A 39-Year Follow-up of the U.K. Oil Refinery and Distribution Center Studies: Results for Kidney Cancer and Leukemia

by Lesley Rushton

This paper presents briefly some of the principal results of a mortality analysis of a cohort of workers employed for at least 1 year between 1950 and 1975 at eight oil refineries and approximately 750 distribution centers in the U.K., together with detailed results for kidney cancer and leukemia. Over 99% of the workers were successfully traced. Their mortality was compared with that of all males in the national population. The mortality from all causes of death is lower than that of the comparison population in both studies, and reduced mortality is also found for many of the major nonmalignant causes of death. In the refinery study, some increased mortality patterns are found for diseases of the arteries, and no healthy worker effect is found in the distribution center study for ischemic heart disease. Mortality from all neoplasms is lower than expected overall in both studies, largely due to a deficit of deaths from malignant neoplasm of the lung. Mortality from malignant neoplasm of the kidney is increased overall in the distribution center study, and in drivers in particular. The mortality from this disease increases with increased time since first exposure. The observed deaths from leukemia are slightly less than expected in the refinery study and slightly more than expected in the distribution center study. One refinery shows increased mortality due to in myeloid leukemia, and mortality is increased among refinery operators. Mortality is also raised in distribution center drivers, particularly for myeloid leukemias, including acute myeloid leukemia.

Introduction

The aim of the Institute of Petroleum (IP) Epidemiological Study was to examine patterns of mortality of employees in oil refineries and distribution centers, taking into account such factors as age and type of occupation. The initial study followed up the employees from 1951 to 1975. This paper describes briefly some of the principal findings from an extension of this follow-up to 1989 and gives detailed information on the leukemia and kidney cancer findings.

Review of the Literature

Many early studies have documented the carcinogenic properties of oil both in experimental studies (1–5) and the occupational field (6–8). Conflicting results have been reported on oil mist exposure, in particular, its effect on lung cancer (9–11). Over 70 papers and unpublished reports document past or on-going studies of the mortality and, less often, the morbidity, of refinery populations. Although there is considerable variation in the dates, length of follow-up period and numbers in the studies, most of them find low overall mortality, which is also reflected in many of the nonmalignant disease groups. Most of the papers focus on malignant disease with increased mortality patterns being found for several malignant disease groups, although with much variation between the studies. A detailed review of these is given in the report of the principal results of the Institute of Petroleum (IP) refinery study (12,13). Four papers (14–17) also provide narrative epidemiological reviews of studies of oil refinery workers.

There have been relatively few studies of workers at oil distribution centers, although they have been included in some broader studies of the oil industry (18–20). Harrington (14) reviews both the petroleum manufacturing industry and the distribution industry with regard to all diseases.

Considerable interest has been shown in the effect of gasoline exposure on the kidneys (21). In a paper given at a 1983 workshop, Phillips (22) reviewed six case–control studies, five (23–27) of which showed a positive association between hydrocarbon exposure and glomerulonephritis, although he pointed out several methodological weaknesses in these studies.

Particular attention has been focused on leukemia (and other diseases of the haematopoietic system) and kidney

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cancer. The association between exposure to benzene and leukemia has been discussed in many studies of populations outside the oil industry (28-30) and increases in mortality have been found in several oil refinery populations (31-34). Nonsignificant excesses were found in blending and packaging plant workers (35) and among producing and pipeline workers (36). Christie (37) reported a significantly increased incidence of leukemia, especially myeloid leukemia, compared with rates obtained from cancer registries.

Although animal studies have shown some association between hydrocarbon exposure and kidney cancer (38,39), an extensive review of this problem in humans at a workshop in 1983 failed to come to any firm conclusion. Generally, any excesses are small (40-42) or show no association (21,43,44).

A few studies of resident populations in areas where the petroleum industry is concentrated have suggested links between certain diseases and the petroleum industry (45-49). However, as Harrington (44) points out, these types of studies are, at best, hypothesis-generating exercises, and should therefore be interpreted with caution.

Several studies have carried out personal air sampling or taken urine samples to investigate the exposure to benzene of workers at bulk marketing terminals (50,51) or service stations (52-56). A proportional mortality study (57) of all deaths over a 10-year period in New Hampshire found high proportional mortality ratios (PMRs) for service station workers for leukemia, suicide, emphysema, and mental conditions. De Silva (58) measured blood lead levels of gasoline pump attendants in Melbourne and concluded that the levels were lower than the accepted level of concern. Other studies have looked at the effect of diesel exhaust emissions (59,60).

**Earlier Reports of the Institute of Petroleum Studies.**

The overall mortality in the previously reported results for the follow-up to 1975 (61,62) was considerably lower than expected in both the IP studies, as was the mortality from stroke, bronchitis, and pneumonia. Heart disease was also low in the refinery study, but there was no evidence of a healthy worker effect for ischemic heart disease in the distribution center study. The lowered mortality from all neoplasms in both studies was due to a large deficit of observed deaths from lung cancer. Increased mortality patterns were found in several refineries for malignant neoplasms of the esophagus, stomach, intestines, and rectum, with significantly more deaths than expected from malignant neoplasms of the nasal cavities and sinus and from melanoma. Mortality from myelofibrosis and diseases of the lymphatic and haematopoietic tissue was slightly raised overall in the distribution center study.

**Methods**

Full details of the feasibility study carried out before the initial data collection, the reasoning behind the choice of data items to be collected, and the analysis methods used are given elsewhere (61,62). Briefly, the study includes all men with a length of service of at least 1 continuous year between January 1, 1950, and December 31, 1975 at eight refineries and approximately 750 distribution centers in the U.K. In this paper the refineries are denoted by A,B,C,D,F,G,H, and J, and the distribution center study companies by 1, 2, and 3.

Detailed information on data collected, tracing and flagging procedures, data validation, comparison populations, and calculation of expected deaths is reported elsewhere (12,13,63,64). Briefly, identification data, dates of employment, last job (or present job for those in employment on January 1, 1976), and National Health Service (NHS) and National Insurance (NI) numbers, where available, were collected for each study member.

In the second follow-up from 1976 to 1989, reported here, data for all the study population still alive on December 31, 1975 were sent to the National Health Service Central Register (NHSCR), which identified those subjects who had since died and provided the death certificates. The records for all the others were then flagged. This flagging procedure enables the NHSCR to identify the study population who die in the future and to provide the death details. This contrasts with the first follow-up in which no attempt at long-term collection of death certificates was made.

The death certificates provide multiple causes of death coded to the relevant International Classification of Disease (ICD) revision. The causes were grouped for analysis into the ICD “A” list. Those who emigrated were assumed to be alive up to the date of emigration, and this date was therefore their study-end date.

As in the analysis of the first follow-up (61,62), the expected deaths were calculated by applying the age- and calendar-period-specific standard death rates to the five-year age- and calendar-period person-years at risk in the study cohort. In the refinery study, the England and Wales rates were used for the six English or Welsh refineries and corresponding Scottish rates for the two Scottish refineries. As the distribution centers are well-scattered throughout the U.K., it was decided, as before, not to analyze the data in Scotland and 10 standard regions in England and Wales separately, as the numbers would be reduced too much for analysis. The rates for England and Wales were thus used in this study.

The standardized mortality ratio (SMR) is calculated from the ratio of observed deaths over the expected deaths multiplied by 100. The 95% confidence interval also has been given for each SMR (19). No formal adjustment has been made to take account of known regional or social class variations in death rates, but these have been used to aid the interpretation of the results.

Two approaches to the analyses were used, as in the previously reported papers (61,65). The first approach, the *a posteriori* approach, involved examination of the patterns and magnitude of mortality using the SMR and its 95% confidence interval. The second *a priori* approach involved using the study to examine hypotheses suggested by other studies.

**Results**

Table 1 shows the status of the total study populations on December 31, 1989. There are 34,569 men in the refinery
study (compared with 34,781 on December 31, 1975), 22,600 alive, 10,193 dead, 1,691 emigrated, and 85 untraced. There are 23,306 men in the distribution center study, 14,168 alive, 8,743 dead, 297 emigrated, and 98 untraced. As before, untraced subjects were not included in the analyses. Included in the alive groups are 1004 men in the refinery study and 723 in the distribution center study whom it was not possible to flag at the NHSCR but who have been traced as alive on December 31, 1989, through the National Insurance records. Those dead include 70 in the refinery study and 66 in the distribution center study for whom it was not possible to obtain a death certificate. In the analyses, all these records are taken as dead, cause unknown. The person-years of observation has increased in the second follow-up by 62% to approximately 93,000 in the refinery study and by 58% to approximately 625,000 in the distribution center.

Mortality Results

The general results from both studies are first described briefly [full details are given elsewhere (12,13,63,64)], followed by a report of the findings for kidney cancer and leukemia. Table 2 gives the observed and expected deaths, the SMR, and the 95% confidence interval for the SMR for all causes of death and all neoplasms for the total refinery and distribution center populations; separately for the first follow-up period, 1951–1975; the second follow-up period, 1976–1989; and the total follow-up period, 1951–1989.

The SMRs for all causes are approximately the same for the two follow-up periods in the refinery study. In the distribution center study, the SMR in the second follow-up period is higher than in the first but still markedly low, showing a continuation of the healthy worker effect. There is a tendency for the all-cause mortality in both studies to increase with increasing time since first exposure and earlier year of starting work. The SMRs for the two follow-up periods for all neoplasms in the refinery study are identical. In the distribution center study, the mortality from all neoplasms is markedly low in the first follow-up period, but the observed deaths are only slightly less than those expected in the second period.

Table 3 gives the observed and expected deaths, SMR, and 95% confidence interval for selected nonmalignant causes of death, separately for the total populations of the two studies. The low overall mortality is also reflected in many of these diseases, such as cerebrovascular disease, hypertensive heart disease, pneumonia, and bronchitis. The mortality is generally low in the nonmalignant diseases for all the job groups except a) laborers/general manual workers in both studies, where it is raised in several disease groups (e.g., cerebrovascular disease, diseases of the arteries, and pneumonia); b) security men in the distribution center study, for whom mortality is raised by about 5%; and c) fire and safety workers, drivers, and storemen in the refinery study, where the observed deaths approximately equal those expected.

In the refinery study, the only large, nonmalignant disease group to show consistently increased mortality patterns across several refineries, age, and job groups is diseases of the arteries. There is a marked trend for increasing mortality with increasing time since first exposure for this disease group. The healthy worker effect in the distribution center study is not reflected in ischemic heart disease. Increased mortality is found in operators, general manual workers, and clerical, administrative, and managerial staff in company 2. The SMRs are particularly high for men between 45 and 55 years old at death and for those between 60 and 70 years old. Mortality increases with increasing calendar period of follow-up until 1975 and then declines.

Table 4 gives the observed and expected deaths, SMR, and its 95% confidence interval for selected malignant neoplasms. The higher mortality in the second follow-up period for all neoplasms in the distribution study is also reflected in many of the individual groups of neoplasms, whereas the opposite trend is generally found in the refinery study. The low mortality from all neoplasms in both studies is largely due to a deficit of observed deaths from malignant neoplasm of the lung, although the trend is for increasing mortality from this disease as the calendar period of follow-up increases. Mortality is slightly increased for malignant neoplasm of the lung for operators and general manual workers in the distribution center study and is raised for riggers, storemen, and laborers in the refinery study.

There are some increased mortality patterns in the refinery study from malignant disease groups, for example, from malignant neoplasms of the stomach, esophagus, intestine, rectum, larynx, and prostate. These tend to be more isolated results and are not consistent across the refineries or job groups. The increased mortality from melanoma found in the first follow-up period in this study has also continued in the second follow-up period, although to a slightly lesser extent, being increased in five of the eight refineries and across several job groups. There are also a few isolated increased mortality patterns in malignant disease groups in the distribution center study, namely, malignant neoplasms of the intestines, larynx, and prostate, and other neoplasms of the lymphoid tissue. Mortality is increased for operators from malignant neoplasm of the prostate in both studies.

Kidney Cancer. The observed deaths from malignant neoplasm of the kidney in the refinery study are approximately the same as those expected (Table 4). No raised mortality patterns are found in any subgroup analyses for this study.

Table 5 gives the observed and expected deaths, SMRs, and 95% confidence intervals for malignant neoplasm of the kidney in the distribution center study by company and
selected subgroups. Mortality is increased overall and, in particular, at companies 2 and 3. The majority of the 53 kidney cancer deaths were coded to ICD 1890, malignant neoplasm of the kidney except pelvis, with only 1 being renal pelvis, 2 ureter, and 2 site unspecified. Mortality from kidney cancer tends to decline as the year of entry increases, with a corresponding increase with the time since first exposure up to 30–39 years. Mortality is increased in drivers, 15 of whom have 20 or more years service. There are 11 other deaths where malignant neoplasm of the kidney is a contributory cause of death (4 of whom are drivers).

**Leukemia.** The mortality from leukemia is slightly increased overall in the distribution center study and slightly lower than expected in the refinery study, both patterns being similar in the two follow-up periods. Table 6 gives the observed and expected deaths, SMRs, and 95% confidence intervals for leukemia by type separately for both studies. Only other myeloid leukemia in the refinery study shows markedly increased mortality (as judged by the confidence interval). Monocytic leukemia in the refin-
ery study and acute myeloid in the distribution center study are increased to a lesser extent. There is a tendency for the mortality from all leukemia to increase with increased time since first exposure in the distribution center study, but there is no clear pattern in the refinery study.

Only one refinery shows increased mortality from leukemia, namely, refinery D, where there are 14 observed deaths from leukemia (E = 8.6, SMR = 164, 95% CI, 89–275). Twelve of these are myeloid leukemias (E = 4.98, SMR = 241, 95% CI, 124–421). This refinery shows excess mortality for acute myeloid leukemia (O = 7, E = 3.3, SMR = 210, 95% CI, 84–433) and other myeloid leukemia (O = 2, E = 0.1, SMR = 1621, 95% CI, 196–5854). Twenty-one of the 68 refinery leukemia deaths are in operators (E = 17.3, SMR = 123, 95% CI, 75–186) and 6 out of the 7 other myeloid leukemias are in operators.

In the distribution center study, increased mortality is found in company 2 for lymphatic leukemia, in particular, chronic lymphatic leukemia (O = 15, E = 8.52, SMR = 176, 95% CI, 99–290) and to a much lesser extent in acute myeloid leukemia (O = 17, E = 13.15, SMR = 129, 95% CI, 75–207). Twenty-two of the 46 deaths from all leukemia from company 2 started work before 1940 (E = 14.1, SMR = 156, 95% CI, 98–236).

Table 7 gives the observed and expected deaths, SMRs, and 95% confidence intervals by type of leukemia for drivers. Mortality from all leukemia is raised in the total distribution center study population and, in particular, at company 2 (O = 21, E = 14.6, SMR = 133, 95% CI, 89–220). Nineteen of the leukemia deaths in drivers are myeloid, with thirteen being acute myeloid.

There are also 15 other deaths in the refinery study and 12 in the distribution center study where leukemia is a contributory cause of death, 17 of these being chronic lymphatic leukemias.

**Discussion**

In both the studies, over 99% of the population was successfully traced. Death certificates were obtained for all but 0.7% of the deaths. Before commenting on the results obtained in this study, it is appropriate to indicate briefly some of the limitations of this type of cohort study, the problems inherent in interpreting the results, and outline some of the possible causes of variation in mortality. These include inaccuracy in diagnosis, classification and coding of the causes of death, and omission of information from the death certificates.

The SMR (and its confidence interval) has been used in this study to describe the patterns of mortality and to search for consistency across variables and subgroups examined. The interpretation of subgroup analyses when the all-cause mortality is low, and the impact of the reanalysis of data in a cohort study after an additional 14 years follow-up needs to be considered. Differences in the workforce or type of work place between the refineries and the three distribution center companies may partly account for noncomparability in the mortality patterns.

The large size of the cohort was the reason that only the last job title for leavers (or current title for those in employment on December 31, 1975) could be collected to define occupational group. In addition, no lifestyle information, such as data on smoking and alcohol, was collected so that caution is necessary when interpreting the results.

The overall relative mortality of the two study populations remains low, continuing to exhibit the healthy worker effect. This lowered mortality is also reflected in many of the numerically large, nonmalignant causes of death such as cerebrovascular disease, pneumonia, and bronchitis. Some of the individual job groups show slightly increased
mortality from specific nonmalignant disease groups, in particular, stroke and heart disease in laborers/general manual workers in both studies, and bronchitis in security men in the distribution center study. However, this mortality is, in general, not greater than that of men of a similar social status in the male population of England and Wales.

The consistently raised mortality from diseases of the arteries in the refinery study and from ischemic heart disease in the distribution center study is more difficult to interpret, being high across several age and job groups. The patterns for these diseases are in contrast to those of most of the heart disease groups, where the mortality is generally low.

Mortality from all neoplasms in both studies is lower than expected, due mainly to marked deficits in malignant neoplasm of the lung. It has been suggested that oil industry employees may smoke somewhat less than the general population (66) and that there is unlikely to be serious confounding of the results due to smoking in studies where this information is not available (67).

As discussed previously, concern has been expressed about increased mortality from such diseases as malignant diseases of the prostate, kidney, and brain; leukemia; and other lymphatic neoplasms (22, 37, 38, 68). In both studies, the slightly increased mortality from malignant neoplasm of the prostate continues in the second follow-up period, with operators again having markedly increased mortality. There are no increased mortality patterns from malignant neoplasm of the brain in either study.

There were no increased mortality patterns from malignant neoplasm of the kidney in the refinery study. A review of the epidemiological evidence from 11 refinery studies (38) suggested that, although they were not generally supportive of an association between kidney cancer and gasoline, there was some evidence of a small kidney cancer excess among older workers, or among workers exposed for long periods. Mortality from malignant neoplasm of the kidney is increased overall in the present distribution center study and in drivers in particular. There is a tendency for the mortality to increase with increasing time since first exposure.

Particular interest has been paid to mortality from leukemia and its possible relation with exposure to benzene and other solvents (28, 30). The total observed deaths from leukemia in both studies are once again similar to those expected. Markedly increased mortality is found in only one refinery, and from myeloid leukemia in particular. Just less than one-third of the leukemia deaths in the refinery study are in operators. In the distribution center study, markedly increased mortality is found in only one company. Nearly half of the leukemia deaths are in drivers, and mortality is increased for drivers for myeloid leukemias, and in particular acute myeloid leukemia. A nested case-control study carried out on the leukemia deaths after the first follow-up period in the refinery study found the risk of leukemia in those with high or medium exposure to benzene to be twice that of those with low exposure (69).

Although the contributory causes of death on the death certificates were coded and entered into the database, no detailed analyses of these have so far been carried out. However, the deaths with a malignant neoplasm as a contributory cause were investigated. The ratio of the number of total mentions of each malignant neoplasm over the number of underlying causes of that disease group in the study population was compared to the ratios from the population of England and Wales (70) and generally found to be similar. The ratios for malignant neoplasms of the kidney and bladder for the distribution center study population are higher than those of England and Wales, which may suggest a possible underreporting of these diseases as the underlying cause of death (71) and may perhaps strengthen concern about increased mortality from malignant neoplasm of the kidney.

The specific issues of concern reported here can be further examined using nested case-control studies. Deaths from leukemia and malignant neoplasm of the kidney could be matched to controls selected from the rest of the study population. Further details such as job history or exposure to potential hazards can then be efficiently obtained for the limited number of cases and controls.

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REFERENCES

1. Berenblum, I., and Shoental, R. Carcinogenic constituents of coal-tar. Br. J. Cancer 1: 157–165 (1947).
2. Gilmah, J. P. W., and Vesselevitch, S. D. Cutting oils and squamous-cell carcinoma. Part II: An experimental study of the carcinogenicity of two types of cutting oils. Br. J. Ind. Med. 12: 244 (1965).
3. Gradiiski, D., Vinot, J., Zissu, D., Limasset, J. C., and Lafontaine, M. The carcinogenic effect of a series of petroleum-derived oils on the skin of mice. Environ. Res. 32: 258–268 (1983).
4. Holland, J. W., Rahn, R. O., Smith, L. H., Clark, B. R., Chang, S. S., and Stephens, T. J. Skin carcinogenicity of synthetic and natural petroleums. J. Occup. Med. 31: 614–618 (1979).
5. Jarvholm, B., and Lavenius, B. Mortality and cancer morbidity in workers exposed to cutting fluids. Arch. Environ. Health. 42: 361–366 (1987).
6. Cruickshank, C. N. D. Occupational dermatitis and industrial skin cancer. Proc. R. Society of Med. 7: 611–612 (1952).
7. Henry, S. A. Cancer of the Scrotum in Relation to Occupation. Oxford University Press, London, 1946.
8. Miller, B. G., Cowie, H. A., Middleton, W. G., and Seaton, A. Epidemiological studies of Scottish oil shale workers: III Causes of death. Am. J. Ind. Med. 9: 433–446 (1986).
9. Decouffe, F. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J. Natl. Cancer. Inst. 61: 1025–1030 (1978).
10. Pasternack, B., and Ehrlich, L. Occupational exposure to an oil mist atmosphere—a twelve year mortality study. Arch. Environ. Health. 25: 286–294 (1972).
11. Moss, E., Scott, T. S., and Atherley, G. R. C. Mortality of newspaper workers from lung cancer and bronchitis 1962–1956. Br. J. Ind. Med. 29: 1–14 (1972).
12. Rushton, L. The Institute of Petroleum Epidemiological Study. Distribution Centre Study Principal Results 1961–1989. Institute of Petroleum, London, 1991.
65. Rushton, L., and Alderson, M. R. An epidemiological survey of eight oil refineries in Britain. Br. J. Ind. Med. 38: 225–234 (1981).
66. Van Peenan, P. F. D., Blanchard, A. G., and Wolkonsky, M. D. Smoking habits of oil refinery employees. Am. J. Public Health. 74: 1408–1409 (1984).
67. Siemiatycki, J., Wacholder, S., Dewar, R., Cardis, E., Greenwood, C., and Richardson, L. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. J. Occup. Med. 30: 617–625 (1988).
68. Reeve, G. R., Bond, G. G., Lloyd, J. W., Cook, R. R., Waxweiler, R. J., and Fishbeck, W. A. An investigation of brain tumors among chemical plant employees using a sample-based cohort method. J. Occup. Med. 25: 387–393 (1983).
69. Rushton, L., and Alderson, M. R. A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers. Br. J. Cancer 43: 77–84 (1981).
70. Office of Population Censuses and Surveys. Mortality Statistics Cause 1986, Series DH2, No.13. Her Majesty's Stationery Office, London, 1988.
71. Wong, O., Rockette, H. E., Redmond, C. K., and Heid, M. Evaluation of multiple causes of death in occupational mortality studies. J. Chronic Dis. 31: 183–193 (1978).