

A case–control study of risk factors for sporadic campylobacter infections in Denmark

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SUMMARY

A case control study comprising 282 cases and 319 matched controls was conducted in Denmark during 1996–7. Two estimates of the odds ratio (OR) were determined for each risk factor with and without ‘protective factors’ fitted into the final model. Consumption of undercooked poultry (OR 4·5; 8·2), consumption of red meat at a barbecue (OR 2·3; 4·1), consumption of grapes (OR 1·6; 2·8) and drinking unpasteurized milk (OR 2·3; 11·8) were identified as risk factors in both models. Frequent consumption of pork chops (OR 4·4) and daily contact with domestic animals and pets were identified as risk factors in one of the two models only. Finally, foreign travel was found to be a significant risk factor (OR 2·5). Seasonal and regional interaction was observed for several risk factors and the time elapsed from interviewing of cases to interviewing of controls seemed to influence the effect of certain seasonal dependent risk factors.

INTRODUCTION

Campylobacter is a common cause of acute bacterial gastroenteritis worldwide, and in some countries the number of registered cases exceeds the number of cases of salmonellosis. Although rarely fatal, campylobacter infections cause considerable morbidity and loss of productivity and may be associated with severe disabling consequences including arthritis and demyelinating disease (Guillain–Barré syndrome) [1–5]. Denmark is among a limited number of countries with comprehensive national laboratory-based surveillance for campylobacter. As in several countries in Europe, North America and Australasia, Denmark has in recent years recorded a marked increase in the incidence of campylobacter infections [6]. From 1992 to 2001 the number of recorded cases increased four-fold, from 1129 to 4620 cases [7]. With an incidence

of 86 cases/100 000 in 2001 Denmark is among the five countries with the highest incidence of reported campylobacter infections worldwide.

The most frequently identified sources of outbreaks of campylobacter are untreated water, contaminated milk and poultry [8]. However, most persons who contract campylobacter infections are not part of recognized outbreaks. These sporadic cases may be associated with a different set of risk factors from those causing outbreaks [8, 9]. To assess the risk factors for sporadic campylobacter infections a number of case–control studies have been conducted in the United States, Europe and New Zealand within the last 20 years. Consumption of poultry and poultry products have in most studies been identified as risk factors [10–15]. Other risk factors include drinking untreated water [13–16], travel to foreign countries [11, 14], consumption of raw or unpasteurized milk [13, 14, 17], consumption of milk from bottles attacked by birds [12, 18, 19], handling and cooking of food, particularly

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raw meat, in relation to barbecuing [10, 14, 16, 20, 21] and contact with food-producing animals and pets [12–14, 16, 22]. These studies suggest that different sources may be of different importance in the various countries and regions. Although the findings from these case–control studies have provided insight into the epidemiology of campylobacter infections, our understanding is still incomplete. The relative importance of the different sources is not well known, and no clear explanation for the increasing incidence of campylobacter infections in many countries has been proposed, although increased consumption of fresh poultry may play an important role. A natural experiment from Belgium and control measures implemented in Iceland point to broilers as a principal source of campylobacteriosis [23, 24].

The objective of the present study was to investigate risk factors for sporadic campylobacter infections in Denmark and thereby potentially identify points where possible control and intervention measures could be established. In this report we present the analysis of risk factors associated with campylobacteriosis. The clinical features and host risk factors including medication and underlying illness will be reported separately.

MATERIALS AND METHODS

This study was designed as a prospective case–control study and was conducted from May 1996 to May 1997. Cases were culture-confirmed patients with campylobacter infection, identified by the examination of samples submitted from hospitals and general practitioners from 9 of the 16 Danish counties. This catchment area corresponds to 70% of the population. During the study period, a weekly number of 20–25 randomly selected patients with culture-confirmed campylobacter were invited to participate by their own physicians. Individuals who agreed to participate were mailed additional information about the study, a consent form and a questionnaire. Patients were requested to complete the questionnaire immediately and sign and return the consent form by mail. If more than one stool sample from a household yielded campylobacter, only the first identified case was enrolled in the study. Cases from recognized outbreaks were not included. Cases were also excluded for the following conditions: not able to establish date of symptom onset, an earlier history of campylobacter infection, unable to speak Danish, if it was likely that the case had been infected due to secondary

transmission or if the case had had recurring diarrhoea in the 4 weeks prior to infection. When the consent from a case was received controls were found through the Danish Civil Registry system (CPR), which is a continuously updated register of all residents in Denmark. Eligible controls were mailed a questionnaire and a consent form. A low response rate was identified at the beginning of the study, so the number of contacted controls was increased from one to three. If none of the controls responded after approximately 10 days, 1–3 new controls were found through the CPR and contacted according to the same procedure. Controls were matched with cases by sex, date of birth and county. The age difference between cases and controls was rarely more than 1 week. Controls were excluded from the study if they had a history of a campylobacter infection or it was likely that they had had a gastrointestinal infection in the preceding month (indicated by diarrhoea or abdominal pain with fever).

Data were collected through telephone interviews using a standard questionnaire. In order to facilitate data collection and reduce interviewer bias all interviews were conducted using a Computer Aided Telephone Interviewing (CATI) system. Data collection regarding food exposures, cooking practices and contact with animals was confined to infections acquired in Denmark, and these individuals were queried about exposure to different foods, cooking and hygiene procedures, preparation methods, contact with animals, household water supply, occupation, use of medication, and underlying illness. In total, 109 exposure variables were included in the study. Cases were also questioned about clinical information and treatment. Cases were interviewed about the 14 days prior to symptom onset and controls about the 14 days prior to interview. For use of medication the exposure period in question was 4 weeks. A parent was interviewed when a case or a control was younger than 15 years of age. When cases or controls were between 15 and 18 years of age they could be interviewed themselves – subject to parental approval. The Danish Scientific Ethical Committee approved the study.

Isolation and identification of patient isolates

Stool specimens were processed on Skirrow's medium or on mCCDA (SSI Diagnostica, Hillerød, Denmark) and incubated microaerobically at 37 °C for 48 h. One colony from each sample was subcultured and identified to the species level using key phenotypic

tests: phase-contrast microscopy (characteristic morphology and mobility), catalase, oxidase, indoxyl acetate hydrolysis, hippurate hydrolysis, susceptibility to nalidixic acid and cephalothin.

Subgroup analysis

To study the effect of delayed enrolment of controls compared to cases, a subgroup of the total study population was examined. This subgroup was defined by a time lag of 30 days or less from interviewing of cases to interviewing of controls.

Statistical analysis

Conditional logistic regression was applied to calculate a matched odds ratio (OR), which, if necessary, were expressed in dichotomous categories. Variables, which reached a significance level of 0.10 or less in the univariate analysis, or variables of special interest, were selected for inclusion in multiple logistic regression. The multivariate conditional logistic regression model was constructed using a forward selection procedure. Variables with a *P* value of 0.05 or less and variables with a confounding effect were kept in the model. All excluded variables were re-entered, to test whether they could be fitted as significant variables in the final reduced model. Two factor interactions were created between significant variables ($P=0.10$) and variables known to be effect modifiers (age, season and geography). The most parsimonious model was then created to explain the data. The statistical software SAS Release v.6.12 (SAS Institute Inc., Cary, NC, USA) was used to analyse the data.

The population attributable risk (PAR) was estimated from the equation

$$\text{PAR} = \frac{n_1 m_0 - m_1 n_0}{m_0 n},$$

where n_0 and n_1 are equal to the numbers of unexposed and exposed cases, respectively, and m_0 and m_1 the numbers of unexposed and exposed controls, with $n_0 + n_1 = n$ and $m_0 + m_1 = m$.

The corresponding $100(1-\alpha)$ percent confidence interval for the unadjusted PAR(25) is

$$\frac{1}{1 + [(1 - \text{PAR})/\text{PAR}]e^{EF}},$$

$$\frac{1}{1 + [(1 - \text{PAR})/\text{PAR}]/e^{EF}},$$

where *EF* is equal to

$$z_{1-\alpha/2} \sqrt{(n_1/m_0 + m_1/mm_0)[m_0m/(n_1m - m_1n)]^2}.$$

RESULTS

Study population

A total of 979 cases were selected to participate in the study; 585 cases and 566 matched controls were interviewed. The case patients represented 27.4% of the 2136 registered cases of campylobacteriosis in Denmark during the study period. A verbal consent was received from the physicians of 856 (87.4%) cases who were subsequently mailed a questionnaire and a consent form. After the interview, 150 (25.6%) cases that met the exclusion criteria were excluded: 86 cases (14.7%) had potentially been part of an outbreak, 37 (6.3%) had recurring diarrhoea, 18 (3.1%) had unknown onset date and 9 (1.5%) cases had incomplete interviews. A total of 2200 controls were invited, and 566 (25.7%) returned a consent-form and were all subsequently interviewed. Of the interviewed controls 72 were excluded: 61 (10.8%) had symptoms of a gastrointestinal infection in the month before interview, 7 (1.2%) had incomplete interviews and 4 (0.7%) had a history of campylobacteriosis. When selecting only matched sets of cases and controls the total study population constituted 282 cases and 319 controls. When confining the study to cases and controls without foreign travel in the month before onset of illness/interview the matched, domestic study population was 217 cases and 236 controls.

The average age of cases were 24 years (range 0–78 years, 25% quantile: 4 years and 75% quantile: 37 years) and 122 (55.7%) were women. There was a mean interval of 118 days (25% quantile: 2 days and 75% quantile: 190 days) between interviews of cases and their matched controls. This time lag was explained by successive invitation of new controls if no one from the first group of invited controls had responded.

Risk factors

Travel abroad in the last month was found to be associated with an increased risk for infection. A total of 52 (18.4%) of 282 cases had been abroad in the month prior to onset of disease compared with 30 (9.4%) of 319 controls (OR 2.51, 95% CI 1.49–4.24).

Table 1. Odds ratios for poultry and poultry product exposures calculated from a case control study on sporadic campylobacteriosis conducted in Denmark 1 May 1996 to 12 May 1997. Cases ($n=217$) and controls ($n=236$) were matched by sex, birthday and county

Risk factor	No. of cases (%)	No. of control (%)	Odds ratio	95% CI
Poultry in general	162 (74.7)	179 (75.8)	0.94	0.62–1.43
Chicken/hen bought in pieces	60 (27.6)	64 (27.1)	1.02	0.69–1.53
Chicken/hen bought whole	83 (38.2)	96 (40.7)	0.90	0.61–1.33
Turkey	70 (32.3)	91 (38.6)	0.77	0.53–1.12
Duck	13 (6.0)	23 (9.7)	0.57	0.27–1.18
Goose*	2 (0.9)	0 (0.0)	—	—
Chicken brands (whole chicken)				
Poussin	7 (3.2)	6 (2.5)	1.50	0.47–4.79
Gourmet chicken†	1 (0.5)	0 (0.0)	—	—
Organic chicken	2 (0.9)	2 (0.8)	1.00	0.14–7.10
'Skrabe' chicken‡	3 (1.4)	8 (3.4)	0.40	0.10–1.50
'Bornholm' rooster§	3 (1.4)	0 (0.0)	—	—
'Graasten' chicken¶	0 (0.0)	0 (0.0)	—	—
Salmonella free chicken	10 (4.6)	13 (5.5)	0.86	0.38–1.98
Frozen – unknown brand	42 (19.4)	46 (19.5)	0.97	0.61–1.55
Chicken of own breed	3 (1.4)	11 (4.7)	0.33	0.09–1.19
Chicken/hen bought in pieces				
Chicken leg	16 (7.4)	30 (12.7)	0.56	0.30–1.04
Chicken supreme	16 (7.4)	16 (6.8)	1.14	0.54–2.42
Chicken giblets	2 (0.9)	1 (0.4)	2.00	0.18–22.06
Chicken wings	4 (1.8)	4 (1.7)	1.00	0.25–4.00
'Saturday mix'¶	20 (9.2)	25 (10.6)	0.85	0.46–1.58
Poultry and preparation				
Eat poultry at barbecue/open fire	11 (5.1)	9 (3.8)	1.27	0.52–3.06
Poultry bought ready to eat	19 (8.8)	14 (5.9)	1.59	0.77–3.27
Poultry reheat/cook in microw. Oven	10 (4.6)	10 (4.2)	1.07	0.44–2.58
Poultry undercooked	15 (6.9)	5 (2.1)	3.50	1.15–10.63

* OR undefined, P value = 0.139.

† Retail brand name, OR undefined, P value = 0.296.

‡ Chickens raised indoor, free access to open space, 56 days old at slaughter.

§ Rooster, 47–49 days old at slaughter, raised indoor, from the island of Bornholm. OR undefined, P value = 0.070.

¶ Retail brand name.

For domestically acquired infections the matched odds ratios for 24 different types of poultry and poultry products, including nine types/brands of whole chicken, are presented in Table 1. In total, 11 of 24 poultry exposures had point estimates of the odds ratio above 1.0 and 10 exposures below 1.0. Undercooked poultry (all types) (OR 3.50, 95% CI 1.15–10.63) was the only exposure significantly associated with campylobacter infection.

Table 2 presents the univariate analyses of risk factors for campylobacter infection related to other exposure variables, with a P value less than 0.10 as a cut-off. Eating beef, organs from pigs, ham and game was more common among controls than cases. Pork chops eaten twice or more in a fortnight was

associated with illness (OR 1.71, 95% CI 1.01–3.27). Meat prepared at a barbecue, which included pork, veal and beef (referred to as 'red meat' in the present paper) was also identified as a risk factor (OR 1.93, 95% CI 1.13–2.94).

Grapes were the only produce that tended to be associated with an increased risk (OR 1.47, 95% CI 0.94–2.13). Raw carrots, raw cabbage and unpeeled apples and pears were more often eaten by controls compared with cases (OR 0.67, 95% CI 0.44–0.99; OR 0.50, 95% CI 0.27–0.90; OR 0.48, 95% CI 0.31–0.73).

Unpasteurized milk was the only milk product which tended to be associated with an increased risk of infection (OR 1.89, 95% CI 0.89–6.16).

Table 2. Odds ratios for foods (other than poultry), water exposures, eating out and contact with animals calculated from case control study on sporadic campylobacteriosis conducted in Denmark 1 May 1996 to 12 May 1997. Cases ($n=217$) and controls ($n=236$) were matched by sex, birthday and county

Risk factor	No. of cases (%)	No. of controls (%)	Odds ratio	95% CI
Red meat				
Roast beef	196 (90.3)	216 (91.5)	0.86	0.27–0.92
Ground beef ≥ 3 times/14 days	71 (32.7)	96 (40.7)	0.67	0.43–1.03
Organs from pigs	8 (3.7)	24 (10.2)	0.37	0.16–0.80
Ham	41 (18.9)	68 (28.8)	0.60	0.39–0.92
Pork chops ≥ 2 times/14 days	29 (13.4)	19 (8.1)	1.71	1.01–3.27
Game	7 (3.2)	19 (8.1)	0.31	0.11–0.84
Meat barbecued	56 (25.8)	35 (14.8)	1.93	1.13–2.94
Fruit and vegetables				
Raw carrots	147 (67.7)	179 (75.8)	0.67	0.44–0.99
Raw cabbage	18 (8.3)	35 (14.8)	0.50	0.27–0.90
Unpeeled apples/pears	140 (64.5)	185 (78.4)	0.48	0.31–0.73
Grapes	77 (35.5)	63 (26.7)	1.47	0.94–2.13
Milk and milk products				
Organic milk	60 (27.6)	84 (35.6)	0.66	0.43–0.99
Cake w/ cream & raw eggs [†]	22 (10.1)	38 (16.1)	0.55	0.31–0.99
Hard cheese	171 (78.8)	199 (84.3)	0.65	0.40–1.05
Unpasteurized milk	20 (9.2)	13 (5.5)	1.89	0.89–4.02
Drinking water				
Private well*	14 (6.5)	8 (3.4)	2.09	0.90–6.16
Bad smell/taste of water	12 (5.5)	3 (1.3)	4.23	1.18–15.04
Eating out				
Restaurant or similar	147 (67.7)	179 (75.8)	0.65	0.40–0.94
Contact with animals				
Contact with cat w/diarrhoea	11 (5.1)	4 (1.7)	3.77	1.03–13.83
Daily contact with kitten [†]	9 (4.1)	1 (0.4)	9.00	1.24–78.08
Daily contact with cow	13 (6.0)	5 (2.1)	3.09	1.09–8.74
Daily contact with pig [‡]	9 (4.1)	4 (1.7)	2.68	0.82–8.81
Daily contact with poultry	24 (11.1)	14 (5.9)	2.11	0.99–4.49

* P value = 0.114.

[†] Cat less than 7 months of age.

[‡] P value = 0.105.

Drinking water, which had a bad taste or smell, in the 14 days prior to illness onset, and having a private well as the household water supply were also associated with increased risk of infection. The latter was however not significant at a 95% level (OR 4.23, 95% CI 1.18–15.04 and OR 2.09, 95% CI 0.90–6.16 respectively).

More thorough cleaning procedures (scalding with water) of different kitchen utensils were reported more frequently by controls than by cases (cutting board: OR 0.68, 95% CI 0.30–1.52, knives: OR 0.48, 95% CI 0.21–1.11 and sink: OR 0.31, 95% CI 0.09–1.12). In addition, controls had more

often been eating at a restaurant in the period prior to the interview (OR 0.65, 95% CI 0.40–0.94).

Contact with a cat either with diarrhoea or daily contact with a kitten (less than 7 month old) was associated with illness (OR 3.77, 95% CI 1.03–13.82 respectively OR 9.00, 95% CI 1.24–78.08). Also daily contact with cattle (OR 3.09, 95% CI 1.09–8.74), pigs (OR 2.68, 95% CI 0.82–8.81) and poultry (OR 2.11, 95% CI 0.99–4.49) increased the risk of infection.

To estimate occupational risks, two categories of hazard were defined: (i) working with children less than 6 years of age, e.g. in a day care or in a preschool

Table 3. Result of multivariate logistic regression analysis of exposures associated with increased or decreased risk of infection identified in case control study on sporadic campylobacteriosis conducted in Denmark, 1 May 1996 to 12 May 1997. Cases ($n=217$) and controls ($n=236$) were matched on sex, birthday and county

Exposures	Model 1: risk factors and 'protective factors'		Model 2: risk factors	
	OR	95% CI	OR	95% CI
Risk factors				
Undercooked poultry	8.24	1.07–63.12	4.52	1.33–15.32
Pork chops ≥ 2 times	4.35	1.39–13.66	—	—
Meat at a barbecue/open fire	4.09	1.53–10.94	2.26	1.30–3.94
Dietary preference of not eating animals' organs	2.63	1.16–5.95	3.45	1.99–5.99
Eating grapes	2.81	1.35–5.87	1.59	0.98–2.56
Unpasteurized milk	11.78	1.97–70.32	2.34	0.94–5.86
Daily contact with kitten	—	—	7.40	0.87–62.79
Daily contact with cow	—	—	1.61	0.47–5.53
Daily contact with pig	—	—	1.80	0.48–6.79
'Protective' factors				
Eat organs from pigs	0.23	0.07–0.77	—	—
Thawing of poultry	0.16	0.03–0.88	—	—
Scalding cutting boards	0.26	0.06–1.17	—	—
Scalding sink	0.82	0.10–6.71	—	—
Drink organic milk	0.39	0.18–0.84	—	—
Unpeeled apples and pears	0.16	0.06–0.41	—	—

Table 4. Estimated OR and 95% confidence interval (CI) for eating barbecue, unpeeled apples/pears or consuming unpasteurized milk, calculated for in-campylobacter-season (June to October) and off-campylobacter-season (November to May). These exposures were identified in the Danish case control study on sporadic campylobacteriosis conducted from 1 May 1996 to 12 May 1997. Cases ($n=217$) and controls ($n=236$) were matched on sex, birthday and county

Interactions	OR	95% CI
Barbecue in season*	3.02	1.60–5.69
Barbecue in off-season*	0.60	0.16–2.30
Unpasteurized milk in season*	0.86	0.25–2.90
Unpasteurized milk in off-season*	9.67	1.83–50.99
Apples/pears in season†	0.04	0.01–0.19
Apples/pears in off-season†	0.73	0.18–2.95

* Estimated from model 2.

† Estimated from model 1.

and (ii) contact with animals or animal products, e.g. animal carcasses or animal faeces. None of these categories was associated with illness.

Table 3 shows the OR derived from two multivariate models: model 1 containing risk factors and exposures which were more frequently observed in controls than in cases ('protective factors') and model 2 containing only risk factors. Eating undercooked poultry, meat barbecued over an open fire, dietary preference of not eating organ meat, eating grapes and drinking unpasteurized milk were found independently associated with campylobacteriosis in both models. In model 1 also pork chops eaten two times or more in a fortnight was identified. In contrast, daily contact with a kitten, daily contact with cattle or pigs was identified in model 2. Eating organs from pigs, thawing of poultry, scalding of cutting boards, scalding sink, drinking organic milk and eating unpeeled apples and pears were found associated with a reduced risk of infection in model 1.

Interactions, subgroups and unmatched analyses

Interactions due to season and geography were identified in both models. Eating meat barbecued over open fire, drinking unpasteurized milk and eating unpeeled apples and pears were modified by the campylobacter season (Table 4). The largest risk from

Table 5. Population attributable risk (PAR) of exposures associated with campylobacteriosis. Calculated from case control study on sporadic campylobacteriosis conducted in Denmark 1 May 1996 to 12 May 1997

Exposures	OR Model 1/model 2*	PAR (%)	95% CI
Travel†	2.51	10.0	5.0–18.9
Undercooked poultry	8.24/4.52	4.9	2.0–11.3
Meat at barbecue	4.09/2.26	12.9	6.2–24.7
Preference of not eating organ meat	2.63/3.45	23.8	15.9–33.9
Grapes	2.81/1.59	12.1	4.3–29.6
Unpasteurized milk	11.78/2.34	3.9	1.0–14.8
Pork chops \geq 2 times	4.35	5.8	1.8–17.0
Daily contact with kitten	7.40	3.7	1.6–8.2
Daily contact with cow	1.61	3.9	1.4–10.6
Daily contact with pig	1.80	2.5	0.6–9.5

* OR estimated from model 1 and model 2 (Table 3).

† Travel was identified as a risk factors in an overall analysis of the data, constituting 282 cases and 319 controls. The other risk factors was identified for a subpopulation containing only domestic cases and controls (217 cases and 236 controls).

eating meat barbecued over open fire was seen from June to October (OR 3.02, 95% CI 1.60–5.69), and the largest risk from drinking unpasteurized milk was by contrast seen from November to May (OR 9.67, 95% CI 1.83–50.99). The reduced risk associated with eating unpeeled apples and pears was most pronounced from June to October (OR 0.04, 95% CI 0.01–0.19).

No interactions with sex and age were identified. However, county of residence was identified as an effect modifier on all risk factors and factors associated with a reduced risk of infection. Due to the low number of residents in several counties it was not possible to estimate the effect of all the interaction terms with these counties. However, residents of two counties in the Western and Northern part of the country had a higher risk of infection from daily contact with cattle, drinking unpasteurized milk, eating grapes and the dietary preference of not eating animal organs, compared to residents of other counties.

In total, 90 cases and 95 controls had a time interval between interviews less than 31 days. In this subpopulation, we observed the same effects and trends, with a few exceptions, as in the total population. However, eating grapes and meat barbecued over an open fire were not significant risk factors at 10% level for this sub-population.

Finally, we conducted an unmatched analysis of the full dataset, while still adjusting for the matching variables. This analysis was prompted by a low proportion of matched sets compared with the overall

case-population (217 matched cases of 585 interviewed, i.e. 37%). The most important food and animal exposures and food preferences was analysed in the unmatched analysis, including 317 domestic cases and 445 controls. The results were, by and large, similar to the main matched analysis. Undercooked poultry (OR 3.83, 95% CI 1.54–9.54), preference for not eating animals' organs (OR 2.55, 95% CI 1.73–3.75), contact with a cow (OR 2.93, 95% CI 1.23–7.02) and contact with a puppy pet (OR 6.06, 95% CI 1.61–22.84) were all associated with an elevated risk of infection.

Calculation of the population attributable risk

The highest population attributable risk (PAR) was for the dietary preference of not eating animals' organs (23.8%) but also traveling abroad, eating barbecued meat and eating grapes had high PARs (10–13%) (Table 5). A PAR between 2.5% and 5.8% was obtained for eating undercooked poultry, drinking unpasteurized milk, eating pork chops two times or more in 14 days as well as having daily contact with a kitten, cattle or pigs.

DISCUSSION

In the investigation of foodborne outbreaks, case control studies with a limited number of cases and controls have often been used successfully to identify the sources of the outbreaks. By contrast, case-control

Table 6. Risk factors for campylobacter infections identified in case-control studies, 1979-98

Location	No. of cases/ No. of controls	Selection of controls. Matching criteria	Interview period case and control*	Risk factors (Odds ratios)	Study period (year)	Ref
Freiburg, West Germany	114/90	Random group of healthy people	Case: 48 h prior to onset Control: —	Consumption of poultry (—)	4 mo (1979-80)	[27]
Denver and Fort Collins, USA	40/71	Nominated by cases as nearest neighbour control or through a city directory. Matched on sex and age	Cases: 7 d prior to onset Controls: 7 d prior to case's onset	Drinking untreated water (10·7) Drinking raw milk (6·9) Eating undercooked chicken (2·8) Cat in household (3·2)	2½ mo (1981)	[13]
Larimer County, Colorado, USA	10/15	Case's household members	Case: 7 d prior to onset Control: 7 d prior to case's onset	Consumption of chicken (—) Handling raw chicken	1 mo (1982)	[21]
Rotterdam, Netherlands	44/54	Living in the same street as cases	Cases: 7 d prior to onset Controls: 7 d prior to enquiry	Eating chicken (—) $P=0\cdot0002$ Eating chicken at barbecue (—) $P=0\cdot0015$ Pork (—) $P=0\cdot048$	4 mo (1982)	[20]
King and southwest Snohomish county, Washington, USA	218/526	Non campylobacter enteritis patient's from same health register as cases. Matched on age group and month of interview	Case: 7 d prior to onset Control: 7 d prior to enquiry (home interview)	Consumption of raw milk (4·6)† Consumption of mushrooms (1·5)‡	18 mo (1982-3)	[17]
Iowa city, Iowa, USA	46/46	Neighbourhood controls nominated by cases. Matched on sex and age group	Cases: 7 d prior to onset Controls: 7 d prior to case's onset	Consumption of raw milk (—)	12 mo (1982-3)	[34]
Three counties, Norway	52/103	Found through government register of all Norwegian residents. Matched on sex and age	Cases: 2 wk prior to onset Controls: 2 wk prior to enquiry	Eating sausages at a barbecue (7·6) Daily contact w/dog (4·3) Eating poultry bought into the house raw (3·2)	18 mo (1989-90)	[10]
Six health districts, UK	29/41	Acute diarrhoeal illness – campylobacter not isolated from faeces. Matched on sex and age group	Case: 10 d prior to onset Control: 10 d prior to case's onset	Drinking milk from milk bottles with tops pecked by birds (15·24)	1 mo (1990)	[18]
Brigend area of South Wales, UK	32/64	Selected from the same GP register as the case. Matched on sex, age and area of residence	Cases: 7 d prior to onset Controls: 7 d prior to case's onset	Consumption or handling of milk from bottles attacked by birds (15·5-42·1)	1 mo (1990)	[19]
Eleven public health laboratories, UK	598/598	Nominated by cases. Matched on age, sex and geography of residence	Case: 10 d prior to onset Control: 10 d prior to case's onset	Occupational exposure to raw meat (9·37) Pet with diarrhoea in household (2·39) Drinking untreated water from lakes, rivers and streams (4·16)	9 mo (1990-1)	[16]

Seven major laboratories, Switzerland	167/282	Was nominated outside household by cases. Matched on sex, ratio	Cases: 5 d prior to onset Controls: 5 d prior to completion of questionnaire	Travel abroad (21·2) Foreign citizenship (6·7) Eating poultry liver (5·7)	11 mo (1991)	[11]
Greater Christchurch area, New Zealand	100/100	Nominated by cases medical practitioner. Sex and age matched	Case: not given Control: not given	Eating poultry at a friends house (3·18) Eating poultry at a barbecue (3·00) Eating undercooked chicken (4·94) Drinking water from a nonurban supply (2·7) Consumption of chicken bought fresh (1·8)	2 mo (1992–3)	[15]
Four urban centres, New Zealand	621/621	Random selection from telephone directories. Matched on sex, age group and home telephone prefix	Case: 10 d prior to onset Controls: 10 d prior to enquiry (home interviews)	Eating raw or undercooked chicken (4·52) Chicken eaten in restaurants (3·85) Overseas travel (4·43) Rainwater as home watersource (2·20) Consumption of raw dairy products (3·10 or 12·00) Contact with puppies (2·67) Contact with cattle/calves (2·29/2·27)	9 mo (1994–5)	[14]
Nottingham Health District, UK	313/512	Nominated by cases. Sex and age group matched	Case: 2 wk prior to onset Controls: — (Cases and controls older than 18 years of age)	Foreign travel (3·4) Diabetes mellitus (4·1) Consuming medication with omeprazole (3·5) and H ₂ and H ₂ antagonists (3·7) Contact with puppies (11·3) Eating chicken (1·4) Drinking milk from bottles damages by a bird (3·3)	14 mo (1994–5)	[12]
Ävlsbor County, Western Sweden	101/198	Through the national population register. Matched on age, sex and area of residence	Case: 2 wk prior to onset Control: 2 wk prior to enquiry	Drinking unpasteurized milk (3·56) Eating chicken (2·29) Eating pork with bones (2·02) or loin of pork (1·83) Barbecuing (1·98) Living/working on a farm (3·06) Daily contact with chickens or hens (11·83)	12 mo (1995)	[29]
Hawaii, USA	211/211	From telephone directories: adding or subtracting of 1 from cases home telephone number. Age and telephone exchange matched	Case: 7 d prior to onset Control: 7 d prior to case's onset	Eating chicken prepared commercially (1·8) Consuming antibiotics (3·3)	5 mo (1998)	[30]

* wk = week, d = days, mo = month.

† Relative risk (RR) reported.

‡ Cooking status of the mushrooms that were eaten was not determined.

studies of small sample size are not well suited for the identification of health effect of relative rare exposures or in situations where the outcome may be caused by a variety of factors [26]. Several case-control studies conducted on sporadic campylobacteriosis within the last 20 years have had relatively short study periods (< 1 year) or a low number of cases and controls [13, 15, 20, 27]. There are therefore reasons to suspect that these studies have been unable to identify relevant risk factors.

In the current study the risk associated with 109 different exposures were evaluated. With a significance level of 95% one could expect 5–6 exposures to be significant just by chance. The selection of exposures to be included in a final model was therefore partly based on a judgment of the biological and epidemiological plausibility of the individual exposures found to be risk factors for campylobacteriosis in the univariate analysis.

Risk factors

Considering that poultry is a major reservoir for campylobacter and that 10–30% of the poultry products are contaminated at retail level in Denmark [28], one of the primary objectives with this study was to examine whether different poultry or poultry products were associated with an increased risk of campylobacteriosis. A wide range of poultry products was associated with an elevated risk of infection, but undercooked poultry (all types) was the only statistically significant risk factor. In 11 of at least 16 case-control studies on sporadic campylobacteriosis conducted during the last 20 years eating poultry was among the most frequently identified risk factor [10–15, 20, 21, 27, 29, 30] (Table 6).

Failure to identify specific poultry products or handling of poultry as risk factors for campylobacteriosis in the current study could be due to a good knowledge of hygiene and handling practices of poultry and chicken in the general Danish population [31, 32]. During the last 10 years the Danish media's attention to salmonella and public health campaigns have informed the public about the risk of salmonella from poultry consumption and handling of poultry. These efforts may have contributed to increased awareness among consumers on proper cooking and handling of poultry and poultry products. Furthermore, we queried food exposure in a 14 days period, which is much longer than the most commonly observed incubation period for campylobacter

infection. This may lead to a non-differential overestimation of exposure levels among cases and controls, and thus conservative estimates of the odds ratio, as discussed elsewhere (Mølbak and Neimann, personal observation).

Failure to identify other poultry related risk factors, may also be associated with a low power to estimate the risk associated with consumption of some specific products, such as poussin, organic chicken, chicken giblets and chicken wings, where the estimated odds ratio had very wide confidence intervals.

Eating meat cooked at a barbecue has been linked to an increased risk of campylobacter infection in previous studies [10, 20]. We found, as expected, that the risk from eating meat barbecued over open fire was highest from June to October. In the present study as well as in the Norwegian study the types of meat in question were beef, veal and pork [10].

Grapes tended to be independently associated with an increased risk of infection. Vegetables and fruit have been associated with an increased, but not significant risk of infection in only one previous study [17]. In a Danish screening study of thermophilic campylobacter in fruit ($n=103$) and vegetables ($n=123$) in 1997 no sample was contaminated [33]. Like meat at a barbecue (see above) eating grapes was not identified in the analysis of the subpopulation. Hence, it is possible that this observation is an artefact. However, grapes are mostly imported from countries with a warm climate, which might have a high prevalence of endemic campylobacteriosis [11], and since grapes are eaten without any cooking, and often unwashed, it may also be possible that grapes could serve as a vehicle for campylobacter.

Drinking unpasteurized milk has been identified as a risk factor for campylobacteriosis in several case-control studies [13, 14, 34]. The higher risk from drinking unpasteurized milk in the cold period could be associated with a seasonal periodicity in carriage rate of thermophilic campylobacter among dairy cows. This is supported by data from the United Kingdom where the carriage rate of campylobacter among dairy cows is higher in the cold months and lowest in the summer months [35, 36].

Drinking water with a bad taste or smell tended to be associated with an elevated risk of infection. Drinking untreated water has been identified as a risk for campylobacteriosis in previous studies [13, 14, 16], and contaminated water is among the most frequently identified single sources of outbreaks with campylobacteriosis [6]. Less than 1% of the registered public

water supply in Denmark comes from surface water – the main supply being ground water, and most drinking water supplies are non-chlorinated. The only recorded community outbreak hitherto with campylobacter from drinking water in Denmark took place in January 1996, involving 110 culture-confirmed cases and an estimated total of 2800 cases [37]. A bad taste or smell of the water initially led to the identification of this outbreak and the cause of the outbreak was a contamination of the community water supply by sewage water. Water is a potential source of sporadic campylobacter infections in Denmark that needs to be further investigated.

An increased risk of campylobacteriosis related to travelling has been identified in at least three other studies [11, 12, 14]. It was not possible in the current study to determine to which extent specific travel destinations contributed to a higher risk of campylobacteriosis. However, most cases had a history of travel to Southern Europe, the Middle East or Asia, which is in agreement with the high-risk travel destinations found in a Swiss study [11]. Campylobacter is known to be a major cause of travellers' diarrhoea [38].

Cats and dogs are known to harbour and excrete campylobacter asymptomatically [39–41]. The playful disposition and lack of 'toilet training' of young pets makes faecal–oral transmission of campylobacter to humans (and especially children) very likely. Pets, both with and without diarrhoea, have in previous studies been shown to be associated with an increased risk for infection [9, 10, 12–14, 16, 42]. Even though an interaction with age was not identified in the current study, the finding that daily contact with a kitten is a risk factor is biologically plausible and in agreement with previous studies.

'Protective factors'

Exposures more predominant among controls than cases ($OR < 1$) are often referred to as protective factors [11, 12, 16, 43]. In the current study three protective factors associated with proper kitchen hygiene or cooking procedures were identified: thawing of poultry, scalding of cutting boards and scalding of sink. It is suggested that thawing of poultry is a proxy measure for consumption of poultry that has been frozen. Freezing of poultry has been shown to have a lethal effect on campylobacter [44]. Scalding different kitchen utensils reduces the risk of cross contamination from meat to non heat-treated food items (e.g. salad). Three food exposures were also identified

as protective: eating pigs' organs, drinking organic milk and eating unpeeled apples and pears. The occurrence of compounds in food, such as antioxidants (e.g. vitamin C), garlic and mustard oil with antibacterial activity against *Campylobacter* spp. or the related bacterium *Helicobacter pylori*, has been published [45]. This makes the finding that certain food items were protective of campylobacteriosis biologically plausible. However, besides a real protective effect, several of the food exposures found to be protective (like drinking organic milk) could also be explained as proxy measures for differences in cooking procedures and food preferences, statistical coincidences, methodological bias including dietary preferences among interested controls, on recall bias [11, 12, 16, 43].

One of the prerequisites for identification of factors protective against infection is that the controls actually have been exposed to the pathogen. Whether the protective factors found in this study are real protective factors, proxy measures of behaviour, or artefacts remains unclear. However, several case controls studies have identified protective factors of a similar kind, and to elucidate this further studies are warranted.

Two models

Because the interpretation of protective factors is complicated we fitted two multivariate models, one including and one excluding protective factors. Five exposures were found to be significantly associated with increased risk of campylobacteriosis in both models. Four exposures were only significant in one model. The OR calculated in model 2 (only risk factors) corresponds to the OR calculated in the univariate analysis. In contrast, the OR calculated in model 1 (risk factors and protective factors) were almost twice as high as the ORs found in the univariate analysis. We suspect that the exposures fitted in model 2 may be more genuinely associated with campylobacteriosis, but we cannot ignore factors found to be significant in model 1 only.

Representativeness of the study population

One of the concerns with the present study was that many of the cases had no matching control with a completed interview. We also had to exclude cases due to foreign travel or with their interview missing even though the controls had been interviewed. In fact, due

to this problem with unbalanced sets, only 37% of the interviewed cases contributed to the matched analysis. Nevertheless, the unmatched analysis based on the full dataset did not reveal additional risk factors, and supported the major findings of the matched analysis.

Due to the seasonality of the incidence in human campylobacteriosis and the seasonal consumption of many food items there are reasons to suspect a bias due to delayed enrolment of controls compared to cases. We therefore analysed a subset of cases and controls with a limited time lag between interviews. Except for two exposures (grapes and unpasteurized milk) the risk factors identified for the total population were also found to be significant in the sub-population. This finding suggests that delayed enrolment of controls might have biased the identification of certain risk factors, i.e. identifying consumption of grapes and red meat at a barbecue as risk factors might be artefacts. In several of the case-control studies conducted on sporadic campylobacteriosis there have been no criteria defined for the time lag from interviewing of cases to interviewing of controls or such criteria have not been reported [10–13, 18, 20]. In studies where enquiry about food exposure among controls was related to the period immediately prior to the interview, delayed enrolment of controls might have constituted a bias [10, 11, 17, 20]. Care should be taken to minimize this type of bias, in particular in a matched design.

The response rate among the controls was low. In a separate publication, we evaluated the representativeness of the controls compared with the Danish population [46]. With regard to some of the protective factors identified in the current study (eating cabbage, carrots, apples and pears and cookies with raw cream) the controls was found to be different from the general population. This was not observed for some of the risk factors (eating chicken and pork chops twice or more in a fortnight). In studies where other procedures for enrolling controls have been adapted, e.g. random digit dialing, the number of initially contacted controls has never been reported nor been discussed [19, 30]. It is easy to suspect that a similarly low response rate among the controls [contacted (by telephone)] has occurred in those studies.

Conclusion

Campylobacter infections in Denmark appear to be acquired from several food and environmental sources. This case-control study identified consumption of

undercooked poultry, red meat prepared at a barbecue, grapes and unpasteurized milk as independent risk factors for campylobacteriosis in Denmark. Furthermore, an elevated risk of infection was found for drinking water with a bad taste or smell and contact with domestic animals and pets. The present study corroborates the findings of many earlier studies of risk factors for sporadic campylobacter infections in other countries. It did not, unfortunately, provide an explanation for the marked increase in campylobacteriosis incidence currently occurring in Denmark and in many other industrialized nations. Research to address this particular question should be given a high priority in future studies of the epidemiology of campylobacter infections.

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