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Association between diesel exposure at work and prostate cancer

by Andreas Seidler, MD,[1] Harald Heiskel, MD,[1] Ralf Bickeböller, MD,[2] Gine Elsner, MD[1]

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Objectives The possible etiologic relevance of occupational factors such as cadmium, cutting oils, diesel fuel and fumes, herbicides, polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls, soot, tar, mineral oil, and solvents to prostate cancer was studied.

Methods A case-referent study design was used to recruit 192 subjects with histologically confirmed prostate cancer and 210 referents who had prostate cancer histologically excluded either in one of two urologic practices (Hamburg and Frankfurt) or in the urological policlinic of the Frankfurt University. Data were gathered with a self-administered questionnaire and analyzed using logistic regression to control for age, region, and cigarette smoking. A job-exposure matrix was used for assigning exposure. For the calculation of dose-years, the duration of contact with specific substances was weighted by the intensity and probability of exposure according to a job-exposure matrix.

Results The analysis of dose-years yielded a statistically significant association between occupational exposure to diesel fuel or fumes and prostate cancer (odds ratio 3.7, 95% confidence interval 1.4—9.8, for subjects exposed to more than 25 dose-years in a comparison with subjects never exposed). For the other substances, no statistically significant differences in exposure were found between the cases and referents. When only jobs with a high exposure probability were used to classify the participants as exposed, only exposure to PAH was significantly associated with prostate cancer.

Conclusions In keeping with results from other studies, this study provides further evidence that exposure to diesel fuel or fumes — possibly mediated through PAH — may be associated with the development of prostate cancer.

Key terms case-referent study, job exposure matrix, occupational exposure, polycyclic aromatic hydrocarbons.

The incidence of prostate cancer is increasing rapidly (1). It is unlikely that the broader use of screening methods can explain this increase entirely, as age-standardized mortality is increasing as well. Nevertheless, little is known about the etiology of prostate cancer. Epidemiologic studies have shown dietary animal fat to play a potential etiologic role (2—3), while vegetable consumption may play a protective role through the effect of dietary phytoestrogens (4—5). In addition, several studies have provided evidence that smoking is associated with the development of prostate cancer (6—7).

The etiologic relevance of occupational factors to date is unclear. For many years, cadmium was believed to be of etiologic importance, but recent studies have not confirmed this relationship (8). Some studies have examined a possible relationship between agricultural jobs and prostate cancer (5, 9). Several studies found a link between prostate cancer and motor exhaust (10), diesel exhaust (11—12), or occupations with exposure to diesel exhaust such as professional driving (13—14) or mining (15). Other studies failed to confirm these associations (16—17). One study (18) actually reported a negative association between transport work and prostate cancer (and no association between truck driving and prostate cancer).

Polycyclic aromatic hydrocarbons (PAH) are the main carcinogenic agents found in diesel exhaust. Some epidemiologic studies have found elevated prostate cancer in occupations with probable PAH exposure such as the rubber industry (19), foundry industry (20), or firefighting (21). Houten et al (22) found a relationship between the occupation of mechanic and prostate cancer. The study conducted by Brownson et al (17) revealed similar, although not statistically significant, results.

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Golka et al (15) found an association between the occupation of miner, but not land transport worker or machinist, and prostate cancer. A large case-referent study found a modest link between PAH exposure and prostate cancer (12, 23). Nadon et al (23) found a statistically significant association between occupations with exposure to PAH from coal and prostate cancer, an association of borderline significance between benzo[a]pyrene exposure or PAH exposure from other sources and prostate cancer, but no association between total PAH exposure or between PAH from wood or gasoline and prostate cancer. Using the same data base, Aronson et al (12) found a relationship between PAH from coal and diesel exhaust and between water transport work and prostate cancer, but not between exposure to PAH from any source and prostate cancer.

The aim of our case-referent study was to elucidate further the possible etiologic relevance of occupational factors such as cadmium, cutting oils, diesel fuel and fumes, herbicides, PAH, polychlorinated biphenyls, soot, tar, mineral oil, and solvents to prostate cancer.

Subjects and methods

Study population

Patients with prostate disease were recruited from 2 urologic practices, one in Hamburg and the other in Frankfurt, and from the urologic policlinic of the Frankfurt University. Participating physicians were asked to identify all patients with prostate biopsies. Subjects with a histological diagnosis of prostate cancer were defined as cases, and those with negative biopsies became the referents. The referents either had prostate hypertrophy with subsequent transurethral prostate resection or had a biopsy to rule out suspected prostate cancer based on elevated prostate-specific antigen levels or rectal examination results. Cases with known multiple primary malignancies or referents with any type of cancer were excluded. Furthermore, subjects with manifest dementia or with an unclear diagnosis were not recruited. Of 272 cancer patients, 192 agreed to participate (71%). Out of 381 referents, 210 agreed to participate (55%).

A self-administrable questionnaire was developed to elicit a complete history of job titles and the subjects' own assessments of the frequency of exposure to the following substances: gasoline, diesel fuel, paints and lacquers, arsenic, benzidine pigments, asbestos, pesticides, organic solvents, silicates, lead, mercury, nickel, chromium, other metals, formaldehyde, cadmium, tar or bitumen. In addition, the subjects were asked about education, car driving, alcohol and coffee consumption, and smoking.

Exposure assessment by job-exposure matrix

The occupations were coded on the basis of the German Federal Statistical Institute's 1992 classification of occupations, on the Registrar General's 1966 classification of occupations, and on the 1968 classification of industries. Coding was performed by 2 of the authors (HH, AS) blind to the case or reference status. The job-exposure matrix constructed by Pannett et al (24) was used for the assignment of exposure regarding the following substances: cadmium; cutting oils; diesel fuel and fumes; herbicides; polychlorinated biphenyls; PAH; soot, tar, mineral oil; and solvents.

The Pannett matrix is based on combinations of industrial and occupational classes that have been cross-tabulated with 50 chemical agents or other exposure factors. For each combination of occupation and industry, the probability (3 grades: none, small proportion of workers, high proportion of workers) and the intensity (3 grades: none, lightly exposed, heavily exposed) of exposure to each of the chemical substances is classified. For example, bus drivers (occupation code 122) with unknown industry (industry code 999.9) are categorized as having a high potential of low diesel exposure, and motor mechanics (occupation code 42) in road passenger transport (industry code 702.X) are classified as having a low potential for high exposure to diesel fuel or fumes. Exposures before 1950 are separately classified. To combine duration of exposure with intensity and probability of exposure, we regarded the semiquantitative exposure classes as quantitative values. Dose-years of exposure were calculated in 2 modes. First, the duration of potential contact with specific substances was weighted by intensity (exposure trivial = weighting factor 0, lightly exposed = weighting factor 1, heavily exposed = weighting factor 2) and probability of exposure (none = factor 0, small proportion = factor 0.5, high proportion = factor 1) according to the job-exposure matrix. Thus 10 dose-years could mean low-level exposure with a high exposure probability (eg, bus drivers exposed to diesel fuel or fumes) for 10 years or, equivalently, low-level exposure with a low exposure probability (eg, steel erectors in coal mining with exposure to diesel fuel or fumes) for 20 years. The subjects were classified into the 3 categories of never exposed (reference category), exposed subjects with ≤25 dose-years, and exposed subjects with >25 dose-years.

In a second analysis, only subjects having held jobs with a high exposure probability were classified as exposed, the subjects classified as having had low exposure for <5 years being regarded as never exposed. Occupational exposures of subjects having held jobs with a low exposure probability for ≥5 years and having held no jobs with a high exposure probability were analyzed as a separate category.

As no direct exposure measurements were available, exposures that were significantly associated with prostate cancer were reanalyzed using another job exposure matrix developed by Seidler et al (25), the Parkinson's disease (PD) matrix. This matrix was developed for use in a case-referent study in Germany in a study of risk factors for Parkinson's disease. The PD matrix uses the same exposure categories as the Pannett matrix. As it was primarily constructed for the assessment of neurotoxic exposures, not all the potentially carcinogenic substances analyzed in this study could be classified by it. In addition, the PD matrix only provides exposure assessment for the occupations held by subjects in the study for which it was developed. Therefore, some occupations could only be assigned to similar, but not identical, occupations with the PD matrix. For this reason, the Pannett matrix was used for the basic analysis and the PD matrix only for an additional examination of the significant results.

A computer program was created to convert the occupational histories of the subjects into exposure indices for the mentioned substances.

Potential confounders

The subjects were asked about their age, education, and smoking status (smoking of cigarettes, cigars or pipes in the present or the past). The mean age at the time of the diagnosis of prostate cancer among the cases was 71.1 (SD 8.6) years, and the mean age at the histological exclusion of prostate cancer among the referents was 69.7 (SD 8.5) years (table 1). Ex-smokers and current smokers (cigarettes, cigars or pipes) were classified as ever smokers (80.2% of the cases, 76.7% of the referents).

All the statistical analyses were adjusted for age, smoking, and place of data collection, referred to as "region" in this text (Hamburg urologic practice, Frankfurt urologic practice, Frankfurt policlinic). As age is known to be strongly associated with the occurrence of prostate cancer, and as the cases were generally older than the referents, we decided to adjust for age. Age was entered into the logistic regression model in 1-year intervals. The mean age of the subjects was about 70 years; therefore, there was no substantial correlation between age and exposure duration. As several studies have found a link between smoking and prostate cancer (6—7), we decided to adjust for smoking. Region was considered to be a potential confounder because of differences in the case-referent ratio according to recruitment center, possibly due in part to variations in the degree of prediagnostics and because occupational exposures differed between the regions. (For example, there were seamen in Hamburg, but not in Frankfurt.)

Statistics

The odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using a logistic regression analysis, adjusted for age, smoking, and region. As a relatively long latency period between a potential carcinogenic initiator or promoter effect and the later diagnosis of

Table 1. Characteristics of the cases and referents.

Characteristic	Cases (N=192)				Referents (N=210)			
	N	%	Mean	SD	N	%	Mean	SD
Age at diagnosis	..	..	71.1	8.6	..	..	69.7	8.5
≤59 years	17	8.9	..	..	29	13.8	..	..
60—69 years	61	31.8	..	..	76	36.2	..	..
70—79 years	76	39.6	..	..	78	37.1	..	..
≥80 years	38	19.8	..	..	27	12.9	..	..
Educational level								
Graduated from high school	23	12.0	..	..	31	15.0	..	..
Secondary school level	52	27.2	..	..	52	25.1	..	..
Elementary level	116	60.4	..	..	124	58.9	..	..
Unknown	1		..	..	3	..	..	..
Region								
Hamburg (urologic practice)	125	65.1	..	..	132	62.9	..	..
Frankfurt (urologic practice)	24	12.5	..	..	42	20.0	..	..
Frankfurt (urologic policlinic)	43	22.4	..	..	36	17.1	..	..
Smoking								
Never	36	18.8	..	..	45	21.4	..	..
Ever	154	80.2	..	..	161	76.7	..	..
Unknown	2	..	..	..	4	..	..	..
Duration of work (years, ≤5 years before diagnosis)	..	..	42.7	7.6	..	..	42.1	8.2
Unknown	4	..	..	..	4	..	..	..
Number of jobs (≤5 years before diagnosis)	..	..	3.9	1.9	..	..	3.7	2.0
Unknown	2	..	..	..	3	..	..	..

prostate cancer was expected, only exposures up to 5 years prior to the diagnosis (considered to be the date of the histologic exclusion of prostate cancer for the referents) were considered.

Results

Self-estimated chemical exposures

The cancer patients and referents did not differ with respect to their own assessment of exposure to cadmium, diesel fuel, pesticides, soot or tar, or solvents (table 2). The cancer patients drove further distances by car than the referents. The odds ratio (OR) for prostate cancer in subjects driving 10 — 30 000 km per year versus those not driving at all was 1.6 (95% CI 0.9—2.6). The OR increased to 2.8 (95% CI 1.1—6.9) for subjects driving 30—50 000 km per year. However, an OR of only 0.5 (95% CI 0.1—1.9) was found for subjects driving more than 50 000 km per year (table 2).

Occupational exposures classified by the Pannett matrix

The analysis of dose-years (exposure duration weighted by probability and intensity of exposure) yielded a statistically significant association between exposure to diesel fuel or fumes and prostate cancer (table 3, left column). The odds ratio for the subjects exposed to diesel fuel or fumes for up to 25 dose-years versus the subjects never exposed at work was 1.1 (95% CI 0.7—1.8); the odds ratio for the subjects exposed for >25 dose-years was 3.7 (95% CI 1.4—9.8). The longest held occupations of the subjects classified as having had >25 dose-years of exposure to diesel fuel or fumes (Registrar General's 1966 classification) were drivers of road transport vehicles (6 cases, 2 referents), motor mechanics or auto engineers (4 cases, 3 referents), deck and engine-room rating, barge or boatmen (4 cases, 0 referents), drivers of other road transport vehicles (2 cases, 0 referents), and drivers, motormen, firemen or railway engineers (1 case, 0 referents). No significant differences between the subjects with prostate cancer and the referents were found for exposure to substances other than diesel fuel or fumes.

When only subjects with a high probability of exposure were regarded as exposed (table 3, right column), the cancer patients were more likely to have been exposed to PAH for >25 years than were the referents (OR 2.1, 95% CI 1.0—4.2). For the other substances examined — including diesel fuel and fumes — this analysis did not reveal a significant association with prostate cancer. The Pannett matrix classified very few subjects as having had a high probability of exposure for >25 years to the substances considered in this study; therefore, the OR values for >25 dose-years of exposure were based on small numbers in this second analysis.

Parkinson's disease matrix analysis

The PD matrix analysis (table 4, left column) revealed a significant association between prostate cancer and exposure to exhaust fumes. The OR for >25 years of exposure versus no exposure was 2.4 (1.2—4.7). The OR values for the other substances analyzed with the PD matrix were not significant or could not be calculated due to the small numbers of subjects exposed. However, there were 5 cases, but no referents, with >25 dose-years of exposure to tar or pitch. Similarly, 6 cases, but no referents, were classified as having been exposed to soot, and 4 cases but no referents with exposure to pyrolytic substances for >25 dose-years. When only subjects with a high exposure probability were regarded as exposed (table 4, right column), an odds ratio of 3.8 (95% CI 1.2—11.4) was calculated for the subjects exposed to exhaust fumes for >25 years. Exposure to tar and pitch for ≤25 dose-years was also significantly associated with prostate cancer (OR 2.6, 95% CI 1.1—6.2) in this analysis; there were no subjects with >25 dose-years of exposure to tar or pitch. The association between ≤25 dose-years of high potential exposure to soot and prostate cancer approached significance (OR 3.1, 95% CI 0.9—10.4); in addition, 2 cases, but no referents, had >25 dose-years of high potential soot exposure. Only a very small number of subjects was classified as being exposed to pyrolytic substances with high probability by the PD matrix.

Table 2. Car driving and self-reported exposure to chemicals. (OR = odds ratio, 95%CI = 95% confidence interval)

Variable	Cases (N)	Referents (N)	Adjusted OR[a]	95% CI
Car driving (km/year)				
Nondriver	39	51	1.0	.
< 10 000 km	39	50	1.0	0.6 — 1.9
10 000 — 30 000 km	94	89	1.6	0.9 — 2.6
>30 000 — 50 000 km	17	11	2.8	1.1 — 6.9
>50 000 km	3	9	0.5	0.1 — 1.9
Occupational or free-time exposures				
Cadmium				
Never	187	201	1.0	
Occasionally	5	8	0.7	0.2 — 2.2
Frequently	-	1	.	.
Diesel fuel				
Never	142	151	1.0	.
Occasionally	26	29	1.0	0.6 — 1.9
Frequently	24	30	0.9	0.5 — 1.6
Pesticides				
Never	153	164	1.0	.
Occasionally	36	37	1.1	0.7 — 1.8
Frequently	3	9	0.4	0.1 — 1.3
Solvents				
Never	119	125	1.0	.
Occasionally	43	61	0.8	0.5 — 1.3
Frequently	30	24	1.2	0.7 — 2.2
Soot, tar				
Never	156	171	1.0	.
Occasionally	25	29	1.0	0.5 — 1.7
Frequently	11	10	1.1	0.5 — 2.8

[a] Adjusted for age, smoking, and region.

Table 3. Exposure to specific substances, classified by the Pannett job-exposure matrix (OR=odds ratio, 95% CI = 95% confidence interval, PAH = polycyclic aromatic hydrocarbons)

Variable	1. Dose-years = intensity × probability × duration				2. Dose-years = intensity × duration (only unexposed subjects[a] and subjects with a high probability of exposure)			
	Cases (N)	Referents (N)	Adjusted OR[b]	95% CI	Cases (N)	Referents (N)	Adjusted OR[b]	95% CI
Cadmium[c]								
0 dose-years	149	165	1.0	.	157	172	1.0	.
> 0 — 25 dose-years	38	39	1.1	0.6 — 1.7	-	-	..	.
> 25 dose-years	1	1	1.2	.	-	-	..	.
Low probability of exposure[d]	-	-	..	.	31	33	1.0	0.6 — 1.7
Unknown	4	5	..	.	4	5	..	
Cutting oils[c]								
0 dose-years	151	163	1.0	.	161	167	1.0	.
> 0 — 25 dose-years	34	34	1.1	0.6 — 1.8	12	8	1.6	0.6 — 4.1
> 25 dose-years	3	8	0.4	0.1 — 1.6	1	5	0.2	<0.1 — 1.7
Low probability of exposure[d]	-	-	..	.	14	25	0.6	0.3 — 1.1
Unknown	4	5	..	.	4	5	..	.
Diesel fuel and fumes[c]								
0 dose-years	118	141	1.0	.	134	155	1.0	.
> 0 — 25 dose-years	53	58	1.1	0.7 — 1.8	23	24	1.1	0.6 — 2.1
> 25 dose-years	17	6	3.7	1.4 — 9.8	-	-	..	.
Low probability of exposure[d]	-	-	..	.	31	26	1.4	0.8 — 2.6
Unknown	4	5	..	.	4	5	..	.
PAH[c]								
0 dose-years	118	145	1.0	.	131	156	1.0	.
> 0 — 25 dose-years	64	55	1.6	1.0 — 2.4	24	14	2.1	1.0 — 4.2
> 25 dose-years	6	5	1.4	0.4 — 4.7	1	1	..	.
Low probability of exposure[d]	-	-	..	.	32	34	1.1	0.6 — 1.9
Unknown	4	5	..	.	4	5	..	.
Herbicides[c]								
0 dose-years	173	186	1.0	.	181	194	1.0	.
> 0 — 25 dose-years	14	16	1.0	0.5 — 2.1	3	9	0.4	0.1 — 1.4
> 25 dose-years	1	3	..	.	-	-	..	.
Low probability of exposure[d]	-	-			4	2	2.2	0.4 — 12.6
Unknown	4	5	..	.	4	5	..	.
Organic solvents[c]								
0 dose-years	107	128	1.0	.	117	134	1.0	.
> 0 — 25 dose-years	72	65	1.3	0.8 — 2.0	24	18	1.5	0.8 — 3.0
> 25 dose-years	9	13	0.8	0.3 — 2.1	4	8	0.6	0.2 — 2.0
Low probability of exposure[d]	-	-	..	.	43	46	1.0	0.6 — 1.7
Unknown	4	4	..	.	4	4	..	.
Polychlorinated biphenyls[c]								
0 dose-years	152	167	1.0	.	159	171	1.0	.
> 0 — 25 dose-years	35	37	1.0	0.6 — 1.8	-	2	..	.
> 25 dose-years	1	1	..	.	-	-	..	.
Low probability of exposure[d]	-	-	..	.	29	32	1.0	0.6 — 1.7
Unknown	4	5	..	.	4	5	..	.
Soot, tar, mineral oil[c]								
0 dose-years	103	110	1.0	.	121	128	1.0	.
> 0 — 25 dose-years	62	70	1.0	0.6 — 1.5	26	15	1.9	0.9 — 3.8
> 25 dose-years	23	26	1.0	0.5 — 1.9	5	12	0.4	0.2 — 1.3
Low probability of exposure[d]	-	-	..	.	36	51	0.7	0.4 — 1.2
Unknown	4	4	..	.	4	4	..	.

[a] Subjects with a low probability of exposure for < 5 years have been regarded as never exposed.
[b] Adjusted for age, smoking, and region.
[c] The missing values were analyzed as a separate category (OR not shown here).
[d] Low probability of exposure for ≥5 years; in the first analysis, these subjects were not classified separately.

Discussion

This case-referent study revealed a statistically significant association between prostate cancer and exposure to diesel fuel or fumes and PAH.

Calculating the power of the study is difficult, as the usage of a semiquantitative job-exposure matrix in the absence of ascertained exposure assessments does not allow for valid prevalence estimates. We assume that the proportion of probands classified as exposed is

Table 4. Exposure to substances containing polycyclic aromatic hydrocarbons, as classified by the PD job-exposure matrix. (PD = Parkinson's disease, OR = odds ratio, 95% CI = confidence interval)

Variable	1. Dose-years = intensity × probability × duration				2. Dose-years = intensity × duration (only unexposed subjects[a] and subjects with a high probability of exposure)			
	Cases (N)	Referents (N)	Adjusted OR[b]	95% CI	Cases (N)	Referents (N)	Adjusted OR[b]	95% CI
Exhaust fumes[c]								
0 dose-years	48	67	1.0	.	52	70	1.0	-
> 0 — 25 dose-years	102	116	1.2	0.8 — 1.9	119	125	1.2	0.8 — 2.0
> 25 dose-years	38	22	2.4	1.2 — 4.7	14	5	3.8	1.2 — 11.4
Low probability of exposure[d]	-	-	..	.	3	5	0.9	0.2 — 3.8
Unknown	4	5	..	.	4	5	..	.
Tar, pitch[c]								
0 dose years	80	99	1.0	.	114	133	1.0	.
> 0 — 25 dose-years	103	106	1.2	0.8 — 1.8	19	9	2.6	1.1 — 6.2
> 25 dose years	5	-	..	.	-	-	..	.
Low probability of exposure[d]	-	-	..	.	55	64	0.9	0.6 — 1.5
Unknown	4	5	..	.	4	4	..	.
Soot[c]								
0 dose-years	85	94	1.0	.	115	130	1.0	.
> 0 — 25 dose-years	97	111	0.9	0.6 — 1.4	10	4	3.1	0.9 — 10.4
> 25 dose-years	6	-	..	.	2	-	..	.
Low probability of exposure[d]	-	-	..	.	61	72	0.9	0.5 — 1.4
Unknown	4	5	..	.	4	4	..	.
Pyrolytic substances[c]								
0 dose-years	88	93	1.0	.	122	130	1.0	.
> 0 — 25 dose-years	96	112	0.8	0.6 — 1.3	1	1	..	.
> 25 dose-years	4	-	..	.	2	-	..	.
Low probability of exposure[d]	-	-	..	.	63	75	0.8	0.5 — 1.3
Unknown	4	5	..	.	4	4	..	.

[a] Subjects with a low probability of exposure for < 5 years have been regarded as never exposed.
[b] Adjusted for age, smoking, and region.
[c] The missing values were analyzed as a separate category (OR not shown here).
[d] Low probability of exposure for ≥5 years; in the first analysis, these subjects were not classified separately.

generally higher than the true exposure prevalences because the job-exposure matrix assignments were based on probability estimates. In our study, an odds ratio of 2 could be detected with a power of 80% for a 14% prevalence of exposure in the reference group. In a Finnish case-referent study on primary liver cancer, industrial hygienists estimated the prevalence of exposure to chemicals classified with the Pannett job-exposure matrix (26). Of the substances considered in our study, only exposure to diesel fuel and fumes (prevalence 28%) had a prevalence higher than 14% in the Finnish study. Equivalent German data are not available. In our study, even if the lowest prevalence of exposure among the referents, that to herbicides (9%, including the referents with a low probability of exposure) were equal to the true prevalence, the power would not be sufficient to detect an odds ratio of 2. Therefore, negative results concerning rare exposures, in our study particularly to herbicides, should be interpreted with caution.

Selection bias

Case-referent studies are open to bias (27). Because this study was not population-based, a patient selection bias cannot be ruled out. Both the cases and the referents were recruited in a urologic practice or policlinic. It cannot be ruled out that subjects with nonmalignant prostate diseases differ in their health seeking behavior. For example, subjects with higher socioeconomic status may contact physicians with relatively mild complaints and could therefore be overrepresented in the reference group. On the other hand, persons with a higher socioeconomic status are more likely to participate in cancer screening programs and may therefore be detected at an earlier stage. To determine whether early cancer diagnosis (possibly through selective participation in screening programs) influenced the results, we excluded cases with low-grade prostate cancer (N=21) from the analysis. This exclusion had no substantial effect on the results. Adjustment for educational status did not substantially influence the results either.

The relatively low response rate could also have led to selection bias. With regard to age, the respondents did not differ from the nonrespondents. Nevertheless, a selectively low participation rate cannot be completely ruled out for the referents exposed to diesel fuel.

Misclassification bias

An analysis of the subjects' own assessment of exposure to specific substances revealed no differences between the cancer patients and the referents. As self-assessment

is a rather subjective indication of exposure to specific substances that is open to both recall bias and misclassification bias (especially when substances are not commonly known to lay persons, such as PAH), a job-exposure matrix was used to classify the occupational exposures. This approach can be criticized as it specifies exposures only crudely (28) and therefore leads to substantial misclassification. Kauppinen et al (26) presented direct data on the magnitude of the misclassification bias of diesel fuel and fumes; the bias was moderate but not as serious as for many other less common agents. The authors suggested that the Pannett job-exposure matrix should be an acceptably valid screening tool outside the United Kingdom, provided exposures in industries and occupations in other countries are similar to its assignment. Our comparison with the PD matrix suggests that this is the case in Germany for the exposures relevant to this study. In addition, as misclassification through the use of a job-exposure matrix is nondifferential with regard to the disease status of the subjects, it tends to lead to an underestimation of risk. If the prevalence of exposure is low, it has been shown that this bias towards unity is more dependent on specificity than on sensitivity (29). Specificity of the job-exposure matrix is increased (albeit with a loss of sensitivity) if only subjects with a high probability of exposure are regarded as exposed. When we analyzed our data using this approach, exposure to diesel fuel and fumes was no longer significantly associated with prostate cancer, but exposure to PAH was. Notably, PAH represent the main carcinogenic component of diesel fuels, although a carcinogenic effect specific for the development of prostate cancer has not yet been shown.

Validity of the exposure assessment

Continuous job-site measurements or biomonitoring results are generally not available to validate results obtained using a job-exposure matrix. However, agreement between the results obtained using 2 different matrices lends further support to the findings. Therefore, we reanalyzed our data using the PD matrix, which we constructed for use in a study concerned with risk factors for Parkinson's disease in Germany (25). This matrix does not allow direct classification of exposure to diesel fuel and fume or PAH, but it does classify exposure to exhaust fumes, tar and pitch, soot, and pyrolytic substances. Concordance between the Pannett and PD matrices was moderate. For example, Pearson's correlation coefficient for the correlation of dose-years of solvent exposure as classified by the Pannett matrix and as classified by the PD matrix is 0.50; the correlation coefficient between the dose-years of diesel exposure according to the Pannett matrix and the dose-years of exposure to exhaust fumes according to the PD matrix is 0.69. Indeed, the results obtained using the PD matrix indirectly support the results revealed by the Pannett matrix, as they show a statistically significant association between prostate cancer and exposure to exhaust fumes, tar or pitch, and soot. Exposure to exhaust fumes generally entails exposure to diesel fumes, and exposure to exhaust fumes, tar, pitch, and soot is related to PAH exposure. The subjects exposed to diesel fuel or fumes for more than 25 dose-years mainly worked as drivers, motor mechanics, auto engineers, or boatmen. This job spectrum suggests that exposure to PAH as a component of inhalatory diesel exhaust may be an important risk factor for prostate cancer, particularly in light of the elevated odds ratios for high potential exposure to PAH, for exposure to exhaust fumes in the PD matrix analysis, and for car driving. However, it is, of course, difficult to identify the biologically relevant agents among the many combinations of substances that constitute workplace exposure definitively using retrospective epidemiologic methods alone.

Biological plausibility

There is some evidence for a possible humorally mediated carcinogenic effect of PAH on parenchymatic organs (30). The carcinogenic effects of some PAH may be associated with the inducibility of certain enzymes such as AHH (aryl hydrocarbon hydroxylase) in the target organs (31—33). Lee et al (34) exposed male rats to diesel emissions for 42 days (20 hours a day) and documented whether the activity of AHH in liver, lung, testicles, and prostate glands was induced. The highest relative increase in AHH activity was observed in the prostate glands. The authors discussed a potential relationship between the inducibility of AHH and the susceptibility to PAH-induced cancers. Therefore, diesel exhausts may exert effects not only on the respiratory or gastrointestinal systems, but also on parenchymatic organs. Cell culture experiments have revealed a relationship between enzymatic metabolism of various PAH and the inducibility of malignant transformations (31, 35—37).

Golden et al (38) reviewed available data regarding the risk of cancer among fire fighters. They pointed out a 30—50% increase in prostate cancer risk consistently found in the majority of studies. The authors concluded that relatively weak but plausible evidence links firefighting to an increased risk of (inter alia) prostate cancer. Although fire fighters are exposed to complex mixtures of potentially carcinogenic substances, among these, PAH have established carcinogenic properties. Thus PAH may be an important factor in the development of prostate cancer, although their exact etiologic role remains unclear (23, 38—40). Liou et al (41) monitored PAH-DNA adducts, as a measure of potential carcinogenic damage associated with exposure to PAH. After adjustment for potential confounders, fire fighters had a statistically significant 4-fold higher risk of detectable

PAH-DNA adduct levels when compared with unexposed referents. This study not only presents evidence for the PAH exposure of fire fighters that could contribute to the elevated prostate cancer risk, but additionally described a novel way of biomonitoring occupational exposure to PAH (41) in future studies.

PAH or other chemical constituents of diesel exhaust, such as certain hydrocarbons, may also have hormonal effects that could have carcinogenic potential. For instance, methyl-cholanthrene, benzo[a]pyrene, and 7,12-dimethyl-1,2-benzanthracene have been shown to have an antiestrogenic effect in estrogen-sensitive human breast cancer cell lines (MCF-7) through binding to the cytosolic aryl hydrocarbon receptor (42—43). The application of estrogenic hormones can slow the proliferation of metastic prostate neoplasms (44). Thus antiestrogenic hormones or the antiestrogenic effects of certain hydrocarbons may promote the growth of initiated cancer cells in the prostate, analogous to the promotor effects of androgens. However, the clinical importance of possible hormonal or other effects of various PAH and other hydrocarbons, particularly on the prostate gland, remains inadequately understood.

Concluding remarks

In keeping with results from other studies, our data provide further evidence that exposure to diesel exhaust — possibly mediated through PAH — may play a potential role in the etiology of prostate cancer. However, there is a need for experimental research to elucidate further the effects of specific PAH and other hydrocarbons on the prostate gland, and to assess the carcinogenic potential of their enzyme-inducing and hormone-imitating effects. In addition, further epidemiologic studies are needed to determine potential carcinogenic exposures relevant to the development of prostate cancer — particularly to PAH and other hydrocarbons — more precisely, ideally including biomarkers in exposure measurement.

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