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ORIGINAL ARTICLE

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Environmental exposure to gasoline and leukemia in children and young adults – an ecology study

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Abstract Benzene is an established cause of leukemia in adults, especially acute non-lymphocytic leukemia (ANLL). A few studies have indicated that exposure to gasoline is a cause of childhood leukemia. The purpose of this study was to investigate if environmental exposure to benzene from gasoline and car exhaust was associated with leukemia in children and young adults. The exposure to gasoline and car exhaust was estimated by the number of cars per area. In this ecology study, data on the incidence of cancer in each municipality of Sweden during an 11-year period (1975–1985) were compared with the number of cars per area. Data on the incidence of cancer for persons aged 0–24 years at diagnosis were collected from the National Swedish Cancer Register. The following diagnoses were studied: non-Hodgkin's lymphoma, acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML). We found an association between AML and car density. In municipalities with more than 20 cars/km^2 the incidence of AML was 5.5 [95% confidence interval (CI) 4.4–6.8, $n = 89$] as compared with 3.4 (95% CI 1.9–5.7, $n = 15$) cases per 1 million person-years in municipalities with less than 5 cars/km^2 ($P = 0.05$). No association was found for the other sites of cancer studied. The association between AML in young adults and car density might be attributable to exposure to benzene from gasoline vapors and exhaust gases, but further investigations are necessary before any definite conclusion can be drawn.

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Introduction

Benzene is an established cause of leukaemia in adults, especially acute non-lymphocytic leukaemia (ANLL). Increased risks have been found in the workplace where the concentrations of benzene in air have measured around 30 mg/m^3 or more (International Agency for Research on Cancer 1982; Rinsky et al. 1987).

An association of childhood cancer, especially leukemia, with residential traffic has been suggested (Savitz and Feirgold 1989). An elevated incidence of childhood leukemia around the Sellafield nuclear reprocessing plant in Great Britain has been found (Wolff 1993). Children near the plant traveled more frequently by car than did children in the reference group, and it was suggested that the increased incidence was caused by exposure to benzene from automotive sources. However, other studies have not found any association between environmental exposure to benzene and cancer. An association between gasoline consumption and leukemia was not found in an ecology study in 19 European countries (Swaen and Slangen 1995). The study, however, was restricted to age groups of over 35 years. No association was found between exposure to engine exhaust and leukemia in a Swedish case-referent study of persons aged 20–54 years (Flodin et al. 1986).

The two major sources of environmental benzene exposure are gasoline exhaust from gasoline-driven cars and tobacco smoke. Exhaust from cars consists of a complex mixture of substances and contains, among other compounds, benzene from unburned gasoline. Gasoline contains benzene in varying concentrations. In Sweden the concentration is currently usually around 3–5% and has been in this range since the 1970s (R. Jarsin, Swedish Petroleum Institute, Stockholm, personal communication). The maximal allowable

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concentration of benzene in gasoline in Sweden has been 5% since 1977. Benzene is also emitted during refuelling of cars and due to leakage from gasoline stations and transportation (Akland 1993; Nordlinder and Ljungkvist 1992; Stenberg et al. 1983).

Varying concentrations of benzene in ambient air have been reported to range from 0.2 $\mu g/m^3$ in remote and rural areas to as high as 349 $\mu g/m^3$ in industrial centers with a high density of automobile traffic (WHO 1993). Measurements in 17 Swedish cities during the winter season 1992/1993 showed 6-month average levels of 3–10 $\mu g/m^3$ (Svanberg et al. 1994). Higher concentrations of benzene have been found inside cars as compared with the outside air (CONCAVE 1994; van Wijnen et al. 1995; Weisel et al. 1992).

The objective of this study was to investigate a possible association between environmental exposure to benzene from gasoline, in car exhaust or due to refuelling, and leukemia in children and young adults. There have not been systematic measurements of exposure to car exhausts or benzene in Sweden that could be used to estimate childhood exposure to these substances. We therefore used the number of cars per area and the amount of gasoline sold per area to estimate the childhood exposure. In this ecology study we investigated if these measures were associated with the incidence of leukemia in persons below the age of 25 years.

Subjects and methods

Data on the incidence of cancer in each municipality ($n = 277$) of Sweden during an 11-year period were compared with the number of cars or amount of gasoline per area, respectively. Data on the incidence of cancer for persons aged 0–24 years at diagnosis for the observation period of 1975–1985 were collected from the National Swedish Cancer Register. The rates were stratified according to age (5-year intervals), sex, and calendar year. The following diagnoses were studied: non-Hodgkin's lymphoma (ICD 9: 200.1), acute lymphocytic leukemia (ALL; ICD 9: 204.0), chronic lymphocytic leukemia (CLL; ICD 9: 204.1), acute myeloid leukemia (AML: ICD 9: 205.0), and chronic myeloid leukemia (CML; ICD 9: 205.1). However, there were only three cases of CLL, making an analysis infeasible. The incidence was calculated by division of the number of cases by the number of persons each year. The population of the municipality on January 1 of each year was used for calculation of the incidence.

From Statistics Sweden we received information on the number of cars as of January 1st, the land area (square kilometers) and the gasoline deliveries (cubic meters) made during the year in all municipalities for the years 1975 and 1985. The "car density" (cars per square kilometer) and the "gasoline density" (cubic meters per square kilometer) were calculated from these figures. From Statistics Sweden we also received data on the smoking habits of pregnant women in all municipalities for the same periods.

Confidence intervals were calculated assuming Poisson distribution (Documenta Geigy 1971); the 95% confidence intervals of rate differences were calculated by approximation to the normal distribution (Rothman 1986). Linear trends of incidence were tested according to a chi-square test (Breslow and Day 1987).

Results

We found a high correlation ($R = 0.998$) between car density and gasoline density, (Fig. 1). Therefore, only car density is reported in the following analysis. The 277 municipalities in Sweden were ranked in 4 groups according to car density (Table 1). There was no difference between the ranks of the municipalities according to car density between 1975 and 1985. The maximal car density was 1026 cars/km^2 (Stockholm), but 90% of the municipalities had a car density of below 47.9 cars/km^2. Large cities had the highest car densities, whereas the lowest values were found in sparsely populated areas in North Sweden. The smoking habits of pregnant women were almost the same in all car-density groups (Table 2).

There seemed to be an association between car density and AML but not the other sites of cancer studied (Table 3). The combined group of municipalities with more than 5 cars/km^2 had a significantly higher rate of AML than did the group with less than 5 cars/km^2 (95% confidence interval 0.1–4.0 cases per million

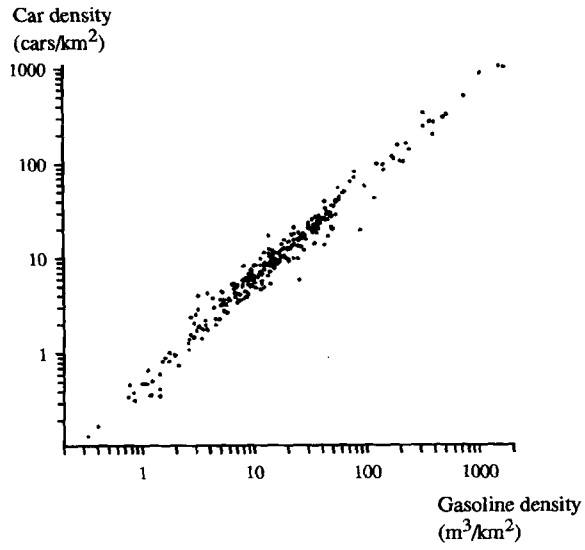

Fig. 1 Correlation between car density and gasoline density as determined in 277 municipalities in Sweden

Table 1 Car density in 1975 as determined in 277 Swedish municipalities

Cars/km^2	Frequency	Percent
<5	82	29.6
5–9	73	26.4
10–19	54	19.5
≥20	68	24.5
Totals	277	100

Table 2 Smoking habits as determined in pregnant mothers in relation to car density in 277 Swedish municipalities

Car-density (cars/km^2)	Smoking mothers (%)	95% CI
<5	30.5	29.5–31.5
5–9	30.0	29.1–31.0
10–19	30.3	29.3–31.3
⩾20	31.5	30.3–32.7

person-years). However, the linear trend was not significant ($\chi^2 = 1.3$). The attributable risk, calculated from the risk estimates in this study, was found to be about 40%, or six cases per year, in Sweden in this age group for car densities above 5 cars/km^2.

Discussion

This study suggests that AML in children might be associated with the car density in their living area. There was no association with other diagnoses. CML is a rather rare tumor in this age group, and only very strong associations could be detected. The power to detect an association between ALL and car density is much higher, as ALL is far more common than AML. A possible cause of the association between AML and car density is exposure to benzene from car exhaust or gasoline vapors. An established cause of AML in adults is benzene exposure (Jacobsson et al. 1993), but other constituents of the exhaust may also be important. A causal association is somewhat supported by similar observations in other studies (Savitz et al. 1988; Wolff 1992).

Car density is probably a crude measure of benzene exposure, but the misclassification would be nondifferential and such a misclassification usually weakens the association (Soran and Gilthorpe 1994). It is therefore improbable that a strong dose-response relationship would be found, and the linear trend detected in the present study was weak. Furthermore, the diagnosis of different types of leukemia may sometimes be difficult. If hospitals in areas with a high car density more often used the diagnosis of AML and hospitals in other areas used other diagnoses, an information bias could occur. However, children with these types of cancer are mainly treated and diagnosed at a few large hospitals in Sweden, making such a bias less probable.

Any factor that is causally related to AML and associated with living in areas with a high car density, i.e., areas with a high population density, is a possible confounder of the association observed between AML and car density. Below we discuss smoking as well as maternal and paternal occupational exposure to benzene and radiation.

Smoking is an important environmental source of exposure to benzene (Hoffman et al. 1989; Wallace 1989; Wallace et al. 1987)). However, there is conflicting evidence about an increased risk for AML in smokers (Brownson et al. 1993; Siegel 1993). In a study of smokers aged 60 years and older there was an increased risk for AML (Sandler 1993). We are not aware of any study that has found that environmental tobacco smoke (ETS) causes AML. If ETS is causally related to AML, it is a possible confounder. However, we found the smoking habits of pregnant women to be similar in municipalities with a low car density and municipalities with a high car density, (Table 2). The fathers' smoking habits are unknown, but it is probable that the smoking habits of the mothers correlate positively with those of the fathers. Furthermore, among nonsmokers living with smokers, only 15% of the benzene exposure was attributable to ETS in a study of adults (Adlerkofer et al. 1995).

Since the 1960s, occupational exposure to benzene in Sweden has almost exclusively involved handling of gasoline or similar petroleum products (Nordlinder 1995). Such exposure has occurred in refineries, transportation, and car repair, which may have occurred more frequently in areas with a high car density. These activities have involved very few women. It is also a rather rare form of exposure in men; we estimate that less than 5% of the male population were exposed to benzene in their workplace during the observation period. Maternal or paternal exposure to benzene therefore seems to be an improbable cause of the observed association between car density and AML.

Table 3 Cancer incidence rates (per 10^6 person-years) as determined between 1975 and 1985 according to diagnosis and car density in persons aged 0–24 years at diagnosis[a]

Site of cancer	Car density (cars/km^2)			
	<5	5–9	10–19	⩾20
Non-Hodgkins lymphoma ($n = 118$)	3.2 (1.85–5.4), $n = 14$	4.3 (2.8–6.4), $n = 24$	3.5 (2.3–5.3), $n = 24$	3.5 (2.6–4.5), $n = 56$
ALL ($n = 657$)	21.1 (17.0–25.8), $n = 92$	19.9 (16.4–24.0), $n = 111$	22.5 (19.1–26.4), $n = 153$	18.6 (11.3–21.4), $n = 301$
AML ($n = 171$)	3.4 (1.9–5.7), $n = 15$	5.4 (3.6–7.7), $n = 30$	5.4 (3.8–7.5), $n = 37$	5.5 (4.4–6.8), $n = 89$*
CML ($n = 36$)	0.5 (0.06–1.7), $n = 2$	1.3 (0.50–2.6), $n = 7$	0.9 (0.32–2.0), $n = 6$	1.3 (0.80–2.0), $n = 21$

* $P = 0.05$ as compared with <5 cars/km^2

[a] 95% confidence intervals are given in parentheses

Children may be exposed to radiation from natural sources, or building material or during medical diagnosis and treatment. No report is available on the relationship between radiation and urbanization in Sweden. Radiation may come from some building material, e.g., concrete made of some minerals rich in uranium. Houses in the sparsely populated areas in North Sweden may more often be made of wood, making building materials a possible confounding factor. Measurements in dwellings in Sweden, however, have shown higher exposure to radon in individual houses than in blocks of flats (Swedish Radiation Protection Institute 1995). The use of radiographs in medical examinations of children or pregnant women may be more prevalent in cities where there is better access to advanced medical equipment. Thus, radiation cannot be totally excluded as a confounding factor. On the other hand, an effect of radiation would probably have influenced the occurrence of cancer at some other sites. As no increased risk was found for cancer at those sites, radiation seems less likely to be a confounder.

The result of this study must be regarded with caution. It was an ecology study, and uncontrolled confounding may have occurred. Thus, we cannot be sure that the association detected between AML and car density was caused by car exhaust or gasoline exposure and not by an effect of confounding. Since other investigators (Savitz and Feirgold 1989; Wolff 1993) have also found an association between traffic and the occurrence of leukemia in children and young adults, further studies seem important.

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