

## DIABETES AND RISK OF NON-HODGKIN LYMPHOMA: A CASE-CONTROL STUDY

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**Aims and background:** We investigated the relation between diabetes and the risk of non-Hodgkin lymphoma, as epidemiological results are controversial and diabetes has been related to the risk of several neoplasms.

**Patients and methods:** We analyzed the combined dataset of two Italian case-control studies conducted in 1985-1997 and 1999-2002. Cases were 671 patients, aged <85 years, with incident, histologically confirmed non-Hodgkin lymphoma, and controls were 1799 patients admitted to hospitals for acute non-neoplastic conditions. Odds ratios were estimated using unconditional multiple logistic regression models including

terms for age, center, sex, residence and educational level. **Results:** No material association between diabetes and non-Hodgkin lymphoma risk was observed, with an odds ratio of 1.12 (95% confidence intervals, 0.70-1.77). No association was found in relation to age at first diagnosis of diabetes, years since diagnosis, or in younger and older subjects at diagnosis of non-Hodgkin lymphoma.

**Conclusions:** The results of the study allow to exclude a strong association between diabetes and non-Hodgkin lymphoma, although the small number of cases with diabetes leaves open the possibility of a moderate direct relation.

**Key words:** case-control studies, diabetes, non-Hodgkin lymphoma, risk factors.

### Introduction

Diabetes has been related to excess risk of several neoplasms, including colorectal<sup>1,2</sup>, liver<sup>3</sup>, pancreatic<sup>4</sup> and endometrial<sup>5</sup>. The possible relation of diabetes with other neoplasms is less clear<sup>6,7</sup>. With reference to non-Hodgkin lymphoma (NHL), a recent analysis of a multicentric case-control study, based on the US Surveillance Epidemiology and End Results (SEER) cancer registries, found no overall association between diabetes mellitus and the risk of NHL, independently of diabetes treatment (no drugs, oral antidiabetic drugs, insulin and their combination), and histological characteristics of NHL<sup>8</sup>.

In an Italian case-control study conducted between 1985 and 1997, we showed that diabetes was not materially related with NHL<sup>9</sup>. In the present analysis, we have combined these data with those of another case-control study conducted in Italy from 1999 to 2002<sup>10</sup>. We were therefore able to provide information also within strata of age, sex and age at diagnosis of diabetes.

### Patients and methods

Two studies were included in the dataset. The first one was conducted in the province of Pordenone and the greater Milan area between 1983 and 1997 and included 446 cases of histologically confirmed NHL (ICD-9 200 and 202) (256 men and 190 women: median age, 58

years; range, 17-79) and 1,295 controls admitted to the same hospitals as cases for a wide range of acute non-neoplastic, non-immunological and non-gynecological conditions (791 men and 504 women: median age, 56 years; range, 17-79)<sup>11,12</sup>. The second study was conducted in the province of Pordenone and in Naples between 1999 and 2002 and included 225 cases of histologically confirmed NHL (120 men and 105 women: median age, 59 years; range, 18-84) and 504 controls (341 men and 163 women: median age, 63 years; range, 18-84)<sup>10</sup>. Overall, the two studies included 671 cases of NHL (376 men and 295 women: median age, 58 years; range, 17-84) and 1,799 controls (1,132 men and 667 women: median age, 58 years; range, 17-85). Of controls, 24% were non-alcohol-related traumas, 26% other orthopedic disorders, 27% surgical conditions, and 21% other miscellaneous illnesses, such as ear, nose and throat, eye, dental or skin disorders.

In both studies, trained interviewers administered a structured questionnaire to cases and controls in the hospital setting including questions on socio-demographic characteristics, anthropometric measures, personal and family history of selected medical conditions, a few selected occupational and environmental exposures, smoking status, and frequency of consumption of selected dietary items, including alcohol and coffee. Information on diabetes and other selected medical conditions was self-reported and included age at diagnosis.

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The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models including terms for study, center, age (quinquennia and continuous variable), sex, area of residence and years of education<sup>13</sup>.

## Results

Diabetes was reported by 29 patients with NHL (4.3%) and 67 controls (3.7%), corresponding to an OR of 1.12 (95% CI, 0.70-1.77) (Table 1). Compared with subjects without diabetes, the OR of NHL was 0.99 in patients diagnosed with diabetes when aged less than 45 years (1 case, 4 controls) and 1.12 in those aged 45 years or older (28 cases, 63 controls); the OR was 1.14 in patients diagnosed with diabetes less than 5 years earlier, 1.09 in those diagnosed 5 to 9 years earlier, and 1.11 in patients diagnosed 10 years earlier or longer. The ORs were not heterogeneous in two strata of age at diagnosis of cancer: in subjects younger than 60 years at diagnosis of cancer, the OR was 1.35 and in subjects aged 60 years or older it was 1.02. The ORs were 0.78 in men and 1.90 in women (not different). Likewise, no significant heterogeneity was observed across strata of study, area of residence or education.

## Discussion

The findings of the study allow us to exclude a strong association between diabetes and NHL, but not a moderate increased risk.

The results on the relation between diabetes and NHL are not consistent. Out of five cohort studies, a British one found no relation between diabetes and NHL<sup>14</sup>, an American study found no relation in women and a slight excess risk in men<sup>15</sup>, and three other studies found a direct association<sup>16-18</sup>. Among case-control studies, a Spanish one found a non-significant higher risk of NHL with diabetes<sup>19</sup>, whereas a Japanese study found a direct association of diabetes only with extranodal lymphomas<sup>20</sup>. A possible association between type-2 diabetes and NHL may be related to endocrine factors, such as insulin-related growth factor, which could enhance cancer progression<sup>19</sup>.

A potential limitation of these data is the use of hospital controls. However, information on medical history is likely to be more comparable when collected in the same setting for cases and controls<sup>13</sup>, and the prevalence

**Table 1 - Distribution of 671 cases of non-Hodgkin lymphoma (NHL) and 1,799 controls and corresponding odds ratios (OR) and 95% confidence intervals (CI), according to selected aspects of diabetes**

	NHL No. (%)	Controls No. (%)	OR <sup>a</sup> (95% CI)
All subjects			
Diabetes			
No	642 (95.7)	1732 (96.3)	1 <sup>b</sup>
Yes	29 (4.3)	67 (3.7)	1.12 (0.70-1.77)
Years since diagnosis <sup>c</sup>			
<5	11 (1.6)	23 (1.3)	1.14 (0.54-2.41)
5-9	6 (0.9)	14 (0.8)	1.09 (0.40-2.93)
≥10	12 (1.8)	30 (1.7)	1.11 (0.55-2.23)
Current age <60 years			
Diabetes			
No	354 (97.3)	944 (98.2)	1 <sup>b</sup>
Yes	10 (2.8)	17 (1.8)	1.35 (0.59-3.11)
Current age ≥60 years			
Diabetes			
No	288 (93.8)	788 (94.0)	1 <sup>b</sup>
Yes	19 (6.2)	50 (6.0)	1.02 (0.58-1.81)
Men			
Diabetes			
No	362 (96.3)	1085 (95.9)	1 <sup>b</sup>
Yes	14 (3.7)	47 (4.2)	0.78 (0.41-1.47)
Women			
Diabetes			
No	280 (94.9)	647 (97.0)	1 <sup>b</sup>
Yes	15 (5.1)	20 (3.0)	1.90 (0.93-3.89)

<sup>a</sup>Estimated from multiple logistic regression models including terms for study, centre, age, sex, area of residence and education; <sup>b</sup>reference category; <sup>c</sup>reference category: subjects without diabetes.

of diabetes among the comparison group (3.7%) was comparable to that of the Italian general population<sup>21</sup>. Furthermore, cases and controls came from similar residential areas, participation rate was almost complete (approximately 95% for cases and controls), and information on medical history was obtained by a satisfactorily reproducible structured questionnaire (k for agreement for diabetes = 0.85)<sup>22</sup>.

Thus, the present work provides additional data to a still open issue, but the small number of cases with diabetes precludes any definite conclusion. Taken together with other available evidence, the results allow to exclude a strong association between diabetes and NHL but are compatible with a moderate excess risk, which, on a population level, would account for a limited proportion of cases.

## References

- Larsson SC, Orsini N, Wolk A: Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*, 97: 1679-1687, 2005.
- Seow A, Yuan JM, Koh WP, Lee HP, Yu MC: Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. *J Natl Cancer Inst*, 98: 135-138, 2006.
- Dellon ES, Shaheen NJ: Diabetes and hepatocellular carcinoma: associations, biologic plausibility, and clinical implications. *Gastroenterology*, 129: 1132-1134, 2005.
- Rousseau MC, Parent M-E, Pollak MN, Siemiatycki J: Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. *Int J Cancer*, 118: 2105-2109, 2006.
- Anderson KE, Anderson E, Mink PJ, Hong CP, Kushi LH, Sellers TA, Lazovich D, Folsom AR: Diabetes and endometrial cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev*, 10: 611-616, 2001.
- La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P:

- A case-control study of diabetes mellitus and cancer risk. *Br J Cancer*, 70: 950-953, 1994.
7. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM: Fasting serum glucose level and cancer risk in Korean men and women. *JAMA*, 293: 194-202, 2005.
  8. Cerhan JR, Bernstein L, Severson RK, Davis S, Colt JS, Blair A, Hartge P: Anthropometrics, physical activity, related medical conditions, and the risk of non-Hodgkin lymphoma. *Cancer Causes Control*, 16: 1203-1214, 2005.
  9. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A: Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. *Eur J Cancer Prev*, 9: 59-64, 2000.
  10. Talamini R, Montella M, Crovatto M, Dal Maso L, Crispo A, Negri E, Spina M, Pinto A, Carbone A, Franceschi S: Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy. *Int J Cancer*, 110: 380-385, 2004.
  11. Franceschi S, Serraino D, Bidoli E, Talamini R, Tirelli U, Carbone A, La Vecchia C: The epidemiology of non-Hodgkin's lymphoma in the North-East of Italy: a hospital based case-control study. *Leukemia Res*, 13: 465-472, 1989.
  12. Tavani A, Negri E, Franceschi S, Talamini R, Serraino D, La Vecchia C: Hair dye use and risk of lymphoid neoplasms and soft tissue sarcomas. *Int J Cancer*, 113:629-631, 2005.
  13. Breslow NE, Day NE: Statistical methods in cancer research. Vol. I, The analysis of case-control studies. International Agency for Cancer Research, Lyon, 1980 (IARC Sci Publ, 32: 5-338).
  14. Swerdlow AJ, Laing SP, Qiao Z, Slater SD, Burden AC, Botha JL, Waugh NR, Morris AD, Gatling W, Gale EA, Paterson CC, Keen H: Cancer incidence and mortality in patients with insulin-treated-diabetes: a UK cohort study. *Br J Cancer*, 92: 2070-2075, 2005.
  15. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ: Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*, 159: 1160-1167, 2004.
  16. Cerhan JR, Wallace RB, Folsom AR, Potter JD, Sellers TA, Zheng W, Lutz CT: Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst*, 89: 314-318, 1997.
  17. Hjalgrim H, Frisch M, Ekblom A, Kyvik KO, Melbye M, Green A: Cancer and diabetes – a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med*, 241: 471-475, 1997.
  18. Weiderpass E, Gridley G, Ekblom A, Nyrén O, Hjalgrim H, Adami HO: Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst*, 89: 816-817, 1997.
  19. Fortuny J, Benavente Y, Bosch R, Garcia-Villanueva M, de Sevilla AF, de Sanjosé S: Type 2 diabetes mellitus, its treatment and risk for lymphoma. *Eur J Cancer*, 41: 1782-1787, 2005.
  20. Natazuka T, Manabe Y, Kono M, Murayama T, Matsui T, Chihara K: Association between non-insulin dependent diabetes mellitus and non-Hodgkin's lymphoma. *BMJ*, 309: 1269, 1994.
  21. La Vecchia C, Decarli A, Franceschi S, Ferraroni M, Pagano R: Prevalence of chronic diseases in alcohol abstainers. *Epidemiology*, 6: 436-438, 1995.
  22. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C: Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. *J Clin Epidemiol*, 54: 902-906, 2001.