Exhibit 285

Cancer Incidence Among Finnish Oil Refinery Workers, 1971–1994

Eero Pukkala, PhD

Cancer incidence between 1971 and 1994 was studied in a cohort of 7,512 men and 1,942 women who had been employed for at least 3 months in a Finnish enterprise that was primarily active in oil refining. The expected numbers of cancer cases were based on the national incidence rates. The standardized incidence ratios (SIR) for overall cancer after 5 years at work was decreased by 12% because of a significant deficit from cancer of the lung in oil refineries (SIR, 0.3; 95% confidence interval [95% CI], 0.1–0.6). There was a significant excess of kidney cancer in males, which was highest among men with at least 5 years of employment in oil refineries (SIR 2.8; 95% CI, 1.6–4.7). Male blue-collar workers had a twofold risk of non-Hodgkin's lymphoma and non-melanocytic skin cancer. Occupational exposure to gasoline may be associated with increased risk of cancer of the kidney.

The International Agency for Research on Cancer (IARC) has evaluated occupational exposures in petroleum refining as "probably carcinogenic to humans" (Group 2A).[1] This limited evidence applies to skin cancer and leukemia. Excess cancers of the kidney, bladder, stomach, and pancreas have been occasionally but not consistently reported in refinery cohorts.[1]

Neste Group is a North European enterprise operating in the oil, energy, and chemicals industries. Before the 1990s, Neste was the only provider of gasoline to the Finnish market. Besides the main field of action of Neste — oil refining — there is a chemical division that develops, manufactures, and markets chemical products: in particular, adhesive resins used in the forest industry and industrial coatings, as well as oxo products used as intermediates for coatings. The production also includes polystyrene and composite materials. Neste employees may have been exposed to several chemicals and work processes listed by IARC evaluations in carcinogenicity groups 1, 2A, and 2B: gasoline manufacturing, benzene, vinyl chloride monomer, 1,3-butadiene, hydrazine, polycyclic aromatic hydrocarbons (PAH), asbestos, nickel, and chromium. The majority of the employees are exposed to benzene, which until the early 1990s constituted 5% by volume of gasoline produced by Neste. The first oil refinery started production in Naantali in 1957 and the other one in Porvoo in 1966; the petrochemical production began in 1970. The head office has always

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1076-2752/98/4008-0675$3.00/0

been located in the Helsinki (capital) area of Finland.

The aim of this study was to evaluate whether employees exposed to various chemicals in oil refining are at an increased risk of cancer. Special attention was paid to cancers with a priori suspected associations.

Material and Methods

The records for all Finnish workers who had been employed by Neste Group for at least 3 months during the period 1967–1982 and who had not died before January 1, 1971, were available from the personnel files of the company. This cohort was cross-checked against the population register of Finland, and the personal identification number and vital status were recorded for every cohort member. All residents of Finland since January 1, 1967, have a unique personal identification number, which is used in all main registers in Finland.

Follow-up for cancer through the files of the population-based countrywide Finnish Cancer Registry was done automatically, using the personal identification number as key. Follow-up for cancer started at the date of first employment (excluding those 3 first months, which were the criteria for inclusion into the study) or on January 1, 1971, whichever was later, and ended at death, at emigration, or on December 31, 1994, whichever occurred first. In the analyses made by occupational subcategories (clerical, technical, and blue-collar workers) or by department (oil refineries in Porvoo and Naantali, Porvoo Chemicals, head office), the beginning of follow-up was defined on the basis of first employment in the category in question. Some persons belonged to more than one subgroup and thus produced person-years for more than one category. Further division was made by the time elapsed since first employment. Relative risks were also calculated as a function of time at work, then the follow-up started on the date when the person had been working the required time (2 or 5 years) in the respective work category. However, the work periods before 1971 and after 1984 were not known.

The numbers of observed cases and person-years at risk were counted, by 5-year age groups, separately for three calendar periods (1971–1978, 1979–1986, and 1987–1994). The expected numbers of cases for total cancer and for specific cancer types were calculated by multiplying the numbers of person-years in each age group by the corresponding average cancer incidence rates in the entire population of Finland during the period of observation. The specific cancer types selected a priori for the analysis included the cancer sites with known or suspected excess risk in earlier studies and other common cancer types to reveal the general cancer pattern among workers of Neste Group.

To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. The statistical significance was tested by the Mantel-Haenszel χ^2 test, on the presumption that the number of observed cases followed a Poisson distribution.

Results

There were 7,512 men and 1,942 women under follow-up in the cohort. The numbers of person-years were 133,312 and 33,553, respectively (Table 1). The mean length of follow-up of a person was thus 17.7 years. Forty percent of the workers had been employed for more than 5 years by Neste Group between 1971 and 1984.

Overall Cancer

During the follow-up period, 241 cancer cases were diagnosed in males and 69 in females; the expected numbers were 253 and 64, respectively. The SIR among male workers was thus 0.95 (95% confidence interval [95% CI], 0.83–1.07), and among women was 1.07 (95% CI, 0.83–1.35). The overall cancer risk decreased with increasing time at work. After 5 working years, the SIR was 0.88 (95% CI, 0.74–1.04; 129 observed cases). The site-specific results for the whole cohort are given in Table 2.

Kidney Cancer

The incidence of kidney cancer was significantly elevated (SIR, 1.97; 95% CI, 1.29–2.88); the SIR

TABLE 1
Number of Workers Under Follow-Up (*n*) and Number of Person-Years at Risk in 1971–1994, by Occupational Category, Department, and Age

Category	Males		Females	
	n	Person-Years	*n*	Person-Years
Total	7,512	133,312	1,942	33,553
Age*				
<30 years	4,571	28,242	1,287	9,207
30–59 years	2,851	97,495	648	22,654
≥60 years	90	7,574	7	1,691
Occupation†				
Clerical	2,268	44,465	1,415	24,827
Technical	1,130	19,226	224	3,591
Blue-collar	5,168	90,839	342	6,093
Department†				
Porvoo Refinery	4,514	79,293	975	16,728
Naantali Refinery	1,199	22,087	243	4,430
Porvoo Chemicals	1,250	15,287	161	1,936
Head office	902	15,255	614	10,203
Unknown	971	19,266	132	2,727

* Age of persons defined at the beginning of follow-up.
† A cohort member may belong to several categories.

TABLE 2
Observed (Obs) and Expected (Exp) Numbers of Cancer Cases and Standardized Incidence Ratios (SIR) With 95% Confidence Intervals (CI) Among Finnish Oil and Chemicals Company Workers (n = 9,454) in 1971–1994, by Site

Primary Site	Obs	Exp	SIR	95% CI
All sites	310	318	0.98	0.87–1.08
Stomach	21	21	1.00	0.62–1.52
Colon	14	15	0.95	0.52–1.59
Rectum	8	11	0.73	0.31–1.43
Liver	2	4	0.54	0.07–1.94
Pancreas	6	10	0.59	0.22–1.27
Larynx	6	5	1.31	0.48–2.84
Lung, bronchus	50	57	0.87	0.65–1.15
Breast	53	23	**1.50**	1.05–2.08
Cervix uteri	1	2	0.57	0.01–3.17
Corpus uteri	3	3	0.86	0.18–2.51
Ovary	3	5	0.66	0.14–1.92
Prostate	15	24	0.63	0.35–1.03
Testis	4	4	0.89	0.24–2.28
Kidney	26	13	**1.97**	1.29–2.88
Bladder	11	13	0.82	0.41–1.47
Skin melanoma	12	14	0.86	0.45–1.51
Other skin*	11	7	1.67	0.84–2.99
Brain/nervous system	19	18	1.08	0.65–1.68
Thyroid	7	6	1.16	0.47–2.39
Soft tissues	2	3	0.63	0.08–2.27
Hodgkin's disease	7	5	1.35	0.54–2.79
Non-Hodgkin's lymphoma	12	10	1.24	0.64–2.17
Leukemia	9	9	1.02	0.47–1.93

* Excludes basal cell carcinoma.

increased to 2.39 (95% CI, 1.37–3.88; 16 cases) with a minimum of 5 years at work. The excess in kidney cancer was attributable to men only (25 observed cases). Among them, the SIR was 2.13 (95% CI, 1.38–3.13) and it was highest in the follow-up category of 5–14 years after first known employment (12 cases; SIR, 2.61; 95% CI, 1.35–4.56). The relative risk of kidney cancer among men did not vary by main type of work: it was 2.31 (95% CI, 1.37–3.64; 18 cases) for blue-collar workers, 2.40 (95% CI, 0.78–5.60; 5 cases) for technical workers, and 2.51 (95% CI, 1.30–4.38; 12 cases) for clerical staff.

The risk of kidney cancer in males was higher in oil refineries (Porvoo: 12 cases, SIR 2.51, 95% CI 1.30–4.39; Naantali: 7 cases, SIR 2.32, 95% CI 0.93–4.78) than in other departments (chemicals: 2 cases, SIR 1.84; head office: 3 cases, SIR 1.79; unknown location: 4 cases, SIR 1.48). In the oil refineries, the SIR among male technical/clerical staff was somewhat higher (combined SIR, 3.13; 95% CI, 1.66–5.34; 14 cases) than among blue-collar workers (SIR, 2.41; 95% CI, 1.25–4.22; 12 cases). However, 6 of the 14 men classified as technical/clerical workers had also worked in blue-collar tasks. The SIR among male workers increased with increasing time at refinery work (Table 3).

Other Cancers

The decrease in overall cancer incidence was attributable to low lung cancer risk after 5 years of work. The deficit was only seen in oil refineries (6 cases observed vs 23 expected; SIR, 0.26; 95% CI, 0.10–0.57). For those workers with less than 5 years of known employment in refineries, the incidence of lung cancer was above the Finnish average (Table 3). There was no difference in lung cancer risk between the blue-collar and clerical/technical staff in the refineries.

The relative risk of breast cancer in women was significantly high (SIR in the whole cohort, 1.50; 95% CI, 1.05–2.08). The relative risk increased by increasing time since first employment. In the follow-up category ≥5 years since first known employment, it was highest among clerical workers (23 cases; SIR, 1.70; 95% CI, 1.08–2.56) or any workers in the head office (14 cases; SIR, 2.29; 95% CI, 1.25–3.84).

There was an non-significant excess in the incidence of non-melanocytic skin cancer (basaliomas excluded) among blue-collar men in the whole cohort (8 cases; SIR, 2.04; 95% CI, 0.88–4.02). Three of the cases were observed during the first 5 years since first known employment (SIR, 9.54; 95% CI, 1.97–27.9). However, the skin cancers of refinery workers were merely found among those with longer employment (Table 3).

Among male blue-collar workers, there was a borderline significant excess of non-Hodgkin lymphomas (11 cases; SIR, 2.01; 95% CI, 1.00–3.59). The SIR was above 1.0 in all departments except the head office. The relative risk decreased with increasing time since first known employment and with increasing time at refinery work (Table 3); all cases were diagnosed in workers less than 60 years of age.

The observed number of leukemias was equal to that expected in the whole cohort (Table 2) and in all subcategories analyzed separately.

Discussion

The cohort consisted of all persons who had worked for Neste Group for at least 3 months during 1967–1982 and who had not died before 1971. From January 1, 1971, onward, the identification of cohort members and follow-up for deaths and emigration were complete for the period of this study. The cancer registration system in Finland is also virtually complete[2]

TABLE 3
Observed (Obs) and Expected (Exp) Numbers of Cancer Cases and Standardized Incidence Ratios (SIR) With 95% Confidence Intervals (CI) Among Male Oil Refinery Workers (n = 7,512) in 1971–1994, by Cancer Site and Duration of Employment*

	Time at Work <5 Years				Time at Work ≥5 Years			
Primary Site	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All sites	67	61.8	1.09	0.84–1.38	82	101.3	0.81	0.64–1.00
Lung, bronchus	15	10.9	1.38	0.77–2.27	6	22.9	**0.26**	0.10–0.57
Kidney	4	2.5	1.58	0.43–4.05	15	5.2	**2.87**	1.61–4.73
Skin, non-melanoma†	1	1.4	1.43	0.17–5.16	5	2.2	2.26	0.73–5.26
Non-Hodgkin's lymphoma	6	2.4	2.48	0.91–5.40	1	3.3	0.30	0.01–3.19
Leukemia	1	2.4	0.41	0.01–2.28	3	2.8	1.09	0.23–3.19

* Only work periods during 1971–1984 were known.
† Excludes basal cell carcinoma.

and the computerized record linkage procedures precise.[3] Therefore, technical incompleteness does not cause bias in the results.

The cohort included also workers with relatively short periods of employment. However, the time periods of employment for those workers employed between 1971 and 1984 were known and could be taken into account in the analysis whenever there were signs of cancer risks possibly associated with work-related exposures. The structure of the basic register did not allow more detailed occupational subcategories than those used in the present analysis. There are plans to study occupational histories and specific exposures in detail for selected cancer sites in further case-referent studies nested in the present cohort.

Bias caused by non-occupational lifestyle factors is possible. In a four-category social grouping used in the 1970 Population Census of Finland,[4] the clerical workers of the present cohort would be primarily classified into the two highest social classes and the blue-collar workers to the two lowest ones. The overall cancer incidence among working-aged Finnish men increases and among women decreases towards the lower social class.[5] Cancers of the kidney and breast typically show higher incidence rates among people of high social class. Hence, the expected numbers for these sites, eg, among clerical workers, would have been somewhat higher if social class–specific reference rates could have been used instead of average incidence rates of the whole Finnish population. Unfortunately, social class–specific rates are not available for the whole follow-up period and for all birth cohorts.

The geographical variation in cancer incidence—highest rates of, eg, cancers of the kidney and breast in southern Finland[6]—is largely attributable to the geographical social class patterns. If the incidence rates of the Helsinki area (where the majority of the cohort members were working) had been used as a reference, the SIRs for cancers of the breast and kidney would have been reduced by about 10%. Use of an alternative reference population would not have changed the conclusions of this study.

The overall cancer incidence rate among workers of the Neste Group was somewhat lower than that in the general population. This deficit was attributable to the very low lung cancer risk in oil refineries. Apparently, male oil refinery workers smoke much less than other men. There are temporal smoking restrictions in oil refineries, and it seems likely that workers with a strong tobacco addiction were not been able or willing to continue in oil refinery work for a longer period. A decreased lung cancer risk (though not as strong as in the Finnish cohort) has been seen in most mortality studies of oil refinery workers.[7]

The SIR of breast cancer was especially high in women who had been working for a longer time in the head office located in one of the most well-to-do areas in Finland. This excess is of the same magnitude as that seen among occupations such as female managers, public relations officers, office cashiers, typists, architects, etc, in any workplace in Finland.[5] One of the main explanations for this risk increase is that career-oriented women tend to have fewer children and delay pregnancy until they are older than women in general. It is unlikely that any occupational exposure would account for the increased risk of breast cancer among employees of the Neste Group.

There was a significant two- to threefold relative risk of kidney cancer among male oil refinery workers in our cohort. This increase came up more than 5 years after first employment, which points toward a causal work-related association. However, the relative risk was higher among technical and clerical workers (SIR, 3.1) than among blue-collar workers (SIR, 2.4). It is known that the incidence of kidney cancer among men in social classes I-II is some 20% above and in social classes II-IV 10% below the average of the economically active

population.[5] If the SIRs for technical/clerical and blue-collar workers are corrected by these factors, respectively, the SIRs in both groups will end up at a rate close to 2.6. Furthermore, almost every second clerical/technical worker with kidney cancer also had some work history in blue-collar occupations. This type of mixture of different types of jobs among kidney cancer patients was essentially more common than that among cohort members in general. The role of specific exposures needs to be confirmed in separate in-depth studies. At the present level of knowledge, it seems justified to conclude that the elevated risk of kidney cancer is probably attributable to occupational exposures in oil refining. The finding does not seem to be explained by the main potential confounder, tobacco smoking, since a deficit of lung cancer was observed. Unleaded gasoline causes kidney cancer in male rats.[8] Increased risk has been described in humans exposed to automotive gasoline.[7,9–11] Constituents of gasoline are thus strong candidates as for the causal agents for the increased risk of renal cancer.

Acknowledgments

Thanks are due to Mrs Annukka Ojamo and Drs Pertti Kaitaniemi and Rolf Ahlberg from Neste Group for creating the basic study cohort and assisting with the qualitative exposure evaluation.

References

1. International Agency for Research on Cancer (IARC). Occupational exposures in petroleum refining: crude oil and major petroleum fuels. In: *IARC Monographs on the Evaluation of Carcinogenic Risks in Humans*, vol 45. Lyon, France: IARC; 1989.
2. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry: experience in Finland. *Acta Oncol.* 1994;33:365–369.
3. Pukkala E. Use of record linkage in small-area studies. In: Elliot P, Guzick J, English D, Stern R, eds. *Geographical and Environmental Epidemiology*. Oxford, UK: Oxford University Press; 1992: 125–131.
4. Central Statistical Office of Finland. *Population Census 1970: Occupation and Social Position. Official Statistics of Finland VI*, C:104, vol IX. Helsinki, Finland: Central Statistical Office of Finland; 1974.
5. Pukkala E. *Cancer Risk by Social Class and Occupation: a Survey of 109,000 Cancer Cases Among Finns of Working Age. Contributions to Epidemiology and Biostatistics,* vol 7. Basel, Switzerland: Karger; 1995.
6. Pukkala E, Gustavsson N, Teppo L. *Atlas of Cancer Incidence in Finland.* [Cancer Society of Finland Publication No. 37.] Helsinki, Finland: Finnish Cancer Registry; 1987.
7. Rushton L. *The Institute of Petroleum Epidemiological Study: Refinery Study Principal Results 1951–1989.* London, England: Thames Polytechnic School of Mathematics, Statistics and Computing; 1991.
8. MacFarland HN, Ulrich CE, Holdsworth CE, Kitchen DN, Halliwell WH, Blum SC. A chronic inhalation study with unleaded gasoline vapor. *J Am Coll Toxicol.* 1984;3:231–247.
9. Partanen T, Heikkilä P, Hernberg S, Kauppinen T, Moneta G, Ojajärvi A. Renal cell cancer and occupational exposure to chemical agents. *Scand J Work Environ Health.* 1991;17:231–239.
10. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cell cancer study. IV: Occupation. *Int J Cancer.* 1995;61:601–605.
11. Lynge E, Andersen AA, Nilsson R, et al. Risk of cancer and exposure to gasoline vapors. *Am J Epidemiol.* 1997;145:449–458.

CHARLES TURNER THACKRAH (1795–1833)

Although his life was shortened by tuberculosis, Thackrah had a profound impact on occupational medicine in the English-speaking world. He was highly trained for his time but chose to practice in Leeds, a city undergoing great transformation because of the Industrial Revolution. (Compare him, for example, with the character Dr Lydgate in George Eliot's *Middlemarch.*) He became interested in occupational health, and in 1831 published the first work on occupational medicine in English: *The Effects of the Principal Arts, Trades and Professions, and of Civic States and Habits of Living, on Health and Longevity, with Suggestions for the Removal of many of the Agents which Produce Disease and Shorten the Duration of Life.* It was a masterpiece, noteworthy for its excellent clinical descriptions of lead toxicity and other disorders, but thoroughly modern in concept, emphasizing prevention and the control of exposure.

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