RECREATIONAL PHYSICAL ACTIVITY AND BRAIN CANCER RISK IN CANADIAN ADULTS

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ABSTRACT

Brain cancer is a debilitating and lethal form of cancer with little known about its prevention. A population-based case-control study was conducted with 643 histologically confirmed incident brain cancer cases and 3106 population controls aged 20-76 years from seven Canadian provinces to assess the impact of recreational physical activity on brain cancer in 1994-1997. Results of significance were in female subjects only. Compared to female subjects in the lowest respective quartiles of moderate, strenuous and total recreational physical activity, subjects in the highest respective quartiles had multi-variable adjusted odds ratios of 0.52 (95% CI: 0.35-0.79), 0.82 (95 CI: 0.56-1.20), and 0.57 (95% CI: 0.37-0.86). Physical activity particularly benefited women who smoked more than 10 pack-years and those with a body mass index below 25 kg/m^2. This study provides further support that physical activity plays an important role in the prevention of disease.

Keywords: brain cancer; physical activity; prevention; case-control

Subject Terms: Cancer-Prevention; Brain-Cancer; Physical Fitness; Case-Control Study

To all my friends and family who have

supported me through the years

~ Thank You!!

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INTRODUCTION

Brain cancer is one of the most debilitating and lethal forms of cancer (Inskip, Linet, & Heineman, 1995; Inskip, 2003). It accounts for only 2% of all cancer cases in Canada but it is one of the most lethal, with a 24% 5-year survival ratio (Canadian Cancer Society [CCS] & National Cancer Institute of Canada, 2007). It was estimated there would be 2,600 new cases of brain cancer in Canada in 2007, with slightly more presenting in males (CCS & National Cancer Institute of Canada, 2007). Increased incidence rates have been reported into the late 1980s (Deorah, Lynch, Sibenaller, & Ryken, 2006; Desmeules, Mikkelsen, & Mao, 1992), after which it appears there has been a slight decline (CCS & National Cancer Institute of Canada, 2007; Deorah et al., 2006). This increase may have been due in part to advancements in early detection and diagnosis technology (Inskip, 2003), but it is unlikely that technological advancement is the only source of this increase (Desmeules et al., 1992).

The etiology of brain cancer is poorly understood (Davis & McCarthy, 2000; Wrensch, Minn, Chew, Bondy, & Berger, 2002), but there is some evidence that various environmental and occupational factors may play a role (Baldwin & Preston-Martin, 2004; Inskip et al., 1995; Pan, Ugnat, Mao, & The Canadian Cancer Registries Epidemiology Research Group, 2005). In childhood brain cancer there is an accepted causal link between utero exposures and the

development of cancer, particularly if the mother was exposed to ionizing radiation and diethystilesterol (Baldwin & Preston-Martin, 2004). Other environmental and occupational exposures have some supporting evidence to their attributed risk to the development of brain tumours (Pan et al., 2005; Zheng, Cantor, Zhang, Keim, & Lynch, 2001).

In addition to ionizing radiation and diethystilesterol, n-nitroso compounds and dietary nitrosamines are potential risk factors (Baldwin & Preston-Martin, 2004; Lee, Wrensch, & Miike, 1997). There is less supporting evidence for pesticides and electromagnetic frequencies (Baldwin & Preston-Martin, 2004). Infectious agents, head injury, medications, and vitamins have also been mentioned in limited literature as potential risk factors (Baldwin & Preston-Martin, 2004; Wrensch, Bondy, Wiencke, & Yost, 1993). Tobacco smoke has been established as a risk factor for several other forms of cancer and other chronic diseases, but there exists little evidence linking tobacco smoke exposure to brain cancer (Baldwin & Preston-Martin, 2004; Lee et al., 1997).

As well as a lack of understanding of risk factors and the etiology of brain cancer, even less is known about the primary and secondary prevention of this disease. A diet high in fresh fruit and vegetables, and rich in vitamin E has been suggested to decrease brain cancer risk in individuals in China (Hu et al., 1999). Physical activity has been shown to have health benefits for several non-communicable diseases (Dishman, Washburn, & Heath, 2004; Dishman et al., 2006), such as cardiovascular disease (Bouchard & Rankinen, 2001; Davey Smith, Shipley, Batty, Morris, & Marmot, 2000; Warburton, Nicol, & Bredin,

2006), type II diabetes (Bouchard & Rankinen, 2001; Warburton et al., 2006), and some forms of cancers such as colon and breast (Friedenreich & Orenstein, 2002; Lee, 2003; Thune & Furberg, 2001; Warburton et al., 2006). Physical inactivity rates are high in developed countries; in Canada, approximately 50% of the adult population does not participate in adequate amounts of physical activity (Warburton et al., 2006). Participation in physical activity has many benefits for individuals. Currently, nothing is known about the effects physical activity can have on the development of or the likelihood an individual will develop brain cancer. Brain cancer rates have declined slightly (CCS & National Cancer Institute of Canada, 2007; Deorah et al., 2006), and due to the debilitating effects of brain cancer, an investigation into potential preventive risk factors, such as physical activity, is warranted.

MATERIALS AND METHODS

Study Population

Participant data was extracted from the National Enhanced Cancer Surveillance System (NECSS) database, which is a multi-component, collaborative project of Health Canada and provincial cancer registries. The NECSS was created to provide a better understanding of the relationship between the environment and cancer. Information from 21,020 Canadians with one of 19 types of cancer and 5,039 population controls aged 20 to 76 years was collected from 1994 to 1997 in eight of 10 provinces in Canada (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island and Saskatchewan) (Pan et al., 2004).

Current analyses were based on 643 incident primary brain cancer cases and 3,106 male and female population controls from all participating provinces except Ontario. Ontario data for cases (N=366) and controls (N=1,933) were excluded from this study due to variation in the collection of physical activity information. Incident cases were recruited and selected following review of pathology reports received by the provincial cancer registries (Pan et al., 2005). All brain cancer cases were histologically confirmed by provincial registries, and defined as C71 according to the *International Classification of Diseases for Oncology, Second Edition* (ICD-O-2). Benign tumours, including meningiomas, were not included. Histologic subtypes were grouped into the following

categories according to the ICD-O-2: astrocytomas, glioblastomas, oliogodendrogliomas, ependymomas, and others. Letters of consent to contact were sent to the physicians of 1,413 identified brain cancer patients. Questionnaires were not sent to 268 cases due to death, and physicians chose not to offer letters to 153 cases. A total of 1,060 (75.0%) brain cancer cases received questionnaires via mail, and 1,042 were subsequently contacted. In total, 643 (61.7%) brain cancer cases completed and returned the questionnaires.

Control subjects had no prior diagnosis of cancer, and were residents of the participating provinces. Frequency matching to the overall NECSS cancer case group was used to select population controls that were similar in age and sex; matching to specific cancer types was not part of the selection. Frequency matching ensured that there would be at least one control for every case within each sex and 5-year age group for any specific cancer site in each province. The selection of population controls varied by province due to differences in data availability, accessibility, and quality. A total of 5,107 potential female and male controls were identified by provincial registries and were mailed the same questionnaire used with cases. Completed questionnaires were returned by 3,106 (60.8%) potential controls; 81 (1.6%) questionnaires were returned because of an old or wrong mailing address, and an updated address could not be obtained.

Data Collection

The same questionnaire and protocol was used by the registries with both cases and controls. Registries attempted to contact cases 1-3 months following diagnosis. When questionnaires were not completed in full telephone follow-up was used. The questionnaires were designed to collect information about cancer risk factors. The majority of questions attempted to capture information about cases and controls personal history two years prior to the time of questioning, this allowed for a more complete picture of cases prior to diagnosis. Demographic information concerning subjects level of education (highest grade achieved and years of post-secondary school), average family income over the last five years, marital status, employment history, residential history, and ethnic group or cultural group was collected. As well, subjects' height and weight two years prior was collected and used to calculate their corresponding body mass index (BMI). BMI was calculated by dividing a subject's weight in kilograms by height in meters squared. Obesity was defined as a BMI of 30 kg/m^2 or more, and overweight was defined as a BMI between 25 kg/m^2 and less than 30 kg/m^2 based on standards set by the World Health Organization (World Health Organization, 2000).

Subjects were also asked about: alcohol consumption two years prior, smoking history (smoked at least 100 cigarettes in lifetime; current smoking status; total years smoked), exposure to specific substances at work or home for more than one year, diet (60-item food frequency questionnaire, eating habits two years prior), history of vitamin and mineral supplement use (during the past

20 years), recreational physical activity two years prior, and reproductive history in women.

Assessment of Physical Activity

The questionnaires collected information about subjects' participation in recreational physical activity two years prior to the interview. Subjects were asked about the history of the frequency and duration of various recreational physical activities. Frequency and duration of activities were assessed by recording session frequency, average time per session, and the season(s) participated in 12 of the most common forms of moderate and strenuous recreational physical activities in Canada (jogging or running, gardening or yard work, home exercise or exercise class, golf, racquet sports, bowling or curling, swimming or water exercise, skiing or skating, bicycling, social dancing, and other strenuous exercise).

Intensity of exercise was estimated by assigning values of metabolic equivalents (METs) to each activity; METs used were adopted from the *Compendium of Physical Activities* (Ainsworth et al., 1993; Ainsworth et al., 2000). A MET was defined as the ratio of the associated metabolic rate for an activity to the resting metabolic rate (Anshel, Freedson, Hamill, & et al., 1991). One MET was equated to the average seated resting energy cost for an adult and was set at 3.5 ml of oxygen per kg per minute. The MET score for each physical activity was multiplied by the midpoint of the reported frequency of the activity. The score was then converted to the frequency per week and summed, creating a combined index of total recreational physical activity per week

(Gammon et al., 1998). Levels of recreational physical activity were then categorized into three levels using the combined index score: moderate (MET ≥3 to ≤ 6), strenuous (MET > 6), and total (moderate plus strenuous). The sums of each category of moderate, strenuous and total (moderate plus strenuous) recreational physical activity were used in the present analysis.

Statistical Analysis

Logistic regression was used to compute the odds ratios and corresponding 95% confidence intervals using the SAS software package (Version 9.1; SAS Institute, Inc., Cary, North Carolina). Physical activity variables were categorized into quartiles using the frequency distribution of the variables among the control population. Potential confounding variables considered in the initial regression model were: age (5-year age group), sex (male/female), province of residence, years of education (continuous), caloric intake (categorical; ≤11,000, 11,000≤15,000, >15,000 k/J per week) , vegetable consumption (continuous; servings/week), fruit consumption (continuous; servings/week), smoking status (never smoked, ex-smoker, current smoker), pack-years of smoking (continuous), alcohol consumption (quartiles; servings per week), body mass index (categorical; ≤25.0, 25.0-29.9, ≥30.0 kg/m^2), and occupational exposure at home and/or work to asbestos, arsenic salts, chromium salts, cadmium salts, asphalt, mineral/lube oil, bezidine, isopropyl oil, dyestuffs, vinyl chloride, pesticides, herbicides, mustard gas, radiation sources, welding, wood dust or other (exposure to at least one/no exposure). The final multivariate model was adjusted for 5-year age group; province of residence; body mass

index; caloric intake; pack-years of smoking; sex; occupational exposure; and alcohol consumption. Quartiles for variables were based on the frequency distribution in the control population.

To identify potential confounders an assessment was conducted using the stepwise selection method where variables were entered and removed from the model via a forward step, which may be followed by one or more backward elimination steps. The stepwise selection method terminated once no further effect could be added to the model or if the effect most recently entered is the only effect removed in the following backward elimination step. A p value of 0.10 was used for entry into and removal from the model. Models were adjusted for province of residence because provincial cancer registries varied in their identification of cases and controls. Although controls were matched by 5-year age group and sex to the entire NECSS sample of cancer types, age and sex were no longer matched when the analysis is limited to brain cancers; models were adjusted for 5-year age group to control for this difference. Tests for trend were conducted on all models of categorized data by treating the different categories as a single ordinal variable. Stratified analysis by brain cancer histologic subtype, and examination of effect modification by pack-years of smoking, BMI, and sex were performed.

RESULTS

A total of 643 (400 men and 243 women) incident brain cancer cases were included in the study. Table 1 displays the histolgic subtypes of brain cancer cases for men and women included in the study. Of the 643 brain cancer cases, 316 (49.1%) were astrocytomas, 155 (24.1%) were glioblastomas, 58 (9.0%) were oligodendrogliomas, 14 (2.2%) were ependymomas, and 100 (15.6%) were classified as "other".

Table 1: Brain cancer cases by histologic subtype, NECSS, Canada, 1994-1997

Histological Type	ICD-O-2 Codes	No. Cases		
		Total	Male	Female
Astrocytoma	9384, 9400-9421	316	198	118
Glioblastoma	9440-9442	155	103	52
Oligodendroglioma	9450-9460	58	32	26
Ependymoma	9391-9393	14	6	8
Others	8000, 8010, 8070, 8481, 8560, 8720, 9085, 9150, 9161, 9220, 9240, 9380, 9382, 9424, 9430, 9470, 9471, 9473, 9500, 9505, 9506, 9530, 9538, 9989	100	61	39

Table 2 compares the distribution of characteristics among brain cancer cases and controls. Compared to controls, brain cancer cases were younger; smoked fewer years (pack-years and total years); had more years of education; had a higher caloric intake; had a higher family income; consumed slightly more

fruit; participated in more recreational physical activity; and were more often exposed to harmful substances. Mean body mass index, alcohol consumption, and vegetable consumption were similar for cases and controls.

Table 3 presents the characteristics of brain cancer cases and controls by levels of total recreational physical activity. There were fewer numbers of current smokers and a higher number of ex-smokers as the level of physical activity increased. Level of recreational physical activity also increased with fruit and vegetable consumption, and caloric intake.

Table 2: Selected characteristics of brain cancer cases and controls, NECSS, Canada, 1994-1997

Characteristic	Cases (N=643)	Controls (N=3106)	*p* value‡
Age (years) (mean (SD*))	49.0 (14.4)	57.1 (13.5)	<0.0001
Female sex (N (%))	243 (37.8)	1464 (47.1)	<0.0001
Never smoked (N (%))	267 (41.5)	1131 (36.4)	0.0003
Ex-smoker (N (%))	209 (32.5)	1277 (41.1)	
Current smoker (N (%))	167 (26.0)	698 (22.5)	
Pack years of smoking (mean (SD))	8.6 (12.2)	12.8 (17.2)	<0.0001
Total years of smoking (mean (SD))	12.4 (14.8)	16.9 (17.6)	<0.0001
Overall average cigarettes smoked/day (mean (SD))	15.3 (9.0)	16.7 (9.8)	0.009
Age (years) at which smoking started (mean (SD))	16.9 (4.5)	17.1 (4.9)	0.36
Years since quitting smoking (mean (SD))	7.5 (11.7)	10.0 (12.9)	<0.0001
Alcohol (srvgs/wk) (mean (SD))	5.1 (10.0)	4.5 (9.1)	0.15
High family income N (%)	125 (25.3)	441 (18.4)	0.0018
Upper-middle family income N (%)	146 (29.5)	780 (32.6)	
Lower-middle family income N (%)	126 (25.5)	586 (24.5)	
Low family income N (%)	98 (19.8)	588 (24.6)	
Body mass index value (weight/kg $(m)^2$) (mean (SD))	25.8 (4.5)	25.9 (4.9)	0.88
Total years of education=Secondary + post	12.7 (3.5)	11.9 (3.7)	<0.0001
Vegetable consumption (srvgs/wk) mean (SD)	21.4 (14.5)	21.2 (14.6)	0.74
Fruit consumption (srvgs/wk) means (SD)	21.5 (17.7)	19.8 (15.2)	0.029
Total recreational PA (MET*-hours/week) (mean(SD))	26.2 (27.5)	23.8 (23.9)	0.039
Moderate recreational PA (mean(SD))	15.4 (16.0)	16.2 (15.4)	0.22
Strenuous recreational PA (mean(SD))	10.8 (19.6)	7.5 (15.9)	<0.0001
Total caloric intake (kJ/wk) (mean (SD))	14420.5 (5757.5)	13504.8 (6485.7)	0.0003
Occupational exposure† (N (%))	304 (47.3)	1252 (40.3)	0.0011

* SD, standard deviation; MET, metabolic equivalent

† Occupational exposure to asbestos, arsenic salts, chromium salts, asphalt, mineral/lube oil, benzidine, isopropyl oil, dyestuffs, vinyl chloride, pesticides, herbicides, mustard gas, radiation sources, welding, wood dust and other at home and/or work

‡ t-test for continuous variables and chi-squared test for categorical variables

Table 3: Characteristics of brain cancer cases and controls by levels of total recreational physical activity, NECSS, Canada, 1994-1997

Characteristic	Levels of total recreational physical activity (MET*-hours/week)							
	<=6.25		6.25<=16.98		16.98<=34.41		>34.41	
	Cases (N=159)	Controls (N=776)	Cases (N=151)	Controls (N=778)	Cases (N=145)	Controls (N=776)	Cases (N=188)	Controls (N=776)
Age (years) (mean (SD*))	49.2 (14.2)	58.8 (12.7)	48.0 (14.6)	56.9 (13.5)	51.2 (14.0)	57.4 (12.9)	47.8 (14.5)	55.5 (14.8)
Female sex N(%)	76 (47.8)	375 (48.3)	61 (40.4)	403 (51.8)	50 (34.5)	380 (49.0)	56 (29.8)	306 (39.4)
Never smoked (N(%)	57 (35.8)	264 (34.0)	69 (45.7)	326 (41.9)	60 (41.4)	263 (33.9)	81 (43.1)	278 (35.8)
Ex-smoker (N(%)	45 (28.3)	301 (38.8)	43 (28.5)	285 (36.6)	59 (40.7)	355 (45.7)	62 (33.0)	336 (43.3)
Current smoker (N(%)	57 (35.8)	211 (27.2)	39 (25.8)	167 (21.5)	26 (17.9)	158 (20.4)	45 (23.9)	162 (20.9)
Pack years of smoking (mean (SD))	11.7 (15.1)	15.4 (19.6)	7.7 (11.7)	12.3 (17.1)	7.5 (10.4)	12.5 (15.6)	7.4 (10.5)	10.9 (15.7)
Occupational exposure† (N (%))	57 (35.8)	277 (35.7)	80 (53.0)	292 (37.5)	68 (46.9)	305 (39.3)	99 (52.7)	378 (48.7)
Alcohol (srvgs/wk) (mean (SD))	4.7 (10.1)	3.9 (8.9)	5.3 (11.4)	4.1 (8.5)	4.9 (7.9)	4.9 (9.6)	5.5 (10.3)	5.2 (9.4)
Body mass index value (weight/kg (m)^2) (mean (SD))	25.7 (5.2)	26.7 (6.2)	25.9 (4.7)	25.7 (4.4)	26.0 (4.3)	25.6 (4.4)	25.8 (3.9)	25.4 (4.2)
Total years of education=Secondary + post (mean (SD))	12.1 (3.8)	10.8 (3.9)	12.8 (3.1)	11.7 (3.6)	13.1 (3.6)	12.3 (3.5)	13.0 (3.5)	12.7 (3.4)
Vegetable consumption (srvgs/wk) mean (SD)	18.3 (11.2)	19.6 (19.7)	21.2 (13.0)	19.3 (9.4)	21.7 (12.9)	22.2 (13.7)	23.9 (18.3)	23.5 (13.3)
Fruit consumption (srvgs/wk) mean (SD)	17.2 (15.0)	17.0 (14.4)	22.0 (15.9)	18.3 (13.5)	20.7 (16.5)	21.2 (15.8)	25.1 (21.1)	22.9 (16.3)
Total caloric intake (kJ/wk) (mean (SD))	13645.3 (6513.9)	12894.6 (9079.9)	14302.4 (5643.1)	13181.32 (5236.5)	14020.2 (4600.3)	13832.5 (5700.5)	15479.8 (5860.0)	14109.1 (5030.2)

*SD, standard deviation; MET, metabolic equivalent;

† Occupational exposure to asbestos, arsenic salts, chromium salts, asphalt, mineral/lube oil, benzidine, isopropyl oil, dyestuffs, vinyl chloride, pesticides, herbicides, mustard gas, radiation sources, welding, wood dust and other at home and/or work.

The risk of brain cancer associated with moderate, strenuous and total levels of recreational physical activity was examined (table 4). Compared to female subjects in the lowest respective quartiles of moderate, strenuous and total recreational physical activity, female subjects in the highest respective quartiles had multi-variable adjusted odds ratios of 0.52 (95 percent confidence interval (CI): 0.35-0.79), 0.82 (95% CI: 0.56-1.20), and 0.57 (95% CI: 0.37-0.86). Brain cancer was significantly associated with moderate and total physical activity (*p* for trend: 0.001 and 0.009). The odds of being a case within the strenuous physical activity reference group (98/678 (14.5%)) compared to higher odds in the moderate (87/366 (23.8%)) and total physical activity (76/366 (20.8%) reference groups may explain the lack of significance found for strenuous physical activity in women. When stratified by gender no statistical significance was found for moderate, strenuous, or total physical activity in men.

Variation in brain cancer risk by tumour type was examined to determine whether activity-related brain cancer risk differs by histologic subtype (table 5). There was no statistical significance found for astrocytomas and glioblastomas. A statistically significant trend (*p* for trend: 0.004) in decreasing brain cancer risk associated with higher total physical activity was found for other types (includes oligodendrogliomas, ependymomas, and cases classified as "other") of brain cancer in women.

Stratified analysis by pack-years of smoking (two categories: ≤10 and >10 pack-years) shows decreased ORs associated with higher total recreational physical activity among women who smoked more than 10 pack-years (table 6).

When stratified by BMI (<25.0, 25.0-29.9, ≥30 kg/m^2), an inverse association between brain cancer risk and total recreational physical activity in subjects with a BMI less than 25 kg/m^2 was observed in women only (table 7). However, ORs ranged from 0.32 and 0.57 in women with a BMI between 25 and 29.9 kg/m^2 but a lack of significance was found, possibly due to small sample size (table 7).

Table 4: Odds ratios for brain cancer risk associated with recreational physical activity, by activity level and sex, NECSS, Canada, 1994-1997

Women (n=1707)					Men (n=2042)				
Physical activity level and MET* - hours/week	Cases (N)	Controls (N)	Multivariable adjusted†		Physical activity level and MET - hours/week	Cases (N)	Controls (N)	Multivariable adjusted†	
			OR*	95% CI*				OR	95% CI
Moderate					Moderate				
0<=4.73	87	366	ref.*	ref.	0<=3.88	103	411	ref.	ref.
4.73<=12.07	57	369	0.56	0.38, 0.83	3.88<=11.60	106	410	0.89	0.63, 1.23
12.07<=23.11	47	365	0.50	0.33, 0.76	11.60<=25.54	100	410	1.02	0.73, 1.41
>23.11	52	364	0.52	0.35, 0.79	>25.54	91	411	0.89	0.63, 1.25
p for trend			0.001		*p* for trend			0.70	
Strenuous					Strenuous				
0	98	678	Ref.	ref.	0	120	705	ref.	ref.
0<=.019	8	59	0.70	0.31, 1.58	0<=0.58	29	116	1.11	0.68, 1.80
0.19<=4.21	71	361	1.02	0.71, 1.46	0.58<=10.91	127	410	1.19	0.88, 1.62
>4.21	66	366	0.82	0.56, 1.20	>10.91	124	411	0.90	0.65, 1.24
p for trend			0.44		*p* for trend			0.70	
Total					Total				
0<=6.06	76	366	Ref.	ref.	0<=6.42	85	411	ref.	ref.
6.06<=15.24	58	366	0.61	0.41, 0.92	6.42<=19.10	102	410	1.02	0.73, 1.44
15.24<=31.35	51	366	0.58	0.38, 0.87	19.10<=37.36	93	411	0.92	0.65, 1.31
>31.35	58	366	0.57	0.37, 0.86	>37.36	120	410	0.93	0.67, 1.31
p for trend			0.009		*p* for trend			0.57	

*MET, metabolic equivalent; OR, odds ratio; CI, confidence interval; Ref., reference

† Odds ratios adjusted for 5-year age group, province of residence, caloric intake, body mass index, pack-years of smoking, occupational exposure, and alcohol consumption

Table 5: Odds ratios for brain cancer risk associated with recreational physical activity, by sex and histologic sub-type, NECSS, Canada, 1994-1997

Histologic subtype	Women (n=1707)					Men (n=2042)				
	Physical activity level (MET*-hours/week	Cases (N)	Controls (N)	Multivariable adjusted†		Physical activity level (MET-hours/week	Cases (N)	Controls (N)	Multivariable adjusted†	
				OR*	95% CI*				OR	95% CI
Astrocytoma										
	0<=6.06	36	366	ref. *	ref.	0<=6.42	37	411	ref.	ref.
	6.06<=15.24	25	366	0.53	0.30, 0.93	6.42<=19.10	53	410	1.22	0.76, 1.95
	15.24<=31.35	26	366	0.59	0.33, 1.04	19.10<=37.36	50	411	1.15	0.72, 1.85
	>31.35	31	366	0.63	0.36, 1.09	>37.36	58	410	1.05	0.65, 1.67
	p for trend			0.16		*p* for trend			0.98	
Glioblastoma										
	0<=6.06	18	366	ref.	ref.	0<=6.42	22	411	ref.	ref.
	6.06<=15.24	11	366	0.52	0.23, 1.17	6.42<=19.10	22	410	0.87	0.46, 1.62
	15.24<=31.35	8	366	0.41	0.17, 1.00	19.10<=37.36	27	411	0.97	0.53, 1.78
	>31.35	15	366	0.76	0.35, 1.61	>37.36	32	410	0.92	0.51, 1.68
	p for trend			0.45		*p* for trend			0.91	
Other types‡										
	0<=6.06	22	366	ref.	ref.	0<=6.42	26	411	ref.	ref.
	6.06<=15.24	22	366	0.85	0.44, 1.64	6.42<=19.10	27	410	0.78	0.44, 1.41
	15.24<=31.35	17	366	0.65	0.31, 1.36	19.10<=37.36	16	411	0.44	0.24, 0.90
	>31.35	12	366	0.31	0.13, 0.71	>37.36	30	410	0.64	0.35, 1.16
	p for trend			0.004		*p* for trend			0.10	

*MET, metabolic equivalent; OR, odds ratio; CI, confidence interval; Ref., reference

† Odds ratios adjusted for 5-year age group, province of residence, caloric intake, body mass index, pack-years of smoking, occupational exposure, and alcohol consumption

‡ Other types include oligodendroglioma, ependymoma and others

Table 6: Odds ratios for brain cancer risk associated with recreational physical activity, by pack-years smoking and sex, NECSS, 1994-1997

Gender and total recreational physical activity (MET*-hours/week)	<=10 pack years of smoking (n=2284)				>10 pack years of smoking (n=1426)			
	Cases (N)	Controls (N)	Multivariable adjusted†		Cases (N)	Controls (N)	Multivariable adjusted†	
			OR*	95% CI*			OR	95% CI
Women								
0<=6.06	52	258	ref. *	ref.	21	103	ref.	ref.
6.06<=15.24	48	275	0.73	0.46, 1.16	8	91	0.38	0.15, 0.92
15.24<=31.35	40	260	0.62	0.38, 1.01	10	102	0.44	0.19, 1.01
>31.35	50	276	0.70	0.44, 1.12	7	90	0.11	0.11, 0.77
p for trend			0.13				0.01	
Men								
0<=6.42	44	160	ref.	ref.	40	245	ref.	ref.
6.42<=19.10	63	191	1.08	0.68, 1.70	38	215	0.94	0.56, 1.58
19.10<=37.36	62	193	1.05	0.66, 1.66	31	213	0.76	0.44, 1.31
>37.36	76	236	0.94	0.60, 1.47	41	171	1.00	0.59, 1.70
p for trend			0.68				0.82	

* MET, metabolic equivalent; OR, odds ratio; CI, confidence interval; Ref., reference

† Odds ratios adjusted for 5-year age group, province of residence, caloric intake, body mass index, occupational exposure, and alcohol consumption

Table 7: Odds ratios for brain cancer risk associated with recreational physical activity, by BMI and sex, NECSS, Canada, 1994-1997

Gender and total recreational physical activity (MET*-hours/week)	Body mass index < 25 (n=1785)				Body mass index 25<30 (n=1393)				Body mass index >=30 (n=548)			
	Cases (N)	Controls (N)	Multivariable adjusted†		Cases (N)	Controls (N)	Multivariable adjusted†		Cases (N)	Controls (N)	Multivariable adjusted†	
			OR*	95% CI*			OR	95% CI			OR	95% CI
Women												
0<=6.06	39	177	ref.*	ref.	22	106	ref.	ref.	12	81	ref.	ref.
6.06<=15.24	37	191	0.70	0.41, 1.20	12	125	0.32	0.14, 0.73	9	49	0.92	0.34, 2.49
15.24<=31.35	29	227	0.48	0.27, 0.85	13	93	0.55	0.25, 1.25	9	44	1.22	0.45, 3.31
>31.35	33	227	0.49	0.28, 0.86	16	99	0.57	0.26, 1.22	7	40	0.97	0.33, 2.88
p for trend			0.007				0.37				0.89	
Men												
0<=6.42	34	144	ref.	ref.	32	185	ref.	ref.	18	77	ref.	ref.
6.42<=19.10	41	171	0.83	0.48, 1.43	47	182	1.17	0.69, 1.99	14	54	1.18	0.52, 2.71
19.10<=37.36	42	168	0.83	0.48, 1.43	37	189	0.95	0.55, 1.65	14	52	1.12	0.49, 2.54
>37.36	44	181	0.62	0.36, 1.08	60	175	1.40	0.84, 2.35	15	53	0.79	0.34, 1.85
p for trend			0.10				0.28				0.64	

* MET, metabolic equivalent; OR, odds ratio; CI, confidence interval; Ref., reference

† Odds ratios adjusted for 5-year age group, province of residence, caloric intake, pack-years of smoking, occupational exposure, and alcohol consumption

DISCUSSION

The present results suggest that participation in any amount of moderate recreational physical activity protects against brain cancer in women. An association between physical activity and brain cancer risk in female subjects who smoked more than 10 pack-years, and in female subjects with a BMI less than 25 kg/m^2 was observed. A decreased risk may be present for women with a BMI between 25 and 30 kg/m^2. Lack of significance was found, although ORs ranged from 0.32 to 0.57 in this group. Small sample size in both the middle and upper BMI categories may signify that women with a lower BMI participate in larger amounts of physical activity. In all present analyses, no association of significance between physical activity and brain cancer risk was found in male subjects.

This study was exploratory in nature, as there has been no previous published literature that examines the preventive effects recreational physical activity may have on the development or likelihood of development of brain cancer in adults. As such, the mechanisms behind the present findings are unknown and only speculative. Other researchers have examined the relationship between physical activity and other forms of cancer (Lee, 2003; Thune & Furberg, 2001), such as lung (Mao, Pan, Wen, Johnson, & Canadian Cancer Registries Epidemiology Research Group, 2003; Steindorf et al., 2006), breast (Lahmann et al., 2007; Slattery et al., 2007), ovarian (Pan, Ugnat, & Mao,

2005) and colon (Johnsen et al., 2006; Wolin et al., 2007). A population-based study using data from the NECSS reported that higher levels of moderate physical activity were inversely related to ovarian cancer risk (Pan et al., 2005). As well, a decreased lung cancer risk, in both men and women, associated with moderate and vigorous physical activity has been reported in another NECSS-based study, with increased protective effects among smokers and individuals with a BMI less than or equal to 30 kg/m^2 (Mao et al., 2003). However, a large European cohort study examining the relationship between physical activity and lung cancer found inconsistent results (Steindorf et al., 2006). Current research highlights the fact that there continues to be uncertainty surrounding the protective role physical activity can play in the development of cancer.

The results of the present study suggest that physical activity did not play a role in the development of brain cancer in men; all results of significance pertained to women only. This sex different may signify variation in the underlying biological mechanism(s) of brain cancer in men and women. It could also point to variation in how physical activity functions biologically in men and women. Further research is required to explain why a physical activity only influences the development of cancer in women.

Research has been conducted examining the impact of physical activity in patients with multiple sclerosis (White & Castellano, 2008). Insulin-like growth factor-1, neutrophins, brain-derived neutrophic factor, and nerve growth factor are proposed to be influenced by physical activity, promoting brain health in patients with multiple sclerosis (White & Castellano, 2008). Immune modulation

is another possible mechanism by which physical activity may influence the development of brain cancer. Physical activity can both positively and negatively influence immune system functioning, but at a certain levels physical activity can enhance the immune system and inhibit cancer development (Westerlind, 2003). Results of the current study identify a relationship between physical activity and brain cancer in women. This relationship may be mediated by the influence physical activity has on the production of female sex steroid hormones (Westerlind, 2003). Brain cancer is complex with poorly understood pathways and mechanisms. Without having a better understanding of the mechanisms behind the disease, it is difficult to determine the precise mechanism(s) physical activity plays in its development.

Limitations

There are several limitations to note regarding this study. Frequency matching was used when selecting population controls. The selection of controls was not matched to individual cancer types. As such, when examining the brain cancer case group, controls were no longer matched and a significant difference in mean age was found. Regarding the collection of physical activity information, subjects were asked questions related to participation in recreational physical activity. Participation in physical activity related to occupation was not addressed in the questionnaire. It is unknown whether participation in recreational physical activity is lower for some subjects because of participation at the workplace. In addition, data from the province of Ontario was excluded from present analyses because of a difference in the type of physical activity information collected. This

was unfortunate because Ontario had both the highest number of brain cancer cases and controls in cornparison to the other participating provinces.

Cases were asked about their participation in physical activity two years prior to the time of the questionnaire administration. Provincial cancer registries were requested to identify cases within 1-3 months following diagnosis, but this may not have been the case as subjects and registries did not identify date of diagnosis; some brain cancer cases may have been identified after a longer period. In addition to not reporting date of diagnosis, registries did not provide the time elapsed between diagnosis and the self-administration of the study questionnaire. As such, some subjects may have been recently diagnosed, with physical activity information correctly reflecting levels prior to diagnosis. Whereas other subjects may have been diagnosed earlier, with physical activity information reflecting levels following diagnosis, this may have been particularly true because of the relatively low incidence rate of brain cancer in Canada. Due to the nature of brain cancer, physical activity levels may be impacted following diagnosis. Finally, as with all studies employing a case-control design, recall bias must be noted; accurately recalling personal information two or more years prior to the date of interview can be a difficult task for most.

Public Health Practice Implications

This population-based study provides preliminary evidence to support a link between physical activity and brain cancer risk, and it is a step forward in the understanding of brain cancer and its development. Further investigation is required to validate the present results to support the benefit of moderate activity in women. Physical activity must become and remain a public health priority for decision-makers in government and in the community. Ensuring access and affordability to physical activities not only improves the health of individuals (Sallis, Bauman, & Pratt, 1998) but also that of the community (Brownson, Baker, Housemann, Brennan, & Bacak, 2001) and society as a whole. There are a variety of opportunities for decision-makers to address the high rates of physical inactivity in Canada, as well as in other developed countries. For instance, incorporating physical environments that are conducive to activity into city and community planning could increase access, or, ensuring that children and adolescents have a sufficient amount of gym/outdoor activity time while in school are two possible means of addressing physical activity in the community.

Conclusion

In summary, this population-based study showed modest evidence of a decreased brain cancer risk among women who participate in recreational physical activity. As well, it adds to the literature supporting the inverse association between physical activity and cancer. Because this is an exploratory study, further investigation is required to examine this association in greater depth. Physical inactivity is a growing problem in developed countries,

particularly in Canada. Participation is beneficial in the prevention of cancer and other chronic diseases and also supports an overall healthy lifestyle. An increase in physical activity among the Canadian population could have a significant public health impact and as such should remain a priority for health decision-makers in Canada.

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