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Increased risk of zoonotic *Salmonella* and *Campylobacter* gastroenteritis in patients with haematological malignancies: a population-based study

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Abstract We hypothesised that haematological malignancies increase the risk of acquiring zoonotic *Salmonella* or *Campylobacter* gastroenteritis. The population-based study comprised all first-time *Salmonella/Campylobacter* gastroenteritis cases in two Danish counties (1991–2003), with age- and gender-matched controls from the background population. We linked the study cohort to registries to obtain data on malignancies, chemotherapy (yes/no), and main comorbidities diagnosed before *Salmonella/Campylobacter* gastroenteritis. Based on this design, we determined incidence rate ratios (IRR) in conditional logistic regression analyses, and we used weighted mean regression curves to evaluate fluctuations in risk 0–5 years after the malignancy diagnosis. Sixty-eight of 13,324 cases (0.5%) and 29 of

26,648 controls (0.1%) had haematological malignancy before their *Salmonella/Campylobacter* gastroenteritis. Comorbidity-adjusted IRR for *Salmonella/Campylobacter* gastroenteritis in patients with haematological malignancy as compared to patients without malignancy were 4.46 [95% confidence intervals (CI), 2.88–6.90] for all individuals, 8.33 (95% CI, 4.31–16.1) for *Salmonella*, and 2.17 (95% CI, 1.15–4.08) for *Campylobacter*. Stratification on chemotherapy treatment did not change these estimates. In time-related analyses, IRR were 7–8 in the first 2 years after the haematological malignancy diagnosis and 4–5 in the following 3 years. Patients with haematological malignancy had increased long-term risk of enquiring *Salmonella* or *Campylobacter* gastroenteritis.

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Introduction

Although behavioural factors, such as travelling, lax hygiene or outdoor cooking, are known to increase the risk of infection with non-typhoid *Salmonella* (hereafter “*Salmonella*”) or thermophilic *Campylobacter* (hereafter “*Campylobacter*”), less is known about the role of host factors other than age, gender and HIV infection [2, 13, 17, 27, 31].

The risk of acquiring *Salmonella* and *Campylobacter* could be increased in patients with haematological malignancies due to immunodeficiency, which is often profound. Case series studies, most of which were published decades ago, reported *Salmonella* infections in hospitalised patients with malignancies [14–16, 22, 23, 29, 38]. To our knowledge, there are no studies on *Campylobacter* in patients with

malignancies except one casuistic study of *Campylobacter jejuni* in a patient with alpha chain disease [19]. Thus, there is a lack of population-based studies that assess the role of haematological malignancies in the acquisition of *Salmonella* and *Campylobacter* infections.

The acquisition of *Salmonella/Campylobacter* infections in HIV patients has been reported to be associated with the degree of immunodeficiency [13, 31], and a similar graded impact could be expected in patients with haematological malignancies. Hence, the aim of our nested case–control study was to assess the risk of acquiring *Salmonella/Campylobacter* gastroenteritis in patients with haematological malignancies, using patients with solid tumours and the age- and gender-matched background population for comparison.

Materials and methods

Setting

The Danish health care system is tax-financed and free of charge for all residents. Initial medical contact is with the general practitioner who may refer the patient to a hospital in the patient's county of residence. The two counties from which cases and controls were retrieved had an average of 1,127,069 residents (21.4% of Denmark's population) during the study period [8].

Retrieval of cases and controls

In the Civil Registration System, all Danish residents have a unique ten-digit personal identification number (the CPR-number, which incorporates age and gender) used for all health contacts, which thus permits linkage between health administrative registries [24].

Data on all *Salmonella*- and *Campylobacter*-positive stool specimens were retrieved from laboratory registries, which contain the patient's CPR-number, bacterial type and date of receipt of stool specimen (specimen date). Date of entry into the study was the specimen date, which, in contrast to the sampling date, was known for all episodes. Cases consisted of all residents with a first-time detection of *Salmonella* or *Campylobacter* in stool specimens in Aarhus County or North Jutland County from 1991 through 2003. Residents with different bacteria isolated within a 7-day period (double infections) were excluded, defining different bacteria as *Salmonella* vs. *Campylobacter* or as different *Salmonella* serotypes.

For each case included in the study, two controls were selected from the population of the two counties through the Civil Registration System. The controls, matched on the specimen date for age (± 1 year), gender and county of

residence, were selected by using the incidence density sampling principle [36].

Data linkage

Using the CPR-number, we linked the data from cases and controls to the Danish Cancer Registry [32] and the Danish National Patient Registry [1]. From the Cancer Registry, we retrieved all first-time diagnoses of malignancy from 1977 to the specimen date, with the omission of basal cell carcinomas. This registry also records whether treatment (chemotherapy, radiation or surgery) is initiated within the first 4 months after diagnosis of the malignancy. From the National Patient Registry with its International Classification of Diseases (ICD) system (ICD-8 in 1977–1993 and ICD-10 thereafter), we retrieved all diagnosed comorbid diseases from 1977 to the specimen date as listed in the Charlson comorbidity index. This index includes 19 disease categories (e.g. cardiovascular disorders, chronic pulmonary disease, diabetes mellitus and malignancies) and assigns points to each of these, with more points associated with more severe disease categories [4]. To avoid redundancy, we excluded the four malignancy disease categories of the Charlson comorbidity index.

For all cases and controls in North Jutland County from 1998 through 2003, we also had data on the number of cultured stool specimens. For these individuals, we compared the number of cultured stool specimens between patient groups to deduce if a possible surveillance bias in patients with malignancies resulted in the culturing of more stool specimens.

Microbiological procedures for stool specimens

In brief, 10 μ L stool specimen was suspended in selenite broth (SSI Diagnostika, Hillerød, Denmark) incubating 18–24 h at 35°C and plated on SSI enteric medium [3] and XLD agar (Oxoid, Basingstoke, UK) for culturing of *Salmonella* (incubating 18–24 h at 35°C) and on mCCDA agar [10] for culturing of *Campylobacter* (microaerophilic incubation 36–48 h at 35°C). The Kauffmann–White scheme was used for serotyping of *Salmonella* [12, 25]. *Campylobacter* was confirmed by microscopy and a positive oxidase and catalase reaction and identified as *C. jejuni/Campylobacter coli*, without differentiation between these two species.

Statistical analysis

The use of the incidence density sampling principle makes the odds ratio (OR) an unbiased estimate of the incidence rate ratio (IRR) for the acquisition of *Salmonella/Campylobacter* [36], which we report for the logistic regression analyses.

We categorised patients with malignancy according to malignancy type (solid tumours or haematological malignancies) and chemotherapy treatment within the first 4 months after the diagnosis of malignancy (given or not given). We used conditional logistic regression analyses to compare the prevalence of these four malignancy groups in cases vs. controls. For each malignancy/chemotherapy group, we computed IRR with 95% confidence intervals (CI) for the acquisition of *Salmonella/Campylobacter* gastroenteritis, using individuals without malignancy as the reference group. In addition to the age- and gender-adjusted model (due to matching), we adjusted for comorbidity and stratified all analyses on *Salmonella* and *Campylobacter*. Moreover, we cross-tabulated the type of haematological malignancy vs. cases and controls.

We computed locally weighted mean regression curves [6] for haematological malignancies and solid tumours to evaluate IRR fluctuations from 0 to 5 years after the malignancy diagnosis. This was computed for all individuals and separately for *Salmonella* and *Campylobacter* cases.

We used the Kruskal–Wallis test to compare the number of cultured stool specimens between individuals with solid tumours, haematological malignancies or no malignancy (within cases and controls) and between cases and controls (excluding controls without stool specimens sampled).

The software program Stata/SE 9.2 for Windows (Stata Corporation, College Station, TX, USA) was used for all analyses.

Ethical considerations

The study was conducted according to the guidelines of the regional scientific ethics committee for use of clinical and laboratory data and approved by the Danish Data Protection Agency (Record no. 2004-41-4004).

Results

Baseline characteristics

There were 13,324 cases and 26,648 controls (Table 1). Cases had more malignancy diagnosed before *Salmonella/Campylobacter* gastroenteritis than controls (OR [95% CI], 1.39 [1.20–1.61]) as well as higher comorbidity, regardless of malignancy status. The distribution of the matched variables age and gender did not differ between cases and controls with malignancy.

Malignancy and chemotherapy distribution among cases and controls

In general, there were minor differences between the two models used in our analyses (Table 2). The IRR for *Salmonella/Campylobacter* gastroenteritis were higher among patients with haematological malignancies compared with patients with solid tumours, which was especially

Table 1 Baseline characteristics of the study cohort

Characteristics	Cases (<i>n</i> =13,324)	Controls (<i>n</i> =26,648)	Crude OR (95% CI) ^a
All individuals			
Age, years			
Median (1st–3rd quartile)	29.7 (17.6–48.1)	29.7 (17.6–48.1)	
Mean (range)	32.8 (0–98.9)	32.8 (0–98.9)	
Females	6,610 (49.6) ^b	13,220 (49.6)	
Comorbidity ^c			
0 points	11,946 (89.7)	24,639 (92.5)	0.71 (0.66–0.76)
1–2 points	1,185 (8.9)	1,822 (6.8)	1.33 (1.23–1.44)
>2 points	193 (1.5)	187 (0.7)	2.08 (1.69–2.56)
Individuals with malignancy			
Age, years			
Median (1st–3rd quartile)	62.5 (50.2–74.9)	62.2 (49.6–74.2)	
Mean (range)	60.4 (1.5–98.9)	61.0 (3.1–95.1)	
Females	172 (52.4)	272 (57.3)	0.82 (0.61–1.10)
Comorbidity ^c			
0 points	225 (68.6)	367 (77.3)	0.64 (0.46–0.89)
1–2 points	76 (23.2)	93 (19.6)	1.24 (0.87–1.77)
>2 points	27 (8.2)	15 (3.2)	2.75 (1.38–5.65)

Cases were all individuals with first-time detection of zoonotic *Salmonella* or *Campylobacter* in stool specimens, Aarhus or North Jutland counties, Denmark, 1991–2003, matched to controls for age (± 1 year), gender and county of residence

^aOdds ratio (95% confidence intervals)

^bNumber (percent)

^cCharlson comorbidity index [4], with malignancy diagnoses excluded

Table 2 Distributions of combinations of malignancy type and chemotherapy treatment among cases and matched controls (cf. Table 1) and results from conditional regression analyses

Patient group	Main malignancy group	Cases	Controls	Incidence rate ratio ^a (95% confidence intervals)	
				Model 1 ^b	Model 2 ^c
All	No malignancy	12,996 (97.5) ^d	26,173 (98.2)	1 (reference)	1 (reference)
	Haematological malignancies, chemotherapy	46 (0.35)	18 (0.07)	5.15 (2.98–8.88)	4.88 (2.82–8.43)
	Haematological malignancies, no chemotherapy	22 (0.17)	11 (0.04)	4.06 (1.97–8.38)	3.77 (1.82–7.81)
	Solid tumours, chemotherapy	31 (0.23)	38 (0.14)	1.66 (1.03–2.67)	1.68 (1.04–2.70)
	Solid tumours, no chemotherapy	229 (1.72)	408 (1.53)	1.15 (0.97–1.36)	1.15 (0.97–1.36)
Zoonotic <i>Salmonella</i>	No malignancy	6,346 (96.8)	12,837 (97.9)	1 (reference)	1 (reference)
	Haematological malignancies, chemotherapy	33 (0.50)	8 (0.06)	8.32 (3.84–18.0)	8.15 (3.75–17.7)
	Haematological malignancies, no chemotherapy	14 (0.21)	3 (0.02)	9.33 (2.68–32.5)	8.82 (2.51–31.0)
	Solid tumours, chemotherapy	16 (0.24)	22 (0.17)	1.47 (0.77–2.79)	1.41 (0.74–2.70)
	Solid tumours, no chemotherapy	148 (2.26)	244 (1.86)	1.24 (1.01–1.54)	1.26 (1.02–1.56)
Zoonotic <i>Campylobacter</i>	No malignancy	6,650 (98.3)	13,336 (98.5)	1 (reference)	1 (reference)
	Haematological malignancies, chemotherapy	13 (0.19)	10 (0.07)	2.60 (1.14–5.93)	2.40 (1.05–5.50)
	Haematological malignancies, no chemotherapy	8 (0.12)	8 (0.06)	2.05 (0.77–5.46)	1.88 (0.70–5.02)
	Solid tumours, chemotherapy	15 (0.22)	16 (0.12)	1.90 (0.94–3.85)	1.99 (0.98–4.03)
	Solid tumours, no chemotherapy	81 (1.20)	164 (1.21)	1.00 (0.76–1.32)	1.00 (0.75–1.31)

^a Because of the incidence density sampling principle [36], odds ratio is an unbiased estimate of the incidence rate ratio for the acquisition of zoonotic *Salmonella/Campylobacter*

^b Adjusted for age, gender and county of residence (due to matching)

^c Model 1, adjusted for Charlson comorbidity index [4], with malignancy diagnoses excluded

^d Number (percent)

notable for *Salmonella*. IRR changed little in relation to chemotherapy treatment, both for solid tumours and haematological malignancies.

Type of haematological malignancy among cases and controls

Cases had less lymphomas and correspondingly more leukaemias and myelomas than controls (Table 3). In contrast, there were no conspicuous differences between *Salmonella* and *Campylobacter* cases (data not shown).

Table 3 Overview of haematological malignancies among cases with *Salmonella/Campylobacter* gastroenteritis and controls (cf. Table 1)

Type of haematological cancer	Cases	Controls
Non-Hodgkin lymphoma	19 (27.9) ^a	14 (48.3)
Hodgkin lymphoma	14 (20.6)	9 (31.0)
Acute myeloid leukaemia	7 (10.3)	1 (3.4)
Chronic myeloid leukaemia	2 (2.9)	0 (0)
Acute lymphatic leukaemia	5 (7.4)	1 (3.4)
Chronic lymphatic leukaemia	10 (14.7)	3 (10.3)
Hairy cell leukaemia	1 (1.5)	1 (3.4)
Multiple myeloma	10 (14.7)	0 (0)
Total	47 (100)	29 (100)

^a Number (percent)

Incidence rate ratios 0–5 years after the diagnosis of malignancy

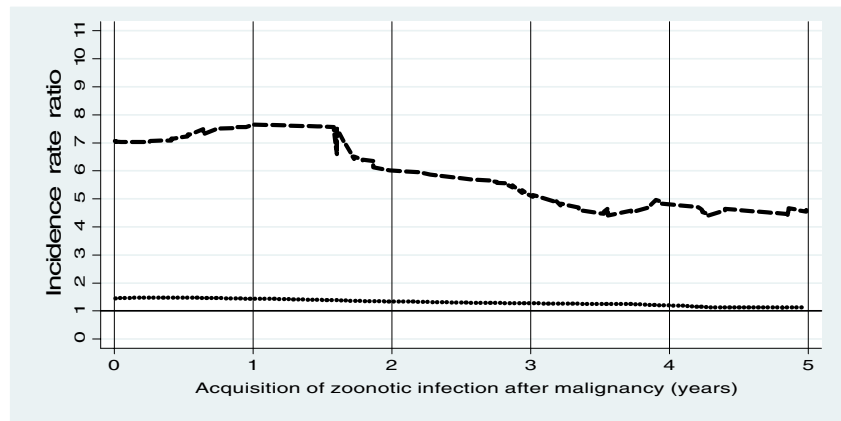
For haematological malignancies, IRR for the acquisition of *Salmonella/Campylobacter* was seven- to eightfold increased within the first 18 months after the diagnosis of malignancy, after which it decreased to a steady level of 4–5 after a 3-year period (Fig. 1a). Concerning *Salmonella*, IRR was 10 immediately after the diagnosis of malignancy, and thereafter, it decreased to a steady level of 6–7 after 3 years (Fig. 1b). As regards *Campylobacter*, IRR fluctuated between 2 and 5, with the highest IRR during the first 2 years after the diagnosis of malignancy (Fig. 1c).

For solid tumours, IRR for the acquisition of *Salmonella/Campylobacter* was 1–1.5 throughout the period, without any time-related increase or decrease, either for all individuals (Fig. 1a), *Salmonella* (Fig. 1b) or *Campylobacter* (Fig. 1c).

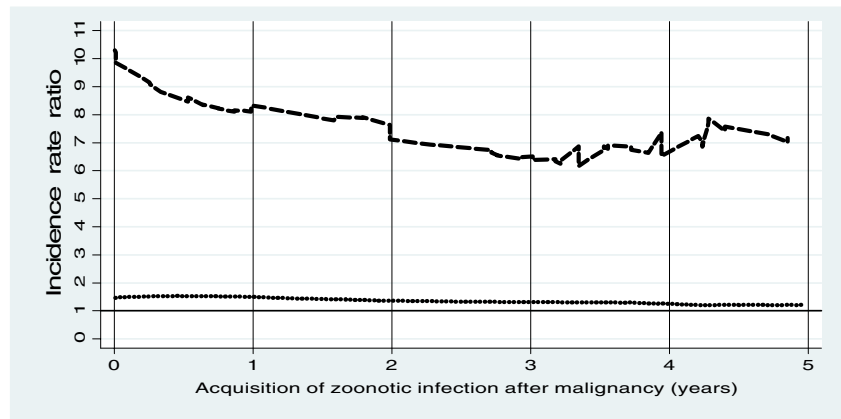
Number of cultured stool specimens to deduce possible surveillance bias

We had access to the number of cultured stool specimens for 8,008 individuals (2,686 cases and 5,322 controls). There were no differences in median number of cultured stool specimens between individuals without malignancy, with solid tumours and with haematological malignancies ($p=0.88$ within cases and $p=0.15$ within controls, data not shown). Among the 187

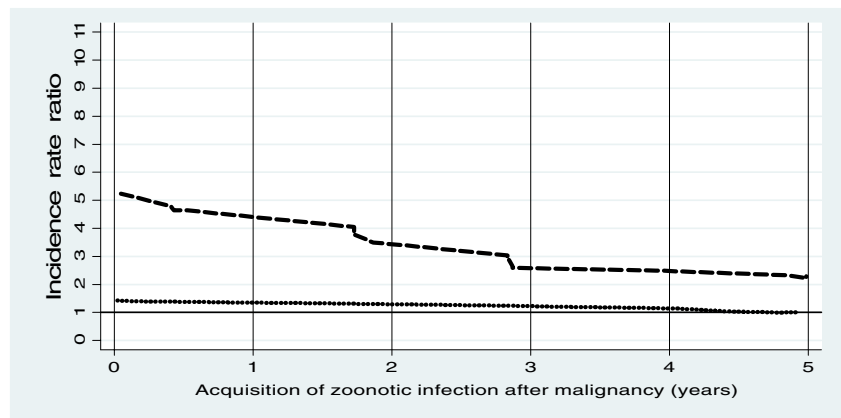
Fig. 1 Zoonotic *Salmonella/Campylobacter* gastroenteritis 0–5 years after haematological malignancy or solid tumours. Locally weighted mean regression incidence rate ratio curves (cases vs. matched controls) for the acquisition of zoonotic *Salmonella/Campylobacter* gastroenteritis 0–5 years after the diagnosis of haematological malignancy (*thick dashed line*) or solid tumours (*thick dotted line*). Incidence rate ratio = 1 shown as *thin solid line*. **a** All cases with zoonotic *Salmonella/Campylobacter* gastroenteritis vs. matched controls. **b** Cases with zoonotic *Salmonella* gastroenteritis vs. matched controls. **c** Cases with zoonotic *Campylobacter* gastroenteritis vs. matched controls



A



B



C

controls (3.5%) with stool sampled from 1998 through 2003, the median number of cultured stool specimens was 2, in contrast to 3 for the 2,686 cases ($p=0.001$, data not shown).

Discussion

We found a higher risk of acquiring *Salmonella/Campylobacter* gastroenteritis in patients with haematological malignancies as

compared to an age- and gender-matched background population. This risk decreased with time since diagnosis of the haematological malignancy, but remained higher even 5 years after. To our knowledge, this is the first study to describe the association between malignancies and *Salmonella/Campylobacter* infections on a population-based level.

The increased risk of *Salmonella/Campylobacter* gastroenteritis among patients with haematological malignancies could be explained either by a higher degree of comorbidity

or conditions that specifically increase the likelihood of acquiring *Salmonella/Campylobacter* gastroenteritis. *Salmonella/Campylobacter* patients had higher general comorbidity than their matched controls, which pertained both to non-malignancy and malignancy conditions. However, we find it unlikely that a generally higher comorbidity could be the decisive factor, especially when time relationships are considered. Thus, haematological malignancy patients seem to be specifically prone to acquiring *Salmonella/Campylobacter* gastroenteritis.

The risk of *Salmonella* was higher in patients with haematological malignancies as compared to *Campylobacter*. *Salmonella* is primarily an intracellular pathogen [7], whereas *Campylobacter* is mainly extracellular [2]. Chronic lymphatic leukaemia and multiple myeloma predominantly suppress the humoral immune system, whereas the other haematological malignancies mainly affect the cellular immunity. However, the complexity of involved immune mechanisms known from in vitro studies [11, 18, 21, 34] may, in addition to the independent impact of chemotherapy, reflect the lack of clear associations between *Salmonella* or *Campylobacter* on the one hand and the type of haematological malignancy on the other (data not shown).

A number of hospital case series studies [9, 14–16, 22, 23, 29, 38] and one surveillance study [5] reported *Salmonella* in patients with malignancies. Though direct comparisons to our study are difficult due to different settings and study designs, a higher risk of *Salmonella* in patients with haematological malignancies as compared to solid tumours was also reported in several of these studies [14, 22, 23, 29, 38].

No study has previously reported *Campylobacter* in malignancy patients, except one casuistic report of *C. jejuni* in a patient with alpha chain disease directly involving the small intestine [19].

The main strengths of this study were the overall high statistical precision, the high validity and completeness (95–98%) of the Danish Cancer Registry [32] and the age- and gender-matched controls from a well-defined population.

Our study also had limitations. First, there is possibly surveillance bias for frail patients groups, which may result in the diagnosis of more *Salmonella/Campylobacter* gastroenteritis. We found, however, no difference in the median number of cultured stool specimens between the malignancy groups, and this indicated that the higher occurrence of *Salmonella/Campylobacter* in patients with haematological malignancies was unlikely to be due to higher vigilance. The under-ascertainment of *Salmonella* or *Campylobacter* infections has been evaluated only in a few studies [28, 35, 37], none of which addressed specific patient groups. Second, we lacked clinical data except preceding comorbidity and treatment within the first 4 months after the diagnosis of malignancy. Due to the

high correlation with the malignancy type (solid tumours or haematological malignancies, cf. Table 2), we did not include chemotherapy as a possible confounder in our multivariable regression model. Moreover, aggravation of the immunodeficiency state during chemotherapy may be part of the pathway between malignancy and *Salmonella/Campylobacter* infection, which excludes its role as a confounder [26]. The main differences were seen between solid tumours and haematological malignancies (cf. Table 2), which supported that the immunosuppressive effect was mainly associated with haematological malignancy. This should, however, be interpreted with caution because we had no data on the type of chemotherapy, treatment beyond 4 months or malignancy duration. Third, the Danish National Patient Registry has lower validity than the Danish Cancer Registry, mainly due to underreporting and possible misclassifications [30], but we believe that this has non-differential implications in our study, which used the Charlson comorbidity index as a general marker of frailty. Fourth, we had no data on behavioural factors. Frailer patients may be less likely to travel abroad, especially to more exotic places with a lower hygienic standard [33], and they may be stricter with food hygiene practices [20], though little is known about such aspects. Fifth, the statistical precision was low in some groups, including patients with haematological malignancies.

Our results mainly have implications for clinicians who should be aware of an increased likelihood of *Salmonella/Campylobacter* gastroenteritis in patients having haematological malignancy and for the patients themselves, for whom safe food production, processing and cooking to reduce food borne bacterial infections are crucial.

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Conflicts of interest None.

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