Leukemia Risk Associated With Low-Level Benzene Exposure

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Background: Men who were part of an Australian petroleum industry cohort had previously been found to have an excess of lympho-hematopoietic cancer. Occupational benzene exposure is a possible cause of this excess.

Methods: We conducted a case-control study of lympho-hematopoietic cancer nested within the existing cohort study to examine the role of benzene exposure. Cases identified between 1981 and 1999 (N = 79) were age-matched to 5 control subjects from the cohort. We estimated each subject's benzene exposure using occupational histories, local site-specific information, and an algorithm using Australian petroleum industry monitoring data.

Results: Matched analyses showed that the risk of leukemia was increased at cumulative exposures above 2 ppm-years and with intensity of exposure of highest exposed job over 0.8 ppm. Risk increased with higher exposures; for the 13 case-sets with greater than 8 ppm-years cumulative exposure, the odds ratio was 11.3 (95% confidence interval = 2.85-45.1). The risk of leukemia was not associated with start date or duration of employment. The association with type of workplace was explained by cumulative exposure. There is limited evidence that short-term high exposures carry more risk than the same amount of exposure spread over a longer period. The risks for acute nonlymphocytic leukemia and chronic lymphocytic leukemia were raised for the highest exposed workers. No association was found between non-Hodgkin lymphoma or multiple myeloma and benzene exposure, nor between tobacco or alcohol consumption and any of the cancers.

Conclusions: We found an excess risk of leukemia associated with cumulative benzene exposures and benzene exposure intensities that were considerably lower than reported in previous studies. No evidence was found of a threshold cumulative exposure below which there was no risk.

Key Words: benzene, occupational exposure, leukemia, lymphoma, multiple myeloma, petroleum industry

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Benzene is present in crude oil, at most stages of petroleum production and distribution, and is a component of gasoline fuels, typically less than 3%. It is also a byproduct of combustion of fuels and other materials such as tobacco, wood, and coal. Benzene is present in indoor environments from activities such as cooking and heating, and it is ubiquitous in urban air at low concentrations. Nonsmokers living in an urban environment are typically exposed to average benzene concentrations in the order of 0.005 ppm.[1]

Benzene is classified as a group 1 human carcinogen by the International Agency for Research on Cancer,[2] and there is general agreement that benzene can cause leukemia in highly exposed individuals.[3] The extent of the risk of leukemia with exposure to low concentrations of benzene (less than 10 ppm) has been debated.[3-11] This debate has centered on 2 issues: whether the exposures were underestimated in previous epidemiologic studies and what model should be used to extrapolate the risk to lower concentrations of benzene, including whether there is a threshold exposure below which there is no risk.

In addition, there is debate about which subtypes of leukemia are associated with benzene exposure. Some but not all authorities consider that acute nonlymphocytic leukemias or, more specifically, acute myeloid leukemia, are the only subtypes clearly associated with benzene exposure.[3,8,9,12,13] Benzene has also been associated with increased risk of

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multiple myeloma,[3,14,15] although this too is disputed.[9,16] A review of 308,000 benzene-exposed workers from 26 cohorts in 5 countries found no increased rate of non-Hodgkin lymphoma.[17] In the U.K., the occupational exposure limit for benzene (maximum exposure limit) is 3 ppm as an 8-hour time-weighted average.[18] This was introduced in 2000 as the first part of a phased reduction to 1 ppm in 2003 in accordance with the Carcinogens Directive of the Council of the European Union.[19] The current American Conference of Governmental Industrial Hygienists' threshold limit value for benzene is 0.5 ppm.[20]

A prospective cohort study of all-cause mortality and cancer incidence in the Australian petroleum industry, known as Health Watch, was established in 1980 at the University of Melbourne for the Australian Institute of Petroleum. In 1999 the study was transferred to the University of Adelaide. The cohort consists of all employees except head office staff and those employed at Australian sites with fewer than 10 employees. Employees in the industry have been surveyed at approximately 5-year intervals using an interviewer-administered job and health questionnaire. This questionnaire obtained information on jobs and tasks, on possible confounding variables (including smoking and alcohol), and on specific health outcomes. The first survey was conducted from 1981-1983 and resulted in an original cohort of 10,979 men and 626 women. More subjects were recruited in the second and subsequent surveys. Approximately 95% of eligible employees in the industry have participated in Health Watch surveys. Employees were recruited into the Health Watch cohort after having served 5 years in the petroleum industry, and they remain in the cohort for life. Copies of death certificates are obtained and cancer incidence is validated through state cancer registries and the treating doctor. Cancer registration in Australia is a legal requirement of pathology laboratories and hospitals. In 1998 the cohort comprised 15,732 men and 1178 women.

Men in the cohort have been shown to have increases in the standardized incidence ratios for leukemia of 2.0 (95% confidence interval [CI] = 1.3-2.9) and for multiple myeloma of 1.9 (95% CI = 1.0-3.3).[21] We designed a case-control study to assess the association between lympho-hematopoietic cancers and occupational benzene exposure among men in the cohort. We report the exposure-response relationships for lympho-hematopoietic cancers, including the subtypes of leukemia, and benzene exposure based on matched analyses.

METHODS

This case-control study is nested within the Health Watch cohort. We estimated the occupational exposure to benzene of the cases and control subjects, drawing on the subject's entire job history and using measured exposures for a wide range of tasks in the petroleum industry.

Cases were defined as men in the Health Watch cohort who reported a newly diagnosed lympho-hematopoietic cancer to Health Watch (either by himself or by his family) that was confirmed by pathology report, cancer registration, letter from a medical practitioner, or death certificate. Registry cases who had not self-reported to Health Watch could be included under the terms of the ethics committee approval only if the man had been lost to follow up or had died.

Seventy-nine cohort members met the definition of lympho-hematopoietic cancer cases. They were identified by searching the cancer registries and through self-report to Health Watch. One man was found in the cancer registry, but under the terms of the ethics approval he could not be a case because he had not self-reported the disease and was not deceased or lost to contact.

All documentation on the cases was reviewed by the investigators and cases were assigned to International Classification of Diseases groupings according to the highest level of evidence (Table 1). For 9 cases with uncertain histology the documentation was reviewed by a hematologist who classified cases using the French-American-British system.[22]

We selected 5 male control subjects for each case. Control subjects were selected randomly from a list of all cohort members who were eligible at the time of diagnosis and matched by year of birth. As a result of the random selection, 5 workers were used as control subjects for more than 1 case, 4 of whom were used in 2 case-control sets and 1 in 3 sets. Thus, the total number of control subjects was 395. One worker selected as a control subject subsequently became a case; this subject was retained as a control subject because he was not diagnosed at the time of selection. As a control subject, his exposure was truncated at the time of the matched-case diagnosis (as with all control subjects). As a case his exposure was estimated up to the time of his diagnosis.

Each subject's smoking, alcohol, and job history had been collected as part of the Health Watch cohort surveillance.[21] For employees interviewed in either the first or second Health Watch surveys in 1981-1983 and 1986-1987, detailed information had been collected only on their current job and jobs held in the previous 5 years. During the third Health Watch survey in 1991-1993, full job histories were obtained for all current employees interviewed. For those Health Watch members no longer employed in the petroleum industry, lists of jobs held in the industry were obtained during the annual health check mail-out in 1994. The lists included job titles, company, site, area of work and dates, but no details of individual tasks or products handled. The job histories were cross-checked with company personnel records. In those instances in which discrepancies were found, the more detailed record (usually the subject's) was used.

TABLE 1. Type of Cancer by Highest Level of Evidence for the Diagnosis

Type of Lympho-hematopoietic Cancer	ICD-9 Code	Highest Level of Evidence: Histology (N = 39)	Doctors' Letters (N = 17)	Cancer Registry Alone (N = 14)	Death Certificate (N = 9)	Total No. (N = 79)
Non-Hodgkin lymphoma	200, 202	14	6	5	6	31
Multiple myeloma	203	8	4	2	1	15
Leukemia	204–208	17	7	7	2	33
Chronic lymphocytic leukemia	204.1	5	5	0	1	11
Chronic myeloid leukemia	205.1	1	1	4	0	6
Acute lymphocytic leukemia	204.0	2	0	0	0	2
Acute nonlymphocytic leukemia*	205.0, 208.0	7	1	2	1	11
Other leukemia†	202.4, 204.9	2	0	1	0	3

*This group includes 9 acute myeloid leukemias and 2 acute undifferentiated leukemias.
†The 3 "other" leukemias were a hairy cell leukemia and 2 unspecified lymphocytic leukemias. ICD-9, World Health Organization International Classification of Diseases, 9th revision.

Cases were not themselves interviewed about their tasks, because this information might have been subject to recall bias. Instead, we interviewed contemporaries at the site who were familiar with the requirements of the job. These surrogate respondents provided information on the tasks that each subject would have performed for each job he had recorded in the job history, the technology used at that time, and products handled. Current and past employees were interviewed, and the interviews were structured using standard questionnaires for each job type based on those developed for previous petroleum industry epidemiologic studies.[23,24] The interviewers had no knowledge of the names and health status of the subjects.

We calculated the benzene exposure of each individual using a task-based algorithm involving the subject's occupational history; previously measured exposures for particular tasks in the Australian petroleum industry; and task-, site-, and period-specific data. This exposure model was similar to those used in some other petroleum industry epidemiologic studies[23,24] but more detailed in that it was task-based and applied to each individual's job history. This provided an estimate of cumulative exposure to benzene in parts per million-years (ppm-years) for each subject. The subjects were divided into geometric exposure groups. The exposure estimation process is described more fully elsewhere.[25,26]

We used the following additional exposure metrics to test the association with risk of leukemia, with and without adjustment for cumulative exposure:

1. Start date: Subjects were divided into 3 groups by their start date in the industry: pre-1965, 1965-1975, and post-1975.
2. Duration of employment: The duration of employment (in participating companies) was defined as the difference between the earliest start date and the latest finish date for each subject, truncated by date of diagnosis. We calculated quintiles of duration with cut-points approximately every 7 years.
3. Whether most of the career was spent as an office worker or as a blue collar worker.
4. Site of longest-held job and highest-exposed job: Each site where a subject worked was allocated to a site type. The period of time and associated exposure for each subject was then allocated to that site type. If a subject worked in the office at a refinery or a distribution terminal, he was included as an office worker rather than being assigned to a site type.
5. Intensity of exposure: We calculated the average exposure intensity (cumulative benzene exposure estimate divided by duration of employment) in ppm for each job. We divided the subjects into geometric exposure intensity groups based on their highest exposed job.
6. Subjects with exposure to benzene concentrate: We identified those subjects who had handled benzene concentrate that is 100% benzene or BTX (benzene-toluene-xylene, which is principally an aromatic fraction derived from coke oven operations, containing approximately 70% benzene).

All odds ratios and 95% confidence intervals are from matched analyses.

The study was carried out with the clearance of Monash University Standing Committee on Ethics in Research Involving Humans, and the Ethics Committees from Melbourne

and Adelaide Universities. All subjects signed a consent form to allow access to their job histories, and cases consented to our contacting their treating doctor for diagnostic details.

RESULTS

The cases and control subjects were well matched demographically (Table 2). They were similar with regard to alcohol consumption and country of birth. Control subjects were slightly more likely than the cases to be exsmokers. The risk of leukemia was not associated with smoking; odds ratios (ORs) were 0.55 (95% CI = 0.18-1.32) for previous smokers and 1.28 (95% CI = 0.52-3.14) for current smokers compared with never-smokers. We estimated the OR for leukemia associated with smoking score (pack-years) and alcohol score (standard drink-years) both as continuous measures. The OR per 100 pack-years was 0.98 (95% CI = 0.80-1.19) and per 1000 drink-years was 0.78 (95% CI = 0.52-1.16).

The ages of the cases at the date of case diagnosis ranged from 26-79 years with a mean of 54 years (Table 2). The mean duration of employment, prior to diagnosis, was 20.4 years (standard deviation, 9.0 y), and ranged from 4.3-43 years. A control subject, employed for only 4.3 years at the time of diagnosis of the case to which he was matched, had satisfied the cohort criteria of being employed in the industry for 5 years or more.

Cases had, on average, a higher lifetime cumulative exposure than control subjects, and a greater proportion of cases were in higher exposure categories (Table 3). The subjects were grouped by cumulative exposure (ppm-years) into 6 geometric groups, and conditional logistic regression (case-matched) was used to calculate stratum-specific ORs (Table 4). No increase in risk for non-Hodgkin lymphoma/multiple myeloma was found with increasing exposure to benzene. However, the ORs for leukemia were found to be elevated for 3 of the 5 exposure groups compared with the lowest (≤1 ppm-years) as illustrated in Figure 1. The highest exposure group (>16 ppm-years) contained 7 of 33 leukemia cases, but only 3 of their 165 matched control subjects. For the 2 highest exposure categories combined (13 case-sets with >8 ppm-years cumulative exposure), the OR was 11.3 (95% CI = 2.85-45.1).

In a comparable study in the U.K. petroleum industry,[27] a cut-point of 4.79 ppm-years was used in the analysis. For comparison purposes we analyzed our data using the same cut-point and obtained an OR of 2.51 (95% CI = 1.1-5.7).

The OR associated with cumulative exposure as a continuous measure was 1.65 (95% CI = 1.25-2.17), which is consistent with an increase of 65% for each doubling of mean cumulative exposure.

There was no association between leukemia (with or without adjustment for cumulative benzene exposure) and date of starting work in industry or duration of employment (Table 5). Blue collar workers had a 3-fold risk of leukemia compared with office workers, but this risk disappeared when adjustment was made for cumulative benzene exposure (data not shown). Subjects who had worked longest at an airport had nearly 4 times the risk of leukemia compared with terminal workers but this result was based on small numbers. This finding did not change after adjustment for cumulative

TABLE 2. Lifestyle and Demographic Characteristics of the Cases and Control Subjects

Characteristic	Control Subjects (N = 395)	All Cases (N = 79)	Types of Cancer			
			Leukemia (N = 33)	NHL/MM (N = 46)	MM (N = 15)	NHL (N = 31)
Age in years; mean (range)	54 (26–76)	54 (26–79)	52 (34–71)	54 (26–75)	55 (39–75)	54 (26–70)
Tobacco; no. (%)*						
Never smoked	125 (32)	28 (35)	11 (33)	17 (37)	8 (53)	9 (29)
Previous smoker	166 (42)	21 (27)	8 (24)	13 (28)	6 (40)	7 (23)
Current smoker	103 (26)	30 (38)	14 (42)	16 (35)	1 (7)	15 (48)
Alcohol; no. (%)						
Never drank	79 (20)	16 (20)	7 (21)	9 (20)	1 (7)	8 (26)
Previous drinker	10 (3)	2 (3)	1 (3)	1 (2)	0	1 (3)
Current drinker	305 (77)	61 (77)	25 (76)	36 (78)	14 (93)	22 (71)
Country of birth; no. (%)						
Australia	259 (66)	56 (71)	25 (76)	31 (67)	10 (67)	21 (68)
UK	75 (19)	14 (18)	4 (12)	10 (22)	3 (20)	7 (23)
Other	60 (15)	9 (11)	4 (12)	5 (11)	2 (13)	3 (10)

*One control did not record smoking data.
NHL/MM, combined non-Hodgkin lymphoma and multiple myeloma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

TABLE 3. Cases and Control Subjects Grouped by Exposure to Benzene Expressed as Cumulative Exposure (ppm-years)

Characteristic	Control Subjects (N = 395)	All Cases (N = 79)	Types of Cancer			
			Leukemia (N = 33)	NHL/MM (N = 46)	MM (N = 15)	NHL (N = 31)
Mean and range of cumulative exposure (ppm-years)	4.7 (0.01–57.3)	7.27 (0.01–52.7)	10.63 (0.09–52.7)	4.85 (0.01–23.4)	4.73 (0.17–23.4)	4.91 (0.01–21.8)
Cumulative exposure (ppm-years); no. (%)						
≤1	138 (35)	18 (23)	3 (9)	15 (33)	4 (27)	11 (35)
>1–2	56 (14)	12 (15)	6 (18)	6 (13)	2 (13)	4 (13)
>2–4	67 (17)	16 (20)	8 (24)	8 (17)	5 (33)	3 (10)
>4–8	64 (16)	12 (18)	3 (9)	9 (20)	2 (13)	7 (23)
>8–16	53 (13)	11 (14)	6 (18)	5 (11)	1 (7)	4 (13)
>16	17 (4)	10 (13)	7 (21)	3 (7)	1 (7)	2 (6)

NHL/MM, combined non-Hodgkin lymphoma and multiple myeloma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

benzene exposure. Similar results were found for those whose highest benzene-exposed job was at an airport.

There was a strong association between leukemia risk and exposure to benzene concentrate that was somewhat reduced when cumulative exposure was controlled for. That is, exposure to benzene concentrate resulted in a higher risk of leukemia than exposure to the same amount of benzene encountered in a more dilute form such as in gasoline.

The proportion of subjects whose highest exposed job was in high-intensity exposure categories was greater for cases than control subjects (Table 5). Exposure intensity in the highest exposed job was strongly related to leukemia risk, with the increase starting at around 0.8-1.6 ppm and with those in the highest exposure category being nearly 20 times more likely to develop leukemia than those who were unexposed. Adjusting for cumulative exposure removed the association between high-intensity exposure and leukemia. However, exposure intensity and cumulative exposure are highly correlated, and goodness-of-fit statistics and the stepwise conditional logistic regression algorithm did not provide unequivocal evidence that would distinguish between the relative contributions of cumulative exposure and exposure intensity to leukemia risk.

The ORs were also calculated by using conditional logistic regression for the leukemia subtypes acute nonlymphocytic leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia (Table 6); such calculations were not possible for acute

TABLE 4. Association of Leukemia and Non-Hodgkin Lymphoma/Multiple Myeloma by Benzene Exposure Group, From Conditional Logistic Regression Analysis

Cumulative Lifetime Benzene Exposure (ppm-years)	Leukemia OR (95% CI)	NHL/MM OR (95% CI)
≤1*	1.0	1.0
>1–2	3.9 (0.9–17.1)	1.1 (0.4–2.9)
>2–4	6.1 (1.4–26.0)	1.2 (0.5–3.0)
>4–8	2.4 (0.4–13.6)	1.3 (0.5–3.2)
>8–16	5.9 (1.3–27.0)	0.8 (0.3–2.6)
> 16	98.2 (8.8–1090)	1.1 (0.3–4.5)

* Reference category.

NHL/MM, combined non-Hodgkin lymphoma and multiple myeloma; OR, odds ratio; CI, confidence interval.

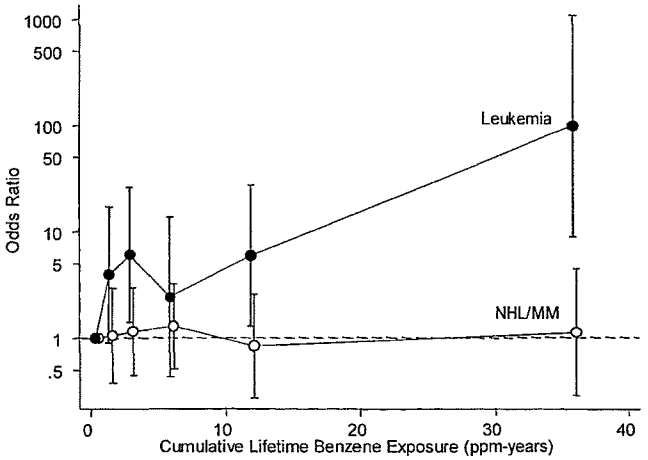

FIGURE 1. Leukemia and Non-Hodgkin Lymphoma/Multiple Myeloma (NHL/MM) odds ratios by geometric benzene exposure groups (ppm-years) displayed at the midpoint of the exposure group. (Circles indicate odds ratios; vertical lines depict confidence intervals).

TABLE 5. Distribution of Exposure Variables for Leukemia Cases and Control Subjects and Results of Matched Analyses of the Risk of Leukemia Using These Variables

Exposure Characteristic	Cases (N = 33) No. (%)	Control Subjects (N = 165) No. (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Start date in industry				
Before 1965†	15 (45)	63 (38)	1.0	1.0
1965–1975	12 (36)	60 (36)	0.6 (0.2–1.9)	0.9 (0.3–3.2)
1975 or later	6 (18)	42 (25)	0.4 (0.1–1.6)	1.0 (0.2–4.8)
Duration of employment truncated at date of diagnosis (y)				
≤11†	15 (19)	77 (19)	1.0	1.0
>11–17	18 (23)	83 (21)	1.2 (0.4–4.0)	0.7 (0.2–2.5)
>17–22.5	12 (15)	81 (21)	1.6 (0.4–5.5)	1.2 (0.3–5.4)
>22.5–29	16 (20)	80 (20)	1.0 (0.2–4.2)	0.4 (0.1–1.9)
>29–43	18 (23)	74 (19)	1.6 (0.4–6.8)	0.4 (0.1–2.7)
Exposure to benzene concentrate				
No†	28 (84)	163 (99)	1.0	1.0
Yes	5 (16)	2 (1)	12.5 (2.4–64)	6.3 (1.1–36)
Exposure intensity group based on highest benzene-exposed job (ppm)				
≤0.1†	5 (15)	65 (39)	1.0	1.0
>0.1–0.2	9 (27)	26 (16)	3.9 (1.2–12.6)	1.2 (0.3–4.9)
>0.2–0.4	4 (12)	25 (15)	2.2 (0.5–9.4)	0.5 (0.1–3.2)
>0.4–0.8	4 (12)	11 (7)	6.6 (1.7–25.7)	0.6 (0.1–6.2)
>0.8–1.6	3 (9)	31 (19)	1.6 (0.4–6.7)	0.2 (0.0–2.0)
>1.6–3.2	6 (18)	6 (4)	5.6 (1.0–31.2)	0.4 (0.0–6.1)
>3.2	2 (6)	1 (1)	20.4 (1.6–270)	1.6 (0.1–38)

*Adjusted for cumulative benzene exposure.
†Reference category.
CI, confidence interval.

lymphocytic leukemia because there were only 2 cases. Because there were relatively few cases of the leukemia subtypes, it was necessary to combine the 3 lowest exposure groups and the 2 highest exposure groups. The ORs in the combined higher exposure group were raised relative to the combined lower exposure group for both chronic lymphocytic leukemia and acute nonlymphocytic leukemia.

DISCUSSION

These data provide strong evidence for an association between previous benzene exposure in the Australian petroleum industry and an increased risk of leukemia. However, we did not find an association of benzene with multiple myeloma or non-Hodgkin lymphoma, which is consistent with previous findings.[9,16,17]

In our data, leukemia seems to be associated with lower cumulative exposures than has been observed in other studies. The estimated cumulative exposures were generally similar to those reported for other petroleum industry studies, except that the most highly exposed subjects in our study had cumulative exposures of less than 60 ppm-years, whereas those in other studies were as high as 220 ppm-years.[27,28]

TABLE 6. Association of Leukemia Subtype With Cumulative Benzene Exposure From Conditional Logistic Regression Analysis

Cumulative Lifetime Benzene Exposure (ppm-years)	Leukemia Subtype ANLL (N = 11)	CLL (N = 11)	CML (N = 6)
≤4*	1.00	1.00	1.00
>4–8	0.52 (0.05–5.0)	2.76 (0.42–18.1)	-
>8	7.17 (1.27–40.4)	4.52 (0.89–22.9)	0.91 (0.08–9.8)

*Reference category.
ANLL, acute nonlymphocytic; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia.

It has been suggested that there might be no increased risk at cumulative exposures below 200 ppm-years[9] or intensity of less than 20-60 ppm.[10] In a recent large cohort study of Chinese workers, the relative risk for all hematologic neoplasms was 2.2 (95% CI = 1.1-4.2) for workers exposed to benzene at estimated average levels of less than 10 ppm.[11] Over a working lifetime this could amount to a cumulative exposure of up to several hundred ppm-years. In our study, the risk of leukemia was increased at all cumulative exposures above 1 ppm-year, with a strong exposure–response relationship. There was no evidence of a threshold.

Leukemia risk in the highest exposure category was 98 (95% CI = 8.8-1090). Combining the 2 highest cumulative exposure groups resulted in an OR of 11.3 (95% CI = 2.85-45.1). This is considerably higher than that observed in a similar petroleum industry study,[28] which found an OR of 2.11 (95% CI = 0.01-138) for leukemia for those in the highest quartile of exposure (8-220 ppm-years). In a similar study,[27] the leukemia OR was 2.13 (95% CI = 0.90-5.03) for those in the highest quintile of exposure (>4.79 ppm-years). In our study, the matched OR for those exposed to greater than 4.79 ppm-years was similar at 2.51 (95% CI = 1.1-5.7).

We found a positive association of benzene exposure with both acute nonlymphocytic leukemia and chronic lymphocytic leukemia. An association between acute nonlymphocytic leukemia and benzene exposure has only been reported previously associated with exposures above 200 ppm-years.[9,16] In a U.K. petroleum industry study,[27] the risk of acute myeloid and monocytic leukemia did not increase with cumulative exposure when analyzed as a continuous variable. However, when categorized into discrete ranges, an odds ratio of 2.8 (95% CI = 0.8-9.4) was found for a cumulative exposure of 4.5-45 ppm-years.[27]

There are a number of possible confounders, including tobacco and alcohol consumption and exposure to other chemicals and radiation. Tobacco and alcohol were not confounding factors in our data. Workers in the petroleum industry are exposed to a wide range of aliphatic and aromatic hydrocarbons found in or derived from crude oil, ranging from natural gas (methane) to bitumen. Known carcinogenic exposures include sunlight, polycyclic aromatic hydrocarbons, asbestos, and possibly other insulating materials. A few, mainly older, workers have had exposure to paint, and some workers in the lubricating oils operations had exposure to white spirit (Stoddard Solvents), methyl ethyl ketone, and toluene. The subjects include some laboratory workers who have had exposure to a number of laboratory reagents.

In 1996, a comprehensive review of risk factors for leukemia concluded that the only confirmed occupational risk factors were exposure to benzene, radiation, and some retroviruses. There is some inconsistent evidence for leukemogenic potential from some pesticides, styrene and butadiene manufacturing, and ethylene oxide.[29] We consider it unlikely that subjects in this study were occupationally exposed to retroviruses or these other agents. Some workers employed in the petroleum extraction, refining, and distribution industries might have used x-ray machines in laboratories or pipe surveys, but the sources are thought to have been well shielded.

The present study has a number of strengths and weaknesses. The diagnoses of the cases were well established. However, the study was based on a relatively small number[79] of lympho-hematopoietic cancer cases, including 33 leukemias of which there were only 11 acute nonlymphocytic leukemias and only 11 chronic lymphocytic leukemias. This limits the power of the study to detect excess risks for leukemia subgroups, particularly when we stratified the subjects by exposure.

The cases were individually age-matched to control subjects, and both were drawn from the same prospective cohort of workers in the Australian petroleum industry. The cohort has been followed for 20 years with serial identification of jobs, smoking habits, and health status. Only 10 of the 474 subjects (2%) had incomplete job histories. Relatively few subjects in the cohort (6%) have been lost to follow up,[21] and vital status was confirmed every 5 years; thus we are confident that the control subjects were selected from an appropriate risk set.

We estimated the subjects' exposure to benzene quantitatively, on an individual basis, with an algorithm based on a substantial body of exposure data from the Australian petroleum industry.[25] The exposure assessment method was validated,[26] but there are always uncertainties and unknown sources of variation in retrospective exposure assessments. Between-worker variation in exposure measurements, resulting from personal factors such as individual work practice, was not included in the exposure assessment reported here. There was also uncertainty about exposures before 1975 because jobs have changed over the years, but the available exposure data used in the algorithm postdated this period. However, the Health Watch cohort is relatively recent compared with other similar studies in which jobs held before 1920 were assessed.[27,28] Most of the subjects in our case-control study started work after 1965; the earliest start date was 1941. This means that jobs have changed less in our study, and for most jobs we were able to identify changes by interviewing contemporary coworkers. These individuals did not have to recall far distant exposure conditions so their uncertainty was reduced.

For 33 cases, including 13 leukemia cases, the complete job history was obtained after lympho-hematopoietic cancer diagnosis. These cases provided information after diagnosis, about jobs held before 1975, thus introducing some potential for recall bias. These subjects' job histories were constructed from the information gathered during the Health Watch surveys and from company records. This was then sent to the

subject for cross-checking. However, the high degree of agreement with the company records suggests that the self-reported job histories were reasonably accurate and that possible recall bias was low. For the remaining 46 cases, either the complete job history was obtained before diagnosis or only the company job history was used because, for example, the case died before the complete job history collection.

All smoking and drinking data were collected before individual diagnoses, thereby avoiding a potential cause of recall bias.

The benzene exposure assessments were carried out without any knowledge of the names and health status of the subjects to reduce observer bias. Detailed information on the circumstances of the exposure was provided, usually by contemporary work colleagues of the cases and control subjects. Some of the site interviewees might have been able to identify the subjects but were instructed not to reveal their names or health status to the interviewer. This could have given rise to some recall bias, because more effort might have been applied to recalling the tasks with benzene exposure for some of the cases because the connection between benzene exposure and lympho-hematopoietic cancer is widely known within the industry. However, it is unlikely that the employees would distinguish between the risk from benzene exposure of different cancers (leukemia compared with multiple myeloma or non-Hodgkin lymphoma). Our finding of increased risk specifically for leukemia but not for multiple myeloma or non-Hodgkin lymphoma suggests that recall and observer biases do not affect our main results.

It is unlikely that the baseline comparison group was incorrectly defined because this was a nested case-control study with the control subjects selected from the cohort matched by age. However, misclassification of only a few cases from the baseline group into higher exposure groups could markedly distort the exposure–response relation. Although the lowest exposed group contained many office workers, there is no strong socioeconomic gradient for risk of leukemia and the analysis of smoking suggested that this was not a confounding exposure. If there was a strong bias in the exposure estimates leading to differential misclassification, this should have affected the results for multiple myeloma and non-Hodgkin lymphoma as well; the questionnaire respondents would have been unlikely to draw a distinction between one form of hematopoietic cancer or another. The fact that no association was found between multiple myeloma/non-Hodgkin lymphoma and benzene exposure suggests that such bias, if present, was small. We cannot rule out the possibility that some bias was introduced in gathering the occupational histories, although such an effect would presumably be small. If such bias occurred, it could not explain the association between leukemia and benzene exposure that was found, but might have exaggerated the exposure–risk relationship and hidden a low-exposure threshold.

In summary, these data demonstrate a strong association between benzene exposure and the risk of acute and chronic leukemia. No association was found between benzene and non-Hodgkin lymphoma or multiple myeloma, or between any of the cancers and tobacco or alcohol consumption. The excess risk of leukemia was associated with lower cumulative exposures and lower exposure intensity than have been observed in other studies. We found no evidence of a threshold cumulative exposure below which there is no risk.

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