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Increased incidence of non-Hodgkin lymphoma in chronic Q fever patients

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Background: Infection with intracellular pathogens possibly plays a role in the development of non-Hodgkin lymphoma (NHL). It has been suggested that *Coxiella burnetii*, the causative agent of Q fever, is associated with development of NHL. We studied the association between chronic infection with *C. burnetii* and NHL.

Material/methods: The incidence rate (IR) of NHL in chronic Q fever patients was compared to the IR of NHL in the overall Dutch population. IR of NHL in chronic Q fever patients was retrieved from the Dutch national chronic Q fever database. For all subjects, period at risk started 1-1-2007 and ended at end of study, death or NHL diagnosis. IR of NHL in the overall Dutch population was obtained from the Dutch integral cancer centre (IKNL), which systematically registers all newly diagnosed malignancies, and Central Bureau of Statistics (CBS). An adjusted relative risk for NHL in chronic Q fever patients was calculated using a negative binomial regression model.

Results: Of 439 chronic Q fever patients (mean age 65 years, male sex 73%), five developed NHL (absolute risk 1.1%, IR 3.01/1000 personyears at risk). Three B-cell chronic lymphocytic leukaemias

(non-hairy cell), one mantle cell lymphoma and one inconclusive subtype of B-cell NHL were observed. Median time from diagnosis of chronic Q fever to diagnosis of NHL was 0.7 years (IQR 0.4 – 2.2). All NHL patients were smokers, three used alcohol. They did not have other known risk factors for NHL. The relative risk for NHL in chronic Q fever patients, adjusted for age and sex, compared to the general population was 4.42 (95% CI 1.31 – 14.95).

Conclusions: Incidence of NHL among chronic Q fever is increased in comparison to the general Dutch population. Causality however is uncertain: chronic inflammation or immunomodulation by *C. burnetii* may induce development of NHL. On the other hand, common risk factors (such as immunocompromised state) may cause both diseases, although no NHL patients with chronic Q fever in this study had such risk factors. Furthermore, since both diseases may have considerable diagnostic delay, we cannot be certain that infection with *C. burnetii* preceded NHL. Finally, there is a risk of detection bias: since chronic Q fever patients are regularly monitored, NHL may be diagnosed earlier in these patients. Despite these drawbacks, clinicians should be aware of the increased incidence of NHL among chronic Q fever patients.

Table 1. NHL cases in chronic Q fever patients and in the overall Dutch population

	Chronic Q fever patients	Overall Dutch population
No. of NHL	5	25,562
Follow-up duration (in personyears)	1,661	116,447,502
Male sex (%)	100	57
Mean age (SD)	75 (8)	64 (14)
Incidence rate (per 1,000 personyears)	3.01	0.22
Relative risk (adjusted for sex and age)	4.42	n/a