	19.1	0.01
Frequent canned foods intake[4] (%)	6.3	5.9	0.88
Drug use (%)	7.8	5.1	0.29
Personal hair dye use (%)	21.9	41.0	0.001>
Exposure to chemicals (%)	19.5	10.5	0.01
Family history of glioma (%)	19.5	5.5	0.001>
Family history of cancer (%)	32.8	34.0	0.82
Supplement use (%)	7.80	15.6	0.03
Physical activity (MET-h/d)	34.8 ± 6.3	33.8 ± 6.3	0.13
Energy (Kcal/d)	2580 ± 560	2561 ± 722	0.79
Nutrient intakes			
Proteins (g/d)	98.2 ± 21.7	97.1 ± 29.7	0.70
Fats (g/d)	61.8 ± 18.6	66.1 ± 21.6	0.05
Saturated fatty acids (g/d)	19.1 ± 7.2	20.7 ± 9.0	0.09
Calcium (mg/d)	1021 ± 260	1122 ± 321	0.01
Vitamin E (mg/d)	5.1 ± 2.5	5.7 ± 3.0	0.03
Vitamin B6 (mg/d)	1.9 ± 0.5	2.0 ± 0.8	0.13
Folate (mcg/d)	349 ± 90	382 ± 302	0.24
Dietary Fiber (g/d)	23.4 ± 11.2	23.0 ± 14.2	0.82
Food groups			
Refined grains (g/d)	501.2 ± 174.7	421.0 ± 182.3	0.001>
Whole-grains (g/d)	176.8 ± 134.0	150.0 ± 108.2	0.04
White meats (g/d)	30.1 ± 13.6	32.6 ± 22.5	0.24
Red meats (g/d)	41.4 ± 27.8	36.0 ± 19.8	0.03
Fruits (g/d)	325.3 ± 99.7	360.8 ± 124.2	0.01
Vegetables (g/d)	257.8 ± 82.6	274.2 ± 86.2	0.08
Dairy products (g/d)	309.2 ± 116.7	355.0 ± 131.5	0.01
Legumes and nuts (g/d)	40.6 ± 22.7	46.0 ± 20.0	0.02
Sugar-Sweetened beverages (g/d)	79.1 ± 67.3	83.5 ± 74.5	0.57

MET = metabolic equivalent.
[1]Farmers were considered as having a high-risk occupation.
[2]Individuals who lived in places near electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.
[3]Individuals who consumed fried food at least twice per week considered as frequent fried food users.
[4]Individuals who used barbecue, microwave and canned foods at least twice per week were considered as frequent users.

including dietary intakes, into account (0.32; 0.14–0.72). Additional adjustments for BMI did not significantly alter the association; such that individuals in the top category of legume and nuts consumption were 66% less likely to have glioma compared with those in the bottom category (0.34; 0.15–0.76).

Discussion

We found an inverse association between legume and nuts consumption and odds of glioma. The association remained statistically significant even after taking other potential confounders, including socioeconomic characteristic, dietary intakes, and BMI into account. This study is the first to examine the association between legume and nuts consumption and odds of glioma in a Middle East country.

Glioma has a low 2-years survival rate and often diagnosed late; which makes treatment less likely to succeed. Therefore, preventive approach, in particular about this disease, is better than treatment approach. In the present case-control study, we found an inverse relationship between legume and nuts consumption and risk of glioma in Iranian adults. This finding was

Table 2. General characteristics of the study participants cross categories of legume and nuts consumption.

	Categories of legume and nuts consumption			
	1	2	3	*P*
Age(years)	43.2 ± 14.1	44.5 ± 14.2	41.1 ± 12.7	0.152
Males (%)	63	59	53	0.256
BMI(Kg/m^2)	26.1 ± 3.9	26.2 ± 3.9	26.2 ± 4.2	0.994
Married (%)	82	75	83	0.426
University graduated (%)	12	17	17	0.394
High-risk jobs[1] (%)	7	2	6	0.208
High-risk residential area[2] (%)	21	28	25	0.422
Duration of cell phone use (years)	3.7 ± 2.4	3.2 ± 2.8	3.4 ± 2.9	0.356
History of exposure to the radiographic X-ray (%)	12	12	6	0.225
History of head trauma (%)	29	40	33	0.199
History of allergy (%)	31.5	26	25	0.472
History of hypertension (%)	3.5	7	2	0.098
History of dental photography (%)	64	45	54	0.010
Current smoker	32	20	11	<0.0001
Frequent fried food intakes[3] (%)	82.5	82	83	0.981
Frequent use of barbecue[4] (%)	16	9	15	0.177
Frequent microwave use[4] (%)	12	14	21	0.127
Frequent canned foods intake[4] (%)	4	6	9	0.308
Drug use (%)	6	6	6	0.967
Personal hair dye use (%)	35	33	36	0.926
Exposure to chemicals (%)	13	13.5	15	0.877
Family history of glioma (%)	13	9	9	0.478
Family history of cancer (%)	29	35	37	0.370
Supplement use (%)	13	9.5	16.5	0.271
Physical activity (MET-h/week)	34.7 ± 6.3	34.1 ± 5.6	33.6 ± 5.4	0.241

MET = metabolic equivalent.
[1]Farmers were considered as having a high-risk occupation.
[2]Individuals who lived in places near electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.
[3]Individuals who consumed fried food at least twice per week considered as frequent fried food users.
[4]Individuals who used barbecue, microwave and canned foods at least twice per week were considered as frequent users.

Table 3. Dietary intakes of study participants across categories of legume and nuts consumption.

	Categories of legume and nuts consumption			
	1	2	3	*P*
Energy (Kcal/d)	2330 ± 518	2595 ± 662	2833 ± 746	<0.0001
Nutrients				
Proteins (g/d)	87 ± 18	97 ± 23	110 ± 35	<0.0001
Fats (g/d)	57 ± 17	65 ± 19	74 ± 23	<0.0001
Saturated fatty acids (g/d)	18 ± 8	20 ± 8	23 ± 9	<0.0001
Calcium (mg/d)	995 ± 253	1084 ± 272	1208 ± 355	<0.0001
Vitamin E (mg/d)	4.6 ± 2.6	5.7 ± 2.8	6.0 ± 2.9	<0.0001
Vitamin B6 (mg/d)	1.7 ± 0.4	2.0 ± 0.6	2.2 ± 0.9	<0.0001
Folate (mcg/d)	309 ± 60	370 ± 121	450 ± 424	<0.0001
Dietary Fiber (g/d)	19 ± 9	25 ± 14	26 ± 15	<0.0001
Food groups				
Refined grains (g/d)	440 ± 177	456 ± 191	447 ± 183	0.789
Whole-grains (g/d)	145 ± 106	158 ± 121	177 ± 126	0.090
White meats (g/d)	29 ± 13	32 ± 11	34 ± 30	0.025
Red meats (g/d)	35 ± 19	35 ± 17	44 ± 30	0.002
Fruits (g/d)	304 ± 102	355 ± 106	398 ± 127	<0.0001
Vegetables (g/d)	236 ± 67	258 ± 67	321 ± 98	<0.0001
Dairy products (g/d)	312 ± 124	344 ± 121	368 ± 134	0.002
Sugar-Sweetened beverages (g/d)	75 ± 65	80 ± 72	93 ± 80	0.137

Comparisons were made using ANOVA.

in agreement with a case-control study in China, in which greatest legume intake, compared with the lowest consumption, was associated with a 60% reduced risk of glioma (14). However, some studies did not find a significant association between legume and nuts consumption and glioma (8, 15–17). In an Australian case-control study, high legume and nuts consumption was not associated with odds of glioma (16). In two American studies, the investigators failed to find any relationship between intake of nuts and risk of glioma (15, 17). Lack of controlling for several well-known potential confounders (such as, exposure to high-dose ionizing radiation, age, family history and diet) and low sample size in the mentioned

Table 4. Multivariable-adjusted odds ratios for glioma across categories of legume and nuts consumption.

	Categories of legume and nuts consumption			
	1	2	3	P_{trend}
Crude	1.00	0.68 (0.41–1.13)	0.52 (0.30–0.88)	0.014
Model 1	1.00	0.63 (0.38–1.06)	0.46 (0.26–0.81)	0.007
Model 2	1.00	0.38 (0.19–0.74)	0.21 (0.10–0.45)	<0.0001
Model 3	1.00	0.46 (0.23–0.94)	0.32 (0.14–0.72)	0.005
Model 4	1.00	0.47 (0.23–0.96)	0.34 (0.15–0.76)	0.008

Model 1: adjusted for age, sex and energy intake.
Model 2: further adjustments were made for physical activity, family history of cancers, family history of glioma, marital status, education, high-risk occupation, high-risk residential area, duration of cell phone use, supplement use, history of exposure to the radiographic X-ray, history of head trauma, history of allergy, history of hypertension, smoking status, exposure to chemicals, drug use, personal hair dye, frequent fried food intake, frequent use of barbecue, canned foods and microwave.
Model 3: additionally adjusted for meats and processed meats, fruits, vegetables, and dairy consumption.
Model 4: Further adjusted for BMI.

studies, compared to that in our study, might explain the discrepant findings. It must also be considered that dietary intakes of Asian people are different from American and Australian people. Asian people almost intake more legume and nuts. Legume and nuts are traditionally used in high amounts in mixed dishes of Middle-Eastern people. Different level of legume and nuts consumption, as well as high exposure to potential risk factors such as red and processed meat intake, alcohol consumption and smoking might also be considered in the interpretation of different findings.

The mechanisms through which legume and nuts consumption might affect risk of glioma are unknown. Legume and nuts are rich sources of proteins, dietary fibers, and vitamins that might affect development and proliferation of brain tumors (10, 12,13, 24). Legume proteins through activating apoptosis process, triggering receptor-mediated signaling pathways and exploring microRNA-modulated cell death might effect glioma (24). Vitamin E, which is highly available in nuts, can lower the expression of cyclin-dependent kinases 2 and four and overexpression of P27, through which it can protect brain cells (25). Nuts contain essential fatty acids, vitamins, minerals, antioxidants and polyphenols which can protect cells against tumors through their antioxidant and anti-inflammatory effects. They can also regulate apoptosis of tumor cells without harming normal cells through increasing levels of free radicals and lipid peroxides, decreasing the expression of the oncogenes Ras and Bcl-2, and enhancing the activity of P53 (26).

This study has several strengths. It is the first study that assessed the relationship between legume and nuts consumption and risk of glioma in the Middle East. We controlled for a wide range of confounders in the present study to reach an independent association between legume and nuts consumption and risk of glioma. Also, new cases of glioma were enrolled in the study to reduce the effect of changing dietary habits. This study has some limitations as well. Because of the case-control design, selection and recall biases cannot be avoided. Previous epidemiological studies have shown that cases generally recall their usual past dietary intakes better than controls. We recruited new cases of glioma to minimize recall bias. We enrolled controls from individuals who were hospitalized in Orthopedic and Surgical departments of the same hospitals or outpatients referring to the same clinics. In hospital-based case-control studies, different patterns of referring cases and controls might result in a greater selection bias. In the current study, FFQ was used for assessing dietary intakes. As we all know, the accuracy of reported dietary intakes by FFQ is lower than those obtained from dietary records or recalls. Therefore, the possibility of misclassification of participants in terms of dietary intakes cannot be excluded.

In this case-control study, we found that legume and nuts consumption was inversely associated with risk of glioma, even after taking potential confounders into account. However, further studies in particular of prospective design are required to confirm these findings.

Conflict of interest

No potential conflict of interest was reported by the author(s).

Authors' Contribution to Manuscript

Hanieh Malmir (HM), Mehdi Shayanfar (MS), Minoo Mohammad-Shirazi (MMS), Giuve Sharifi (GS), and Ahmad Esmaillzadeh (AE) designed the research; HM and MS conducted the research; HM and MS performed statistical analysis; HM and AE wrote the paper; AE had responsibility for final content. All authors read and approved the final manuscript.

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