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Contacts with animals and humans as risk factors for adult brain tumours. An international case–control study

F. Ménégoz[a,*], J. Little[b], M. Colonna[a], A. Arslan[c], S. Preston-Martin[d], B. Schlehofer[e], M. Blettner[f], G.R. Howe[g], P. Ryan[h], G.G. Giles[i], Y. Rodvall[j], W.N. Choi[k,✠]

[a]Registre du cancer de l'Isère, 21 Chemin des Sources, 38240 Meylan, France
[b]Department of Medicine and Therapeutics, University of Aberdeen Medical School, Foresterhill, Aberdeen, UK
[c]International Agency for Research on Cancer, Lyon, France
[d]University of Southern California School of Medicine, Los Angeles, CA, USA
[e]Unit of Environmental Epidemiology, Deutsches Krebsforschungzentrum, Heidelberg, Germany
[f]Department of Epidemiology and Medical Statistics, University of Bielefeld, Germany
[g]Division of Epidemiology, Columbia University School of Public Health, New York, NY, USA
[h]Department of Public Health, University of Adelaide, Australia
[i]Anti Cancer Council of Victoria, Australia
[j]Institute for Environmental Medicine, Stockolm, Sweden
[k]Manitoba Cancer Treatment and Research Foundation, Manitoba, Canada

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Abstract

While numerous studies have addressed the possible role of farming and related exposures as risk factors for brain tumours in adults, few of them have examined the potential effect of exposure to farm animals or pets. In an international multicentre case–control study, we investigated whether residence on a farm, contact with animals, or working in occupations with a high degree of potential contact with animals or humans were associated with brain tumours. Using a common questionnaire, 1177 cases of glioma, 330 with meningioma and 2478 controls from eight centres were interviewed about the exposures and, in particular, about their contacts with nine species of animals: dairy cattle, beef cattle, pigs, horses, sheep, goats, poultry, dogs and cats. Living or working on a farm was not a risk factor, for either glioma or meningioma. Except in some centres, there was no relationship between having contacts with farm animals or pets and the risk of brain tumour, for either type of tumour or either sex. In relation to seven industrial groups involving frequent human and/or animal contacts, no association was apparent for either glioma or meningioma. In relation to 25 occupational groups with potential frequent contact with humans and/or animals, for glioma there was a reduced risk for biological technicians (Odds Ratio (OR)/=0, $P=0.01$), and general farm workers (OR=0.66, 95% Confidence Interval (CI): 0.5–0.9). For meningioma, there was an increased risk for cooks (OR=2.0; CI: 1.2–3.4). With some exceptions, these results indicate no association between either the type of brain tumour and contacts with animals, or with occupations that include a high level of contact with animals or a high level of contact with humans.

Keywords: Brain neoplasms; Farm; Animals; Occupation

1. Introduction

Among the potential risk factors for chronic diseases to which farm workers are exposed, contacts with animals have received considerable attention. A number of infectious agents transmissible from animals to humans have effects on the central nervous system or meninges, for example, listeria infections, brucellosis, salmonella infections, leptospirosis, yersinia infections, Q fever, rabies, the arboviruses and toxoplasmosis [1]. It is possible that some of these agents might be involved in the aetiology of brain tumours. In experimental animals, brain tumours can be induced by several types of viruses [2], including Rous sarcoma virus, polyomaviruses (notably Simian Virus (SV) 40, JC, BK) and adenoviruses (notably type 1 and type 12) [3–6]. In a hospital-based study in Minneapolis-St Paul (USA) Schuman

* Corresponding author. Tel.: +33-4-7690-7610; fax: +33-4-7641-8700.

E-mail address: registre.cancer.isere@wanadoo.fr (F. Menegoz).

✠ Deceased.

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and colleagues [7] reported a higher frequency of the presence of antibodies to *toxoplasma gondii* in cases with brain tumours, particularly those with astrocytoma, than in controls. Ryan and colleagues [8], in a study of subjects from Adelaide and Melbourne in Australia, some of whom are included in the present report, found no association between toxoplasma antibodies and glioma, but there was a positive association with meningioma. In one study of brain tumours in children, a positive association with reported contact of the index child with animals, and sick pets in particular, was reported [9], but this has not been observed in other studies [10]. Although in several studies of brain tumours in adults, the associations with farm residence or agricultural work has been investigated [11–43], few have assessed possible relationships with either contact with pets or farm animals. With regard to pets, no association with either ownership [15,23] or contact with sick pets [11] has been observed. The results of the five studies in which either livestock farming was distinguished from other types of farming or contacts with farm animals were investigated were inconsistent [30,34–37]. Contacts with animals have been investigated as possible risk factors for other types of cancer, notably leukaemia in children [44] and adults [34,37,45,46] and testicular tumours [47]. Therefore, one of the hypotheses investigated in an international collaborative study of brain tumours in adults was that contact with animals increases the risk of developing these tumours.

As infections are also transmitted from person to person, it is possible that occupations in which there is a high level of contact with people might increase the risk of having a neuro-oncogenic infection. Some studies suggest that there is an increased risk of brain tumours in those who work in education and healthcare [18,19,40,48,49]. This hypothesis was also investigated in this collaborative study.

2. Patients and methods

An international multicentre population-based case–control study on postulated risk factors for primary brain tumours in adults was carried out under the coordination of the International Agency for Research on Cancer (Lyon, France). Data on glioma were obtained in eight centres (Adelaide, Grenoble, Heidelberg, Los Angeles, Melbourne, Stockholm, Toronto and Winnipeg) and on meningioma from six centres (all except Los Angeles and Melbourne). All centres followed the same international study protocol, including a standardised questionnaire, study design, conduct and analysis. Minor differences in study design and conduct between the participating centres due to differing local circumstances are described in detail elsewhere [50,57]. Histologically-confirmed cases aged between 20 and 80 years diagnosed mostly in the late 1980s (range 1980–1991) were ascertained from neuro-surgical clinics or cancer registries. Verification of the completeness of case ascertainment was carried out either by cross-checks with cancer registries or with pathology departments, showing that with few exceptions, all incident cases were included in the study. A total of 106 cases had to be excluded because of an interval of more than 12 months between diagnosis and interview ($N=53$), inability to identify matched controls ($N=17$), lack of histological confirmation ($N=2$), unknown date of diagnosis, or missing information on years of schooling ($N=34$). Thus, the data included in the present paper relate to a total of 1177 cases of glioma (ICD-O 191; World Health Organization (WHO), 1976) and 330 cases of meningioma (ICD-O 192.0).

Population-based controls were recruited in each centre using different methods according to local circumstances. Individual matching on age and sex was used in Grenoble, Los Angeles, Melbourne, Stockholm and Winnipeg. Frequency matching on the same variables was used in Adelaide, Heidelberg and Toronto. Some centres also matched on ethnic group (Los Angeles) or by geographical region (Australian centres). Because of the differences in the matching methods, *post hoc* individual matching was performed in order to establish a uniform database for the analysis of the combined data set (Table 1). Controls were matched with cases by 5-year age group, sex and study centre. Data from a total of 2478 controls were obtained. When analysing animals as potential risk factors, 257 controls could not be matched with a case and therefore were not included in the combined analysis. If there were appropriate matches, controls were used in the analyses of both types of tumour. Thus, 1975 controls were included in the combined analysis of glioma and 1120 controls in the combined analysis of meningioma. When analysing occupation, in order to increase the power of the study, both sexes were put together.

A standardised questionnaire was developed by the study group and translated as appropriate. In most of the centres, information was collected in face to face interviews by specially trained interviewers. Self-administered questionnaires were used for all subjects in the Swedish component of the study and in some subjects in Melbourne, because of the difficulties of interviewing subjects over a wide geographical area. When index subjects were not available for interview, information was obtained by interview with a proxy (315 glioma cases, 10 meningioma cases, 88 controls).

Information was sought on residence or work on a farm and about contact with animals. Subjects were asked if they had ever come into contact with animals of specified types at least twice a month for a total of at

Table 1
Numbers of cases and controls, and participation rates, by centre

	Glioma		Meningioma		Participation rate (%)	
	Cases *n*	Matched controls *n*	Cases *n*	Matched controls *n*	All cases	All controls
Adelaide	107	417	61	371	90	63
Grenoble	61	122	54	108	74	59
Heidelberg	113	414	78	386	98	72
Los Angeles	93	93	–	–	62	69
Melbourne	404	405	–	–	66	63
Stockholm	153	152	81	80	81	83
Toronto	169	220	26	115	46	50
Winnipeg	77	152	30	60	45	50
Total	1177	1975	330	1120	73	74

least 12 months on a farm or elsewhere. The specific types of animal considered were dairy cattle, beef cattle, pigs, horses, sheep, goats, poultry, dogs and cats. In addition, a complete occupational history was obtained. The nature of the various types of work in which the subject had been engaged was coded according to International Standard Industrial Classification of all economic activities (ISIC, United Nations, 1971) and the job title according to the International Standard Classification of Occupations (ISCO, International Labour Office, 1968). Subjects were also asked about their history of infections, including medically diagnosed toxoplasmosis. As risks associated with infections might arise from contacts with humans, as well as from contacts with animals, we looked at occupations having a potentially high frequency of contacts with humans.

In order to estimate Odds Ratio (OR) and their 95% Confidence Intervals (95% CI), unconditional logistic regression (ULR) analysis was performed, with adjustment for age, sex, centre and years of schooling. As previous analyses of the combined data set had shown that cases were less educated than controls [50], and this marker of socio-economic status might be associated not only with case–control status, but also with contact with animals and occupation, years of schooling was included in the models as a potential confounder. As allowed by the design of the study, conditional logistical regression (CLR) analysis was also performed [58]. This analysis took into account the variable numbers of cases and controls in the matched sets. As both methods yielded similar results, only the results of the unconditional logistic regression analysis are presented.

For most variables, missing values were rare. We therefore excluded missing values from the analysis, as this had little effect on the power of statistical tests. We did not assume that no answer was equivalent to 'no contact'.

Heterogeneity between centres was tested by fitting centre-exposure interaction terms and comparing the corresponding deviance between models using likelihood ratio tests. When the P value of the test statistic was less than 0.10, centre-specific results are also presented and possible reasons for the heterogeneity are discussed.

When investigating age at first contact with a farm, we used subjects born on a farm as the reference group and ranked other subjects into quintiles according to their age at first contact.

In the analyses of the occupational data, we identified both ISIC and ISCO codes which we considered *a priori* would have high levels of potential contact with animals or with people. For instance, farmers, butchers, cooks and veterinarians were considered to potentially have high levels of contact with animals or animal tissue, and doctors, teachers, dentists, nurses and medical technicians to potentially have high levels of contact with humans or human tissue. As our primary hypothesis refers to a possible causal relationship between infection and brain tumours, we describe a 'high level of potential contact', as 'potential biological exposure'. Occupations specifically associated with potential exposure to fish or fish products, or with potential exposure to the skin or hides of animals which had already been processed (e.g. fourriers, leather workers) were excluded from this part of the study.

In order to test whether there could be a generic effect of either type of exposure, two broad categories were defined: one for occupations with potential biological exposure to animals and one for occupations with potential biological exposure to humans, based on the ISIC and ISCO codes described above.

3. Results

3.1. Living or working on a farm

443 people with glioma, 145 with meningioma and 952 controls reported ever having once lived or worked on a farm. No association with glioma was apparent (OR for men 0.97, 95% CI: 0.78–1.57; for women 1.22, 95% CI: 0.95–1.57). In addition, the OR for meningioma was

1.54 (95% CI: 0.91–2.58) for men and 0.94 (95% CI: 0.67–1.32) for women. There was no increase of the risk with an increasing length of the time having lived or worked on a farm. In view of observations that the long-term effects of infections may depend on the age of exposure, we analysed the age at which the subject first lived or worked on a farm. For meningioma, compared with those born on a farm (OR = 1), the risk of disease decreased with decreasing age of first contact (OR per quintile 0.86, 95% CI: 0.76–0.98, $P_{(trend)}$ 0.024). This was more pronounced for men than women.

3.2. Contacts with animals

For glioma, the OR associated with contact with the nine classes of animal specified in the questionnaire were in the range of 0.9–1.0 for men and 0.8–1.0 for women (Table 2). Heterogeneity between the centres was observed for contact with dairy cattle, dogs and cats in men and contacts with sheep in women. The test for heterogeneity of the association for contact with pigs or horses in men and dogs in women was also of borderline statistical significance. The heterogeneity of association for these groups of animals was, in part, due to the elevated OR in Winnipeg for contact with dairy cattle, pigs and cats, but not in most of the other centres (Table 3). The heterogeneity of the association for contact with horses in men was due to a low OR in Heidelberg, for contact with sheep in women due to a low OR in Los Angeles and for contact with dogs in women due to a low OR in Adelaide.

The OR of meningioma associated with contact with the various classes of animals in men varied between 0.6 and 1.9 (Table 4). None of the OR differ significantly from unity. The highest OR were associated with contact with sheep (OR 1.89, 95% CI: 0.93–3.85) and horses (OR 1.61, 95% CI: 0.91–2.85). The lowest OR were observed for

Table 2
Contacts with animals as risk-factors for glioma, International Collaborative Study of Brain Tumours in Adults, 1980–1991

Animal type	Men				Women			
	Number exposed				Number exposed			
	Cases	Controls	OR[a] (95% CI)	*P* Value for heterogeneity[b]	Cases	Controls	OR[a] (95% CI)	*P* Value for heterogeneity[b]
	N = 636	*N* = 1030			*N* = 541	*N* = 945		
Dairy cattle	196	359	0.97 (0.76–1.24)	0.02	145	297	0.94 (0.72–1.24)	0.43
Beef cattle	137	248	0.94 (0.72–1.22)	0.19	93	203	0.81 (0.59–1.22)	0.41
Pigs	148	284	0.93 (0.71–1.21)	0.11	128	268	1.01 (0.75–1.36)	0.38
Horses	197	344	0.96 (0.76–1.23)	0.11	155	301	0.90 (0.69–1.17)	0.39
Sheep	111	189	0.96 (0.71–1.28)	0.83	72	157	0.81 (0.58–1.13)	0.08
Goats	64	121	0.91 (0.63–1.30)	0.73	47	117	0.84 (0.57–1.25)	0.26
Poultry	253	489	0.89 (0.70–1.14)	0.54	216	469	0.85 (0.66–1.10)	0.21
Dogs	432	712	0.96 (0.72–1.29)	0.08	396	686	0.91 (0.67–1.24)	0.11
Cats	380	624	0.99 (0.77–1.28)	0.08	339	619	0.84 (0.65–1.10)	0.68

95% CI, 95% Confidence Interval; OR, Odds Ratio; ULR, unconditional logistic regression.
[a] Model (ULR) with: age (six levels), centre (eight centres for men, seven centres for women) + years of schooling + exposure.
[b] Model (ULR) with: age (six levels), centre (eight centres for men, seven centres for women) + years of schooling + exposure + (centre exposure).

Table 3
Centre-specific odds ratios associated with contacts with animals for which there was evidence of heterogeneity between centres, International Collaborative Study of Brain Tumours in Adults, 1980–1991

	Odds ratio (95%CI)							
	Adelaide	Grenoble	Heidelberg	Los Angeles	Melbourne	Stockholm	Toronto	Winnipeg
Gliomas in males								
Dairy cattle	0.72 (0.39–1.31)	0.44 (0.19–1.02)	0.73 (0.40–1.33)	–	1.11 (0.73–1.68)	1.19 (0.62–2.27)	0.43 (0.10–1.86)	3.26 (1.43–7.46)
Pigs	0.55 (0.28–1.11)	0.43 (0.17–1.11)	0.79 (0.43–1.46)	–	1.15 (0.70–1.88)	1.16 (0.59–2.32)	1.55 (0.43–5.51)	2.4 (1.02–5.65)
Horses	0.75 (0.42–1.36)	0.50 (0.20–1.29)	0.44 (0.22–0.92)	–	1.28 (0.87–1.90)	1.37 (0.71–2.62)	0.79 (0.24–2.60)	1.31 (0.59–2.95)
Dogs	0.64 (0.28–1.45)	0.47 (0.16–1.38)	0.77 (0.43–1.40)	–	1.41 (0.82–2.40)	1.66 (0.88–3.16)	0.52 (0.12–2.26)	0.34 (0.09–1.26)
Cats	0.88 (0.44–1.76)	0.43 (0.18–1.05)	0.73 (0.40–1.32)	–	1.11 (0.73–1.69)	0.87 (0.46–1.64)	2.58 (0.54–12.28)	2.69 (1.12–6.46)
Gliomas in females								
Sheep	0.48 (0.22–1.02)	0.68 (0.15–3.09)	0.88 (0.28–2.73)	0.23 (0.07–0.74)	1.05 (0.59–1.86)	1.15 (0.41–3.24)	2.64 (0.53–13.20)	2.02 (0.54–7.51)
Dogs	0.42 (0.20–0.89)	1.25 (0.36–4.33)	1.05 (0.56–1.95)	1.65 (0.66–4.15)	0.65 (0.33–1.25)	1.01 (0.67–1.52)	0.01 (0–287)	0.66 (0.18–2.36)
Meningiomas in women								
Dogs	1.89 (0.63–5.71)	0.28 (0.10–0.78)	0.7 (0.38–1.24)	–	–	1.91 (0.90–4.07)	–	0.49 (0.08–2.89)

contact with cats (OR 0.61, 95% CI: 0.34–1.06) and dogs (OR 0.66, 95% CI: 0.34–1.26). No heterogeneity between the centres was apparent for any of the associations with meningioma in men. In women, the OR for meningioma associated with contact with animals of the different types varied between 0.7 and 0.9. The OR associated with contact with horses was statistically significantly less than unity (OR 0.66, 95% CI: 0.46–0.94). Heterogeneity between the centres was apparent for the association with contact with dogs (Table 3). This seems, in part, attributable to a low OR in the data from Grenoble.

We investigated the potential effect of contact with any animals. No effect was apparent for glioma, whereas for meningioma, the OR were decreased, but not statistically significant (for men 0.45, 95% CI: 0.19–1.07; for women 0.84, 95% CI: 0.47–1.52). For both sexes together, the OR was 0.73 (95% CI: 0.45–1.17).

We also considered the possible effect of the number of types of animals with which the subject was in contact. There was no association for either type of tumour.

Contacts with these different classes of animals could have been occupational, as a result of having pets or a result of residence or holidays on farms. Therefore, we stratified the analysis according to whether or not the subjects had worked in occupations involving exposure to animals or animal products. With two exceptions, men having occupational contacts with animals had about the same risk of glioma as those who did not. The OR of glioma for men who had been in contact with poultry and who had potentially had occupational

Table 4
Contacts with animals as risk-factors for meningioma, International Collaborative Study of Brain Tumours in Adults, 1980–1991

Animal type	Men				Women			
	Number exposed				Number exposed			
	Cases	Controls	OR[a] (95% CI)	P Value for heterogeneit[b]	Cases	Controls	OR[a] (95% CI)	P Value for heterogeneity[b]
	N = 89	N = 480			N = 241	N = 640		
Dairy cattle	44	197	1.26 (0.72–2.23)	0.70	89	234	0.93 (0.65–1.31)	0.51
Beef cattle	30	128	1.13 (0.64–2.00)	0.95	60	158	0.78 (0.53–1.16)	0.26
Pigs	35	160	1.07 (0.60–1.92)	0.79	84	222	0.85 (0.59–1.22)	0.20
Horses	39	180	1.61 (0.91–2.85)	0.70	68	219	0.66 (0.46–0.94)	0.18
Sheep	18	87	1.89 (0.93–3.85)	0.83	34	109	0.88 (0.55–1.39)	0.69
Goats	16	72	1.28 (0.63–2.57)	0.34	26	90	0.85 (0.51–1.40)	0.45
Poultry	49	267	1.24 (0.68–2.25)	0.97	119	355	0.80 (0.57–1.14)	0.29
Dogs	56	307	0.66 (0.34–1.26)	0.48	161	438	0.88 (0.61–1.28)	0.01
Cats	47	274	0.61 (0.34–1.06)	0.30	152	408	0.90 (0.63–1.29)	0.73

OR, Odds Ratio; 95% CI, 95% Confidence Interval.
[a] Model (ULR) with: age (six levels), centres (six centres) + years of schooling + exposure.
[b] Model (ULR) with: age (six levels), centres (six centres) + years of schooling + exposure + (centre exposure).

Table 5
Associations between brain tumours and work in industries potentially involving contact with humans or animals, International Collaborative Study of Brain Tumours in Adults, 1980–1991 (both sexes combined)

Isic code	Industry	Glioma			Meningioma		
		Cases (n = 1177)	Controls[a] (n = 2478)	OR[b] (95% CI)	Cases (n = 330)	Controls[c] (n = 2299)	OR[b] (95% CI)
11	Agriculture and hunting	158	407	0.86 (0.69–1.07)	57	340	1.06 (0.76–1.50)
3111	Slaughtering, preparing and preserving meat	21	55	0.92 (0.54–1.59)	3	48	0.40 (0.12–1.34)
3112	Manufacture of dairy products	16	35	0.82 (0.43–1.53)	4	24	1.07 (0.35–3.22)
3231	Manufacture of leather	6	18	0.80 (0.29–2.16)	3	16	1.22 (0.33–4.57)
9331	Medical dental and other health services	140	283	1.01 (0.79–1.29)	37	208	0.94 (0.62–1.41)
9332	Veterinary services	0	4	0.00 ($P = 0.31$)[d]	1	0	0.00 ($P = 0.13$)[d]
9591	Barber and beauty shop	15	38	0.70 (0.36–1.36)	7	28	1.21 (0.51–2.89)

ISIC, International Standard Industrial Classification; OR, Odds Ratio; 95% CI, 95% Confidence Interval.
[a] All controls for eight centres are included.
[b] Model (ULR) with: age (six levels), centre (eight centres for glioma, six for meningioma), sex + years of schooling + ISIC group.
[c] All controls for six centres are included.
[d] Fisher's Exact test on unadjusted data.

exposure to animals was 1.40 (95% CI: 0.82–2.40) compared with 0.80 (95% CI: 0.60–1.06) for those without occupational exposure. The OR associated with contact with dogs and occupational exposure to animals was 0.56 (95% CI: 0.27–1.18), compared with 1.08 (95% CI: 0.78–1.51) for those without occupational exposure.

In women, for whom contacts with animals have no effect on the risk of glioma as a whole (Table 2), there was a significant decrease of the risk associated with contact with dairy (OR 0.49, 95% CI: 0.24–0.99) and beef cattle (OR 0.45, 95% CI: 0.22–0.91) if they had occupational exposure to animals.

Among men who had occupational exposure to animals, the OR for meningioma was 5.1 (95% CI: 1.02–25.5) for those with contact with horses. The elevated risk of meningioma in men associated with contact with sheep appeared to be confined to those who had not held occupations involving potential exposure to animals (OR 3.17, 95% CI: 1.24–8.10). The OR for women having contacts with poultry and occupational contacts with animals, was 0.31 (95% CI: 0.12–0.81).

3.3. Industries involving contact with humans or animals

The main industries considered were agriculture and hunting, food manufacture and medical and personal services. Seven groups (ISIC classification) were identified as potentially involving frequent human and/or animal contacts. None of the OR for glioma or meningioma associated with ever having worked in any of these seven industrial groups was significantly different from unity (Table 5).

3.4. Occupations involving contact with humans or animals

53 groups of occupations (ISCO classification) with potentially frequent contact with humans and/or animals were identified *a priori*. As there were no cases (or

Table 6
Associations between brain tumours and occupations potentially involving contact with humans or animals, International Collaborative Study of Brain Tumours in adults, 1980–1991 (both sexes combined)

Isco code	Occupation	Glioma			Meningioma		
		Cases ($n=1177$)	Controls[a] ($n=2478$)	OR[b] (95% CI)	Cases ($n=330$)	Controls[c] ($n=2299$)	OR[b] (95% CI)
0–54.20	Biological technician	0	12	0.00 ($P=0.01$)[d]	0	6	0.00 ($P=1.00$)[a]
5.31	Cooks	48	91	1.04 (0.71–1.53)	25	69	2.02 (1.20–3.38)
6–1	All farmers together	168	444	0.85 (0.69–1.04)	63	370	1.05 (0.76–1.45)
6–12.40	Livestock farmers	5	5	1.34 (0.36–4.99)	0	1	0.00 ($P=1.00$)a
6–12.50	Dairy farmers	7	6	1.27 (0.41–3.94)	0	0	0.00 ($P=1.00$)a
6–12.60	Poultry farmers	2	8	0.34 (0.07–1.71)	0	3	0.00 ($P=1.00$)a
6–21	General farm workers	76	279	0.66 (0.50–0.88)	44	247	1.03 (0.71–1.49)
6–24	Livestock workers	14	21	1.16 (0.56–2.39)	1	16	0.64 (0.08–5.20)
6–25	Dairy farm workers	7	11	1.02 (0.37–2.77)	0	7	0.00 ($P=0.63$)a
6–26	Poultry farm workers	4	10	0.93 (0.27–3.24)	1	6	0.78 (0.09–7.00)
7–6	Tanners, felmongers and pelt dressers	1	11	0.29 (0.04–2.19)	1	11	0.80 (0.10–6.73)
7–73	Butcher and meat preparers	18	28	1.35 (0.71–2.19)	2	23	0.78 (0.17–3.53)
7–74	Food preservers	3	9	0.66 (0.17–2.62)	1	7	0.54 (0.06–4.60)
7–75	Dairy product processors	6	15	0.78 (0.29–2.14)	3	13	1.56 (0.42–5.82)
0–54.30	Medical science technicians	6	12	1.38 (0.46–4.10)	0	11	0.00 ($P=0.38$)a
0–61, 0–63	Medical doctor, dentists	12	28	0.93 (0.45–1.94)	0	21	0.00 (P=0.10)a
0–71, 0–73, 0–75	Nurses, midwives, opticians, physiotherapy	64	139	1.05 (0.75–1.47)	27	110	1.13 (0.70–1.82)
0–72	Nurses aids	33	63	1.22 (0.76–1.94)	6	47	0.65 (0.26–1.58)
1–31	University teachers	15	44	0.61 (0.32–1.15)	2	28	0.45 (0.10–2.05)
1–32	Secondary education teachers	37	82	0.97 (0.63–1.49)	8	57	0.87 (0.39–1.92)
1–33	Primary education teachers	33	64	1.20 (0.75–1.92)	14	50	1.85 (0.95–3.59)
1–34	Pre-primary education teachers	10	25	0.77 (0.35–1.71)	8	23	1.83 (0.76–4.42)
1–35	Special education teachers	6	9	1.21 (0.40–3.72)	1	5	0.99 (0.11–8.99)
1–39	Teachers nos	16	20	1.65 (0.81–3.39)	2	15	0.94 (0.20–4.40)
5–70	Hair dressers, barbers	16	40	0.72 (0.38–1.37)	10	30	1.47 (0.69–3.16)
	'Biological exposure' to animals	231	571	0.86 (0.71–1.05)	84	470	1.10 (0.82–1.48)
	'Biological exposure' to humans	195	437	0.95 (0.76–1.17)	67	338	1.07 (0.77–1.49)

ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification.
[a] All controls for eight centres are included.
[b] Model (ULR) with: age (six levels), centre (eight centres for glioma, six for meningioma), sex + years of schooling + ISIC group.
[c] All controls for six centres are included.
[d] Fisher's Exact test on unadjusted data.

controls) for many occupations, we describe our results for 25 ISCO groups only. Because of the small number of cases, analyses were done for both sexes together. An analysis was also performed for each sex, but is not presented here. The OR for glioma associated with ever having worked in one of the 25 ISCO groups ranged between 0.0 and 1.7, with 13 below unity (Table 6). The only statistically significant departures from unity (at the 0.05 level) were for an absence of biological technicians amongst cases and a deficit of general farm workers (OR 0.66, 95% CI: 0.50–0.88). The OR for the group of occupations having potential exposure to animals or animal products was 0.86 (95% CI: 0.71–1.05).

The OR for meningioma varied between 0.0 and 2.0, with 17 of the 25 ISCO groups having ORs less than unity. The only significant result at the 0.05 level was an excess for cooks (OR 2.02, 95% CI: 1.20–3.38). The elevation of risk was apparent only in women (OR 2.24, $P=0.005$), and not in men (OR 0.76, $P=0.79$). There were elevated OR for primary education teachers (OR 1.85, 95% CI: 0.95–3.59) and pre-primary education teachers (OR 1.83, 95% CI: 0.76–4.42). The OR for other categories of teacher were not elevated. The majority of teachers were women, and similar results were obtained when the analysis was restricted to women. More generally, the variable 'biological exposure to humans', was not associated with either glioma nor meningioma.

4. Discussion

The strengths of the present study are that it was based on large numbers of cases and controls from whom data had been obtained by standardised protocols. This enabled us to conduct specific analyses for glioma and meningioma and by sex. The important differences between these histological types in terms of age and sex distribution [51,52] suggest that the risk factors might be different. Another strength of the study is that it is possible to assess heterogeneity of associations between different geographical areas.

Our study does not support the hypothesis of an increased risk of brain tumours among people who had ever lived or worked on a farm. In particular, there is no association in the analysis based on occupational history when jobs were classified according to the environment in which the work was performed (ISIC codes) or the nature of the work (ISCO codes). In 27% of our glioma cases, and 4% of controls, data were obtained from proxies. Excluding the proxy data had little effect on the risk estimates.

In some previous studies, based on death certificates, using cancer registry records or proxy respondents, higher risks for brain tumours among farmers were reported [12,26,28,32,53,54]. In a meta-analysis of the results of 33 studies of brain tumours and farming published between 1981 and 1996, significant heterogeneity in the association was found [55]. Overall, the meta-analysis suggested that there was a weak association between brain tumours and farming. No analysis was done by histological type. In an analysis restricted to female farmers, no association with brain tumours was found.

Contact with animals has been suggested as possibly increasing the risk of brain tumours [56]. In our study, contact with animals was not a rare event. Contact with goats was the most infrequent situation, but still involved more than 10% of the controls. Contacts with dogs and cats were frequent (70–80%) and the most common contact with farm animals was for poultry (55–60%). Contacts with other farm animals ranged from 20 to 50%. In general, we observed no effect of being in contact with an animal, for both sexes and both histological types. However, there was significant heterogeneity between centres for gliomas in men (five species) and women (two species). One possible explanation is that the underlying causal factor might differ between countries, perhaps because of differences in the presence of infection or susceptibility in the animal and/or human host. Another possible explanation is that contact with animals is associated with different exposures in different countries (e.g. the relationship between social class and animal contact may be different between countries). The findings might also be attributable to chance, especially in the context of multiple testing.

Most previous studies of the potential effect of animals as risk factors for brain tumours deal with the disease in children. In the literature, we found nine studies assessing the association between brain tumours and contact with pets. Six were directed toward brain tumours in children, and three towards adult brain tumours [11,15,23]. In none of the latter three studies were contacts with pets found to be risk factors. Few previous studies have investigated contact with farm animals. In one study [30], there was an increased risk of brain tumours for dairy farmers and sheep handlers, and in another for livestock farmers [35]. We found no association between contact with any animals (among the nine species studied) and brain tumours. In addition, we found no increase of the risk with increasing number of animal types with which the subject was in contact. Thus, our study does not support the idea of a generic risk factor resulting from contact with animals.

We considered that it was important to distinguish between contacts with animals as a result of occupational activity and other contacts. Occupational contact may be with substantially larger numbers of animals of the same type, and more frequent, compared with contact resulting from leisure activity. Because of the structure of our questionnaire, in those with occupational contact, we were not able to distinguish the types of animal with which there was occupational contact from the type with which there was contact as a result of leisure activities.

In general, the risks of both glioma and meningioma associated with contact with animals were similar or lower for those who had held jobs involving potential exposure to animals than in those who had not held such jobs. Thus, no dose relationship was observed in these analyses. The only exceptions to this pattern were a modest excess of glioma in men who had been in contact with poultry, and a more pronounced excess risk of meningioma in men who had been in contact with horses (OR 5.1, 95% CI: 1.02–25.5). There is no obvious explanation for this finding. The study does not support the hypothesis that animal infections are associated with brain tumour development. Moreover, in another analysis of these data, only one case of glioma, one case of meningioma and three controls reported ever having toxoplasmosis [57].

With regard to occupations potentially involving contact with humans, no overall elevation in risk was observed. Moreover, some elevation of the risk of meningioma was observed for pre-primary and primary education teachers. This was not apparent for other categories of the teaching profession. An excess in risk associated with teaching has not been reported in other studies. The absence of a general effect of occupations potentially involving exposure to humans or human tissues does not support previous reports of an increased risk of brain tumours in anatomists, pathologists, embalmers, physicians, dentists and dental assistants [54]. The absence of any overall increase in the risk of glioma or meningioma associated with reported contact or potential contact with animals or humans appears to be consistent with the lack of increase in risk with reported infectious diseases in the analysis of other data collected in this collaborative study [57].

In conclusion, our study does not support the hypothesis that living or working in a farm increases the risk of brain tumour. In previous reviews or meta analysis, considerable methodological differences between studies were noted. Some were not able to distinguish between gliomas and meningiomas. Some were not population-based and therefore selection bias may have affected the results. Others were based on mortality data, and might not have reliably distinguished secondary and primary tumours. In the present study, information was not obtained on the duration or intensity of exposure, and this may have impeded the detection of an association. In future studies of this issue, this information should be sought in a design which is a population-based study of newly incident cases.

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