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Nested case-control study of leukaemia, multiple myeloma, and kidney cancer in a cohort of petroleum workers exposed to gasoline

Otto Wong, Lisa Trent, Fran Harris

Abstract

***Objectives*—This nested case-control study was based on data in a cohort study of more than 18 000 petroleum distribution workers exposed to gasoline, which contains about 2%–3% benzene. Risks of leukaemia, acute myeloid leukaemia, multiple myeloma, and kidney cancer were examined relative to exposure to gasoline.**

***Methods*—For each case, up to five individually matched controls were selected. Analyses based on the Mantel-Haenszel procedure as well as univariate and multivariate conditional logistic regression were performed for each disease category. Jobs with similar exposures were grouped into homogeneous categories for analysis. Several quantitative indices of exposure to gasoline were used in the analyses: duration of exposure, cumulative exposure, frequency of peak exposure, and time of first exposure.**

***Results*—No increased risks for the four cancers were found for any job category. Analyses with logistic regression models based on duration of exposure, cumulative exposure, and frequency of peak exposure did not show any increased risk or exposure-effect relation. Time of first exposure to gasoline was also found to be unrelated to the four diseases under investigation.**

***Conclusion*—Exposure to gasoline or benzene at the concentrations experienced by this cohort of distribution workers is not a risk factor for leukaemia (all cell types), acute myeloid leukaemia, multiple myeloma, or kidney cancer.**

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Keywords: leukaemia; multiple myeloma; kidney cancer; gasoline; benzene

The present nested case-control study is based on data in a cohort mortality study of more than 18 000 United States land based or marine distribution workers with exposure to gasoline, which contains about 2%-3% benzene. The overall results of the cohort study are summarised in table 1. For further details, readers are referred to the previous reports.[1 2] In the original study design, it was proposed that case-control analyses for certain diseases of interest should be performed as well as the cohort analyses. The diseases initially chosen included total leukaemia, acute myeloid leukaemia (AML), multiple myeloma (because of benzene in gasoline), and kidney cancer (because of previous animal studies). In this

Table 1 Observed and expected deaths, SMRs (95% CIs) by cause among petroleum distribution workers exposed to gasoline in the United States

Causes of death	*Observed*	*Expected*	*SMR*	*95% CI*
All malignant neoplasms	1081	1384.42	0.78**	0.74 to 0.83
Cancer of buccal cavity and pharynx	20	42.06	0.48**	0.29 to 0.73
Cancer of digestive organs and peritoneum	289	383.64	0.75**	0.67 to 0.85
Cancer of oesophagus	29	33.86	0.86	0.57 to 1.23
Cancer of stomach	41	69.14	0.59**	0.43 to 0.80
Cancer of large intestine	118	128.94	0.92	0.76 to 1.10
Cancer of rectum	23	42.38	0.54**	0.34 to 0.81
Cancer of biliary passages and liver	20	24.60	0.81	0.50 to 1.26
Cancer of pancreas	57	76.52	0.74*	0.56 to 0.96
Cancer of respiratory system	388	468.46	0.83**	0.75 to 0.92
Cancer of larynx	15	20.35	0.74	0.41 to 1.22
Cancer of bronchus, trachea, and lung	373	444.18	0.84**	0.76 to 0.93
Cancer of bone	5	5.97	0.84	0.27 to 1.96
Cancer of skin	23	21.99	1.05	0.66 to 1.57
Cancer of prostate	88	113.94	0.77*	0.62 to 0.95
Cancer of testes and other urinary organs	2	6.06	0.33	0.04 to 1.19
Cancer of bladder	33	46.01	0.72	0.49 to 1.01
Cancer of kidney	24	32.69	0.73	0.47 to 1.09
Cancer of brain and central nervous system	26	34.26	0.76	0.50 to 1.11
Cancer of thyroid and other endocrine glands	2	2.49	0.80	0.10 to 2.90
Cancer of lymphatic and haematopoietic tissue	89	129.14	0.69**	0.55 to 0.85
Non-Hodgkin's lymphoma	19	45.23	0.42**	0.25 to 0.65
Hodgkin's disease	6	12.62	0.48	0.18 to 1.05
Multiple myeloma	17	21.52	0.79	0.46 to 1.24
Leukaemia	43	53.75	0.80	0.56 to 1.07
Acute myeloid leukaemia	18	15.38	1.17	0.69 to 1.85
Benign neoplasms	13	16.92	0.77	0.41 to 1.31
Diseases of blood and blood forming organs	10	15.43	0.65	0.31 to 1.19

*p<0.05; **p<0.01.

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Table 2 Comparison of mean exposure indices between cases and controls

Cancer	Duration of employment (years)	Duration of exposure (years)	Cumulative exposure (ppm-years THC)	Peak exposure (cumulative frequency)
Leukaemia:				
Cases	25.6	21.8	814	5832
Controls	27.9	24.4	819	6074
Acute myeloid leukaemia:				
Cases	27.1	23.2	773	4895
Controls	29.5	23.4	837	5513
Multiple myeloma:				
Cases	27.9	21.7	672	8178
Controls	27.9	25.3	800	6383
Kidney cancer:				
Cases	25.0	23.3	618	3456
Controls	26.6	23.2	866	3701

THC=total hydrocarbons.

report, we present results from the nested case-control study.

Methods and materials

The major refinement in exposure assessment in the case-control study was the development of more specific and more homogeneous job categories and exposure estimates than those in the cohort study. In the cohort study, four broad job categories were used among land based workers: terminal operators, drivers, loaders, and other terminal jobs.[3] In the case-control study, terminal operators were further broken down into four more specific groups: plantmen, warehousemen, labourers, and mechanics; and other terminal jobs into: clerks or office workers, foremen or supervisors, maintenance or yard workers, and other jobs. Quantitative exposure estimates were developed for these job categories, and used in constructing individual exposure profiles for the land based workers. Although marine jobs were also re-examined in the case-control study, because of the nature of marine jobs, only three new marine job categories were added, and few workers were classified in these new categories (pumpers, captains, and masters). For this reason, it was determined that no new information would result from case-control analyses of the marine workers. Thus, the case-control study was limited to the land based workers only.

In the nested case-control study, cases were identified from both the underlying and contributory causes of death listed on death certificates. The number of cases for the four cancers and the corresponding eighth revision of international classification of diseases (ICD-8) codes were as follows: 35 cases of leukaemia (all cell types, 204–207), 13 cases of acute myeloid leukaemia (205.0), 11 cases of multiple myeloma (203), and 12 cases of kidney cancer (189).

For each case, up to five controls were selected from the remaining cohort—that is, among workers who were still alive at the end of the study and dead workers whose death certificates did not mention any of these four diseases. Controls were randomly selected with the following restrictions. To ensure an equal opportunity for potential exposure, the controls must be alive at the time of death of the corresponding case. Furthermore, they were individually matched to the corresponding case according to the following criteria: same company, date of birth (within 2 years), and same sex.

In the cohort study an extensive assessment of exposure to gasoline was performed.[3] Exposure to gasoline was expressed in terms of parts per million (ppm) of total hydrocarbons (THCs), which represent a mixture of chemicals including aromatic and aliphatic hydrocarbons. One constituent of particular interest is benzene. According to data presented by the International Agency for Research on Cancer,[4] there is a high correlation between air concentrations of THCs and benzene from gasoline, and under various conditions, the ratio between the two is about 100:1.6.

In the case-control analyses, several exposure variables were used: duration of employment, duration of exposure, job category, cumulative exposure (product of concentration and duration of exposure expressed as ppm-years in terms of THCs or benzene), cumulative frequency of peak exposure (defined as an episode of exposure in excess of 500 ppm THCs for 15–90 minutes), and year of first exposure ($\leqslant$1948 v $\geqslant$1949). The interest in year of first exposure stems from the finding that the recommended standard for benzene before 1947 was 100 ppm, which was reduced to 50 ppm in 1947, and further reduced to 35 ppm in 1948. Thus, around 1947–9 the recommended benzene standard underwent considerable reduction.

The Mantel-Haenszel χ^2 procedure (based on individually matched sets) was used to analyse job categories and year of first exposure. Univariate and multivariate conditional logistic regression procedures were used to analyse continuous variables such as years of exposure and cumulative exposure. In the analyses, exposures of controls were truncated at the time of death of the corresponding case.

Table 3 Relative risk (95%CI) by cancer site and job category

Job (ever)	Leukaemia	Acute myeloid leukaemia	Multiple myeloma	Kidney cancer
Plantmen	0.83(0.40 to 1.72)	1.17(0.35 to 3.91)	0.55(0.15 to 2.10)	0.81(0.22 to 2.95)
Warehousemen	0.54(0.12 to 2.40)	0	1.82(0.32 to 10.4)	1.79(0.32 to 9.95)
Labourers	0.96(0.26 to 3.51)	2.42(0.21 to 27.4)	0	1.79(0.32 to 9.95)
Mechanics	0.83(0.30 to 2.34)	0.91(0.17 to 4.80)	0.45(0.05 to 3.81)	0
Clerks or office	0.53(0.18 to 1.58)	0.33(0.04 to 2.62)	0.29(0.04 to 2.28)	0.87(0.24 to 3.16)
Foremen or supervisors	1.36(0.59 to 3.18)	1.12(0.30 to 4.18)	1.92(0.43 to 8.59)	2.08(0.60 to 7.26)
Maintenance	0	0	0	1.27(0.13 to 12.5)
Drivers	0.77(0.35 to 1.71)	0.42(0.13 to 1.44)	0.91(0.21 to 3.96)	1.15(0.32 to 4.19)
Loaders	0.79(0.09 to 6.82)	0	1.00(0.11 to 9.51)	5.73(0.88 to 37.3)
Others	0.89(0.41 to 1.92)	0.62(0.17 to 2.25)	0.80(0.21 to 3.06)	1.87(0.54 to 6.29)

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Table 4 Univariate conditional logistic regression analysis for kidney cancer, leukaemia, acute myeloid leukaemia, and multiple myeloma

Model	*Variables in the model*	*β*	*SE (β)*	χ^2	*p Value*	*RR**
Leukaemia:						
1	Duration of employment (y)	−0.026112	0.020450	1.631	0.202	0.97
2	Duration of exposure (y)	−0.013375	0.018340	0.532	0.466	0.99
3	Cumulative exposure (ppm-y THC)	−0.000003	0.000318	0.000	0.993	1.00
4	Frequency of peak exposure	−0.000006	0.000034	0.028	0.868	1.00
5	Year of first exposure†	−0.549856	0.553380	0.987	0.320	0.58
Acute myeloid leukaemia:						
1	Duration of employment (y)	−0.031112	0.034410	0.818	0.366	0.97
2	Duration of exposure (y)	0.002738	0.029530	0.009	0.926	1.00
3	Cumulative exposure (ppm-y THC)	−0.000032	0.000527	0.004	0.951	1.00
4	Frequency of peak exposure	−0.000007	0.000055	0.015	0.901	1.00
5	Year of first exposure†	−0.315322	0.948050	0.111	0.739	0.73
Multiple myeloma:						
1	Duration of employment (y)	0.000244	0.038260	0.000	0.995	1.00
2	Duration of exposure (y)	−0.038776	0.034580	1.257	0.262	0.96
3	Cumulative exposure (ppm-y THC)	−0.000536	0.000732	0.536	0.464	1.00
4	Frequency of peak exposure	0.000046	0.000052	0.790	0.374	1.00
5	Year of first exposure†	0.644938	1.125110	0.329	0.567	1.91
Kidney cancer:						
1	Duration of employment (y)	−0.027584	0.039670	0.484	0.487	0.97
2	Duration of exposure (y)	0.001030	0.035180	0.001	0.977	1.00
3	Cumulative exposure (ppm-y THC)	−0.000477	0.005243	0.827	0.363	1.00
4	Frequency of peak exposure	−0.000011	0.000066	0.028	0.867	1.00
5	Year of first exposure†	−1.115231	0.815680	1.869	0.172	0.33

*RR corresponds to an increment of 1 unit of the independent variable.
†$\leq$1948 v $\geq$1949.
THC=total hydrocarbons.

Results

For most cases, we were able to select five matched controls. For one case of AML, no eligible control could be found. For the remaining cases of AML, five controls were selected for each. For leukaemia (all cell types), as well as the case of AML with no controls, one case had only three controls. Five controls were selected for each of the remaining cases of leukaemia, multiple myeloma, and kidney cancer.

Four key exposure variables (duration of employment, duration of exposure, cumulative exposure, and frequency of peak exposure) were compared between the cases and controls for the four disease categories (table 2). The cases had similar or slightly lower means of these four exposure variables than had the controls.

Table 3 shows the Mantel-Haenszel relative risks (RRs) for the four disease categories by ever or never job category. No significantly increased risk of leukaemia was detected for any job category. For AML, except for the category labourers, which consisted of only one case, no job category showed any excess. For multiple myeloma, no significant excess was found. However, for those who had ever been foremen or supervisors, the RR was 1.92 (based on three cases, p>0.05; 95% CI 0.43 to 8.59). For kidney cancer, no significant excess was found for any job category. However, non-

Table 5 Multivariate conditional logistic regression analysis for leukaemia, acute myeloid leukaemia, multiple myeloma, and kidney cancer

Model	*Variables in the model*	*β*	*SE(β)*	χ^2	*p Value*	*RR**
Leukaemia:						
1	Duration of exposure (y)	−0.015262	0.019680	0.601	0.438	0.98
	Cumulative exposure (ppm-y THC)	0.000089	0.000332	0.071	0.789	1.00
2	Duration of exposure (y)	−0.016621	0.022130	0.564	0.453	0.98
	Frequency of peak exposure	0.000011	0.000041	0.071	0.790	1.00
3	Cumulative exposure (ppm-y THC)	0.000031	0.000362	0.007	0.933	1.00
	Frequency of peak exposure	−0.000007	0.000039	0.035	0.852	1.00
Acute myeloid leukaemia:						
1	Duration of exposure (y)	0.003672	0.031160	0.014	0.906	1.00
	Cumulative exposure (ppm-y THC)	−0.000053	0.000562	0.009	0.924	1.00
2	Duration of exposure (y)	0.006950	0.035440	0.038	0.845	1.01
	Frequency of peak exposure	−0.000014	0.000066	0.046	0.831	1.00
3	Cumulative exposure (ppm-y THC)	0.000000	0.000602	0.000	1.000	1.00
	Frequency of peak exposure	−0.000007	0.000063	0.012	0.914	1.00
Multiple myeloma:						
1	Duration of exposure (y)	−0.033747	0.038630	0.763	0.382	0.97
	Cumulative exposure (ppm-years THC)	−0.000218	0.000755	0.083	0.773	1.00
2	Duration of exposure (y)	−0.098083	0.052870	3.441	0.064	0.91
	Frequency of peak exposure	0.000153	0.000089	2.980	0.084	1.00
3	Cumulative exposure (ppm-y THC)	−0.001226	0.001040	1.381	0.240	1.00
	Frequency of peak exposure	0.000088	0.000065	1.850	0.174	1.00
Kidney cancer:						
1	Duration of exposure (y)	0.007465	0.035870	0.043	0.835	1.01
	Cumulative exposure (ppm-y THC)	−0.000502	0.000550	0.831	0.362	1.00
2	Duration of exposure (y)	0.003560	0.037650	0.009	0.925	1.00
	Frequency of peak exposure	−0.000013	0.000070	0.036	0.850	1.00
3	Cumulative exposure (ppm-y THC)	−0.000510	0.000566	0.810	0.368	1.00
	Frequency of peak exposure	0.000012	0.000069	0.033	0.857	1.00

*RR corresponds to an increment of 1 unit of the independent variable.
THC=total hydrocarbons.

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significant increases were reported for loaders, foremen or supervisors, warehousemen, and labourers. Analyses by job category with a minimum duration of 5 or 10 years showed similar results, and will not be presented in this report.

As discussed earlier, based on a consideration of the reduction in recommended benzene standards in 1947 and 1948, the risk of developing the four diseases among those first exposed before 1949 was compared with that among those exposed thereafter. The RRs (95% CIs) were: 0.73 (0.32 to 1.66) for leukaemia, 0.92 (0.22 to 3.89) for AML, 1.39 (0.27 to 7.33) for multiple myeloma, and 0.52 (0.16 to 1.73) for kidney cancer.

Results based on univariate conditional logistic regression are shown by disease category in table 4. In these univariate analyses, only one exposure variable was in the logistic model. Based on these univariate models, no association was found between any of the exposure variables and any of the four diseases.

Results of the multivariate conditional logistic regression analyses are presented in table 5. In these models, various combinations of exposure variables were used—such as, duration of exposure and frequency of peak exposure, cumulative exposure, and frequency of peak exposure, etc. No significant association was detected between the exposure variables and any of the diseases in the multivariate logistic regression models.

Discussion

In the case-control study, job categories and exposure estimates were further refined, resulting in 10 more specific job categories. For example, the broad job category terminal operators, which was used in the cohort study previously, was broken down into additional categories, including plantmen, warehousemen, labourers, mechanics, foremen or supervisors, and maintenance or yard workers. Exposures within these subcategories were more homogeneous than those in the previous overall category terminal operators.

Analysis by newly developed job categories did not find any significantly increased risk for any of the four diseases. However, non-significant excesses were detected among foremen or supervisors for leukaemia, multiple myeloma, and kidney cancer. From the exposure point of view, the category foremen or supervisors is considered to be a group with low exposure. On the other hand, among other job categories examined, mechanics and maintenance or yard workers were considered to have higher exposure than the others. Neither of these two groups showed an excess in leukaemia (all cell types), AML, multiple myeloma, or kidney cancer. Thus, the excesses found among foremen or supervisors could not be explained in terms of their level of exposure.

As well as job categories, other exposure variables were used in the case-control analyses. Included in the logistic regression analyses were several quantitative exposure indices. Analyses based on univariate logistic regression did not indicate any relation between the diseases of interest and quantitative gasoline or benzene exposure indices. As these exposure indices correlated with one another, multiple logistic regression models were also used. For example, cumulative exposure was highly dependent on duration of exposure. In one of the models, both cumulative exposure and duration of exposure were analysed simultaneously. Again, no associations between any of the four disease categories and any of the exposure indices were found. These case-control analyses based on logistic regression confirmed the findings based on subcohort analyses of standardised mortality ratio (SMR) and proportional hazards models reported in the original cohort study.[1 2]

A similar conclusion was reached in a nested case-control study of lymphohaematopoietic cancers in Canadian distribution workers.[5] Exposures were assessed in terms of cumulative exposure and intensity of exposure. No relations between exposure to total hydrocarbons (or benzene) and any of the lymphatic and haematopoietic cancers (leukaemia, multiple myeloma, non-Hodgkin's lymphoma) were found. For example, for exposure to benzene, the odds ratios for multiple myeloma were 1.00, 0.44, 1.44, and 0 for cumulative exposure categories 0.0–0.90, >0.90–9.9, >9.9–9.99, and >9.99 ppm-years, respectively.

Exposures to benzene among distribution workers were relatively low. For example, one of the most highly exposed jobs in distribution workers was driver for small terminals from 1950 to 1965: 8 hour time weighted average (8 h TWA) of 210 ppm THCs, which is about 3–4 ppm benzene. By contrast, in populations of workers reported to have an increased risk of AML in previous studies, exposure to benzene was much higher. For example, it was reported that shoemakers in Turkey, who used solvents containing up to 88% benzene, were exposed to concentrations of benzene in air as high as 650 ppm,[6] and Pliofilm workers in Ohio to peaks as high as 750 ppm and 8 h TWAs as high as 260 ppm.[7] Recently, based on the Pliofilm study and with exposure values which were most likely underestimated, Wong reported that no excess AML was found among workers with cumulative exposure to benzene <200 ppm-years.[8] Had more realistic exposure estimates been used, the AML threshold would most likely be in the range of 370–530 ppm-years. Among distribution workers in our study, on the other hand, cumulative exposure was up to 8000 ppm-years of THCs or 128 ppm-years of benzene. Thus, exposure to benzene in this cohort was not sufficient to increase the risk of AML. This statement is supported by the lack of an exposure-effect relation based on analyses in the cohort study and case-control study.

For multiple myeloma, no association with exposure to gasoline was found in this case-control study. Suggestions for an association between exposure to benzene and multiple myeloma came primarily from the study of Pliofilm workers in Ohio.[9] Although a significant increase of multiple myeloma was found in that study in a previous update, the increase

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was only marginally significant. More importantly, three of the four cases of multiple myeloma in the Pliofilm study were short term workers, including one who worked at the factory for 4 days, and no exposure-response relation was found. Based on the most recently updated data, the increase in multiple myeloma was no longer significant.[8] The conclusion of no association between exposure to gasoline or benzene and multiple myeloma is further supported by several population based case-control studies and a recent comprehensive review of studies of petroleum workers.[10–15]

For kidney cancer, analyses in the nested case-control study indicate that the risk of developing kidney cancer is not related to exposure to gasoline or benzene. As indicated in table 2, the cases of kidney cancer and their controls had similar exposures. Based on the more refined job classification in the case-control study, no job category was found to be significantly related to risk of kidney cancer. The finding of a fivefold risk ratio for loaders was based on only two cases of kidney cancer, and the risk ratio was not significant. More importantly, based on logistic regression analyses, none of the exposure indices were found to be associated with an increased risk of kidney cancer. Thus, little interpretation can be attached to the isolated finding of a non-significant increased risk ratio in loaders. Taking all the results into consideration, the analyses in the nested case-control study indicate that exposure to gasoline is not related to an increased risk of kidney cancer. A similar case-control study of kidney cancer in petroleum workers concluded that no increased risk of kidney cancer resulted from exposure to gasoline.[16]

Exposure information in the case-control analyses was limited to employment in the petroleum industry. No information on lifestyle, previous medical histories, or information on employment outside the petroleum industry was available to control potential confounding effects. Many substances as well as personal factors have been reported to be associated with an increased risk of the diseases under investigation. Unfortunately, it was beyond the scope of this case-control study to collect information on these confounding factors.

Conclusion

In this nested case-control study, more specific and more homogeneous job classifications and exposure estimates than those used in the original cohort study were developed and used in the analysis. Based on the results of this case-control study, we conclude that exposures to gasoline or benzene at the concentrations experienced by this cohort of distribution workers are not significant risk factors for leukaemia (all cell types), AML, multiple myeloma, or kidney cancer.

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