

MADAR TALIBOV

# Occupational Exposures and Risk of Adult Leukemia

A population based study  
in the Nordic countries



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**ACADEMIC DISSERTATION**

To be presented, with the permission of  
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*Supervised by*

Professor Eero Pukkala  
University of Tampere  
Finland  
Docent Susanna Lehtinen-Jacks  
University of Tampere  
Finland

*Reviewed by*

Associate Professor Shelley Harris  
University of Toronto  
Canada  
Docent Tea Lallukka  
University of Helsinki  
Finland

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## Abstract

Leukemia is a cancer of blood, which originates from malignant transformation of hematopoietic progenitor cells. Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) are four major types of leukemia. A number of genetic, life-style, therapeutic and environmental factors have been linked to an increased risk of leukemia. However, the evidence to date is inconsistent on majority of these factors. The aim of this study was to evaluate associations between various occupational exposures and adult leukemia.

This study was based on the Nordic Occupational Cancer Studies (NOCCA). The NOCCA study includes 14.9 million persons from Denmark, Finland, Iceland, Norway and Sweden. These persons were 30-64 years old when they participated in one or more computerized censuses, which took place in 1990 or before in the Nordic countries. Census records provided information on age, gender, marital status, education, occupation and industry. These records were linked to national cancer registries for information on leukemia. The linkage was done by using unique personal identity codes.

In Study I, all cases of AML ( $n=18,811$ ), CLL ( $n=20,462$ ), and all other non-specified leukemia (“Other leukemia”) ( $n=15,570$ ) diagnosed between 1961 and 2005 in the Nordic countries were grouped into 53 occupational categories and one group of economically inactive persons. Study II included 15,332 incident cases of AML and 76,660 controls matched for year of birth, sex and country. Study III consisted of 13,435 AML cases and 67,175 matched controls. Finally, Study IV included 5,022 airline workers (1,535 cockpit crew and 3,487 cabin crew members) from Finland.

The exposure estimates for solvents in Study II were obtained by using NOCCA job-exposure matrix (NOCCA-JEM). The estimates for extremely low-frequency magnetic fields (ELF-MF) and electrical shocks in Study III were obtained by using ELF-MF and electrical shock job exposure matrices (JEM). In Study IV, NOCCA-JEM based cosmic radiation exposure estimates were compared against individual dose estimates from Radiation and Nuclear Safety Authority, Finland (STUK). Individual doses were estimated by using the software package CARI-6 and European Program Package for the Calculation of Aviation Route Doses (EPCARD) computer programs.

In Study I, the relative incidences of AML, CLL and “Other leukemia” were described by standardized incidence ratios (SIR). In Studies II and III, hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated by using conditional logistic regression models. In Study IV, intraclass correlation coefficient (ICC) and Bland-Altman plot were used for continuous exposures, and proportion of agreement (PA) and kappa statistics (both Cohen’s kappa and weighted kappa) were used for categorical exposures as agreement measures.

Study I showed that leukemia incidence in some occupational groups was slightly elevated compared to the incidence in the overall study population. AML risk was increased among drivers (SIR=1.16, 95% CI 1.07-1.26) and food workers (SIR=1.13, 95% CI 1.01-1.27). CLL risk was elevated among farmers (SIR=1.09, 95% CI 1.04-1.14) and clerical workers (SIR=1.07, 95% CI 1.01-1.14). Risk of “Other leukemia” was increased among seamen, other health workers, chemical process workers, and sales agents. In some occupational groups significantly reduced risk of leukemia was observed. For example, forestry workers had reduced risk of AML, seamen had reduced risk of both AML and CLL, and fishermen had reduced risk of other non-specified leukemia. No evidence of increased AML risk was observed for occupational exposure to solvents, ELF-MF, electrical shock and working in electric/electronic occupation in Studies II and III. Study IV demonstrated large disagreement between cosmic radiation estimates from NOCCA-JEM and STUK. The Bland-Altman plot showed that NOCCA-JEM underestimated true cosmic radiation exposure on average by about 9 mSv, and NOCCA-JEM estimates could be about 28 millisievert (mSv) below and 10 mSv above true dose estimates. A low correlation was observed (intraclass correlation (ICC) 0.37, 95% CI 0.01-0.61) for continuous measures of radiation exposure, while the agreement between categorical exposure estimates was moderate (Cohen’s kappa statistic 0.46 and weighted kappa 0.43).

In conclusion, the observed small leukemia excess in some occupational categories may be associated with exposure to specific occupational chemical and non-chemical agents. However, our studies on solvents, ELF-MF, and electrical shocks did not demonstrate any associations with adult leukemia. Study IV showed substantial disagreement between NOCCA-JEM based and individual cosmic radiation exposure estimates among airline workers suggesting that NOCCA-JEM can lead to exposure misclassification of cosmic radiation exposure in NOCCA studies.

# Tiivistelmä

Leukemia (kreik. *valkoverisyyys*) on verisyöpä, veren valkosolujen syöpä. Sen neljä yleisintä muotoa ovat akuutti myeloominen leukemia (engl. lyhenne AML), akuutti lymfaattinen leukemia (ALL), krooninen myeloominen leukemia (CML) ja krooninen lymfaattinen leukemia (CLL). Vaikka monilla geneettisillä ja elintapoihin ja –ympäristöön liittyvillä tekijöillä on arvioitu olevan yhteyttä leukemian riskiin, useimmissa tapauksissa näyttö on epäyhtenäistä. Tutkimukseni tavoitteena on arvioida eräiden ammattialtistusten yhteyttä aikuisten leukemiariskiin.

Tutkimus pohjautuu pohjoismaisen ammattisyöpätutkimussarjan (Nordic Occupational Cancer Studies, NOCCA) yhteensä 14,9 miljoonan islantilaisen, norjalaisen, ruotsalaisen, suomalaisen ja tanskalaisten henkilön aineistoon. Näiden henkilöiden ammattitiedot 30-64 vuoden iässä löytyvät digitalisoidusta väestölaskentatiedostoista vuosilta 1960-1990 (vaihtelevasti maasta riippuen). Tutkimushenkilöille haettiin henkilötunnusen avulla syöpätiedot vuoteen 2003-2005 asti kansallisista syöpärekistereistä.

Tutkimuksen I aineistona olivat kaikki AML-tapaukset (n=18 811), CLL-tapaukset (n=20 462), ja kolmantena ryhmänä kaikki loput leukemiatapaukset (n=15 570), jotka oli todettu Pohjoismaissa ensimmäisen käytettäväissä olevan väestölaskentatiedon jälkeen ja viimeistään vuonna 2005. Syövät luokiteltiin 53 ammattiluokkaan ja erilliseen ammatissa toimimattomien ryhmään. Tutkimukseen II ei voitu ottaa mukaan Tanskan aineistoa, jolloin siihen jäi 15 332 AML-tapausta. Heille haettiin yhteensä 76 660 syntymävuosi-, sukupuoli- ja maakaltaistettua verrokkia. Tutkimuksessa III oli 13 435 AML-tapausta ja 67 175 verrokkia. Tutkimus IV rajautui suomalaiseen lentohenkilöstöön, joista 1 535 oli lentäjiä ja 3 487 matkustamohenkilökuntaa.

Tutkimuksessa II käytetyt liuotinaltistusarviot perustuvat NOCCA-tutkimuksessa kehitettyyn ammattialtistusmatriisiin (NOCCA-JEM). Tutkimuksessa III käytetyt erittäin matalataajuuisen magneettikenttäaltistuksen (ELF-MF) ja sähköaltistuspiikkien määräarvioiden pohjaksi räätälöitiin Hollannissa erillinen ammattialtistusmatriisi (JEM). Tutkimuksessa IV verrattiin NOCCA-JEM-pohjaisia kosmischele säteilylle altistumisen arvioita yksilökohtaisiin säteilymittaustietoihin, joita oli saatavissa Säteilyturvakeskuksesta (STUK). Yksilöannokset estimoitiin CARI-6 ja EPCARD (European Program Package for the Calculation of Aviation Route Doses) -ohjelmistoilla.

Tutkimuksessa I AML:n, CLL:n ja muun leukemian riskiä kuvattiin vakioidulla ilmaantuvuussuhteella (standardized incidence ratio, SIR). Tutkimuksissa II ja III määritettiin riskitihetyssuhteet (hazard ratio, HR) 95 %:n luottamusväliseen (95% CI) ehdollisten logististen regressiomallien avulla. Tutkimuksessa IV käytettiin (kahden käytetyn altistumisen arvointimenetelmän yhtäpitävyyden mittareina) luokansisäisiä korrelatiokertoimia (intraclass correlation coefficient, ICC) ja Bland-Altmanin kuvaajia jatkuville altistusmuuttujille, sekä yhtäpitävyyden suhteellisia osuuksia (proportion of agreement, PA) ja kappakerrointa (sekä Cohenin kappa että painotettu kappa) luokitelluille altistusmuuttujille.

Tutkimus I osoitti leukemian ilmaantuvuuden olevan hieman väestökeskiarvoa suurempi eräissä ammattiluokissa. AML:n riski oli koholla autonkuljettajilla ( $SIR=1,16$ , 95% CI 1,07-1,26) ja elintarviketyöntekijöillä ( $SIR=1,13$ , 95% CI 1,01-1,27) ja CLL:n riski maanviljelijöillä ( $SIR=1,09$ , 95% CI 1,04-1,14) ja konttorityöntekijöillä ( $SIR=1,07$ , 95% CI 1,01-1,14). Muiden leukemiatyyppejen riski oli suurentunut merimiehillä, kemian prosessityöntekijöillä ja myyntiedustajilla. Metsureilla AML:n riski, merimiehillä AML:n ja CLL:n riskit, sekä kalastajilla muiden leukemiatyyppejen riski, olivat tilastollisesti merkitsevästi tavanomaista pienempiä. AML:n riski ei liittynyt liuotinaltistuksiin (tutkimus II) eikä magneettikenttä- tai sähköaltistuksiin (tutkimus III).

Tutkimus IV osoitti, että kosmisen säteilyn altistusestimaatit poikkeavat selvästi toisistaan riippuen siitä, onko arvion lähteenä NOCCA-JEM (ryhmätason ammattialtistumatriisi) vai Säteilyturvakeskuksen mittausaineisto (yksilökohtaiset säteilymittaustiedot). Bland-Altman kuvaajat osoittivat, että NOCCA-JEM:iin perustuvat altistusarviot olivat keskimäärin 9 mSv alhaisempia kuin yksilöllisiin mittautietoihin perustuvat arviot. NOCCA-JEM:iin perustuvat arviot saattoivat olla noin 28 mSv matalampia ja 10 mSv korkeampia kuin yksilöllisiin mittautietoihin perustuvat arviot. Jatkuvien altistusmuuttujien välinen korrelaatio oli matala (ICC 0,37, 95% CI 0,01-0,61), kun taas yhtäpitävyys luokiteltujen altistusmuuttujien välillä oli kohtalainen (Cohenin kappa 0,46 ja painotettu kappa 0,43).

Tutkimuksessa havaitut välttelut ammattialakohtaisessa leukemia ilmaantuvudessa olivat melko pieniä ja voisivat johtua työhön liittyvistä kemikaali- tai muista altistuksista. Havaintojemme mukaan ilmiön selittäjiä eivät ole liuotinaltistukset, magneettikentät eivätkä sähköaltistukset. Arvioitaessa lentohenkilökunnan altistumista kosmiselle säteilylle altistusarvioissa havaittiin selviä eroja NOCCA-JEM:n ja yksilöllisiin mittautietoihin perustuvien arvioden välillä. NOCCA-JEM saattaa siksi johtaa kosmista säteilyä koskevan altistustiedon virheluokittelun.

## List of original publications

This dissertation is based on the original articles listed below, which are referred in the text by their Roman numerals (I to IV). In addition to the material contained in these original articles, some previously unpublished data are also presented in this doctoral thesis.

- I Talibov, M., Kautiainen, S., Martinsen, J.I., Kjaerheim, K., Lynge, E., Sparen, P., Tryggvadottir, L., Weiderpass, E., Pukkala, E. (2012). Occupation and leukemia in Nordic countries. *JOEM*, 54(12), 1527-1532.
- II Talibov, M., Lehtinen-Jacks, S., Martinsen, J.I., Kjaerheim, K., Lynge, E., Sparen, P., Tryggvadottir, L., Weiderpass, E., Kauppinen, T., Kyrrönen, P., Pukkala, E. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries. *Scand J Work Environ Health*, 40(4), 420-426.
- III Talibov, M., Guxens, M., Pukkala, E., Huss, A., Kromhout, H., Slotje, P., Martinsen, J.I., Kjaerheim, K., Sparen, P., Weiderpass, E., Tryggvadottir, L., Uuksulainen, S., Vermeulen, R. (2015). Occupational exposure to extremely low-frequency magnetic fields and electrical shocks and acute myeloid leukemia in four Nordic countries. *Cancer Causes Control*, 26, 1079-1085.
- IV Talibov, M., Salminen, R., Lehtinen-Jacks, S., Auvinen, A. (2016). Estimation of occupational cosmic radiation exposure among airline personnel: agreement between the Nordic Occupational Cancer study job-exposure matrix and individual dose measurements., *Am J Ind Med*, submitted on 24 June 2016.

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# Abbreviations

ALHC	aliphatic and alicyclic hydrocarbon solvents
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
ANLL	acute non-lymphocytic leukemia
ARHC	aromatic hydrocarbon solvents
BENZ	benzene
BMI	body mass index
CHC	chlorinated hydrocarbon solvents
CI	confidence interval
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
DDT	4,4-Dichlorodiphenyltrichloroethane
ELF-MF	extremely low-frequency magnetic field
EMF	electromagnetic field
EPCARD	European Program Package for the Calculation of Aviation Route Doses
ERR	excess relative risk
FINJEM	Finnish Job-Exposure Matrix
FORM	formaldehyde
HR	hazard ratio
Hz	Hertz
ICC	intraclass correlation coefficient
ICD	International Classification of Diseases
IRAD	ionizing radiation
ISCO	International Standard Classification of Occupations
JEM	job-exposure matrix
MCH	methylene chloride
MDS	myelodysplastic syndrome
µg	microgram
µT	micro-Tesla
mSv	millisievert
NOCCA	Nordic Occupational Cancer Studies

NOCCA-JEM	Nordic Occupational Cancer Studies job-exposure matrix
NYK	Nordic Classification of Occupations
OR	odds ratio
OSOL	other organic solvents
PER	perchloroethylene
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
RR	relative risk
SEER	Surveillance, Epidemiology, and End Results Program
SIR	standardized incidence ratios
SMR	standardized mortality ratio
STUK	Radiation and Nuclear Safety Authority, Finland
TCE	1,1,1-trichloroethylene
TOLU	toluene
TRI	trichloroethylene

# 1 Introduction

Leukemia is a cancer of blood, which originates from malignant transformation of hematopoietic progenitor cells (Linet, Devesa, & Morgan, 2006). It may develop from either myeloid or lymphoid progenitor cells. The four major types of leukemia are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL) (Linet et al., 2006).

Leukemia is characterized by accumulation of malignant blood cells in bone marrow and infiltration into other organs, thereby replacing healthy tissues (Miller & Grodman, 2001). This results in suppression of hematopoietic and immune systems, and manifestation of typical symptoms such as fatigue, fever, malaise and bruising.

In the Nordic countries in 2013, the highest incidence of AML adjusted for world standard population was observed in Denmark for males (3.5 per 100,000), and in Iceland for females (3.9 per 100,000) (Engholm et al., 2015). The incidence of CLL was the highest in Norway (5.7 per 100,000) and Denmark (5.6 per 100,000) for males, and in Denmark for females (3.1 per 100,000). The incidences of ALL and CML were substantially lower in all Nordic countries (Engholm et al., 2015).

Leukemia caused 9.3 million disability-adjusted life years (DALY) in the world (GBD, 2015a). 78% of this occurred in developing and only 22% in developed countries. Leukemia ranked tenth for cancer incidence and ninth for cancer deaths in the world in 2013 (GBD, 2015a). Studies investigating economic burden of leukemia are sparse, and low incidence and the fact that it mainly affects patients older 60 years of age may have contributed to sparse attention to this disease (Redaelli, Botteman, Stephens, Brandt, & Pashos, 2004). The economic burden of leukemia is primarily from inpatient and pharmaceutical costs, and costs due to productivity losses (Redaelli et al., 2004). The economic burden of CLL in Germany was about 201 million euros per year for the sickness funds and 322 million for society (Blankart et al., 2013). Also the burden of AML on society is significant despite its low incidence (Redaelli et al., 2004). According to Blankart et al (2013), the economic burden of CLL is considerably lower compared to common diseases

(e.g. diabetes, chronic obstructive pulmonary disease). However, the treatment costs per CLL case are approximately twice higher than the treatment costs per case with common diseases. It is expected that the economic and societal burden of leukemia will continue to grow with the aging population and increasing incidence of leukemia (Blankart et al., 2013).

The causes of leukemia remain largely unknown. Previous studies have linked some genetic and life-style factors, various drugs and diagnostic procedures, viruses, and environmental factors with increased risk of adult leukemia.

Occupational exposures constitute a major part of environmental exposures. Among occupational exposures, benzene (BENZ) and ionizing radiation (IRAD) are the most widely accepted risk factors of adult leukemia. Occupational exposure to BENZ has mainly been linked to acute non-lymphocytic leukemia (ANLL) (Divine & Hartman, 2000; Guenel, Imbernon, Chevalier, Crinquand-Calastreng, & Goldberg, 2002; Hayes et al., 1997), but some studies also demonstrated associations with other leukemia subtypes (Glass et al., 2003; Hayes et al., 1997; Huebner, Wojcik, Rosamilia, Jorgensen, & Milano, 2004). The leukemogenic effect of occupational ionizing radiation exposure has been demonstrated in studies of radiologists and X-ray technicians (Smith & Doll, 1981), airline pilots (Gundestrup & Storm, 1999) and military servicemen exposed to atomic bomb tests (Caldwell, Kelley, Zack, Falk, & Heath, 1983; Darby et al., 1988). Formaldehyde, electromagnetic field and solvents are among other occupational exposures suspected as a risk factor of adult leukemia (Hauptman et al., 2003; Strom, Oum, Gbito, Garcia-Manero, & Yamamura, 2012; Theriault et al., 1994).

The main objective of this study was to assess associations between various occupational exposures and adult leukemia. The study population was an occupational cohort from four Nordic countries. The cohort members were employed between 1920s and 2000s and leukemia cases were diagnosed between 1961 and 2005. Data from various registries such as census records, cancer registries and population registries, were used to collect information on sex, date of birth, death and emigration; date of diagnosis; education; and occupation.

## 2 Review of literature

The purpose of literature review was to collect background information on adult leukemia and risk factors with main focus on occupational factors. The Medline database search engine was accessed via Ovid and used to search the literature. Leukemia, occupation, environmental exposure, pollutant, chemical, radiation, benzene, solvent, formaldehyde among others were used as keywords for extracting relevant papers from the database. Reference lists of articles selected from Medline database were further examined for additional literature relevant to the current research. Papers were restricted to English language and adult leukemia. The review was performed from July 2015 to October 2015.

### 2.1 Classification and overview of leukemia

Leukemias are subdivided into acute and chronic types (Miller & Grodman, 2001). Acute leukemias are characterised by rapid proliferation of leukemic cells with impaired maturation and chronic leukemias are characterized by expanded population of cells that proliferate but retain their ability to differentiate. Leukemias are also divided into myeloid and lymphocytic types depending on which cell type is affected (Linet et al., 2006). Myeloid leukemia type originates in myeloid progenitor cells that give rise to platelets, monocytes, erythrocytes and granulocytes, and lymphocytic type develops in lymphoid progenitor cells that differentiate into lymphocytes.

The latest version (10<sup>th</sup> revision, volume 2) of international classification of diseases (ICD) has grouped leukemia into lymphoid leukemia (C91), myeloid leukemia (C92), monocytic leukemia (C93), other leukemia of specified cell type (C94) and other leukemia of unspecified cell type (C95) (WHO, 2010).

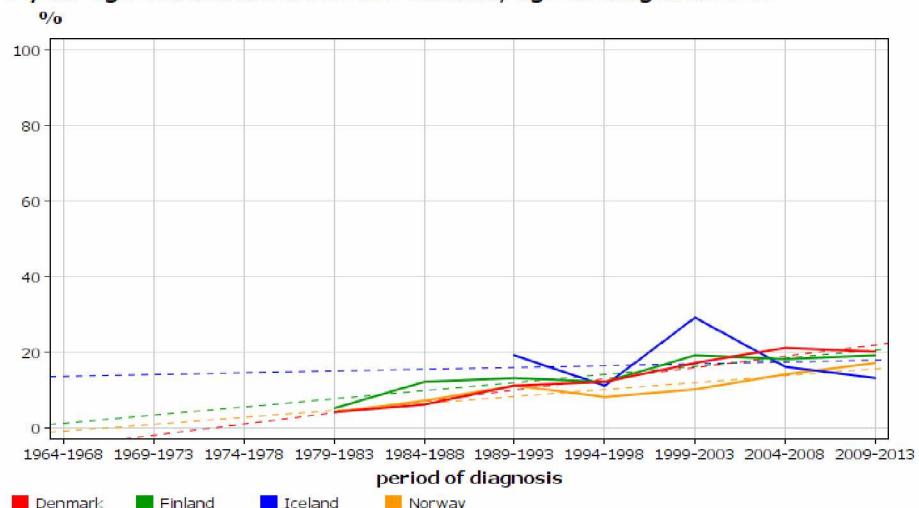
The clinical manifestation of leukemias is a result of accumulation of leukemic cells in bone marrow, and infiltration into bloodstream and other organs (Miller & Grodman, 2001). In acute leukemias, rapid accumulation of malignant cells in bone marrow results in suppression of hematopoiesis, anemia, thrombocytopenia and

neutropenia. In chronic leukemias, proliferated leukemic cells gradually replace healthy tissue in bone marrow, spleen and lymph nodes. Fatigue, malaise, fever, bruising are some of the typical symptoms of leukemia and clinical presentation varies across subtypes (Miller & Grodman, 2001).

The poorest prognosis is observed for AML compared to other leukemia subtypes. 5-year relative survival of AML in the United States significantly improved from 6.2 % in 1975-1977 to 26.8% in 2006-2012 according to U.S. SEER program (Howlader et al., 2016). Survival of CML improved from 21.8% to 65.9%, and of ALL from 40.6% to 70.7% during the same period. A modest improvement of CLL survival (from 67.1% to 85.1%) was also observed. In general, survival of all leukemia subtypes among younger patients is considerably better compared to older patients (Howlader et al., 2016). Better survival among younger patients is attributed to their having more chemo-sensitive disease (Hills & Burnett, 2011), intense induction treatment, better management of short-term toxicity and a reduction in relapse rates (Andersson et al., 2010). Older patients are more likely to be offered palliative care rather than intensive curative therapy because of differences in the biology of their disease and co-morbidities (Burnett et al., 2009, Burnett et al., 2010).

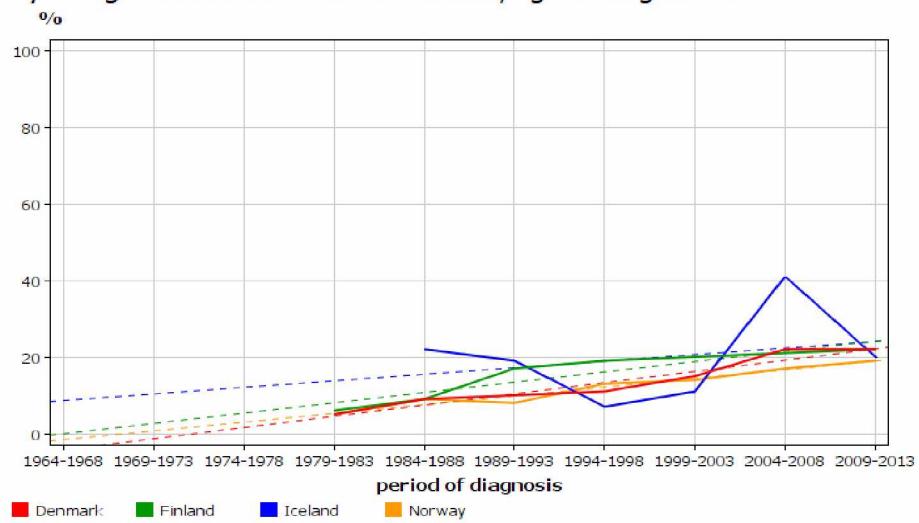
Leukemia survival has substantially improved also in the Nordic countries during the last few decades (Engholm et al., 2015) (Figure 1). The poorest 5-year survival was observed for AML and the highest survival was observed for lymphoid leukemia types (Figure 1).

**Acute myeloid leukaemia: Male**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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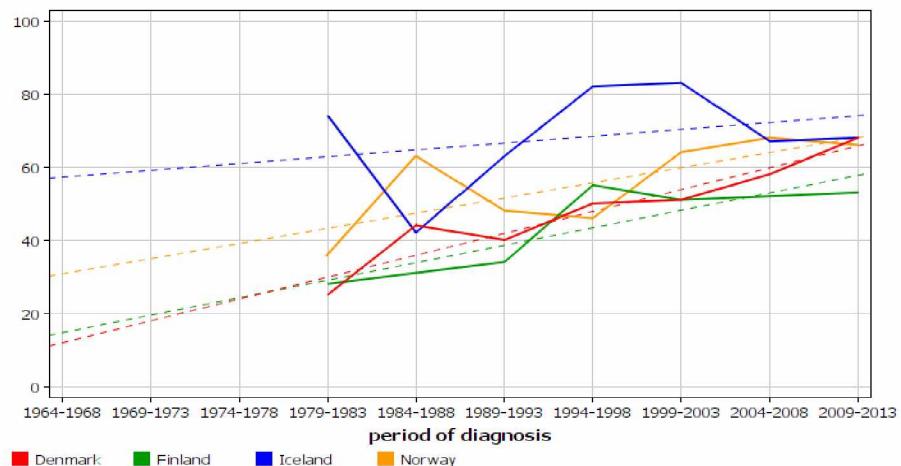
**Acute myeloid leukaemia: Female**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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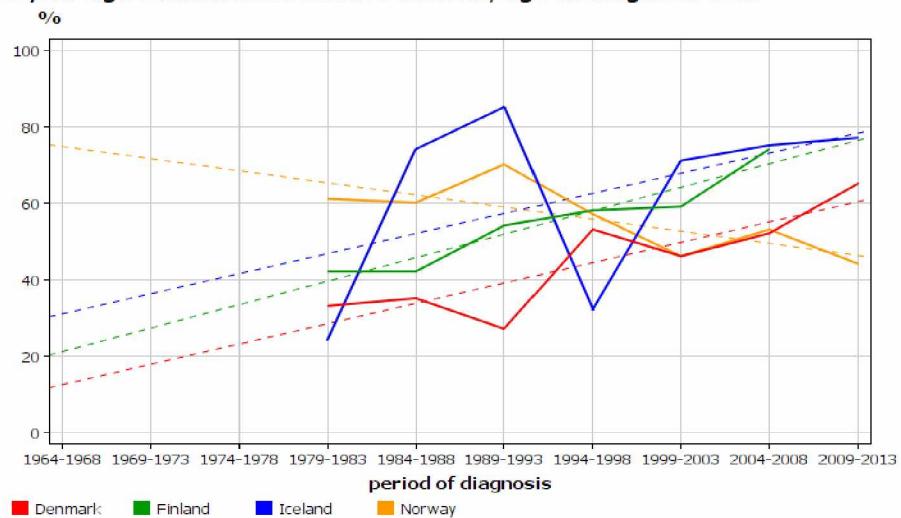
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**Acute lymphatic leukaemia: Male**  
**5-year age standardised relative survival, age at diagnosis 0-89**  
 %



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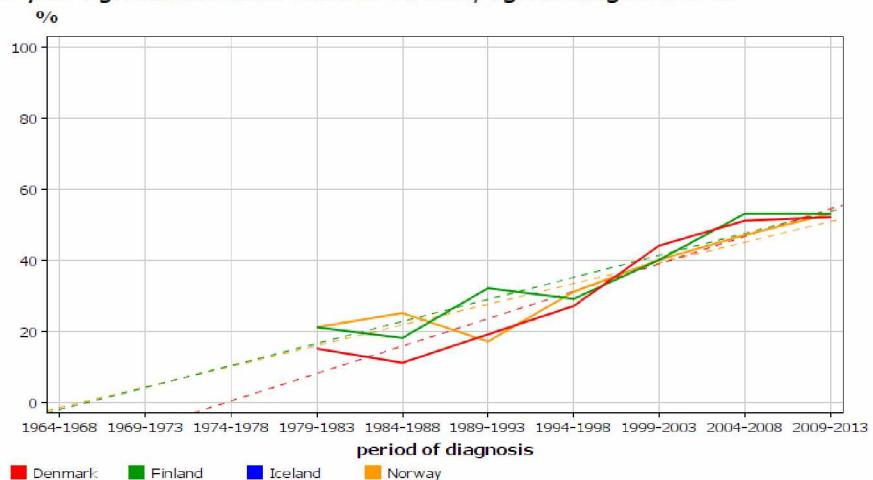
**Acute lymphatic leukaemia: Female**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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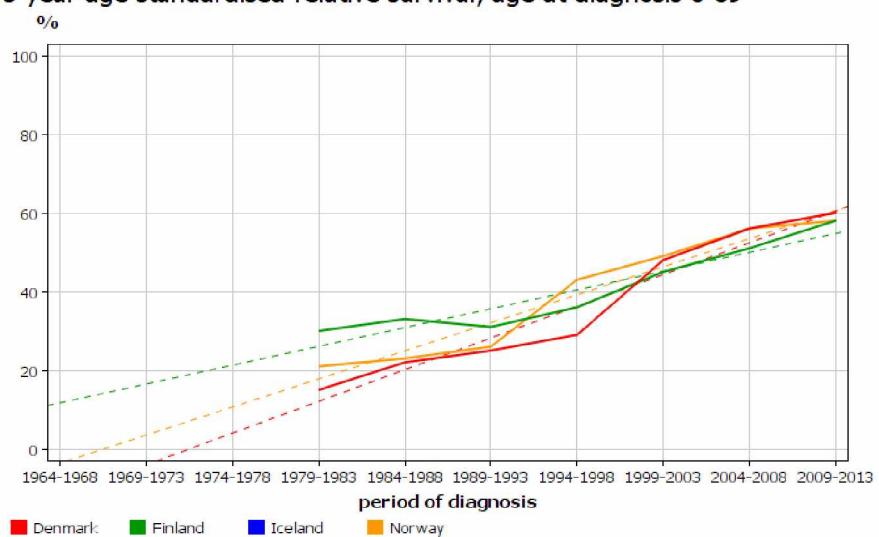
(Figure 1 continues on the next page)

**Chronic myeloid leukaemia: Male**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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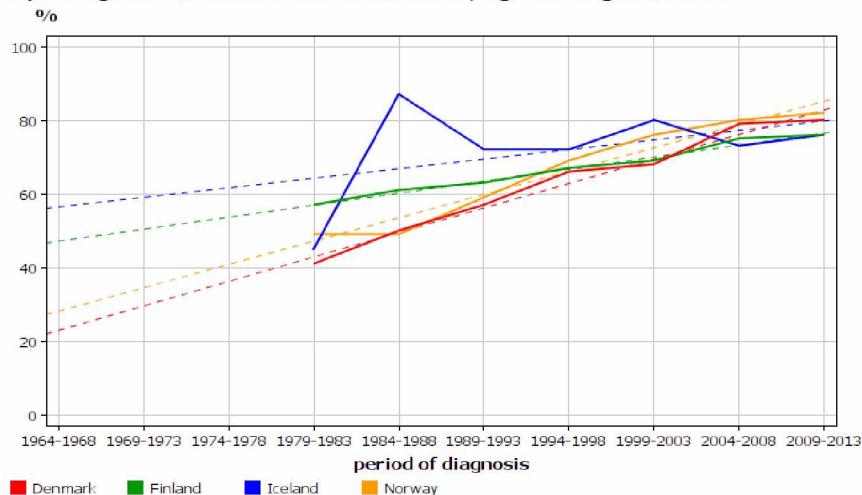
**Chronic myeloid leukaemia: Female**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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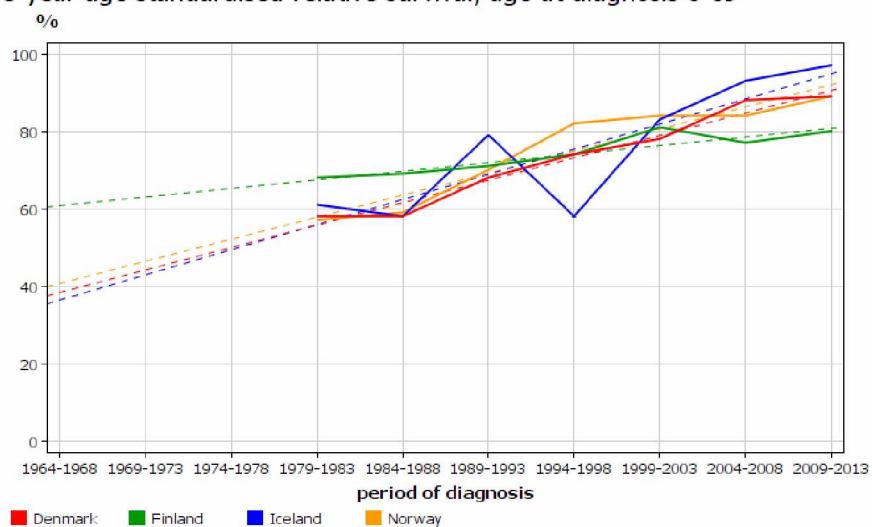
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**Chronic lymphatic leukaemia: Male**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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**Chronic lymphatic leukaemia: Female**  
**5-year age standardised relative survival, age at diagnosis 0-89**



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Figure 1. Five-year age standardized relative survival of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) in the Nordic countries (Engholm et al, 2015).

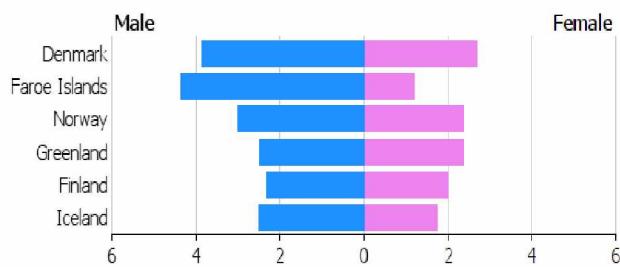
## 2.2 Epidemiology of leukemia

*Geographical patterns.* There were 414,000 incident cases and 265,100 deaths of leukemia worldwide in 2013 (GBD, 2015a; GBD, 2015b). Age-standardized incidence rates and deaths rates (per 100,000) were higher in developed countries than developing countries (age-standardized incidence rates 8.15 vs 5.09; deaths rates 4.78 vs 3.46) (GBD, 2015a). In 2013, the lowest incidence rate due to leukemia was reported for sub-Saharan Africa and the highest for North America, Australia and Western Europe (GBD, 2015a).

Incidence rates of AML vary about three-fold internationally and are the highest in white populations in North America, Oceania, northern and western Europe, and in Hispanics in Los Angeles (Douer et al., 1996; Tomas & Fernandez-Ranada, 1996). The lowest AML rate is observed in Asians, particularly Chinese (Shanghai) and Indians (Bombay). The highest CML rates are observed among Italian males, Australians, African Americans, Los Angeles Hispanics and the lowest rates are among Asians (Parkin, Whelan, Ferlay, & Teppo, 2002). The rates of ALL are the highest among Hispanics in Los Angeles, Spain, northern Italy and in whites in New Zealand (Parkin et al., 2002). The lowest ALL incidences are observed among Israeli Jews, Japanese, Indians (Bombay) and Chinese (Shanghai). International variation of incidence rates is the highest for CLL among all leukemia subtypes (Parkin et al., 2002). The highest CLL rates are observed in whites in New Zealand, Italy, North America and the lowest rates are observed in Japan, China (Shanghai), India (Bombay).

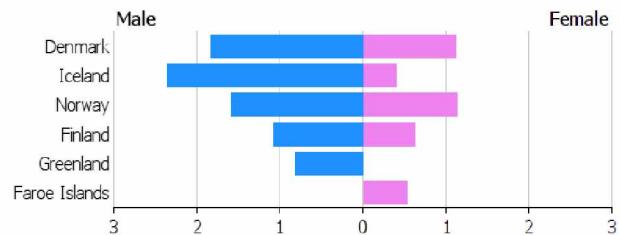
In the Nordic countries, the AML incidence rate in 2013 among males was the highest in Faroe Islands and Denmark, and among females in Denmark (Engholm et al., 2015) (Figure 2). Incidence of CML was the highest in Iceland and Denmark for males, and in Denmark and Norway for females. The highest rates for CLL were observed in Norway, Denmark and Iceland for males, and in Denmark and Norway for females. The incidence of ALL was the highest in Iceland and Greenland in females, and Faroe Islands for males (Figure 2).

Acute myeloid leukaemia, Incidence (2004-2013)  
 ASR (World) age 20-85+



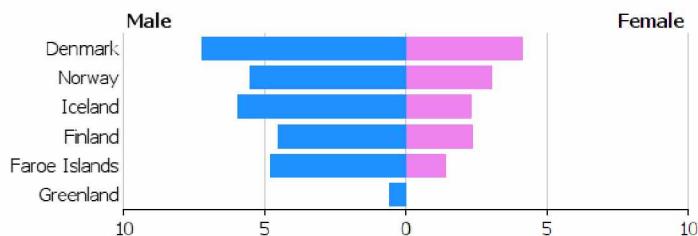
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Chronic myeloid leukaemia, Incidence (2004-2013)  
 ASR (World) age 20-85+



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Chronic lymphatic leukaemia, Incidence (2004-2013)  
 ASR (World) age 20-85+



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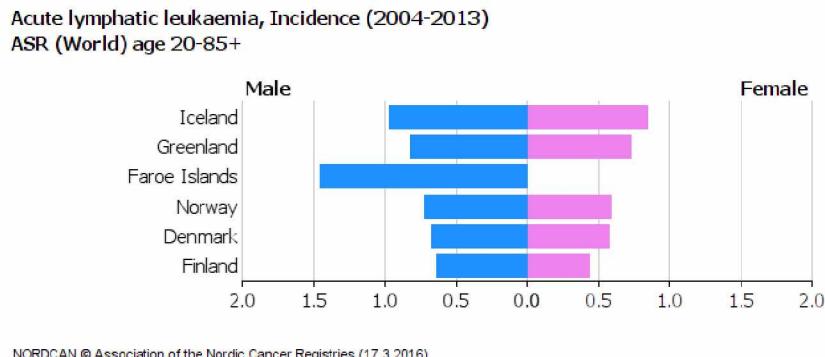


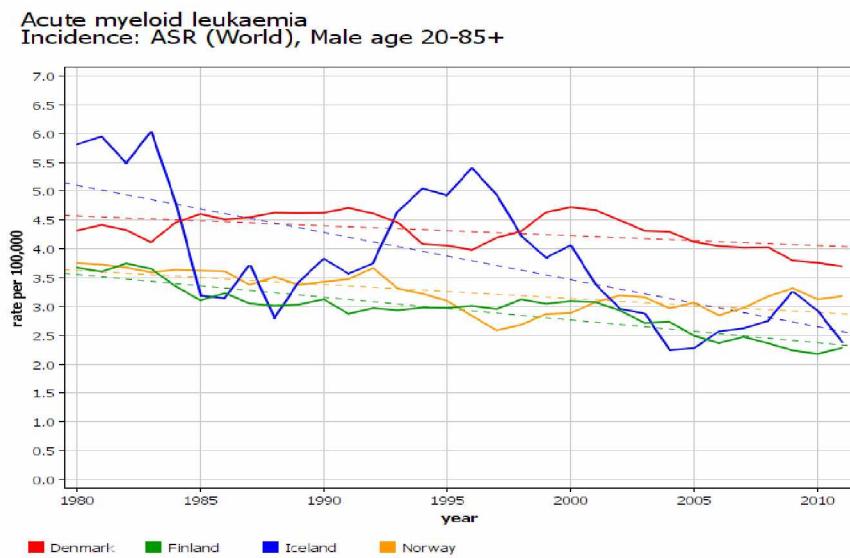
Figure 2. Incidence (per 100 000 person-years) of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL) by country and sex in the Nordic countries in 2004-2013 (NORDCAN data). Adjusted for world standard population (Engholm et al, 2015).

*Time-trend.* Age-standardized mortality rate of overall leukemia has decreased by about 20% from 5.2 in 1990 to 4.1 in 2013 (GBD, 2015b). However, overall deaths due to leukemia increased from 223,800 in 1990 to 265,100 in 2013, and corresponding incidence rates increased from 297,000 to 414,000, mainly because of global population growth and aging during the past decades (GBD, 2015a; GBD, 2015b).

Age-standardized AML incidence rates in both sexes were higher among whites compared to African Americans in all periods from 1970s to 1990s (Ries et al., 2003). The rate of AML in all groups slightly increased through 1994-2000 compared to previous years. CML rates were uniquely increased in African Americans in both sexes compared to white Americans (Ries et al., 2003). CML rates among African Americans increased from 1973-1979 and 1987-1993 for males and between 1973-1979 and 1980-1986 for females, then declined for both sexes. The rate of ALL has increased over time for all four race-sex groups with the higher rates observed for white Americans. The rate of CLL was higher for whites than African Americans and very small increase was observed during 1973-1979 and 1987-1993, which followed by a decline in 1987-1993 and 1994-2000 (Ries et al., 2003).

The incidence of AML for both sexes has been the highest in Denmark and decreased in all Nordic countries from 1980 to 2013 (Engholm et al., 2015) (Figure 3). CML rate increased in Norway and Denmark, but decreased in other Nordic

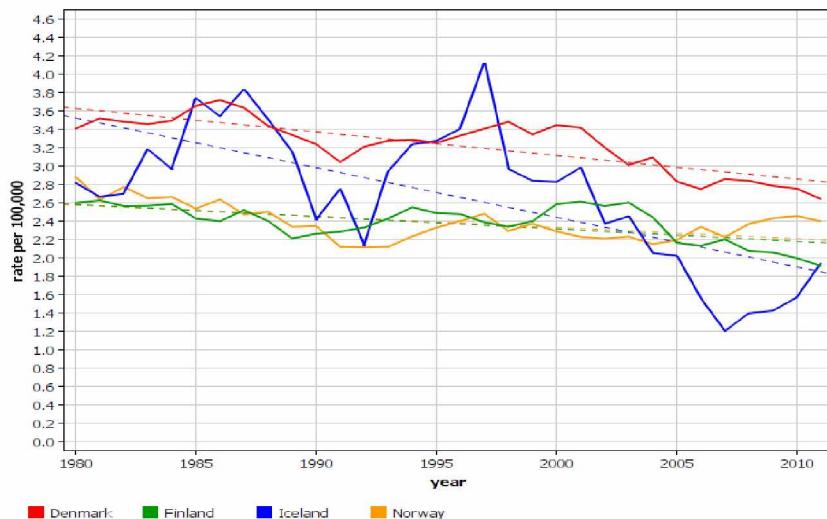
countries among females. Among males, CML rate increased in Iceland, but decreased in Finland and Denmark. Incidence of CLL increased in Denmark, Iceland, and Norway, and decreased in Finland in both sexes. Small increases of ALL rates were observed among females in Norway and Denmark, among males in Norway and Iceland. ALL rate decreased in Finland for both sexes (Figure 3).



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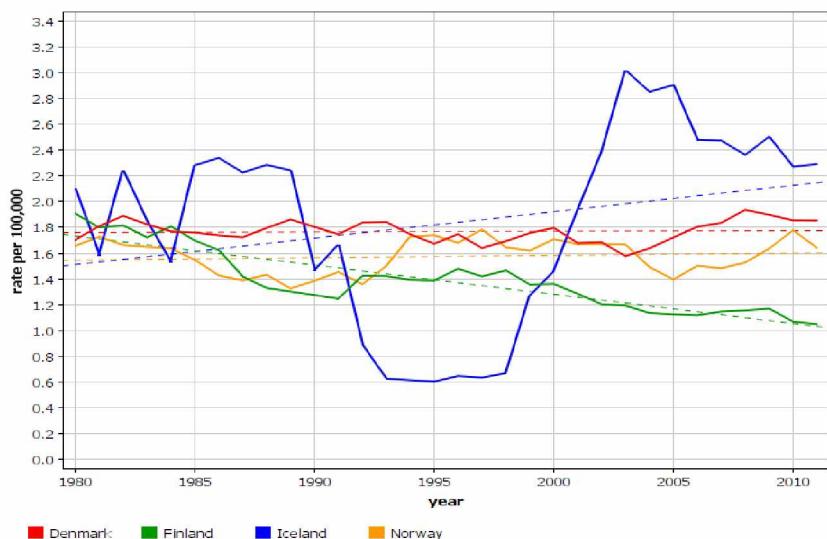
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**Acute myeloid leukaemia**  
 Incidence: ASR (World), Female age 20-85+



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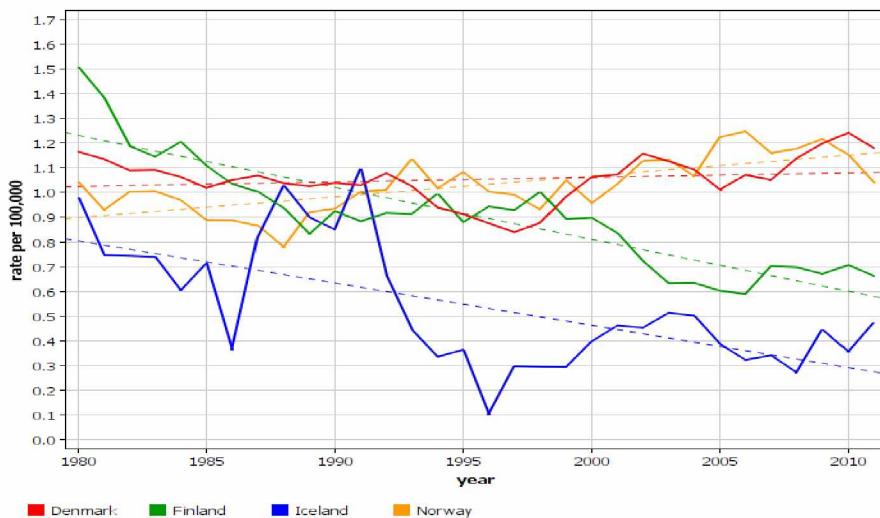
**Chronic myeloid leukaemia**  
 Incidence: ASR (World), Male age 20-85+



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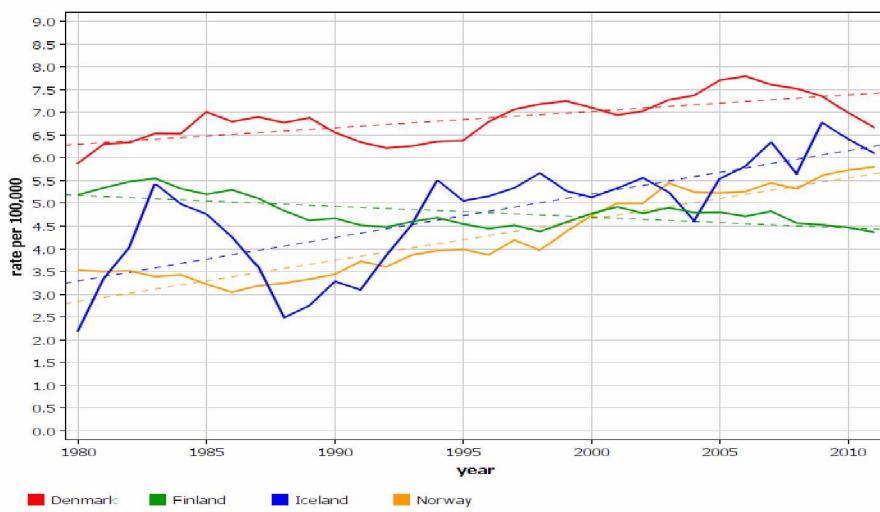
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**Chronic myeloid leukaemia**  
 Incidence: ASR (World), Female age 20-85+



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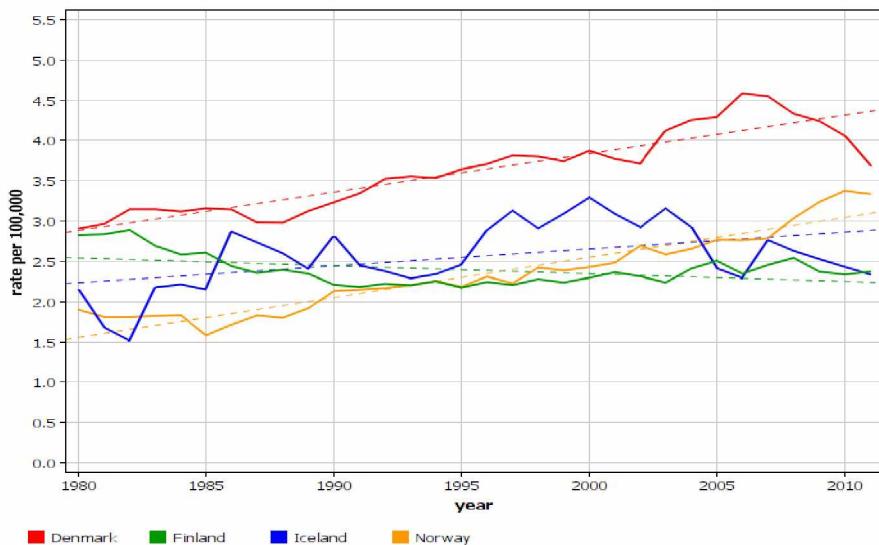
**Chronic lymphatic leukaemia**  
 Incidence: ASR (World), Male age 20-85+



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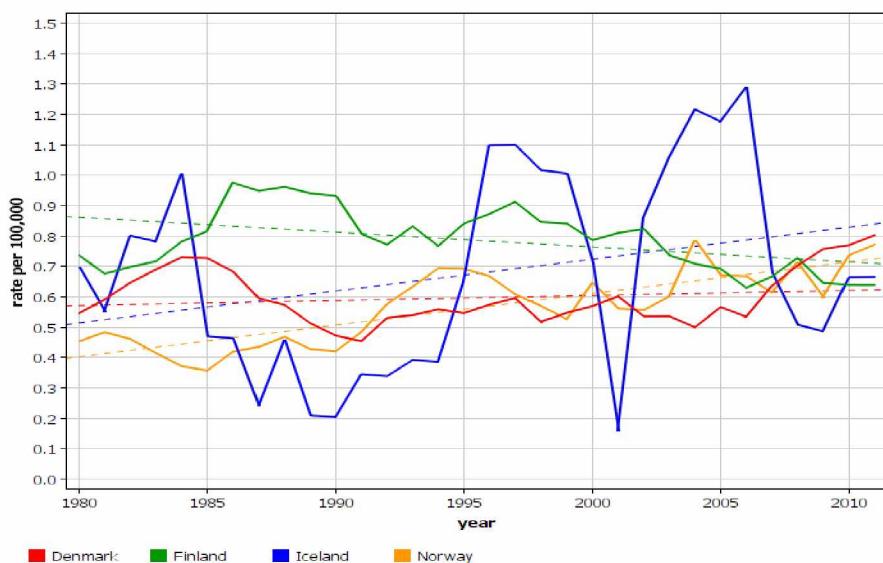
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**Chronic lymphatic leukaemia**  
Incidence: ASR (World), Female age 20-85+



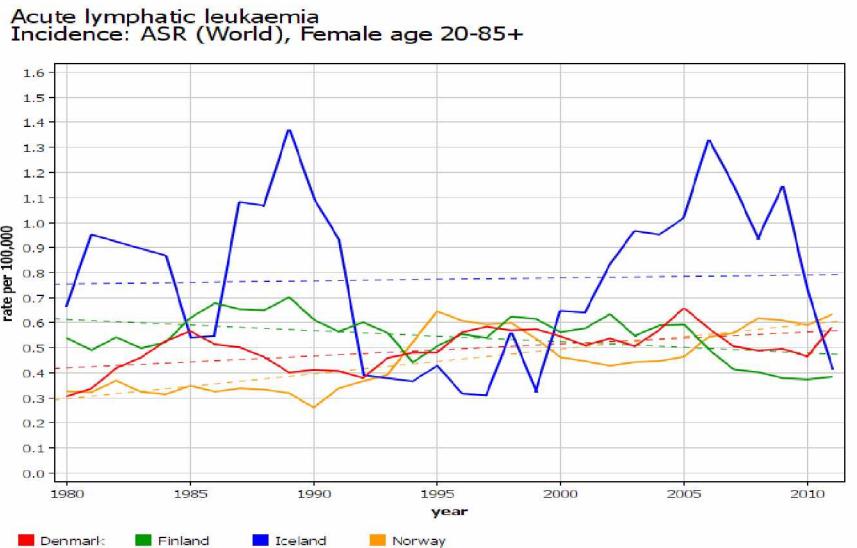
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**Acute lymphatic leukaemia**  
Incidence: ASR (World), Male age 20-85+



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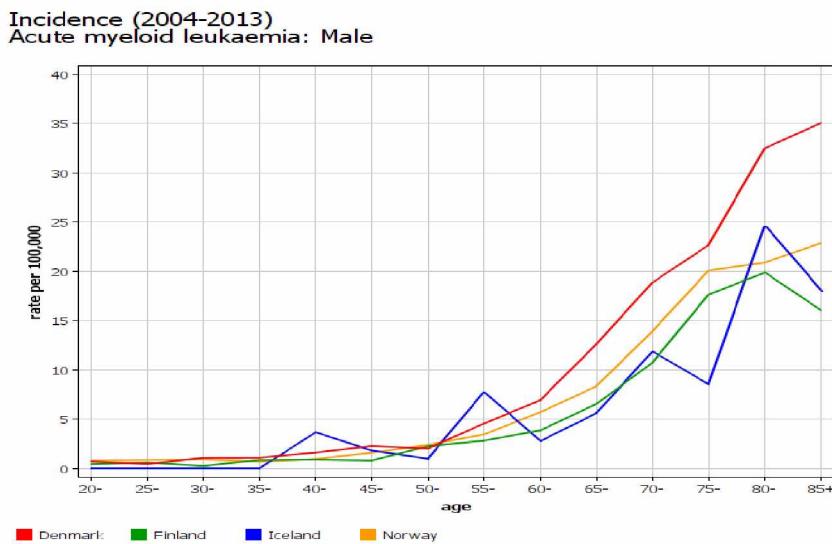
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Figure 3. Five-year average incidence (per 100 000 person-years) of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL) by country, sex and time period (1980-2013) in Nordic countries (NORDCAN data). Adjusted for world standard population (dashed lines show trends) (Engholm et al, 2015).

*Age-specific patterns.* In the US, myeloid leukemias account for about 45% of all leukemias (Ries et al., 2003). AML incidence rapidly increases after the age 40 years. There are no sex-specific differences in AML rates among middle-aged white and African Americans, while among elderly persons, higher rates among whites compared to African Americans are observed. The rates of CML exponentially increase in both races and sexes throughout life. Generally, the rate of CML is higher among African Americans than white Americans for both sexes. Lymphoid leukemias constitute about 47% of all leukemias in the U.S. (Ries et al., 2003). Over 70% of all childhood leukemias are lymphocytic, predominantly ALL. Among persons aged >65 years, about 46% of leukemias are lymphocytic, most of which is CLL. ALL incidence rate has two distinct age-specific peaks. The first peak corresponds to the age 2-4 years followed by sharp decline during adolescence and early adulthood. The second peak occurs at older ages, which is lower than the first peak. CLL is very uncommon before the age 30 years and the difference in incidence between white and African Americans is very small among middle-age persons. The

rate increases exponentially between ages 30 and 60 years and then a small increase is observed in older ages (Ries et al., 2003).

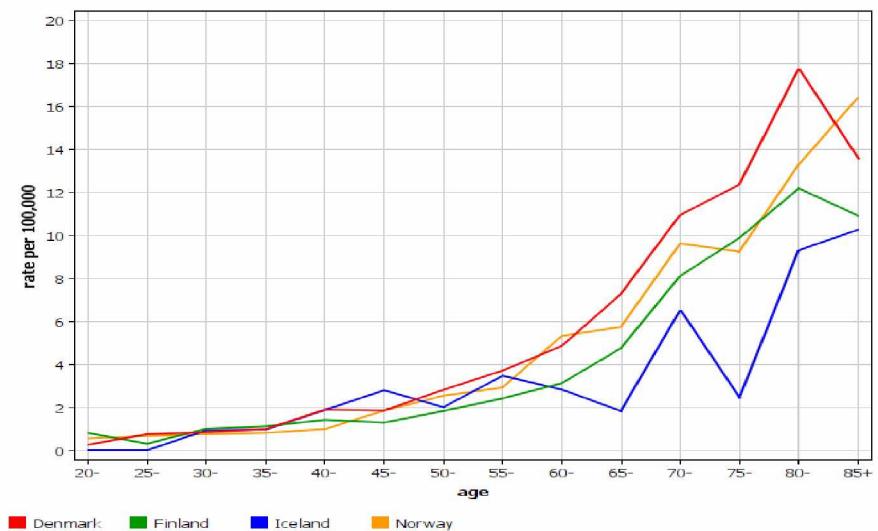
Figure 4 shows age-specific pattern of leukemia incidences in adult populations (age 20+ years) of the Nordic countries during 2004-2013. Incidences of all leukemia types seem to rapidly increase from age 60-65 years for both sexes (Engholm et al., 2015) (Figure 4).



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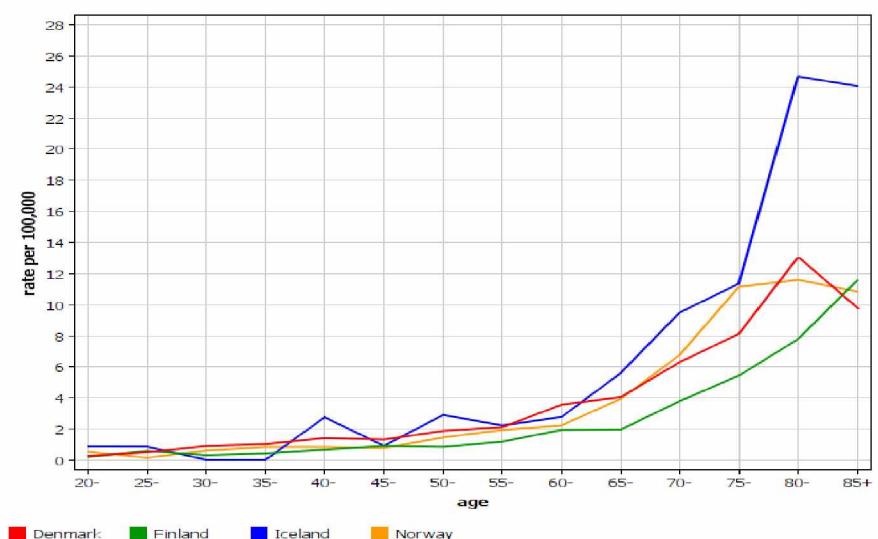
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**Incidence (2004-2013)  
Acute myeloid leukaemia: Female**



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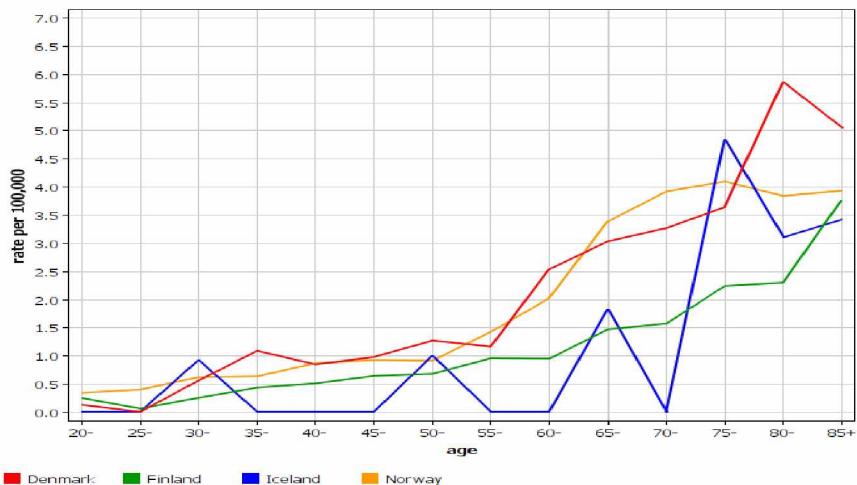
**Incidence (2004-2013)  
Chronic myeloid leukaemia: Male**



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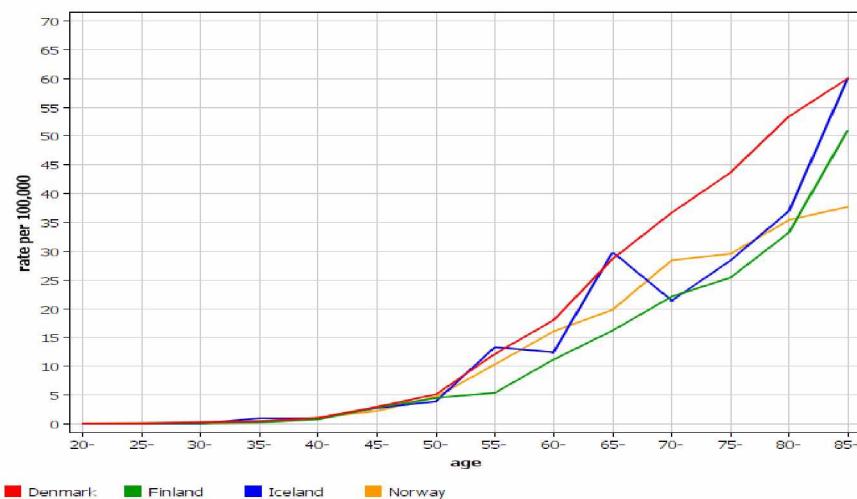
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**Incidence (2004-2013)**  
**Chronic myeloid leukaemia: Female**



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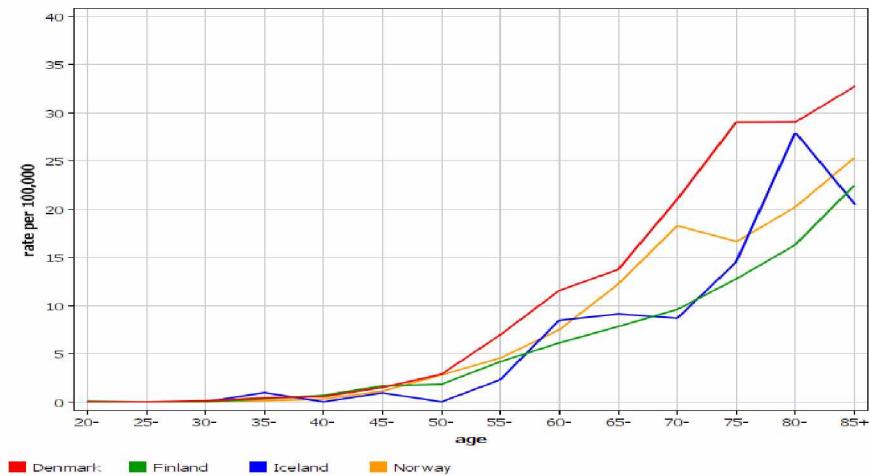
**Incidence (2004-2013)**  
**Chronic lymphatic leukaemia: Male**



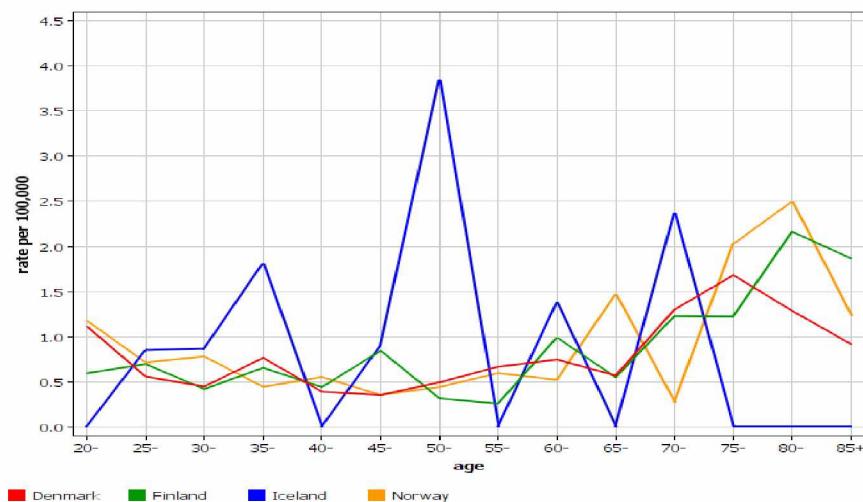
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**Incidence (2004-2013)**  
**Chronic lymphatic leukaemia: Female**

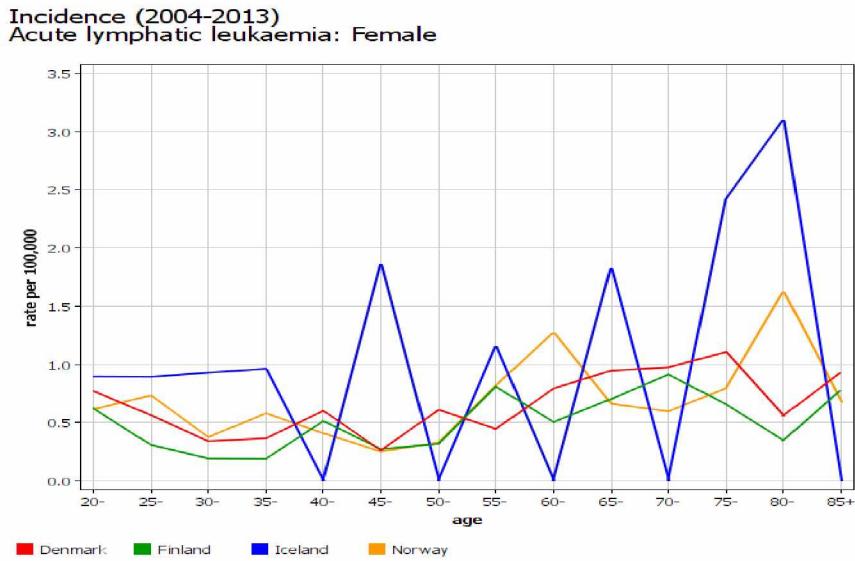


**Incidence (2004-2013)**  
**Acute lymphatic leukaemia: Male**



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Figure 4. Incidence (per 100 000 person-years) of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL) by country, sex and age in 2004-2013 in Nordic countries (NORDCAN data) (Engholm et al, 2015).

## 2.3 Risk factors of leukemia

A broad range of factors linked to adult leukemia can be grouped into genetic, life-style, therapy-related and environmental factors (Zeeb & Blettner, 1998). Some of these factors can be included in more than one group. For example, exposure to ionizing radiation may be included in environment, occupation, and therapy/diagnostics (Table 1).

Table 1. Potential risk factors of adult leukemia.

Group	Examples
Genetic	Down syndrome, Klinefelter syndrome, Philadelphia chromosome etc.
Life-style	Smoking, diet, body mass index etc.

<b>Group</b>	<b>Examples</b>
Therapy-related	Radiotherapy, chemotherapy, diagnostic radiology etc.
Environmental	Occupation, chemical and non-chemical agents.

### 2.3.1 Genetic factors

The genetic predisposition to leukemia is supported by evidence from family history studies and studies of genetic abnormalities. In a Texas case-control study, family history of lymphoma, multiple myeloma, myelodysplastic syndrome and leukemia in the first-degree relatives significantly increased the risk of AML both among women ( $OR=2.75$ , 95% confidence interval [95% CI] 1.20-6.32) and men ( $OR=3.06$ , 95% CI 1.47-6.37) (Strom et al., 2012).

Down syndrome, Philadelphia chromosome, Fanconi anemia, and Klinefelter syndrome are among genetic abnormalities that have been studied in relation to leukemia. The risk of leukemia was 10-fold among persons with Down syndrome in a Finnish cohort study (Patja, Pukkala, Sund, Livanainen, & Kaski, 2006). Although the risk was more obvious in younger ages, it remained elevated throughout life. In another study of persons with Down syndrome, significant rate ratios of 18.9 (95% CI 10.4-31.5) for leukemia, 22.2 (95% CI 10.9-40.6) for lymphoid leukemia and 17.2 (95% CI 5.5-40.9) for myeloid leukemia were observed (Goldacre, Wotton, Seagroatt, & Yeates, 2004). In a mortality study between 1988 and 1999 among 14,781 persons with Down syndrome, a  $SMR=17$  (95% CI 11-25) was observed for leukemia (Day, Strauss, Shavelle, & Reynolds, 2005). Philadelphia chromosome (usually translocation 9/22) was found in the majority of CML cases. It was suggested that its presence alone may not lead to CML, but it induces an early step in leukemia development (Greaves, 1997, as cited in Zeeb & Blettner, 1998). An association between Klinefelter syndrome and leukemia was suggested in some case reports (Keung, Buss, Chauvenet, & Pettenati, 2002; Mamunes, 1961), but it was not confirmed in larger studies (Horsman, Pantzar, Dill, & Kalousek, 1987; Price, Clayton, Wilson, Collyer, & De Mey, 1985). In a prospective Danish cohort study, 696 men with Klinefelter syndrome were followed-up from 1943 to 1991 and no excess leukemia risk was observed (Hasle, Mellemgaard, Nielsen, & Hansen, 1995). An excess incidence of leukemia was observed among 279 patients with ataxia telangiectasia compared to general population in a French cohort study (Suarez et

al., 2015). In a retrospective cohort of North American patients with Fanconi anemia, the ratio of observed to expected cases was 785 (observed=9) for leukemia (Rosenberg, Green, & Alter, 2003).

### 2.3.2 Life-style factors

Cigarette smoking, alcohol intake, obesity, dietary intake are among life-style related factors, which have been studied in relation to adult leukemia.

In a Texas case-control study, statistically significantly increased risk of AML was observed for being a current smoker (men: OR=1.60, 95% CI 1.08-2.38; women: OR=1.93, 95% CI 1.26-2.97) (Strom et al., 2012). Similarly, current smoking was significantly associated with AML (OR=1.4, 95% CI 1.1-1.8) in a Canadian population based case-control study, but no increased risk was observed for other leukemia subtypes (Kasim, Levallois, Abdous, Auger, & Johnson, 2005). In an analysis by the number of cigarette packs smoked per year, leukemia risk remained elevated with positive dose-response relationship in both studies (Kasim et al., 2005; Strom et al., 2012). The risk of AML decreased by increasing number of years since quitting smoking and no association with AML was reported for those quitting smoking for >28 years before the date of interview (Kasim et al., 2005). Second hand smoking was not associated with AML risk in a study by Strom et al. (2012). The risk of smoking-related AML was restricted to a subgroup with t(8;21) (q22;q22) translocation but not to other groups in a study by cytogenetic groups, suggesting that AML risk due to smoking may vary by chromosomal abnormalities (Moorman, Roman, Cartwright, & Morgan, 2002). In 2004, the IARC concluded that there is a sufficient evidence for the causality between active smoking and AML (IARC, 2004).

Obesity was statistically significantly associated with increased risk of leukemia in a Canadian case-control study (Kasim et al., 2005). Odds ratio for all leukemias was 1.3 (95% CI 1.1-1.5) for body mass index (BMI) =25-30 kg/m<sup>3</sup>, and 1.6 (95% CI 1.3-1.9) for BMI≥30 kg/m<sup>3</sup> compared to BMI<25 kg/m<sup>3</sup>. Analysis by leukemia cell-types showed that the risk of AML, CML, ALL and CLL were increasing with BMI with a significant trend (Kasim et al., 2005). The risk of CML was also reported to increase with BMI in a study by Strom, Yamamura, Kantarjian, & Cortes-Franco (2009). In this study, the risk remained elevated for both males and females and different age groups in a detailed analysis. Weight gain was also consistently associated with increased CML risk and the strongest association was observed for gaining >1 kg/year between 25 and 40 years of age (OR=3.63, 95% CI 1.46-9.04) (Strom et al., 2009). Strom et al. (2012) observed significantly increased risk of AML

for  $\text{BMI} \geq 30 \text{ kg/m}^2$  among women ( $\text{OR}=1.62$ , 95% CI 1.06-2.47) but not men ( $\text{OR}=1.24$ , 95% CI 0.91-1.79).

In a Texas case-control study, overall AML risk was significantly decreased among those who consumed dark-green vegetables, seafood, and nuts/seeds; and it was significantly increased among greatest consumers of red meat (Yamamura, Oum, Gbito, Garcia-Manero, & Strom, 2013). Among men, AML risk was the lowest among those whose consumption was in the highest quartile for fruits ( $\text{OR}=0.25$ , 95% CI 0.10-0.69), poultry ( $\text{OR}=0.28$ , 95% CI 0.10-0.78), and seafood ( $\text{OR}=0.39$ , 95% CI 0.16-0.96) compared to those in the lowest quartile. Among women, risk was the lowest among those whose consumption was in the highest quartile of dark-green vegetables ( $\text{OR}=0.28$ , 95% CI 0.12-0.68), orange vegetables ( $\text{OR}=0.40$ , 95% CI 0.17-0.96), and nuts/beans ( $\text{OR}=0.26$ , 95% CI 0.11-0.60) (Yamamura et al., 2013). Vegetable intake was also associated with decreased risk of adult leukemia ( $\text{OR}=0.30$ , 95% CI 0.18-0.50) in a Chinese multicenter case-control study (Liu, Holman, Jin, & Zhang, 2015a). In this study, intakes of fruit, red meat and poultry was not associated with leukemia risk. Dietary fiber, carotenoids, vitamins B1, B2, and C, niacin, and folate were significantly associated with reduced risk. Dietary intake of animal fat, deep-fried and smoked foods was associated with elevated leukemia risk (Liu et al., 2015a). Fruit or vegetable intake was not associated with leukemia in a study by Kasim et al. (2005), and none of the selected dietary factors (red and processed meat, poultry, offal, fish, dairy products, vegetables, and seeds/nuts) was associated with leukemia risk in a European Prospective Investigation into Cancer and Nutrition study (Saberi et al., 2014). In a Chinese multicenter case-control study, significantly decreased leukemia risk was observed among those who consumed green tea (Liu, Zhang, Xie, Jin & Holman, 2015b). Compared with non-tea drinkers, the adjusted odds ratios were 0.50 (95% CI 0.27-0.93), 0.31 (95% CI 0.17-0.55) and 0.53 (95% CI 0.29-0.99) for those, who, respectively, consumed green tea  $>20$  years,  $\geq 2$  cups daily and dried tea leaves  $>1000$  g annually (Liu et al., 2015b).

The effect of alcohol intake on development of AML was not supported in previous studies (Brown, Gibson, Burmeister, Schuman, Everett, & Blair, 1992; Hinds, Kolonel, Lee, & Hirohata, 1980; Williams & Horm, 1977). In an Italian multicenter case-control study, a non-significant increased risk of all leukemias, AML, CLL and ALL was observed for the highest quartile ( $>31 \text{ g/day}$ ) of alcohol intake (Gorini et al., 2007). In this study, the risk of CML was significantly increased in the highest quartile ( $>27.7 \text{ g/day}$ ) of wine intake (2.13, 95% CI 1.01-4.50).

However, a recent systematic review and meta-analysis did not support increased leukemia risk among alcohol drinkers (Rota et al., 2014).

### 2.3.3 Therapy related factors

Adult leukemia sometimes occurs following a primary neoplasm. The most frequently reported primary cancers preceding secondary leukemia are lymphomas and breast cancer (Fianchi et al., 2015; Howard et al., 2007). However, there is evidence also for other cancer types such as testicular cancer and prostate carcinoma (Travis et al., 2000).

In a number of studies, this phenomenon has been linked to certain types of chemotherapy drugs and radiotherapy administered to patients treated for primary cancers (Boivin, 1990; Kyle, 1982). However, it is often difficult to attribute an observed risk of secondary leukemia to a particular therapy-related factor, because various chemotherapeutic drugs are usually administered in combination with radiotherapy (Kröger et al., 2003). Alkylating agents, platinum-containing anti-cancer drugs, topoisomerase II-inhibitors, anti-tumor antibiotics are among chemotherapeutic drugs that have been linked to secondary leukemia.

Alkylating agents have been linked to AML but not ALL in an Italian multi-center (GIMEMA) study (Pagano et al., 2000). In a case-control study nested in an international cohort of 18,567 one-year survivors of testicular cancer, a significantly increased risk of secondary leukemia ( $OR=3.2$ , 95% CI 1.5-8.4) was observed among patients receiving cisplatin for cumulative dose of 650 mg (Travis et al., 2000). Larger cumulative doses of cisplatin (1000 mg) were linked to significantly increased 6-fold risk in that study. However, no increased leukemia risk was observed for other chemotherapeutic agents such as etoposide and bleomycin (Travis et al., 2000). Mitoxantrone administered breast cancer patients had significantly increased risk of secondary AML and myelodysplastic syndrome (MDS) ( $RR=10.1$ , 95% CI 3.5-16.7) and AML alone ( $RR=14.1$ , 95% CI 2.8-25.4) compared to the general population in a study by Saso et al. (2000). Kröger et al. (2003) also observed secondary AML cases emerging after about 57 months of follow-up in a group of 305 breast cancer patients who received mitoxantrone-based high dose chemotherapy. Some of topoisomerase II-inhibitor drugs (e.g. anthracyclines) were linked to increased risk of secondary acute promyelocytic leukemia (APL) following 3-years treatment of breast carcinoma (Beaumont et al., 2003). The lag-time following treatment with topoisomerase II-inhibitors is about 2 years and MDS usually does not precede secondary leukemia (LeBeau et al., 1986; Felix, 1998).

The evidence for radiation therapy of cancer seems to be weaker than that for chemotherapy. In an Italian cohort study of breast cancer patients undergoing radiotherapy with either tele-cobalt unit or linear accelerator, an elevated risk of secondary leukemia (RR=6.67, 95% CI 0.76-58.00) was observed during two or more years following the treatment (Zhang, Becciolini, Biggeri, Pacini, & Muirhead, 2011). In another cohort study (Kaplan, Malmgren, & Atwood, 2011), breast cancer patients receiving both combination of radiotherapy and chemotherapy, and radiotherapy alone were at increased risk of AML and MDS/AML compared to population incidence data. In that study, the risk of AML seemed to be restricted in women younger 65 years (RR=5.32, 95% CI 1.31-14.04) than women older 65 years (RR=2.38, 95% CI 0.73-5.61). In a cohort study based on data from eight national cancer registries from North America and Europe, the risk of leukemia was 3-fold among patients receiving radiotherapy (mean dose 12.6 Gy) to pelvis, abdomen and chest and the risk significantly increased by administered dose (Travis et al., 2000). However, no increased leukemia risk was observed among thyroid cancer patients following iodine-131 therapy (De Vathaire et al., 1997). Radiotherapy for diseases other than cancer has also been linked to elevated leukemia risk. For example, enhanced rate of leukemia was observed among patients injected radium-224 for the treatment of ankylosing spondylitis (Wick, Nekolla, Gaubitz, & Schulte, 2008; Wick, Atkinson, & Nekolla, 2009). Median lag-time after radiotherapy was reported to be longer than that following chemotherapy in an Italian study (Fianchi et al., 2015).

Patients undergoing radiation diagnostics may also be at risk of subsequent leukemia, however, the evidence is weaker than that for radiation therapy. Diagnostic radiation involves radiation doses lower than that received during radiation therapy. Assessment of exposure to diagnostic radiation maybe challenging as it heavily relies on patient's memory that may span for a long time. Diagnostic X-ray has been linked to leukemia risk in small case-control studies (Flodin, Fredriksson, Persson, & Axelson, 1990; Preston Martin, Thomas, Yu, & Henderson, 1989). Conversely, no leukemia risk was observed in a larger study of tuberculosis patients who repeatedly received fluoroscopy (Davis, Boice, Hrubec, & Monson, 1989). Among radioactive contrast agents, thorotrast, is a well-known leukemia risk factor. It is an alpha-emitting contrast that was widely used in the world between 1920 and 1950 for various diagnostic procedures (Ron, 2003). Epidemiologic follow-up studies of patients receiving thorotrast consistently showed an increased leukemia risk (Dos Santos Silva, Jones, Malveiro, & Swerdlow, 1999; Mori et al., 1999; Nyberg et al., 2002; Van Kaick et al., 1999).

## 2.3.4 Environmental factors

Environmental risk factors have received widespread attention in epidemiological studies of adult leukemia (Zeeb & Blettner, 1998). These factors include various chemical and non-chemical agents, and exposure to these factors is common in occupational settings. Because occupational groups are commonly used as a proxy for specific occupational exposures, they are also discussed in this chapter.

### 2.3.4.1 Occupational groups

Increased incidence and mortality of adult leukemia has been observed in various occupational groups. Farming and farming related jobs, rubber industry workers, shoe workers, and petroleum workers are the occupational groups most commonly linked to excess leukemia incidence and mortality.

Excess leukemia (ANLL and ALL) risk was reported among meat industry workers (abattoir and butchers) in New-Zealand (Bethwaite, McLean, Kennedy, & Pearce, 2001). The risk among abattoir workers was confined to those working more than two years ( $OR=4.9$ , 95% CI 1.5-15.6) and having direct contact with animals or animal products ( $OR=5.2$ , 95% CI 1.2-22.2). The risk among butchers was observed among butchers working in abattoir ( $OR=4.8$ , 95% CI 1.1-20.0) but not among retail/wholesale butchers and meatpackers ( $OR=1.2$ , 95% CI 0.4-3.6) (Bethwaite et al., 2001). In a Canadian population based case-control study, subjects occupationally exposed to beef cattle were at significant leukemia risk ( $OR=2.0$ , 95% CI 1.2-3.3) and the risk was confined to a group of workers with duration of working with beef cattle for more than 30 years ( $OR=3.0$ , 95% CI 1.4-6.3). Other animal-related occupations (e.g. dairy cattle, poultry, horses, pigs, and fish) were not linked with excess leukemia risk in this study (Fritschi, Johnson, Kliwer, Fry, & the Canadian Cancer Registries Epidemiology Research Group, 2002). The risk of ALL, CLL and AML was elevated among farmers in Ireland (Kelleher et al., 1998) and the risk of CLL was increased among animal breeding farmers in Italy (Amadori et al., 1995).

Excess deaths due to leukemia ( $SMR=219$ , 95% CI 109-392) were observed among rubber industry workers in Germany. The risk was confined to workers hired during 1950-1959 and having work experience for more than 10 years (Straif et al., 1998). Rubber workers were at increased leukemia risk also in an Italian multi-center case-control study (Costantini et al., 2001). Non-significantly increased risk of overall leukemia and AML among petroleum workers was restricted to workers hired before

1950 (Raabe, Collingwood, & Wong, 1998). In this study, the risk peaked during 1960s and no more elevation was observed after 1980. The risk of leukemia among shoe workers ( $SMR=536$ , 95% CI 111-1566) was restricted to shoe workers first hired between 1950 and 1959 when benzene exposure was substantial (Fu et al., 1996). Restriction of leukemia risk to earlier but not recent periods may be due to reduction of level of some carcinogenic agents at work places over time as a result of strict regulations of exposure limits (Wong, Harris, & Smith, 1993).

Increased leukemia risk was also observed among painters, material handlers, metal processors, printers ( $OR=3.20$ , 95% CI 1.5-9.77), management, business and finance workers, sales managers, engineers, radiological technologists, automobile manufacture workers ( $OR=2.50$ , 95% CI 1.17-5.34), food and beverage industry ( $OR=1.61$ , 95% CI 1.02-2.56), airline workers (Band et al., 1996; Robinson et al., 2015; Wong, Harris, Armstrong, & Hua, 2010; Yoshinaga, Aoyama, Yoshimoto, & Sugahara, 1999).

It is difficult to attribute an excess leukemia risk in an occupational group to particular agent because workers in the same occupation are usually exposed to a diverse group of chemical and non-chemical factors simultaneously. For example, farmers and farmworkers may be occupationally exposed to pesticides and various biological agents from animals. Petroleum, rubber industry workers, painters, printers and shoe makers may be exposed to benzene and other solvents. For some other occupations such as sales managers, business and finance workers there are no known chemical and non-chemical factors.

In many studies of occupational groups (e.g. airline pilots, shoe manufacturing workers, petroleum refinery workers), statistically significant decreased overall mortality, compared to general population, was reported (Band et al., 1996; Fu et al., 1996; Raabe et al., 1998). In some studies, reduced mortality was observed for some specific cancers (e.g. cancer of liver, rectum, buccal cavity and pharynx) (Raabe et al., 1998). Decreased mortality in these studies is believed to result from the healthy worker effect because comparisons were usually made with the general population. This suggests that if expected cases were estimated from a comparable population (e.g. employed population), the risk estimates would have probably been larger. In fact, a cancer mortality study among radiological technologists in Japan showed no increased risks for leukemia when expected cases were estimated using the general population of Japan. However, when professional and technical workers were used as a standard population, leukemia risk reached a statistically significant level ( $SMR=1.75$ , 95% CI 1.07-2.71) (Yoshinaga et al., 1999).

### 2.3.4.2 Chemical factors

*Benzene.* Benzene is used in the manufacture of other chemicals (e.g. cyclohexane, cumene, phenol, aniline, and styrene) and as a component of dyes, rubber, detergents, pesticides, gasoline etc. (ATSDR, 2007; IARC, 2012; Williams, Panko, Unice, Brown, & Paustenbach, 2008). Occupational exposure to benzene occurs via inhalation or dermal absorption of solvents in rubber and paint manufacturing industries; during crude oil refining and chemical manufacturing (IARC, 2012). The level of benzene exposure may differ across occupational categories. For example, in rubber, shoe and paint manufacturing it is higher than in oil industry (IARC, 2012).

Benzene exposure may also occur in a non-occupational setting from gasoline filling-stations, tobacco smoke, air contaminated with benzene (from industrial sources, heavy traffic areas etc.) (ATSDR, 1997). Compared to occupational exposure, non-occupational benzene exposure is generally very low. For example, outdoor air concentrations of benzene in the U.S. was 0.02 parts per billion (ppb) (0.06 microgram ( $\mu\text{g}$ )/ $\text{m}^3$ ) in rural area, and 112 ppb (356  $\mu\text{g}/\text{m}^3$ ) in an urban area (ATSDR, 1997). In an urban area exposure was the highest around gasoline filling-stations and heavy motor-vehicle traffic. Amount of benzene per cigarette ranged from 5.9 to 75  $\mu\text{g}$  in mainstream smoke and from 345 to 653  $\mu\text{g}$  in sidestream smoke (ATSDR, 1997). Average airborne benzene exposure ranges from 3.7 to 41  $\mu\text{g}/\text{m}^3$  in the UK (Duarte-Davidson, Courage, Rushton, & Levy, 2001). Residential exposure to benzene may also occur from drinking contaminated water or eating contaminated food (IARC, 2012). The level of benzene intake via ingestion is considerably lower than intake from ambient air (ATSDR, 1997).

In high concentrations, benzene can suppress bone marrow cell proliferation and lead to hematologic disorders (IARC, 2012). In 1982, IARC classified benzene as Group-1 carcinogen (IARC, 2012).

The first suggestion of leukemogenic effect of benzene exposure came from a case report in 1928 (Delore & Borgomano, 1928) and was followed by other case reports (Aksoy, Din Col, Erdem & Din Col, 1972; Aksoy, Erdem & Din Col, 1974; Vigliani, 1976). These studies were followed by a large number of industry- and population-based cohort and case-control studies. In this summary, characteristics and results from industry-based studies found through the literature review are presented and discussed (Table 2).

The strongest epidemiologic evidence was observed for an association between high benzene exposure levels and non-lymphocytic leukemia (ANLL) (Divine & Hartman, 2000; Glass et al., 2003; Guenel et al., 2002; Hayes et al., 1997). There is also some evidence for other leukemia subtypes (Glass et al., 2003; Hayes et al., 1997;

Huebner et al., 2004). In an Italian case-control study, benzene exposure was associated with CLL, but not with AML (Costantini et al., 2008).

Excess leukemia risk was reported for various benzene exposure levels. Evidence seems to be stronger for high exposure levels, but for low levels the results are inconsistent. For example, Collins, Ireland, Buckley, and Shepperly (2003) observed increased risk of leukemia and ANLL for peak levels  $>100$  parts per million (ppm), Aksoy et al., (1972) for average exposure  $>25$  ppm. In a Chinese multi-industrial cohort, risk of leukemia subtypes was elevated at average levels  $<10$  ppm, and increased by increasing exposure level and duration of exposure (Hayes et al., 1997). Leukemia risk was evident among gas- and electric-utility workers with cumulative exposures  $\geq 16.8$  ppm-years and average intensity of  $<1$  ppm (Guenel et al., 2002). In a Pliofilm cohort study, workers exposed to benzene levels  $>200$  ppm-years were at increased AML risk (Wong, 1995). In a study of Australian, Canadian and UK petroleum workers with cumulative exposure 10 ppm-years equivalent to average exposure intensities of 0.2-0.3 ppm, no evidence of leukemia risk was observed (Schnatter, Glass, Tang, Irons, & Rushton, 2012). Cancer incidence between 1971 and 1994 was studied in a cohort of Finnish oil refinery workers, and no increased risk of leukemia was observed (SIR=1.02, 95% CI 0.47-1.93) (Pukkala, 1998). Rushton and Romaniuk (1997) observed a weak association between myeloid leukemia and cumulative benzene exposure levels  $<45$  ppm-years in a study of petroleum marketing and distribution workers in the UK. In a large Texas cohort of oil refinery workers, an increased SMR (259.6, 95% CI 112.1-511.5) was observed for ALL but not for other leukemia cell-types (Satin et al., 1996).

The temporal pattern of risk suggested that the risk of leukemia from benzene exposure was higher in earlier periods and increased by duration of exposure. Sathiakumar et al. (1995) reported increased risk of AML for oil and gas production workers (OR=2.8, 95% CI 1.1-7.3). This risk was restricted to employees hired for over 32 years (highest tertile of employment duration) (OR=8.7, 95% CI 2.0-37) and there was a consistent trend of ORs with increasing duration of employment (Sathiakumar et al., 1995). In Texaco crude oil workers, risk of AML was higher among those first employed before 1940 (Divine & Hartman, 2000) and in a multi-industrial cohort in China, workers hired before 1972 had higher ANLL risk (Hayes et al., 1997). Similarly, significantly increased mortality from ANLL and ALL was observed in Baton Rouge workers (ExxonMobil refinery/petrochemical workers) before and during World War II, but not after (Huebner et al., 2004). Authors suggested two possible explanations: first, wartime exposures and production processes might have been different than during later periods; second those worked

at plant might have had poorer health than those who were recruited to active military service (Huebner et al., 2004). Among Norwegian offshore workers the risk of leukemia and AML was more evident for the first exposure during 1981-1985 compared to 1986-2003 (Kirkeleit, Riise, Bråteit, & Moen, 2008). Among gas and electric utility workers, the risk seemed to be restricted to persons first exposed before 1960 (Guenel et al., 2002). In a Texas cohort study of petroleum workers, leukemia risk seemed to be restricted to those hired before 1950 (Wong, Harris, Rosamilla, & Raabe, 2001). The temporal pattern of leukemia risk among benzene exposed workers can be related to strict regulation of exposure limits in some countries. For example, in the US, 8-hour daily time-weighted average benzene exposures were reduced from 100 ppm to 50 ppm in 1947, and from 50 ppm further down to 35 ppm in 1948 (Wong et al., 1993).

Lag-time analyses in some studies indicated that relatively recent but not too distant benzene exposures were related to adult leukemia. In a study of gas and electric utility workers (Guenel et al., 2002) the risk was observed for 2, 5 and 10 years lag-time. In a recent cohort study of rubber hydrochloride workers, RR of leukemia was the highest in the 10 years immediately after exposure and risk gradually decreased to background levels in 20 years and more after exposure (Richardson, 2008). In a Chinese multi-industrial cohort, exposures occurring less than 10 years before diagnosis were more strongly related to the leukemia risk (Hayes et al., 1997).

Despite being based on similar occupational group (e.g. petroleum workers), some studies reported an increased risk of leukemia (Divine & Hartman, 2000; Glass et al., 2003; Kirkeleit et al., 2008), while others did not (Lewis et al., 2003; Rushton, 1993, Rushton & Romaniuk, 1997). Inconsistent results were observed even in studies based on the same cohort. For example, strong evidence for ANLL and CLL was reported in a case-control study nested in Australian Health Watch cohort (1981-1996) (Glass et al., 2003). However, in an updated follow-up of the same cohort through 31 December 2001 no evidence was observed (Gun, Pratt, Ryan, & Roder, 2006). In an updated follow-up (1970- 1997) of ExxonMobil refinery/petrochemical workers, significantly increased risk of ANLL was observed, which was not evident in previous update (1970-1992) (Huebner et al., 2004). Potential explanations for inconsistencies include accuracy of disease status ascertainment and exposure measurement, differences in study designs, study populations and exposure metrics.

Although the results of individual studies did not provide strong evidence, the most recent reviews supported an association between occupational benzene exposure and AML, CLL, CML and ALL (Vlaanderen, Lan, Kromhout, Rothman,

& Vermeulen, 2011; Vlaanderen, Lan, Kromhout, Rothman, & Vermeulen, 2012). One of explanations for this discrepancy is the fact that these review studies provided only pooled risk estimates for “any occupational benzene exposure” vs “background benzene exposure”, and overall estimates could have been influenced by large estimates from single studies. The authors selected this general approach because they wanted to also include studies that did not provide stratum-specific risk estimates but only overall estimates. However, it seems that more detailed analysis could have been performed in many cases. For example, Vlaanderen et al. (2011) reported a summary meta-RR of 2.32 (95% CI 1.55-3.47) for AML based on six studies, which authors classified as studies with the best quality of exposure assessment (Group A studies). Among these studies, a statistically significant overall risk estimate (SMR=5.03, 95% CI 1.84-10.97) based on only six observed cases was observed only in a Pliofilm cohort study (Wong, 1995). All of the remaining studies reported non-significantly increased overall AML risk (Bloemen et al., 2004; Collins et al., 2003; Glass et al., 2003; Hayes et al., 1997; Rushton & Romaniuk, 1997). It is possible that the overall pooled risk estimate in this analysis could have been influenced by a single estimate from Wong (1995). All of these six studies provided stratum-specific risk estimates for various exposure levels, and pooled estimates for various exposure levels in this specific analysis would probably be more informative than overall pooled estimate.

Table 2. Cohort and case-control studies of occupational benzene exposure and adult leukemia (AML – acute myeloid leukemia; CML – chronic myeloid leukemia; ALL – acute lymphocytic leukemia; CLL – chronic lymphocytic leukemia; ANLL – acute non-lymphocytic leukemia; CMML - chronic myelomonocytic leukemia; OR – odds ratio; SMR – standardized mortality ratio; RR – relative risk; ppm – parts per million).

Reference	Country, follow-up <sup>a</sup>	Study population/Industry	Outcomes	Exposure assessment <sup>b</sup>	Main findings
<b>Case-control study</b>					
Sathiakumar et al., 1995	USA, 1976-1990	69 leukemia cases and 284 matched controls selected from employees at large petroleum company.	Leukemia, AML	Qualitative	The association with AML was observed for oil and gas production workers (OR=2.8, 95% CI 1.1-7.3). It was restricted for workers hired for more than 32 years (highest tertile of employment duration) (OR=8.7, 95% CI 2.0-37). Also significantly increasing risk trend was observed for employment duration in oil and gas production.
Schnatter et al., 1996	Canada, 1964-1983	16 leukemia cases 64 controls nested in petroleum distribution workers.	Leukemia	Semi-quantitative	No evidence of leukemia risk (OR=1.002).
Rushton & Romaniuk, 1997	UK, -1991	91 cases and 364 controls nested in petroleum marketing and distribution workers cohort.	Leukemia, AML, ALL, CML, CLL	Semi-quantitative	Non-significantly increased risk of AML without a clear trend was observed for cumulative exposures <45 ppm-years. The risk of AML also seemed to increase from zero 10 year lag-time. The job history data was incomplete and sometimes it had to be

<b>Reference</b>	<b>Country, follow-up<sup>a</sup></b>	<b>Study population/industry</b>	<b>Outcomes</b>	<b>Exposure assessment<sup>b</sup></b>	<b>Main findings</b>
					supplemented from other sources, such as medical and pension records, and interviews.
Guenel et al., 2002	France, 1978-1989	72 cases and 285 controls nested in gas- and electric-utility workers.	Leukemia, AML, CML, ALL, CLL	Semi-quantitative	OR=3.6 (95% CI 1.1-11.7) for leukemia at cumulative exposure >16.8 ppm-years. For some of subtypes non-significantly increased risk observed.
Glass et al., 2003	Australia, 1981-1994	79 cases and 395 controls nested in Australian petroleum workers (Health Watch Cohort).	Leukemia, CLL, CML, ALL, ANLL	Semi-quantitative	OR=7.17 (95% CI 1.27-40.4) for ANLL and OR=4.52 (95% CI 0.89-22.9) for CLL at cumulative lifetime exposure >8 ppm-years. No association for cumulative lifetime exposures <8 ppm-years. The number of exposed cases were small.
Costantini et al., 2008	Italy, 1991-1993	586 cases and 1,278 controls from 11 provinces in Italy.	Leukemia, AML, CLL	Qualitative	Non-significant risk for CLL (OR=1.8, 95% CI 0.9-3.9), and no evidence for AML (OR=0.9) for medium/high exposure.
Gross et al., 2012	China, 2003-2007	36 cases and 72 controls selected from 28 hospitals	CMMI	Semi-quantitative	No evidence of increased risk.
Schnatter et al., 2012	Australia, Canada, UK, -2006	370 cases and 1587 controls nested within Australia, Canada and UK petroleum workers cohorts.	AML, CML, ALL	Semi-quantitative	Non-significantly increased risk estimates were observed for some exposure metrics.
<b>Cohort study</b>					

<b>Reference</b>	<b>Country, follow-up<sup>a</sup></b>	<b>Study population/Industry</b>	<b>Outcomes</b>	<b>Exposure assessment<sup>b</sup></b>	<b>Main findings</b>
McCraw et al., 1985	USA, 1973-1982	All white male employees at the Wood River Refinery.	AML, CML, ALL, CLL	Qualitative	SMR=394 (95% CI 172-788) for AML, for other cell-types no increased risk was observed.
Rushton, 1993	UK, 1950-1975	34,569 oil refinery and 34,781 distribution workers (males).	AML, ALL, CLL, CML, monocytic leukemia, other leukemia	Qualitative	All SMR estimates were non-significant, except for other leukemia (SMR=678, 95% CI 273-1397) based on 7 cases.
Wong et al., 1993	USA, 1946-1985	18,135 petroleum distribution workers (land-based terminal and marine workers).	Leukemia, AML, CML, ALL, CLL	Semi- quantitative	No evidence of leukemia by various exposure metrics. Only non-significantly increased risk for AML (SMR=1.5, p-value>0.05).
Wong, 1995	USA, 1940-1987	Cohort of workers employed at two Goodyear plants in Ohio in the manufacture of Pliofilm (rubber hydrochloride).	AML	Semi-quantitative	SMR=27.21 (95% CI 3.29-98.24) for cumulative exposure levels 200-400 ppm-years, SMR=98.37 (95% CI 20.28-287.65) for levels >400 ppm-years. Overall SMR=5.03 (95% CI 1.84-10.97). There were only 2 observed cases in the category 200-400 ppm-years and 3 cases in the category >400 ppm-years.
Wong & Raabe, 1995	USA, UK, 1937-1989	208,000 petroleum workers from US and UK.	AML, ALL, CML, CLL	Qualitative	No evidence of leukemia risk. SMR=0.96 (95% CI 0.81-1.13) for AML; SMR=0.89 (95%

Reference	Country, follow-up <sup>a</sup>	Study population/Industry	Outcomes	Exposure assessment <sup>b</sup>	Main findings
					CI 0.68-1.15) for CML; SMR=1.16 (95% CI 0.81-1.61) for ALL. Authors attributed the lack of association to low levels of benzene exposure in study population.
Satin et al., 1996	USA., 1937-1987	17,844 employees of a large Texas refinery cohort.	Leukemia, AML, CML, ALL, CLL	Qualitative	SMR=259.6 (95% CI 112.1-511.5) for ALL was observed. For other cell-types no increased risk reported. SMR for AML was 62.7 (95% CI 30.1-115.3). Analyses stratified by sex and employment duration did not show any significantly increased risk for leukemia.
Yin et al., 1996	China, 1972-1987	74,828 exposed and 35,805 unexposed subjects.	Leukemia, AML, CLL, CML, ALL	Qualitative	RR=2.6 (95% CI 1.3-5.7) for leukemia; RR=3.1 (95% CI 1.2-10.7) for AML.
Hayes et al., 1997	China, 1972-1987	74,828 exposed and 35,805 unexposed workers (multi-industrial cohort).	Leukemia, ANLL, other leukemia	Semi-quantitative	RR=3.0 (95% CI 1.0-8.9) for ANLL; the risk seemed to be restricted among those hired before 1972 but not evident in later periods. ANLL risk was statistically significantly increased for average exposure 10-24 ppm (RR=5.8), but not for <10 ppm (RR=3.2) and ≥25 ppm (RR=4.1); for exposure duration <10 years (RR=4.3) but not ≥10 years

Reference	Country, follow-up <sup>a</sup>	Study population/industry	Outcomes	Exposure assessment <sup>b</sup>	Main findings
					(RR=2.8); and for cumulative exposures >40 ppm-years. No significant trend of increasing ANLL risk was observed and the number of cases was less than 15 in all stratified analyses.
Divine et al., 1999	USA, 1947-1993	28 840 workers of Texaco mortality study	Leukemia, AML, CLL, CML, ALL	Qualitative	Mortality of leukemia and cell-types was not increased in the cohort. SMR=155 (95% CI 93-243) for AML for those employed before 1950 and SMR=30 (95% CI 0-168) for those employed after 1950.
Divine & Hartman, 2000	USA, 1946-1994	24,124 crude oil production workers (Texaco cohort).	Leukemia, AML, CLL, CML, ALL	Qualitative	SMR=1.92 (95% CI 1.10-3.13) for AML and the risk was restricted among those first employed before 1940 and worked >20 years.
Wong et al., 2001a	USA, 1945-1996	7,543 Beaumont, Texas petroleum refinery workers.	Leukemia, AML, CLL, CML, ALL	Qualitative	Overall results did not show association (leukemia SMR=1.39, 95% CI 0.99-1.90).
Wong et al., 2001b	USA, 1959-1997	3,328 workers who were employed at the Mobil (now ExxonMobil) Torrance, California.	AML, CML, ALL, CLL	Qualitative	SMR=74.4 (95% 1.9-414.3) for CLL; SMR=45.4 (95% 1.1-252.8) for AML; SMR=195.6 (95% CI 23.7-706.6) for CML. For ALL there were 0 observed cases and SMR was not estimated. No risk pattern was

<b>Reference</b>	<b>Country, follow-up<sup>a</sup></b>	<b>Study population/industry</b>	<b>Outcomes</b>	<b>Exposure assessment<sup>b</sup></b>	<b>Main findings</b>
					observed by time since hire or employment duration.
Collins et al., 2003	USA, 1940-1997	4,172 male and 245 female workers of chemical plant in Illinois.	Leukemia, ANLL, CLL	Semi-quantitative	No significantly increased risk was observed for leukemia. SMR for ANLL was 4.1 (95% CI 95% CI 0.5-14.9) for >40 days exposure to peak exposure levels (>100 ppm). No significantly increased ANLL risk was observed for cumulative exposures <1 ppm-years (SMR=1.4, 95% CI 0.1-5.1); 1-6 ppm-years (SMR=2.7, 95% CI 0.3-9.9), >6 ppm-years (SMR=2.2, 95% CI 0.3-8.1). The number of observed cases were small (<5) in all ANLL analyses and there was a limited exposure information for 1940s and 1950s.
Lewis et al., 2003	Canada, 1964-1994	25,292 petroleum workers.	Leukemia, ANLL, CLL, ALL, AML	Qualitative	No evidence of leukemia risk.
Bloemen et al., 2004	USA, 1940-1996	2,266 chemical workers from Michigan.	Leukemia	Semi-quantitative	SMR for leukemia was 1.14 (95% CI 0.59-1.99), for ANLL 1.11 (95% CI 0.30-2.83), for CLL 0.42 (95% CI 0.01-2.36). There was no significantly increased SMR for ANLL in the analyses of duration, cumulative exposure

Reference	Country, follow-up <sup>a</sup>	Study population/Industry	Outcomes	Exposure assessment <sup>b</sup>	Main findings
					and average intensity and the number of exposed cases was mainly <5 in all stratified analyses.
Huebner et al., 2004	USA, 1970-1997	7,637 Baton Rouge (Illinois) and 7,007 Baytown (Texas) workers of two ExxonMobil refinery/petrochemical workers.	Leukemia, ANLL, CLL, ALL, CML	Qualitative	Risk of ANLL seemed to be increased in Baytown cohort (SMR=2.13, 95% CI 1.10-3.73) but not in Baton Rouge; the risk of CLL was increased in Baton Rouge (SMR=2.42, 95% CI 1.16-4.45) but not Baytown cohort.
Gun et al., 2006	Australia, 1980-2001	16,547 males and 1,356 females (Australian Health Watch cohort).	Leukemia, AML, CLL, ALL, CML	Semi-quantitative	No evidence of increased risk of leukemia subtypes.
Kirkeleit et al., 2008	Norway, 1981-2003	27,919 offshore petroleum workers and 366,114 referent group from general population.	Leukemia, AML, ALL, CML, CLL	Qualitative	RR=2.89 (95% CI 1.25-6.67) for AML among upstream offshore workers, for other job categories no risk was observed.
Richardson, 2008	USA, 1940-1965	1,845 rubber hydrochloride workers.	leukemia	Semi-quantitative	Leukemia risk seemed to be increased (RR=1.19, 95% CI 1.10-1.29) at 10 ppm for about 10 years duration and showed decreasing tendency for duration >10 years. Benzene exposures accrued at age ≥45 years seemed to be more strongly associated

<b>Reference</b>	<b>Country, follow-up<sup>a</sup></b>	<b>Study population/industry</b>	<b>Outcomes</b>	<b>Exposure assessment<sup>b</sup></b>	<b>Main findings</b>
					with leukemia than exposures accrued at younger ages.

<sup>a</sup> Follow-up period corresponds either to the time period of exposure assessment or case diagnosis in case-control studies.

<sup>b</sup> Semi-quantitative exposure measurement was based on job-history data that were converted to numeric exposure either by using job-exposure matrix or expertise of industrial hygienist; qualitative measurements grouped subjects into exposed and unexposed and did not provide numeric exposure estimates.

*Formaldehyde.* Formaldehyde has a large number of industrial uses and is found in many consumer products (NTP, 2010). Its primary use in industry is in production of resins. Occupational exposure to formaldehyde may occur among manufacture workers of resins, furniture, plastics, fiberglass, histologists and pathologists, embalmers, foundry and construction workers and many other occupational groups. The main source of exposure is through inhalation of formaldehyde gases present indoors (NTP, 2010). Non-occupational exposure may occur from many home products such as furniture, carpets, fiberglass products, latex paints, fingernail hardeners, grocery bags, paper towels etc. (ATSDR, 2010). Based on sufficient evidence for nasopharyngeal cancer, formaldehyde has been classified as a Group 1 carcinogen (IARC, 2006). In 2009, the IARC working group reaffirmed carcinogenicity of formaldehyde for humans and concluded that evidence for leukemia, particularly myeloid type, is sufficient (Baan et al., 2009).

Studies of occupational formaldehyde exposure and leukemia were mainly cohort studies based on either professional groups (e.g. embalmers, pathologists, and anatomists) or industrial workers. These studies are summarized in Table 3.

The strongest evidence was observed in a cohort study of U.S. formaldehyde industry workers ( $RR=3.46$ , 95% CL 1.27-9.23) (Hauptmann, Lubin, Stewart, Hayes, & Blair, 2003) and a case-control study of U.S. embalmers ( $OR=11.2$ , 95% CL 1.3-95.6) (Hauptman et al., 2009). In a cohort study of industrial workers, the risk of leukemia and myeloid leukemia was statistically significantly increased for peak exposures  $>2$  ppm, non-significantly increased for average intensity  $>0.5$  ppm and duration of exposure  $>15$  years. Cumulative exposure was not associated with leukemia risk (Hauptmann et al., 2003). In a case-control study of embalmers, the risk of myeloid leukemia and AML increased by duration of working in jobs with embalming ( $>20$  years), cumulative formaldehyde exposures greater than 9253 ppm-hours, and number of embalming ( $>1422$ ). Also average intensity and peak exposure seemed to predict increased risk (Hauptmann et al., 2009). Little evidence for lymphatic leukemia was observed in both studies. Association between formaldehyde exposure and leukemia was also suggested in mortality studies of embalmers, garment workers (Hayes, Blair, Stewart, Herrick, & Mahar, 1990; Walrath & Fraumeni, 1984). However, Coggon, Ntani, Harris, and Palmer (2014) and Pira, Romano, Verga, and La Vecchia (2014) did not observe any evidence of increased risk of leukemia from formaldehyde exposure in cohorts of British chemical workers and Italian laminated plastic factory workers respectively.

Beane Freeman et al. (2009) updated a cohort study of industrial workers (Hauptmann et al., 2003) with additional 10 years follow-up. In this update, risk estimates for leukemia and myeloid leukemia diminished and became non-significant. This could reflect either increased precision of risk estimates due to accrual of additional cases or relatively short induction period following formaldehyde exposure (Beane Freeman et al., 2009). Diminished risk of leukemia was also observed in an update of 11,098 U.S. formaldehyde exposed garment workers (Meyers, Pinkerton, & Hein, 2013). In this study, risk was elevated only among workers first hired before 1963, but not after. Also the risk was restricted to longer time since first exposure ( $>20$  years) and duration ( $>10$  years).

One of major limitations in studies of formaldehyde was an accuracy of exposure measurement. Because no data on exposure measurement were available, exposure estimates were derived merely based on the knowledge of industrial hygienist in some studies (Beane Freeman et al., 2009; Hauptmann et al., 2003). In a case-control study of embalmers, exposure was estimated using predictive models based on duration, year of exposure, availability and type of ventilation at work place and other predictors of exposure (Hauptman et al., 2009). The latter was collected through interviewing next of kin of deceased subjects and there was a likely recall bias. Despite having individual measurements for some years, some studies did not derive numeric exposure estimates (Meyers et al., 2013; Pinkerton, Hein, & Stayner, 2004).

Bosetti, McLaughlin, Tarone, Pira, and La Vecchia (2008) reviewed cohort studies of formaldehyde through 2006, and found a pooled relative risk of 1.39 (1.15-1.68) for leukemia. Schwick, Zhang, Smith, Smith, & Steinmaus (2010) also observed increased risk for leukemia (RR=1.53, 1.11-2.21) and for AML (RR=2.47, 1.42-4.27) in a review study of formaldehyde exposure. However, another review concluded that evidence for an association between formaldehyde and lymphohematopoietic malignancies including AML was inconsistent across studies and there was little evidence for a dose-response relationship (Checkoway, Boffetta, Mundt, & Mundt, 2012).

Table 3. Cohort and case-control studies of occupational formaldehyde exposure and adult leukemia (AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia; RR – relative risk; SMR – standardized mortality ratio; PMR – proportional mortality ratio; CI – confidence interval).

Reference	Country, Follow-up <sup>a</sup>	Study population/industry	Outcome	Exposure assessment <sup>b</sup>	Main findings
<b>Case-control study</b>					
Hauptman et al., 2009	USA, 1960-1986	168 lympho-hematopoietic cases and 265 matched controls from embalmer cohort.	Myeloid leukemia	Semi-quantitative	Evidence was the strongest for myeloid leukemia, significantly increasing trend by duration of employment was observed. Cumulative exposure and number of embalming were also predictors of the risk.
<b>Cohort study</b>					
Walrath & Fraumeni, 1984	California, US, 1916-1978	1,046 male and 63 female embalmers.	Leukemia	Qualitative	Overall PMR was 175 ( $p<0.05$ ). When the duration of exposure was estimated by length of licensure, PMR was 221 ( $p<0.05$ ) for duration of more than 20 years. For duration less than 20 years PMR was 124 ( $p>0.05$ ).
Hauptman et al., 2003	USA, 1966-1994	25,619 workers from 10 plants.	Leukemia, myeloid leukemia	Semi-quantitative	The risk of leukemia, particularly myeloid leukemia, increased by peak exposures and average intensity of exposure, but not cumulative exposure categorized by 60 <sup>th</sup> and 80 <sup>th</sup> percentile cut-points.
Pinkerton et al., 2004	USA, 1955-1998	11,039 garment workers/2 plants from Georgia and 1 from Pennsylvania	Leukemia, myeloid leukemia	Qualitative	SMR for leukemia and myeloid leukemia was non-significantly elevated. The risk seemed to be restricted in a category of duration >10 years, time

Reference	Country, Follow-up <sup>a</sup>	Study population/Industry	Outcome	Exposure assessment <sup>b</sup>	Main findings
					since first exposure >20 years, first exposure before 1963.
Beane Freeman et al., 2009	USA, -2004	25,619 workers employed in 10 plants producing or using formaldehyde	Myeloid leukemia	Semi-quantitative	Peak exposures >4 ppm seemed to increase the risk of all leukemia and AML.
Meyers et al., 2013	USA, 1955-2008	11,098 garment workers from Georgia and Pennsylvania	Leukemia, myeloid leukemia, AML, CLL	Qualitative	Non-significantly increased risk of leukemia, myeloid leukemia and AML was observed in this study. The risk was restricted to year of first employment before 1963, time since first exposure >20 years, duration of exposure >10 years, and exposure windows (exposures from 2 to 20 years accrued at any age).
Coggon et al., 2014	England and Wales, 1941-2012	14,008 chemical workers at six factories	Leukemia, myeloid leukemia	Semi-quantitative	This study did not provide evidence for leukemia or myeloid leukemia.
Pira et al., 2014	Italy, 1947-2011	2,750 laminated plastic workers (2,227 men and 523 women)	Leukemia	Qualitative	No evidence of leukemia overall. Many exposure metrics were used in this study and no clear pattern of the risk was observed.

<sup>a</sup> Follow-up period corresponds either to the time period of exposure assessment or case diagnosis in case-control studies.

<sup>b</sup> Semi-quantitative exposure measurement was based on job-history data that were converted to numeric exposure either by using job-exposure matrix or expertise of industrial hygienist; qualitative measurements grouped subjects into exposed and unexposed and did not provide numeric exposure estimates.

*Pesticides.* Pesticides are widely used to protect crops from insects, plants and molds. Farmers are among a group of occupations with the highest occupational pesticide exposure. However, because of wide use of pesticides, exposure to these agents is also ubiquitous in a general population, with a major exposure route being through ingestion of food contaminated with pesticides (Barr et al., 2005; Barr et al., 2010). Despite consisting of diverse group of chemicals, only some of specific pesticides were classified as probably carcinogenic (Group 2A: captfol, nonarsenical insecticides, 4,4-Dichlorodiphenyltrichloroethane (DDT), glyphosate etc.) or possibly carcinogenic (Group 2B; chlordane, dichlorvos, heptachlor etc) to humans (IARC, 1991; IARC, 2016).

The link between exposure to pesticides and leukemia has been studied among farmers, agricultural workers and pesticide manufacturers (Adegoke et al., 2003; Brown et al., 1990). Overall, there appears to be weak evidence for an association between pesticide exposures and leukemia. Brown et al. (1990) observed significantly elevated leukemia risks for exposure to specific animal insecticides including the organophosphates crotoxyphos ( $OR=11.1$ , 95% CI 2.2-55.0), dichlorvos ( $OR=2.0$ , 95% CI 1.2-3.5), and famphur ( $OR=2.2$ , 95% CI 1.0-5.0), and the pyrethrins ( $OR=3.7$ , 95% CI 1.3-10.6), nicotine ( $OR=1.6$ , 95% CI 1.0-2.6) the organochlorines methoxychlor ( $OR=2.2$ , 95% CI 1.0-5.0), and DDT ( $OR=1.3$ , 95% CI 1.0-1.8).

A major limitation of the pesticide studies was the inability to evaluate specific groups of pesticides and leukemia subtypes due to scarcity of data. Some studies grouped the study population into exposed vs unexposed (Acquavella, Delzell, Cheng, Lynch, & Johnson, 2004; Adegoke et al., 2003), while others provided numeric exposure estimates based on a job-exposure matrix (Steenland, Piacitelli, Deddens, Fingerhut, & Chang, 1999).

In a cohort study of alachlor manufacturers, an increased risk ( $SMR=1165$ , 95% CI 141-4210) was observed for CML (Acquavella et al., 2004). In a population-based case-control study of agricultural workers, increased risk of leukemia ( $OR=1.2$ , 95% CI 1.0-1.5) and CLL ( $OR=1.4$ , 95% CI 1.1-1.9 was observed for farmers compared to non-farmers (Brown et al., 1990). Analysis of specific group of pesticides suggested that the risk may be restricted to specific animal insecticides (e.g. organophosphates, chlorinated hydrocarbons), but not herbicides, fungicides or crop insecticides (Brown et al., 1990). In an Italian multi-center case-control study, an increased risk of leukemia was observed for women exposed to nitro-derivatives ( $OR=5.6$ , 95% CI 1.2-29.5), dinocap ( $OR=8.5$ , 95% CI 1.7-62.7) and phosphoroamidon (5.4, 95% CI 1.4-30.4), and for men exposure to insecticide oils ( $OR=11.7$ , 95% CI 2.8-79.5) (Miligi et al., 2003). Differences in perception of the

risk and in attitudes towards using protective equipment, different exposure patterns in different cultivation situations were suggested as potential explanations for sex-specific differences in risk estimates, though the role of chance could not be excluded. A recent cohort study of chemical manufacturers and pesticide sprayers in UK did not find any evidence of risk associated with exposure to phenoxy herbicides and leukemia (Coggon, Ntani, Harris, Jayakody, & Palmer, 2015).

A review of cohort studies of pesticide manufacturing workers yielded a pooled relative risk of leukemia (pooled-RR=1.60, 95% CI 1.02-2.52) and myeloid leukemia (pooled-RR=6.99, 95% CI 1.96-24.90) for ever exposure to phenoxy herbicides unlikely to have been contaminated with dioxins and furans (Van Maele-Fabry, Duhayon, Mertens, & Lison, 2008). Merhi et al. (2007) reviewed case-control studies of hematopoietic cancers in pesticide related occupations and observed overall leukemia risk (pooled-OR=1.35, 95% CI 0.91-2.0) in pesticide related occupations.

*Other chemicals.* Ethylene-oxide, butadiene, styrene, cadmium, polyvinyl chloride, and solvents are other chemicals that have been studied in relation to leukemia. A positive association between ethylene-oxide exposure and lymphoid leukemia was observed in a cohort study of ethylene-oxide workers (Stayner et al., 1993). However, a review based on 10 cohort studies with 29,800 workers did not show evidence of such association (summary SMR=1.06, 0.73-1.48) (Shore, Gardner, & Pannett, 1993).

In an updated cohort study of US synthetic rubber industry workers, potentially exposed to styrene-butadiene, increased mortality due to leukemia was observed among a specific group of workers (polymerization, coagulation, laboratory work and maintenance labor) (Sathiakumar et al., 2005). The length of employment and time since hire also seemed to be related to the risk in that study. However, in a mortality cohort study of styrene exposed reinforced plastic boatbuilding industry workers, no excess leukemia deaths was found (Ruder, Ward, Dong, Okun, & Davis-King, 2004).

In a cancer mortality cohort study based on the Third National Health and Nutrition Examination Survey (NHANES III), suggestive evidence of increased risks from cadmium exposure were observed (Adams, Passarelli, & Newcomb, 2011). Increased mortality due to leukemia was observed among polyvinyl chloride workers in Taiwan (Hsieh et al., 2011).

In a case-referent study, about 6-fold increased risk of leukemia associated with solvent exposure was reported (Flodin et al., 1981). Also in a Texas case-control study, occupational solvent exposure was statistically significantly linked to increased AML risk with dose response relationship in women (OR=4.18, 95% CI 2.28-7.64)

and in men ( $OR=4.26$ , 95% CI 3.00-6.04) for medium/high exposures (Strom et al., 2012). In a population-based case-control study in Shanghai, toluene exposure was associated with increased risk of adult leukemia. Dose-response relationship with increasing exposure duration was also observed ( $OR=2.9$ , 95% CI 1.3-6.7 for  $\geq 15$  years duration,  $p$  for trend=0.02) (Adegoke et al., 2003). However, these findings for solvent exposure are inconsistent with findings from other studies (Clavel et al., 1998; Lehman & Hein, 2006).

#### 2.3.4.3 Non-chemical factors

Two major types of non-chemical factors, which has been linked to adult leukemia are ionizing radiation and electromagnetic fields (EMF).

*Ionizing radiation.* Ionizing radiation (IRAD) carries sufficient energy to ionize atoms in the human body and induce chemical changes that maybe harmful for the functioning of cells (IARC, 2000). Until the end of nineteenth century, humans were exposed only to radiation from natural sources (e.g.  $\gamma$ -radiation,  $\alpha$ -emitting radon).  $\gamma$ -radiation may originate from outer space (also known as cosmic radiation) or from radioactive atoms (radionuclides) present in earth. Man-made radiation was introduced by discovery of X-rays by Wilhelm Röntgen in 1895, and many new sources of radiation have been discovered since then (IARC, 2000). Man-made radiation has found its application in diagnostics and treatment of diseases, production of weapons and electricity from nuclear power plants. The general population can be exposed to man-made radiation as a result of fallout from facilities where radionuclides are used or when they are subject to the treatment and diagnosis involving ionizing radiation. Persons working in such facilities are occupationally exposed to IRAD, usually in low doses (IARC, 2000).

Effect of IRAD on leukemia has been studied extensively. High-dose radiation exposure has been studied in the context of Hiroshima-Nagasaki atomic bomb survivors and Chernobyl accident emergency and clean-up workers. In a Life Span Study (LSS) of atomic bomb survivors followed up from 1950 to 1990, excess relative risk (ERR) of leukemia per Sievert (Sv) was 4.62 (95% CI 3.28-6.40) and attributable risk was 53.7% (Pierce, Shimizu, Preston, Vaeth, & Mabuchi, 1996). In an evaluation of hematopoietic cancer incidence among Hiroshima-Nagasaki atomic bomb survivors during 1950-1987, about 50% of all leukemia was attributable to radiation (Preston et al., 1994). Both studies concluded that there was a strong evidence for association between IRAD and all leukemia subtypes except adult T-

cell leukemia. Risk of radiation-induced leukemia among Chernobyl emergency workers of Russian cohort was similar to atomic bomb survivors (Ivanov et al., 2012). In that study, average ERR of leukemia was 4.98 per Gray (Gr) during the period 1986-1997, that is about 7-10 years since the exposure onset of cohort members. No statistically significant risk was observed for CLL and for leukemia during the years 1998-2007. The main conclusion was that leukemia-induced risk was limited on time after exposure (Ivanov et al., 2012).

The evidence for low dose radiation exposure is less consistent than that for high doses. Effect of low-dose radiation on leukemia has been studied among nuclear industry workers, uranium miners, medical personnel, airline workers and military servicemen. Increased leukemia risk among radiologists and X-ray technicians employed during the first half of the 20<sup>th</sup> century was reported in studies of British (Smith & Doll, 1981) and US radiologists (Matanoski, Sartwell, Elliot, Tonascia, & Sternberg, 1984). Leukemia mortality was also elevated among US (RR=1.64, 0.42-6.31) and Japanese (SMR=1.75, 1.07-2.71) radiologic technologists first employed before 1950 and 1960 but not later periods (Mohan et al., 2003; Yoshinaga et al., 1999). Richardson & Wing (2007b) observed a positive association between IRAD and leukemia mortality in a study of Savannah River Site nuclear weapon industry workers. Although individual studies among nuclear industry workers by Boice et al. (2006) and Matanoski et al. (2008) did not produce statistically significantly increased risk, a combined analysis of cohorts of nuclear workers yielded a small risk elevation (Cardis et al., 1995; Muirhead et al., 1999). Significantly increased incidence of AML (SIR=5.1, 1.03-14.91) was reported among Danish male jet cockpit crew members flying more than 5,000 hours but not among those flying less than 5,000 hours (Gundestrup & Storm, 1999). Excess risk of myeloid and overall leukemia was also observed in studies of military servicemen exposed to atomic weapon tests (Caldwell et al., 1983; Darby et al., 1988). However, low-dose ionizing radiation was not linked to adult leukemia among medical and research laboratory personnel, workers handling uranium and military personnel in some recent studies (Ahn, Park & Koh, 2008; Lie, Kjaerheim, & Tynes, 2008; Mohner, Gellissen, Marsh, & Gregoratto, 2010). Some studies observed increased risk with borderline significance (Mohner, Lindtner, Otten, & Gille, 2006; Richardson, Wing, & Wolf, 2007a).

*Non-ionizing radiation.* Exposure to electromagnetic fields (EMF) may occur both occupationally and residentially (IARC, 2002). The main sources of residential exposure to EMF are multiple grounded current-carrying plumbing and/or electrical circuits, appliances and nearby powerlines, including lines supplying electricity to individual homes (IARC, 2002). Exposure to EMF at workplace greatly varies across

occupations. Floderus et al. (1993) measured EMF at 1015 different workplaces by using personal dosimeters and average exposure exceeding 1 micro-Tesla ( $\mu$ T) was very rare. Occupations with the highest EMF exposure included train (railroad) drivers, lineman, sewing machine users, logging workers, welders, electricians, power station operators and sheet metal workers (Floderus et al., 1993).

Occupational or residential exposure to EMF has been considered as a risk factor for leukemia since 1979, when association between household wiring and childhood leukemia was observed (Wertheimer & Leeper, 1979). Since then, there have been many studies of both residential and occupational exposure to EMF with highly inconsistent results. In an industrial cohort study, statistically significantly increased risk of leukemia and acute leukemia (PMR=136 and PMR=162) was observed (Milham, 1985). In a case-control study nested within three cohorts of electric utility workers (1 from France, 2 from Canada), occupational exposure to 50-60 Hertz (Hz) magnetic fields was significantly associated with AML (Theriault et al., 1994). In a Swedish case-control study, occupational but not residential exposure to magnetic fields (at levels  $\geq 0.2 \mu$ T) has been linked to acute myeloid and chronic lymphocytic leukemia (Feychting, Forssen, & Floderus, 1997). These findings were further supported by findings for exposure to extremely low-frequency magnetic fields (ELF-MF) (Kheifets, Monroe, Vergara, Mezei, & Afifi, 2008; Roosli et al., 2007). Significantly elevated risk (HR=2.15, 95% CI 1.06-4.35) with dose-response was observed for AML following occupational exposure to ELF-MF in a prospective Netherlands Cohort Study (Koeman et al., 2014). There have also been a number of studies in which no evidence was observed (Floderus et al., 1993; Kheifets, London, & Peters, 1997; Kheifets et al., 1999; Willet, McKinney, Fear, Cartwright, & Roman, 2003).

In summary, the current literature review suggests that evidence for a leukemogenic effect of occupational exposure agents is mainly inconsistent. The strongest evidence seems to have accumulated for benzene, while for other exposure agents there have been limited studies. Exposure estimation in most of previous studies seems to have been a major challenge. Some of these studies could not estimate exposure quantitatively and merely grouped subjects into exposed and unexposed. The quality of exposure data was variable within the studies that provided quantitative exposure estimates, because numeric exposure values by job title and employment years was limited in most of the studies. Finally, the quality of leukemia data across studies was also variable because diverse sources of information such as health insurances, deaths certificates, medical/pathology records, pension benefits were used.

## 2.4 Exposure measurement in occupational studies

In epidemiology, the term exposure denotes any of subject's attributes or any agent with which he/she may come in contact that may be relevant to his or her health (Armstrong, White & Saracci, 1992). The objective of exposure measurement is to characterize the nature, dose (amount) and temporal pattern of exposure (Armstrong et al., 1992). The nature of exposure variable should be as specific as possible, isolating components of a broader class of exposure. Dose can reflect a total accumulated dose (cumulative exposure), rate (e.g. number of exposure episodes per day), peak exposure (the highest exposure level), and average exposure (cumulative exposure divided by duration of exposure). The most common exposure metrics used in studies included in this review were cumulative exposure, average exposure, peak exposure, duration of exposure, and start date of exposure/employment (Collins et al., 2013; Glass et al., 2003; Hayes et al., 1997). According to its relationship to exposed subjects, exposure dose can be described as available, administered, absorbed, or active dose (Armstrong et al., 1992). Available dose is measured in the external subject's environment. Administered dose or intake is the actual amount of agent coming into contact with the subject's body. How much of available dose becomes administered dose, depends on subject's physiology and behavior. From a biological point of view, administered dose can only be a surrogate for absorbed dose or uptake, which is an amount of agent that actually enters the body. Absorbed dose in its turn, is a surrogate for active or biologically effective dose at the sites in the body (e.g. organs, tissues, cells, molecules), which are the specific targets of agents (Armstrong et al., 1992).

Each exposure should also be characterized as to when it first began and ended, and how it was distributed over time (e.g. continuous, periodic). Characterizing temporal patterns of exposure is essential, because duration of exposure determines cumulative exposure and a critical time window (etiologically relevant exposure period) for many diseases. Inclusion of exposures outside of critical time window into exposure variable may lead to misclassification of exposure (Rothman, 1981).

Exposure measurement methods range from objective measurement methods on human attributes or environment (e.g. blood, urine, ambient air) to methods that may depend on subject's capacity to recall information or accuracy of recorded data. The latter is the most commonly used method in occupational studies, because objective measurements on past exposures are rarely available. For example, in most studies included in this review, exposure information was based on the work history of subjects. Work history information was obtained through employment records,

labor organizations, social security administration or self-report. In some mortality cohort studies, exposure could not be estimated quantitatively. Instead, subjects were categorized to exposed and unexposed (Yin et al., 1996; Divine & Hartman, 2000; Huebner et al., 2004). In other studies, quantitative exposure estimates for each study participant were derived from work history information either by using job-exposure matrices (JEMs) or an occupational hygiene specialist assigned exposure values. The quality of exposure information was also variable within studies with quantitative exposure estimates. For example, in a study by Bloemen et al. (2004), data on ambient benzene concentrations were available for each department in a plant. In a study by Collins et al. (2003), such information was limited only to some departments. In a Chinese multi-industrial cohort, ambient air measurements were further categorized into various time periods (e.g. 1949-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-84 and 1985+) to account for time variation of benzene exposure (Hayes et al, 1997). In an Italian multi-center case-control study, no ambient benzene estimates were available, and exposure estimates were assigned by industrial hygienists based on only work history information (Costantini et al., 2008).

Exposure measurement error is a difference between measured exposure variable and the true exposure. It is one of the major sources of bias in epidemiological studies and can lead to spurious conclusions about the relationship between exposure and disease (Armstrong et al., 1992). Exposure measurement error can result from a number of reasons including differential recollection of exposure history by subjects (recall bias) and data collector's knowledge of the subject's disease status (interviewer bias). Validity and reliability measures are often used as a benchmark for evaluation of the degree of exposure measurement error. Validity refers to the capacity of an exposure variable to measure the true exposure in a population of interest. Reliability generally refers to the reproducibility of a measure, that is, how consistently a measurement can be repeated on the same subjects. Intramethod reliability is a measure of reproducibility of an instrument, either applied in the same manner to the same subjects in two or more different times (test-retest reliability) or applied by two or more data collectors to the same subjects (inter-rater reliability). Intermethod reliability is a measure of ability of two different instruments, which measure the same exposure, to yield similar results on the same subjects (Armstrong et al., 1992). There are various measures of reliability, and the choice of the measure depends on type of exposure variables (continuous or categorical) and study design (intramethod or intermethod reliability). The most common reliability measures used for continuous variables are Pearson and Spearman correlation coefficients, intraclass correlation coefficient (ICC), Bland-

Altman plot, and reliability measures for categorical variables include the proportion of agreement (PA), Cohen's kappa and weighted kappa. The most common validity measures are sensitivity and specificity.

Intermethod reliability is quite often used in occupational studies to compare exposure measurement instrument under the study to a more accurate method, and the studies of this type are sometimes also called validity or intermethod agreement studies (Armstrong et al., 1992). For example, validity of JEM for estimation of occupational exposure to iron, lead and copper was assessed in a case-control study of association between neurologic disease and occupational metal exposure (Rybicki, Johnson, Peterson, Kortsha, & Gorell, 1997). In this study, JEM estimates were compared against individual estimates derived by an industrial hygienist from the work history of each participant. In an Australian community-based case-control study of the association of medical conditions, family and reproductive history, diet and occupational exposures with glioma, FINJEM estimates were compared with estimates assigned by industrial hygiene panel (Benke et al., 2001). In a retrospective Netherlands Cohort Study, validity of three various JEMs (asbestos JEM, DOMJEM, FINJEM) was assessed for the estimation of asbestos, welding fumes and polycyclic aromatic hydrocarbons (PAHs) exposure by comparisons with case-by-case expert assessment (Offermans et al., 2012). In a study by Grajewski, Atkins, and Whelan (2004), self-reported flight hours were compared with airline company records to assess validity of self-reporting.

### 3 Aims of the study

The overall aim of the current study was to examine a variation of adult leukemia by occupational groups, to assess associations between specific occupational agents and adult leukemia, and to assess a reliability of the Nordic Occupational Cancer Studies Job-Exposure Matrix (NOCCA-JEM). The specific aims were as follows:

1. To describe occupational variation of AML, CLL and all other non-specified leukemia incidences in Denmark, Finland, Iceland, Norway and Sweden (Study I).
2. To assess associations between solvents, ELF-MF, electrical shocks and electric/electronic occupations and adult leukemia in employed populations of Finland, Iceland, Norway and Sweden (Studies II and III).
3. To assess an agreement between NOCCA-JEM and individual dose measurements for estimation of occupational cosmic radiation exposure among the Finnish airline personnel (Study IV).

## 4 Materials and methods

### 4.1 Study population

#### 4.1.1 Nordic Occupational Cancer Studies (NOCCA) cohort

The Nordic Occupational Cancer Study (NOCCA) cohort was a source population from which individual study populations in Studies I, II and III were drawn. A detailed description of NOCCA cohort can be found in Pukkala et al. (2009). A summary of that description is provided in this chapter.

The NOCCA cohort consists of 14.9 million persons from five Nordic countries: 2 million from Denmark, 3.4 million from Finland, 100,000 from Iceland, 2.6 million from Norway and 6.8 million from Sweden.

All of these persons participated in computerized censuses, which took place in 1990 or before in the Nordic countries. Computerized censuses occurred on 9 November 1970 in Denmark; 31 December 1970, 1980 and 1990 in Finland; 31 January 1981 in Iceland; and 1 November 1960, 1970 and 1980 in Norway. In Sweden the 1960, 1970 and 1990 censuses took place on 1 November and the 1980 census on 15 September.

Information on personal identity code, name, address, marital status, education, economic activity, occupation, and industry was collected by means of self-administered questionnaires for each person in NOCCA cohort during censuses. In Iceland, all persons born in 1964 or before had to fill out self-administered questionnaire personally, whereas in other Nordic countries, the heads of households filled it out on behalf of all members of household and dwelling.

#### 4.1.2 Individual study populations

The Study I was an occupational cohort study. A sampling unit in this study was a number of observed and expected cases of AML, CLL and all other non-specified leukemia types defined as “Other leukemia” in categories of:

- country (Finland, Denmark, Iceland, Norway and Sweden)
- sex (male and female)
- occupational groups (53 groups and one group of economically inactive persons)
- period (9 five-year periods from 1961 to 2005)
- age (12 five-year age groups from age 30 years)

In total, 18,811 AML, 20,462 CLL and 15,570 “Other leukemia” cases diagnosed from 1961 to 2005 in NOCCA cohort were included into the Study I. AML cases were from Finland, Denmark, Iceland, Norway and Sweden. CLL and “Other leukemia” cases were from Finland, Iceland, Norway and Sweden. Because the categories of CLL and “Other leukemia” in Denmark could not be defined, the cases from this country were not included.

The Study II employed a case-control design nested in NOCCA cohort. It included all incident cases of AML that occurred between 1961 and 2005 in the Nordic countries. Five controls per each case were randomly selected from NOCCA cohort. Cases and controls were individually matched by year of birth, sex and country. Cases could have a previous history of any type of cancer before developing AML and controls could have any type of cancer other than AML. In total, 15,332 AML cases and 76,660 controls were selected from NOCCA cohort. Out of these, 350 cases (2.3%) and 2,155 (2.8%) controls were excluded because they were either younger than 20 years old or did not have any occupational record.

Study III employed the same study design as Study II. The only difference was that in Study III, cases and controls who did not have a previous history of any cancer were included. As a result, 13,435 AML cases and 67,175 controls were selected for this study. Because of large exposure uncertainty before the World War II, only those persons who started their employment career in 1945 and later periods were included in the main analysis. This resulted in inclusion of 5,409 AML cases and 27,045 controls into the main analysis.

The Study IV was an intermethod agreement study, which included all 5,022 airline workers (1,535 cockpit crew and 3,487 cabin crew members) from Finland. The other occupational groups potentially exposed to cosmic radiation were miners and health workers (e.g. radiologists). Miners were not included because individual data on radiation exposure for this occupational group were limited. Health workers were not included because NOCCA-JEM assigns a zero value to this group due to a low prevalence (<10%) of radiation exposure among health workers.

The data used for Studies I through III were linkage-based. Therefore, no ethical statement was required for the implementation of these studies. Ethical statement

was not also required for Study IV because direct contact with study participants was not needed and personal identification numbers were not used. Therefore, information used in Study IV could not be linked to any particular person. In addition, the Study IV did not deal with health outcome, but with exposure information. Obtaining personal consent from each study participant would be very laborious due to a large number of subjects, and furthermore, consent could not be obtained from persons who were already deceased.

## 4.2 Information on outcome

Information on leukemia status was obtained by linking census records of each study participant to cancer registries of the Nordic countries by using personal identity numbers. Personal identity numbers were given to all persons in Sweden in 1947, in Iceland in 1953, in Norway in 1964, in Finland in 1967 and in Denmark in 1968 (Pukkala et al., 2009).

Cancer registries in the Nordic countries was described in Pukkala et al. (2009) and summarized below. Cancer registry in Denmark is the oldest in the Nordic countries and was established in 1942. Notification of Danish cancer cases come from hospital departments, and are supplemented by reports from practicing specialists and autopsy reports. Cancer registry in Finland was established in 1953 and reporting of cancer cases has been compulsory since 1961. Finnish cancer cases were registered based on reports from clinical and pathological departments, private clinics, general practitioners and death registry records. Cancer registry in Iceland started in 1955, and case notification was based on reports from pathology laboratories complemented by information from cytology and hematology laboratories, hospitals, health centers, and deaths certificates. Registration of cancer in Norway was established in 1953 and reports of cancer cases came from the same sources as in Finland and Iceland. In Sweden, reporting of cancer cases during the period 1958-1982 was based on reports from hospitals and pathologists. Private practitioners were required to report cancer cases since 1983. Unlike other Nordic countries, Sweden does not use death certificates information for cancer registry.

## 4.3 Information on exposure

### 4.3.1 Occupational groups

Study participants are classified into more than 300 specific occupations in NOCCA cohort. These occupations are coded according to national adaptations of the Nordic Occupational Classification (NYK) (Arbeidsdirektoratet, 1958) in Finland, Norway and Sweden. NYK is based on the International Standard Classification of Occupations (ISCO) from 1958 (ILO, 1962). The first digit of NYK code indicates the major occupational category, two-digit level indicates about 70 minor occupations and three-digit level more than 300 specific occupations (Pukkala et al., 2009). The national NYK codes are different across the Nordic countries, however, the principle of coding is similar. A national adaptation of ISCO-68 (ILO, 1968) was used in Iceland for occupational coding, while Denmark used a special Danish nomenclature (Pukkala et al., 2009). Validity studies in the Nordic countries indicated reasonable accuracy of occupational classification based on census records (OECD, 1997; Schmidt, 2004; Terlinden, 2005).

In the Study I, more than 300 specific occupational groups in NOCCA cohort were combined into 53 broader job titles and a group of economically inactive persons. The definition for economic activity varied across countries. Persons who were gainfully employed at the time of census or were temporarily absent from work due to illness or military service were classified as economically active in Denmark and Sweden. In Finland, persons who were gainfully employed or employed at least half of industry's normal working hours or were temporarily absent were classified as economically active. In Iceland, persons who were gainfully employed the week before 1981 census or temporarily absent due to vacation or illness were classified as economically active. In Norway, economically active persons had to be gainfully employed for at least 100 hours during 1970 and 1980 censuses, and for 1960 census they were defined based on having an occupation (Pukkala et al., 2009). Occupational classification was based on the first census record a person participated in when s/he was aged 30-64 years old. The reason for combining specific occupations into broader groups was to avoid small numbers of cancer cases in categories of occupation.

### 4.3.2 Nordic Occupational Cancer Studies Job-Exposure Matrix

JEMs were developed for estimating occupational exposure agents in occupational epidemiology studies. They are commonly used when occupational history data are available but individual exposure estimates cannot be obtained for each study participant.

NOCCA-JEM was used in Studies II, III and IV to convert job titles of study participants to specific occupational agents. NOCCA-JEM is based on the Finnish job-exposure matrix (FINJEM) (Kauppinen et al., 2009). FINJEM was constructed for occupational epidemiology studies in Finland in 1990s (Kauppinen, Toikkanen, & Pukkala, 1998). It has three dimensions: agent, occupation and period. The agent-dimension of FINJEM includes over 80 chemical, physical, microbiological, ergonomic and psychosocial factors. The occupation-dimension includes all 311 occupations used for occupational classification in the Finnish census records. Finally, time-dimension consists of periods: 1945-59, 1960-84, 1985-94, 1995-97, 1998-2000 and 2001-03 (Kauppinen et al., 1998). Each cell in FINJEM characterizes exposure agent by proportion of exposed workers (P) and mean exposure intensity (L). The latter is expressed as the annual mean exposure concentration during working-hours in workroom air. Both P and L are based on FINJEM exposure measurement data, which includes over 4,000 measurements based on tens of thousands of samples (Kauppinen et al., 1998). The minimum level of L for chemical agent in FINJEM is defined as occupational inhalatory level exceeding background levels originating from non-occupational exposure (Kauppinen et al., 1998).

Two exposure experts from Finland, two from Norway, and one from each Sweden, Denmark and Iceland were recruited to create NOCCA-JEM by modifying FINJEM (Kauppinen et al., 2009). Information on exposed occupations and exposure prevalence (P) in NOCCA-JEM is based on the knowledge of those experts and FINJEM prevalence estimates. NOCCA-JEM exposure intensity (L) was derived from FINJEM intensity estimates and exposure measurement data from the Nordic countries (Kauppinen et al., 2009).

FINJEM estimates were directly adopted for Norway, Iceland, Sweden and Denmark if the difference between country-specific P and L values from these countries was within 50% and 150% of corresponding FINJEM values (Kauppinen et al., 2009). Otherwise, FINJEM values had to be modified for each country. If prevalence of chemical agent was less than 5% and prevalence of non-chemical agent was less than 10% for all periods, such agents were not included in NOCCA-JEM. The values for non-chemical agents were available only for the period 1985-94, because no reliable data were available for other periods (Kauppinen et al., 2009).

FINJEM period 1960-84 was split into two NOCCA-JEM periods because it was believed that exposure levels and agents may have changed in 1970s. FINJEM periods after 1995 was not assessed because their relevance in cancer studies may be small due to long latency period required for the development of cancer after exposure (Kauppinen et al., 2009).

Consequently, the adoption procedure resulted in a new three-dimensional matrix NOCCA-JEM (Kauppinen et al., 2009). NOCCA-JEM provides values for 28 chemical and non-chemical factors. It covers 4 periods: 1945-59, 1960-74, 1975-84, and 1985-94 for chemical and only 1985-94 period for non-chemical agents. Finally, NOCCA-JEM includes 492 occupational categories for men and 447 for women in Denmark, 311 in Finland, 374 in Iceland, 322 in Norway, and 296 in Sweden (Kauppinen et al., 2009).

### 4.3.3 Solvent exposure

In Study II, occupational solvent exposure was estimated by linking occupational titles to NOCCA-JEM. Exposure estimation based on NOCCA-JEM offers various exposure metric options. For example, average life-time exposure can be derived from annual exposures ( $L$ ) over entire working career and duration of exposure. It is also possible to estimate peak exposure by selecting the highest  $L$  value that a subject was exposed during working career. Such estimates are commonly used in studies of acute conditions. However, in studies of chronic conditions with long latency periods (e.g. cancer), cumulative exposure is the recommended exposure metric (Kauppinen et al., 2009). Cumulative exposures to solvents as well as other covariates were estimated by first assigning  $P$  and  $L$  values of the exposure to the occupation held by an individual and then multiplying it to the duration ( $T$ ) during which individual worked in that occupation. If a given subject had more than one occupation during working career, it was assumed that he/she changed an occupation in the middle between two available census records. It was also assumed that working career started at the age 20 and ended at the age 65 years in this study. Codes for missing occupational records were imputed from the nearest available census records. The imputation procedure used in this study is explained in detail in Appendix 1.

In the analyses, cumulative exposures were categorized into background, low, moderate and high exposure levels. Background level corresponded to zero exposure, low level to exposure values between zero and 50<sup>th</sup> percentile, moderate

level to exposure values between 50<sup>th</sup> and 90<sup>th</sup> percentile, and high level to exposure values above 90<sup>th</sup> percentile of exposure distribution among exposed cases/controls.

Altogether, this procedure was repeated for the following solvents: BENZ, toluene (TOLU), perchloroethylene (PER), methylene chloride (MCH), trichloroethylene (TRI) and 1,1,1-trichloroethane (TCE) as individual solvents; and aliphatic and alicyclic hydrocarbon solvents (ALHC), aromatic hydrocarbon solvents (ARHC) and chlorinated hydrocarbon solvents (CHC) and other organic solvents (OSOL) as grouped solvents.

#### 4.3.4 Extremely low-frequency magnetic fields

Occupational exposure values to ELF-MF were obtained by linking job titles of subjects to ELF-MF job-exposure matrix (ELF-MF JEM). ELF-MF JEM is a modified version of job-exposure matrix developed by Bowman, Touchstone, and Yost (2007, as cited in Koeman et al., 2013). The latter provides time-weighted intensity in  $\mu\text{T}$  of low-frequency magnetic field exposure by occupation based on available measurement data. However, it does not take into account the proportion of exposure by job. To incorporate proportion of exposure into job-exposure matrix, Koeman et al. (2013) first categorized exposure intensities into background (i.e. very low), low and high levels by using distributional cut-off points 0.15  $\mu\text{T}$  and 0.30  $\mu\text{T}$ . These levels were then up- or downgraded by two industrial hygienists based on the estimated probability of exposure per job. The resulting levels were classified as background, low and high (Koeman et al., 2013).

The following exposure metrics were used for ELF-MF exposure:

1. Ever exposure to low and high levels versus background levels. Because some study participants changed occupation during working career, they could be in more than one ELF-MF exposure level. Such persons were grouped into their highest possible exposure level. For example, if a person had a job with low ELF-MF exposure for some years and then moved to the one with high exposure levels, he/she was classified into high exposure level.
2. Exposure duration of ever low or high and ever high ELF-MF levels expressed in years. Risk associated with each 10-year increase in exposure duration was estimated.
3. Cumulative exposure. Weights reflecting the multiplicative nature of exposure distribution were assigned to each ELF-MF exposure level: 0 for background, 1 for low, and 4 for high levels. These weights were then

multiplied by duration of exposure to the corresponding level. Finally, all multiplications were summed up for the entire working career to estimate cumulative ELF-MF exposure for each subject. The working career in Study III was assumed to start at the age 20 years and end at the age 60 years. In the analyses, cumulative exposure to ELF-MF was categorized into four levels by using tertiles of exposure distribution among exposed controls. The first level corresponded to zero exposures; the second level included exposure values between zero and the first tertile; the third level included values between the first and the second tertiles; and the fourth level corresponded to values higher than the second tertile.

BENZ, TOLU, TRI, MCH, ALHC, TCE, formaldehyde and ionizing radiation were used as co-factors in the Study III. All co-factors were estimated by using the NOCCA-JEM. The list of occupations with high levels of ELF-MF exposure in the NOCCA cohort is described in Table 4.

Table 4. Occupations with high level of extremely low-frequency magnetic field (ELF-MF) exposure and high risk of electrical shocks in the Nordic Occupational Cancer Studies (NOCCA) cohort.

Occupation	ELF-MF	Electrical shock
Airline pilots etc.	+	-
Assisting construction workers	-	+
Bench carpenters	-	+
Bricklayers, plasterers and tile setters	-	+
Building occupations	-	+
Cabinetmakers and joiners etc.	-	+
Cold- and hot-rolling metal workers	+	-
Concrete shutterers and finishers	-	+
Construction carpenters	-	+
Cookers and furnacemen (chemical processes)	+	-
Crane operators	+	-
Deck crew	-	+
Electric machine fitters (high voltage)	+	+
Electric machine operators	+	-
Electrical and electronic equipment assemblers	-	+
Electricians	+	+
Electronics and telecommunications workmen	-	+
Fitter-assemblers etc.	-	+
Forestry supervisors	+	-

Occupation	ELF-MF	Electrical shock
Forestry workers and lumberjacks	+	-
Foundry workers	+	+
Glaziers	-	+
Heat treaters, hardeners, temperers etc.	+	-
Insulation workers	-	+
Lighthouse keepers	-	+
Machine and engine mechanics	-	+
Machine setter operators (not in textile industry) riggers	+	+
Maintenance crews and supervisors	-	+
Metal plating and coating work	+	-
Metal smelting furnace men	+	-
Occupations in smelting, metallurgical and foundry workers	+	-
Plumbers	-	+
Radio and TV transmitter, other electrical work	-	+
Railway engine drivers, steam engine firemen	+	-
Reinforced concrete layers, stonemasons etc.	-	+
Rod layers	-	+
Sheet metal workers	-	+
Smiths	+	-
Stone cutters	+	-
Telegraphists, radio communications operators etc.	+	-
Telephone installation crew, linemen and cable jointers	-	+
Welders and flame cutters	+	+
Wire and pipe drawers	+	-
Wooden boat builders, coach-body builders etc.	-	+

#### 4.3.5 Electrical shock

Electrical shock exposure was estimated by linking occupational history to electrical shock JEM. Huss, Vermeulen, Bowman, Kheifets, & Kromhout (2013) developed electrical shock JEM based on electrical injury risk by occupation in five European countries. In that study, electrical injury data were obtained from various registries

in Germany, United Kingdom (UK), Austria, Switzerland and Netherlands. In Germany, data were obtained from Social Accident Insurance on electrical injuries at work for the years 2005-2008 and occupational data are based on 4-digit ISCO-88 classification (Standke, 2007). Electrical injury data in the UK was provided by the Health and Safety Executive for the years 2007-2009 and accidents were coded in the British Standard Occupational Classification (SOC) 2000 (Huss et al., 2013). This was translated to ISCO-88 by using translation available online (Lambert, 2005) and by hand checking the assigned occupations. Huss et al. (2013) retrieved injury data in Austria from the Austrian Workers' Compensation Board database, which included data for the period 2005-2009. In this database, occupations were classified based on ISCO-08, which were translated to ISCO-88 using the correspondence table provided by International Labor Organization (ILO) (ILO). The Swiss Accident Insurance provided electrical injury data for the period 2003-2008 and occupations were classified according to ISCO-88. Data from Netherlands were from the Dutch Labor Inspectorate. This provided injury data for the years 1998-2004, names of job titles and industry that were translated into ISCO-88 (Huss et al., 2013). Huss et al. (2013) found minor differences in definition of electrical injury between the countries and most of them followed the definition of the European Statistics on Accidents at Work, which defines electrical injury as an accident resulting in at least three consecutive days of inability to work (excluding the day of the accident) or death (EUROSTAT). The denominator data consisted of the number of workers per ISCO-88 job category and country, which was retrieved from the European Statistics for the year 2001 (EUROSTAT). Because the denominator data was in 3-digit level occupational codes, the numerator data was also collapsed into 3-digit level ISCO-88 occupations. Consequently, electrical injury rates and 95% confidence intervals were calculated by occupation for each country and year (Huss et al., 2013). These rates were then pooled to estimate summary rates for each occupation by using random effect models. The resulting rates were categorized into background, low and high categories by using 75<sup>th</sup> and 90<sup>th</sup> percentile values of the distribution of electrical injury rates as cut-points. Finally, electrical injury had to be reported from at least two countries in low category, and from at least three countries in high category (Huss et al., 2013).

Both ELF-MF JEM and electrical shock JEM were developed for job titles based on ISCO-88 classification. Because job titles in NOCCA cohort are based on NYK codes, ISCO-88 based ELF-MF and electrical shock JEMs had to be translated to NYK codes. This was achieved by using existing automated crosswalk (Van Tongeren et al., 2013). These translations did not lead to large inconsistencies in

exposure values due to one-to-many and many-to-one code translations because the coding systems are very similar in classifications (Koeman et al., 2013).

The list of occupations with high risk of electrical shock in the NOCCA cohort is described in Table 4.

#### 4.3.6 Electric and electronic occupations

In Study III, study subjects were also grouped into electric/electronic occupations by using two classifications used in previous epidemiological studies (Deapen & Henderson, 1986; Feychtung, Jonsson, Pedersen, & Ahlbom, 2003).

Deapen and Henderson (1986) used electrical/electronic occupation classification to study the link between trauma induced by electrical shocks and amyotrophic lateral sclerosis. They classified occupation as electrically related if occupation was likely to expose the worker to electricity. This work was performed in consultation with an occupational medicine physician familiar with job duties. Occupations selected as electrically related were: electrical and electronic engineers; electrical and electronic engineering technicians; electricians; electrician apprentices; electric power linemen and cablemen; air conditioning, heating and refrigeration repairmen; data processing machine repairmen; household appliance and accessory installers and mechanics; office machine repairmen; radio and television repairmen; power station operators; telephone installers and repairmen; telephone linemen and splicers; welders and flame cutters; conductors and motormen, urban rail transit; and assemblers (Deapen & Henderson, 1986).

Feychtung et al. (2003) studied association between occupational magnetic field exposure and neurodegenerative diseases. In that study, occupations defined as electrical/electronic were: railway engine drivers; glass, pottery, tile work; welders; forest workers and log-drivers; electricians; radio and television assemblers and repairmen; telephone and telegraph installers and repairmen.

The list of electrical and electronic occupations in the NOCCA cohort is shown in Table 5. Two exposure metrics were used for electric/electronic occupations: 1) ever versus never exposed; 2) duration of ever exposed in years.

Table 5. Electrical/electronic occupations in the Nordic Occupational Cancer Studies (NOCCA) cohort.

Occupation	Classification	
	DM Deapen et al <sup>a</sup>	M Feychting et al <sup>b</sup>
Canal, harbor and ferry watchmen	+	-
Electric machine fitters (high voltage)	+	+
Electric machine operators	+	+
Electrical and electronic equipment assemblers	+	+
Electrical engineering technicians	+	-
Electrical engineers	+	-
Electricians	+	+
Electronics and telecommunications workmen	+	+
Radio and TV transmitter, other electrical work	+	-
Railway engine drivers, steam engine firemen	+	-
Technicians in mechanical engineering	+	-
Telegraphists, radio communications operators etc.	+	+
Telephone installation crew, linemen and cable jointers	+	+
Welders and flame cutters	+	-

<sup>a</sup>Deapen DM, Henderson BE (1986) A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 123(5):790-799.

<sup>b</sup>Feychting M, Jonsson F, Pedersen NL, Ahlbom A (2003) Occupational magnetic field exposure and neurodegenerative disease. Epidemiol 14(4):412-419.

#### 4.3.7 Cosmic radiation exposure

In the Study IV, reliability of NOCCA-JEM was assessed for estimation of cosmic radiation exposure among Finnish aircrew members by using individual dose estimates from STUK as a reference. STUK was established in 1958 with a task of inspecting radiation facilities in hospitals (STUK). Nowadays, STUK regulates the use of radiation in nuclear power plants, health care, industry, research and training. Operation of STUK is strictly controlled by the Finnish legislation and safety guidelines (STUK).

STUK individual dose estimates were derived from flight profile of each study participant. Airline companies must estimate annual cosmic radiation dose for each airline worker and report it to STUK (STUK, 2013). Estimation of individual cosmic radiation dose for airline workers has been compulsory in Finland since 2001. Therefore, individual dose estimates were available from 2001 to 2014. Airline

companies currently estimate individual doses by using CARI-6 software, but in earlier periods European Program Package for the Calculation of Aviation Route Doses (EPCARD) software was also used by some companies. CARI-6 was developed by the US Federal Aviation Authority (CARI-6) and is based on the LUIN radiation transport program (Friedberg et al., 1992; O'Brien et al., 1992). EPCARD was developed by Helmholtz Zentrum Munchen and approved by Civil Aviation Authority in Germany (Bottollier-Depois, 2012). CARI-6 and EPCARD computer programs calculate effective dose of cosmic radiation received by an individual during a flight. Effective dose is estimated as a function of flight route, aircraft type, altitude and latitude, and calendar period. Based on the time of the flight, programs take into account effect of changes in earth's magnetic and solar activity. If flight information is available, programs can estimate cosmic radiation effective dose from earlier periods. For example, CARI-6 can estimate effective dose from January 1958 (CARI-6). NOCCA-JEM based cosmic radiation estimates were derived by linking occupational information of study participants to NOCCA-JEM. The procedure was similar to the one that was used in Study II for estimation of solvent exposure, and it is described in Section 4.2.3.

Continuous and categorical dose estimates were used in Study IV. Continuous estimates were expressed as cumulative exposure, which was estimated as a sum of annual doses during the follow-up 2001-2014. Categorical doses were obtained by categorizing continuous estimates by using tertile based cut-points. In this study tertiles of NOCCA-JEM based dose estimates were used as cut-points for both NOCCA-JEM and STUK estimates. The resulting exposure categories were: <6 mSv for low, 6-12 for medium and >12 mSv for high levels.

## 4.4 Statistical analysis

### 4.4.1 Descriptive statistics

Descriptive statistics included estimates of frequencies of study participants by demographic indicators and exposures of interest (solvents in Study II; ELF-MF, electrical shock and electrical/electronic occupations in Study III; cosmic radiation exposure among Finnish aircrew members in Study IV).

#### 4.4.2 Standardized incidence ratios

In Study I, incidences of AML, CLL and “Other leukemia” in 53 occupational categories and a group of economically inactive persons were compared with corresponding incidences in entire national study populations. Observed number of AML, CLL and “Other leukemia” cases and person-years were stratified into 5-year age groups and 5-year calendar periods by categories of occupation, country and gender. Expected number of cases in each of these strata were derived from stratum-specific incidence rates in the entire study population and corresponding person-years. Standardized incidence ratios (SIR) were estimated for each occupation as a ratio of observed to expected number of cases, and 95% CIs by assuming Poisson distribution of observed cases. Analyses stratified by age groups, calendar periods, countries, time since first hired and duration of employment were performed to evaluate consistency of the main results. Poisson trend test (Breslow & Day, 1987) was performed to assess statistical significance of observed trends across subgroup levels in stratified analyses.

#### 4.4.3 Conditional logistic regression models

Hazard ratios (HR) and 95% CIs were estimated for exposures of interest by fitting conditional logistic regression models in Studies II and III. Covariates were selected by using a “purposeful variable selection” method for categorical variables (Hosmer & Lemeshow, 2013). According to this procedure, several steps of variable selection were followed to arrive at final effect models. In the first step, each covariate was examined through univariate analyses and selected variables with likelihood-ratio test p-value less than 0.25. In the next steps, variables selected in Step 1 and clinically significant variables were included into multivariate analyses. Consequently, contribution of each variable into full model was evaluated by comparing reduced model (model without variable of interest) with full model by using a partial likelihood-ratio test. These steps resulted in the decision to include formaldehyde (FORM) and ionizing radiation into the final effect models as co-variates. To avoid multicollinearity, highly correlated variables were included into separate models. Using the purposeful variable selection method described, resulted in two final main effect models in Study II:

1. All covariates except for ARHC were included in the final main effect model  
(Model1=BENZ+TOLU+ALHC+TRI+TCE+MCH+PER+OSOL+IRAD+FORM).
2. All covariates except for BENZ and TOLU were included  
(Model2=ARHC+ALHC+TRI+TCE+MCH+PER+OSOL+IRAD+FORM).

Age and sex-specific stratified analyses were conducted in Study II to evaluate effect modification of the main results with age and sex.

The main exposures of interest in Study III were ELF-MF, electrical shock and electrical/electronic occupation. Final main-effect models were defined separately for each of these exposures. All models were adjusted for BENZ, TOLU, ALHC, TRI, TCE, MCH, PER, OSOL, IRAD and FORM. Adjusting variables were selected based on the same procedure used in Study II.

To assess the robustness of the main results, a series of sensitivity analyses were conducted in Studies II and III. Analyses with various exposure lag-time assumptions were the main sensitivity analyses. In this approach, it was assumed that there is a latency period between exposure and leukemia, and exposures occurring during this period were unlikely to have an effect on leukemia risk. Analyses with 0, 3, 5, 7, 10, 20 years lag-time in Study II, and analyses with 0, 10 and 20 years lag-time in Study III were conducted. Results from analysis with 10 years lag-time in Study II, and from analyses with 0 years (no lag-time) in Study III were used as the main results.

Other sensitivity analyses included, analyses with various onset and end of working career (e.g. from age 20 to 65 years in Study III), estimation of exposure by using only average intensities (L) (Study II). Because Icelandic data included occupational information only from one census (1981 census), sensitivity analysis by excluding Icelandic data (n=684, 0.85%) was also conducted (Study III). Finally, analysis by excluding economically inactive persons was conducted (n=4931, 6.1%) (Study III).

#### **4.4.4 Agreement indices**

Spearman correlation, Bland-Altman plot and intraclass correlation coefficient (ICC) were used for the assessment of reliability of continuous NOCCA-JEM dose estimates. Bland-Altman plot illustrates differences of measurements against their

mean (Bland & Altman, 1999). It is a more powerful graphical tool than simple correlation plot because it shows magnitude of difference, systematic differences and whether there is any trend of differences. ICC estimates proportions of total variation due to true differences between estimates and due to measurement error, and it is based on mean squares obtained by applying analysis of variance (ANOVA) models (Deyo, Diehr, & Patrick, 1991).

For categorical exposures, proportion of agreement (PA) and kappa statistic were estimated. PA was estimated by dividing a sum of frequencies in agreement cells by total number of observations. It provides an estimate of proportion of exact concordance between two measurements across all measurements (Fleiss, Levin, & Paik, 2003). However, it cannot take into account chance agreement between the measurements (Szklo & Nieto, 2014). Therefore, kappa statistic and weighted kappa were also estimated. Kappa statistic is a proportion of observed agreement not due to chance in relation to the maximum non-chance agreement (Cohen, 1960). Weighted kappa is used for ordered categorical data (Szklo & Nieto, 2014). It is based on assigning weights to different levels of disagreement. In Study IV, medians of NOCCA-JEM dose categories were used as weights. Hence, the weights corresponded to median values of 3 mSv for low level, 9 mSv for medium, and 14 mSv for high levels.

Subgroup analyses separately for cockpit and cabin crew members, males and females, persons younger and older 50 years were also conducted.

All analyses (Studies I through IV) were conducted by using R statistical software (various releases from 2.11 to 3.2.0).

## 5 Results

### 5.1 Characteristics of study populations

The majority of AML and CLL cases in Study I were from Sweden (35.9% and 57.4%) and Norway (24.7% and 21.2%). Males constituted 60.2% and females 39.8% of CLL cases. There were no substantial sex-specific differences for AML cases (51.5% males vs 48.5% females). The majority of AML (76.0%) and CLL (82.6%) cases were older than 60 years.

Studies II and III included all AML cases diagnosed in four Nordic countries between 1961 and 2005, and their matched controls. Demographic characteristics of study populations in Studies II and III are shown in Table 6. Removing secondary AML cases from dataset did not result in large differences in demographic characteristics of study populations in Studies II and III. The majority of cases were from Sweden (~45%) and Norway (~31%), a smaller proportion from Finland (~23%) and only less than 1% from Iceland (Table 6). In both studies, over 60% of AML cases were 60 years old or older at index date, and more than 85% of study participants were born before 1941. The proportion of male AML cases was slightly greater than the proportion of female cases in both studies.

Occupational solvent exposure was very rare in a study population of Study II (Table 7). The prevalence of low and moderate solvent exposure was less than 4% whereas the prevalence of high exposure levels was less than 1%. Solvent exposure was more common among males than females.

About 40% of subjects were ever exposed to low ELF-MF exposure levels and about 7% to high levels. Approximately, 18% of case/controls were at low risk and 15% at high risk of electrical shocks at workplace. Overall less than 6% of participants worked in electrical/electronic occupations. Sex-specific analyses showed that mainly men constituted high exposure levels. There were about 12% of males in high ELF-MF exposure category compared to only about 1% females, and about 26% of men were at high risk of electrical shocks compared to only about 2% females. A similar pattern was observed for electrical/electronic occupations where about 7% of men were ever employed in electrical/electronic job compared to only 1.5% women (Table 8).

The study population in Study IV consisted of 1,535 cockpit and 3,487 cabin crew members. Over 60% of study participants were 30-50 years old and the mean age at the end of follow-up was 44 years old. 94.9% of cockpit crew were males and 86.7% of cabin crew were females. The median cumulative cosmic radiation exposure according to STUK was 18.5 mSv among cockpit crew members and 14.5 mSv among cabin crew members. The respective median NOCCA-JEM dose estimates were 9.0 mSv and 8.0 mSv. 61.1% of cockpit crew had cumulative individual dose greater than 12 mSv compared to 54.8% of cabin crew members. Individual doses were set to zero for 2% of study population because they had annual doses below 0.1 mSv due to few or no flights.

Table 6. Demographic characteristics of study populations (AML cases and controls) in Studies II and III.

Characteristic	Study II				Study III			
	Case		Control		Case		Control	
	n	%	n	%	n	%	n	%
Sex								
male	7751	51.7	38642	51.9	6967	51.9	34835	51.9
female	7231	48.3	35863	48.1	6468	48.1	32340	48.1
Country								
Finland	3484	23.3	17419	23.4	3099	23.1	15494	23.1
Iceland	109	0.7	479	0.6	114	0.8	570	0.8
Norway	4606	30.7	22928	30.8	4277	31.8	21385	31.8
Sweden	6783	45.3	33679	45.2	5945	44.3	29725	44.3
Age at index <sup>a</sup>								
20-29	139	0.9	690	0.9	163	1.2	832	1.2
30-39	458	3.1	2271	3.1	529	3.9	2612	3.9
40-49	1163	7.8	5758	7.7	1200	8.9	6018	8.9
50-59	1991	13.3	9881	13.3	1980	14.7	9902	14.7
60-69	3558	23.8	17687	23.7	3427	25.5	17188	25.5
70-79	4836	32.3	24089	32.3	4068	30.3	20281	30.3
≥80	2837	18.9	14129	18.9	2068	15.4	10342	15.4
Year of birth								
≤1910	3350	22.4	16682	22.4	3058	22.8	15290	22.8

Characteristic	Study II				Study III			
	Case		Control		Case		Control	
	n	%	n	%	n	%	n	%
1911-1920	4042	26.9	20138	27.0	3524	26.2	17620	26.2
1921-1930	3677	24.5	18293	24.6	3257	24.2	16285	24.2
1931-1940	2000	13.4	9926	13.3	1809	13.5	9045	13.5
1941-1950	1406	9.4	69.75	9.4	1310	9.8	6550	9.8
1951-1960	507	3.4	24.91	3.3	477	3.6	2385	3.6
<i>Total</i>	14982	100.0	74505	100.0	13435	100.0	67175	100.0

<sup>a</sup> index date is defined as a date of case diagnosis

Table 7. Distribution of occupational solvent exposure among acute myeloid leukemia (AML) cases and controls (Study II) (ppm – parts per million).

Agent <sup>a</sup> (ppm/year)	Male				Female				Total			
	Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%
<i>Aliphatic and alicyclic hydrocarbon solvents</i>												
background	7154	92.3	35651	92.3	7138	98.7	35352	98.6	14292	95.4	71003	95.3
≤17.5	320	4.1	1572	4.1	33	0.5	171	0.5	353	2.4	1743	2.3
17.5-300	227	2.9	1075	2.8	56	0.8	318	0.9	283	1.9	1393	1.9
>300	50	0.6	344	0.9	4	0.1	22	0.1	54	0.4	366	0.5
<i>Aromatic hydrocarbon solvents</i>												
background	7237	93.4	36164	93.6	7064	97.7	34976	97.5	14301	95.5	71140	95.5
≤9.3	265	3.4	1182	3.1	97	1.3	479	1.3	362	2.4	1661	2.2
9.3-275	197	2.5	1000	2.6	59	0.8	362	1.0	256	1.7	1362	1.8
>275	52	0.7	296	0.8	11	0.2	46	0.1	63	0.4	342	0.5
<i>Benzene</i>												
background	7074	91.3	35308	91.4	7100	98.2	35147	98.0	14174	94.6	70455	94.6
≤3.7	350	4.5	1513	3.9	80	1.1	486	1.4	430	2.9	1999	2.7
3.7-13.6	264	3.4	1420	3.7	46	0.6	213	0.6	310	2.1	1633	2.2
>13.6	63	0.8	401	1.0	5	0.1	17	0.0	68	0.5	418	0.6
<i>Toluene</i>												
background	7037	90.8	35129	90.9	7149	98.9	35420	98.8	14186	94.7	70549	94.7
≤42.4	366	4.7	1653	4.3	58	0.8	301	0.8	424	2.8	1954	2.6

Agent <sup>a</sup> (ppm/year)	Male				Female				Total			
	Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%
42.4-612	277	3.6	1477	3.8	19	0.3	125	0.3	296	2.0	1602	2.2
>612	71	0.9	383	1.0	5	0.1	17	0.0	76	0.5	400	0.5
<i>Trichloroethylene</i>												
background	7238	93.4	35883	92.9	7099	98.2	35144	98.0	14337	95.7	71027	95.3
≤16.2	239	3.1	1400	3.6	63	0.9	360	1.0	302	2.0	1760	2.4
16.2-121	225	2.9	1115	2.9	50	0.7	258	0.7	275	1.8	1373	1.8
>121	49	0.6	244	0.6	19	0.3	101	0.3	68	0.5	345	0.5
<i>1,1,1-trichloroethane</i>												
background	6977	90.0	34555	89.4	7109	98.3	35165	98.1	14086	94.0	69720	93.6
≤5.6	489	6.3	2528	6.5	77	1.1	458	1.3	566	3.8	2986	4.0
5.6-12.7	211	2.7	1131	2.9	33	0.5	186	0.5	244	1.6	1317	1.8
>12.7	74	1.0	428	1.1	12	0.2	54	0.2	86	0.6	482	0.6
<i>Methylene chloride</i>												
background	7180	92.6	35764	92.6	7168	99.1	35508	99.0	14348	95.8	71272	95.7
≤9.9	285	3.7	1429	3.7	41	0.6	209	0.6	326	2.2	1638	2.2
9.9-64.6	228	2.9	1123	2.9	21	0.3	144	0.4	249	1.7	1267	1.7
>64.6	58	0.7	326	0.8	1	0.0	2	0.0	59	0.4	328	0.4
<i>Perchloroethylene</i>												
background	7648	98.7	38110	98.6	7162	99.0	35446	98.8	14810	98.9	73556	98.7
≤12.1	60	0.8	313	0.8	29	0.4	159	0.4	89	0.6	472	0.6

Agent <sup>a</sup> (ppm/year)	Male				Female				Total			
	Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%
12.1-106	41	0.5	206	0.5	26	0.4	175	0.5	67	0.4	381	0.5
>106	2	0.0	13	0.0	14	0.2	83	0.2	16	0.1	96	0.1
<i>Other organic solvents</i>												
background	7487	96.6	37374	96.7	7177	99.3	35596	99.3	14664	97.9	72970	97.9
≤83.8	134	1.7	579	1.5	33	0.5	181	0.5	167	1.1	760	1.0
83.8-357	104	1.3	543	1.4	19	0.3	74	0.2	123	0.8	617	0.8
>357	26	0.3	146	0.4	2	0.0	12	0.0	28	0.2	158	0.2

<sup>a</sup> cut-points correspond to 50<sup>th</sup> and 90<sup>th</sup> percentile of exposure distribution among exposed cases/controls.

Table 8. Distribution of occupational extremely low-frequency magnetic field (ELF-MF) exposure, electrical shock risk and electrical/electronic occupation among acute myeloid leukemia (AML) cases and controls.

Agent	Male				Female				Total			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	2917	100	14585	100	2492	100	12460	100	5409	100	27045	100
<b>Extremely low-frequency magnetic fields</b>												
Ever exposed to												
background levels	1475	50.6	7094	48.6	1398	56.1	6733	54.0	2873	53.1	13827	51.1
low levels	1090	37.4	5608	38.5	1075	43.1	5599	44.9	2165	40.0	11207	41.4
high levels	352	12.1	1883	12.9	19	0.8	128	1.0	371	6.9	2011	7.4
Cumulative exposure <sup>a</sup>												
0 unit-years	1475	50.6	7094	48.6	1398	56.1	6733	54.0	2873	53.1	13827	51.1
1-16.2 unit-years	425	14.6	2235	15.3	566	22.7	2997	24.1	991	18.3	5232	19.3
16.2-29.9 unit-years	405	13.9	2003	13.7	366	14.7	1829	14.7	771	14.3	3832	14.2
29.9-159.9 unit-years	612	21.0	3253	22.3	162	6.5	901	7.2	774	14.3	4154	15.4
<b>Electrical shocks</b>												
Ever exposed to												
background levels	1571	53.9	7672	52.60	2055	82.5	10010	80.3	3626	67.0	17682	65.4
low levels	582	20.0	3008	20.6	398	16.0	2218	17.8	980	18.1	5226	19.3
high levels	764	26.2	3905	26.8	39	1.6	232	1.9	803	14.8	4137	15.3
Cumulative exposure <sup>a</sup>												
0 unit-years	1571	53.9	7672	52.6	2055	82.5	10010	80.3	3626	67.0	17682	65.4
1-19.9 unit-years	321	11.0	1829	12.5	286	11.5	1649	13.2	607	11.20	3478	12.9
19.9-45.7 unit-years	424	14.5	2108	14.5	125	5.0	678	5.4	549	10.1	2786	10.3

Agent	Male				Female				Total			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%	n	%	n	%
45.7-159.9 unit-years	601	20.6	2976	20.4	26	1.0	123	1.0	627	11.6	3099	11.5
<b>Electric/electronic occupations</b>												
Ever exposed (yes vs. no) <sup>b</sup>	281	9.6	1404	9.6	37	1.5	185	1.5	318	5.9	1589	5.9
Ever exposed (yes vs. no) <sup>c</sup>	144	4.9	742	5.1	28	1.1	144	1.2	172	3.2	886	3.3

<sup>a</sup> cut-points correspond to tertiles of exposure distribution among exposed controls

<sup>b</sup> classification based on Deapen & Henderson, 1986

<sup>c</sup> classification based on Feychtig et al, 2003

## 5.2 Risk of adult leukemia by occupation

In Study I, statistically significantly increased incidences of AML were observed in drivers (observed cases [n]=555, SIR=1.16, 95% CI 1.07-1.26) and food workers (n=287, SIR=1.13, 95% CI 1.01-1.27) compared to the entire study population during follow-up from 1961 to 2005. The risk of CLL was elevated in clerical workers (n=1086, SIR=1.07, 95% CI 1.01-1.14) and farmers (n=1746, SIR=1.09, 95% CI 1.04-1.14). The risk of "Other leukemia" was statistically significantly increased in chemical process workers (SIR=1.18, 95% CI 1.01-1.38), other health workers (SIR=1.22, 95% CI 1.02-1.47), seamen (SIR=1.24, 95% CI 1.04-1.49) and sales agents (SIR=1.15, 95% CI 1.06-1.25).

In some occupational groups the risk of leukemia was significantly decreased. For example, the risk of AML among forestry workers (SIR=0.85, 95% CI 0.73-0.99) and seamen (SIR=0.79, 95% CI 0.64-0.97) was statistically significantly decreased. Among seamen, also the risk of CLL was decreased (SIR=0.79, 95% CI 0.65-0.96). The incidence of "Other leukemia" among fishermen was significantly lower than the incidence in entire study population (SIR=0.68, 95% CI 0.53-0.85).

Analysis by year of first employment showed that excess risk of AML was restricted to drivers first hired before 1940 (SIR=1.15, 95% CI 1.00-1.33) and between 1940 and 1960 (SIR=1.21, 95% CI 1.08-1.35) (Table 9). AML risk was also restricted to sales agents (SIR=1.22, 95% CI 1.07-1.39), clerical workers (SIR=1.14, 95% CI 1.03-1.27) and public safety workers (SIR=1.31, 95% CI 1.02-1.67) first hired before 1940, and to food workers (SIR=1.75, 95% CI 1.22-2.43) and building caretakers (SIR=1.31, 95% CI 1.04-1.63) first hired after 1960. The risk of AML risk significantly decreased by year of first employment for sales agents, clerical workers, and increasing trend for food workers and building caretakers. The risk of CLL was restricted to clerical workers (SIR=1.16, 95% CI 1.05-1.28), farmers (SIR=1.09, 95% CI 1.03-1.16) and engine operators (SIR=1.21, 95% CI 1.01-1.45) first hired before 1940, and to teachers first hired after 1960 (SIR=1.20, 95% CI 1.01-1.43) (Table 9).

Analysis by duration of employment indicated statistically significantly increased AML risk among drivers (SIR=1.17, 95% CI 1.07-1.28), sales agents (SIR=1.12, 95% CI 1.02-1.23) and welders (SIR=1.27, 95% CI 1.01-1.59) employed for more than 30 years (Table 10). Also excess risk of CLL among clerical workers (SIR=1.07, 95% CI 1.01-1.14) and farmers (SIR=1.09, 95% CI 1.04-1.14) were restricted to those with employment duration of more than 30 years (Table 10). The risk of AML

among assistant nurses was restricted for duration less than 30 years with significant decreasing trend of the risk by duration of employment (Table 10).

Table 9. Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) by year of first employment in selected occupational categories (observed cases – Obs; p-trend – p-value for Poisson trend test).

Occupation	-1940			1940-1960			1960-			p-trend
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	
<i>AML</i>										
Religious workers	76	1.13	0.89-1.42	102	1.21	1.00-1.47	64	0.87	0.67-1.12	0.13
Clerical workers	353	1.14	1.03-1.27	571	1.03	0.95-1.12	203	0.95	0.83-1.09	0.04
Sales agents	234	1.22	1.07-1.39	210	1.02	0.89-1.17	66	0.93	0.72-1.18	0.02
Drivers	186	1.15	1.00-1.33	305	1.21	1.08-1.35	64	0.97	0.75-1.24	0.46
Public safety workers	67	1.31	1.02-1.67	59	0.97	0.74-1.25	22	1.04	0.65-1.58	0.17
Building caretakers	227	1.00	0.88-1.14	285	1.11	0.99-1.25	81	1.31	1.04-1.63	0.04
Food workers	104	0.95	0.78-1.15	148	1.11	0.99-1.25	35	1.75	1.22-2.43	<0.01
Textile workers	128	0.83	0.70-0.99	140	0.93	0.79-1.10	22	1.01	0.63-1.53	0.26
<i>CLL</i>										
Clerical workers	407	1.16	1.05-1.28	505	1.03	0.94-1.12	174	1.03	0.89-1.19	0.09
Farmers	1095	1.09	1.03-1.16	589	1.07	0.99-1.16	62	1.17	0.90-1.50	0.99
Engine operators	115	1.21	1.01-1.45	116	0.87	0.73-1.04	48	1.25	0.92-1.66	0.49
Religious workers	84	0.95	0.76-1.17	120	1.20	1.00-1.44	84	1.16	0.92-1.43	0.19
Teachers	147	0.94	0.80-1.10	252	1.04	0.92-1.18	129	1.20	1.01-1.43	0.04
Plumbers	23	0.61	0.39-0.92	57	1.03	0.78-1.33	17	1.22	0.71-1.96	0.02
Seaman	44	0.80	0.58-1.08	45	0.72	0.53-0.96	14	1.11	0.61-1.86	0.60

Table 10. Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) by duration of employment in selected occupational categories (observed cases – Obs; p-trend - p-value for Poisson trend test).

Occupation	≤15 years			15-30 years			>30 years			p-trend
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	
<i>AML</i>										
Smelting workers	3	6.85	1.41-20.02	9	0.79	0.36-1.49	127	0.92	0.77-1.09	0.28
Assistant nurses	3	1.66	0.34-4.84	48	1.38	1.02-1.83	127	0.93	0.78-1.11	0.01
Clerical workers	6	0.86	0.32-1.88	147	0.93	0.79-1.09	974	1.07	1.00-1.14	0.11
Sales agents	2	1.01	0.12-3.63	44	0.84	0.61-1.13	464	1.12	1.02-1.23	0.09
Drivers	2	0.92	0.11-3.34	59	1.09	0.83-1.40	494	1.17	1.07-1.28	0.55
Welders	2	3.88	0.47-14.03	11	0.92	0.46-1.65	78	1.27	1.01-1.59	0.79
<i>CLL</i>										
Clerical workers	1	2.10	0.05-11.70	66	1.13	0.87-1.44	1019	1.07	1.01-1.14	0.58
Farmers	0	0.00	0.00-27.48	36	1.18	0.83-1.64	1710	1.09	1.04-1.14	0.66

### **5.3 Risk of adult leukemia and occupational exposure to solvents**

There was no strong evidence for an increased risk of AML associated with occupational exposure to solvents in Study II. The largest risk was observed among workers in the highest decile of toluene exposure (1.35, 95% CI 0.74-2.46) in the main analysis with 10 year lag-time. The HR estimate for toluene remained elevated also in analyses with other lag-time assumptions, and the highest estimate was observed in analysis with no lag-time (1.86, 95% CI 1.06-3.28).

Among other solvents, ARHC (1.18, 95% CI 0.76-1.86) and trichloroethylene (1.12, 95% CI 0.83-1.49) had small non-significantly increased hazard ratios. The overall AML risk associated with benzene exposure was not elevated in Study II. However, there was some indication of increased risk among women (2.02, 95% CI 0.58-7.04) and persons younger 50 years old (2.24, 95% CI 0.99-5.08) for the highest decile of benzene exposure.

In general, HR estimates were the highest in the analyses with short lag-time (e.g. 3, 5 and 10 years) (Appendix 2) and tended to decrease towards null in the analyses with 15 or 20 year lag-time. Sex- and age-specific differences in HR estimates were observed for some solvents. However, none of sex- and age-specific association between solvent exposure and AML was statistically significant.

### **5.4 Risk of adult leukemia and occupational exposure to low-frequency magnetic field and electrical shock**

There was no evidence for an association between occupational ELF-MF exposure, electrical shock and AML in Study III. The HR estimate for ever exposure to high levels of ELF-MF was 0.88 (95% CI 0.77-1.01), high risk of electrical shock was 0.94 (95% CI 0.85-1.05).

The HR for “ever working in electrical/electrical occupation” based on Deapen and Henderson (1986) classification was 1.02 (95% CI 0.88-1.17) and based on Feychting et al. (2003) classification was 0.98 (95% CI 0.81-1.18).

The main results of this study were not sensitive to various lag-time assumptions (Appendix 3), exclusion of Iceland and economically inactive persons from the analyses or inclusion of subjects who started employment career before 1945.

## 5.5 Agreement between NOCCA-JEM and individual dose measurements for estimation of occupational cosmic radiation exposure among Finnish airline personnel

A strong positive relationship between continuous STUK and NOCCA-JEM dose estimates was observed (Spearman correlation; rho=0.90; 95% CI 0.89-0.91) (Figure 5). However, a normal curve fitted to the data was systematically different from the line of equality. The latter shows where the normal curve would be if two measurements would have perfectly matched. The ICC was low (0.37, 95% CI 0.01-0.61). The Bland-Altman plot showed that mean difference between STUK and NOCCA-JEM was -9.3 mSv (95% CI [-9.6]--[-9.6]) and the negative sign of the estimate indicated underestimation. The upper limit of agreement was 10.1 (95% CI 9.6-10.6) and the lower limit of agreement was -28.7 (95% CI [-29.1]--[-28.2]). NOCCA-JEM tended to underestimate individual dose estimates higher than about 20 mSv and overestimate very small values.

Analyses of categorical data showed that PA was 64% (95% CI 62%-65%). The kappa statistics was 0.46 (95% CI 0.44-0.48) and weighted kappa was 0.43 (95% CI 0.42-0.44). Figure 6 demonstrates ranking of measurements into low, medium and high categories by NOCCA-JEM and STUK. The shaded areas correspond to agreement and non-shaded to disagreement cells. There are many observations in disagreement cells (Figure 6).

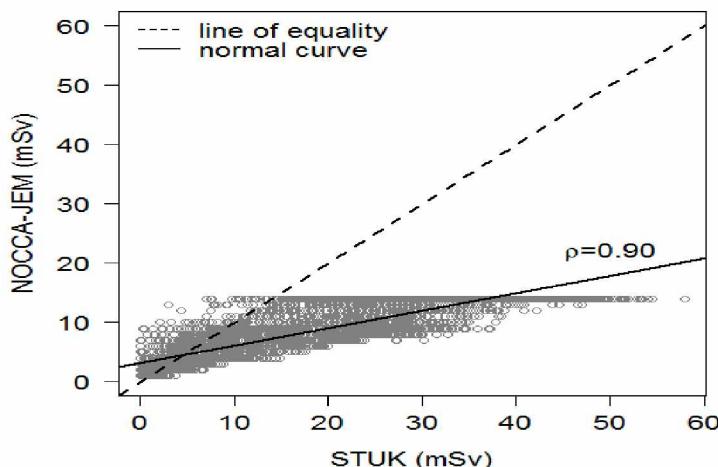


Figure 5. Scatter plot of ionizing radiation exposure estimates by the Nordic Occupational Cancer Studies Job-Exposure Matrix (NOCCA-JEM) and STUK-Radiation and Nuclear Safety Authority, Finland (mSv – millisievert;  $\rho$  – Spearman correlation coefficient).

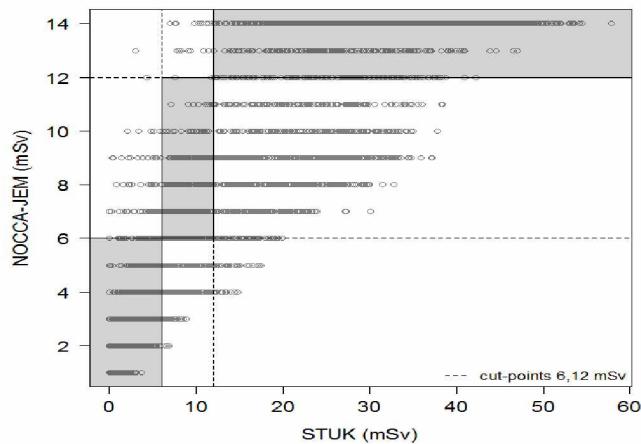


Figure 6. Distribution of ionizing radiation exposure by dose categories estimated by the Nordic Occupational Cancer Studies Job-Exposure Matrix (NOCCA-JEM) and STUK-Radiation and Nuclear Safety Authority, Finland (mSv – millisievert; shaded areas correspond to agreement cells; dose categories are:  $\leq 6$  mSv, 6-12 mSv,  $> 12$  mSv).

## 6 Discussion

### 6.1 Summary of the main findings

The findings from this study supports previous evidence that adult leukemia risk may be associated with specific occupational categories such as drivers, food workers, sales agents, clerical workers, welders, building caretakers, engine operators and farmers. It appeared that leukemia risk in some occupational categories was limited to particular years of the first employment and duration of employment.

Another finding of this study is a lack of association between occupational exposure to solvents, ELF-MF and electrical shock and working electric/electronic occupations and leukemia in workers. Surprisingly, this study did not demonstrate an elevated risk for occupational benzene exposure, which is a widely accepted risk factor of leukemia.

Accurate exposure estimation is a prerequisite for achievement of valid results in epidemiological studies. Therefore, assessment of reliability of NOCCA-JEM for occupational cosmic radiation exposure measurement was an essential complement to the current research study. Our findings indicated that NOCCA-JEM had substantial disagreement with individual dose measurements for estimation of cosmic radiation exposure among Finnish aircrew members.

### 6.2 Limitations of the study

In Study I, over 300 specific job titles were combined into broader 53 occupational categories and a group of economically inactive persons to allow for sufficient number of observed and expected cases. However, this approach could have reduced specificity of the study. In addition, occupations for each study participant were classified based on a single census (the first census during which subject was 30 years or older) ignoring potential change of job during employment career.

Despite advantages of NOCCA-JEM, its application is limited by potential exposure misclassification. Exposure misclassification is inherent to all JEMs

because exposure prevalence is rarely 100% and there is usually an exposure variation in an occupation (Kauppinen et al., 2009). However, JEMs cannot account for such variation of exposure and assign a group average estimate to all persons within an occupational category (Siemiatycki, 1996; Teschke et al., 2002). Assigning group averages instead of true values to all workers may lead to Berkson error, which reduces the power of the study, but does not dilute the risk estimates (Armstrong, 1998). Berkson error can make it more likely that true associations are not detected (Armstrong, 1998). The Study IV suggested that NOCCA-JEM is unlikely to introduce Berkson error for cosmic radiation because average estimate assigned by the NOCCA-JEM was different from true average estimates among cockpit and cabin crew members. However, analysis of categorical exposure in Study IV suggested that using NOCCA-JEM for deriving categorical cosmic radiation exposure may lead to exposure misclassification. In Studies II & III, misclassification of continuous cumulative exposures was not related to disease status of study participants because the same exposure measurement method (NOCCA-JEM) was applied to both cases and controls. This suggests that exposure misclassification of cumulative exposures in Studies II & III was likely to be non-differential. According to a commonly used overly simplistic approach that non-differential misclassification always leads to a bias towards the null, one would argue that the true risk estimates were likely to be stronger than those observed in Studies II & III. This could be true for dichotomous exposure variables. However, exposure variables in Studies II & III were multilevel ordinal variables created by categorizing continuous cumulative exposures. Non-differential misclassification of ordinal multilevel exposures does not necessarily attenuate positive risk estimates towards the null. The direction and magnitude of such bias depends on level of risk, exposure distribution, and misclassification rate (Birkett, 1992; Brenner, 1992; Correa-Villasenor, Stewart, Franco-Marina, & Seacat, 1995; Dosemeci, Wacholder, & Lubin, 1990; Rosner, 1996; Weinberg, Umbach, & Greenland, 1994). When exposure variables have three levels, non-differential exposure can bias risk estimates away from null only in the middle exposure category (Correa-Villasenor et al., 1995). The upward bias in the middle exposure level can occur when misclassification rate is small in the reference category (e.g. low level), and it is moderate to high in middle and high exposure categories, and the risk increases with true exposure. When misclassification rate is too high in non-adjacent exposure levels, a crossover bias can occur in middle and high exposure levels (Correa-Villasenor et al., 1995). In this circumstance, a detrimental risk ( $OR>1$ ) will appear to be protective ( $OR<1$ ), and conversely, a true protective risk will appear to be detrimental. Furthermore, depending on the shape of exposure

distribution, categorization of continuous exposures with non-differential measurement error into multilevel ordinal exposure variables can produce differential misclassification in ordinal exposure variables (Delpizzo & Borghesi, 1995; Flegal, Keyl, & Nieto, 1991). Therefore, exposure misclassification of multilevel ordinal exposure variables in Studies II & III could even be differential.

Another potential source of exposure misclassification in this study is related to limited job history data. Job history of study participants was available only from 1970, 1980 and 1990 censuses in Finland; 1981 census in Iceland; 1960, 1970 and 1980 censuses in Norway; and 1960, 1970, 1980 and 1990 censuses in Sweden. Annual job histories for the entire employment career were imputed from these census records by assuming that subjects changed their occupation in the middle between two censuses. This assumption was probably the weakest for Iceland because annual job history data in this country was imputed from a single census record for the entire working career. However, the Icelandic part of the data constituted only a small proportion of all study participants (<1%). Therefore, inaccuracies in job histories from Iceland did not affect overall risk estimates. This was evident in sensitivity analysis in Study III, when the main results did not change after exclusion of Icelandic data from analysis. This assumption may not hold true also for persons with high occupational mobility. However, earlier studies indicated a low percentage of occupational mobility in Nordic countries. In a study analyzing occupational mobility in Finland, 85% of male and female employees worked in the same occupation in 1975 and 1980 (Kolari, 1989). The comparison was also made between 1980 and 1985 census records in the same study, and very stable labor market in Finland was demonstrated. Pukkala et al. (2009) estimated occupational stability proportion of subjects in the NOCCA cohort and observed higher stability among men than women, and in occupational categories where a long education was required. This evidence suggests that our results are unlikely to be biased by limited job history information.

A low prevalence of exposures in a study population was also a shortcoming in this study. Because most of the exposures of interest in the study population were very rare, it was impossible to define high exposure levels including only truly high exposures. Any attempt to do so resulted in very small number of exposed persons in the high category. Therefore, percentile-based cut-points were used for categorization to avoid small numbers. The main limitation of this approach is that the highest category included cumulative exposures with large differences in magnitude. Figure 7 shows a distribution of cumulative benzene and ionizing radiation exposures among exposed cases and controls in AML data with percentile-

based categorization options. The distribution for both benzene and ionizing radiation is highly positively skewed with majority of exposed persons having small exposures. Vertical dashed-dot lines correspond to tertile cut-points, and dashed lines to 50<sup>th</sup> and 90<sup>th</sup> percentile cut-points of exposure distribution among exposed subjects. When the second tertile is used as a cut-point for high exposure category, the values for benzene range from 7.3 ppm to 42.9 ppm, and for ionizing radiation from 4.9 mSv to 28.4 mSv in the highest category. A difference between minimum and maximum values included in the category is about 6-fold. When 90<sup>th</sup> percentile is used as a cut-point for high exposure category, the values for benzene range from 13.6 ppm to 42.9 ppm, and for ionizing radiation from 12.5 mSv to 28.4 mSv. In this case, a difference is about 2-3 fold. Therefore, by using percentiles as cut-points for exposure levels, it is implicitly assumed that exposure values with such large differences have identical effects on leukemia risk (Bennette & Vickers, 2012).

Family history of leukemia, smoking and other life-style related factors could not be controlled for in Studies I through III, because there was no data on these factors. Although potential confounding effect of these factors on the risk estimates cannot be excluded, it is unlikely these are strong confounders.

Finally, reliability of NOCCA-JEM was assessed only for cosmic radiation because there were no individual estimates for other occupational exposures. In addition, radiation estimates were available only for the period 2001-2014 and not for entire working career of study participants. This limits generalization of agreement estimates found in Study IV.

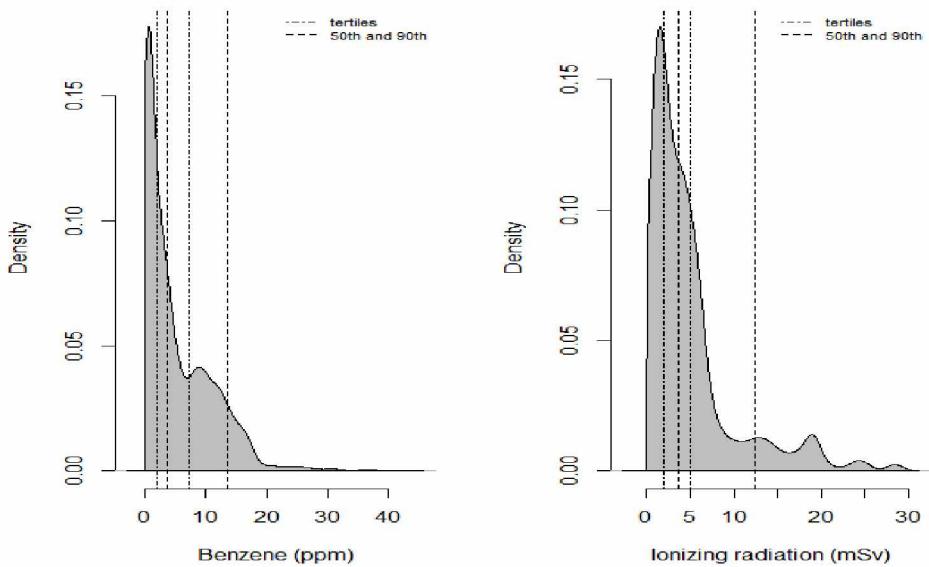


Figure 7. Distribution of cumulative benzene and ionizing radiation exposure among exposed acute myeloid leukemia (AML) cases and their matched controls (ppm – parts per million; mSv – millisievert).

### 6.3 Strengths of the study

One of the main advantages that NOCCA studies offer is completeness and accuracy of cancer incidence data. Cancer registries in the Nordic countries are famous for their accurate cancer registration (Pukkala, 2009). Several studies indicated high-quality coverage of cancer incidence in Denmark since 1943. For example, comparison between hospital discharge and Danish Cancer Society data in 1977 showed that 95% of cancer cases were registered in both sources (Osterlind & Jensen, 1985). Cancer incidence registration was moved from Danish Cancer Society to the National Board of Health in 1997. This was done to make cancer registration procedure electronically and part of other national registration. Eventually, this resulted in considerable delays of both cancer incidence and mortality registration and the newest available data in 2008 was a data from 2003. The impact of this

change on accuracy of cancer registration in Denmark is unknown (Pukkala et al., 2009).

A study comparing cancer registry data with Economic and Medical Information system conducted in 1976 showed 98% completeness of cancer registration in Norway (Lund, 1981). There was a small underreporting of cancer cases mainly for leukemia and multiple myeloma. 86.5% of all cancer cases registered in Norway since 1953 are histologically verified and only 1.3% of cancer cases are based on death certificate alone (Larsen, Småstuen, Parkin, & Bray, 2007).

In a linkage study, a Finnish cancer registry data was compared to the national hospital discharge records for the period 1985-1988. This study demonstrated 99% completeness of the Finnish cancer registry and about 10% underreporting were for neoplasms of central nervous system, CLL and multiple myeloma (Teppo, Pukkala, & Lehtonen, 1994). The main reason for underreporting was a slow reporting of newly diagnosed cancer cases. Most of these cases were later reported via the normal registration procedure (Teppo et al., 1994). Slowness of reporting was also observed in other Nordic countries (Storm, Manders, Sporgel, Bang, & Jensen, 1990; Vidarsdottir, Stefansdottir, Jonsdottir, Jonasson, & Tryggvadottir, 2008).

A recent linkage of hospital discharge information with Icelandic cancer registry indicated 99% completeness of cancer registry data in Iceland (Vidarsdottir et al., 2008).

The difference between the Swedish cancer registry and registries of other Nordic countries is that death certificates have not been used as a source of data in Sweden (Pukkala et al., 2009). Validation studies linking deaths certificates with Swedish cancer registry showed a maximum of 4.5% underreporting mainly for prostate cancer, stomach cancer, myeloma and leukemia (Barlow, Westergen, Holmberg & Talback, 2009; Mattson, 1984). The small underreporting of leukemia cases in some Nordic cancer registries is unlikely to bias the results in the current study because this underreporting is not related to occupation (Pukkala et al., 2009). If underreporting was related to occupation, then selection bias could occur.

Another advantage of the current study is that personal identity numbers were used to link information from various sources (census records, cancer registry, and population registry). This ensured complete ascertainment of relevant events for each study participant (Pukkala et al., 2009). If needed, additional information from many other sources can also be obtained for study participants through linkage by using identity numbers.

Numeric exposure estimates for more than twenty chemical and non-chemical occupational factors was possible to generate by using NOCCA-JEM. This was an

advantage over studies categorizing subjects merely into exposed and unexposed. In addition, NOCCA-JEM has an advantage over JEMs, which are based on questionnaire data. It is because exposure estimates in NOCCA-JEM are derived from individual measurement data, and NOCCA-JEM provides estimates for more than 300 specific occupations.

Finally, this study was the first to provide direct evidence for reliability of NOCCA-JEM through comparison with individual dose estimates from STUK. Individual dose estimates from STUK registry were estimated by using CARI-6 and EPCARD software, which are among the best available methods for calculation of effective dose. A validation study comparing CARI-6 effective dose estimates with in-flight dosimeter measurements of ambient dose equivalent demonstrated an excellent agreement between two methods (O'Brien et al., 2003). Another validation study showed better than  $\pm 20\%$  agreement for EPCARD compared with measured doses (Lindborg et al., 2004).

## 6.4 Comparison with findings from previous studies

The occupational category of food workers in the Study I included cannery workers, butchers and sausage makers, dairy makers, processed food workers among others. Therefore, our results for food workers can be compared to results for meat industry workers from previous studies. Observed AML risk among food workers in this study is consistent with but considerably smaller than risk estimates observed in Bethwaite et al. (2001) and Fritschi et al. (2002). Our findings for drivers are consistent with but also smaller than findings from study of the Finnish workers exposed to diesel or gasoline engine exhaust (Guo et al., 2004), which were followed-up from 1971 to 1995. Guo et al. (2004) observed increased leukemia risk ( $SIR=1.29, 1.02-1.60$ ) for Finnish male truck drivers, but not for bus, taxi and motor vehicle/tram drivers. Observed excess CLL risk among farmers in this study is consistent with but considerably smaller than findings for farmers in Ireland ( $SIR=1.88, 1.34-2.56$ ) (Kelleher et al., 1998) and animal breeding farmers ( $OR=3.05, 1.12-8.32$ ) in Italy (Amadori et al., 1995). Observed reduced leukemia risk among forestry workers, seamen and fishermen in this study is consistent with previous studies showing reduced risk for some specific occupational groups (Band et al., 1996; Fu et al., 1996; Raabe et al., 1998). The literature review in this study did not yield an evidence in support of CLL risk among clerical workers. As opposed to previous studies (Band et al., 1996; Costantini et al., 2001; Robinson et al., 2015; Wong et al., 2010; Yoshinaga et al., 1999), this study did not show positive

associations between adult leukemia and printers, painters, shoe and leather workers, electrical workers and mechanics, despite workers in these occupations maybe exposed to high benzene exposure levels. One explanation for the lack of association and observed smaller associations in the Study I is that relatively broad occupational categories were used, which probably included both exposed and unexposed persons. If the incidence rate among unexposed members of occupational category was lower than that in general population, and rates for exposed persons were higher, these rates would cancel each other out when averaged over the occupational category (Breslow & Day, 1987). Another potential explanation is that we cannot completely exclude the healthy worker effect because expected cases were derived from population which included large proportion (~26% in leukemia data) of economically inactive persons. Those who have been in active employment for many years were more likely to have a better health than economically inactive persons. Finally, observed increased risk restricted to particular period of first employment is consistent with a number of previous studies (Fu et al., 1996; Raabe et al., 1998; Straif et al., 1998).

The Study II did not demonstrate clear evidence for an association between occupational solvent exposure and AML. The highest risk estimate was observed for toluene exposure, which was statistically non-significant in the main analysis (10 year lag-time analysis). However, the risk for toluene was statistically significantly increased ( $HR=1.86$ , 95% CI 1.06-3.28) in a sensitivity analysis (no lag-time analysis). This finding is consistent with but smaller than the risk estimate for toluene ( $OR=2.6$ , 1.0-6.9) from a population-based case-control study in Shanghai (Adegoke et al., 2003). Our results did not indicate any evidence for benzene exposure. This is consistent with results from Italian multi-center case-control study (Constantini et al., 2008) and Australian, UK and Canadian petroleum workers study (Schnatter et al., 2012), but contrasts a strong positive relationship observed in previous individual studies and meta-analyses (Adegoke et al., 2003; Divine & Hartman, 2000; Guenel et al., 2002; Hayes et al., 1997; Vlaanderen et al., 2011; Vlaanderen et al., 2012).

Occupational exposure to ELF-MF, electrical shock and working in electric/electronic occupation was not associated with increased risk of AML in this study. In general, there is weak evidence for association between ELF-MF and AML. In a meta-analysis by Kheifets et al. (2008), a small increased meta-relative risk was observed for AML. This risk estimate was based on mainly older studies, while the recent studies demonstrated a marginal increase of AML risk. Koeman et al. (2014) observed a modest increased risk of AML in a prospective Netherlands Cohort Study. In that study, ELF-MF exposure was estimated using the same JEM as was

used in our Study III. To our knowledge, our study was the first to assess the association between electrical shock and AML.

The Study IV is consistent with previous studies assessing accuracy of JEM in estimation of various occupational exposures. For example, in a study by Rybicki et al. (1997), low sensitivity (21% for copper, 0% for lead and 16% for iron) was observed for JEM in estimation of exposure values of three metals. In addition, this study demonstrated a substantial bias (greater than 50% towards null) of true OR estimates by JEM (Rybicki et al., 1997). Only a poor to fair agreement ( $\kappa=0.07$  for formaldehyde, 0.33 for lead, 0.46 for insecticides, 0.12 for aromatic hydrocarbons, 0.28 for chlorinated hydrocarbons) was observed between FINJEM and industrial hygiene panel in an Australian community-based case-control study (Benke et al., 2001). In a retrospective Netherlands Cohort Study by Offermans et al. (2012), weighted kappa for estimation of asbestos exposure for asbestos JEM was 0.10 (95% CI 0.05-0.13), for DOMJEM was 0.29 (95% CI 0.23-0.32) and for FINJEM was 0.23 (95% CI 0.19-0.29). The highest weighted kappa (95% CI 0.70 [0.65-0.74]) was observed for FINJEM for estimation of welding fumes (Offermans et al., 2012). There is however, indirect evidence for validity of FINJEM. In a study of occupational silica dust exposure, FINJEM was able to replicate a known association with dose-response relationship between silica dust and lung cancer (Pukkala et al., 2005).

## 7 Summary and conclusions

In conclusion, this population-based epidemiological study showed that adult leukemia incidence in some occupational categories is statistically significantly higher than the incidence in general populations of Nordic countries. For some of these occupations, increased leukemia risk may be linked to specific occupational exposures. For example, food workers include wide range of specific occupations, which are potentially exposed to benzene, solvents and infectious agents from animal populations. Drivers are occupationally exposed to gasoline and diesel exhaust fumes. Increased risk of CLL among farmers might be related to either pesticides, which are commonly used in this occupational category, or infectious agents that can be transmitted to humans from animal populations. We are not aware of any occupational exposures as potential leukemia risk factors for categories of clerical workers and sales agents. Restriction of leukemia risk in particular time periods of first employment maybe related to higher exposure levels during that period.

This study did not provide clear evidence of an increased leukemia risk for occupational exposure to solvents, ELF-MF and electrical shocks and working in electric/electronic occupations. There was no increased risk also for benzene exposure, which is a widely accepted leukemia risk factor. Some explanations for the lack of association for benzene exposure are potential exposure misclassification by NOCCA-JEM, and low prevalence of high benzene exposures in the study population. There was some variation of risk estimates by sex and age. This may reflect either a true risk variation in these subgroups or maybe simply due to chance.

The reliability study of NOCCA-JEM for cosmic radiation exposure demonstrated substantial disagreement with individual level exposure data. This suggests that NOCCA-JEM may lead to substantial exposure measurement error and misclassification in studies of occupational cosmic radiation exposure. Studies conducted in Australia and Netherlands (Benke et al., 2001; Offermans et al., 2012) indicated poor to moderate validity of FINJEM for estimation of lead, asbestos, welding fumes, aromatic hydrocarbons, chlorinated hydrocarbons and insecticides. These results are apparently true also for NOCCA-JEM, because NOCCA-JEM estimates were mainly derived from FINJEM estimates (Kauppinen et al., 2009). However, generalization of these results to Nordic setting maybe limited because

these studies were based on data from Australia and Netherlands (Benke et al., 2001; Offermans et al., 2012). There is also an indirect evidence of FINJEM validity suggesting that it is quite accurate in estimating some specific exposure agents. For example, FINJEM was able to replicate a known association and exposure-response relationship between silica dust exposure and lung cancer (Pukkala et al., 2005). Further studies based on the Nordic data are needed to assess reliability of NOCCA-JEM for estimation of other specific occupational agents.

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## 10 Appendix 1. Imputation of missing job history data

A figure below is based on AML data used in Study III. It shows proportions of missing job history data during census years 1960, 1970, 1980 and 1990. The largest missing job history was observed for censuses in 1960 (24.4%) and in 1990 (27.1%), whereas it was less than 3% for the remaining censuses (Figure 8). Dark blue areas of bars indicate proportions of missing job history due to unavailable censuses. For example, 90.7% of missing job history during 1960 census was because the whole census was not available for Finland and Iceland in 1960, and 88.9% of missing job history in 1990 was because there were no census records at all for Norway and Iceland in 1990. In 1970, census records were not available only for Iceland.

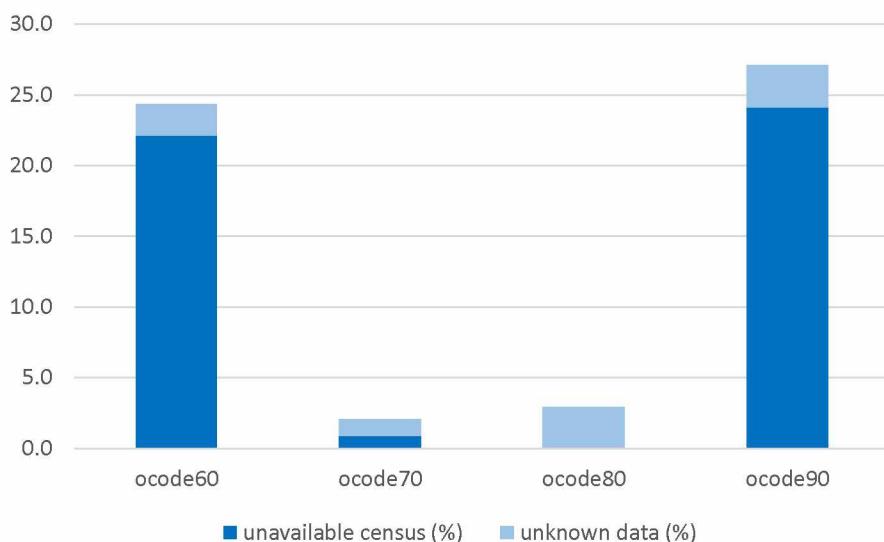


Figure 8. Missing job history in Study III (ocode60 – occupational code in 1960 census; ocode70 – occupational code in 1970 census; ocode80 – occupational code in 1980 census; ocode90 – occupational code in 1990 census; dark blue area corresponds to missing values due to unavailable census and light blue cells to missing values due to unknown data).

Occupational codes for missing years were imputed based on the nearest available census years by assuming that a person changed occupation in the middle between

available census records. The earliest possible exposure start in the Study III was on 01.01.1945 and the latest exposure end was on 31.12.2005. Therefore, all imputations of missing occupational codes were made between these dates. Imputations of job history data for each possible combination of missing occupational codes is presented in the table below. Cells with “plus” sign indicate available occupational code and “minus” sign unavailable code.

Occupational code				Imputation of missing codes
1960	1970	1980	1990	
-	-	-	+	ocode90 1945-2005
+	-	-	+	ocode60 1945-1974; ocode90 1975-2005
+	-	-	-	ocode60 1945-2005
-	+	-	-	ocode70 1945-2005
-	-	+	-	ocode80 1945-2005
+	-	+	-	ocode60 1945-1969; ocode80 1970-2005
-	+	+	-	ocode70 1945-1974; ocode80 1975-2005
+	+	-	-	ocode60 1945-1964; ocode70 1965-2005
-	-	+	+	ocode80 1945-1984; ocode90 1985-2005
-	+	-	+	ocode70 1945-1979; ocode90 1980-2005
+	-	+	+	ocode60 1945-1969; ocode80 1970-1984; ocode90 1985-2005
+	+	-	+	ocode60 1945-1964; ocode70 1965-1979; ocode90 1980-2005
+	+	+	-	ocode60 1945-1964; ocode70 1965-1974; ocode80 1975-2005
-	+	+	+	ocode70 1945-1974; ocode80 1975-1984; ocode90 1985-2015
+	+	+	+	ocode60 1945-1964; ocode70 1965-1974; ocode80 1975-1984; ocode90 1985-2005

## 11 Appendix 2. Analyses with 0 and 5 years lag-time in Study II.

Table 11. Hazard ratios (HR) and 95% confidence intervals (95% CI) of acute myeloid leukemia associated with exposure to solvents and other co-factors.  
[ppm-parts per million]

Agent <sup>a</sup> (ppm/year)	0 years lag-time					5 years lag-time				
	Cases	Controls	HR	95% CI	p for trend	Cases	Controls	HR	95% CI	p for trend
<i>Aliphatic and alicyclic hydrocarbon solvents</i>										
≤17.5	348	1739	0.89	0.70-1.15	0.75	364	1738	0.97	0.76-1.24	0.83
17.5-300	310	1522	0.98	0.75-1.27		293	1470	0.94	0.72-1.23	
>300	65	430	0.56	0.33-0.93		60	402	0.57	0.34-0.97	
<i>Aromatic hydrocarbon solvents <sup>b</sup></i>										
≤9.3	368	1711	1.12	0.95-1.30	0.53	371	1694	1.14	0.98-1.33	0.42
9.3-275	251	1391	0.89	0.74-1.09		256	1384	0.92	0.76-1.12	
>275	94	457	1.13	0.78-1.63		81	406	1.20	0.81-1.78	
<i>Benzene</i>										
≤3.7	453	2122	1.07	0.88-1.29	0.34	454	2077	1.03	0.85-1.25	0.47
3.7-13.6	316	1645	0.91	0.73-1.13		309	1634	0.86	0.69-1.07	
>13.6	77	459	0.81	0.57-1.13		75	451	0.85	0.59-1.19	
<i>Toluene</i>										

Agent <sup>a</sup> (ppm/year)	0 years lag-time					5 years lag-time				
	Cases	Controls	HR	95% CI	p for trend	Cases	Controls	HR	95% CI	p for trend
≤42.4	434	2055	1.11	0.90-1.37	0.49	439	2009	1.16	0.94-1.44	0.62
42.4-612	316	1669	1.06	0.83-1.35		309	1645	1.06	0.83-1.36	
>612	86	433	1.86	1.05-3.26		80	423	1.53	0.84-2.77	
<i>Trichloroethylene</i>										
≤16.2	310	1889	0.91	0.77-1.08	0.10	322	1839	0.99	0.84-1.17	0.17
16.2-121	293	1450	1.10	0.93-1.31		281	1408	1.10	0.93-1.31	
>121	69	365	1.06	0.79-1.42		69	359	1.08	0.80-1.44	
<i>1,1,1-trichloroethane</i>										
≤5.6	557	2886	0.92	0.79-1.08	0.59	580	2932	0.92	0.79-1.08	0.61
5.6-12.7	278	1636	0.79	0.66-0.96		264	1531	0.76	0.63-0.93	
>12.7	138	697	0.91	0.71-1.15		111	592	0.84	0.65-1.08	
<i>Methylene chloride</i>										
≤9.9	296	1430	1.20	0.97-1.48	0.47	301	1433	1.14	0.92-1.40	0.46
9.9-64.6	331	1692	1.09	0.88-1.35		313	1597	1.10	0.89-1.37	
>64.6	63	362	0.88	0.49-1.57		62	349	1.08	0.58-1.99	
<i>Perchloroethylene</i>										
≤12.1	85	514	0.90	0.69-1.17	0.39	86	501	0.89	0.69-1.16	0.35
12.1-106	76	381	0.98	0.74-1.30		75	380	0.97	0.73-1.29	
>106	18	124	0.69	0.38-1.24		18	111	0.79	0.44-1.45	
<i>Other organic solvents</i>										
≤83.8	158	774	0.99	0.81-1.19	0.51	163	765	1.06	0.87-1.28	0.52
83.8-357	134	651	0.91	0.69-1.21		130	627	1.00	0.75-1.34	

Agent <sup>a</sup> (ppm/year)	0 years lag-time					5 years lag-time				
	Cases	Controls	HR	95% CI	p for trend	Cases	Controls	HR	95% CI	p for trend
>357	37	212	0.95	0.57-1.57		31	198	0.87	0.51-1.49	

<sup>a</sup> Occupationally unexposed individuals were used as a reference group in all analyses.

<sup>b</sup> HR estimates for aromatic hydrocarbon solvents are from Model 2, all other HR are from Model 1.

## 12 Appendix 3. Analyses with 5 and 10 years lag-time in Study III.

Table 12. Hazard ratios (HR) and 95% confidence intervals (95% CIs) of occupational exposure to low-frequency magnetic fields and acute myeloid leukemia.

Agent	5 years lag-time					10 years lag-time				
	Cases	Controls	HR	95% CI	p for trend	Cases	Controls	HR	95% CI	p for trend
<b>Extremely low-frequency magnetic fields</b>										
<i>Ever exposed to</i>										
Background levels	2915	14380	1.00			3036	15043	1.00		
Low levels	2125	10723	0.99	0.93-1.06		2017	10157	1.00	0.94-1.07	
High levels	369	1942	0.95	0.83-1.09	0.58	356	1845	0.97	0.85-1.12	0.85
Duration of ever low/high exposed (HR/10 years) <sup>a</sup>	5409	27045	0.99	0.97-1.03		5409	27045	0.99	0.97-1.03	
Duration of ever high exposed (HR/10 years) <sup>a</sup>	5409	27045	0.99	0.93-1.06		5409	27045	0.99	0.93-1.08	
Cumulative exposure <sup>b</sup>										
Background (0 unit-years)	2915	14380	1.00			3036	15043	1.00		
1-16.2 unit-years	1153	5702	1.01	0.94-1.09	0.50	1240	6234	1.00	0.93-1.08	0.97

Agent	5 years lag-time					10 years lag-time				
	Cases	Controls	HR	95% CI	p for trend	Cases	Controls	HR	95% CI	p for trend
16.2-29.9 unit-years	690	3589	0.97	0.88-1.07		593	3016	0.99	0.90-1.11	
≥29.9 unit-years	651	3374	0.97	0.87-1.08		540	2752	0.99	0.89-1.12	

<sup>a</sup> The risk associated with 10-year increase in duration of exposure.

<sup>b</sup> Tertiles of exposure distribution among exposed controls used as cutoff points.

## Occupation and Leukemia in Nordic Countries

*Madar Talibov, MSc, Susanna Kautiainen, PhD, Jan Ivar Martinsen, PhD, Kristina Kjaerheim, PhD, Elsebeth Lyng, PhD, Per Sparén, PhD, Laufey Tryggvadottir, PhD, Elisabete Weiderpass, PhD, and Eero Pukkala, PhD*

**Objective:** We studied occupational variation of the risk of acute myeloid leukemia, chronic lymphocytic leukemia, and other leukemia in Nordic countries. **Methods:** The study cohort comprised 15 million persons older than 30 years who participated in the population censuses in 1960, 1970, 1980/1981, 1990, or all of these years in five Nordic countries. Standardized incidence ratios (SIRs) were estimated for 53 occupations and one group of economically inactive persons. **Results:** Significantly increased risks were observed for acute myeloid leukemia among drivers (SIR = 1.16; 95% confidence interval [CI], 1.07–1.26) and food workers (SIR = 1.13; 95% CI, 1.01–1.27); for chronic lymphocytic leukemia among farmers (SIR = 1.09; 95% CI, 1.04–1.14) and clerical workers (SIR = 1.07; 95% CI, 1.01–1.14); and for other leukemia among seamen (SIR = 1.24; 95% CI, 1.04–1.49), “other health workers” (SIR = 1.22; 95% CI, 1.02–1.47), chemical process workers (SIR = 1.18; 95% CI, 1.01–1.38), and sales agents (SIR = 1.15; 95% CI, 1.06–1.25). **Conclusion:** Observed modest occupational variation of leukemia risk might be associated with occupational or lifestyle factors.

**L**eukemia is a heterogeneous group of malignancies. It is classified as either lymphocytic or myelogenous according to which kind of blood cell is affected. Both types have acute and chronic forms. Incidence of leukemia among the elderly in Nordic countries increased between the 1950s and 1970s, when the increase began to level off (Fig. 1).<sup>1</sup>

Increased risk of leukemia may be associated with a wide range of occupational agents such as ionizing radiation, electromagnetic fields, benzene, ethylene oxide, styrene, butadiene, and pesticides, among others. However, the evidence is not consistent.<sup>2</sup> Proposed mechanisms through which such agents act is complex. This study aimed to evaluate occupational variation of the risk of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and all other leukemia combined (“other leukemia”) in Nordic countries.

### METHODS

The Nordic Occupational Cancer (NOCCA) study cohort was based on populations in one or more censuses in Denmark, Finland, Iceland, Norway, and Sweden who participated in population censuses from 1960, 1970, 1980/1981, 1990, or all years and were 30 to 64 years old at the beginning of follow-up and living in the country on January 1 after the census. Person-years were calculated until the

From the School of Health Sciences (Ms Talibov and Drs Kautiainen and Pukkala), University of Tampere, Tampere, Finland; Cancer Registry of Norway (Drs Martinsen, Kjaerheim, and Weiderpass), Oslo, Norway; Centre of Epidemiology and Screening (Dr Lyng), Institute of Public Health, University of Copenhagen, Denmark; Department of Epidemiology and Biostatistics (Drs Sparén and Weiderpass), Karolinska Institute, Stockholm, Sweden; Icelandic Cancer Registry (Dr Tryggvadottir), Reykjavik, Iceland; Finnish Cancer Registry (Dr Pukkala), Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland.

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Address correspondence to: Madar Talibov, MSc, School of Health Sciences, University of Tampere, FI-33014, Tampere, Finland (Madar.Talibov@uta.fi). Copyright © 2012 by American College of Occupational and Environmental Medicine

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date of emigration, death, or to December 31 of the following years: 2003 in Denmark and Norway, 2004 in Iceland, and 2005 in Finland and Sweden. Information about economic activity, occupation, and industry was recorded for each individual during the censuses, and questionnaires were centrally coded and computerized in the national statistical offices.<sup>3</sup>

In Finland, Norway, and Sweden the occupations were coded to more than 300 categories according to national adaptations of International Standard Classification of Occupations from 1958. In Iceland, the occupations were coded according to national adaptation of International Standard Classification of Occupations 1968, and a special national nomenclature was used for occupational coding in Denmark.<sup>3</sup> Original national codes were converted to relatively specific but not too narrow occupational titles with 53 categories (Table 1).

Information about cancer was obtained from the cancer registries of the Nordic countries, which are fairly similar, on the basis of notification from clinical and pathologic departments, general practitioners, private clinics, and death registries. In our data set, leukemia cases were classified as AML, CLL, and other leukemia. For Denmark, the categories of CLL and other leukemia were not defined, and therefore subtype-specific results are presented only for AML.

We present our results as standardized incidence ratios (SIRs), which were computed as the ratio of the observed number of cases to the expected number of cases in strata defined according to 5-year age category, 5-year period, sex, and country. To estimate the expected number of cases, incidence rates were multiplied by the respective numbers of person-years at risk. The 95% confidence intervals (CIs) for SIR estimates were calculated by assuming Poisson distribution for observed cases.

To evaluate the consistency and trends of SIR estimates, we combined the data to broader calendar periods (1961–1975, 1976–1990, and 1991–2005) and age groups (30–44, 45–59, and ≥60 years). A Poisson regression trend test<sup>4</sup> was performed to assess the significance of observed trends of SIR estimates across age and calendar periods.

### RESULTS

The cohort consisted of 14.9 million individuals from the five Nordic countries; 2.0 million from Denmark, 3.4 million from Finland, 100,000 from Iceland, 2.6 million from Norway, and 6.8 million from Sweden. In total, 18,811 cases of AML, 20,462 cases of CLL, and 15,570 cases of other leukemia occurred during the follow-up from 1961 to 2005. The number of person-years accumulated by the end of follow-up was 384.4 million. For the analysis related to CLL and “other leukemia,” excluding Denmark, the number of person-years was 333.5 million.

Table 1 shows the overall SIR estimates for AML, CLL, and other leukemia in 53 occupational categories and in the group of economically inactive persons. During the follow-up, 555 cases of AML occurred among drivers (SIR = 1.16; 95% CI, 1.07–1.26) and 287 cases occurred among food workers (SIR = 1.13; 95% CI, 1.01–1.27). The incidence of CLL was significantly higher than that of the population average in the occupational categories of farmers (SIR = 1.09; 95% CI, 1.04–1.14) and clerical workers (SIR = 1.07; 95% CI, 1.01–1.14).

**TABLE 1.** Observed Number and Standardized Incidence Ratios for AML, CLL, and Other Leukemia by Occupational Categories in Nordic Countries

Occupational Category	AML			CLL			Other Leukemia		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Technical workers, etc	662	0.98	0.91–1.06	889	0.98	0.92–1.05	616	0.98	0.91–1.06
Laboratory assistants	36	1.23	0.86–1.71	17	0.75	0.44–1.20	22	1.07	0.67–1.63
Physicians	65	1.22	0.94–1.55	61	1.06	0.81–1.37	36	0.83	0.58–1.15
Dentists	27	1.07	0.70–1.56	24	0.83	0.53–1.24	29	1.35	0.91–1.94
Nurses	130	0.96	0.81–1.14	99	0.97	0.79–1.18	84	0.91	0.73–1.13
Assistant nurses	178	1.03	0.89–1.19	156	1.00	0.85–1.17	142	1.03	0.87–1.21
Other health workers	112	0.88	0.73–1.06	100	0.91	0.75–1.11	113	<b>1.22</b>	<b>1.02–1.47</b>
Teachers	506	1.02	0.93–1.11	528	1.04	0.95–1.13	370	0.93	0.84–1.03
Religious workers, etc	242	1.08	0.95–1.23	288	1.10	0.98–1.23	206	0.96	0.84–1.10
Artistic workers	57	0.91	0.69–1.17	83	1.10	0.87–1.36	58	1.03	0.78–1.34
Journalists	33	1.17	0.81–1.65	32	0.92	0.63–1.30	28	1.06	0.70–1.52
Administrators	528	1.04	0.95–1.13	513	1.02	0.94–1.11	348	0.95	0.86–1.06
Clerical workers	1127	1.05	0.99–1.11	1086	<b>1.07</b>	<b>1.01–1.14</b>	826	1.02	0.95–1.09
Sales agents	510	1.09	1.00–1.19	697	1.04	0.97–1.12	562	<b>1.15</b>	<b>1.06–1.25</b>
Shop workers	788	1.01	0.94–1.08	611	1.01	0.93–1.09	424	0.92	0.84–1.01
Farmers	1380	0.98	0.93–1.03	1746	<b>1.09</b>	<b>1.04–1.14</b>	1099	0.97	0.91–1.03
Gardeners	508	0.97	0.89–1.06	637	0.98	0.91–1.06	485	1.01	0.92–1.10
Fishermen	108	0.83	0.69–1.00	111	0.83	0.69–1.00	69	<b>0.68</b>	<b>0.53–0.85</b>
Forestry workers	160	<b>0.85</b>	<b>0.73–0.99</b>	287	0.95	0.85–1.07	196	0.90	0.78–1.04
Miners and quarry workers	46	1.03	0.75–1.37	68	0.97	0.75–1.23	56	1.11	0.84–1.45
Seamen	95	<b>0.79</b>	<b>0.64–0.97</b>	103	<b>0.79</b>	<b>0.65–0.96</b>	118	<b>1.24</b>	<b>1.04–1.49</b>
Transport workers	179	1.03	0.89–1.19	240	1.04	0.92–1.18	146	0.97	0.83–1.14
Drivers	555	<b>1.16</b>	<b>1.07–1.26</b>	594	1.03	0.95–1.12	395	0.97	0.88–1.07
Postal workers	200	1.01	0.88–1.16	208	0.94	0.82–1.08	157	0.91	0.78–1.06
Textile workers	290	0.89	0.79–1.00	307	0.89	0.80–1.00	250	0.93	0.82–1.05
Shoe and leather workers	48	0.92	0.68–1.22	50	0.76	0.56–1.00	61	1.19	0.91–1.53
Smelting workers	139	0.92	0.78–1.09	167	0.92	0.79–1.07	137	1.05	0.89–1.24
Mechanics	658	0.97	0.90–1.05	892	0.98	0.92–1.05	635	1.00	0.93–1.08
Plumbers	74	0.98	0.77–1.23	97	0.91	0.74–1.11	72	0.97	0.76–1.22
Welders	91	1.23	0.99–1.51	117	0.99	0.83–1.19	91	1.12	0.90–1.37
Electrical workers	272	1.03	0.91–1.16	349	1.00	0.90–1.11	254	1.03	0.91–1.17
Wood workers	539	0.97	0.89–1.06	739	1.00	0.93–1.07	491	0.92	0.84–1.01
Painters	128	0.97	0.82–1.15	177	1.00	0.86–1.16	109	0.86	0.71–1.04
Other construction workers	298	0.98	0.87–1.10	333	0.96	0.86–1.07	246	0.99	0.87–1.12
Bricklayers	69	0.86	0.67–1.09	75	0.89	0.70–1.12	70	1.18	0.92–1.49
Printers	79	0.80	0.63–1.00	119	1.05	0.88–1.26	84	1.00	0.79–1.23
Chemical process workers	143	1.07	0.91–1.26	171	1.01	0.87–1.17	151	<b>1.18</b>	<b>1.01–1.38</b>
Food workers	287	<b>1.13</b>	<b>1.01–1.27</b>	213	0.92	0.80–1.05	165	0.96	0.82–1.12
Beverage workers	14	0.89	0.49–1.49	4	1.15	0.57–2.05	9	1.20	0.55–2.27
Tobacco workers	10	1.20	0.58–2.21	11	1.07	0.29–2.75	3	1.01	0.21–2.94
Glass makers, etc	145	0.88	0.75–1.04	184	0.97	0.84–1.12	151	1.07	0.91–1.26
Packers	287	1.01	0.90–1.13	359	0.96	0.87–1.06	293	1.03	0.92–1.16
Engine operators	200	1.04	0.91–1.19	279	1.05	0.93–1.18	182	0.95	0.82–1.10
Public safety workers	148	1.11	0.94–1.30	182	1.09	0.94–1.26	134	1.13	0.95–1.34
Cooks and stewards	121	1.02	0.85–1.22	138	1.02	0.86–1.21	114	1.03	0.86–1.24
Domestic assistants	243	0.99	0.87–1.12	222	1.03	0.90–1.17	187	0.97	0.84–1.12
Waiters	95	0.83	0.67–1.02	113	0.99	0.82–1.19	91	0.99	0.80–1.22
Building caretakers	593	1.08	1.00–1.17	440	0.96	0.87–1.05	387	1.06	0.96–1.17
Chimney sweeps	8	1.25	0.54–2.45	11	1.19	0.59–2.12	4	0.62	0.17–1.59
Hairdressers	53	0.85	0.63–1.11	51	0.86	0.64–1.13	44	0.95	0.69–1.27
Launderers	55	0.83	0.63–1.08	61	0.99	0.75–1.27	50	1.05	0.78–1.39
Military personnel	88	1.20	0.96–1.48	100	1.09	0.89–1.33	60	0.98	0.75–1.26
Other workers	521	0.98	0.90–1.07	544	1.00	0.92–1.09	406	0.97	0.88–1.07
Economically inactive	4883	0.99	0.96–1.02	4779	0.99	0.96–1.02	4054	1.02	0.99–1.05

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Obs, observed number of cases; SIR, standardized incidence ratio.  
The data given in bold indicates significant estimates.

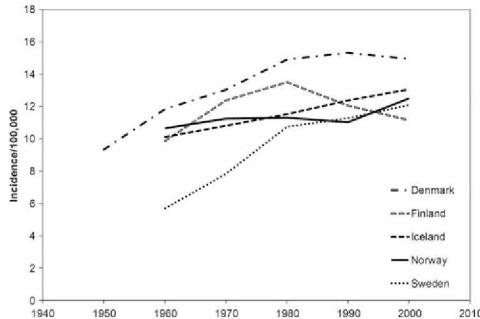
**TABLE 2.** Observed Number and Standardized Incidence Ratio for AML, CLL, and Other Leukemia by Period and Selected\* Occupational Categories in Nordic Countries

Type of Leukemia	Occupation	1961–1975			1976–1990			1991–2005			$P_{\dagger}$
		Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	
AML	Drivers	44	1.22	0.89–1.64	224	1.12	0.98–1.28	287	1.18	1.05–1.32	0.83
	Food workers	21	0.92	0.57–1.40	113	1.03	0.86–1.24	153	1.26	1.08–1.48	0.06
	Seamen	13	0.87	0.46–1.49	40	0.80	0.57–1.09	42	0.76	0.55–1.03	0.67
	Forestry workers	11	0.59	0.30–1.06	77	0.86	0.68–1.08	72	0.90	0.71–1.14	0.28
CLL	Farmers	180	1.01	0.87–1.17	851	1.13	1.06–1.21	715	1.07	0.99–1.15	0.99
	Clerical workers	92	1.61	1.30–1.97	331	1.00	0.90–1.11	663	1.06	0.98–1.14	0.05
	Seamen	15	1.10	0.62–1.82	40	0.82	0.59–1.12	48	0.71	0.53–0.94	0.15
Other leukemia	Seamen	29	1.17	0.79–1.68	35	1.04	0.73–1.45	54	1.46	1.09–1.90	0.25
	Other health workers	17	1.38	0.81–2.22	36	1.24	0.87–1.71	60	1.17	0.89–1.51	0.55
	Chemical process workers	39	1.03	0.73–1.41	58	1.23	0.93–1.59	54	1.26	0.95–1.65	0.35
	Sales agents	128	1.14	0.96–1.36	192	1.11	0.96–1.28	242	1.20	1.06–1.36	0.56
	Fishermen	26	0.74	0.48–1.08	24	0.66	0.42–0.98	19	0.63	0.38–0.98	0.59

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Obs, observed number of cases; SIR, standardized incidence ratio.

\*Only occupations with significantly increased and decreased overall SIR estimates are shown.

†Poisson trend test.

**FIGURE 1.** Incidence rates (per 100,000 person-years) of leukemia in Nordic countries, among those aged 30 to 85 years, adjusted to the world standard population. Tabulation is based on NORDCAN data.<sup>1</sup>

Statistically significantly increased risk for other leukemia was observed among chemical process workers (SIR = 1.18; 95% CI, 1.01–1.38), other health workers (SIR = 1.22; 95% CI, 1.02–1.47), seamen (SIR = 1.24; 95% CI, 1.04–1.49), and sales agents (SIR = 1.15; 95% CI, 1.06–1.25). Significantly decreased SIRs were observed among forestry workers and seamen for AML; seamen for CLL; and fishermen for other leukemia.

There was a tendency of increasing SIR over time for AML among food workers (Table 2). The risk of CLL among clerical workers was only elevated in 1961 to 1975. The other associations were quite stable over the periods.

Stratification by age (Table 3) showed that the SIR of AML among food workers and SIR of other leukemia among other health workers were mainly elevated in those younger than 60 years. There was some indication of increasing trend toward older ages for AML among drivers and for other leukemia among seamen, but none of the trends were statistically significant. We did not observe any

significant difference of the SIRs across sexes and countries (Tables 4 and 5).

## DISCUSSION

To our knowledge, this study is one of the largest to explore associations between occupational affiliation and leukemia. The strengths of this study include reliable ascertainment and high coverage of leukemia cases<sup>5–8</sup> and the high accuracy of occupational coding in Nordic countries.<sup>3</sup> The linkages between the census data, the mortality and emigration data, and the cancer incidence data were based on the unique personal identity codes used in registries of all Nordic countries.

The information about occupations was based on national censuses from 1960 to 1990. Occupations were classified on the basis of the first census records for each person at the age of 30 years or older. In Finland, occupation-specific standardized mortality ratios were calculated in two ways: first on the basis of one single census (1980) and then restricted to persons who had stayed in the same occupation in subsequent censuses. The standardized mortality ratio estimates were practically identical.<sup>9</sup> We believe that these results, based on occupation in one census, give, in most instances, results similar to those we would have obtained from categorizations, based on occupational titles kept in several censuses. The follow-up in this study started with the occupation held at the age of 30 years or older to avoid misclassification due to career development in the beginning of work life.

In general, there was quite little variation of the SIR estimates. We observed significantly elevated risk of AML among drivers and food workers. Drivers included car, taxi, van, bus, motorcycle, and truck drivers. Some of them are occupationally exposed to diesel exhaust, which is emitted as a result of combustion of diesel fuel. Some particles of diesel exhaust such as benzene, butadiene, ethylene oxide, and styrene are carcinogenic to humans.<sup>10</sup> There is evidence from previous studies that exposure to benzene causes AML in humans.<sup>11,12</sup> Occupational exposure to butadiene, ethylene oxide, and styrene also has been linked to leukemia; however, the evidence is inconsistent.<sup>13–15</sup> Age-specific pattern of the risk among drivers suggests that AML occurrence might depend on the duration of exposure to benzene.

**TABLE 3.** Observed Number and Standardized Incidence Ratio for AML, CLL, and Other Leukemia by Age and Selected\* Occupational Categories in Nordic Countries

Type of Leukemia	Occupation	30–44			45–59			≥60			P†
		Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	
AML	Drivers	32	0.99	0.68–1.40	119	1.11	0.93–1.33	404	1.19	1.08–1.31	0.26
	Food workers	14	1.26	0.69–2.11	63	1.40	1.08–1.79	210	1.06	0.93–1.21	0.09
	Seamen	3	0.37	0.08–1.08	21	0.79	0.49–1.21	71	0.83	0.65–1.05	0.25
	Forestry workers	10	1.32	0.63–2.43	20	0.67	0.41–1.03	130	0.87	0.73–1.03	0.82
CLL	Farmers	7	0.96	0.39–1.97	191	1.13	0.98–1.30	1548	1.09	1.04–1.15	0.76
	Clerical workers	16	0.84	0.48–1.37	250	1.14	1.01–1.29	820	1.06	0.99–1.14	0.71
	Seamen	0	0.00	0.00–2.56	28	1.07	0.71–1.55	75	0.73	0.58–0.92	0.08
Other leukemia	Seamen	8	1.00	0.43–1.97	29	1.10	0.74–1.58	81	1.33	1.05–1.65	0.29
	Other health workers	19	1.42	0.86–2.22	45	1.46	1.07–1.96	49	1.01	0.75–1.33	0.09
	Chemical process workers	9	1.16	0.53–2.20	33	1.14	0.78–1.60	109	1.20	0.99–1.45	0.82
	Sales agents	47	1.19	0.88–1.59	142	1.13	0.96–1.33	373	1.16	1.05–1.28	0.98
	Fishermen	5	0.92	0.30–2.14	17	0.80	0.46–1.28	47	0.62	0.46–0.83	0.25

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Obs, observed number of cases; SIR, standardized incidence ratio.

\*Only occupations with significantly increased and decreased overall risk estimates are shown.

†Poisson trend test.

**TABLE 4.** Observed Number and Standardized Incidence Ratio for AML, CLL, and Other Leukemia by Sex and Selected\* Occupational Categories in Nordic Countries

Type of Leukemia	Occupation	Male			Female			Obs	SIR	95% CI
		Obs	SIR	95% CI	Obs	SIR	95% CI			
AML	Drivers	542	1.16	1.07–1.26	13	0.93	0.50–1.60	180	1.14	0.99–1.32
	Food workers	180	1.14	0.99–1.32	107	1.11	0.92–1.34			
	Seamen	94	0.79	0.64–0.96	1	3.75	0.09–20.90			
	Forestry workers	157	0.85	0.73–0.99	3	1.14	0.23–3.32			
CLL	Farmers	1 553	1.09	1.03–1.14	193	1.13	0.98–1.30	461	1.09	0.99–1.19
	Clerical workers	461	1.09	0.99–1.19	625	1.06	0.98–1.15			
	Seamen	103	0.80	0.66–0.96	0	0.00	0.00–17.16			
Other leukemia	Seamen	118	1.24	1.04–1.49	0	0.00	0.00–18.00	38	1.41	1.00–1.94
	Other health workers	38	1.41	1.00–1.94	75	1.14	0.90–1.43			
	Chemical process workers	136	1.18	1.00–1.40	15	1.19	0.67–1.97			
	Sales agents	477	1.17	1.07–1.28	85	1.08	0.86–1.34			
	Fishermen	66	0.65	0.50–0.83	3	3.20	0.66–9.36			

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Obs, observed number of cases; SIR, standardized incidence ratio.

\*Only occupations with significantly increased and decreased overall risk estimates are shown.

Food workers included such occupations as cannery workers, butchers and sausage makers, dairy makers, and processed food workers, among others. Some of these occupational subgroups can be exposed to benzene in the workplace. For example, benzene is used as a solvent in production of rubber cement, which is widely used in the cannery industry. There was some indication of an increasing trend of SIR among food workers over calendar periods. We did not observe significant risk elevation among other benzene-exposed occupational groups such as shoe and leather workers and printing, painting, and rubber industry workers.

The incidence of CLL was significantly higher in occupational categories of farmers and clerical workers than in the average population. Some, but not all, epidemiological studies have found an association between farming and leukemia.<sup>16–18</sup> Two major groups of risk factors were proposed as causes of hematologic malignancies

among agricultural workers: The first group includes various chemicals such as pesticides, herbicides, and related substances. The second group includes various animal viruses.<sup>19</sup> Clerical workers included secretaries and clerical workers in banks and insurance companies, accounting and bookkeeping clerks, and other types of office works. We are not aware of any exposure in this occupational category that could put clerical workers at leukemia risk.

We found significantly increased SIR for other leukemia among chemical process workers, seamen, sales agents and other health workers. Chemical process workers included distillers, cooks, and furnacemen, wood grinders, pulp mill workers, paper and cardboard mill workers, and other occupations related to chemical processing. Chemical process workers are exposed to a wide range of chemical agents including benzene, formaldehyde, toluene, and other solvents, which might explain the increased risk. We did not

**TABLE 5.** Observed Number and Standardized Incidence Ratio for AML, CLL, and Other Leukemia by Country and Selected\* Occupational Categories in Nordic Countries

Type of Leukemia	Occupation	Denmark			Finland			Iceland			Norway			Sweden		
		Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
AML	Drivers	122	1.08	0.90–1.29	105	1.17	0.97–1.42	3	1.11	0.23–3.24	121	1.08	0.90–1.29	204	1.26	1.10–1.45
	Food workers	86	1.02	0.81–1.25	42	1.41	1.02–1.91	11	1.47	0.73–2.63	81	1.14	0.90–1.42	67	1.08	0.84–1.37
	Seamen	11	0.71	0.35–1.27	14	1.48	0.81–2.49	1	1.08	0.03–6.02	57	0.75	0.57–0.97	12	0.67	0.34–1.16
	Forestry workers	8	1.24	0.54–2.45	42	0.95	0.68–1.28	0	0	0.00–89.13	43	0.75	0.54–1.01	67	0.84	0.65–1.07
CLL	Farmers	—	—	—	549	1.05	0.97–1.14	12	1.35	0.70–2.36	503	1.22	1.12–1.33	682	1.03	0.96–1.11
	Clerical workers	—	—	—	224	1.14	1.00–1.30	11	1.23	0.62–2.21	221	0.99	0.87–1.13	630	1.08	1.00–1.17
	Seamen	—	—	—	13	0.90	0.48–1.54	0	0.00	0.00–4.02	51	0.67	0.50–0.88	39	1.02	0.73–1.40
Other leukemia	Seamen	—	—	—	11	1.10	0.55–1.97	1	1.05	0.03–5.83	69	1.19	0.93–1.51	37	1.39	0.98–1.92
	Other health workers	—	—	—	33	1.36	0.93–1.90	0	0.00	0.00–9.07	20	0.96	0.59–1.48	60	1.27	0.97–1.64
	Chemical process workers	—	—	—	20	1.05	0.64–1.62	0	0.00	0.00–11.19	39	1.13	0.81–1.55	92	1.24	1.00–1.53
	Sales agents	—	—	—	87	1.11	0.89–1.37	3	1.25	0.26–3.67	134	1.32	1.11–1.56	338	1.11	1.00–1.23
	Fishermen	—	—	—	6	1.54	0.57–3.36	2	0.51	0.06–1.85	49	0.65	0.48–0.86	12	0.64	0.33–1.12

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Obs, observed number of cases; SIR, standardized incidence ratio.

\*Only occupations with significantly increased and decreased overall risk estimates are shown.

observe risk elevation among other solvent-exposed occupational groups such as mechanics, smelting workers, building caretakers, painters, or printers. The occupational category of "seamen" included all kinds of seamen, from deck crew to ship pilots. Among these occupational subgroups, only engine room crew is exposed to diesel exhaust, which might explain the increased risk. Professionals associated with finance and sales, business service agents, and trade brokers were combined into the category of sales agents. "Other health workers" included veterinarians, pharmacists, and physiotherapists, among others. It is possible that they are exposed to some carcinogenic agents at workplace, but we cannot name any specific exposures.

Other occupational factors implicated in the etiology of leukemia are ionizing radiation, electromagnetic fields, and formaldehyde.<sup>20–22</sup> In our cohort, physicians and miners were occupationally exposed to low doses of ionizing radiation; electrical workers were exposed to electromagnetic fields; and nurses, forestry workers, textile workers, shoe and leather workers, foundry workers, welders, and wood workers were exposed to formaldehyde. We did not observe significant elevation of leukemia risk in any of these occupational categories.

Among other suspected factors, cigarette smoking has been weakly associated with leukemia, especially the myeloid type,<sup>23,24</sup> and the findings were highly controversial. However, being common and having a high variation between occupations, smoking is likely to affect our results to some extent; part of the excess AML risk seen among drivers and food workers is probably due to smoking.

Chromosome aberrations such as Philadelphia chromosome, Down syndrome, Klinefelter syndrome, ataxia telangiectasia, Bloom syndrome, and Fanconi anemia also have been associated with leukemia.<sup>25</sup> These conditions are rare and not clustered in certain occupations; therefore, we do not think that our results could be confounded by chromosomal disorders.

It has been demonstrated that the use of broader occupational categories is not always an adequate surrogate for occupational factors.<sup>26</sup> Some of the occupational categories in this study are heterogeneous and may therefore hide occupational risks.<sup>3</sup> However, the aim of this study was to describe the variation in leukemia risk among occupations. If the aim was to study the effect of specific occupational factors on leukemia risk, we should go for more specific occupational categories.

The magnitude of chance findings related to multiple comparisons is another issue to be considered in this type of study. Because we had five independent, country-specific observations for each cancer–occupation combination, we could judge reasonably well which findings are due to chance and which are true ones. For example, variation of the SIRs by leukemia type among the seamen was quite uniform in the country-specific analyses.

## CONCLUSIONS

This study provides evidence that there is modest variation in the incidence of leukemia between occupations. Some of the highest incidences could be at least partly attributed to occupational factors.

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## Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries

by Madar Talibov, MSc,<sup>1</sup> Susanna Lehtinen-Jacks, PhD,<sup>1</sup> Jan Ivar Martinsen,<sup>2</sup> Kristina Kjærheim, PhD,<sup>2</sup> Elsebeth Lynge, PhD,<sup>3</sup> Pär Sparén, PhD,<sup>4</sup> Laufey Tryggvadottir, PhD,<sup>5</sup> Elisabete Weiderpass, PhD,<sup>2, 4, 6, 7</sup>, Timo Kauppinen, PhD,<sup>8</sup> Pentti Kyrrönen,<sup>9</sup> Eero Pukkala, PhD<sup>1, 9</sup>

Talibov M, Lehtinen-Jacks S, Martinsen JL, Kjærheim K, Lynge E, Sparén P, Tryggvadottir L, Weiderpass E, Kauppinen T, Kyrrönen P, Pukkala E. Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries. *Scand J Work Environ Health*. 2014;40(4):420–426. doi:10.5271/sjweh.3436

**Objective** The aim of the current study was to assess the relation between occupational exposure to solvents and the risk of acute myeloid leukemia (AML).

**Methods** Altogether, this study comprises 15 332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961–2005 and 76 660 controls matched by year of birth, sex, and country. Occupational records were linked with Nordic Occupational Cancer Study job exposure matrix (JEM) to estimate quantitative values for 26 occupational exposure factors. Hazard ratios (HR) with 95% confidence intervals (95% CI) were estimated by using conditional logistic regression models.

**Results** We did not observe statistically significantly increased risk for exposure to any of the solvents. HR estimates for high levels of toluene (HR 1.35, 95% CI 0.74–2.46), aromatic hydrocarbon solvents (ARHC) (HR 1.18, 95% CI 0.76–1.86), and moderate-to-high levels of trichloroethylene were slightly but non-significantly elevated. We did not observe an association between benzene exposure and AML in this study.

**Conclusions** This study did not provide clear evidence for an association between occupational solvent exposure and AML. There was some indication for an excess risk in the groups of workers exposed to toluene, trichloroethylene, and ARHC.

**Key terms** aromatic hydrocarbon solvent; benzene; cancer; JEM; job exposure matrix; Nordic Occupational Cancer Study; toluene; trichloroethylene.

Acute myeloid leukemia (AML) is a cancer of blood and bone marrow. It accounts for approximately 25% of all leukemias among adults (1).

While the etiology of AML is poorly understood, it has been linked to genetic disorders, physical and chemical exposures, radiation exposure, chemotherapy, and viruses (2, 3).

There is a general consensus that benzene can cause AML in humans (4–8). Some previous studies suggested an association between exposure to solvents and AML (9–11).

The aim of this study was to assess the relation between occupational solvent exposure and AML.

<sup>1</sup> School of Health Sciences, University of Tampere, Tampere, Finland.

<sup>2</sup> Cancer Registry of Norway, Oslo, Norway.

<sup>3</sup> Centre of Epidemiology and Screening, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark.

<sup>4</sup> Department of Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden.

<sup>5</sup> Icelandic Cancer Registry, Reykjavik, Iceland.

<sup>6</sup> Institute of Community Medicine, University of Tromsø, Tromsø, Norway.

<sup>7</sup> Samfundet Folkhälsan, Helsinki, Finland.

<sup>8</sup> Finnish Institute of Occupational Health, Helsinki, Finland.

<sup>9</sup> Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland.

Correspondence to: Madar Talibov, School of Health Sciences, University of Tampere, FI-33014, Tampere, Finland. [E-mail: Madar.Talibov@uta.fi]

## Methods

The current study employed a case-control design nested in the Nordic Occupational Cancer Study (NOCCA) cohort. The NOCCA cohort consists of 14.9 million individuals from Finland, Iceland, Norway, Denmark, and Sweden who participated in population censuses in 1960, 1970, 1980/1981, and/or 1990. As we had no access to the individual records from Denmark, their data were not included.

Occupational information was obtained from computerized census records from 1960 and later censuses in Sweden and Norway and from 1970 and later censuses in Finland. In Iceland, the only computerized census record was available for 1981 census. Personal identity codes were used to link census records with the data from cancer registries and national population registries for information on cancer, death, and emigration. Each person was followed-up until the date of emigration, death or 31 December of the following years: 2005 in Finland, 2004 in Iceland, 2003 in Norway, 2003 in Denmark, and 2005 in Sweden. A detailed account of the NOCCA cohort was given in Pukkala et al (12).

All incident AML cases diagnosed from 1961–2005 were extracted from the NOCCA cohort. Five controls per case were randomly selected among persons who were alive and free from AML on the date of diagnosis of the case (hereafter the “index date” of the case-control set). Cases and controls could have a history of any cancer other than AML and were matched for the year of birth, sex, and country. Persons with minimum age of 20 years at index date, and having occupational information from at least one census record, were included in the present study.

For each case and control, the exposure to solvents and other occupational factors was estimated based on conversions of occupational codes to quantitative amounts of exposures with the NOCCA job exposure matrix (JEM). National experts from the Nordic countries developed the NOCCA JEM on the basis of the Finnish JEM (13). It covers more than 300 specific occupations, 29 exposure agents and 4 periods: 1945–59, 1960–74, 1975–84, and 1985–94. Exposure agents are characterized by the proportion of exposed (P) and the mean level of exposure among the exposed persons (L) in a specific occupation and time period. The NOCCA JEM was described in detail in Kauppinen et al (14).

We quantified exposure to benzene, toluene, perchloroethylene, methylene chloride, trichloroethylene, and 1,1,1-trichloroethane as individual solvents; and aliphatic and alicyclic hydrocarbon solvents (ALHC), aromatic hydrocarbon solvents (ARHC), chlorinated hydrocarbon solvents (CHC), and other organic solvents (OSOL) as grouped solvents. In addition to this, we

**Table 1.** Individual/grouped solvents and co-factors with measurement units. [PPM= parts per million of agent; mg/m<sup>3</sup>=milligram of agent in cubic meter of workroom air; f/cm<sup>3</sup>=fibers of asbestos in cubic centimeter of workroom air; µg/m<sup>3</sup>=microgram of agent in cubic meter of workroom air; µmol/l=micromoles of lead in liter of blood; mSv=annual equivalent radiation dose in millisieverts.]

Agent	Unit
Solvent	
Aliphatic and alicyclic hydrocarbon solvents	ppm
Aromatic hydrocarbon solvents	ppm
Benzene	ppm
Toluene	ppm
Chlorinated hydrocarbon solvents	ppm
Methylene chloride	ppm
Perchloroethylene	ppm
Trichloroethylene	ppm
1,1,1-trichloroethane	ppm
Other organic solvents	ppm
Co-factor	
Animal dust	mg/m <sup>3</sup>
Asbestos	f/cm <sup>3</sup>
Benz(a)pyrene	µg/m <sup>3</sup>
Bitumen fumes	mg/m <sup>3</sup>
Chromium	µg/m <sup>3</sup>
Diesel engine exhaust	mg/m <sup>3</sup>
Iron	mg/m <sup>3</sup>
Formaldehyde	ppm
Gasoline	ppm
Nickel	µg/m <sup>3</sup>
Lead	µmol/l
Quartz dust	mg/m <sup>3</sup>
Sulphur dioxide	ppm
Ionizing radiation	mSv
Wood dust	mg/m <sup>3</sup>
Welding fumes	mg/m <sup>3</sup>

quantified exposure to 16 other agents which were considered as potential co-factors in the analysis (table 1).

The procedure for quantifying cumulative exposure was as follows. For each occupational code, a corresponding value of the product of proportion and level of exposure ( $P \times L$ ) from NOCCA JEM file was assigned. This value was then multiplied by employment period (T) in years during which the subject was in that occupation. The procedure was repeated for all exposure factors.

Employment period was assumed to start at the age of 20 and end at 65 years. If there were different occupational codes in census records for a given person, the individual was assumed to have changed occupation in the middle of the known census years. In such a case, the exposure history of the persons consisted of more than one  $P \times L \times T$  value. Cumulative exposure for these individuals was estimated by summing up all of their  $P \times L \times T$  values over the entire working career. Assuming that AML develops over a number of years, and recent exposures are less relevant than those which took place in the past, we conducted main analyses in which all exposures that occurred during the last ten years before the index date were not counted.

We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for each solvent by conditional logistic regression. We selected values corresponding to the 50<sup>th</sup> and 90<sup>th</sup> percentiles of cumulative exposure distribution among all exposed case/control subjects as cut-off points for categorization. We defined exposure values of 0–50<sup>th</sup> percentile inclusive as “low”, 50–90<sup>th</sup> percentile inclusive as “moderate”, and >90th percentile of exposure distribution as “high”. Individuals with 0 exposure were used as the reference group. Test for trend was performed for a dose-response relationship between exposure factors and AML.

Variable selection for the final main-effect models was based-on the “purposeful covariate selection” procedure (15). Benzene and toluene were highly correlated with ARHC. Therefore, we selected two alternative main-effect models. In Model 1, we included benzene and toluene but not ARHC; and in Model 2, we included ARHC but neither benzene nor toluene. All other solvents were included in both models, and they were also adjusted for ionizing radiation and formaldehyde as co-factors. The results from both models were similar. Therefore, we present only the results of Model 1, except for the ARHC results, which can only come from Model 2.

Analyses stratified by age and sex was conducted to explore potential age- and sex-specific interactions with exposure. Age at index was categorized into two broad levels: <50 and ≥50 years, because only a small proportion of subjects (11–12%) were <50 years (table 2).

Finally, all analyses were done with different lag-time assumptions (0, 3, 5, 7, 10, and 20 years).

## Results

Altogether, 15 332 cases and 76 660 controls were identified during the study period (table 2). Of these, 350 cases (2.3%) and 2155 controls (2.8%) were excluded because they were either <20 years or had no occupational record. The proportion of male subjects was 52%, and 45% of the cases and controls were from Sweden. About 90% of case/controls were born before 1940, and the mean age at AML diagnosis was about 67 years (table 2).

We did not observe statistically significantly increased risk or dose-response relationship for any solvent exposure and AML (table 3). The highest risk estimate was observed for toluene levels >90<sup>th</sup> percentile of exposure distribution (HR 1.35, 95% CI 0.74–2.46). Risk estimates associated with exposure to high levels of ARHC and high and moderate levels of trichloroethylene were slightly elevated. Similarly, a small increase in risk estimates for exposure to high levels of ionizing radiation and formaldehyde were also observed.

**Table 2.** Demographic characteristics of acute myeloid leukemia cases and controls.

Characteristic	Cases		Controls	
	N	%	N	%
<b>Sex</b>				
Male	7751	51.7	38 642	51.9
Female	7231	48.3	35 863	48.1
<b>Country</b>				
Finland	3484	23.3	17 419	23.4
Iceland	109	0.7	479	0.6
Norway	4606	30.7	22 928	30.8
Sweden	6783	45.3	33 679	45.2
<b>Age at index date <sup>a</sup></b>				
20–29	139	0.9	690	0.9
30–39	458	3.1	2271	3.1
40–49	1163	7.8	5758	7.7
50–59	1991	13.3	9881	13.3
60–69	3558	23.8	17 687	23.7
70–79	4836	32.3	24 089	32.3
≥80	2837	18.9	14 129	18.9
<b>Year of birth</b>				
≤1910	3350	22.4	16 682	22.4
1911–1920	4042	26.9	20 138	27.0
1921–1930	3677	24.5	18 293	24.6
1931–1940	2000	13.4	9926	13.3
1941–1950	1406	9.4	6975	9.4
1951–1960	507	3.4	2491	3.3
Total	14 982	100	74 505	100

<sup>a</sup>Index date is defined as a date of diagnoses for the case and a date of diagnoses of the matched case for the control within each risk set.

Sex-specific risk estimates associated with exposure to high levels of toluene were higher among men than women (table 4). In contrast, HR estimates for ARHC, benzene, methylene chloride, and trichloroethylene were more pronounced among women than men.

Analysis stratified on age showed that HR estimates of AML associated with exposure to some solvents might be higher in younger ages (table 5). For example, the risk of AML was more than two-fold among benzene- and methylene-chloride-exposed individuals <50 years, whereas it was close to one among those ≥50 years.

Analysis with different lag-time assumptions showed that HR estimates for toluene were 1.86 (95% CI 1.06–3.28) with 0 lag-time and 1.62 (95% CI 0.89–2.96) with 20 year lag-time. HR for ARHC and trichloroethylene remained elevated from 0–10-year-lag-time and decreased towards null with 20-year-lag-time (data not shown).

## Discussion

The results from this study showed some suggestive evidence for an association between AML and solvent exposure but not consistently in both genders. There was non-significant excess risk for toluene, ARHC, and

**Table 3.** Hazard ratios (HR) and 95% confidence intervals (95% CI) of acute myeloid leukemia associated with exposure to solvents and other co-factors. [Ppm=parts per million; mSv=millisieverts].

Agent <sup>a</sup> (ppm/year)	Cases	Controls	HR	95% CI	P-value for trend
Solvents					
Aliphatic and alicyclic hydrocarbon solvents					
≤17.5	353	1743	1.01	0.79–1.29	
17.5–300	283	1393	1.08	0.82–1.42	
>300	54	366	0.64	0.38–1.08	0.76
Aromatic hydrocarbon solvents <sup>b</sup>					
≤9.3	362	1661	1.10	0.98–1.25	
9.3–275	256	1362	0.99	0.80–1.24	
>275	63	342	1.18	0.76–1.86	0.56
Benzene					
≤3.7	430	1999	1.02	0.84–1.24	
3.7–13.6	310	1633	0.88	0.71–1.11	
>13.6	68	418	0.80	0.56–1.15	0.33
Toluene					
≤42.4	424	1954	1.17	0.94–1.45	
42.4–61	296	1602	1.01	0.79–1.30	
>612	76	400	1.35	0.74–2.46	0.49
Trichloroethylene					
≤16.2	302	1760	0.93	0.79–1.09	
16.2–121	275	1373	1.12	0.94–1.33	
>121	68	345	1.12	0.83–1.49	0.08
1,1,1-trichloroethane					
≤5.6	566	2986	0.89	0.76–1.04	
5.6–12.7	244	1317	0.86	0.71–1.05	
>12.7	86	482	0.81	0.61–1.08	0.58
Methylene chloride					
≤9.9	326	1638	1.01	0.82–1.25	
9.9–64.6	249	1267	1.06	0.84–1.34	
>64.6	59	328	1.06	0.58–1.94	0.43
Perchloroethylene					
≤12.1	89	472	1.07	0.83–1.38	
12.1–106	67	381	0.83	0.61–1.12	
>106	16	96	0.72	0.39–1.34	0.39
Other organic solvents					
≤83.8	167	760	1.09	0.90–1.33	
83.8–357	123	617	0.96	0.71–1.30	
>357	28	158	1.08	0.61–1.90	0.48
Co-factor					
Ionizing radiation (mSv/year)					
≤3.6	27	159	0.84	0.56–1.27	
3.6–12.5	27	121	1.09	0.72–1.67	
>2.5	7	31	1.12	0.49–2.55	0.89
Formaldehyde					
≤0.171	580	3241	0.89	0.81–0.97	
0.171–1.6	485	2571	0.92	0.83–1.03	
>1.6	136	628	1.17	0.91–1.51	0.07

<sup>a</sup> Occupationally unexposed individuals were used as a reference group in all analyses.

<sup>b</sup> HR estimates for aromatic hydrocarbon solvents are from Model 2, all other HR are from Model 1.

trichloroethylene. We did not observe an association between exposure to benzene and AML unlike many earlier studies (4–8).

The evidence for an increased risk of AML from exposure to organic solvents other than benzene is inconsistent. The recent studies by Kaufman et al (10) and Strom et al (11) suggested an increased risk of AML following solvent exposure. However, both studies had limitations with exposure assessment. In the former study, the authors combined benzene, gasoline, and other solvents into a single group due to a small number of exposed subjects. In the latter, exposure information was collected via personal interviews and was, therefore, subject to a recall bias. In an Italian multicenter case-control study no association between exposure to solvents and AML was found (16). Excess risk of AML from benzene exposure could be identifiable already at 10 ppm/year exposure levels according to Vlaanderen et al (8). The estimated cumulative benzene exposure in our study exceeded 13.6 ppm/year for 68 cases and 418 controls (table 3). These numbers are so high that our study is unlikely to lack power and miss an effect should one exist in our data.

Observed age and sex-specific variation in risk estimates could result from effect of physiological differences by age and sex on pharmacokinetics (absorption, distribution, metabolism, elimination) of solvents (17–21). However, we cannot exclude the possibility of chance findings.

When interpreting our results, the following limitations need to be considered. Because this study was based on general populations of the Nordic countries, only a small percentage of study population had considerable exposure to solvents. This constrained our choice of cumulative exposure categorization. Another potential limitation of the present study is exposure misclassification, which may arise from two sources. First, the generic JEM has a poor sensitivity and a failure to account for heterogeneity in exposure levels within jobs (22, 23). Work history data is a second factor likely to contribute to exposure misclassification. Individual work histories were based on census records that are a snapshot of a job held by individual at the time of the census. The data did not provide information on the changes of the job or tasks during the entire working career of an individual. In this study, we assumed that an individual held his/her occupation until the mid-year between two censuses. Finally, we could not control for smoking and genetic factors that have previously been linked to AML (24–27). However, lung cancer risk was not elevated in the majority of occupational groups with solvent exposure (12), suggesting that the smoking rate among solvent-exposed individuals was unlikely to be higher than the general population. In addition, genetic factors are very rare and unlikely to be related to solvent exposure. Therefore, smoking and

**Table 4.** Sex-specific hazard ratios (HR) and 95% confidence intervals (95 % CI) of acute myeloid leukemia associated with exposure to solvents with sex-specific variation of HR estimates. [ppm=parts per million].

Agent <sup>a</sup> (ppm/year)	Males					Females				
	Cases	Controls	HR	95% CI	P-value for trend	Cases	Controls	HR	95% CI	P-value for trend
<b>Aromatic hydrocarbon solvents <sup>b</sup></b>										
≤9.3	265	1182	1.14	0.99–1.32		97	479	1.04	0.81–1.32	
9.3–275	197	1000	1.02	0.79–1.30		59	362	1.13	0.62–2.03	
>275	52	296	1.17	0.67–2.02	0.49	11	46	1.67	0.71–3.96	0.72
<b>Benzene</b>										
≤3.7	350	1515	1.12	0.87–1.44		81	486	0.86	0.60–1.22	
3.7–13.6	264	1414	0.89	0.69–1.18		45	213	1.10	0.69–1.74	
>13.6	63	405	0.76	0.51–1.13	0.18	5	17	2.02	0.58–7.04	0.59
<b>Toluene</b>										
≤42.4	366	1647	1.17	0.90–1.51		58	301	0.87	0.54–1.42	
42.4–61	277	1483	1.02	0.77–1.36		19	125	0.63	0.29–1.31	
>612	71	383	1.41	0.73–2.75	0.32	5	17	0.85	0.17–4.35	0.35
<b>Trichloroethylene</b>										
≤16.2	239	1400	0.92	0.77–1.09		63	360	1.15	0.71–1.85	
16.2–121	225	1117	1.09	0.91–1.32		50	258	1.41	0.85–2.36	
>121	49	242	1.10	0.79–1.54	0.08	19	101	1.52	0.71–3.26	0.61
<b>Methylene chloride</b>										
≤9.9	255	1301	0.99	0.76–1.28		41	201	1.24	0.79–1.96	
9.9–64.6	258	1251	1.12	0.86–1.47		21	152	0.78	0.45–1.37	
>64.6	58	326	1.14	0.59–2.19	0.23	1	2	1.66	0.10–28.8	0.58

<sup>a</sup> Occupationally unexposed individuals were used as a reference group in all analyses.<sup>b</sup> HR estimates for aromatic hydrocarbon solvents are from Model 2, all other HR are from Model 1.**Table 5.** Age-specific hazard ratios (HR) and 95% confidence intervals (95 % CI) of acute myeloid leukemia associated with exposure to solvents with age-specific variation of HR estimates. [ppm=parts per million].

Agent <sup>a</sup> (ppm/year)	<50 years					≥50 years				
	Cases	Controls	HR	95% CI	P-value for trend	Cases	Controls	HR	95% CI	P-value for trend
<b>Aromatic hydrocarbon solvents <sup>b</sup></b>										
≤3.3	39	197	1.03	0.72–1.49		199	806	1.25	1.06–1.47	
3.3–110	25	163	0.67	0.33–1.33		256	1389	0.95	0.80–1.11	
>110	10	37	1.75	0.62–4.95	0.94	152	773	1.05	0.72–1.54	0.53
<b>Benzene</b>										
≤1.34	55	255	1.07	0.66–1.71		173	836	1.05	0.82–1.36	
1.34–5	29	219	0.69	0.36–1.29		222	1033	0.97	0.76–1.24	
>5	18	44	2.24	0.99–5.08	0.65	311	1663	0.82	0.63–1.07	0.25
<b>Toluene</b>										
≤16.9	47	252	0.96	0.49–1.88		213	1019	1.13	0.88–1.44	
16.9–220	40	197	1.39	0.62–3.11		336	1601	1.33	1.01–1.75	
>220	11	49	1.27	0.30–5.38	0.63	149	838	0.78	0.53–1.15	0.51
<b>Trichloroethylene</b>										
≤5.62	38	229	0.84	0.53–1.35		88	562	0.87	0.66–1.14	
5.62–24.9	35	178	1.03	0.65–1.64		194	1043	1.07	0.87–1.31	
>24.9	11	43	1.28	0.62–2.63	0.40	279	1423	1.08	0.90–1.29	0.13
<b>Methylene chloride</b>										
≤5.58	50	220	1.12	0.64–1.97		164	875	0.93	0.72–1.20	
5.58–17.5	29	187	0.75	0.37–1.51		217	1067	1.05	0.81–1.36	
>17.5	11	43	2.31	0.83–6.41	0.76	163	841	1.15	0.84–1.57	0.48
<b>Other organic solvents</b>										
≤33.6	21	98	1.15	0.67–1.98		82	346	1.19	0.92–1.56	
33.6–144	18	77	1.48	0.65–3.40		80	434	0.95	0.73–1.24	
>144	3	21	0.88	0.18–4.25	0.56	114	559	1.81	1.13–2.91	0.58

<sup>a</sup> Occupationally unexposed individuals were used as a reference group in all analyses.<sup>b</sup> HR estimates for aromatic hydrocarbon solvents are from Model 2, all other HR are from Model 1.

genetic factors could have only a little, if any, confounding effect on our estimates.

To our knowledge this was the largest study to assess the relationship between occupational exposure to solvents and AML, which covered the general populations of four Nordic countries. By linking occupational records to the NOCCA JEM, we were able to generate quantitative exposure estimates for 26 work-related agents. It enabled us to explore exposure-response relations beyond the analysis of crude categorization ("exposed" versus "non-exposed") or analysis by occupational groups. In addition, we were able to control for exposure to multiple agents and variation of exposure levels over time.

In conclusion, this study did not provide a clear evidence for an association between occupational solvent exposure and AML. There was some indication for an excess risk among those exposed to toluene, trichloroethylene, ARHC.

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