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Occupational exposure to meat and risk of lymphoma: A multicenter case-control study from Europe

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Several studies have suggested an increased risk of lymphoma among workers exposed to meat, without conclusive evidence. We conducted a multicenter case-control study during 1998–2004 in the Czech Republic, France, Germany, Ireland, Italy and Spain, including 2,007 cases of non-Hodgkin lymphoma, 339 cases of Hodgkin lymphoma and 2,462 controls. We collected detailed information on occupational history and assessed exposure to meat in general and several types of meat *via* expert assessment of the questionnaires. The odds ratio (OR) of non-Hodgkin lymphoma for ever occupational exposure to meat was 1.18 (95% confidence interval [CI] 0.95–1.46), that for exposure to beef meat was 1.22 (95% CI 0.90–1.67), and that for exposure to chicken meat was 1.19 (95% CI 0.91–1.55). The ORs were higher among workers with longer duration of exposure. An increased risk among workers exposed to beef meat was mainly apparent for diffuse large B-cell lymphoma (OR 1.49, 95%CI 0.96–2.33), chronic lymphocytic leukemia (OR 1.35, 95% CI 0.78–2.34) and multiple myeloma (OR 1.40, 95%CI 0.67–2.94). The latter 2 types were also associated with exposure to chicken meat (OR 1.55, 95% CI 1.01–2.37, and OR 2.05, 95%CI 1.14–3.69). Follicular lymphoma and T-cell lymphoma, as well as Hodgkin lymphoma did not show any increase in risk. Occupational exposure to meat does not appear to represent an important risk factor of lymphoma, although an increased risk of specific types of non-Hodgkin lymphoma cannot be excluded.

Key words: meat workers; epidemiology; lymphoma

The lymphomas are a diverse group of malignant neoplasm of the lymphatic system. Conditions involving immunological dysregulation, including severe immunodepression (*e.g.*, AIDS) and autoimmunitary disorders and transplants are known to increase the risk of lymphoma.[1] In addition to the Human Immunodeficiency virus, other infectious agents, including the Hepatitis C virus, Epstein-Barr virus, and Human T-cell leukemia/lymphoma virus cause lymphoma in humans.[1] Most developed countries, including those in Europe and in North America, have experienced an increased incidence of lymphoma and in particular of non-Hodgkin lymphoma during the past 20 years.[1] In the same period, the criteria for diagnosis and classification of lymphoma have changed but this fact alone does not account completely for the increase in incidence rates of non-Hodgkin lymphoma.[2]

Several studies have suggested the possibility of an increased cancer risk of lymphoma among workers exposed to meat, including but not limited to slaughterhouse workers, butchers, food/meat processors, supermarket meat workers, farmers and cooks.[3–16] Other studies, however, have reported no association between risk of lymphoma or lympohaematopoetic neoplasms and employment as meat worker,[17–24] although some of these included a small number of exposed cases.[18,19,22] Working in the meat industry entails several potentially hazardous exposures, including in particular bacterial or viral agents. Animal viruses with oncogenic potential are of particular interest, because of potential exposure *via* blood, urine and feces of animals.[4,10,11,13,17] They include viruses such as ALV and REV, which are known to cause B-cell lymphoma and B-cell lymphoproliferative disease in chickens, and BLV, which causes bovine enzootic leucosis in cattle and sheep.[25] The potential for transmission of these animal viruses to other species under natural circumstances has been poorly investigated.[26] Currently, there is very little known about the effects of these potential oncoviruses in humans.

Increasing knowledge of the heterogeneity in genetics and pathology of the lymphomas proves the necessity of subtype-specific etiological research.[27] However, given the relative rarity of specific lymphoma subtypes, this approach requires large-scale investigations. We have studied the risk of lymphoma among workers exposed to meat in a large-scale multi-center European case-control study.

Methods

A case control study was conducted between 1998 and 2004 in the Czech Republic, France, Germany, Ireland, Italy and Spain. Participants were 17 years of age and older and provided informed consent for participation. A full occupational history was collected *via* a standardized questionnaire, along with information on leisure time activities, residence, personal and familial medical history, and lifestyle habits including sun exposure, tobacco smoking and alcohol drinking. Cases were cytologically or histologically confirmed and diagnoses were classified using the WHO classification.[27] The reliability of the diagnosis was checked by central review of 20% of the slides from each center. In Germany and Italy, controls were selected from a random sample of population registries while in the 4 remaining countries hospital-based controls were recruited: they had a range of diagnoses, not related to

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infectious diseases, immunological conditions or cancer. No single diagnostic category made up more than 10% of the total number of controls in each center. Participation rate was 88% in cases, 81% in hospital controls and 52% in population controls.

Cases and controls were matched by age, sex and recruitment center. In the Czech Republic and Germany the matching was at the individual level while in the remaining countries it was at the group level.

A standard questionnaire was prepared and translated into the language of each country and trained local professionals were used for questionnaire administration. In the occupational part of the questionnaire, cases and controls were asked about all jobs they held for at least 1 year. Job titles and place of employment were coded using ISCO codes[28] and NACE codes,[29] respectively. Detailed information was collected for each job on tasks, machinery used, and contact with specific agents. Specialized questionnaires, including one for meat workers, were administered whenever the study subject had held a relevant job: they included detailed questions tailored to fit the tasks performed by each participant during their employment and to provide information on opportunities for exposure to specific agents. Specific questions for meat workers included the type and number of animals being slaughtered or processed, the specific tasks performed, the opportunity of contact with body fluids and the use of chemicals.

Local expert groups, including chemists, industrial hygienists and occupational physicians performed the occupational exposure assessment in each center. A coder's manual was made available to experts at all centers. The manual defined exposures, rules of coding and quantitative cut points. At the beginning of the study a training program for the experts involved in coding was conducted, so that they could familiarize themselves with the methodology and could standardize assessment among centers. This approach has been developed in previous studies of similar design and considered a reliable method of detailed exposure assessment. Assessments were conducted regularly on subsets of common questionnaires to ensure reproducibility between centers.[30]

Based on the information collected in the questionnaire, the experts assessed exposure to 55 occupational agents and groups of agents, including contact with meat (and meat products) in general as well as contact with beef, chicken, pork, lamb, meat from other animals and fish. For each agent, they indicated their level of confidence (classified as possible, probable and definite) that the exposure actually occurred. Experts also estimated frequency of exposure as percentage of total working time (3 categories: <5%, 5–30%, and >30%) and the intensity of exposure on an ordinal scale (low, medium and high). For the purpose of this analysis, we constructed the following exposure indices (for meat in general and for specific meat types): (*i*) ever exposure; (*ii*) duration of exposure (the total time the subject worked in an exposed occupation, categorized as 1–5, 6–15, and >15 years), (*iii*) weighted duration of exposure (product of the frequency and duration, classified as <6 months, 6 months to 1 year, and >1 year) and (*iv*) intensity of exposure. In addition to the evaluation of the role of occupational exposure to meat in lymphomagenesis, we conducted an analysis based on job titles as markers of exposure, so that lymphoma risks could be assessed according to duties typical to each occupation.

Multiple logistic regression models were fitted to the data and odds ratios (OR) along with 95% confidence intervals (CI) were estimated. The initial analyses were first adjusted for age, sex, education and center. The final regression models included also an index of cumulative exposure to organic pesticides (a suspected risk factor of lymphoma,[31] that was also included in the exposure assessment). Stratified analyses were performed for sex, age, country and type of controls. We initially assessed education for confounding, but found it not to be a factor so it was not included in the final stratified model. Several participants were exposed to more than 1 type of meat, so when evaluating the effects of that exposure all other types of meat were adjusted for in the analysis, using the same exposure dimension. Fish was excluded from the general "meat" category. Tests for trend were conducted for duration and weighted duration of meat by fitting a continuous variable across exposure categories.

The number of cases and controls included in this analysis is slightly lower than that of subjects included in previous reports of the same study[32,33] because of missing data on occupational exposures.

TABLE I – SELECTED CHARACTERISTICS OF THE STUDY POPULATION

	Cases (*N* = 2,346)		Controls (*N* = 2,462)	
	N	%	*N*	%
Sex				
Men	1,314	56.0	1,320	53.6
Women	1,032	44.0	1,142	46.4
Age group				
≤45 years	598	25.5	619	25.1
46–55 years	387	16.5	435	17.7
56–65 years	572	24.4	586	23.8
≥66 years	789	33.6	822	33.4
Country				
Czech Republic	291	12.4	303	12.3
France	297	12.7	276	11.2
Germany	703	30.0	710	28.8
Ireland	202	8.6	207	8.4
Italy	262	11.2	336	13.6
Spain	591	25.2	630	25.6
Education				
Low	1,079	46.0	1,122	45.6
Medium	936	39.9	1,001	40.7
High	330	14.1	339	13.8
Missing	1	0.00	0	0.00
Exposure to organic pesticides				
Never	2,172	92.6	2,301	93.5
Ever	174	7.4	161	6.5
Lymphoma subtype				
Hodgkin lymphoma	339	14.5		
Non-Hodgkin lymphoma[1]	2,007	85.5		
B-cell	1,868	93.1[2]		
Diffuse large B-cell lymphoma	537	28.7[3]		
Follicular lymphoma	250	13.4[3]		
Chronic lymphocytic leukemia/small cell lymphocytic lymphoma	413	22.1[3]		
Other and unspecified B-cell non-Hodgkin lymphoma	391	20.9[3]		
Multiple myeloma	277	14.8[3]		
T-cell	133	6.6[2]		

[1]Including 6 cases of lymphoma not otherwise specified.–[2]Percentage of total non-Hodgkin lymphoma.–[3]Percentage of total B-cell non-Hodgkin lymphoma.

Results

A total of 2,346 cases and 2,462 controls were included in the analysis. Their distribution of selected characteristics is given in Table I. The proportion of male amongst cases was slightly higher than that of females, which was expected. The distribution of non-Hodgkin lymphoma subtypes among cases was dominated by B-cell lymphoma (94.1%), diffuse large-B cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and multiple myeloma were the most common subtypes. The distribution of cases and controls according to age, sex, center, education and pesticide exposure was very similar.

Table II presents the results on risk of Hodgkin and non-Hodgkin lymphoma for exposure to any type of meat: the OR of Hodgkin lymphoma for ever exposure was 1.06 (95% CI 0.65–1.71). No trend was detected according to duration of exposure, weighted duration of exposure or intensity of exposure. The corre-

TABLE II – ODDS RATIO OF HODGKIN LYMPHOMA AND NON-HODGKIN LYMPHOMA FOR INDICATORS OF EXPOSURE TO MEAT

	Controls	Hodgkin lymphoma			Non-Hodgkin lymphoma		
		Cases	OR	95% CI	Cases	OR	95% CI
Never Exposed (reference group)	2,273	315	1.00	–	1,823	1.00	–
Ever Exposed	189	24	1.06	0.65–1.71	184	1.18	0.95–1.46
Duration of exposure							
≤5 years	52	12	1.14	0.57–2.30	49	1.25	0.84–1.86
6–15 years	62	8	0.98	0.44–2.20	52	1.04	0.71–1.51
≥16 years	73	4	1.02	0.36–2.90	82	1.27	0.92–1.76
p-value of test for linear trend				0.90			0.13
Weighted duration of exposure							
≤6 months	62	14	1.54	0.79–2.99	57	1.10	0.76–1.59
7 months to 1 year	35	3	0.60	0.17–2.13	40	1.39	0.87–2.20
>1 year	90	7	0.84	0.37–1.91	86	1.17	0.87–1.59
p-value of test for linear trend				0.75			0.13
Intensity of exposure							
Low	84	11	1.05	0.52–2.12	85	1.24	0.91–1.70
Medium	70	10	1.19	0.56–2.49	66	1.11	0.79–1.57
High	35	3	0.80	0.23–2.74	32	1.14	0.70–1.85

OR, odds ratio, adjusted for age, sex, center, and cumulative exposure to pesticides; CI, confidence interval.

TABLE III – ODDS RATIO OF ALL NON-HODGKIN LYMPHOMA FOR EXPOSURE TO SPECIFIC TYPES OF MEAT—ALL NHL

	Beef meat				Chicken meat				Pork meat			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Never Exposed (Ref group)	1,823	2,273	1.00		1,823	2,273	1.00		1,823	2,273	1.00	
Ever Exposed	117	108	1.22	0.90–1.67	1,36	129	1.19	0.91–1.55	145	143	1.09	0.83–1.42
Duration of exposure												
≤5 years	40	37	1.45	0.92–2.31	30	40	0.97	0.60–1.58	39	41	1.25	0.80–1.96
6–15 years	29	43	0.79	0.47–1.31	42	41	1.21	0.78–1.88	44	58	0.84	0.55–1.28
≥16 years	48	28	1.63	0.93–2.88	64	48	1.36	0.90–2.06	61	43	1.28	0.81–2.03
p-value of test for linear trend (with ref cat)			0.23				0.11				0.54	
Intensity of exposure												
Low	60	59	1.26	0.86–1.83	71	68	1.24	0.88–1.75	70	72	1.15	0.82–1.62
Medium	42	35	1.22	0.73–2.04	47	46	1.11	0.72–1.71	55	52	1.03	0.68–1.58
High	15	14	0.91	0.35–2.40	18	15	1.22	0.56–2.65	20	19	0.89	0.40–1.94
p-value of test for linear trend (with ref cat)			0.36				0.29				0.78	

	Mutton meat				Other meat			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Never Exposed (Ref group)	1,823	2,273	1.00		1,823	2,273	1.00	
Ever Exposed	63	71	0.99	0.66–1.47	52	47	1.07	0.67–1.70
Duration of exposure								
≤5 years	21	20	1.35	0.71–2.56	13	15	0.92	0.41–2.06
6–15 years	21	27	0.87	0.46–1.62	13	10	1.16	0.48–2.81
≥16 years	21	24	0.80	0.41–1.57	26	21	1.19	0.62–2.28
p-value of test for linear trend (with ref cat)			0.60				0.58	
Intensity of exposure								
Low	31	41	0.90	0.55–1.47	24	30	0.82	0.47–1.45
Medium	22	21	1.11	0.57–2.14	17	8	1.97	0.80–4.90
High	10	9	1.29	0.42–4.00	10	9	1.09	0.34–3.51
p-value of test for linear trend (with ref cat)			0.80				0.57	

OR, odds ratio adjusted for age, sex, center, cumulative exposure to pesticides and other types of meat; CI, confidence interval.

sponding OR of non-Hodgkin lymphoma was 1.18 (95% CI 0.95–1.46): also for this group of lymphoma, no trend was apparent for any indicator of exposure.

When the analysis on non-Hodgkin lymphoma was repeated for specific types of meat (Table III), the OR for ever exposure to beef meat was 1.22 (95% CI 0.95–1.67), and the OR for ever exposure to chicken meat was 1.19 (95% CI 0.91–1.55). The remaining meat types, namely pork meat and mutton meat, showed either no effect or small nonsignificant increases in lymphoma risk. Exposure for more than 15 years to beef meat resulted in an OR of 1.63 (95% CI 0.93–2.88). An increase in risk was also observed for long-term exposure to chicken meat (OR = 1.36, 95% CI 0.90–2.06). The results on intensity of exposure did not suggest a difference among meat types.

In the analyses stratified by lymphoma type, whose results are reported in Table IV, an increased risk among workers exposed to beef meat was mainly apparent for diffuse large B-cell lymphoma (OR = 1.49, 95%CI 0.96–2.33), chronic lymphocytic leukemia/small lymphocytic lymphoma (OR = 1.35, 95% CI 0.78–2.34), and multiple myeloma (OR = 1.40, 95%CI 0.67–2.94). Stronger increases in risk were observed for each of these 3 subtypes after 16 years or more of exposure (OR 2.00, 95% CI 0.87–4.61; OR

TABLE IV – ODDS RATIO OF LYMPHOMA SUBTYPES FOR EXPOSURE TO ANY TYPE OF MEAT, BEEF MEAT AND CHICKEN MEAT

	Unexposed (reference category)	Any type of meat			Beef meat			Chicken meat		
		Exposed	OR	95% CI	Exposed	OR	95% CI	Exposed	OR	95% CI
Controls	2,273	189	1	–	108	1	–	129	1	–
B-cell	1,693	175	1.21	0.97–1.51	113	1.26	0.92–1.72	130	1.22	0.93–1.60
Multiple myeloma	254	23	0.99	0.62–1.56	13	1.40	0.67–2.94	20	2.05	1.14–3.69
CLL/SLL	369	44	1.34	0.93–1.91	26	1.35	0.78–2.34	37	1.55	1.01–2.37
Diffuse large B-cell lymphoma	485	52	1.35	0.97–1.87	39	1.49	0.96–2.33	32	1.12	0.71–1.76
Follicular lymphoma	229	21	1.10	0.68–1.77	14	1.12	0.55–2.26	19	1.30	0.72–2.33
T-cell	125	8	0.71	0.34–1.48	3	0.94	0.23–3.79	6	1.13	0.42–3.06

OR, odds ratio adjusted for age, sex, center, cumulative exposure to pesticides and (in the analysis for exposure to beef and chicken meat) other types of meat; CLL/SLL, chronic lymphocytic leukemia/small cell lymphocytic lymphoma; CI, confidence interval.

2.51, 95% CI 1.12–5.66; and OR 2.75, 95% CI 0.60–12.6, respectively). Exposure to chicken meat resulted in an increased risk of multiple myeloma (OR 2.05, 95% CI 1.14–3.69, that was increased to 2.43, 95% CI 1.00–5.91 for 16 or more years of exposure) and chronic lymphocytic leukemia/small lymphocytic lymphoma (OR 1.55, 95% CI 1.01–2.37, that was increased to 2.06, 95% CI 1.17–3.63 for 16 or more years of exposure). Follicular lymphoma, T-cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma did not show any increase in risk for either total meat exposure or exposure to specific types. For sake of comparability with previous studies, we conducted an analysis on the category of "non-Hodgkin lymphoma" defined by ICD-10 (*i.e.*, comprising all subtypes listed in Table I except chronic lymphocytic leukemia/small lymphocytic lymphoma and multiple myeloma): the OR for exposure to any type of meat and to beef meat were 1.16 (95% CI 0.91–1.48) and 1.19 (95% CI 0.85–1.67), respectively.

In an analysis stratified by gender, women showed an increased risk of non-Hodgkin lymphoma for exposure to meat in general (OR 1.37, 95% CI 1.01–1.85) and beef meat and chicken meat in particular (OR 1.47, 95% CI 0.95–2.28, and OR 1.50, 95% CI 1.03–2.18, respectively), while men did not show an elevated risk (OR 1.00, 95% CI 0.74–1.36; OR 0.95, 95% CI 0.58–1.55, and OR 0.93, 95% CI 0.60–1.43, respectively) (Table V). Stratification of the analysis by age did not suggest any heterogeneity in risk estimates. A stratified analysis by country showed that an elevated risk of non-Hodgkin lymphoma for exposure to meat was present in Czech Republic (OR 1.52, 95% CI 0.72–3.25), Germany (OR 1.49, 95% CI 1.01–2.21) and Italy (OR 2.22, 95% CI 1.04–4.73), but not (or only modestly) in France (OR 1.06, 95% CI 0.57–2.00), Ireland (OR 1.21, 95% CI 0.63–2.31) and Spain (OR 0.70, 95% CI 0.46–1.05). This difference is not explained by a different distribution of lymphoma types by country (results not shown in detail). Only 33 cases of non-Hodgkin lymphoma and 49 controls were classified as ever occupationally exposed to fish (OR 0.85 95% CI 0.54–1.34).

We repeated the analysis after excluding cases and controls with low confidence in the assessment of exposure to meat, but the results were similar to those reported above (OR of non-Hodgkin lymphoma for exposure to all types of meat 1.19, 95% CI 0.96–1.48; based on 182 exposed cases and 185 exposed controls).

The analysis by job title did not reveal any clear pattern, as the number of cases and controls employed in specific occupations entailing exposure to meat was small. In particular, 31 cases and 28 controls were ever employed as butchers or meat preparers (OR 1.14; 95% CI 0.68–1.91).

Discussion

The results of this case control study do not support the hypothesis that occupational exposure to meat is an important cause of either Hodgkin or non-Hodgkin lymphoma. However, we observed an excess risk of diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma and multiple myeloma for occupational exposure to beef meat and—for the latter 2—to chicken meat. Although suggestive of a possible association between specific types of meat and specific types of non-Hodgkin lymphoma, these results need to be interpreted with caution because they might have occurred by chance and in most cases do not reach the formal level of statistical significance. Our findings need to be replicated before any conclusion can be drawn.

Our study included a relatively large number of cases of specific lymphoma subtypes: the small number of cases was an important limitation in several previous studies of lymphoma among meat workers.[10,15,17,19,22] Despite the fact that the analysis of several subtypes of B-cell non-Hodgkin lymphoma increases the probability of detecting a significant association by chance, our results support the hypothesis that B-cell lymphoma subtypes are etiologically heterogenous. In our study, the evidence of an association with meat exposure—and specifically beef and chicken meat—was stronger for chronic lymphocytic leukemia/small cell lymphocytic lymphoma than for other B-cell malignancies. With the exception of 2 studies based on small series of cases of chronic lymphocytic leukemia[10] and follicular lymphoma,[12] no other information is available in the literature on risk of specific types of lymphoma among workers exposed to meat.

Most of the available evidence on risk of Hodgkin lymphoma among meat workers comes from a series of studies among US workers exposed to meat in various industries.[3,9–11,13,17,24] Although a positive association was reported among some of these workers,[3,11,13] other analyses were not suggestive of an association.[9,10,17,24] The limited data from studies in other countries do not support an association.[16,21] Similarly, our results add to the evidence against a role of meat exposure in Hodgkin lymphomagenesis. In addition to a case-control study nested in a cohort of US workers, which reported a strong association with multiple myeloma risk,[13] only 2 studies have reported results on risk of multiple myeloma among workers exposed to meat[10,34]: their results were based on few cases and lacked the power to identify a weak association: the possibility of a small increase risk of multiple myeloma among meat workers is supported by our results. The results on risk of T-cell non-Hodgkin lymphoma are limited by the small number of cases, but they did not suggest an association of occupational meat exposure.

Meat workers have the opportunity for exposure to biological agents of animals. Neoplasms of the haematopoietic and lymphatic systems may be induced by viral agents in both cattle and chickens[9]: zoonotic viruses which are specific to beef cattle and chicken including BLV and newly identified herpes viruses, including that responsible for Marek's disease[35] may play an etiologic role. Infection of humans by these viruses, however, has not been demonstrated, albeit antibodies reactive against BLV have been recently identified in humans.[36] On the other hand, in a recent study, no evidence for viral BLV DNA was found in leukemia samples.[37] Since the increased risk of some types of B-cell non-Hodgkin lymphoma was specifically linked in our study to ex-

TABLE V – ODDS RATIO OF LYMPHOMA FOR EXPOSURE TO MEAT BY SEX

	Controls	Hodgkin lymphoma			Non-Hodgkin lymphoma		
		Cases	OR	95% CI	Cases	OR	95% CI
Men							
Never Exposed (reference group)	1,222	171	1.00		1,043	1.00	
Ever Exposed	98	13	1.07	0.56–2.07	87	1.00	0.74–1.36
Duration of exposure							
≤5 years	26	6	1.20	0.45–3.22	26	1.29	0.74–2.25
6–15 years	31	4	0.85	0.27–2.66	19	0.69	0.39–1.24
≥16 years	41	3	1.23	0.36–4.20	41	1.04	0.67–1.63
p-value of test for linear trend			0.86			0.85	
Weighted duration of exposure							
≤6 months	34	7	1.42	0.56–3.57	24	0.80	0.47–1.37
7 months to 1 year	18	1	0.44	0.05–3.75	19	1.14	0.59–2.21
>1 year	46	5	1.02	0.37–2.78	43	1.08	0.70–1.65
p-value of test for linear trend			0.98			0.79	
Intensity of exposure							
Low	34	4	0.88	0.28–2.78	31	1.01	0.61–1.67
Medium	42	7	1.34	0.54–3.30	35	0.93	0.58–1.47
High	22	2	0.86	0.19–3.94	21	1.13	0.62–2.09
p-value of test for linear trend			0.81			0.92	
Women							
Never Exposed (reference group)	1,051	144	1.00		780	1.00	
Ever Exposed	91	11	1.05	0.52–2.15	97	1.37	1.01–1.85
Duration of exposure							
≤5 years	26	6	1.11	0.41–3.04	23	1.19	0.66–2.11
6–15 years	31	4	1.17	0.38–3.62	33	1.39	0.84–2.30
≥16 years	32	1	0.70	0.09–5.32	41	1.57	0.97–2.52
p-value of test for linear trend			0.99			0.02	
Weighted duration of exposure							
≤6 months	28	7	1.72	0.65–4.53	33	1.46	0.87–2.45
7 months to 1 year	17	2	0.74	0.15–3.55	21	1.65	0.86–3.16
>1 year	44	2	0.61	0.14–2.68	43	1.26	0.82–1.95
p-value of test for linear trend			0.69			0.08	
Intensity of exposure							
Low	50	7	1.20	0.49–2.95	54	1.40	0.94–2.09
Medium	28	3	0.96	0.26–3.62	31	1.38	0.82–2.34
High	13	1	0.70	0.08–5.80	11	1.12	0.49–2.55
p-value of test for linear trend			0.93			0.11	

Note: only results for NHL in the paper. OR, odds ratio, adjusted for age, sex, center, and cumulative exposure to pesticides; CI, confidence interval.

posure to beef meat, BLV or other cattle-specific agents could be suggested as a possible etiological agent. The risk appeared to be particularly elevated in individuals who were exposed to beef for more than 15 years. Heterogeneity of results by gender detracts from a causal interpretation; however, it can be also explained by differences in exposure circumstances experienced by men and women, which were not captured by the expert assessment.

The study results were adjusted for exposure to other meat types in order to control for potential reciprocal confounding of the various meat types during analysis, and beef and chicken remained the main exposures that showed a raised risk for lymphoma. It should be stressed however that misclassification of exposure might have occurred among types of meat, which would results in underestimation of the risk in analyses adjusted for the other types of meat. In a study from Canada, beef cattle farmers were the only group who exhibited excess risk of non-Hodgkin lymphoma.[15]

This study has many advantages over previous studies beyond its large sample size, especially the detailed exposure assessment. Previous studies have identified a lack of valid information on individual exposure as a major problem.[16,21] Following direct interviews based on a standardized protocol, experts at each center conducted case-by-case assessments of exposure. To minimize information bias the questionnaires used in each country were standardized and translated, and all interviewers completed rigorous training on survey administration. Prior to conducting the individual assessments of exposure all experts were also trained and each center conducted subsequent tests to insure inter-rater reliability and the reproducibility of results.[30] The fact that exposure to meat was not self-reported but was assessed by groups of experts who were blind of case-control status reduces the opportunity for recall bias, a common problem in retrospective case-control studies. Furthermore, potential confounding by other suspected risk factors of lymphoma, such as organic pesticides, was controlled for in the analysis.

A limitation of the current study is that some selection bias might have occurred: this suspicion is reinforced by the differences in results seen according to the method of control recruitment, as the increased risk for exposure to meat was mainly present in Germany and Italy, where controls were drawn from the general population. An increased prevalence of infection with animal-borne viruses in the general population does not seem a likely explanation for the weaker association observed in countries where hospital-based controls; however, infection prevalence might be higher in hospital patients than in the general population. Heterogeneity in exposure circumstances, on the other hand, might have contributed to the pattern of country-specific results.

In conclusion, our study suggested that individuals employed in occupations entailing exposure to meat are not likely to experience a large increase in lymphoma risk, although a weak effect might be present for diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma and multiple myeloma. A similarly elevated risk was not seen for other types of non-Hodgkin lymphoma, or for Hodgkin lymphoma. However, there results are not sufficient to establish a role of animal viruses in the etiology of specific types of human lymphoma.

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