

# Prostate Cancer Incidence in Relation to Time Windows of Exposure to Metalworking Fluids in the Auto Industry

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**Background:** Exposure to metalworking fluids has been previously associated with prostate cancer mortality in a cohort of autoworkers. Our objective was to further explore this finding in a study of prostate cancer incidence in the same cohort, with reduced misclassification of outcome.

**Methods:** We conducted a nested case-control study in the General Motors cohort of autoworkers. Incident cases of prostate cancer ( $n = 872$ ) were identified via the Michigan Cancer Registry from 1985 through 2000. Controls were selected using incidence-density sampling with 5:1 ratio. Using cumulative exposure ( $\text{mg}/\text{m}^3\text{-years}$ ) as the dose metric, we first examined varying lengths of lags (0–25 years). Then, we evaluated consecutive windows of exposure: 25 or more years before risk age, and fewer than 25 years. We used penalized splines to model the relative risk as a smooth function of exposure, and adjusted for race and calendar year of diagnosis in a Cox model.

**Results:** Risk of prostate cancer increased with exposure to soluble and straight fluids 25 years or more before risk age but not with exposure in the last 25 years. The relationship with soluble fluids was piecewise linear, with a small increase in risk at lower exposures followed by a steeper rise. By contrast, the relationship with straight fluids was linear, with a relative risk of 1.12 per  $10 \text{ mg}/\text{m}^3\text{-years}$  of exposure (95% confidence interval = 1.04–1.20).

**Conclusions:** Exposure to oil-based fluids, soluble and straight, is modestly associated with prostate cancer risk among autoworkers, with a latency period of at least 25 years.

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Prostate cancer is the most commonly diagnosed malignancy in men and the second leading cause of cancer deaths in western countries. In the last 2 decades, the incidence of prostate cancer has increased worldwide, with a particular steep increase in the United States, partly because of serum prostate-specific antigen (PSA) screening.<sup>1–3</sup> There is approximately a 30-fold difference among countries in prostate cancer incidence rates, with the highest rates found in the United States and the lowest in China.<sup>3</sup> In the United States, African-Americans have the highest incidence rates, followed by whites, and then Asian-Americans.<sup>4,5</sup> These international and ethnic/racial variations in prostate cancer incidence, combined with a shift of risk patterns caused by migration to developed countries, suggest that both environmental and genetic factors play important roles in the etiology of this disease.

Thurston et al<sup>6</sup> recently examined the relationship between prostate cancer mortality and exposure to metalworking fluids in a nested case-control study in the United Autoworkers/General Motors (UAW-GM) cohort of 46,400 autoworkers. Metalworking fluids are complex mixtures used in the auto-manufacturing industry to lubricate, cool, prevent rust, and carry away metal parts during machining and grinding operations. These fluids can be grouped into 3 categories: (1) straight oils, which are undiluted mineral and fatty oils; (2) soluble fluids, which are water emulsions of mineral oils; and (3) synthetic fluids, which are organic compounds such as glycols or ethanalamines. Components present in metalworking fluids, such as polyaromatic hydrocarbons (present in straight and soluble fluids), alkanolamines, and nitrosamines have been classified by IARC as possible human carcinogens, group 2B.<sup>7,8</sup> Moreover, in a literature review of health effects of metalworking fluids, National Institute for Occupational Safety and Health concluded that there was substantial evidence linking exposure with cancers of the larynx, rectum, and pancreas, and less consistent evidence for cancers of esophagus, stomach and prostate.<sup>9,10</sup> Findings from Thurston et al<sup>6</sup> suggested that metalworking fluids exposure may also be linked to prostate cancer, based on a nonlinear relationship between cumulative exposure to soluble fluids (with 30 years lag) and prostate cancer deaths. The

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relative risk increased modestly at lower exposures, followed by a steeper rise in risk for higher cumulative exposures.

The goal of this study was to further consider the previous findings of a nonlinear association between prostate cancer mortality and exposure to metalworking fluids in the UAW-GM cohort,<sup>6</sup> by examining recently collected data from newly diagnosed cases of prostate cancer in the same cohort. The objectives of this study were to explore latency by defining cumulative exposure in consecutive time windows and adjust for potential confounding that occurs between exposure windows and by using a flexible regression approach based on penalized splines to examine relationships between 3 types of metalworking fluids (straight, soluble, and synthetic), and the incidence of prostate cancer.

## METHODS

### Subjects

This is a nested case-control study in a cohort of 31,648 hourly employed male members of the UAW-GM, who worked at least 3 years before 1 January 1985 in 3 plants in Michigan, and were still alive on this date (subset of the UAW-GM cohort described by Eisen et al<sup>11</sup>). Study subjects had been hired between 1921 and 1981 and followed for cancer incidence from 1985 through 2000. Information on vital status was available for the original UAW-GM cohort from 1985 through 1994. Vital status was recently updated from 1995 through 2000 for a 10% random sample of the UAW-GM cohort via the National Death Index, for the purpose of another study using a case-cohort approach.<sup>12</sup> We used this information to select a group of controls as described below.

For this study, incident cases of prostate cancer ( $n = 872$ ) in the UAW-GM cohort were identified via the Michigan Cancer Registry from 1 January 1985 through 31 December 2000; the vital status of these cases was also reported by the Registry. Eligible controls were selected using incidence density sampling from among coworkers who remained at risk (ie, free of disease), by the age of diagnosis of the case, with a sampling ratio 5:1. Eligible controls for cases that were diagnosed from 1985 through 1994 were selected from the entire cohort. Controls for those cases diagnosed from 1995 through 2000 were selected from the 10% random sample of the UAW-GM cohort with updated vital information, to make sure that controls were still alive in the calendar year in which they achieved risk age (the age of the case). (These controls were presumably free of prostate cancer, since the entire UAW-GM cohort had been linked to the Michigan Cancer Registry to identify incident cases.) No other matching factors were used.

### Exposure Assessment

Detailed exposure assessment is described elsewhere.<sup>13</sup> In summary, industrial hygiene measurements for 3 types of

metalworking fluids, as well as historical information on metalworking fluids use in specific operations, were collected from plant records and corporate databases. The absolute levels of exposures were based on both personal breathing zone and general area samples collected by researchers.<sup>14</sup> A scale factor was calculated for each metalworking fluids type and operation (grinding and machining) based on the ratio of company measurements to those collected by research industrial hygienists in the 1980s. These scale factors were multiplied by study measurements to generate past exposure concentrations of metalworking fluids aerosol in each unique plant, department, and job.<sup>13</sup> For our study, metalworking fluids exposures for subjects who were still actively employed at the end of 1994 were updated to 2000, assuming no changes in exposure levels during the last 6-year period of additional follow-up.

### Data Analysis

Cumulative exposure to soluble, straight, and synthetic metalworking fluids ( $\text{mg}/\text{m}^3\text{-years}$ ) was the dose metric used. It was accumulated in several ways. First, we calculated total cumulative exposure as a time varying variable for each subject from hire until risk age. This was the sum of the calendar time-specific estimates of total mass particulate for each job in which he had worked, weighted by the time spent in each job. After examining total cumulative exposure, we lagged exposures for 10, 15, 20, and 25 years to account for latency. After examining lags, we also evaluated consecutive time windows of exposure: 25 or more years before (early window), and less than 25 years before risk age (later window). This approach allows recent exposures to contribute to prostate cancer risk, and also controls for potential confounding of one window by another.

We used penalized splines in a Cox model to allow the relationship between exposure windows of each type of metalworking fluids and the log relative risk of prostate cancer incidence to be a smooth function. When the smooth functions of time windows of exposure are incorporated into the Cox model, the natural log (Ln) hazard ratio is expressed as:

$$\text{Ln}\{\lambda(t|X_i)/\lambda_0(t)\} = \sum_j [s_{1j}(X_{1ij}(t)) + s_{2j}(X_{2ij}(t))] + Z_i\beta_k$$

for subject  $i$  at time  $t$  (age is the time variable used in this Cox model);  $j = 1-3$  for soluble, straight, and synthetic fluids;  $X_{1ij}(t)$ ,  $X_{2ij}(t)$  are cumulative exposures in early and later window;  $s_{1j}$ ,  $s_{2j}$  are penalized splines of these exposure variables; and  $Z_i$  is a vector of 2 other covariates (race and calendar year of diagnosis) included in the final model. For the calendar year of diagnosis 2 dummy variables were defined to capture 3 time periods: 1985–1989, 1990–1994, and 1995–2000. We adjusted for other metalworking fluids types because autoworkers in our study had exposures to

more than one fluid type simultaneously. We considered race a potential confounder since incidence rates of prostate cancer are higher among African-American subjects compared with whites, and metalworking fluids exposure varied by race. Incidence rates of prostate cancer have increased with year of diagnosis from 1985 through 2000, while metalworking fluid exposure levels have decreased during the follow-up period.

The S-PLUS function *pspline* (S-PLUS 2000; Insightful Corporation, Seattle, WA) was used to fit penalized splines in a Cox model. We could not smooth all 6 exposure variables simultaneously (ie, 2 exposure windows for each fluid type) with available software. Therefore, we proceeded sequentially by smoothing early and later exposure windows for one type of metalworking fluids, including linear terms for exposures of the other 2 fluid types. Penalized splines were implemented by fitting regression splines, using penalized least squares, with a penalty on coefficients of adjacent knots.<sup>15</sup> Ruppert<sup>16</sup> has shown that the resulting fit of penalized spline is insensitive to the number and location of knots as long as they are relatively dense. In a similar recent application, penalized splines were insensitive to change in the number and location of knots.<sup>17</sup>

We used the S-PLUS default setting for number and location of knots in *pspline* function; there are n knots equally spaced across the range of X (exposure), where n = 2.5 times the degrees of freedom. We selected the optimal degrees of freedom for penalized splines for exposure windows of each metalworking fluid by minimizing Akaike Information Criterion (AIC) value of Cox models. These models included penalized splines for exposure windows of one of the 3 types of metalworking fluids, while adjusting linearly for the other 2 types. Chi-squared tests for the linear and nonlinear components of the *pspline* function (provided in the model output) were used to determine whether a spline or a linear function was more appropriate for the exposure variables that we smoothed on.

We used conditional logistic regression to examine linear relationships between prostate cancer incidence and exposure windows of soluble, straight and synthetic fluids, adjusting for race and calendar year of diagnosis, using *proc phreg* in SAS (SAS Institute, Cary, NC) to estimate relative risks (RRs) and 95% confidence intervals (CIs). Potential confounding was assessed for each exposure, fitting models using each main effect and then controlling for change in parameter estimates of exposure variables when other variables entered or left the models. Goodness of fit was assessed by AIC.

### RESULTS

There were 872 incident cases of prostate cancer in the UAW-GM cohort diagnosed from 1985 through 2000. (Fifty-eight of the cases who had died by the end of 1994 were included in the previously published mortality study.<sup>6</sup>) On

average, cases were 70-year-old at diagnosis (Table 1). The percentage of African-American subjects was higher among cases (27%) compared with controls (15%). Cases were hired 2 years later than controls, but the mean age of hire was similar (about 30 years). On average, calendar year of diagnosis for cases was 2 years later compared with the calendar year in which controls achieved risk age (similar age with cases' age at diagnosis). Duration of employment was slightly higher among cases.

When we examined total cumulative exposure, most cases and control subjects had been exposed to soluble metalworking fluids (88 and 90%, respectively), almost 56% of both groups had been exposed to straight oils, and fewer

**TABLE 1.** Characteristics of Prostate Cancer Cases and Controls in the Cohort of Autoworkers Exposed to Metalworking Fluids

	Cases (n = 872)	Controls (n = 4375)
Age at diagnosis (years); Mean ± SD	70.4 ± 8.9	
Race; %		
White	58	64
African-American	27	15
Unknown	15	21
Plant; %		
Plant 1	47	40
Plant 2	27	36
Plant 3	26	24
Year of birth		
Mean ± SD	1923 ± 10.1	1920 ± 9.8
Range	1893–1949	1890–1949
Year of hire		
Mean ± SD	1953 ± 11.6	1951 ± 11.4
Range	1925–1981	1921–1980
Age at hire (years)		
Mean ± SD	30.2 ± 9.4	30.9 ± 9.5
Range	16.5–60.5	15.5–63.2
Calendar year of diagnosis*		
Mean ± SD	1993 ± 3.8	1991 ± 3.7
Range	1985–2000	1985–2000
Duration of employment (years)		
Mean ± SD	23.2 ± 11.3	20.9 ± 11.5
Range	3.0–51.9	3.0–49.9
Vital Status as of 2000; %		
Alive	61	56
Dead	39	41
Unknown	—	3

\*Calendar year of diagnosis for cases, and calendar year in which controls achieved risk age (similar age with cases' age at diagnosis).

(28% and 26%, respectively) had been exposed to synthetic fluids. Table 2 provides results of linear exposure-response models for prostate cancer incidence and cumulative exposure to 3 types of metalworking fluids with 4 different lags: 0, 10, 20, and 25 years. For soluble and straight metalworking fluids the strength of association increased slightly with the longest lag periods. Because model fit was best for lag 25, we chose 25 years before risk age as the cut-point for exposure windows. This decision was also supported by the previously reported evidence for a 30-year lag for soluble metalworking fluids exposure and prostate cancer mortality,<sup>6</sup> together with a high 5-year survival rate (95%) for prostate cancer.<sup>18</sup> Table 3 presents the distribution of cumulative exposures to soluble, straight, and synthetic fluids for the early and later exposure windows for cases and controls. As observed for all 3 types of metalworking fluids, the distribution was right-skewed and the mean and maximum values were higher for the early window. The correlation coefficients between the 2 exposure windows were 0.26 for soluble, 0.37 for straight, and 0.47 for synthetic fluids.

Optimal degrees of freedom for penalized splines were explored by minimizing the AIC for the Cox models, using smooth functions for both exposure windows simultaneously, and each exposure window separately (for one type of metalworking fluid, adjusting linearly for exposure windows of the other 2 fluids, race, and calendar year of diagnosis). For straight and synthetic fluids, results were consistent using both methods. For straight oils, AIC was minimized for penalized splines with 1.7 and 1.5 degrees of freedom for the early and later window, respectively. For synthetic fluids the degrees of freedom for the 2 exposure windows were 2.4 and 1.6. For soluble metalworking fluids, AIC was minimized for 12.7 and 12.5 degrees of freedom for early and later exposure window, respectively, when we smoothed simultaneously on both exposure windows. By contrast, when we smoothed one exposure window at a time, the optimal degrees of freedom were 1.4 and 1.2 for the early and later window. As a

compromise between over-fitting (high degrees of freedom) and over-simplifying (low degrees of freedom) we present penalized splines with 3 degrees of freedom for the 2 exposure windows for soluble fluids.

Figure 1A and 1B show the log relative risk of prostate cancer incidence as a smooth function of cumulative exposure to soluble metalworking fluids in 2 windows, 25 or more years, and less than 25 years before risk age. Relative risk of prostate cancer increased with increasing cumulative exposure in the early window, 25 years or more before risk age (Fig. 1A). The exposure-response curve was nonlinear, with a small increase in risk for lower exposures, followed by a steeper rise in risk above 200 mg/m<sup>3</sup>-years. However, due to the sparseness of the data above 200 mg/m<sup>3</sup>-years, the confidence bands were large. In the later window (less than 25 years), there was a V-shaped exposure-response relationship, but the confidence bands were wide and included the null (Fig. 1B).

For straight metalworking fluids, the relationship was linear in the early window over the cumulative exposure range, 0 to 80 mg/m<sup>3</sup>-years, followed by a flatter curve above that value (Fig. 1C). The sparseness of exposure data in the flatter region of the exposure-response curve was reflected by the wide confidence bands, and indicated that a linear relationship was most appropriate. In the later window, risk of prostate cancer decreased with increasing cumulative exposure, but with wide confidence bands (Fig. 1D). For synthetic fluids, the confidence bands for penalized splines in both exposure windows were quite large, consistent with no exposure-response relationships (Fig. 1E and 1F).

On the basis of these findings, we selected a final model that included penalized spline with 3 degrees of freedom for cumulative exposure to soluble metalworking fluids in the early window. This model also included linear terms for cumulative exposure to soluble fluids in the later window, cumulative exposures to straight oils, and synthetic fluids (in both time windows), and race, as well as 2 dummy variables

**TABLE 2.** Linear Exposure-Response Models for Prostate Cancer Incidence in Relation to Cumulative Exposure to Metalworking Fluids With Different Lagging Periods (Years)

Cumulative Exposure* (mg/m <sup>3</sup> -years)	Lag 0 RR (95% CI)	Lag 10 RR (95% CI)	Lag 20 RR (95% CI)	Lag 25 RR (95% CI)
Soluble fluids	1.02 (0.99–1.05)	1.02 (1.00–1.05)	1.03 (1.00–1.06)	1.03 (1.00–1.07)
Straight fluids	1.05 (0.99–1.11)	1.05 (0.99–1.11)	1.06 (1.00–1.13)	1.09 (1.01–1.16)
Synthetic fluids	1.05 (0.88–1.25)	1.04 (0.87–1.25)	1.06 (0.87–1.29)	1.09 (0.86–1.37)
Model fit AIC <sup>†</sup>	2730.33	2729.83	2728.28	2724.86

\*Cumulative exposure was used as a continuous variable; risk is expressed as change in RR per 10 mg/m<sup>3</sup>-years of cumulative exposure.

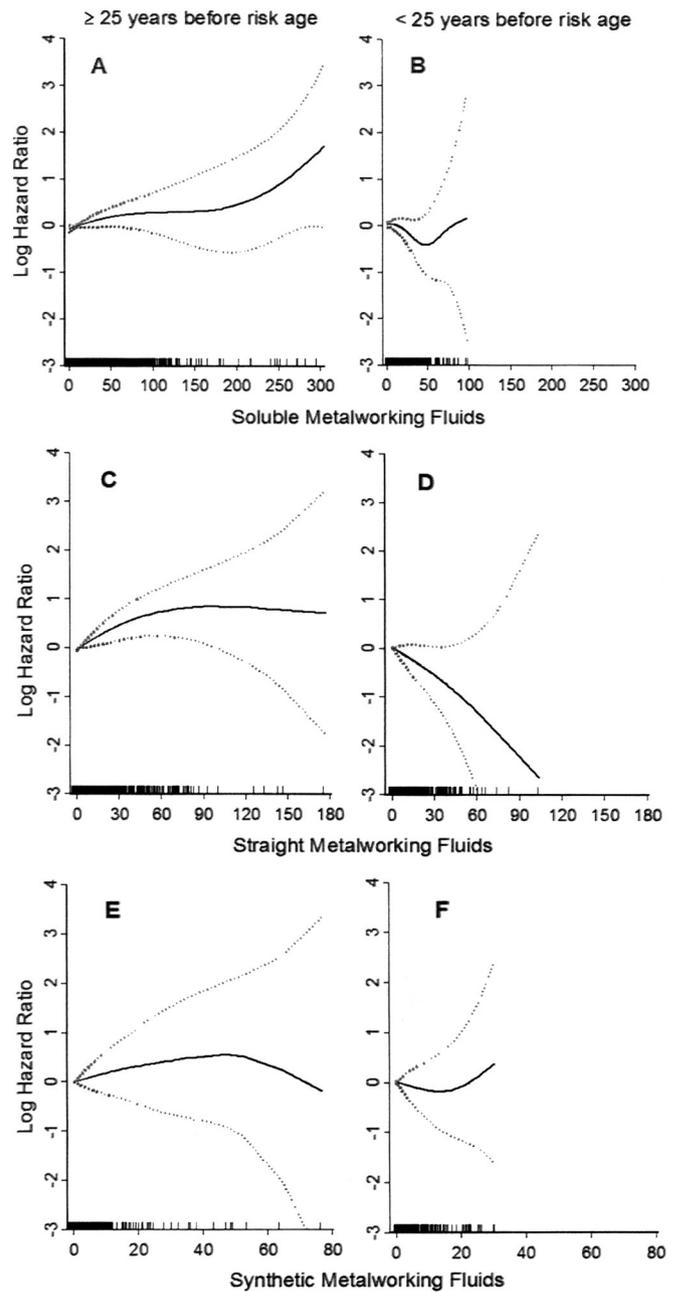
<sup>†</sup>AIC value for the model without any covariate was 3049.24.

Each Cox model included cumulative exposure to 3 types of metalworking fluids, race, and calendar year of diagnosis.

**TABLE 3.** Distribution of Time Windows of Cumulative Exposure to 3 Types of Metalworking Fluids Among Prostate Cancer Cases and Controls

	Cases	Controls
<b>Soluble fluids (mg/m<sup>3</sup>-years)</b>		
≥25 yr prior to risk age		
Mean ± SD	15.5 ± 27.2	13.4 ± 23.8
Min	0	0
50 percentile	6.4	5.1
99 percentile	118.2	109.6
Max	296.4	323.3
<25 yr before risk age		
Mean ± SD	4.9 ± 8.3	5.6 ± 9.7
Min	0	0
50 percentile	1.6	1.2
99 percentile	37.2	46.1
Max	76.3	98.2
<b>Straight fluids (mg/m<sup>3</sup>-years)</b>		
≥25 yr before risk age		
Mean ± SD	3.9 ± 12.9	2.6 ± 9.5
Min	0	0
50 percentile	0	0
99 percentile	69.6	49.0
Max	177.5	145.2
<25 yr before risk age		
Mean ± SD	1.3 ± 4.5	1.4 ± 5.5
Min	0	0
50 percentile	0	0
99 percentile	24.1	27.9
Max	44.2	103.8
<b>Synthetic fluids (mg/m<sup>3</sup>-years)</b>		
≥25 yr before risk age		
Mean ± SD	0.64 ± 3.4	0.55 ± 2.8
Min	0	0
50 percentile	0	0
99 percentile	10.5	9.5
Max	52.6	77.1
<25 yr before risk age		
Mean ± SD	0.36 ± 1.8	0.40 ± 1.9
Min	0	0
50 percentile	0	0
99 percentile	6.5	9.4
Max	29.8	30.3

for calendar year of diagnosis. Results of this model are presented in Table 4 with the RRs estimated at selected values of soluble fluids exposure in the early window (corresponding to Fig. 1A). For other linear-exposure terms in this model, risk was expressed as change in RR per 10 mg/m<sup>3</sup>-years of exposure. In relation to soluble fluids, pros-



**FIGURE 1.** Log relative risk of prostate cancer in Cox models with penalized splines of cumulative exposure to metalworking fluids in 2 windows ≥25 years, and <25 years before risk age (solid lines). A–B, Soluble fluids; degrees of freedom were 3 for both windows. C–D, Straight fluids; degrees of freedom were 1.7 for ≥25 years and 1.5 for <25 years window. E–F, Synthetic fluids; degrees of freedom were 2.4 and 1.6 for each window, respectively. Models are adjusted for exposure windows of other types of metalworking fluids, race, and calendar year of diagnosis. Rugs represent the distribution of exposure data. Dotted lines represent 95% point-wise confidence bands. Reference value for the y-axis is a natural-log relative risk of zero that is equivalent to a RR of 1.0.

**TABLE 4.** Final Model for Prostate Cancer Incidence in Relation to Time Windows of Exposure to 3 Types of Metalworking Fluids

	RR (95% CI)
Soluble fluids (mg/m <sup>3</sup> -years)	
≥25 yr before risk age*	
0 <sup>†</sup>	1.00
10	1.06 (1.01–1.11)
50	1.29 (1.00–1.46)
100	1.41 (0.99–2.00)
270	3.41 (1.05–11.10)
<25 yr before risk age <sup>‡</sup>	0.95 (0.86–1.06)
Straight fluids (mg/m <sup>3</sup> -years)	
≥25 yr before risk age <sup>‡</sup>	1.12 (1.04–1.20)
<25 yr before risk age <sup>‡</sup>	0.86 (0.71–1.03)
Synthetic fluids (mg/m <sup>3</sup> -years)	
≥25 yr before risk age <sup>‡</sup>	1.10 (0.84–1.43)
<25 yr before risk age <sup>‡</sup>	0.97 (0.57–1.63)
Race	
White <sup>†</sup>	1.00
African-American	1.83 (1.51–2.21)
Unknown	0.77 (0.62–0.97)
Calendar year of diagnosis <sup>§</sup>	
1985–1989 <sup>†</sup>	1.00
1990–1994	2.34 (1.91–2.88)
1995–2000	5.50 (4.41–6.99)

\*Nonlinear exposure-response relationship using penalized spline with 3 degrees of freedom; predicted risk is expressed at selected observed values of cumulative exposure.

<sup>†</sup>Reference category.

<sup>‡</sup>Linear exposure-response relationships; risk is expressed as change in RR per 10 mg/m<sup>3</sup>-years of cumulative exposure.

<sup>§</sup>Calendar year of diagnosis for cases, and calendar year in which controls achieved risk age (similar age with cases' age at diagnosis).

tate cancer risk in the early window increased modestly in the lower range of exposure, with a RR of 1.29 at 50 mg/m<sup>3</sup>-years, followed by a steeper rise for higher exposures with a RR of 3.41 at 270 mg/m<sup>3</sup>-years. By contrast, the relationship with straight oils in the early window was linear with RR of 1.12 (95% CI = 1.04–1.20) per 10 mg/m<sup>3</sup>-years. There were null relationships with exposure in the later window for both soluble and straight fluids. For synthetic fluids there were null exposure-response relationships with wide confidence intervals in both windows. Based on the estimates of this model, African-Americans had an 83% increased relative risk of prostate cancer compared with whites.

## DISCUSSION

We examined exposure-response relationships for 2 consecutive windows of exposure to soluble, straight, and synthetic metalworking fluids, and prostate cancer incidence

using penalized splines in a Cox model. Risk of prostate cancer increased modestly with increasing exposure to soluble and straight fluids that occurred 25 years or more before risk age, but not with exposure in the later 25 years. The relationship between soluble fluids and prostate cancer incidence was nonlinear, with smaller increases in risk for lower exposures, followed by a steeper rise. By contrast, the relationship with straight oils in the early window was linear with a relative risk of 1.12 per 10 mg/m<sup>3</sup>-years.

This study was based on newly identified incident cases with an overlap of only 58 cases (6%) with the prostate cancer mortality study in the same UAW-GM cohort.<sup>6</sup> The observed nonlinear relationship between soluble fluids and prostate cancer incidence is consistent with the previous results, in which there was a piecewise linear relationship between cumulative exposure to soluble fluids (with a 30-year lag) and prostate cancer deaths.<sup>6</sup> To check the impact of the overlapping cases, we deleted these 58 cases and their respective controls and refit the final model. The predicted relative risks for cumulative exposure to soluble metalworking fluids in the early window were not different, providing further evidence for consistency between the 2 findings, and supporting a causal relationship. For straight oils, the results between studies are less consistent. Thurston et al<sup>6</sup> found no association with prostate cancer mortality, although in a previous analysis of the full cohort, Tolbert et al<sup>19</sup> reported a dose-response trend for duration of exposure to straight oils, with a RR of 1.52 (95% CI = 1.01–2.29) for 7.5 years or more of exposure duration.

The advantage of using incident cases rather than deaths is that misclassification of outcome is reduced; the 5-year survival rate is 95% for prostate cancer, and men with prostate cancer usually die of other causes.<sup>18</sup> Given this fact, we expected to find stronger exposure-response relationships using incidence data. For prostate cancer, however, the use of incidence does not guarantee complete case ascertainment. Although PSA testing is widely available, the test has imperfect sensitivity. In addition, biopsies can fail to detect the presence of tumor in men with elevated PSA levels.<sup>20</sup> Misclassification of these undetected prostate cancer cases as controls, however, would attenuate the observed associations.<sup>21</sup> Another potential bias introduced by using incidence data, is that because prostate cancer cases diagnosed via PSA screening are in the early stages of disease, exposures that affect carcinogenesis at a later stage may not be detected.<sup>21</sup> Thus, the lack of association with metalworking fluid exposure in the later window may be an underestimate. However, our positive finding with early exposure is not subject to this source of bias.

Brown and Delzell<sup>22</sup> examined the relationship between employment in motor vehicle manufacturing and prostate cancer mortality in a nested case-control study in a cohort of Ford Motor Company autoworkers with a follow-up

through 1987. They found a 50–90% excess in prostate cancer mortality for workers employed in core and mold making, metal melting and pouring operations. In a recent updated follow-up of their cohort, Delzell et al<sup>23</sup> reported a 28% excess mortality for prostate cancer among workers employed in casting operations. Workers in these jobs have potential exposure to metal dusts, fumes, and polyaromatic hydrocarbons (PAH), but no direct exposure to metalworking fluids. Since the associations were weak, the authors attributed their findings to chance and to unmeasured confounding by nonoccupational risk factors for prostate cancer such as diet and family history.<sup>22,23</sup> A limitation in the Ford cohort study was that prostate cancer mortality was evaluated only in broad production and job groups, and not in relation to specific exposures such as metalworking fluids.

We did not have information on other risk factors for prostate cancer. The strongest unmeasured risk factor is family history of prostate cancer, which is associated with both increased risk and earlier onset of disease in first-degree relatives (RRs range from 1.7 to 3.7).<sup>24</sup> Other risk factors such as diet, fat intake, alcohol consumption, smoking, and vitamins, have been investigated but the evidence is not clear. Vitamin D and calcium intake, especially from dairy products, have been associated with increased risk of prostate cancer.<sup>25</sup> There is no clear association between cigarette smoking and prostate cancer,<sup>26</sup> and only very heavy alcohol consumption ( $\geq 7$  drinks/d) has been associated with an excess risk of prostate cancer.<sup>27,28</sup> Some of the unmeasured lifestyle risk factors might have differed among autoworkers by exposure levels, and possible confounding could partly explain the attenuated exposure-response relationships. However, Kriebel et al,<sup>29</sup> using data from the UAW-GM cohort, have recently shown that in retrospective cohort studies, where information on potential confounding factors is often missing, it is unlikely that either systematic or chance differences in lifestyle factors would cause as much as 20% change in the relative risk estimates of the exposure-disease relationships.

In our study, prostate cancer incidence was associated with exposure to straight and soluble metalworking fluids. This suggests the possibility that an agent (or more than one agent) common to these 2 types of fluids may be associated with prostate cancer. In metalworking industries, PAH were present to varying degrees in both straight and soluble fluids, but not synthetic fluids, with higher concentrations in straight oils.<sup>30</sup> Increased risk of prostate cancer has been observed in several occupational groups with exposure to PAH, such as power plant operators, motor vehicle drivers, machinery maintenance workers, repairman, machinists, longshoreman, and railroad industry workers.<sup>31–33</sup> Aronson et al<sup>32</sup> found excess risk of prostate cancer in relation to PAH compounds and to liquid fuel combustion products, whereas Seider et al<sup>33</sup> found excess risk in relation to diesel fuel and fumes, soot, tar and pitch. Thus the observed associations with soluble and

straight fluids in the early window could be due to the PAH content, which was higher in metalworking fluids before the 1970s, and has decreased over time due to better refining of mineral oils. Besides PAH, other chemical compounds that are formed during chlorination of base oils, such as chlorinated paraffin, have shown carcinogenic effect in animal studies.<sup>34</sup> These chlorinated compounds may react during use of metalworking fluids to form other potentially carcinogenic substances, such as dioxins.<sup>30</sup>

In conclusion, results of this study provide further evidence that exposure to soluble and straight metalworking fluids is associated with prostate cancer among autoworkers, with a modest increase in the relative risk. Data support a latency period of at least 25 years.

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