Changing work life and cancer risk in the Nordic countries (NOCCA)

Project description by Eero Pukkala (August 2006)

> The main changes to the protocol during the first 18 months of work (funded by NCU grants 2004 and 2005) are highlighted with blue colour. In general, along with the increasing facts of the actual possibilities offered by the data, the project appears to have even better views than estimated in the earlier applications, and accordingly the project now includes more components and more committed researchers than in the beginning.

1. Background

The pooled analysis of census-derived job titles and cancer registry data from Denmark, Finland, Norway and Sweden has represented a successful and efficient approach to produce important results on occupational cancer (Andersen et al., 1999). It included 54 job titles and 32 cancers. The large data and reliable information on occupation allowed identification of risk occupations even in rare cancers such as nasal cancer given as an example of the results (Fig. 1). The only confirmed occupational risk factors for nasal cancer are leather dust and wood dust, and the highest standardized incidence ratios (SIR) among all 54 occupations studied were seen among shoe and leather workers (SIR 2.9, 95% CI 1.5-5.3) and wood workers (SIR 1.9, 95% CI 1.6-2.2).

This study will now be updated and expanded. Exposure to known and suspected carcinogens and other work-related hazards such as work stress, shift work, lack of physical activity and reduced/postponed parity do to career planning can be estimated via the application of a job-exposure matrix (JEM). Nordic job-exposure matrix will be based on the national matrix developed in Finland (Kauppinen et al., 1998; Pukkala et al. 2005). Using this matrix, the cancer risks attributable to the occupation-related hazards and changes in the work-related risks over a period of three or four decades can be calculated in a dose-response manner for the entire Nordic population.

We will especially focus on women, who today comprise a large fraction of economically active work-force but whose occupational hazards have rarely been studied.

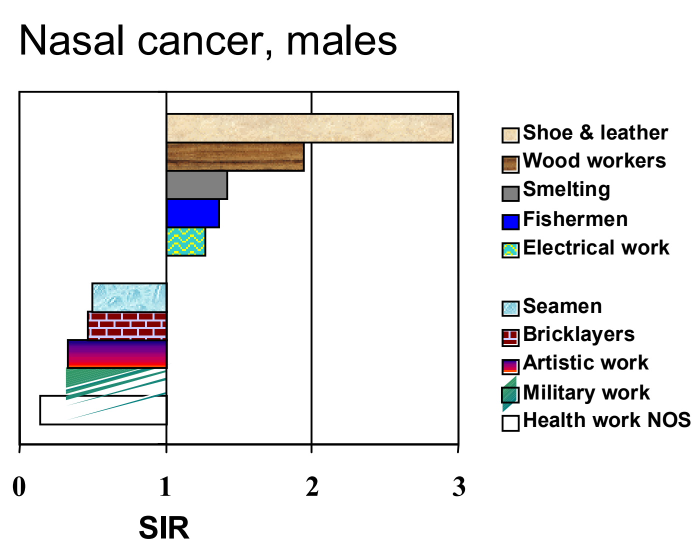

Figure 1. Occupations with highest and lowest standardised incidence ratio (SIR) of nasal cancer in the Nordic countries, 1971-1991. SIR 1.0 = whole population (Andersen et al., 1999)**.**

2. Scientific value

The pooled database from the Nordic countries presents several features that make it a unique resource for research on occupational cancer:

(i) it covers all persons who have reached working ages in five countries;

(ii) the follow-up after occupational exposures is several decades;

(iii) data on occupation (basis for exposure estimate) and cancer data are almost complete and of high quality;

(iv) the proportion of economically active women is high;

(v) data on potential confounders such as smoking, parity and obesity can be obtained.

This type and quality of analysis cannot be done in any other part of the world. Many of the results to be achieved will be are novel findings or have importance in confirmation of earlier findings from earlier small studies.

3. Data

The earlier analysis was based on occupations from population census 1970 and follow-up of cancer incidence until 1987 in Denmark, 1990 in Finland, 1991 in Norway and 1989 in Sweden.

The available data will be expanded in several ways:

(1) update of follow-up until 2003;

(2) use of 1960 and 1980 censuses;

(3) addition of data from Iceland;

(4) application of a job-exposure matrix.

(5) use of data on potential confounders;

(6) assessment of the relationship between reproductive habits, physical activity and occupation in women;

(7) expansion of the list of neoplasms to be studied.

3.1 Update of follow-up for cancer incidence

The follow-up will be updated in each of the countries. All Nordic cancer registries estimate to have their incidence data ready up to the end of 2003 before October 2005. This expansion will bring more than a million additional observed cancer cases, thus increasing substantially the statistical power, which opens unique possibilities in particular for less frequent neoplasms which have hardly ever been studied in the context of occupational exposures (Table 1).

3.2 Use of 1960 and 1980 censuses

The previous analysis was based on job recorded in each country at the census conducted around 1970. However, comparable information from all countries is available for the censuses conducted around 1980. These can be incorporated in the database, allowing to the estimate duration of exposure. In Norway and Sweden also occupations in 1960 are available in computerized files.

3.3 Addition of data from Iceland

Iceland was not included in the previous analysis (Andersen et al., 1999). Its addition is now possible, based on data from 1981 census, and will contribute at least 1,200,000 person-years or observation and 6,000 cases of cancer to the analysis. Furthermore, it will increase the scope for inter-country comparisons of the results. The preliminary results from Iceland indicate that the data available are of high quality. The Icelandic results are strong enough for conclusions related to common phenomena such as increased risk of lung cancer (SIR=1.52, 95% CI 1.20-1.89) among fishermen or decreased risk of lung cancer (SIR=0.52, 95% CI 0.38-0.68) among male farmers but in most instances combining with the result pattern from the other Nordic countries makes interpretation essentially easier.

3.4 Application of a job-exposure matrix

A job-exposure matrix will be prepared that in the first phase (which is now virtually ready) will comprise job title specific estimates of exposure to following 23 agents: asbestos, crystalline silica, nickel and its compounds, lead and its compounds, chromium and its compounds, iron and its compounds, welding fumes, diesel exhaust, benzo-a-pyrene, wood dust, formaldehyde, aliphatic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other solvents, gasoline, animal dust, bitumen fumes, sulphur dioxide, ultraviolet radiation, ionising radiation, physical workload, and night work.

This matrix will include country-specific assessments and separate assessments for men and women. The inclusion of census data from 1960 and 1980 might require time-specific assessments. The matrix has been prepared by a team comprising industrial hygienists from each Nordic country who have had several days of joint meetings and created similar comprehensive matrices for the Nordic countries that was first prepared for Finland (FINJEM; Kauppinen et al., 1998) and now covers almost 100 occupation-related factors and allow quantitative cumulative exposure estimation and precise timing of relative exposure and lag (Pukkala et al. 2005).

3.5 Use of data on potential confounders

Surveys are available in the Nordic countries on distribution of important confounders, namely tobacco smoking, alcohol drinking and body mass index, by categories comparable to those used to classify occupation. It is therefore possible to derive ecological data on potential confounders of the associations between occupational agents and specific neoplasms. Such data can be used to adjust the risk estimates for the occupational agents, as it has been recently done for tobacco smoking in analyses of the Finnish and the Norwegian data (Pukkala et al. 2005; Haldorsen et al., 2004). A pilot phase to assess the quality and comparability of these data will be required.

Denmark also has a data set of annual samples of 20,000 persons available for 2-5 years period around the 1970, the 1980 and the 1990 censuses that can be used for a control on a detailed group basis (Engholm et al., 1996) and another data set of 9231 persons covering smoking habits in specific occupational groups (Arbejdsmiljøgruppen 1974).

A person has been hired by NOCCA to search relevant data sources In Iceland.

3.6 Assessment of the relationship between reproductive habits, physical activity and occupation in women

There are socioeconomic differences in reproductive cancers, with breast, ovarian and endometrial cancers being more common in women of high socio-economic status (Pukkala & Weiderpass, 1999). It is likely that socioeconomic differentials in most aspects of reproductive behavior, account for some of the socioeconomic variation in the risk of female cancers (Pukkala, 1995; Kogevinas et al., 1997). It is unclear, however, what is the contribution of delayed pregnancies vs. other reproductive habits (*e.g.*, reduced breastfeeding). Mean age at having the first child have increased in the last fifty years from 23.9 years in 1945 to 28.5 in 2001 in Sweden, and similar trends have occurred in the other Nordic countries. The project will study this phenomenon in two steps:

(i) to compare systematically reproductive habits in women employed in different occupations and in non-employed women in the five countries;

(ii) to assess the contribution of these differences on risk of breast, ovarian and endometrial cancers.

Information on parity will be obtained from the Swedish Multi-Generation Register as well as from population registries and medical birth registers available in most Nordic countries. There is a file including complete fertility history for all Danish women born from 1930 onwards (Danø et al. 2005), and the average number of children and age at first birth have been calculated for each occupation in the entire female population in Finland in 1985 (Pukkala 1995).

We will also study the impact of the effect of sedentary work that is strongly related to risk of breast cancer and has to be taken into account when estimating risks connected to parity. Lack of physical activity is estimated to cause soon more cancers than all known carcinogenic work-related agents together. Estimates on physical activity at work and at leisure has already been created for occupational categories in Finland (Lynge et al., 1989, Rintala et al., 2002) and similar data collection needs to be done for other countries.

3.7 Expansion of the list of neoplasms

The systematic analysis of cancer risk by job title in the previous analysis was based on a standard list of 32 primary sites. Owing to the increased statistical power, the list will be expanded and focused to specific histological subtypes if necessary due to diverging aetiology (Table 1). For example, the suspected occupational risk factors of squamous cell carcinoma of the oesophagus are very different from those of adenocarcinoma of the same organ. We will also do stage-specific analyses to separate the roles of varying level of diagnostic activity levels between occupations (typically reflected in non-symptomatic, localized cancers) and real difference in risk.

4. Analysis

The standard analytic approach will comprise the calculation of country-specific observed numbers and expected numbers (based on national incidence rates) of cancer cases, from which standardized incidence ratios (SIRs) and 95% confidence intervals are derived. Country-specific results will be pooled according to a fixed-effects model.

Additional analytical approaches will include:

- multivariate (*e.g.*, Poisson regression-based) analysis, taking into account concomitant exposure to several agents;
- adjustment for potential confounders (tobacco smoking, alcohol consumption, obesity and reproductive factors): this requires acquisition of data from each country;
- time-related exposures, taking into account changes in exposure status between censuses (in the case data from 1960 and 1980 censuses will be added) and changes in work conditions over time.

The job-exposure matrix is in principle an efficient tool to analyse the effects of many occupational exposures on cancer risk. The estimates of the relative risk (RR) associated with these factors based on JEM are fairly valid, given that certain conditions regarding exposure distribution in the study cohorts are fulfilled. However, when the exposure levels are highly variable across individuals within an occupational group of interest, the RR estimates of exposure effects are prone to the *ecological bia*s. Recent advances in statistical methodology and computational facilities provide new possibilities to control this bias and obtain more valid RR estimates. The modern statistical approaches are based on *hierarchical* or *multi-level models*, and the interesting quantities are estimated using MCMC simulation methods (Gilks & Richardson, 1992; Wakefield & Salway, 2001; Richardson & Best, 2003).

The NOCCA data offer good possibilities for fruitful application of advanced statistical methods to improve the validity of estimation of true exposure effects. The practical experience so far suggests that in most instances the ecological bias is modest. Nevertheless, there may be extreme situations in which the exposure within an occupational group is so heterogeneous that a careful of control this heterogeneity is needed. Therefore a group of statisticians, coordinated by Esa Läärä from University of Oulu, Finland, will be created to develop and apply these methodologies within the NOCCA network.

5. Organization

The project will be carried out by a group of epidemiologists, complemented by a group of industrial hygienists from all Nordic countries. Table 2 shows the principal investigators who also compose the study steering group, their main tasks and planned main work months during a 3-year project period 2005-2007.

The SIR analysis will be conducted at the Norwegian Cancer Registry. The analysis of reproductive factors will be conducted at the Karolinska Institute. The multivariate analyses that combine data on occupational hazards of interest, occupational co-exposures and life-style confounders to occupation-specific observed and expected numbers of cases will be mainly done using the procedure developed and tested by the Finnish Cancer Registry (Pukkala et al. 2005). This procedure allows us to define the lag between exposure and outcome and take into account ages of exposure as well as historical changes in work conditions.

All epidemiologists will meet at least four times to define the strategy for the analysis and to review the results. The overall results on cancer rates by job titles will be reported in a monograph similar to the earlier one (Andersen et al., 1999). The end result of the team of occupational hygienists will be a publication on prevalence of carcinogenic agents in the work environment in the Nordic countries. Another parallel publication will focus on socio-economic differences in cancer incidence, using same data base as the work based on occupational titles; this work gains from collaboration with Swedish project "Social mobility and cancer" coordinated by Pär Sparén and a newly funded Norwegian project coordinated by Bjørgulf Claussen.

Once the basic data on both numbers of cancers and prevalence of occupational hazards exist, deep-in dose-response analyses on selected occupational hazards, physical activity and reproductive factors can be started and will be published as separate articles in peer-reviewed journals. We have budgeted six smaller work-meetings related to these specific studies, each of which will have unique power in comparison to any earlier study on the same topic. These numerous sub-studies will link NOCCA projects to numerous researchers and institutes not listed in Table 2. The list of specific studies to be done first includes following topics:

- Hairdressers and non-Hodgkin lymphoma (hairdressing/dyes/barbers)
- Outdoors occupations (UV-radiation) and risk and survival of non-Hodgkin lymphoma
- Solvents and non-Hodgkin lymphoma
- Outdoors' occupations and breast cancer
- Sulphur/bitumen/wood dust and lung cancer (with smoking, asbestos and SES as covariates)
- Night work/shift work and breast cancer
- Asbestos/dust and ovarian cancer
- Gasoline/diesel exhaust and kidney cancer (obesity one possible covariate)
- Obesity/alcohol and oesophageal cancer
- Electromagnetic fields and gastrointestinal cancers
- Physical activity and colorectal cancer

The study started in 2005 and is expected to last about 3 years; however the series of the agent and cancer specific dose-response analyses will continue in 2008 and later.

6. References

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Table 1: Cancer sites to be included in the analyses of NOCCA project.

Nro	ICD-7 or own code	Site
0	140-207	All malignant neoplasms *[exclude in situ cancers from all sites]*
1	140	Lip
2	141	Tongue
3	142	Salivary glands
4	143-144	Oral cavity
5	145-148	Pharynx
6	145	oropharynx
7	146	nasopharynx
8	150	Oesophagus
9	150A	oesophagus, adenoca
10	151	Stomach
11	151.1	cardia
12	152	Small intestine
13	153	Colon
14	154	Rectum, rectosigma
15	155.0	Primary liver
16	155H	hemangiosarcoma
17	155.1	Gall-bladder, biliary tract
18	157	Pancreas
19	160	Nose
20	160A	nose, adenoca
21	161	Larynx
22	162,163	Lung
23	162A	lung, adenoca
24	162S	lung, small cell
25	162E	lung, squamous cell
26	162O	lung, other
27	1622,158M	Mesothelioma in pleura/peritoneum *[C38 in ICD-O; based on morphology]*
28	170	Breast
29	170D	breast, ductal
30	170L	breast, lobular
31	171	Cervix uteri (invasive)
32	172	Corpus uteri
33	173	Choriocarcinoma
34	175.0	Ovary
35	175.1	Tuba
36	176.0	Vulva
37	176.1	Vagina
38	177	Prostate
39	178	Testis
40	178S	testis, seminoma
41	178N	testis, non-seminoma
42	179.0	Penis
43	180	Kidney
44	180.1	renal pelvis
45	181	Bladder, ureter, urethra
46	190	Melanoma of the skin
47	190.6	skin melanoma, upper limbs
48	191	Non-melanoma skin cancer
49	191.6	non-melanoma of the skin, upper limbs
50	192	Eye
51	192M	melanoma
52	193	Brain and nervous system
53	193G	glioma
54	193M	meningeoma
55	194	Thyroid
56	194F	thyroid, follicular
57	194P	thyroid, papillary
58	195.0	Glandula suprarenalis
59	195.1	Glandula parathyreiodea
60	195.2	Thymus
61	195.3	Hypophysis
62	195.4	Corpus pineale
63	196	Bone
64	196C	bone, chondrosarcoma [
65	197	Soft tissue
66	197F	soft tissue, fibrosarcoma
68	197L	soft tissue, liposarcoma
69	199	Other/unknown site
70	200,202	Non-Hodgkin's lymphoma
71	201	Hodgkin's disease
72	203	Multiple myeloma
73	204	Leukaemia
74	204CLL	chronic lymphocytic
75	204AML	acute myeloid
76	191 or 205	Mycosis fungoides (lymphoma)

Not included above:
(exclude these cancers from "All sites" and above categories but make a separate category out of them)

90	*175B*	*Ovary, borderline tumour*
91	*181P*	*Papilloma of the bladder*
92	*191B*	*Skin, basal cell carcinoma*

Table 2. Tasks, timing, responsible participants

Task [timing]	Responsible person	Institution
General coordination of the project [Jan 2005-Dec 2007+]	E. Pukkala*	Finnish Cancer Registry
Update of census -cancer follow-up [Feb 2005-Sep 2006]		
Denmark	E. Lynge*	Copenhagen University
Iceland	L. Tryggvadottír	Icelandic Cancer Registry
Finland	E. Pukkala*	Finnish Cancer Registry
Norway	K. Kjærheim*	Norwegian Cancer Registry
Sweden	L. Barlow	Swedish Cancer Registry
Creation of job-exposure matrix [Aug 2005-Sep 2006]		
Denmark	J. Hansen	Danish Cancer Society
Iceland	V. Kristjánsson	Administration of Occup. Safety and Health
Finland	T. Kauppinen# /P. Heikkilä	Finnish Institute of Occupational Health
Norway	K. Lenvik/ T. Woldbæk	Statens Arbeidsmiljoinstitutt
Sweden	N. Plato	Karolinska Hospital
Data on confounders [Aug 2005-Dec 2007]		
Denmark	E. Lynge	Copenhagen University
Iceland	H. Gunnarsdottír*	Administration of Occup. Safety & Health.
Finland	E. Pukkala	Finnish Cancer Registry
Norway	A. Andersen	Norwegian Cancer Registry
Sweden	P. Sparén*#	Karolinska Institute
Analysis of **occupation-specific cancer rates** [Dec 2005-January 2007]	J.I. Martinsen#	Norwegian Cancer Registry
Analysis related to **reproductive habits** [2006-2007]	P. Sparén*#	Karolinska Institute
Development of **statistical methods** [Oct 2006-2007]	E. Läärä#	University of Oulu
Dose-response multivariate analyses of single exposures and cancers, new statistical approaches [2006-2007]	T. Haldorsen E. Weiderpass Vainio E. Pukkala*# P. Boffetta + many others (specialists of respective topics)	Norwegian Cancer Registry Karolinska Institute Finnish Cancer Registry IARC
Linking the project to the instances gaining from the results (globally)	P. Boffetta#	IARC

* Coordinator of national NOCCA activities

\# Coordinator of the main sub-project