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OCCUPATIONAL EXPOSURE TO CHEMICALS AND CANCER

Cecilia Videnros

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Occupational exposure to chemicals and cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Cecilia Videnros

Principal Supervisor:
Assistant Professor Jenny Selander
Karolinska Institutet
Institute of Environmental Medicine
Unit of Occupational Medicine

Co-supervisors:
Professor Per Gustavsson
Karolinska Institutet
Institute of Environmental Medicine
Unit of Occupational Medicine

PhD, MD Carolina Bigert
Karolinska Institutet
Institute of Environmental Medicine
Unit of Occupational Medicine

Opponent:
PhD, MD Ingrid Mehlum
National Institute of Occupational Health
Oslo, Norway

Examination Board:
Associate Professor Jette Möller
Karolinska Institutet
Department of Public Health Sciences
Division of Public Health Epidemiology

Professor Kamila Czene
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Associate Professor Kåre Eriksson
Umeå University
Department of Public Health and Clinical Medicine
Division of Occupational Medicine

To the love of my life, Lars, for your support and endless love.
And to our beautiful baby girl Leona for making me realize
what life is all about.

ABSTRACT

We spend a lot of our time at work and the exposures in our work environment have a great influence on our health. Certain occupational groups, like firefighters, are exposed to a large number of chemicals and an increased risk of cancer has been reported in this group. Also, the association between certain chemicals and cancer types have been studied, like organic solvents and breast cancer. However, there is still a need for better understanding on chemicals' possible effect on the cancer risk. The aim of this thesis was therefore to investigate the association between occupational exposure to chemicals and the risk of cancer, focusing on breast cancer, women's most common form of cancer, and firefighters, a male-dominated occupation where workers are exposed to a large number of chemicals.

Data for this thesis were derived from Malmö Diet and Cancer study (MDCS) and a cohort of firefighters in Stockholm. Papers I, II and III are based on MDCS and paper IV is based on the firefighter cohort. MDCS is a prospective cohort study following 17 035 women born 1923-1950 and living in Malmö during the recruitment years 1991-1996. Diagnoses of breast cancer were identified through the Swedish Cancer registry from inclusion to 2013. Occupational history (three latest occupations) was self-reported at baseline and two different job-exposure matrices were used to estimate the chemical exposure. For paper III an occupational hygienist made a case-by-case exposure assessment based on additional occupation data in the questionnaire. For paper IV a cohort of 1080 men working as firefighters in Stockholm for at least one year between 1931-1983 were followed from 1958-2012 for cancer diagnoses.

Paper I showed that white-collar workers had an increased risk of breast cancer, even after adjusting for risk factors related to lifestyle and reproduction. Papers II and III showed that women exposed to chemicals in their occupational environment had an increased risk of breast cancer that appeared to be correlated with duration of exposure. Specifically in paper III, women exposed to chlorinated hydrocarbon solvents and oil mist had an increased risk of breast cancer. Paper IV showed an overall low risk for cancer among firefighters. However, an increased risk for stomach cancer was found that could possibly be related to their occupational exposures.

This thesis gives some support to the hypothesis that organic solvents are associated with breast cancer. It also indicates that the exposure limit for oil mist might need revision by the Swedish Work Environment Authority since results show that women exposed under the set limit have an increased risk of breast cancer. Our results suggest that the exposure assessment using a JEM in combination with a case-by-case estimation by an occupational hygienist gave an improved risk estimate, compared to only using a JEM.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals I-IV:

I. **Kullberg C***, Selander J, Albin M, Borgquist S, Manjer J, Gustavsson P. Female white-collar workers remain at higher risk of breast cancer after adjustments for individual risk factors related to reproduction and lifestyle. Occup Environ Med. 2017;74(9):652-8.

II. **Videnros C***, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, Manjer J, Gustavsson P. Postmenopausal breast cancer and occupational exposure to chemicals. [Manuscript submitted]

III. **Videnros C***, Selander J, Wiebert P, Albin M, Plato N, Borgquist S, Manjer J, Gustavsson P. Risk of breast cancer among women exposed to chemicals, a nested case-control study using improved exposure estimates. [Manuscript submitted]

IV. **Kullberg C***, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, Bigert C. Cancer incidence in Stockholm firefighters 1958-2012: an updated cohort study. Int Arch Occup Environ Health. 2018;91(3):285-91.

* *Cecilias last name was changed in 2018 from Kullberg to Videnros.*

CONTENTS

LIST OF ABBREVIATIONS

AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CI	Confidence interval
CHC	Chlorinated hydrocarbon solvents
FINJEM	Finnish job-exposure matrix
FoB-80	Population and Housing Census 1980
HR	Hazard ratio
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IGF	Insulin-like growth factor
JEM	Job-exposure matrix
MDCS	Malmö Diet and Cancer Study
NOCCA	Nordic Occupational Cancer Study
NYK	Nordic occupational classification
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
PCB	Polychlorinated biphenyls
SIR	Standardized incidence ratio
WHO	World Health Organization

1 BACKGROUND

We spend a lot of our time at work and the exposures in our work environment have a great influence on our health. In 2002, around 2 million deaths globally were attributed to occupationally-related diseases,[1] and according to a Finnish study from 2001 7% of all deaths in Finland in ages 25-74 years were work related.[2] The exposures in our work environment have changed over time due to the changing work situation, with new types of jobs, changing legislations and technological advancements.[3] Unfortunately, hazardous exposures in the work environment still exist, and the knowledge of how these exposures affect our health is still not fully understood; therefore, the need for new research in the field is needed.

1.1 OCCUPATIONAL EXPOSURE TO CHEMICALS

Several occupational groups are today exposed to a wide range of chemicals through their everyday work.[2] Occupations or industrial sectors that are especially exposed are: (i) production or application of pigments, dyes, paints, cements, pesticides, cleaning products etc.; (ii) production of rubber, plastics, textiles, cosmetics; (iii) agriculture, metallurgy and food processing industry; (iv) painters, metal workers, health care workers, hairdressers and firefighters.[4,5]

There are many different types of chemicals and they are absorbed by the body in different ways. Chemicals can be in liquid, gas or solid form and be either synthetically manufactured or occur naturally. They are taken up by the body through inhalation, absorption through skin, ingestion or injection; inhalation and skin absorption are the most common routes of exposure at workplaces.[6]

Chemical exposure can cause a wide range of diseases such as respiratory diseases, allergy, cancer, developmental disorders, musculoskeletal diseases, cardiovascular diseases and perinatal conditions among others.[7] The International Agency for Research on Cancer (IARC) has classified over 100 chemicals as carcinogenic or probably carcinogenic to humans.[8] The cancer burden is increasing in the world and it has been estimated that 5-8% of all cancers are attributable to occupational exposures.[2,9]

1.2 CANCER

Cancer is essentially an uncontrolled division of cells in the body that leads to tumour development.[10] Chemicals can cause tumour development either direct or indirect; if the chemical carcinogen affect the DNA directly it is a genotoxic carcinogen, while a non-genotoxic chemical carcinogen is a carcinogen that increases the risk of cancer in another way, e.g. through cell division. Chemical carcinogens can also be divided into initiating and promoting agents.[11] Initiators and promotors do not cause tumours by themselves, but both are needed for a tumour to develop. An initiator weakens the cell and makes it more susceptible for other carcinogenic agents. The initiator causes DNA damage and therefore most initiators are genotoxic. A promotor increases the cell division in a weakened cell that has previously been in contact with an initiator. When the cells proliferate in an uncontrolled way progression is possible which then give rise to tumour development. An agent could be both an initiator and a promotor and are then called complete carcinogens.[11]

1.3 BREAST CANCER

1.3.1 Epidemiology

Breast cancer is the most common cancer among women and accounts for 12% of all incident cancer cases worldwide, and 25% of all cancer cases among women.[12] The incidence varies greatly throughout the world (Figure 2), with the highest numbers in North America, Australia and Western Europe.[12,13] Breast cancer incidence has increased in Sweden as well as worldwide, and has over the last 50 years especially increased in traditionally low-incidence Asian countries.[14] These trends may reflect a secular change in reproductive pattern and lifestyle factors that affects breast cancer risk.[14] The prognosis for breast cancer is good [15] and one reason is the increasing trend of mammography screening that has resulted in early detection and treatment of tumours.[16]

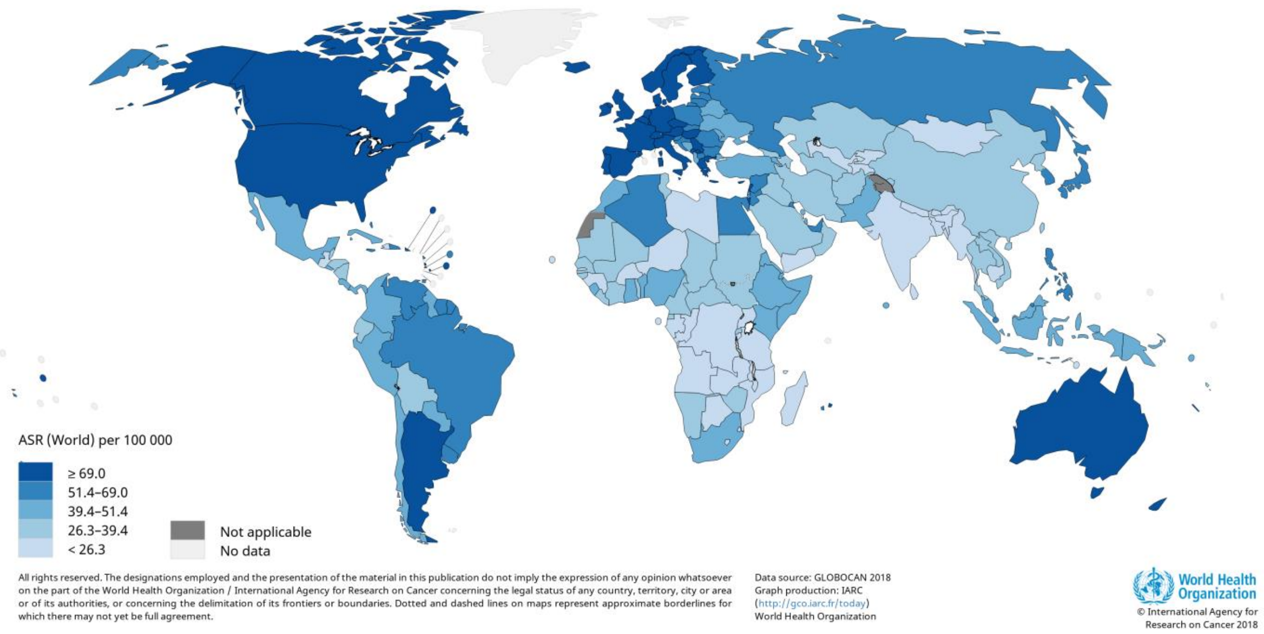


Figure 2. Estimated breast cancer incidence worldwide in 2018. Age-standardized rates per 100.000. WHO/IARC 2018.[17]

1.3.2 Risk factors for breast cancer

1.3.2.1 Hormonal factors

Many established risk factors for breast cancer are associated with hormonal factors related to reproduction and it has been hypothesized that the risk is proportional to endogenous and exogenous exposures to oestrogen.[14] Parity is associated with breast cancer, and women who have had one full-term pregnancy have up to 25% lower risk of breast cancer compared with nulliparous women.[14,18,19] Furthermore, the risk seem to decrease with each child [20] and women with five or more children have about half the risk of nulliparous women.[19] It has been proposed that during every pregnancy there is a shift of more stem cells to a stage where they become resistant, or less sensitive, to carcinogenic stimuli.[21] The age at first full-term pregnancy also affects the risk of breast cancer, independently of number of children, where an increased age is associated with increased risk.[19] Breastfeeding has been shown to be protective of breast cancer, and a review of 47 epidemiological studies found that the risk decreased by 4.3% for each 12 months of breastfeeding.[20] Other hormonal risk factors are early menarche and late menopause, probably due to a larger lifetime exposure to endogenous hormones.[14,20,22] A review of risk factors for breast cancer found 9% decreased risk of premenopausal breast cancer and 4% lower risk for postmenopausal breast cancer for each year the menarche was postponed.[20]

Exogenous hormones such as oral contraceptives and hormone replacement therapy (HRT) have been associated with breast cancer.[18] Women taking oral contraceptives have an increased risk of breast cancer; however, former users of oral contraceptives had only little, if any, increased risk.[14,18] Oral contraceptives contain concentrations of the hormones oestrogen and progesterone that are higher than produced by the body during a normal ovulation cycle.[14] Women who ever used HRT seem to have only a slightly increased risk of breast cancer; however, the risk increases significantly for current users of HRT and for long time users.[14,18] The risk is higher for combined hormonal therapy, including both oestrogen and progesterone.[23]

1.3.2.2 Genetics

Family history of breast cancer is an important risk factor.[14] About 10% of all cases are thought to be due to genetic factors, of which mutations in breast cancer genes 1 and 2 (BRCA1 and BRCA2) are crucial.[24] Carriers of these genes have a 45-65% chance of developing breast cancer by the age of 70.[25] However, BRCA1 and BRCA2 are relatively uncommon in the population with around 0.11% being carriers.[26]

1.3.2.3 Lifestyle factors

There are several lifestyle factors that affect the risk of breast cancer.[14] Alcohol consumption is a strong risk factor, and the risk increases around 7% per unit of alcohol (10g pure alcohol) consumed per day.[27] Alcohol consumption is associated with higher levels of sex hormones, which may partly explain the link between alcohol and breast cancer.[28] Tobacco smoking, however, does not show any association with breast cancer.[19]

Increased body fat percentage, measured by BMI, is associated with increased risk for postmenopausal breast cancer but decreased risk for premenopausal breast cancer.[14] Because breast cancer is more common among postmenopausal women compared to premenopausal women, overall body fat is linked to excess cases in the population.[14] The link between body fat and breast cancer can partly be explained by higher levels of oestrogen that are produced by the fatty tissue.[29] Physical activity has been discussed as a protective factor for breast cancer.[14] One possible explanation for decreased risk among physically active women may be decreased body fat as a result from the physical activity, and thus decreased body fat and lower oestrogen levels being the active mechanism rather than physical activity.[14]

1.3.2.4 Other risk factors

Increased height is related with increased risk of breast cancer.[14] Average height is substantially greater in populations with higher rates of breast cancer, and within populations 10 cm greater height increases the risk of breast cancer by 10%.[19] The mechanism behind this association is not known, but the increased insulin-like growth factor 1 (IGF-1) in the body might influence the risk of breast cancer.[14,30]

1.3.2.5 Occupational risk factors for breast cancer

Several studies have noted a difference in breast cancer risk between occupational groups. These findings go back to the 18th century when Ramazzini noted an increased risk of breast cancer among nuns.[31]. Their high risk is probably due to the reproductive characteristics, such as nulliparity and lack of breastfeeding.[31,32]

Several studies have shown a link between night-shift work and breast cancer.[5,33,34] Exposure to light at night is associated with higher levels of sex hormones since it disturbs the circadian system, which suppresses melatonin production, and melatonin is thought to reduce circulating oestrogen.[35] This could possibly explain nurses’ and flight attendants’ high risk of breast cancer.[36-39] However, the studies on night-shift work is not entirely conclusive and a meta-analysis recently found no link between night-shift work and breast cancer, based on several large cohort studies.[40] Other explanations for nurses’ high risk of breast cancer might be their exposure to carcinogens such as ionizing radiation,[41] ethylene oxide[42], chemotherapeutic drugs[43] and electromagnetic fields.[44]

Several chemical exposures are known to increase the risk of breast cancer. IARC classified a number of chemicals carcinogenic to the breast, such as ethylene oxide, dieldrin (insecticide) and polychlorinated biphenyls (PCB).[45] Ethylene oxide is used to sterilize medical equipment and in the production of other chemicals, which are related to occupations in the medical field and in chemical production.[42,46] Several studies have seen an increased risk among chemists, and also among laboratory technicians in contact with chemicals compared to laboratory technicians not handling chemicals.[47,48] Dieldrin is a pesticide that was previously banned, but still may remain in the environment which individuals still can be exposed to, especially those in agriculture-related occupations.[49] PCBs were commonly used in electrical equipment, like transformers and capacitors, before being banned; however, they may still be found in the environment.[50] Chemically-exposed occupational groups like hairdressers have, according to a meta-analysis, a 6% increased risk of breast cancer, which might be related to exposure to hair dye that contains potential carcinogens like organic solvents and formaldehyde, among others.[51,52] A review found an increased risk in occupations with exposure to organic solvents, which was supported by several other studies.[47,53,54] Organic solvents are thought to increase the risk of breast cancer due to their lipophilic characteristics and the breast tissues' high number of lipid cells.[55] Once stored in surrounding fat tissues, organic solvents can migrate into the lobules and then be transported to the ductular system.[55]

A clear socioeconomic trend is seen, where women working in high socioeconomic occupations have higher risk of breast cancer compared to women working in low socioeconomic occupations. This increased risk in high socioeconomic occupations have not been fully understood but the reproductive characteristics such as later pregnancies and fewer children which are related to longer education have been discussed as a contributory factor.[56] However, several studies lack good confounding control, and therefore new studies with high quality confounding control is needed to investigate this further.

1.4 FIREFIGHTERS

Firefighting is a physically demanding occupation with high exposure to chemical agents that can put the firefighter at risk. The work tasks consist largely of putting out fires, which is mainly divided into knockdown and overhaul.[5] During knockdown, firefighters control and extinguish the fire. Knockdown of large fires may last a long time; however, most fires are extinguished within 10 minutes.[5] During overhaul, any remaining small fires are extinguished. The environment during overhaul is not as hot or as smoky as during knockdown, but still contains products of combustion from small fires or smouldering material and dust.[5] Firefighters are also called out on other emergency accidents and can spend a lot of time not fighting fires.[5] In order to become a firefighter and to remain an employee, there are mandatory physical tests that the firefighters need to pass. In Sweden there are certain regulations to control firefighters’ physical form and capacity for work.[57]

1.4.1 Occupational exposures

Firefighters are, through their extreme work environment, exposed to a wide range of chemicals, including known and possible carcinogens.[5] The fire smoke often contain benzene, 1,3-butadiene, formaldehyde and polycyclic aromatic hydrocarbons (PAHs) and may be inhaled or absorbed through the skin.[5] Firefighters may also be exposed to asbestos, crystalline silica and PCBs depending on the characteristics of the fire site[5] as well as diesel exhaust from firefighting vehicles.[58] Because of firefighters’ extreme work environment with heat, fumes and, at times, lack of oxygen, extensive protective gears are worn when fighting fires.[59] However, these protective gears are often removed during the overhaul stage and fire leaders standing on a distance from the fires do not always use the gear provided.[59] Apart from the chemical exposure many firefighters work in shifts, which could disrupt the circadian rhythm and potentially be a cancer risk.[5]

1.4.2 Firefighters’ risk of cancer

In recent years, firefighters’ risks of cancer have attracted more attention. In 2006, a review of 32 studies and meta-analysis of 26 studies by LeMasters et al. found a probable increased risk of cancer for firefighters.[60] Several previous studies had indicated this,[58,61-63] but this large meta-analysis put firefighters’ working situation in focus for the media, researchers and in their own national association.

In 2010, IARC classified the occupational exposure as a firefighter as possibly carcinogenic to humans (Group 2B), based on limited evidence in humans and inadequate evidence in experimental animals.[5] This classification was made based on several previous studies and reviews. LeMasters et al. found a probable increased risk for multiple myeloma, non-Hodgkin lymphoma, prostate cancer and testicular cancer as well as a possible increased risk for several additional cancers (cancer of the brain, rectum, buccal cavity and pharynx, stomach, colon, leukaemia and skin melanoma).[60] Another comprehensive review and meta-analysis conducted by IARC in 2010 found strongest evidence for non-Hodgkin lymphoma, prostate cancer and testicular cancer.[5]

Recent studies also seem to support the findings that firefighters have an increased risk of several types of cancer. A study from Nordic Occupational Cancer (NOCCA) in 2014 including 15 million people in the five Nordic countries showed an increased risk for prostate cancer, skin melanoma, non-melanoma skin cancer and adenocarcinoma of the lung but a reduced risk for testicular cancer.[64]

Since the occupational conditions can vary in different parts of the world, it is important to also look at and study national conditions. A Swedish study conducted in 1994 on firefighters who worked in Stockholm, Sweden during at least one year from 1931-1983 showed an increased risk for some cancer types.[61] Cancer incidence was studied from 1958-1986 using the Swedish Cancer Registry and with the Stockholm population as reference.[61] The results showed an increased risk for stomach cancer and a tendency for increasing brain and stomach cancers with increasing number of fires fought.[61] Further studies are needed in order to confirm these results and to investigate Swedish firefighter's risk of cancer.

2 AIM

The aim of this thesis was to investigate the association between occupational exposure to chemicals and the risk of cancer, focusing on breast cancer, women's most common form of cancer, and firefighters, a male-dominated occupation were workers are exposed to a large number of chemicals.

2.1 RESEARCH QUESTIONS

I. Is the higher risk of breast cancer in white-collar workers compared to blue-collar workers caused by risk factors related to reproduction and lifestyle? (**Paper I**)

II. Is occupational exposure to chemicals associated with an increased risk of breast cancer? (**Paper II** & **Paper III**)

III. Is working as a firefighter associated with an increased risk of cancer? (**Paper IV**)
  - Which cancer types are in excess?
  - Is the cancer risk dependent on work duration?

3 MATERIAL AND METHODS

This thesis is based on two studies; “Malmö Diet and Cancer study” (MDCS) and “Stockholm firefighters”. Paper I, II and III are based on MDCS and paper IV is based on “Stockholm firefighters”. Figure 3 illustrates an overview of all four papers and the methods and materials used.

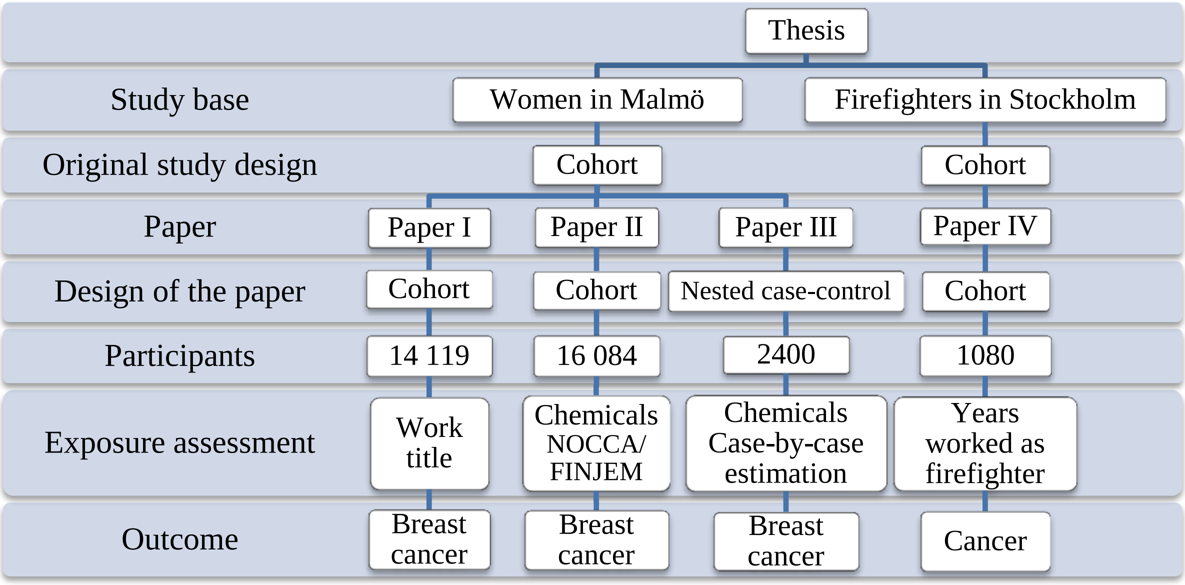


Figure 3. Overview of study design, number of participants, exposure assessment and outcome measures in the studies included in this thesis.

3.1 MALMÖ DIET AND CANCER STUDY

MDCS is a population based prospective cohort study that was initiated in 1991.[65] The overall aim was to study the association between dietary factors and cancer incidence. The study population was defined as Swedish inhabitants (with a registered Swedish identification number) born 1923-1950, who lived in the city of Malmö during 1991-1996. Active recruitment (personal letter invitation) and passive recruitment (pamphlets and posters in public areas, advertisement in newspapers, tv etc.) were used. Of 74 138 eligible persons, 24 851 had unknown address or did not respond, 16 942 declined to participate and 4247 were excluded due to language problems, retardation or incomplete questionnaire. In total 28 098 persons participated in the MDCS.

3.1.1 Study design

The design of MDCS is a prospective cohort design and this design was used in paper I and paper II. Women were enrolled during 1991-1996 and then followed up until a breast cancer diagnosis, death, migration or end of follow-up in December 31, 2013, whichever occurred first. Women with a previous breast cancer diagnosis or prevalent diagnosis at baseline were excluded. The women were considered to be at risk from baseline if postmenopausal. If premenopausal, the women were at risk at the time they became postmenopausal. Menopausal status was assessed using both questionnaire data and medical records. A woman was classified as postmenopausal if: (i) she had undergone bilateral oophorectomy or (ii) she had undergone hysterectomy and was 55 years or older or (iii) the above criteria was missing and she confirmed that the menstruation had ceased two years prior to baseline or (iv) the above criteria was absent and she was 55 years or older. For paper III a nested case-control design was used in order do a case-by-case estimation of the exposure. Each case was matched with two controls on age and the selection of controls was density based.

3.1.2 Study participants

While MDCS contained 28 098 participants, further exclusions were made to modify for our three studies that had the common objectives to investigate occupational exposures and the risk of postmenopausal breast cancer. All men were excluded (n=11 063) as well as all prevalent cases of breast cancer and women who remained premenopausal throughout the entire follow-up period (n=694), as well as women who were never employed in an occupation during the entire follow-up period (n=247). Premenopausal women were excluded from our studies due to low numbers and the difficulty to analyse them in respect to different risk factors for breast cancer,[66] e.g. high BMI decreases the risk of premenopausal breast cancer while it increases the risk of postmenopausal breast cancer.[66] This resulted in a population of 16 084 women who became the study population for paper II. Paper I had further restrictions on occupational history, where women working less than 10 years in an occupation were excluded (n=2222), resulting in a study population for paper I of 14 119 women. Paper III used a nested case-control design, intending to use all 1088 breast cancer cases in the MDCS cohort. However, 239 cases were excluded due to missing baseline questionnaires that were needed for the case-by-case exposure assessment. The baseline questionnaires were accidently lost during a clean-up at Lund University which resulted in a total of 849 cases. When investigating which questionnaires that were lost, no difference or overrepresentation of any characteristics were found, indicating that it was a random sample of questionnaires that were lost, and, therefore, their exclusion should not have introduced any bias in the study. The 849 breast cancer cases that were left were matched with two controls per case, resulting in 1698 controls. Exclusion criteria for paper III were women with no self-reported work history (n=42), diagnosis of breast cancer before baseline (n=50) and premenopausal status until end of follow-up (n=55). A total of 2400 women were included in paper III. See Figure 4 for an overview of the study participants in paper I, II and III.

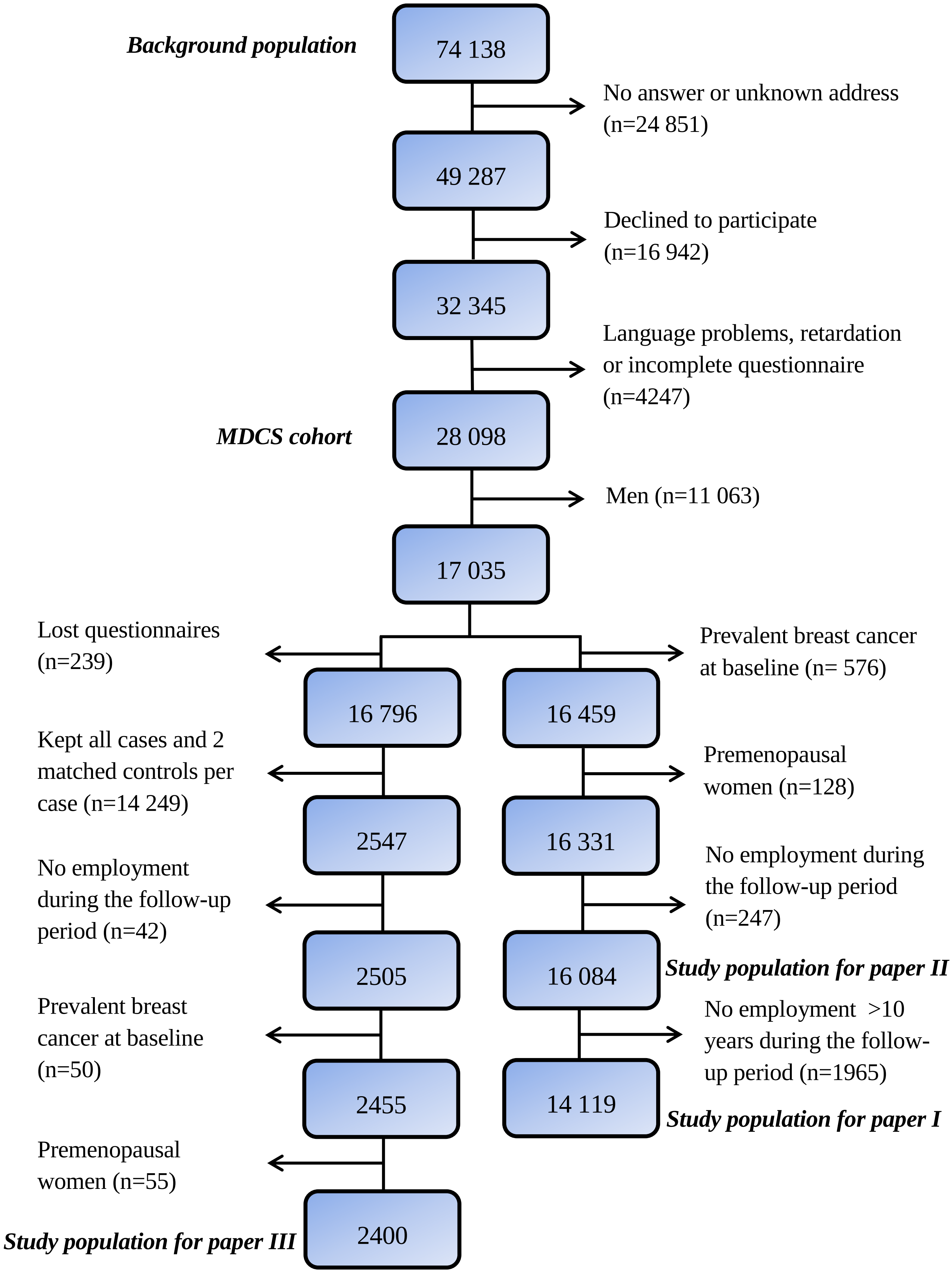


Figure 4. Study participants in the MDCS cohort

3.1.3 Data collection

All participants in the study visited the MDCS centre twice for data collection. At the first visit healthcare personnel did a baseline examination where height and weight were measured, along with instructions on how to fill in the questionnaire. On the second visit the questionnaires were collected and any questions regarding the questionnaire could be asked. At the same time an interview regarding dietary habits took place.[67] For this study the information in the baseline questionnaire and the measurements for height and weight were used. Questions on lifestyle included alcohol consumption, tobacco use, physical activity and education among others. Questions on alcohol consumption were asked regarding the previous 30 days using the validated questionnaire AUDIT.[68] Physical activity was measured with several questions estimating the time of physical activity performed outside of work and multiplied with an intensity factor for each activity. The questions were asked regarding the 12 months prior to baseline, taking seasonal changes into account. The questionnaire also contained an extensive set of questions regarding reproductive and hormonal factors such as age at menarche, parity, age at first child, months of breastfeeding per child, hormonal replacement therapy (HRT), oral contraceptive use and age at menopause.

3.1.4 Exposure assessment

3.1.4.1 Job title

The baseline questionnaire collected detailed information about the participants' three latest occupations such as job title, work tasks and the employment years. The occupations were coded according to the job classification scheme FoB-80 (Population and Housing Census 1980) which is based on NYK (Nordic version of the International Standard Classification of Occupations).[69] FoB-80 contains a total of 349 occupations on 3 digit level. For paper I the occupational title, the first 3 digits of FoB-80, was used as exposure variable. The FoB-80 classification scheme is organized with 11 main groups of occupations according to socioeconomic position, low codes have high socioeconomic status and high codes have low socioeconomic status. We also made a classification of white- and blue-collar workers, where white-collar workers were women in occupational sectors 0,1,2,3 and blue-collar workers were women in sectors 4, 5, 6, 7-8, 90-94 and 98. White-collar workers perform professional, managerial or administrative work, often in an office setting while blue-collar workers are workers who perform manual labour of different kinds. See Table 1 for the FoB-80 occupational sectors and division into white- and blue-collar workers.

Table 1. Main occupational sectors in FoB-80 (Population and Housing Census 1980) and division into white- and blue-collar workers

Code	Occupational sector	Group
0.	Professional, technical and related work	White-collar workers
1.	Administrative and managerial work	
2.	Bookkeeping and clerical work	
3.	Sales work	
4.	Agricultural, forestry and fishing work	Blue-collar workers
5.	Mining and quarrying work	
6.	Transportation and communications work	
7-8.	Production work	
90-94.	Service work	
98.	Armed forces	
99.	Unidentifiable occupations	

3.1.4.2 Job-exposure matrix

For paper II chemical exposures were estimated using the occupational information given in the baseline questionnaire. With information on job title and employment years two different kind of job-exposure matrices were used, NOCCA and FINJEM.[70 71] A job-exposure matrix assigns each occupation an intensity level (in ppm or mg/m^3) and a proportion of the employees exposed for each chemical exposure and occupation. The matrix is also divided into different time periods in order to take changes over time into account. The matrices are developed together with several occupational hygienists who have made actual measurements on many different occupational sites. Figure 5 illustrates a sample from a job-exposure matrix.

FoB 80 code	**Occupational title**	**Exposure**	**Unit**	**Proportion exposed** 1945-1959	**Intensity level** 1945-1959	**Proportion exposed** 1960-1974	**Intensity level** 1960-1974
011	Chemists, physicists	CHC	ppm	0.10	15	0.12	11
014	Laboratory technicians	CHC	ppm	0.08	15	0.08	12.5
040	Registered nurses	CHC	ppm	0.01	5	0.01	0.1
701	Spinners, weavers	CHC	ppm	0.05	10	0.03	10

Figure 5. A sample from FINJEM, showing exposure to Chlorinated hydrocarbon solvents (CHC) for different occupational groups and during two different time periods.

Chemicals of interest for our study that were available in NOCCA was: 1,1,1-trichloroethane, benzene, benzo(a)pyrene, bitumen fumes, diesel exhaust, gasoline exhaust, methylene chloride, perchloroethylene, toluene and trichloroethylene. Chemicals used from FINJEM were aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents (including alcohols, ketones, esters, glycol ethers etc.), fungicides, herbicides, insecticides, polycyclic aromatic hydrocarbons (PAH), gasoline exhaust and oil mist.

In paper II exposure to chemicals were divided into ever exposed and never exposed as well as duration analysis of 1-10 years of exposure and >10 years of exposure. A woman was classified as ever exposed if she had been employed at least 1 year in an occupation where at least 5% were exposed to any of the chemicals we included in the analysis. A limit of 5% was chosen to avoid misclassification of exposure, e.g. 0.3% of nurses were exposed to chlorinated hydrocarbon and this entire occupational group would be considered exposed if there was no restriction. Cumulative exposures to chemicals were also used as exposure measurements in paper II, calculated as intensity level stated in JEM x proportion exposed in JEM x years worked in the exposed occupation added over all work periods. The women were then divided dichotomously at the median into high and low cumulative exposure.

3.1.4.3 Case-by-case estimation

For paper III chemical exposure was assessed with the estimation from the job-exposure matrices and a case-by-case evaluation made by an occupational hygienist. Since paper III only contained a smaller part of the cohort with 2400 participants, a case-by-case evaluation of the exposure was possible. An occupational hygienist read through the baseline questionnaires and based on the work task description in free text changed the proportion exposed (probability) to 0 if the woman was not exposed, 1 if she was exposed or kept it at the original level if unsure. In paper III mean intensity was calculated and dichotomized at the median for the analyses. Mean intensity was calculated as the sum of intensity level stated in JEM x proportion exposed x years worked in the exposed occupation added over all work periods / total working years.

3.1.5 Outcome assessment

In papers I, II and III the outcome variable was first-time diagnosis of invasive breast cancer. The women had to be diagnosed during the follow-up period 1991-2013. The breast cancer cases were identified through the Swedish Cancer Registry, a national registry to which it is mandatory to report all incident cancer cases in Sweden. The Swedish Cancer Registry, therefore, has a coverage of 99% of all Swedish breast cancer cases.[72] In the registry, breast cancer cases were identified with ICD-7 code = 170 (International Classification of Diseases, 7th Revision). Figure 6 illustrates the data collected for MDCS.

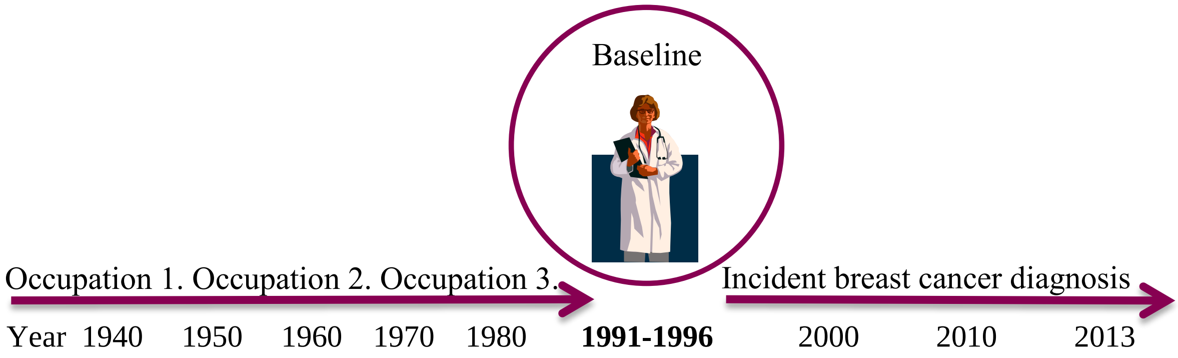


Figure 6. Data collection in MDCS

3.1.6 Statistical approach

Confounding variables for all three papers in MDCS were selected based on a priori knowledge from literature and statistical analysis. A priori knowledge from literature was used to select plausible confounders that were then tested in the statistical model. The selected variables that were not significant in the univariate model or had estimates that changed more than 10% in the multivariate analysis were rejected from the final model. Appendix 1 to paper 1 presents a table of the statistical analyses made for this confounder selection.[73] Confounding risk factors included in the final model were age (45-49, 50-54, 55-59, 60-64, 65-69, 70-74), age at first term pregnancy (<20, 20-24, 25-29, 30-34, 35+), parity (0, 1, 2, 3, ≥4), months of breastfeeding per child (0, 1-5, 6-12, ≥13), hormone replacement therapy (HRT) (no treatment, progesterone, oestrogen, combined treatment), alcohol consumption (0, 1-14, 15-30, >30 gram/day), physical activity at work (quartiles), height (<160, 160-169, ≥170 cm) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30). BMI was calculated as kg/m^2 and categorised according to the WHO standard.[74] Variables considered but not included in the final model were age at menarche, oral contraceptive use, heredity, smoking and education.

Imputations were made on breastfeeding data for women who had data for at least one child but missing data for another. The mean number of breastfeeding months for that woman was used as imputation. Missing data on the confounding factors are presented in Table 1, paper II and are relatively few since women not handing in the questionnaire were excluded and the participants met personnel from the study several times.

Chi-square tests were used in all three papers to compare the distributions of risk factors for breast cancer between white/blue-collar workers in paper I, chemically exposed/non exposed in paper II and cases/controls in paper III. Cox proportional hazards models were used in paper I to the estimate hazard ratio (HR) for breast cancer in each individual occupation versus all other groups. For papers II and III we wanted to estimate the risk or odds for breast cancer among chemically exposed/never chemically exposed and those who had 1-10 years of exposure and >10 years of exposure. Cox proportional hazards models were used in paper II and logistic regression in paper III. Since we were using matched controls for our cases in paper III we performed both conditional and unconditional logistic regression. The analyses showed no significant difference in the results and we therefore used unconditional logistic regression for improved power.

In paper II we performed a sensitivity analysis using a Cox proportional hazards model including only women who were premenopausal at baseline, to make sure they were only exposed during fertile ages. Trend tests were calculated using Cox proportional hazards models in paper II and logistic regression in paper III. A variable was created assigning the unexposed group a value of 0, the short/low exposed group a value of 1 and the long/high exposed group a value of 2, using the unexposed group as a reference. Pearson correlation analyses were used to investigate correlations between chemical agents and chemical groups in both paper II and III.[75] Population attributable fraction was calculated in paper II using the formula AF=proportion of cases exposed to risk factor x (RR-1/RR).[76]

All statistical analyses in paper I, II and III were performed with STATA version 13.0 with the α-level for significance tests set at 0.05.[77]

3.1.7 Ethical consideration

Data for these studies are registered-based data and previously collected data from a big cohort in Malmö, Sweden. Using secondary data is in some ways ethically less problematic. The data handled for this thesis did not contain any personal identification numbers or names. However, certain ethical issues still had to be considered. When reporting the findings it was important not to report results that could reveal the identity of any participants, e.g. not report too small subgroups or occupational groups with very few employed women. It was especially important to consider the privacy since handling sensitive data about women's health and cancer diagnoses.

The study, resulting in paper I, II and III, was approved by the Regional Ethics Review Board in Stockholm (Dnr: 2014/233-31/4).

3.2 STOCKHOLM FIREFIGHTERS

Our study on cancer incidence in Stockholm firefighters is an update and extended follow-up of a previous cohort study.[61] The original study on cancer among firefighters examined both the cancer mortality and cancer incidence in Stockholm firefighters. The follow-up period for that study was 1951-1986.

3.2.1 Study design

Our study, as well as the original study, has a cohort design. The cohort included all men who worked as a firefighter for at least 1 year during the years 1931-1983 in Stockholm, Sweden. The cohort was identified through annual enrolment records kept at each of the 15 fire stations in Stockholm. The men were followed from 1 January 1958, when the National Cancer Registry in Sweden was established, to 31 December 2012. The total follow-up period was 54 years, adding 26 years of follow-up to the original cohort.

3.2.2 Study participants

In total 1153 men had been employed as firefighters in Stockholm during the years 1931-1983. Of these, 63 men had died or emigrated before baseline in 1958 and 10 men were excluded due to a working period of less than 1 year, resulting in a study population of 1080 men.

3.2.3 Data collection

The birth year of each firefighter was extracted from the enrolment records and thus the age of the firefighter could be calculated. The original cohort also collected data on number of fires fought for each firefighter; however, this data was not available for the extended follow-up. Figure 7 illustrates the data collected for this study.

3.2.4 Exposure assessment

Employment duration was used as a proxy for cumulative exposure in our study. All fire stations kept enrolment record of their employees and information on employment duration could therefore be extracted. The employment period could contain years worked before 1931 up until 2012, as long as the firefighter had been employed at least 1 year during the inclusion years 1931-1983. Employment duration was divided into 10-year groups; 1-9, 10-19, 20-29 and ≥30 years of employment.

3.2.5 Outcome assessment

The outcome in our study was cancer incidence. All first time cancer diagnosis for each specific cancer site was included. The cancer diagnoses were identified using the ICD7-codes (International Classification of Diseases, 7th Revision) from the Swedish Cancer Registry. It is compulsory for every health care provider in Sweden to report all incident cases of cancer to this registry which leads to a high national coverage for all cancer types of approximately 96%.[72] Certain cancer types have an even higher coverage.

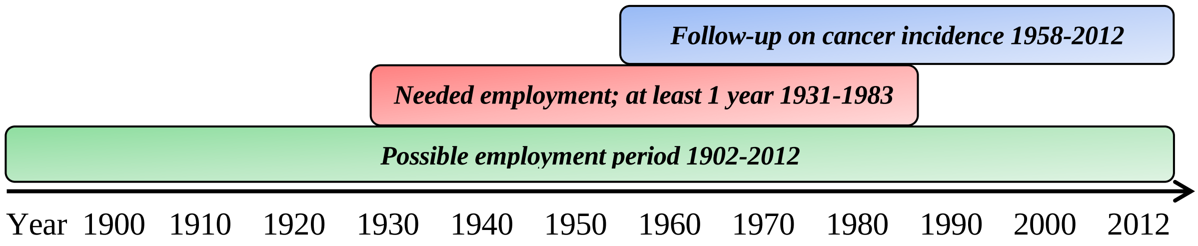


Figure 7. Data collection in the study of Stockholm firefighters

3.2.6 Statistical approach

Standardized incidence ratio (SIR) was calculated for all cancer sites combined and for each specific cancer site. Expected number of cases was calculated from the general male population of Stockholm, using the person year method. Cancer incidence was analysed and stratified on age (<50, 50-64 and ≥65 years old), starting year of employment (1903-1939, 1940-1959, 1960-1983) and employment duration (1-9, 10-19, 20-29 and ≥30 years of employment). Trend tests were calculated using a log-linear Poison model adjusted for age. All statistical analyses were performed with SAS software.

3.2.7 Ethical consideration

All statistical analyses were performed on de-identified data and the study subjects were not contacted. Only registry data were used and no examination or other requirements were asked from the participants, reducing the possible harm to a minimum. The study on firefighters in Stockholm was approved by the Regional Ethics Review Board in Stockholm (Dnr: 2013/2126-31/3 and 2015/787-32).

4 RESULTS AND DISCUSSION

The results presented here are mainly taken from the papers I, II, III and IV, mostly presented in a new approach. However, some new results are also presented. For more detailed results, please see each respective paper.

4.1 MALMÖ DIET AND CANCER STUDY

The study population in MDCS consisted of 17 035 women. Some participants were excluded to fit the aim of each specific paper, which is why the presented numbers in some of the tables will vary marginally from each other.

4.1.1 Baseline characteristics

The characteristics for all the women in the MDCS are presented in Table 2. During the follow-up period from 1991-2013, 1126 incident cases of breast cancer in the cohort were detected, which represent 7% of all women. It should be noted that this is over a long time period of 22 years. Each woman reported on her three latest occupations and the time period for these in the baseline questionnaire. Table 2 shows that the average duration of each employment for these women were 18 years. Around 9% were exposed to any of the chemicals we measured during their working life up until baseline.

Table 2. Characteristics of the women in the MDCS cohort, N=17 035

	n	**%**
Breast cancer diagnoses during follow-up (1991-2013)	1126	7
Ever exposed[a] to chemicals in their occupation	1562	9
Treated with hormone replacement therapy	3058	18
	Mean	**Range**
Employment duration for each occupation (years)	18	1-61
Age at baseline	57	45-74
Parity	2	1-13
Age at first child	25	14-46
Months of breastfeeding	5	0-36
Alcohol consumption (g/day)	7	0- 178
Body Mass Index	25	14-51

a. Ever exposed is classified as being employed in an occupation where at least 5% is considered exposed to any of the following chemical groups; organic solvents, pesticides, fumes and oil mist.

4.1.2 Occupational groups and the risk of breast cancer

The results presented in Table 3 show an increased risk of breast cancer for white-collar workers (occupational sectors 0, 1, 2 and 3) compared to blue-collar workers (occupational sectors 4, 5, 6, 7-8, 90-94 and 98) with a significant HR of 1.25 (95% CI 1.06-1.47). The trend of increasing HR for breast cancer with increased socioeconomic position is apparent in Table 3. The light colours represent low HR and dark colours represent high HR. When observing the results a trend of lighter colours are observed in the lower part of the table and darker colours in the upper part of the table, indicating the trend that several previous studies also have found, that breast cancer is more common among women with higher socioeconomic position.[47 52 78-85] What is notable is that despite the adjustment for all the reproductive and lifestyle confounders, the trend is still present (second column in Table 3). This indicates that there are other factors not yet accounted for that explain this increased risk. Pudrovska et al. have put forward an alternative explanation that discusses life-course stress approach.[82] White-collar workers generally have higher level of job authority leading to a more stressful occupational environment which could cause chronically increased cortisol levels and therefore increase the risk of breast cancer. Another study also found an association between job-strain and increased risk of breast cancer.[86] One other possible explanation for the socioeconomic trend is the higher participation in the mammography screening and thus higher detection of breast cancer among women with higher socioeconomic position.

Differences in risk were also noted between the occupational sectors and occupational groups. The occupational sectors 0–2, professionals, administrative work and bookkeeping all showed elevated HRs, while sectors 3, 6, 7–8, 90–94 including sales, transportation work, production and service showed lower HRs, however all statistically non-significant. The occupational group of registered nurses had an unadjusted elevated risk of breast cancer of HR 1.48 (95% CI 1.07-2.05) that changed marginally when adjusting for confounders (HR 1.51, 95% CI 1.08-2.08). These results indicate that registered nurses have an increased risk of breast cancer that is not due to the reproductive or lifestyle factors, but rather occupational exposures. Several previous studies have found an increased risk of breast cancer among nurses.[78 81] Nurses are exposed to several potential carcinogens such as chemotherapeutic agents, ionising radiation and ethylene oxide which could potentially explain the excess risk. Many nurses also work night shifts, which disrupt the hormone levels in the body and might increase the risk of breast cancer.[33 38] A study on nurses from Iceland showed the highest risk of breast cancer among nurses handling cytotoxic drugs and among paediatric nurses, and a low risk of breast cancer for nurses in primary health care.[87] A likely explanation to nurses' increased risk of breast cancer could be a combination of these occupational-specific exposures.

Table 3. Hazard ratio for breast cancer for women who worked ≥ 10 years

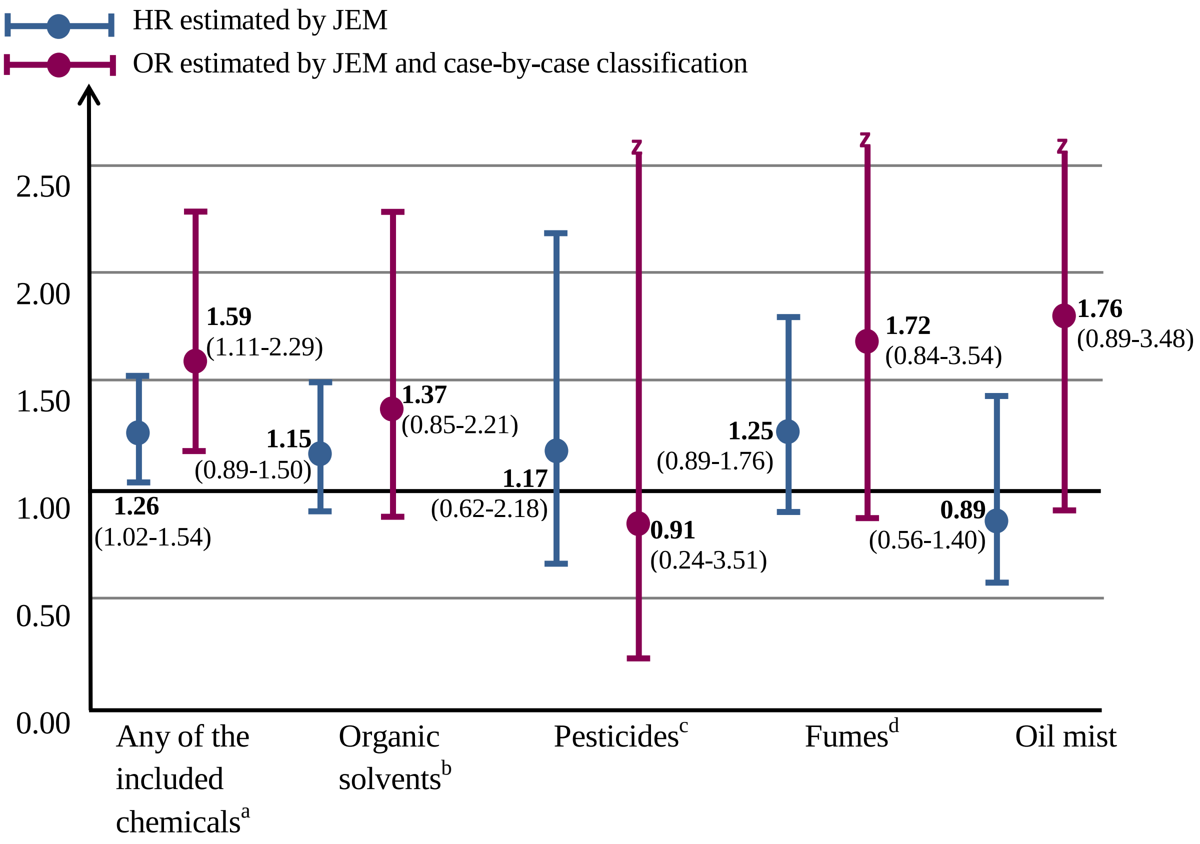
Occupation[a]	**N total**[b] **(14 119)**	**N cases (897)**	**HR**[c]	**95% CI**	**HR adj**[d]	**95% CI**
White-collar workers[e]	9860	669	1.27	(1.09-1.47)	1.25	(1.06-1.47)
Blue-collar workers[f]	4194	225	1.00	-	1.00	-
0. Professional and technical work	4522	294	1.06	(0.92-1.21)	1.00	(0.86-1.15)
00. Engineering work	242	20	1.33	(0.85-2.07)	1.38	(0.88-2.15)
04. Health and nursing work	1732	106	0.97	(0.79-1.19)	0.99	(0.80-1.22)
040. Registered nurses	420	38	1.48	(1.07-2.05)	1.51	(1.08-2.08)
05. Educational work	1326	98	1.22	(0.99-1.50)	1.12	(0.90-1.40)
052. Teachers of theoretical subjects	260	26	1.57	(1.06-2.32)	1.37	(0.90-2.05)
09. Other professionals	684	43	1.00	(0.73-1.35)	0.90	(0.66-1.24)
1. Administrative work	475	35	1.19	(0.85-1.67)	1.14	(0.80-1.62)
10.Government legislative	204	17	1.39	(0.86-2.25)	1.20	(0.72-2.00)
11. Business administrative	271	18	1.05	(0.66-1.67)	1.08	(0.67-1.75)
2. Bookkeeping	4017	276	1.14	(0.99-1.31)	1.14	(0.99-1.32)
20. Bookkeeping and cashier	909	58	1.00	(0.77-1.30)	1.08	(0.83-1.42)
29. Clerical work	3108	218	1.16	(1.00-1.35)	1.14	(0.97-1.34)
3. Sales work	1820	102	0.88	(0.72-1.08)	0.90	(0.73-1.11)
33. Other sales work	1600	92	0.91	(0.73-1.13)	0.93	(0.75-1.17)
4. Agricultural and forestry	103	7	1.07	(0.51-2.25)	1.18	(0.56-2.49)
5. Mining and quarrying work	0	0	-	-	-	-
6.Transportation and communications work	712	40	0.88	(0.64-1.21)	0.88	(0.64-1.22)
65. Postal service	509	22	0.68	(0.44-1.03)	0.64	(0.41-0.99)
7-8. Production work	1309	75	0.95	(0.75-1.21)	0.96	(0.75-1.23)
71. Sewing work	437	17	0.65	(0.40-1.05)	0.63	(0.37-1.05)
88. Packing and storage	227	15	1.09	(0.65-1.81)	1.08	(0.63-1.83)
90-94. Service work	2877	163	0.88	(0.74-1.04)	0.93	(0.78-1.11)
91. Housekeeping	1548	84	0.84	(0.67-1.05)	0.89	(0.70-1.12)
92. Waitresses	203	14	1.11	(0.66-1.89)	1.13	(0.65-1.96)
93. Caretaking and cleaning	694	39	0.89	(0.65-1.23)	0.95	(0.68-1.34)
94. Other service work	381	21	0.88	(0.57-1.36)	0.91	(0.58-1.42)
98. Armed forces	4	0	-	-	-	-

a. Occupational group coded according to FoB80. (Population and Housing Census 1980)
b. A woman can be included up to three times. 14 119 women had 16 013 working periods ≥ 10 years.
c. Hazard ratio for breast cancer in each occupation vs. all other occupations. Adjusted for age.
d. Adjusted for age, parity, age at first child, months of breastfeeding per child, hormonal replacement therapy, physical activity, alcohol consumption, height and BMI.
e. White-collar workers: Occupational sectors 0, 1, 2, 3.
f. Blue-collar workers: Occupational sectors 4, 5, 6, 7-8, 90-94, 98.

HR > 1.29
HR 1.20-1.29
HR 1.10-1.19
HR 1.00-1.09
HR 0.90-0.99
HR 0.80-0.89
HR 0.70-0.79
HR < 0.69

4.1.3 Chemical exposure and breast cancer

Figure 8 is a merge of results from paper II and III. The OR and HR are presented for women ever exposed to any of the main chemical groups that we included in the analysis. The results from the cohort and the case-control study both showed that women ever exposed to at least one of these chemicals had a statistically increased risk of breast cancer (HR=1.26, 95% CI 1.02-1.54 and OR=1.59, 95% CI 1.11-2.29). However, even though many of the chemical groups and chemical agent showed an increased risk, none were statistically significant. The confidence intervals were in many cases wide due to lack in power. It is a clear trend, and especially in the "any chemical exposure" group, that the case-control results showed a higher risk than the results from the cohort study. This is discussed more in detail further down.



a. Exposed in the occupational environment to any of the following chemicals; Organic Solvents (aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, methylene chloride, 1,1,1-trichloroethane, other organic solvents), Pesticides (fungicides, herbicides, insecticides), Fumes (polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust), Oil mist, trichloroethylene, perchloroethylene, gasoline, benzo(a)pyrene,
b. Aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents
c. Fungicides, herbicides, insecticides
d. Polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust

Figure 8. Hazard ratio (95% CI) and Odds ratio (95% CI) for breast cancer among women exposed to chemicals in their occupational environment, estimated through a JEM (n=16 084) and a JEM in combination with a case-by-case classification (n=2400).

The duration analysis shows a significant increased risk of breast cancer with increased duration of exposure to chemicals. Figure 9 illustrates the risk of breast cancer for women who were exposed to at least one of the chemicals we included in the analysis. The trend is significant in both the cohort study and in the case-control study (p=0.01, p=0.01). Furthermore, women exposed for more than 10 years to at least one of these chemicals had an increased risk of HR 1.43 (95% CI 1.10-1.85) in the cohort study and OR 1.88 (95% CI 1.20-2.96) in the case-control study.

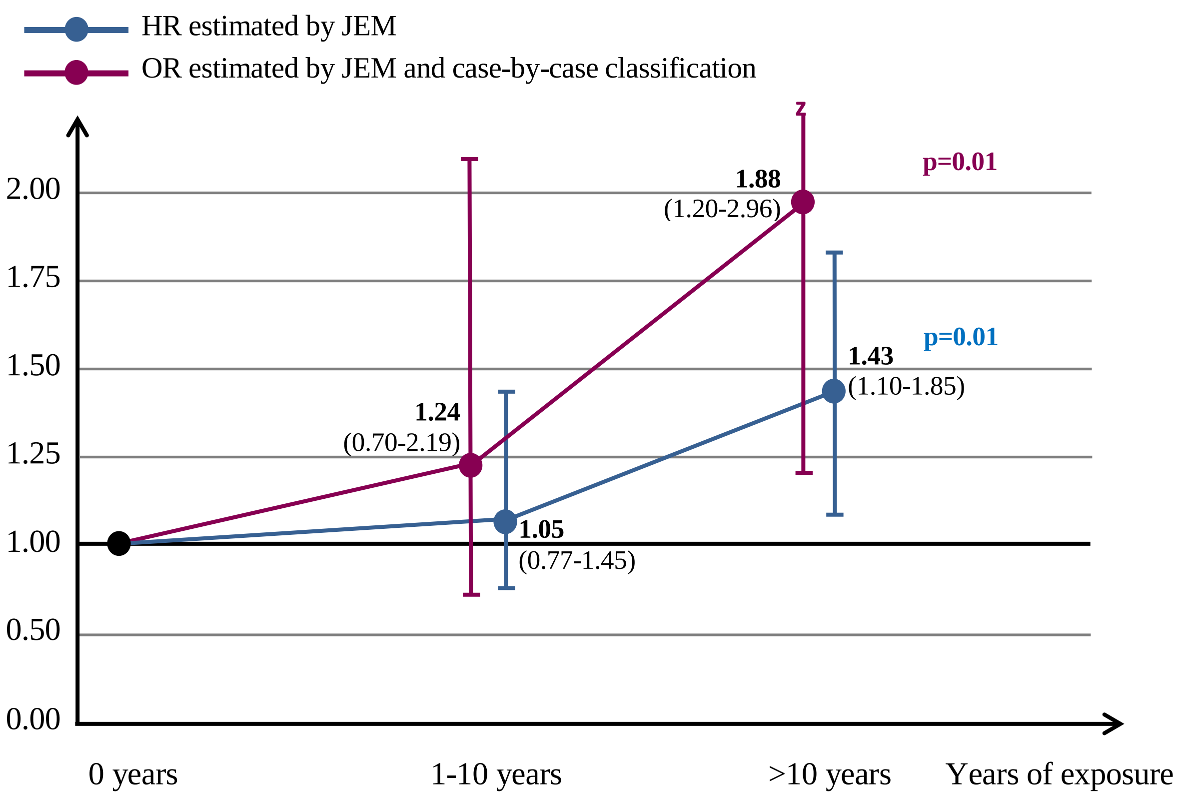


Figure 9. Hazard ratio (95% CI) and Odds ratio (95% CI) for breast cancer among women exposed to any of the main chemical groups (organic solvents, pesticides, fumes or oil mist) for 0, 1-10 or >10 years, estimated through a JEM (n=16 084), and a JEM in combination with a case-by-case classification (n=2400).

Specifically, women exposed to diesel exhaust >10 years had, in the cohort study, a statistically significant increased risk of breast cancer (HR 1.69, 95% CI 1.01-2.82). The results have some support in previous studies. One cohort study from the USA found an increased risk of breast cancer (RR 1.53, 95% CI 1.00-2.33) for women reporting occupational exposure to engine exhaust[88], and another study found increased risk for women exposed to traffic engine exhaust (OR 2.57, 95% CI 1.16-5.69)[89]. Nevertheless, most previous studies on breast cancer and diesel exhaust found no correlation.[90-92] IARC have classified exposure to diesel exhaust as carcinogenic to humans based on evidence for urinary bladder cancer and lung cancer, however lacking enough evidence for breast cancer.

Two significant positive trends of duration were noted among the chemical groups or single agents, for oil mist and chlorinated hydrocarbon solvents. As shown in Figure 10 both of them had a significant trend in the case-control study but not in the cohort study.

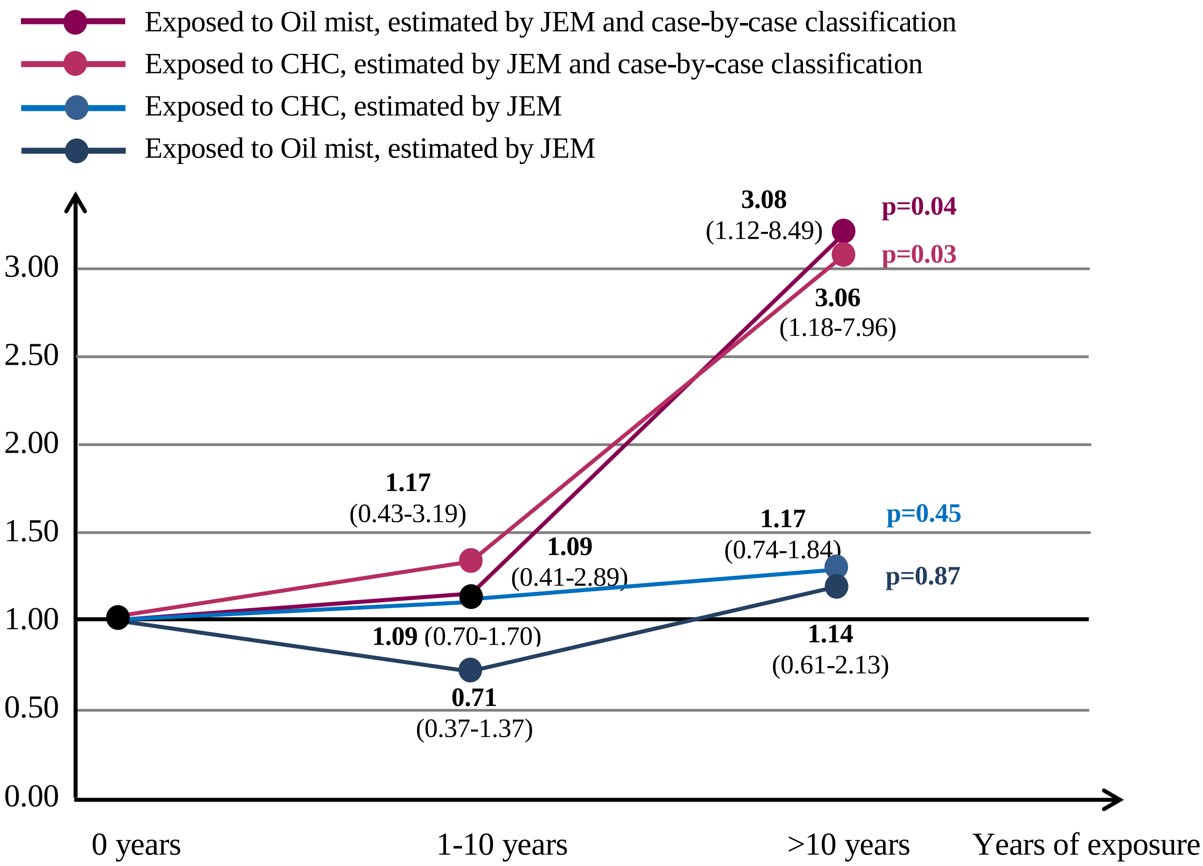


Figure 10. Hazard ratio (95% CI) and Odds ratio (95% CI) for breast cancer among women exposed to Oil mist or Chlorinated hydrocarbon solvents (CHC) for 0 years, 1-10 years or >10 years, estimated through a JEM (n=16 084), and a JEM in combination with a case-by-case classification (n=2400).

Women exposed to oil mist for more than 10 years had an increased OR of 3.08 (95% CI 1.12-8.49), but only a non-significant increased risk of 1.17 (95% CI 0.74-1.84) in the cohort study. A similar trend was shown for chlorinated hydrocarbon solvents where women exposed for more than 10 years had a significant OR of 3.06 (95% CI 1.18-7.96), but only a non-significant increased risk of 1.14 (95% CI 0.61-2.13) in the cohort study. The findings of exposure to organic solvents and increased risk of breast cancer are supported by previous studies.[47,53,55,93-96] In our sample, the women exposed to organic solvents with breast cancer diagnoses were mainly exposed in the occupations: registered nurses, laboratory technicians, spinners and weavers.

When comparing the results from the cohort and the case-control study, it is clear that the risks are higher in the case-control study than the cohort study both in the ever-analyses and in the duration-analyses. The major difference between the two studies is the exposure assessment. In the cohort study a JEM was used to estimate each woman's chemicals exposure while the case-control study also used a case-by-case assessment performed by an occupational hygienist blinded to the cancer status. The exposure assessment made from the occupational hygienist is most likely more accurate than just using a JEM and therefore the results from the case-control study could be more reliable. It is likely that the JEM used in the cohort study introduced a non-differential misclassification of exposure that lead to an attenuation of the results towards an OR of 1.00. However, the results using the JEM were in line with the results using the case-by-case classification, indicating that the JEM is a good enough instrument to use when individual estimates are not feasible.

The mean intensity level (intensity level stated in JEM x proportion exposed x years worked in the exposed occupation / total working years) was calculated in the case-control study. There was no clear overall trend of increased intensity of exposure and increased risk of breast cancer, concluding that duration seemed to be of more importance than mean intensity or cumulative exposure for the risk of breast cancer.

There was, however, one statistically significant intensity trend seen in the analyses. Increased intensity of exposure to oil mist increased the risk of breast cancer (p=0.04). Women exposed to a high intensity of oil mist exposure (0.09-1.80 mg/m^3) with a mean intensity of 0.46 mg/m^3 had a significantly increased risk of breast cancer (OR 2.70, 95% CI 1.09-6.68). The exposure limit for oil mist in Sweden today is 1.00 mg/m^3.[57] This is notable since our results indicate that women exposed to 0.46 mg/m^3 have an increased risk of breast cancer. Oil mist exposure among women occurs mainly among textile workers and could be an exposure from spinner's oil in spinning machines or dyeing processes. The exposure limit to oil mist should be overseen and perhaps re-evaluated by the Swedish Work Environment Authority in order not to cause harm.

4.2 STOCKHOLM FIREFIGHTERS

Our study on Stockholm firefighters is an extended follow-up of a previous cohort study.[61] The results from our study, with some comparisons to the original study, are presented below.

4.2.1 Baseline characteristics

Our extended cohort consisted of 1080 Swedish men who worked at least 1 year as a firefighter in Stockholm between the years 1931-1983. Characteristics of the cohort are presented in table 4. The mean duration of their employment ranged from 1-44 years with a mean length of 26 years. Many of the firefighters started their career early in life with a mean age of 25 years, however they were followed up later in life with a mean age of 38 years. During our follow-up from 1958-2012, 256 cases of cancer were identified in the cohort.

Table 4. Characteristics of the Stockholm firefighting cohort, N=1080

	Mean	**Range**
Birth year	1925	1881-1960
Age at employment	25	17-57
Age at start of follow-up	38	18-77
Starting year of employment	1951	1902-1983
Employment duration (years)	26	1-44

4.2.2 Cancer incidence among firefighters

Figure 11 presents the SIR for firefighters included in the full follow-up, the former follow-up and in the extended follow-up only. The SIR for all cancer types in our extended follow-up was 0.67 (95% CI 0.56-0.79) and for the full follow-up 0.81 (95% CI 0.71-0.91). This was an unexpected finding and in contrast to many other studies on cancer risk among firefighters.[5 64 97 98] The low cancer risk among firefighters in our cohort study could potentially be explained by the healthy worker bias. All men applying for a job in firefighting must pass a physical test in order to be accepted, as well as regularly pass physical tests.[57] This special requirement makes the firefighter in better physical health than the general population. The overall low cancer risk might also be explained by the left truncation bias. The enrolment to the original cohort started in 1931, but our outcome could only be studied from 1958. Therefore, all firefighters who got sick, died or quit as firefighters between 1931-1958 were excluded from our cohort, leaving a slightly healthier cohort at start of follow-up.

More specifically, firefighters had a statistically low risk for prostate cancer (SIR 0.68 95% CI 0.52-0.87) and skin melanoma (SIR 0.30 95% CI 0.06-0.88). These are to an extent surprising results since previous studies have found an increased risk of prostate cancer among firefighters[60] and that shift work possibly could lead to an increased risk of prostate cancer according to IARC.[5] One possible explanation to our findings could be that Swedish firefighters fight fewer fires and are disturbed less at night which leads to less impact on the circadian rhythm, although we do not have this kind of information and therefore it is purely speculative. One other explanation might be firefighters' high physical activity, which is thought to be a protective factor for prostate cancer.[99] The lower risk of skin melanoma among firefighters are also surprising results. The main risk factor for skin melanoma is sun exposure, and firefighters might have less sunburn due to wearing heavy protection clothes when working.

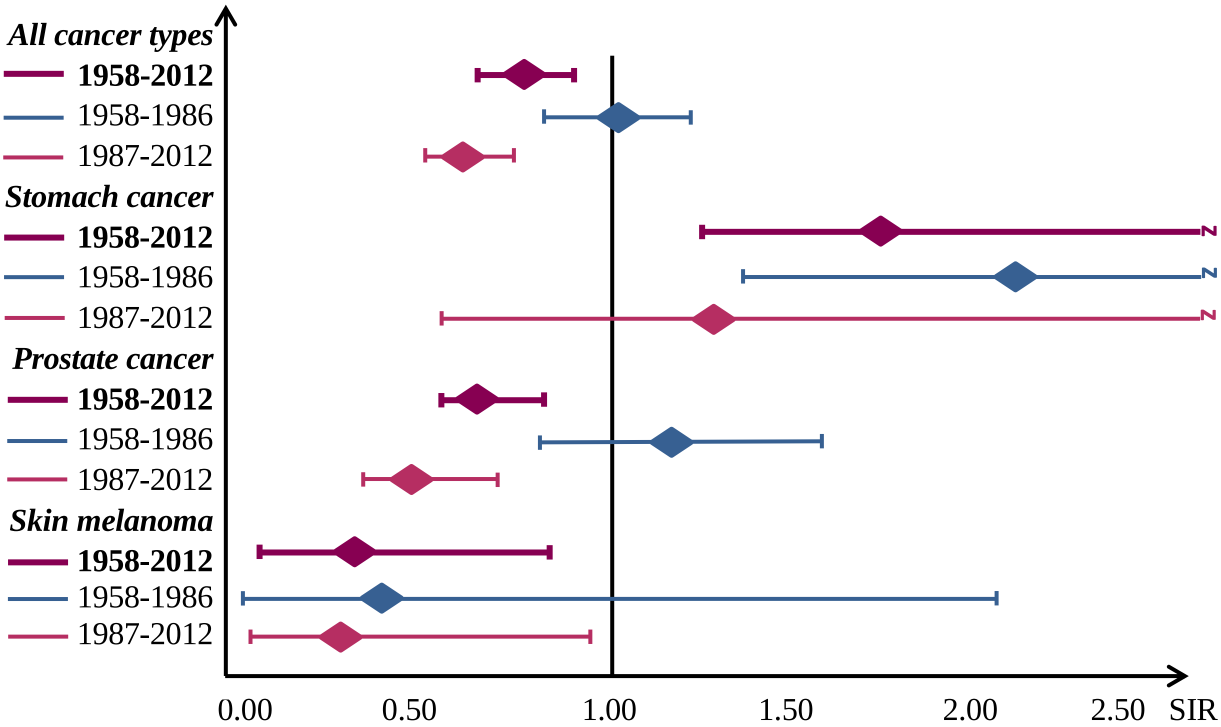


Figure 11. Standardized incidence ratio (SIR) reported for the full follow-up; 1958-2012, for the former follow-up; 1958-1986 and for the extended follow-up only; 1987-2012.

Our study showed an increased risk of stomach cancer (SIR 1.89 95% CI 1.25-2.75) for firefighters. The former follow-up from 1958-1986 found an association between numbers of fires fought and increased risk of stomach cancer, indicating that occupational exposure is involved in the aetiology.[61] The increased risk of stomach cancer among firefighters was also supported by the LeMasters review.[60] Known risk factors for stomach cancer are helicobacter pylori infection, tobacco smoking, occupational exposure in rubber production industry and ionizing radiation.[100] Some evidence is also found indicating that lead compounds, asbestos, nitrate salted fish and pickled vegetables are risk factors for stomach cancer.[100] A recent meta-analysis by Lee et al. showed an association between occupational crystalline silica exposure and increased risk of stomach cancer.[101] Exposure to rubber compounds, asbestos or crystalline silica dust are possible exposures for firefighters if the fire site hold these materials. A review from Raj et al. showed that employees in "dusty occupations" had an increased risk of stomach cancer.[102] Firefighters are often surrounded by dust when tearing down burning material and during overhaul, the last stage of the firefighting.

Even though the overall risk of cancer was low among firefighters, analysis showed a statistically significant trend (p=0.03) of increased risk of cancer with increased employment duration as a firefighter. Since the analysis method takes age into account by the person-year method, the trend seen is likely not confounded by age, but is likely an effect by the occupational exposures firefighters are exposed to.

4.3 METHODOLOGICAL CONSIDERATIONS

Results from observational studies can never be fully understood or interpreted correctly unless having discussed the methodological issues. Below follows an attempt to highlight and discuss the methodological strengths and weaknesses of the papers and studies included in this thesis.

4.3.1 Strengths

Three out of four papers are based on the MDCS, which is a prospective cohort study. This study design is superior to many other study designs, especially when studying cancer outcome which has a long latency period. Since all women were disease-free at baseline we could ensure that the exposure occurred before the outcome, something that is crucial when trying to establish causality. The cohort was followed for a long time, between 17-22 years depending on the year of inclusion. One other strength with this study was the reliable source used for the outcome assessment. First time diagnoses of breast cancer were collected from the Swedish Cancer Registry, which is a national registry with coverage on breast cancer cases of 99% and a total coverage on all cancer types of 97%.[72] The extensive set of individual and reproductive factors that were collected in this cohort study was also a great strength. Few studies have such detailed information of reproductive factors. It is crucial in epidemiological studies to have good information on possible confounding factors and to control for these in order to understand the true association between the studied exposure and outcome. The questionnaire was filled in at baseline and the participant handed in the questionnaire at a personal meeting with the healthcare personnel which contributed to a good response. The participants were quite old at baseline (mean age 57), leaving an almost complete occupational exposure history for each woman. The strengths of the study on firefighters were also the long follow-up time, (up to 54 year) from the Swedish Cancer Registry. The use of registry data for both the outcome and exposure makes the missing data and loss to follow up very limited. We were able to capture almost all firefighters employed in Stockholm during the time period we were interested in.

4.3.2 Random errors

As mentioned earlier, all observational studies have methodological problems that need to be considered. The errors in an observational study can be divided into random and systematic errors. Random errors are the variability in the data and can often be solved with a bigger sample size. As Figure 12 shows, a study with small random errors has high precision, however not necessarily high validity.

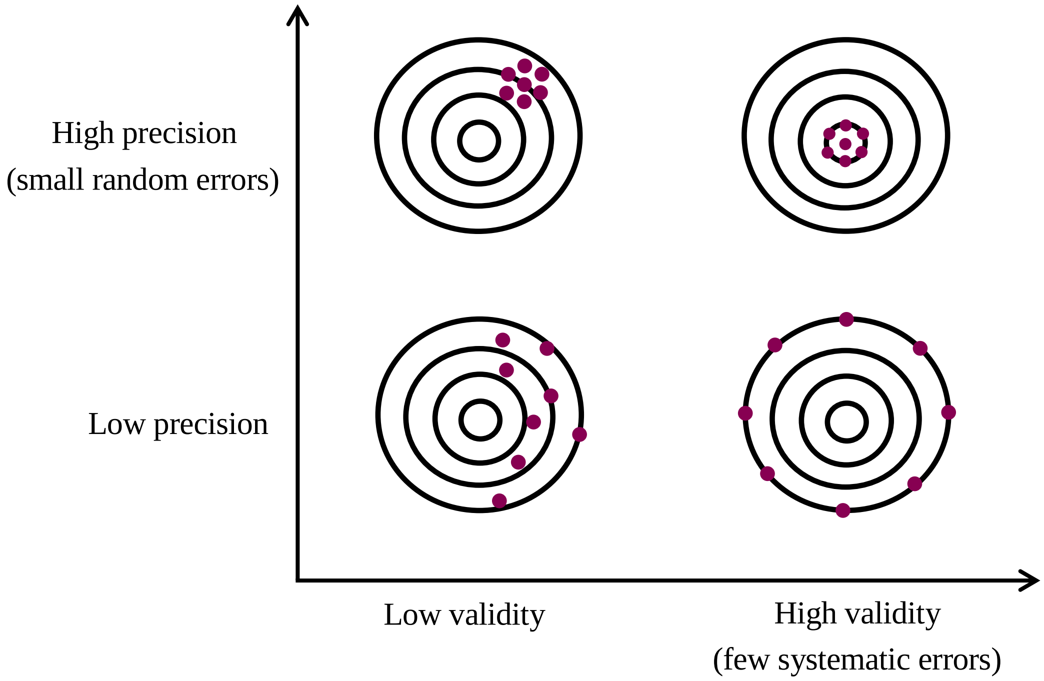


Figure 12. Validity and precision

The MDCS cohort consist of a relatively large study population of around 17 000 women, which reduces the chance findings. However, when studying a rare chemical exposure or subgroups the results were more affected by the random errors which also were shown in wider confidence intervals. In the study on Stockholm firefighters it was clear that even though the follow-up time was long, the study population was too small to detect enough cancer cases in many of the rare forms of cancer. As a result the random errors were larger than preferred.

4.3.3 Systematic errors

Systematic errors are consistent, repeatable errors that are associated with the design or collection of data. It can be divided into selection bias, information bias and confounding.

4.3.3.1 Selection bias

Selection bias could occur when selecting participants for a study or by factors that influence the study participation. If the selection of participants or the will to participate is distorted and the association between the exposure and outcome differ between the two groups, it can introduce a selection bias. Selection bias is often common in case-control studies when both the exposure and the outcome have taken place and the cases and controls volunteer themselves to participate. Our case-control study was nested within a cohort study and since the participants themselves volunteered to participate before the outcome had taken place the risk of selection bias was small.

In the study on firefighters in Stockholm there is a risk of selection bias, specifically healthy worker effect. Since the analysis in that study are comparing a working population, firefighters, to the general population of Stockholm that contain both working and non-working men, it is likely that the firefighters are healthier and have lower risk of our studied outcome cancer. All Swedish firefighters must pass a mandatory physical test to be employed but also to stay employed as a firefighter. Our results indicated that we could have had a healthy worker bias that influenced the low risk of cancer seen in our paper.

There is also a possibility of left truncation bias in the study of Stockholm firefighters.[103] The enrolment started in 1931, however the follow up did not start until 1958 when the cancer registry was established. Therefore, all firefighters who died or were diagnosed with cancer between 1931 and 1958 were excluded from the study, leaving a slightly healthier cohort at start.

4.3.3.2 Information bias

Information bias refers to biases that occur when collecting information about or from the participants and they are categorized incorrectly. If the information bias is related to the outcome (e.g. only the cases are misclassified) it is called differential misclassification, while non-differential misclassification refers to errors that occur regardless of the studied outcome.

Recall bias is a common type of information bias that often occurs in case-control studies. The cases have a tendency of remembering their exposure to a higher extent, often leading to an overestimation of the results. However, the cases in our nested case-control study reported their exposure before becoming a case. This resulted in no chance of recall bias in our case-control study.

There is possible risk of non-differential misclassification of exposure in the MDCS. In paper II the exposure is assessed using a JEM which assign all women in the same occupation the same level of chemical exposure. Naturally not all women in an occupation are exposed to the same level of exposure due to different work tasks, regulations etc. The JEM measures exposure on group level which is then applied on individual level, introducing misclassification of exposure to the participants. However, since there is no difference in respect to cancer diagnosis, the misclassification is non-differential and therefore leads to an attenuation of the results toward a HR of 1.00 in our case.

The nested case-control study used a refined exposure assessment, adding the case-by-case classification of an occupational hygienist in addition to the JEM. This reduced the risk of a misclassification of exposure. However, it could have introduced a differential misclassification of exposure if the occupational hygienist knew and was influenced by the cancer status of the participants when classifying their exposure. Aware of this risk we had the occupational hygienist blinded to the case status for the exposure assessment.

The risk of misclassification of the outcome is small but it still exists. The diagnosis of cancer tumours in Sweden are made after thorough medical examinations of a physician and are classified according to ICD codes. Even though the registry has a very good coverage of close to 100%, there is still a chance that cancer tumours can go undetected if the person does not seek help in time or dies from another cause.

4.3.3.3 Confounding

A confounder is a variable that is associated with both the exposure and the outcome and could cause a false association. Confounders could be adjusted for in the statistical analysis if that data are available. If not adjusted for, it often leads to an over- or underestimation of the true effect.

There is a possibility of detection bias in the MDCS. In paper I we discuss the increased risk of breast cancer among women with higher socioeconomic position. There is a possibility that this result might be affected by detection bias since women with higher socioeconomic position have a greater tendency to seek care and therefore more tumours are likely to be detected. However, in an attempt to control for this, we adjusted the results for education which is a strong predictor of socioeconomic position, without any effect on the breast cancer risk.

In almost all studies there is a chance of residual confounding, confounding factors that for different reasons were not adjusted for. In MDCS night-shift work could have been a potential residual confounder. Studies suggest that night-shift work might increase the risk of breast cancer and at the same time it is common in certain occupational groups, like nurses. In paper I we detected an increased risk of breast cancer among nurses, which then potentially could be due to the confounding factor night-shift work. Residual confounding could also appear when the confounders adjusted for have been poorly measured and therefore have low validity. In our study, many of the reproductive and lifestyle factors were asked with several questions or complete questionnaires (like AUDIT) to get a good and correct estimate.

In paper IV we had very limited information on each firefighter, therefore, there is a big chance of residual confounding. Smoking could have been a possible confounder since associated with the exposure (employment as a firefighter) and the outcome (cancer). Since firefighters are an overall healthier occupational group there are many other possible confounders related to health and lifestyle. For example, one possible risk factor for prostate cancer is sedentary lifestyle,[99] and since we found significantly decreased risk for prostate cancer among firefighters, this might be a possible confounder and explain the low risk we found.

4.3.4 Power calculations

Power calculations were done for the nested case-control study on the MDCS material. The objective was to study if occupational exposure to chemicals would increase the risk of breast cancer. An assumption was made that 2% of the women in the cohort were exposed to chemicals, based on a Swedish yearly report on occupational health.[104] With 2% of the women exposed, an odds ratio of 1.8 could be detected with 80% power at 95% significance level.[105]

No specific power calculation was made for our follow-up on firefighter's risk of cancer. Adding follow-up time and therefore new cases to the already existing study would however only improve the power further.

4.3.5 Generalizability

The internal generalizability is dependent on the systematic errors in the study and few systematic errors increase the internal generalizability. The external generalizability reflects how well a study could be generalizable to other settings and populations. Our study on firefighters in Stockholm can be generalized to other firefighters in Stockholm. However, it might have a lower generalizability to firefighters worldwide since the exposure can differ substantially. This is especially true in countries where little protective gear is worn.

The same argument is true for the MKCS where, for instance, exposure as a nurse in Malmö is very similar to the ones of a nurse in Stockholm. However, the occupational exposures might differ between countries and therefore a somewhat lower generalizability could be expected.

4.4 FUTURE RESEARCH

This thesis tried to investigate the relationship between occupational chemical exposure and the risk of cancer. We have contributed to a small piece of the puzzle, but there are many pieces left to get an understanding of the full picture. In the society we live in today, the occupational structure and working conditions are going through a major change. Many occupations are today performed by computers, some are created for on-demand needs like home-delivery of all kinds. These changed conditions and structures also lead to new occupational exposures that need to be understood and studied. In the field of occupational chemical exposures, there is also an evolvement towards new exposures in form of new chemical agents that comes mainly from production work. Since a lot of production work has been relocated to Asia over the last decades, it is important to study occupational environment and the health of employees not only in Europe but worldwide.

More specifically, since results from our study indicated an increased risk of breast cancer for women exposed to oil mist under the exposure limit set by the Swedish Work Environment Authority, further research on oil mist as a potential risk of breast cancer should be investigated.

5 CONCLUSION

The risk of breast cancer differs between occupational groups and is more common among white-collar workers compared to blue-collar workers. Previous studies suggest that lifestyle and reproductive factors explain this difference in risk. However, our results suggest that there is still a significantly increased risk for breast cancer among white-collar workers, and the risks were only marginally attenuated after adjusting for reproductive and lifestyle factors. This suggests that there might be exposures related to the occupation causing an increased risk of breast cancer.

Our results showed an increased risk of breast cancer among women exposed to chemicals. The risk seemed to increase with duration of exposure. Specifically, women exposed to chlorinated hydrocarbon solvents and oil mist seemed to have an increased risk of breast cancer. The results also indicated that the exposure limit for oil mist set by the Swedish Work Environment Authority might be too high to protect women from breast cancer. Further studies are needed to confirm these results. Our results suggest that the exposure assessment using a JEM in combination with a case-by-case estimation by an occupational hygienist gave an improved risk estimate, compared to only using a JEM.

Firefighters had an overall low risk of cancer, which could be due to potential confounding and healthy worker effect. However, the risk seemed to increase with longer employment duration, indicating an effect of carcinogens in their occupation. Our results showed an increased risk of stomach cancer, which is supported by previous large studies. Firefighters increased risk of stomach cancer could possibly be related to their occupational exposures when fighting fires.

6 POPULÄRVETENSKAPLIG SAMMANFATTNING

Vi tillbringar en stor del av vår vakna tid på arbetet och arbetsmiljön har därför en stor möjlighet att påverka vår hälsa. En av alla skadliga exponeringar som kan förekomma på arbetsplatsen är kemikalier av olika slag. Exponering för kemikalier kan ge olika typer av skador där cancer är en av de allvarligaste konsekvenserna. Uppskattningsvis beror 5–8% av alla cancerfall på exponeringar i arbetsmiljön. Vissa yrkesgrupper, som t.ex. brandmän, har uppmärksammats extra mycket i media och inom forskning då de utsätts för stora mängder kemikalier i sitt arbete. Även specifika kemikalier i relation till vissa cancerformer har fått stor uppmärksamhet som till exempel sambandet mellan organiska lösningsmedel och bröstcancer. Syftet med den här avhandlingen var att undersöka sambandet mellan exponering för kemikalier i arbetet och risken för cancer.

Material till avhandlingen är hämtat från Malmö Kost och Cancer studie (MKC) samt en kohort av brandmän i Stockholm. Artikel I, II och III är baserade på MKC och artikel IV är baserat på kohorten med Stockholms brandmän. MKC är en kohortstudie där 17 035 kvinnor födda 1923-1950 och boende i Malmö under rekryteringsåren 1991-1996 är inkluderade. Kvinnorna följdes upp på bröstcancerstatus i Svenska Cancerregistret från inkludering till 2013. Yrkeshistorik med kvinnornas tre senaste yrken självrapporterades i ett frågeformulär vid baslinjen och med hjälp av en jobb-exponeringsmatris uppskattades varje kvinnas kemiska exponering. För artikel III genomförde en yrkeshygieniker en individuell bedömning av varje kvinnas exponering, baserat på detaljerad yrkesinformation i frågeformuläret. Artikel IV använde en kohort på 1080 män som arbetade som brandmän i Stockholm minst ett år mellan 1931-1983. De följdes upp i Svenska Cancerregistret avseende alla typer av cancer mellan 1958-2012.

Avhandlingens resultat visar att kvinnliga tjänstemän (white-collar workers) hade en ökad risk för bröstcancer jämfört med arbetare (blue-collar workers), även efter justering för hormonella- och livsstilsfaktorer. De kvinnor som var exponerade för kemikalier i sitt arbete hade en ökad risk för bröstcancer och risken verkade öka med ökad exponeringstid. Mer specifikt hade kvinnor som var exponerade för klorerade lösningsmedel och oljedimma en ökad risk för bröstcancer. Brandmän hade generellt en låg risk för cancer jämfört med genomsnittet för män i Stockholm och framförallt var risken låg för prostatacancer och malignt melanom i huden. Brandmän hade däremot en ökad risk för magcancer som tros kunna bero på deras yrkesmässiga exponering för kemikalier.

Avhandlingen ger ett visst stöd för hypotesen om att exponering för lösningsmedel ger ökad risk för bröstcancer. Det arbetshygieniska gränsvärdet för oljedimma kan behöva revideras av Arbetsmiljöverket då resultaten i avhandlingen pekar på att kvinnor som idag är exponerade för värden under exponeringsgränsen har en ökad risk för bröstcancer. Användningen av jobb-exponeringsmatriser har vissa metodologiska nackdelar men är ändå ett bra alternativ när enskilda exponeringsbedömningar inte är genomförbara.

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