

Table 2.10. Case-control studies of exposure to benzene and non-Hodgkin lymphoma

| Reference, study location and period | Characteristics of cases | Characteristics of controls | Exposure assessment | Organ site (ICD code) | Exposure categories | No. of exposed cases | Odds ratio (95% CI)* | Adjustment for potential confounders | Comments |
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| Franceschi <i>et al.</i> (1989) Italy | 232 NHL cases below the age of 80 with histologically confirmed NHL, diagnosed within two yr before the interview, at a cancer centre and all general hospitals in the area under surveillance. 208 interviewed. | 401 patients below age 80 admitted as inpatients for a wide spectrum of acute Conditions (excluding haematological) to the same hospitals. | Patients were asked to indicate, in addition to an occupational history, whether they had ever been exposed to 20 potentially cancerogenic chemical or physical agents, including benzene. | NHL 200, 202 | Benzene and solvents | 15 | 1.1 (0.6–2.3) | Age and sex. | |
| Scherr <i>et al.</i> (1992) USA | 379 cases of non-Hodgkin lymphoma newly diagnosed January 1, 1980, through May 31, 1982, among residents of the Boston Standard Metropolitan Statistical Area treated in any of nine participating hospitals. 303 (80%) participated. | For each case, a control of the same sex and age (within 1 yr), town, and precinct of residence was selected from town residency lists. Of 423 potential controls, 303 were interviewed. | Home interviews. Each subject was asked about his or her current or most recent job, the job held 15 yr ago, major occupation, second most major occupation, and up to two occupations in which he or she was exposed to any of several specific agents. | NHL 200, 202 | Exposure to benzene | | 1.2 (0.5–2.6) | | Numbers of cases exposed and referent not specified. Prevalence of benzene exposure in the population 4%. |

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| Gérin <i>et al.</i> (1998) Canada | Between 1979 and 1986, 4576 eligible men cases of 19 cancer sites (215 NHL) ascertained from all the large hospitals in Montreal 3730 (82%) agreed to participate; 82% of responses were obtained from the subject and the rest from a next-of-kin. | Men selected from electoral lists of the Montreal area, age-stratified to the age distribution of cancer patients. Of 740 selected, 533 (71%) were interviewed. For each case series, a pooled control group was formed by the addition of an additional 533 cancer controls selected randomly from eligible cancer cases to the 533 population controls. | Interviewers obtain a detailed description of each job the subject had in his working lifetime; chemists noted their confidence that the exposure occurred (possible, probable, definite), the frequency of exposure (less than 5% of the time, 5–30%, more than 30%), and the concentration of the agent in the environment (low, medium, high). These were then combined into exposure categories. | NHL 200, 202 | Benzene Unexposed Low Medium/high | 187 19 9 | 1.0 0.6 (0.4–1.0) 0.8 (0.4–1.6) | Age, family income, ethnic group, cigarette smoking, and respondent status. | |

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| Persson & Fredrikson (1999) Sweden | 106 and 93 cases of NHL age 20–80, born in Sweden, included in two earlier studies identified from a Department of Oncology and a regional cancer registry respectively, response rates 96% and 90%. | 479 controls randomly selected from the population registers of the same geographic areas as the cases.. | Mailed questionnaire including information about occupational exposures. | NHL 200, 202 | Occupational exposure to benzene | 3 | 0.8 (0.1–3.8) | Age, sex | Referent not specified |
| Mao <i>et al.</i> (2000) Canada | 1469 of 1955 newly diagnosed, histologically confirmed NHL cases (764 men and 705 women) between 1994 and 1997 in eight Canadian provinces ascertained through cancer registries. | 5073 population controls, of 8 104 selected in 5 provinces from the Provincial Health Plan database, in one from the Ministry of Finance property assessment database and in two by random digit dialling. | Mailed questionnaires were used to obtain data on exposure at work (or home) to any of 17 chemicals for at least one yr including benzene. | NHL 200, 202 | Occupational exposure to benzene: Men None Any Women None Any | 330 36 555 5 | 1.0 1.2 (0.8–1.9) 1.0 0.6 (0.2–1.8) | 10-yr age groups, province, body mass index (< 20, 20–27. and > 27), and consumption of milk for both sexes, and education for women. | |

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| Fabbro-Peray <i>et al.</i> (2001) France | 627 incident cases of histologically confirmed malignant lymphomas diagnosed between 1 January 1992 and 31 December 1995 were identified from hospitals serving the region. All cases were French, living in Languedoc-Roussillon at the time of diagnosis, 18 yr or older, man or woman. and had negative serology for human immunodeficiency virus. Response rate 82%. 445 cases were classified as NHL, 72 HD (exclude | Two controls per case were randomly selected from electoral lists, stratified by county and size of municipalities, but unmatched. All controls were French, living in Languedoc-Roussillon, at least 18 yr old, and man or woman. Of 1 249 controls identified, 1 025 (52%) were interviewed | Personal interviews initially, then by telephone. The questionnaire requested information on chemical exposures, including benzene. | NHL 200, 202 | Self-reported exposure to benzene: No Yes Cumulative number of d exposed Never erratic ≤ 810 d > 810 d | 423 22 433 4 8 | 1.0 2.0 (1.1–3.9) 1.0 1.7 (0.4–6.8) 5.7 (1.4–23.2) | Age, sex, urban setting, and education level. | |

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| Blair <i>et al.</i> (2003) USA | All cases of non-Hodgkins lymphoma in the cancer registry of Iowa between March 1981 and October 1983, and from a surveillance network of hospitals in Minnesota from October 1980 to September 1992. 622 of 715 man cases age 30 or more participated. | Population-based controls frequency-matched to cases by 5-yr age group, vital status at the time of the interview, and state of residence. Controls for cases less than 65 yr of age were selected by random digit dialing, controls for cases 65 yr or older were selected from listings provided by the Health Care Financing Administration, and controls for deceased cases were selected from state death certificate files. Response rates 77–79% | Personal interviews of 438 cases and 184 next of kin of cases and 1 245 controls (425 with next of kin). Detailed occupational history, with job exposure matrix for specific exposures. | NHL 200, 202 | Benzene Low | 141 | 1.1 (0.8–1.4) | Age, state, smoking, family history of malignant lymphoproliferative diseases, agricultural exposure to pesticides, use of hair dyes, direct or surrogate respondent. | Referent for OR not specified. |
| | | | | | Benzene High | 12 | 1.5 (0.7–3.1) | | |
| | | | | | Follicular lymphoma Benzene Low | 53 | 1.3 (0.9–1.9) | | |
| | | | | | Follicular lymphoma Benzene High | 5 | 1.9 (0.7–5.3) | | |
| | | | | | Diffuse lymphoma Benzene Low | 45 | 1.2 (0.8–1.8) | | |
| | | | | | Diffuse lymphoma Benzene High | 4 | 1.8 (0.6–5.4) | | |
| | | | | | Other lymphoma Benzene Low | 43 | 0.8 (0.5–1.2) | | |
| | | | | | Other lymphoma Benzene High | 3 | 0.9 (0.3–3.1) | | |

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| Dryver <i>et al.</i> (2004) Sweden | 1414 consecutive cases of pathology-confirmed NHL patients over 18 yr of age at diagnosis were identified in the south Swedish regional tumour registry between 1990 and 1998, 1249 were contacted and 925 participated. After exclusions 859 remained in the analysis. | 2820 age, sex and parish-matched individuals were concurrently identified using the Swedish unique person identification number and sent the same questionnaires., 1943 (69%) returned completed questionnaires. After exclusions 1 310 remained in the analysis. | Self-administered questionnaire including information regarding occupations and exposures to gasoline and solvents. Using a job-exposure matrix, additional information on exposures (including to benzene) was derived. | NHL 200, 202 | Self-reported exposure to: Gasoline exposure ≥ 5 yr versus < 5 yr | 78 45 | 1.5 (1.0–2.0) 1.9 (1.2–3.1) | | Referent not stated No analysis of specific exposure to benzene. |

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| Fritschi <i>et al.</i> (2005) Australia | 1230 cases age 20–74 notified to the Central Cancer Registry of New South Wales (NSW) with incident NHL first diagnosed between 1 January 2000 and 31 August 2001 and resident in NSW or the Australian Capital Territory (ACT). Of potentially eligible cases 144 were deceased; 842 were approached for interview, 717 responded. | 1687 potential controls were randomly selected from the NSW and ACT Electoral Rolls to approximately match the expected distributions of cases with respect to age, sex and region of residence. After exclusions 1 136 who could be contacted were approached, 694 agreed. | Self-administered questionnaire mailed to each subject including a detailed lifetime occupational history. 28 jobs and 16 industries were identified, an occupational hygienist, who was blind to case status of the subject, allocated modules to jobs considered likely to have significant exposures. The modules were completed by a computer assisted telephone interview, with exposures allocated by an occupational hygienist. | NHL 200, 202 | Benzene Unexposed | 626 | 1.0 | Age, sex, state and ethnic origin. | |
| | | | | | Exposed | 68 | 1.1 (0.8–1.6) | | |
| | | | | | Non-substantial | 66 | 1.2 (0.8–1.7) | | |
| | | | | | Substantial | 2 | 0.3 (0.0–1.5) | | |
| | | | | | | 1.0 | | | |
| | | | | | p for trend | | | | |

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| Kato <i>et al.</i> (2005) USA | 722 women newly diagnosed with NHL between 1 October 1995 and 30 September 1998 identified through a rapid case ascertainment system coordinated with the NYS Cancer Registry. Participation rate after informed consent 56% (376 cases) | Population-based controls frequency-matched to the projected age distribution of the cases and selected from an age-stratified random sample from the NYS Department of Motor Vehicles driver’s license files for those under age 65 (248, 30% participation), and from the Health Care Financing Administration beneficiary files for those age 65 yr or older (215, 67% participation). | Telephone interviews included occupational exposure to benzene. | NHL 200, 202 | No solvent exposure Benzene exposed | 285 7 | 1.0 1.5 (0.4–5.7) | Age at index date, family history of hematologic cancer, college education, surrogate status, yr of interview, body mass index 10 yr before interview, average frequency of use of pain-relieving drugs, total number of episodes of systemic antibiotic use, total number of uses of household pesticide products and duration of work involving pesticide exposures. | Next-of-kin were interviewed for 20.5% of the cases and 3.2% of the controls. |

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| Miligi <i>et al.</i> (2006) Italy | 1428 newly diagnosed cases of malignant lymphoma (of 1 719 ascertained) in men and women age 20 to 74 yr in 1991–1993 were identified in 8 areas in Italy, identified through periodic surveys of hospital and pathology departments as well as in some specialized haematology centres | 1530 controls (of 2086 identified) formed by a random sample of the general population in the areas under study stratified by sex and 5-yr age groups. | In-person interviews primarily at the interviewee’s home. The questionnaire included a detailed occupational history (including collection of detailed data on specific jobs) and extraoccupational exposure to solvents. Industrial hygiene experts assessed a level of probability and intensity of exposure to groups or classes of solvents and certain individual substances. | NHL 200, 202, 204.1 | Benzene: Unexposed (to any solvent) Very low/low Medium/high p for trend Duration of exposure for medium/high: ≤ 15 yr > 15 yr p for trend | 820 49 58 39 14 | 1.0 0.6 (0.4–0.9) 1.6 (1.0–2.4) 0.44 1.2 (0.7–2.0) 2.9 (0.9–9.0) 0.09 | Age, sex, education, and area. | Cases of CLL were included with NHL. For the 20 cases assessed as diffuse follicular NHL the OR for medium/high level benzene exposure was 2.4 (95% CI: 1.3–4.5). |

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| Seidler <i>et al.</i> (2007) Germany | 710 patients with lymphoma (participation rate 87%), identified in six participating areas. 115 had Hodgkins lymphoma, 554 B NHL and 35 T NHL. | 710 sex, region and age-matched (\pm 1 yr of birth) population control drawn from the population registration office (44% participation rate). | Personal interview including job title, industry, and specific job tasks. A trained industrial physician subsequently assessed the intensity and frequency of exposure to specific chlorinated and aromatic hydrocarbons (including benzene). | NHL 200, 202 | B-NHL | | | Age, sex, region, smoking and alcohol consumption | German component of the Epilymph study (See Cocco <i>et al.</i> , 2010) |
| | | | | | Benzene ppm/yr | | | | |
| | | | | | 0 | 459 | 1.0 | | |
| | | | | | 0- \leq 8.6 | 41 | 0.9 (0.6–1.4) | | |
| | | | | | 8.6- \leq 130 | 39 | 1.0 (0.6–1.5) | | |
| | | | | | > 130 | 11 | 1.0 (0.4–2.3) | | |
| | | | | | T-NHL | | | | |
| Benzene ppm/yr | | | | | | | | | |
| 0 | 26 | 1.0 | | | | | | | |
| 0- \leq 8.6 | 3 | 1.2 (0.3–4.4) | | | | | | | |
| 8.6- \leq 130 | 3 | 1.7 (0.5–6.1) | | | | | | | |
| > 130 | 1 | 1.7 (0.2–15.0) | | | | | | | |

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| Wang <i>et al.</i> (2009) USA | 832 cases of Non-Hodgkins lymphoma in women age 21–84 diagnosed in Connecticut, 1996–2000, 601 (72%) interviewed. | Women with Connecticut addresses frequency matched by age to cases and recruited by random digit dialing from among women aged less than 65 yr (69% participation) or by random selection from centres for Medicare and Medicaid Service files for women aged 65 yr or older (47% participation). 717 controls interviewed. | In person interviews collected lifetime occupational histories on jobs held for at least a yr. Exposure to organic solvents and formaldehyde associated with each job assessed by linking the coded occupational data with a job-exposure matrix by industrial hygienists. | NHL 200, 202 | Diffuse Large B-Cell Lymphoma: Benzene exposure | | | Age, family history of haematopoietic cancers, alcohol consumption, and race. | For all NHL (which included CLL – see Table 2.8) the OR for medium to high intensity of benzene exposure was 1.5 (95% CI: 0.9–2.4), based on 34 cases. |
| | | | | | Never | 149 | 1.0 | | |
| | | | | | Ever | 40 | 1.2 (0.8–1.8) | | |
| | | | | | Average intensity: | | | | |
| | | | | | Low | 25 | 1.0 (0.6–1.7) | | |
| | | | | | Medium-high | 15 | 1.8 (0.9–3.4) | | |
| | | | | | p for trend | | 0.04 | | |
| | | | | | Follicular Lymphoma: Benzene exposure | | | | |
| | | | | | Never | 107 | 1.0 | | |
| | | | | | Ever | 29 | 1.3 (0.8–2.0) | | |
| Average intensity: | | | | | | | | | |
| Low | 18 | 1.1 (0.6–1.8) | | | | | | | |
| Medium-high | 11 | 1.8 (0.9–3.7) | | | | | | | |
| p for trend | | 0.18 | | | | | | | |

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| Cocco <i>et al.</i> (2010) (Epiymph study – 6 European countries) | All consecutive adult patients first diagnosed with lymphoma 1998–2004 resident in the referral area of the participating centres. 2 348 cases provided informed consent, overall participation 88% | Controls from Germany and Italy were selected by random sampling from the general population, and matched to cases by sex, 5-yr age group, and residence area. The other 4 centres used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases and immuno-deficient diseases. 2 462 controls provided informed consent, participation rate 52% for population controls and 81% for hospital. | Trained interviewers conducted in-person interviews with cases and controls, using the same structured questionnaire translated to the local language. Questions included information on a list of all fulltime jobs held for 1 yr or longer. Industrial hygienists in each participating centre coded the occupations and industries. | NHL 200, 202 | B-cell lymphoma: | | | Age, sex, education and centre. | Only subjects whose exposure was assessed with high degree of confidence were included in the analysis. | |
| | | | | | Benzene | Unexposed | 1061 | | | 1.0 |
| | | | | | | All exposed | 118 | | | 1.1 (0.8–1.4) |
| | | | | | | Low | 34 | | | 0.9 |
| | | | | | | Medium | 29 | | | 1.1 |
| | | | | | | High | 55 | | | 1.3 |
| | | | | | | p for trend | | | | 0.34 |
| | | | | | DLBCL: | | | | | |
| | | | | | Benzene | Unexposed | 325 | | | 1.0 |
| | | | | | | All exposed | 28 | | | 0.9 (0.6–1.4) |
| | | | | | | Low | 9 | | | 0.8 |
| | | | | | | Medium | 8 | | | 1.0 |
| | | | | | | High | 11 | | | 0.9 |
| | | | | | | p for trend | | | | –0.67 |
| Follicular lymphoma: | | | | | | | | | | |
| Benzene | Unexposed | 140 | 1.0 | | | | | | | |
| | All exposed | 17 | 1.6 (0.9–2.9) | | | | | | | |
| | Low | 5 | 1.3 | | | | | | | |
| | Medium | 8 | 3.0 | | | | | | | |
| | High | 4 | 1.0 | | | | | | | |
| | p for trend | | 0.10 | | | | | | | |

NHL, non-Hodgkin lymphoma; ppm, parts per million; yr, year or years