IARC HANDBOOKS

ABSENCE OF EXCESS BODY FATNESS

VOLUME 16

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, 5–12 April 2016

LYON, FRANCE - 2018

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

2.2.18 *Primary tumours of the brain and central nervous system*

Primary tumours of the brain are a relatively uncommon group of heterogeneous neoplastic diseases with variable natural histories from benign to malignant. There are about 130 histological types arising from the many cell types that support and line the brain tissue and the central nervous system. Primary brain tumours occur across the age spectrum, from childhood through adulthood. The most common type, which arises from the glial cells, is called glioma and accounts for approximately 30% of all brain tumours in adults (Wiedmann et al., 2013). In turn, gliomas are of at least three types – astrocytoma, oligodendroglioma, and ependymoma – and are graded into four grades (1 and 2 are low-grade; 3 and 4, also known as glioblastoma multiforme, are high-grade) (Ricard et al., 2012).

The next most common group is meningioma, which accounts for approximately 20% of brain tumours. Many of these are benign and slow-growing, but – as occurs with other brain tumour types – benign tumours can undergo malignant transformation.

Established risk factors for brain tumours include hereditary conditions, such as neurofibromatosis, and ionizing radiation.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and brain cancers, including meningioma, was *inadequate*.

(a) *Cohort studies of tumours of the brain and central nervous system combined*

Essentially all of the evidence of associations between measures of body fatness and primary brain tumours applies to tumours in adulthood.

Five large prospective cohort studies reported associations between BMI and cancers of the brain and central nervous system in terms of incidence or mortality without specifying the histological type (Table 2.2.18a; Calle et al., 2003; Oh et al., 2005; Samanic et al., 2006; Reeves et al., 2007; Bhaskaran et al., 2014). There is consistently no evidence of associations between BMI and the development of all brain tumours. [This observation was robust when restricting the analyses to non-smokers only (Reeves et al., 2007; Bhaskaran et al., 2014).]

(b) *Cohort studies of glioma*

Five cohort studies (all in European and North American populations) (Benson et al., 2008; Moore et al., 2009; Michaud et al., 2011; Edlinger et al., 2012; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of glioma (Table 2.2.18a). There is consistently no evidence of associations between BMI and the development of glioma. One study stratified by low- and high-grade glioma and reported no difference.

The NIH-AARP cohort study (Moore et al., 2009) reported on the associations between recalled BMI at age 18 years and the development of glioma later in life and noted a positive association (P = 0.003) [the numbers of cases in the upper BMI categories were small; n = 11 for BMI of 30–34.9 kg/m^2, and no cases in the highest category of BMI ≥ 35 kg/m^2].

(c) *Cohort studies of meningioma*

Five cohort studies (all in European and North American populations) (Jhawar et al., 2003; Benson et al., 2008; Johnson et al., 2011; Michaud et al., 2011; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of meningioma (Table 2.2.18a). All reported statistically significant or borderline significant positive associations, with increased risks ranging from 1.4 to 2.13.

Two cohort studies (Johnson et al., 2011; Michaud et al., 2011) reported on associations between baseline waist circumference and meningioma incidence. In both, significant positive associations were noted.

(d) Case–control studies

See Table 2.2.18b.

Two case–control studies (Cabaniols et al., 2011; Little et al., 2013) examined relationships between BMI and risk of glioma, and no associations were found. Two further case–control studies, one in women only (Claus et al., 2013) and the other in men only (Schildkraut et al., 2014), examined relationships between BMI and meningioma and found positive associations in both studies, similar to those found in the cohort studies.

A meta-analysis (Niedermaier et al., 2015), including 2982 meningioma cases from 12 cohort and case–control studies reported positive associations with meningioma: with normal weight as the reference group, the relative risk was 1.21 (95% CI, 1.01–1.43) for overweight and 1.54 (95% CI, 1.32–1.79) for obesity.

Table 2.2.18a Cohort studies of measures of body fatness and cancers of the brain and central nervous system

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Brain and central nervous system combined							
Calle et al. (2003) Cancer Prevention Study II population-based cohort USA 1982–1998	404 576 Men Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 370 461 68 – 	 1.00 0.98 (0.85–1.13) 0.79 (0.61–1.03) – [0.14]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat intake, vegetable intake; in women, also adjusted for HRT use	
	495 477 Women Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 467 213 64 12 – 	 1.00 1.02 (0.87–1.21) 1.10 (0.84–1.44) 0.74 (0.42–1.32) – [0.96]		
Oh et al. (2005) Korean civil servants and teachers from the Korea National Health Insurance Corporation Republic of Korea 1992–2001	781 283 Men Incidence	Brain	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [P_{trend}]	 4 105 69 32 21 3 	 1.07 (0.39–2.93) 1.00 1.09 (0.79–1.50) 0.84 (0.55–1.28) 1.47 (0.90–2.38) 1.79 (0.57–2.66) [0.241]	Age, smoking status, alcohol consumption, frequency of regular exercise, family history of cancer, area of residence	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	Brain ICD-7: 193.0	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 519 353 46 	 1.00 1.03 (0.89–1.18) 0.86 (0.63–1.16) [> 0.5]	Age, year, smoking	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	Brain ICD-10: C71	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 113 133 143 83 99	 1.14 (0.95–1.38) 1.00 (0.84–1.19) 1.27 (1.08–1.50) 1.19 (0.96–1.47) 1.08 (0.88–1.32) 1.01 (0.81–1.26)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity Where appropriate: time since menopause, HRT use	Similar results when restricting to never-smokers or excluding the first 2 yr of follow-up
	1.2 million Women Mortality		BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 123 143 158 90 131	 1.17 (0.98–1.40) 1.00 (0.85–1.18) 1.29 (1.10–1.51) 1.18 (0.96–1.45) 1.31 (1.10–1.56) 1.17 (0.95–1.43)		
Bhaskaran et al. (2014) United Kingdom Clinical Practice Research Database United Kingdom 1987–2012	5.24 million Men and women Incidence	Brain and central nervous system	BMI per 5 kg/m^2	2974	1.04 (0.99–1.10)	Age, diabetes status, smoking, alcohol consumption, calendar year, SES	Very similar risk estimates for never-smokers (n = 1359 incident cases)
Glioma							
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Glioma ICD-O: 9380–9481	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 259 241 106	 1.00 1.20 (1.01–1.44) 1.07 (0.84–1.34) [0.10]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Moore et al. (2009) NIH-AARP cohort USA (8.2 years)	270 395 Men and women Incidence	Glioma ICD-O-3: 9380–9460	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 4 82 95 46 9	 1.66 (0.59–4.64) 1.00 0.90 (0.67–1.22) 1.29 (0.89–1.86) 0.74 (0.37–1.48) [0.95]	Age at baseline, age squared, sex, race, highest level of education, marital status	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Moore et al. (2009) (cont.)			BMI at age 18 yr < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 26 175 24 11 – 	 0.69 (0.45–1.05) 1.00 1.04 (0.67–1.59) 3.74 (2.03–6.90) – [0.003]		No significant associations observed with BMI at age 35 yr or at age 50 yr
Michaud et al. (2011) EPIC cohort From 1999 (8.4 years)	380 775 Men and women Incidence	Glioma ICD-O-2: 9380–9460, 9505	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 13 125 147 55 	 1.08 (0.60–1.92) 1.00 1.04 (0.81–1.34) 1.06 (0.76–1.48) [0.80]	Age, country, sex, education level	
			WC, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 73 82 73 90 	 1.00 0.90 (0.65–1.24) 0.82 (0.59–1.16) 0.97 (0.69–1.35) [0.81]	Age, country, sex, education level, height	
Edlinger et al. (2012) Metabolic Syndrome and Cancer Project (Me-Can) Austria, Norway, Sweden 1972–2005	578 462 Men and women Incidence	Low-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 21 16 21 24 16	 1.00 0.69 (0.33–1.42) 0.90 (0.46–1.77) 1.00 (0.51–1.95) 0.66 (0.31–1.38)	Year of birth (in decades), cohort, smoking status	
		High-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 65 72 82 99 92	 1.00 0.98 (0.68–1.43) 1.06 (0.73–1.52) 1.23 (0.87–1.75) 1.14 (0.80–1.64)		

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway From 1991 (23.5 yr)	74 242 Men and women Incidence	Glioma ICD-O-3: 9380–9480	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 6 79 49 14	 0.67 (0.29–1.56) 1.00 0.88 (0.61–1.27) 1.04 (0.58–1.85) [0.87]	Age, sex	
Meningioma							
Jhawar et al. (2003) Nurses' Health Study USA 1.2 million person-years	121 700 Women Incidence	Meningioma (self-reported)	BMI < 22 22–24.9 ≥ 25 [P_{trend}]	 22 31 58	 1.00 1.10 (0.61–1.97) 1.61 (0.96–2.70) [0.06]	Age, menopausal status, postmenopausal HRT use	
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Meningioma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 154 120 84	 1.00 1.01 (0.79–1.29) 1.40 (1.08–1.87) [0.03]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Johnson et al. (2011) Iowa Women's Health Study USA 291 021 person-years	27 791 Women Incidence	Meningioma ICD-9: 192.1, 192.3, 225.2, 225.4, 237.6	BMI 18.5–24.9 25–29.9 30–34.0 ≥ 35 [P_{trend}] WC (in) < 30.25 30.26–33.50 33.51–37.75 > 37.75 [P_{trend}]	 41 36 35 13 22 20 35 44	 1.00 0.92 (0.59–1.44) 2.14 (1.36–3.36) 1.99 (1.06–3.71) [0.0007] 1.00 0.92 (0.50–1.69) 1.56 (0.92–2.67) 2.13 (1.28–3.56) [0.0006]	Age	BMI at age 18 yr and at age 30 yr not associated with risk

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Michaud et al. (2011) EPIC cohort From 1999 (8.4 yr)	380 775 Men and women Incidence	Meningioma	BMI			Age, country, sex, education level	
			< 20	7	1.00 (0.46–2.19)		
			20–24.9	70	1.00		
			25–29.9	87	1.34 (0.97–1.86)		
			≥ 30	39	1.48 (0.98–2.23)		
			[P_{trend}]		[0.05]		
		Meningioma	WC, quartiles			Age, country, sex, education level, height	
			Q1	32	1.00		
			Q2	45	1.18 (0.73–1.88)		
			Q3	41	1.06 (0.65–1.72)		
			Q4	66	1.71 (1.08–2.73)		
			[P_{trend}]		[0.01]		
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway 23.5 yr	74 242 Men and women Incidence	Meningioma ICD-O-3: 9530–9539	BMI			Age, sex	When stratifying by sex, positive associations (borderline significant) observed in women only
			< 20	6	0.82 (0.35–1.92)		
			20–24.9	59	1.00		
			25–29.9	51	1.22 (0.83–1.80)		
			≥ 30	22	1.48 (0.89–2.45)		
			[P_{trend}]		[0.08]		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES: socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.18b Case–control studies of measures of body fatness and cancers of the brain and central nervous system

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Glioma					
Cabaniols et al. (2011) France 2005	122 Men and women Hospital	BMI in recent past < 25 ≥ 25	 49	 1.00 0.70 (0.41–1.18)	Age, sex
Little et al. (2013) USA 2004–2012	643 Men Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 133 311 191	 2.47 (0.63–9.70) 1.00 1.26 (0.94–1.69) 1.26 (0.91–1.75) [0.67]	Age, race, education level, state of residence
	460 Women Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 10 203 136 111	 0.80 (0.34–1.87) 1.00 0.95 (0.70–1.29) 1.11 (0.98–1.03) [0.63]	
	643 Men Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 34 391 182 29	 0.67 (0.41–1.09) 1.00 1.16 (0.89–1.52) 0.77 (0.45–1.31) [0.054]	
	460 Women Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 69 324 39 23	 0.68 (0.48–0.96) 1.00 1.39 (0.85–2.27) 1.66 (0.85–3.23) [0.004]	

Table 2.2.18b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Meningioma					
Claus et al. (2013) USA 2006–2011	1127 Women Population	BMI < 23.4 23.4–26.6 26.6–30.9 ≥ 30.9 [P_{trend}]	 303 237 269 308	 1.00 1.06 (0.83–1.35) 1.13 (0.89–1.45) 1.29 (1.01–1.65) [0.04]	Race, education level, menopausal status, age at menopause, age at menarche, number of full-term pregnancies, age at first live birth, ever use of OC, ever use of HRT, ever use of fertility medications, smoking, alcohol consumption, breastfeeding, geographical location
Schildkraut et al. (2014) USA 2006–2012	456 Men Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 84 206 102 58	 1.00 1.66 (1.17–2.34) 1.92 (1.28–2.90) 1.64 (1.02–2.64)	Age, race

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; OC, oral contraceptive; yr, year or years

References

Benson VS, Pirie K, Green J, Casabonne D, Beral V; Million Women Study Collaborators (2008). Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *Br J Cancer*, 99(1):185–90. doi:10.1038/sj.bjc.6604445 PMID:18560401

Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L (2014). Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*, 384(9945):755–65. doi:10.1016/S0140-6736(14)60892-8 PMID:25129328

Cabaniols C, Giorgi R, Chinot O, Ferahta N, Spinelli V, Alla P, et al. (2011). Links between private habits, psychological stress and brain cancer: a case-control pilot study in France. *J Neurooncol*, 103(2):307–16. doi:10.1007/s11060-010-0388-1 PMID:20835749

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*, 348(17):1625–38. doi:10.1056/NEJMoa021423 PMID:12711737

Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM (2013). Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. *J Neurosurg*, 118(3):649–56. doi:10.3171/2012.9.JNS12811 PMID:23101448

Edlinger M, Strohmaier S, Jonsson H, Bjørge T, Manjer J, Borena WT, et al. (2012). Blood pressure and other metabolic syndrome factors and risk of brain tumour in the large population-based Me-Can cohort study. *J Hypertens*, 30(2):290–6. doi:10.1097/HJH.0b013e32834e9176 PMID:22179083

IARC (2002). Weight control and physical activity. Lyon, France: IARC Press (IARC Handbooks of Cancer Prevention, Vol. 6). Available from: http://publications.iarc.fr/376.

Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ (2003). Sex steroid hormone exposures and risk for meningioma. *J Neurosurg*, 99(5):848–53. doi:10.3171/jns.2003.99.5.0848 PMID:14609164

Johnson DR, Olson JE, Vierkant RA, Hammack JE, Wang AH, Folsom AR, et al. (2011). Risk factors for meningioma in postmenopausal women: results from the Iowa Women's Health Study. *Neuro Oncol*, 13(9):1011–9. doi:10.1093/neuonc/nor081 PMID:21750006

Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, et al. (2013). Anthropometric factors in relation to risk of glioma. *Cancer Causes Control*, 24(5):1025–31. PMID:23456313

Michaud DS, Bové G, Gallo V, Schlehofer B, Tjønneland A, Olsen A, et al. (2011). Anthropometric measures, physical activity, and risk of glioma and meningioma in a large prospective cohort study. *Cancer Prev Res (Phila)*, 4(9):1385–92. doi:10.1158/1940-6207.CAPR-11-0014 PMID:21685234

Moore SC, Rajaraman P, Dubrow R, Darefsky AS, Koebnick C, Hollenbeck A, et al. (2009). Height, body mass index, and physical activity in relation to glioma risk. *Cancer Res*, 69(21):8349–55. doi:10.1158/0008-5472.CAN-09-1669 PMID:19808953

Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF (2015). Body mass index, physical activity, and risk of adult meningioma and glioma: a meta-analysis. *Neurology*, 85(15):1342–50. doi:10.1212/WNL.0000000000002020 PMID:26377253

Oh SW, Yoon YS, Shin SA (2005). Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol*, 23(21):4742–54. doi:10.1200/JCO.2005.11.726 PMID:16034050

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D; Million Women Study Collaboration (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*, 335(7630):1134. doi:10.1136/bmj.39367.495995.AE PMID:17986716

Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K, Delattre JY (2012). Primary brain tumours in adults. *Lancet*, 379(9830):1984–96. doi:10.1016/S0140-6736(11)61346-9 PMID:22510398

Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr (2006). Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*, 17(7):901–9. PMID:16841257

Schildkraut JM, Calvocoressi L, Wang F, Wrensch M, Bondy ML, Wiemels JL, et al. (2014). Endogenous and exogenous hormone exposure and the risk of meningioma in men. *J Neurosurg*, 120(4):820–6. doi:10.3171/2013.12.JNS131170 PMID:24484233

Wiedmann M, Brunborg C, Lindemann K, Johannesen TB, Vatten L, Helseth E, et al. (2013). Body mass index and the risk of meningioma, glioma and schwannoma in a large prospective cohort study (the HUNT Study). *Br J Cancer*, 109(1):289–94. doi:10.1038/bjc.2013.304 PMID:23778522