

## Tobacco use, body mass index and the risk of malignant lymphomas—A nationwide cohort study in Sweden

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In the search for risk factors involved in the etiology of lymphoproliferative malignancies there is still inconsistent evidence regarding effects of smoking tobacco, and the role of smokeless tobacco is poorly investigated. New evidence indicates that excess body weight increases the risk of NHL and HD. To determine if tobacco use of various forms and high Body Mass Index (BMI) affect the occurrence of these neoplasms, we conducted a prospective cohort study on over 330,000 Swedish construction workers included in the Construction Industry Working Environment and Health program. Information on smoking, snuff dipping, height and weight was gathered by self administered questionnaires together with personal interviews. Cancer incidence was ascertained through the year 2000 by record linkage to the nationwide Swedish Cancer Registry, Migration Registry and Cause of Death Registry. At the end of follow up, 1,309 subjects had been diagnosed with NHL (including chronic lymphocytic leukemia) and 205 with HD respectively. Age adjusted incidence rate ratios were computed using Cox proportional Hazard regression modeling. Smoking cigarette, pipe or cigar was not associated with NHL or HD. There was no evidence indicating a relation between quantity and duration of smoking and NHL or HD risk. No link was found between NHL and usage of smokeless tobacco. Having a BMI of 30 or higher did not convey excess risk of developing NHL or HD compared to normal weight (BMI 18.6–24.9). We conclude that tobacco smoking and high BMI do not entail an increased risk of NHL and HD. Our findings of a relation between the duration of snuff dipping and HD need further investigation.

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**Key words:** non-Hodgkin's lymphoma; Hodgkins disease; smoking-tobacco; moist snuff; body mass index

Over the past decades, there has been controversy regarding the impact of tobacco use on the development of lymphatic malignancies. Although studies conducted within this area are not sparse, results have been largely inconsistent. In part, the conflicting results might reflect the various designs and sizes of the studies, study type and subjects, interview compliance and if information was obtained from study subjects or their next of kin.

Tobacco smoke is known to comprise a number of components, including benzene, lead and polonium<sup>1–3</sup> affecting the immune system by means such as increasing mean leukocyte counts,<sup>4–5</sup> most strongly correlated to neutrophils and CD4+ cells,<sup>5</sup> and altered T-cell function.<sup>6</sup> Moreover smoking has been correlated to lowered levels of immunoglobulins, lysozyme as well as a decrease in the total number of NK-cells in long time smokers.<sup>7</sup>

Whereas several studies have suggested smoking to be associated with NHL<sup>8–11</sup> and HD,<sup>8,12</sup> others have failed to confirm these results.<sup>13–19</sup> More recent studies have indicated this relation to be particularly strong for follicular lymphoma and high grade lymphomas.<sup>9,17,20</sup>

Overweight and obesity has become a globally accelerating health issue related to increased morbidity and mortality around the world.<sup>21</sup> High body mass index (BMI) has, in some reports,<sup>22–24</sup> been suggested as a potential risk factor for lymphoproliferative diseases but results are conflicting.

We here present the results from a large prospective cohort study on Swedish construction workers, with the objective of investigating the role of tobacco use and BMI on development of lymphomas.

## Material and methods

### Subjects

Established in 1968, the Construction Industry's Organization for Working Environment Safety and Health,<sup>25</sup> provided outpatient medical services to construction workers throughout Sweden from 1969 through 1992. The organization was a joint venture launched by construction trade unions and the Swedish Construction Employers' Association. The basic units were stationary and mobile clinics, typically staffed by a few nurses and a physician. The main activity was preventive health check-ups, offered to all blue and white collar employees within the building industry through regular invitations (every second year during the first years, every third year thereafter) as well as visits to or advertisements at virtually all major construction sites. On average each cohort member underwent 2.6 health check-ups. Commencing with visits in 1971, data from these health check-ups were compiled in a computerized central registry.<sup>25</sup> All together, the study cohort constitutes 386,000 persons, visiting the clinics from 1971 to 1992.

### Exposure information

Prior to 1975 a self-administered 200-item questionnaire was used, including information on workplace exposures, tobacco smoke and snuff usage. In each record, measured height and weight were included. The answers obtained from the questionnaires were double-checked by a nurse. In the year 1975 to 1977, no exposure information on smoking was collected. From 1978 and onwards, more detailed information on smoking and snuff dipping was obtained through personal interviews by a nurse. A total of 14,928 individuals were lost to follow up, leaving 371,072 subjects first registered during the period 1971 through 1992 with detailed recorded smoking habits. The quality of the smoking data has been reviewed previously.<sup>26</sup> Because of the lack of smoking data from 1975–1977, only the subjects visiting the clinic during this period were excluded from our analyses. Furthermore, 1,224 individuals with cancer before entry and 5,627 workers with incorrect national identification number were excluded. A total of 335,612 individuals were considered eligible for data analyses. Less than 5% ( $n = 17,691$ ) of the registered persons were women, yielding 36 cases of NHL, 8 cases of HD and 6 cases of CLL respectively. Men and women were analyzed separately. A minor part of data addressing tobacco use has been previously analyzed and published.<sup>16</sup> That study included exposure information from 1971–1975. Thus there is an overlap of 550 cases of NHL, 169 cases of CLL and 136 cases of HD analyzed in both reports.

**Novelty and impact of the paper:** Our study is to our knowledge the first to show an association between HD and long term snuff dipping and one of the largest of its kind. Further, it gives convincing statistical evidence against an excess risk of NHL or HD regarding overweight, obesity or smoking tobacco.

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### Follow-up

The 10-digit national registration number assigned to all Swedish residents is a unique personal identifier, and was used for follow up by linkage to the national Cause of Death Registry, which includes information on date and cause of death, Migration Registry (date of emigration), when applicable, and Cancer Registry. Subsequent checks have revealed incorrect national registration numbers in less than one in 1,000 of the subjects. The Swedish Cancer Registry, initiated in 1958 receives reports of, as well as codes malignant neoplasms according to the International classification of Diseases, Seventh Edition (ICD 7). By law, pathologists and physicians report all incident cases of cancer to the registry, resulting in an overall completeness of 99%.<sup>27</sup>

Each worker of the complete cohort was followed from date of entry until emigration, death, date of cancer diagnosis or December 31st 2000, whichever occurred first, for a total of 6,804,539 person years of observation.

### Statistical analyses

The Cox proportional Hazard regression model was used to estimate crude and age adjusted Incident Rate Ratios (IRR) and corresponding 95% Confidence Intervals (CI), with consideration to the variation of independent variables over time. Likelihood ratio and Chi square tests were applied to revise prior probabilities and compare observed frequencies with expected frequencies. Subjects were stratified into eight age groups of five year intervals. BMI was categorized as follows: less than 18.5 kg/m<sup>2</sup> was underweight, 18.6–24.9 kg/m<sup>2</sup> normal weight, 25–29.9 kg/m<sup>2</sup> overweight and >30.0 obese. One cigarette was assessed to contain one gram, and one cigar on average six grams of tobacco. Smoking and snuff use status and duration were established at date of entry (first visit). According to the WHO classification from 2000<sup>28</sup> chronic lymphocytic leukaemia (CLL) is classified as an NHL-subtype and we therefore chose to analyze NHL and CLL both separately (data not shown) and as a single entity. All analyses were conducted using Intercooled STATA 8.2 (StataCorp. 2003. Stata Statistical Software: Release 8.2 College Station, TX: Stata Corporation).

### Results

The subjects of our cohort had a mean age at entry of 44.65, range (14–82) years. On average, the follow up time for these subjects was 19.1 person years, range (0–31.3) years. Out of the male subjects, 286,596 (85%) were ever tobacco users, 94,244 (28%) stated to ever have used moist snuff and 192, 352 (58%) had at some point used smoking tobacco (cigarettes, pipe or cigar). Moreover, 30% were pure cigarette smokers, 5% pure pipe smokers and 12% used snuff only. Mixed users consisted 23% of the male workers. Among women in the cohort, 48% used cigarette exclusively, 0.13% sole cigar, 0.07% were pure snuff dippers and 0.79% mixed users.

At the end of follow up, the study population had yielded 1,309 histologically verified cases of NHL and 205 persons were diagnosed with HD.

Table I (a) presents IRR of NHL and corresponding 95% CI for male subjects, adjusted for age, BMI and tobacco use respectively. We observed no association between former (IRR = 1.01, 95% CI = 0.85–1.21) or current (IRR = 1.00, 95% CI = 0.87–1.15) usage of smoking tobacco combined, compared with never smokers. Moreover, we found no evidence that risk of NHL is positively associated with being ever cigarette smoker relative to never tobacco user (IRR = 1.00, 95% CI = 0.86–1.16). Nor did ever use of pipe tobacco, cigar smoking or mixed tobacco use have any significant effect on the risk of NHL in relation to those who were never users. Our analyses showed no increased risk of NHL when comparing “ever” with “never” users of moist snuff. We did not observe evidence of an increased risk of NHL in overweight (IRR = 1.05, 95% CI = 0.93–1.18) or obese individuals (IRR = 0.95, 95% CI = 0.75–1.21).

The corresponding results for HD in male workers are also shown. (Table Ia) IRR for HD and all types of smoking tobacco combined as well as cigarette, cigar and pipe analyzed separately were close to the null. Estimates of IRR for an association with ever snuff dipping showed no significant effect (IRR = 0.88, 95% CI = 0.49–1.58). Risk of HD when having a BMI classified as overweight (IRR = 0.81, 95% CI = 0.58–1.12) or obese (IRR = 1.48, 95% CI = 0.86–2.57) did not differ significantly from being of normal weight. Trend tests for IRRs by BMI were performed resulting in a *p* value of 0.65 regarding NHL and 0.75 for HD.

Table I (b) shows IRR of NHL and HD adjusted for age, tobacco use and BMI, together with corresponding 95% CI among women in the cohort. There was no link between any of the types of tobacco investigated and NHL nor HD. Further, no significant association could be found between NHL, HD and divergence in BMI.

As Table II displays, we found no association between NHL and the number of cigarettes smoked per day among male individuals. Accordingly, smoking more than 80 gram pipe tobacco or one cigar daily was not related to a higher risk of NHL (IRR = 0.86, 95% CI = 0.58–1.27). The analyses did not reveal any evidence of increasing NHL incidence with the number of years of exposure to smoking tobacco, nor did time since smoking cessation have any significant influence on the risk of NHL. Similarly, no association could be observed for dose and duration of the different types of smoking tobacco and HD. (Table 2) Comparisons of never users of oral snuff with exposures for up to 30 years and >30 years respectively pointed to results close to the null for NHL. We observed a statistically significant risk for HD (IRR = 3.78, 95% CI = 1.23–11.60) in snuff dippers with exposures for more than 30 years.

### Discussion

In this cohort study, we could not find any evidence of an etiologic role of exposure to tobacco smoke and development of NHL in male and female Swedish construction workers. Furthermore NHL was not related to the frequency, duration and recency of smoking in men. Similarly, no relationship was observed for HD. No excess risk neither for NHL nor HD was correlated with BMI classified as overweight or obese.

Our study provides additional strength to results from several previous publications addressing tobacco smoking and NHL, but it also conflicts with some reports on women. For instance, a case-control study conducted in France did not observe an increased risk of NHL in men, but the risk was elevated for female current smokers compared to women who were never smokers.<sup>29</sup> Combined analyses of three population-based case-control studies observed no association between NHL and tobacco use overall or cigarette smoking, however when investigating men and women separately a suggestive relationship could be seen in women, but not in men.<sup>19</sup> In line with our results, a study of a cohort of Iowa women did not show any excess risk of NHL for neither current nor former smokers.<sup>18</sup> In contrast, one population-based case-control study<sup>10</sup> presented a significantly higher risk of NHL associated with pipe and cigar smoking, but not for cigarette smoking, nor any dose-response relationship for number of cigarettes smoked. A large multicenter study provided support for a slightly increased risk of NHL. However a positive link in ever smoking women was perceived for follicular lymphoma.<sup>17</sup> Other publications<sup>18,20,29–30</sup> have contributed results of close resemblance. In a pooled analysis of nine case-control studies<sup>31</sup> smoking was associated with a slightly increased risk of NHL overall. When stratified by lymphoma subtype, a greater risk of follicular lymphoma was observed for current smokers, increasing even more for subjects smoking 36 pack years or more (OR = 1.45, 95% CI = 1.15–1.82). Some of the reports supporting the hypothesis of smoking tobacco as a possible risk factor for NHL development were lim-

**TABLE 1a** – ESTIMATED INCIDENCE RATE RATIOS (IRR) TOGETHER WITH CORRESPONDING 95% CONFIDENCE INTERVALS (95% CI) FOR NON-HODGKIN'S LYMPHOMA (INCLUDING CHRONIC LYMPHOCYTIC LEUKAEMIA) AND HODGKIN'S DISEASE (HD)<sup>1,2</sup> AMONG MEN

Tobacco use and BMI Type/level	Number of individuals	Number of person years, accumulated (in millions)	Number of cases (NHL including CLL)	IRR (95% CI) Age adjusted (NHL including CLL)	Number of cases Hodgkin's disease	IRR (95% CI) Age adjusted Hodgkin's disease
Never tobacco users (reference)	102,443	1.98	337	1.0	49	1.0
Smoking tobacco						
Ex	33,721	0.80	209	1.01 (0.85–1.21)	22	1.18 (0.70–1.98)
Current	107,552	2.29	455	1.00 (0.87–1.15)	73	1.32 (0.91–1.90)
Cigarette smoker						
Ever	99,530	2.04	357	1.00 (0.86–1.16)	66	1.32 (0.91–1.91)
Cigar smoker						
Ever	1,972	0.05	13	0.82 (0.46–1.45)	3	2.48 (0.77–8.02)
Pipe smoker						
Ever	17,097	0.40	146	1.08 (0.88–1.31)	11	1.07 (0.55–2.09)
Snuff dipper						
Ever	40,981	1.81	66	0.77 (0.59–1.01)	15	0.88 (0.49–1.58)
Mixed users						
Ever	76,689	0.08	348	0.98 (0.84–1.14)	53	1.24 (0.83–1.83)
BMI						
<18.5	4,779	0.09	5	0.57 (0.23–1.36)	1	0.38 (0.05–2.73)
18.6–24.9	210,529	4.24	651	1.0	126	1.0
25–29.9	102,033	2.11	528	1.05 (0.93–1.18)	54	0.81 (0.58–1.12)
≥30	15,404	0.31	78	0.95 (0.75–1.21)	15	1.48 (0.86–2.57)

<sup>1</sup>Adjusted for tobacco use (BMI data) and BMI (smoking data). –<sup>2</sup>All Likelihood Ratio tests were nonsignificant.

**TABLE 1b** – ESTIMATED INCIDENCE RATE RATIOS (IRR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (95% CI) FOR NON-HODGKIN'S LYMPHOMA (INCLUDING CHRONIC LYMPHOCYTIC LEUKAEMIA) AND HODGKIN'S DISEASE (HD)<sup>1,2</sup> AMONG WOMEN

Tobacco use and BMI Type/level	Number of individuals	Number of person years, accumulated (in thousands)	Number of cases (NHL including CLL)	IRR (95% CI) Age adjusted (NHL including CLL)	Number of cases Hodgkin's disease	IRR (95% CI) Age adjusted Hodgkin's disease
Never tobacco users (reference)	778	14.19	27	1.0	5	1.0
Smoking tobacco						
Ex	124	2.20	2	0.55 (0.13–2.32)	1	1.05 (0.12–8.99)
Current	614	10.85	13	0.75 (0.38–1.47)	2	0.38 (0.72–2.00)
Cigarette smoker						
Ever	724	12.80	14	0.68 (0.35–1.31)	3	0.50 (0.12–2.11)
Cigar smoker						
Ever	2	0.02	0	$8.13 \times 10^{-15}$ (~0)	0	$2.59 \times 10^{-07}$ (~0)
Snuff dipper						
Ever	1	0.016	0	$1.36 \times 10^{-15}$ (~0)	0	$8.72 \times 10^{-16}$ (~0)
Mixed users						
Ever	12	0.23	1	2.69 (0.36–19.8)	0	$1.53 \times 10^{-16}$ (~0)
BMI						
<18.5	42	0.76	0	$5.81 \times 10^{-15}$ (~0)	1	3.05 (0.35–26.58)
18.6–24.9	909	16.60	23	1.0	5	1.0
25–29.9	389	6.95	12	1.06 (0.52–2.18)	2	2.13 (0.37–12.26)
≥30	154	2.62	7	1.58 (0.66–3.81)	0	1.15e-15 (0~)

<sup>1</sup>Adjusted for tobacco use (BMI data) and BMI (smoking data). –<sup>2</sup>All Likelihood Ratio tests were nonsignificant.

ited by the fact that they are based on rather few cases and the use of next of kin interviews.

Although HD and NHL are classified as two distinguished disease entities, they share some etiological and clinical patterns.<sup>32</sup> It has therefore been a topicality to give HD some notice in the issue of tobacco use and cancer risk. Our data give some indication that tobacco smoke might increase the risk of developing HD. However, the results are based on rather small number of cases and are not statistically significant. Inconsistent with our findings, three previous case-control studies<sup>13–14,17</sup> and one cohort study,<sup>16</sup> a population based case-control study<sup>12</sup> observed an elevated risk of HD (OR = 1.8).

As of today, the number of studies addressing smokeless tobacco use and lymphoid malignancies are extremely sparse. We did not reveal any correlation regarding snuff dipping and NHL. These findings are consistent with an earlier report by Adami *et al.*<sup>16</sup>

According to our analyses, snuff dipping does not entail any excess risk of HD. However, the interesting finding of an almost four-fold significantly elevated risk in male subjects being snuff dip-pers for more than 30 years was based solely on four cases, thus limiting the statistical power of that result. Usage of oral smokeless tobacco is gaining popularity throughout the western world espe-

cially with adolescents.<sup>33–34</sup> Tobacco in the form of Swedish moist oral snuff (snus) is today highly prevalent in the Swedish male population, and has been increasing during the past decades from 22% to 30%.<sup>35</sup> The proposal that usage of smokeless tobacco might lead to smoking behavior<sup>36–37</sup> has been of major concern, however some results suggest snuff dipping to be more closely related to cessation of smoking (*i.e.* ex-smokers become snuff dippers).<sup>35,38</sup>

We detected no positive association regarding NHL and being overweight or obese. Impaired immune function, effects on cell proliferation and nutritional factors are some of the postulated putative biological mechanisms, but the ethological role of these factors have not been fully verified. Two case-control studies<sup>22–23</sup> have reported a relationship between overweight, obesity and NHL, one of which in particular found a link with diffuse large cell and follicular lymphoma.<sup>22</sup> In contrast, results from a Scandinavian case-control study,<sup>39</sup> showed no association with risk of overall NHL, or with any NHL subtype, supporting the results of a cohort study by Cerhan *et al.*<sup>40</sup> Another cohort study found a positive association to NHL in women, but not in men.<sup>24</sup>

Our analyses showed that individuals classified as overweight or obese had no greater risk of HD compared to those of normal weight. A cohort study on hospitalized patients<sup>24</sup> has reported an



**TABLE II** – ESTIMATED AGE- AND BODY MASS INDEX- ADJUSTED INCIDENCE RATIOS (IRR), TOGETHER WITH CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR NON-HODGKIN'S LYMPHOMA (INCLUDING CHRONIC LYMPHOCYTIC LEUKAEMIA) AND HODGKIN'S DISEASE (HD)<sup>1,2</sup> AMONG MEN

	Person years (millions)	Number of cases (NHL including CLL)	IRR (95%CI) (NHL including CLL) Age and BMI adjusted	Number of cases Hodgkin's disease	IRR (95%CI) Age and BMI adjusted Hodgkins disease
Never tobacco users (reference)	1.98	337	1.0	49	1.0
Dose cigarettes					
<10	1.36	276	1.02 (0.87–1.20)	31	0.95 (0.60–1.49)
11–20	0.96	179	1.04 (0.86–1.25)	40	1.73 (1.14–2.63)
>20	0.15	22	0.72 (0.47–1.11)	5	1.34 (0.53–3.38)
Dose pipe g/w					
<80	0.84	262	1.06 (0.90–1.26)	21	0.93 (0.54–1.61)
>80	0.03	13	1.38 (0.79–2.4)	2	2.34 (0.56–9.76)
Dose cigars/day					
≥1	0.10	28	0.86 (0.58–1.27)	3	1.16 (0.35–3.82)
Years of smoking					
≤15	1.57	184	0.97 (0.80–1.16)	51	1.39 (0.93–2.07)
16–25	0.77	191	1.09 (0.91–1.31)	21	1.08 (0.64–1.83)
26–max	0.67	279	0.97 (0.82–1.16)	22	1.22 (0.68–2.20)
Time since cessation of smoking (years)					
Smoke stop ≤10	0.51	123	1.06 (0.86–1.30)	16	1.29 (0.73–2.29)
Smoke stop >10	0.22	81	0.94 (0.73–1.21)	6	1.01 (0.41–2.49)
Years snuffer					
1–30	0.64	49	0.81 (0.60–1.11)	11	0.70 (0.36–1.37)
>30	0.04	16	0.69 (0.41–1.15)	4	3.78 (1.23–11.60)

<sup>1</sup>Adjusted for tobacco use (BMI data) and BMI (smoking data). –<sup>2</sup>All Likelihood ratio tests were nonsignificant.

increased risk of HD in males, while Chang *et al.*<sup>39</sup> failed to confirm any association. Interestingly, a large scale cohort study<sup>41</sup> investigating the impact of BMI on the risk of total cancer incidence and mortality found a U-shaped association between BMI and cancer occurrence. Also, in this study, the impact of low BMI on cancer incidence was stronger among current smokers than never smokers.

The major strengths of this study are the large scale, the thoroughness in obtaining data together with the extensive follow up through record linkage by the unique and 100% accurate national identification numbers. In our study cohort, 28% of the men were ever snuff dippers compared to 20% of the Swedish male population stating to be daily users of oral moist snuff.<sup>38</sup> Since there is no individual information of snuff use among the general population in Sweden, the very detailed and prospectively collected exposure information in our cohort gives a remarkable opportunity to shed further light on the disputed carcinogenic effects of snuff dipping. These extended analyses, including an additional nine years of follow up and evaluation of BMI, resulting in new incident cancer cases and a greater number of total person years, provide the statistical power to detect even small dissimilarities or trends in risk assessment. In our analysis, we used only information obtained at the first visit, to avoid potential bias if failure to show up in the following check-up were to be related to smoking status and outcome of cancer. Moreover, not all workers had more than one check up, which would obstruct statistical analyses of

multiple visits. Risk factors of lymphoma, such as immunosuppressive status, immunosuppressive therapy, autoimmune diseases and a history of Epstein–Barr infection, were not controlled for in the analysis and might have exerted a confounding effect. However, in order to explain our results, such confounding should have acted towards the null (*i.e.*, smokers being less likely to be exposed to the risk factors than were the nonsmokers) and should have been as strong as the risk factors themselves. We consider unlikely that both conditions were present in our data. Since the cancer registry does not provide information about histological subtype according to accepted classification systems,<sup>42</sup> our analyses did not investigate the diverse NHL subtypes separately.

In conclusion, our cohort study does not contribute any evidence of an effect of tobacco smoking in the occurrence of HD, or non-Hodgkin lymphomas combined. An association between overweight, obesity and lymphoid malignancies is not unlikely and needs further investigation. Finally, our novel finding of an increased risk of HD with long term snuff dipping in males needs to be verified by additional studies, but is most certainly a topic of interest, considering the rapidly increasing number of users of oral moist snuff.

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