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A Case-Control Study of Occupational Exposure to Metalworking Fluids and Bladder Cancer Risk Among Men

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Abstract

Objectives—Metalworking has been associated with an excess risk of bladder cancer in over 20 studies. Metalworking fluids (MWFs) are suspected as the responsible exposure, but epidemiologic data are limited. We investigated this association among men in the New England Bladder Cancer Study using state-of-the-art, quantitative exposure assessment methods.

Methods—Cases (n=895) and population controls (n=1,031) provided occupational histories during personal interviews. For selected jobs, exposure-oriented modules were administered to collect information on use of three MWF types: (1) straight (mineral oil, additives), (2) soluble (mineral oil, water, additives), and (3) synthetic (water, organics, additives) or semi-synthetic (hybrid of soluble and synthetic). We computed odds ratios (ORs) and 95% confidence intervals (CIs) relating bladder cancer risk to a variety of exposure metrics, adjusting for smoking and other factors. Non-metalworkers who had held jobs with possible exposure to mineral oil were analyzed separately.

Results—Bladder cancer risk was elevated among men who reported using straight MWFs (OR=1.7, 95% CI=1.1–2.8); risk increased monotonically with increasing cumulative exposure (p=0.041). Use of soluble MWFs was associated with a 50% increased risk (95% CI=0.96–2.5). ORs were nonsignificantly elevated for synthetic/semi-synthetic MWFs based on a small number

of exposed men. Non-metalworkers holding jobs with possible exposure to mineral oil had a 40% increased risk (95% CI=1.1–1.8).

Conclusions—Exposure to straight MWFs was associated with a significantly increased bladder cancer risk, as was employment in non-metalworking jobs with possible exposure to mineral oil. These findings strengthen prior evidence for mineral oil as a bladder carcinogen.

Metalworking has been associated with an increased risk of bladder cancer in over 20 epidemiologic studies.(1–21) It was first suggested in 1983 that exposure to metalworking fluids (MWFs) might be responsible for this increased risk.(2;3) MWFs are used in metal machining to lubricate, cool, and remove debris from the surfaces of metal parts that are being drilled, ground, milled, or otherwise machined. MWF can be categorized into broad types based on their composition – straight (mineral oil plus additives), soluble (mineral oil emulsified in water, plus additives), synthetic (water with organics and additives, no oil), and semi-synthetic (a hybrid of soluble and synthetic fluids) – but the groups overlap in their components.(22) Some components are known or suspected carcinogens, such as polycyclic aromatic hydrocarbons (PAHs) in straight and soluble MWFs and nitrosamines in soluble, semi-synthetic, and synthetic MWFs.(22–25) In 1988, the National Institute for Occupational Safety and Health found “substantial evidence” for an increased risk of cancer at several sites, including bladder, for “at least some of the MWFs used before the mid-1970s.”(26) MWFs were assigned a medium priority for review by the International Agency for Research on Cancer (IARC).(27)

Studies that have directly addressed MWF exposure and bladder cancer incidence or mortality have yielded mixed results; some observed positive associations,(28;29) others reported borderline or weak evidence for an elevation in risk,(30;31) and others found no association.(32;33) Only one previous study, the United Auto Workers-General Motors (UAW-GM) cohort, examined bladder cancer risk using quantitative measures of exposure to the individual MWF types, reporting an elevated risk for straight, but not soluble or synthetic, MWFs.(28) While this study was an important advancement in research on MWFs, it was not possible to control for smoking. In addition, the exposure settings were limited to three large auto manufacturing plants in Michigan,(34) leaving unanswered questions about MWF exposure in other settings, including small machine shops that are prevalent throughout the world.

Previously, we reported on the relationship between occupation, industry, and bladder cancer risk in the New England Bladder Cancer Study, a large, population-based case-control study conducted in Maine, Vermont, and New Hampshire. We detected elevated risks among male precision metalworkers (odds ratio [OR]=2.2, 95% confidence interval [CI]=1.4–3.4) and metalworking/plasticworking machine operators (OR=1.6, 95% CI=1.01–2.6), and a 70% increase in risk among men who used MWFs in one or more jobs (OR=1.7, CI=1.1–2.5).(21) Here, we expand upon that analysis by conducting an in-depth exposure assessment for the individual MWF types and estimating bladder cancer risk using quantitative exposure metrics.

Methods

Study Population

The study population has been described previously.⁽²¹⁾ Briefly, all residents newly diagnosed with a histologically-confirmed carcinoma of the urinary bladder (including carcinoma *in situ*) at ages 30 to 79 years between September 1, 2001 and October 31, 2004 (Maine and Vermont) or January 1, 2002 and July 31, 2004 (New Hampshire) were eligible. Rapid patient ascertainment was conducted through hospital pathology departments, hospital cancer registries, and state cancer registries. We interviewed 1,213 cases (65% of 1,878 eligible cases). Of non-participating cases, 50% refused, 22% were deceased, 12% were too ill, 5% did not speak English, 5% had a physician refusal, and 5% were unlocatable. Based on a diagnostic slide review by the study's expert pathologist, we excluded 20 patients identified as not having bladder cancer and 22 patients with non-urothelial carcinoma, leaving 1,171 incident cases with urothelial carcinoma.

Controls aged 30 to 64 years were selected randomly from Department of Motor Vehicle (DMV) records in each state, and controls aged 65 to 79 years were selected from beneficiary records of the Centers for Medicare and Medicaid Services (CMS). Controls were frequency matched to cases by state, gender, and age at diagnosis (within 5 years). We interviewed 1,418 (594 DMV and 824 CMS) controls (65% of eligible DMV and 65% of eligible CMS controls). Of non-participating controls, 70% and 65% of DMV and CMS controls, respectively, refused; 24% of DMV and 11% of CMS controls were unlocatable; 3% of DMV and 10% of CMS controls did not speak English; 1% of DMV and 7% of CMS controls were too ill; and 1% of DMV and 7% of CMS controls were deceased.

All respondents gave written informed consent to participate. The study protocol was approved by the National Cancer Institute Special Studies Institutional Review Board and the human subjects review boards of each participating institution.

Exposure Assessment

Interview—Participants completed a mailed residence and work history calendar. During the subsequent home visit, a trained interviewer administered a computer-assisted personal interview that included a lifetime occupational history and questions about demographics, tobacco use, drinking water source, family history of cancer, urinary tract infections, analgesic use, hair dyes, diet, and other exposures. The interviewer recorded information on all jobs held for at least 6 months since age 16, excluding unpaid jobs and absentee business ownership. For each job, participants were queried about the employer name and location; year started and ended; work schedule; type of business; products made or services provided; and the participant's main tasks and activities, tools and equipment used, and chemicals and materials handled. Based on responses to these questions, a job- or industry-specific questionnaire module may have been administered for jobs held for at least 1,000 hours to collect information about exposures of interest.

Seven job modules elicited detailed information about MWF use: machinist, industrial machine repairer, welder, tool and die maker, sheet metal worker, plumber, and electrician. People reporting these jobs were asked how often they machined metals and the frequency

with which they used "straight cutting oils or oils that look and feel like motor oil," "soluble cutting oils or oils that are milky white," and "synthetic cutting oils or oils that feel like water and may be brightly colored, such as green or blue." Because semi-synthetic and synthetic fluids may be similar in appearance and feel, we included only one question to cover both fluid types and grouped them together in the exposure assessment (hereafter referred to as "synthetic" MWFs). Information provided in response to these questions was used as a basis for assessing direct exposure to each MWF type. Several other modules (including managers, engineers, janitors, assembly workers, laborers, and production inspectors) also contained general questions that may have been relevant to MWF exposure.

Estimating probability, frequency, and intensity of exposure—For each job, industrial hygienists estimated the probability, frequency, and intensity of direct exposure to each MWF type. Exposure *probability* (0 to 1) reflects the likelihood that the individual was exposed. The exposure *frequency* is the hours/week that the MWF was estimated to have been used, and the exposure *intensity* is an estimate of the average concentration of the MWF aerosol in the subject's breathing zone (milligrams per cubic meter, mg/m³). Estimates of probability and intensity varied by decade. A confidence score ranging from 1 (low) to 4 (high) was assigned to each probability, frequency, and intensity estimate to reflect the quality of information upon which it was based. We also assessed whether the individual was likely to have been indirectly exposed (from working in proximity to others machining) to each MWF for each job and decade (yes/no). Exposure assessors had no knowledge of case/control status.

Our approaches for assigning probability, frequency, intensity, and confidence scores are discussed in detail elsewhere.(35;36) Briefly, prior to the assessment, all possibly exposed jobs were assigned to one of 11 job groups (7 corresponding to the names of the questionnaire modules that ask about MWF use, plus by-stander in a metalworking industry or maintenance shop, non-machining production in a metalworking industry, miscellaneous MWF jobs, and farmer).(36) Then, for a given job, if questions about MWF use had been asked, assigning a probability and frequency of exposure to each MWF was based directly on the subjects' responses. However, modules were not administered for all potentially MWF-exposed jobs, such as those held for fewer than 1,000 hours. In addition, modules other than "machinist" did not ask about use of MWFs if metal machining was performed for fewer than 5 hrs/wk. If questions about machining and/or types of MWFs used were not asked or answered, the probability and frequency of MWF use were estimated by the industrial hygienists. First, if the respondent reported metal machining, the probability of use for each MWF was based on the MWF's share of the overall U.S. MWF production volume during each decade in which the job was held. Second, if information on metal machining was unavailable, the industrial hygienists estimated the probability of use for each MWF by multiplying (1) the MWF's share of the overall U.S. MWF production volume (as above) by (2) the proportion of jobs in the assigned job group that machined based on responses to the question about machining for other jobs in that group. Frequencies were the median frequencies reported for jobs in the corresponding job group.(35)

To estimate exposure intensity, industrial hygienists developed a multivariate model relating airborne MWF aerosol measurements to determinants of exposure based on data in the

literature. (35;37;38) This model was used to derive exposure estimates (in mg/m^3) as a function of several exposure determinants: type of MWF, decade, type of industry (auto, autoparts, small machine shops), and type of operation (grinding or other non-grinding machining). Each job with a non-zero probability of direct MWF exposure was assigned the most appropriate category for each determinant. When information on determinants of exposure was unavailable from the questionnaire responses, intensity was inferred from the corresponding job group or based on the judgment of the industrial hygienists.

Developing exposure metrics—For each MWF type, individuals were assigned to categories of probability of exposure hierarchically. If they said that they had used the MWF in response to a questionnaire module, they were considered “definitely exposed.” People who were not definitely exposed to that MWF were categorized as “probably exposed” if the probability of use was 0.5–0.99 for any job/decade, and “possibly exposed” if the highest probability of use for any job/decade was >0 and <0.5 . The remaining individuals were considered “indirectly exposed” to that MWF if they had been assessed as having indirect exposure in any job.

For subjects classified as probably or definitely exposed to a MWF, two additional exposure metrics were calculated: *hours of exposure*, defined as the sum, across all jobs with an exposure probability ≥ 0.5 , of the hours using that MWF; and *cumulative exposure* ($\text{mg}/\text{m}^3 \cdot \text{hours}$), defined as the sum, across all jobs with exposure probability ≥ 0.5 , of the product of the job-specific intensity (mg/m^3), frequency of MWF use (hrs/week), and duration in weeks for each of those jobs.

Identifying the referent group—For the referent group, we selected individuals assessed as having no direct or indirect exposure to any MWF. Their job histories were further reviewed to determine if they included any non-metalworking jobs possibly involving other sources of exposure to mineral oil (e.g., some pesticide sprayers, textile workers, painters, roofers, pavers, concrete workers). If so, the individual was removed from the referent group and assigned to a separate group called “possible exposure to mineral oil.” The rationale is that mineral oil is contained in many MWFs and is a suspected bladder carcinogen.

Statistical Analysis

Analyses were performed using the statistical software SAS Version 9.2 (SAS Institute, Cary, NC). We describe the associations between the exposure metrics for each MWF and bladder cancer risk using odds ratios (ORs) and 95% confidence intervals (CIs) computed from unconditional logistic regression models with adjustment for age (<55 years, 55–64 years, 65–74 years, 75+ years), race (white only, Native American/white, other races), state, smoking status (never, occasional [<100 cigarettes over the lifetime], former, current), and employment in a high-risk occupation for bladder cancer (other than those involving MWF or mineral oil exposure, ever/never). Separate models were developed with categories of probability, hours of exposure, and cumulative exposure for each MWF type. For straight and soluble MWFs, exposed participants were categorized in tertiles, with cut points based on the combined distribution of values among cases and controls. For synthetic MWFs, with

fewer exposed participants, two exposed groups were used with cut points set at the median among cases and controls combined. We conducted additional analyses incorporating the confidence scores and further adjustment by duration of smoking, and evaluated associations stratified by smoking status.

Because many participants were exposed to more than one MWF type, we estimated the risk associated with exposure to each MWF type adjusted for exposure to the other MWFs. To do this, we developed a model that included all MWF types, with each MWF entered as a categorical variable with the following levels: “0” if the individual did not have probable or definite direct exposure to that MWF, otherwise as one of the cumulative exposure categories used in the MWF-specific models. The model also included terms (as yes/no variables) for only possible exposure to any MWF, only indirect exposure to any MWF, and possible mineral oil exposure, and the same confounders as in the MWF-specific models. Tests for trend were performed by modeling the median value for each category among controls as continuous. All statistical tests were two-sided, with $\alpha=0.05$ taken as a measure of statistical significance.

Results

Of the 1,171 cases and 1,418 controls interviewed, 13 cases and 16 controls were excluded because they had no qualifying jobs or had missing information on potential confounders, leaving 1,158 cases (895 men, 263 women) and 1,402 controls (1,031 men, 371 women). We excluded women because few were exposed to MWFs. The response rates for men were similar to those of the study population overall (65% for both cases and controls). Selected characteristics of the men in the analysis are shown in Table 1. Demographic characteristics were similar for cases and controls. Cases were more likely than controls to have smoked. The overall distribution of MWF exposure probabilities appeared similar between cases and controls, with 70% of both assessed as having no direct or indirect exposure. However, more cases than controls were assessed as having possible exposure to mineral oil in non-metalworking jobs.

Men with definite direct exposure to any MWF had a statistically significant, 60% increase in bladder cancer risk (OR=1.6, 95% CI=1.03–2.4) (Table 2). Those assessed as “possibly” or “probably” exposed to MWFs did not have an elevated risk. Men with only indirect exposure had a marginally significant elevation in risk (OR=1.5, 95% CI=0.95–2.4). Men with no direct or indirect exposure to MWFs, but with possible exposure to mineral oil in non-metalworking jobs, had a 40% significant increase in risk (OR=1.4, 95% CI=1.1–1.8).

Compared to the referent group, men with definite direct exposure to straight MWFs had a significant, 70% increase in bladder cancer risk (OR=1.7, 95% CI=1.1–2.8). Definite exposure to soluble MWFs was associated with a 50% increase of marginal statistical significance (OR=1.5, 95% CI=0.96–2.5). Men with probable or definite exposure to synthetic MWFs had elevated ORs; however, the numbers were small and the associations were not significant.

Among men with probable or definite direct exposure to MWFs, while there were no clear trends by hours of exposure for any of the MWFs, we did observe a significant, monotonic trend ($p=0.041$) of increasing risk with increasing cumulative exposure ($\text{mg}/\text{m}^3 \cdot \text{hours}$) to straight MWFs (OR in highest category=2.2, CI=1.02–4.8) (Table 3). Risk was slightly elevated in the highest category of cumulative exposure to soluble MWFs (OR=1.5, CI=0.8–2.8), with no significant trend ($p=0.133$). For synthetic MWFs, risk was elevated in the lower, but not the higher, category of cumulative exposure; numbers were small in both exposure categories and ORs were not significant.

These findings did not change meaningfully when we took the confidence scores into account by excluding (1) all years with a direct probability confidence score of 1, or (2) all men with a probability, frequency, or intensity confidence score of 1 anywhere in their job history. Further adjustment for smoking by adding smoking duration to the models did not meaningfully change the results.

As is typically observed for metalworkers, most of the exposed men in our study population had exposure to more than one type of MWF. For example, of the control subjects with probable/definite direct exposure to synthetic MWFs, 71% also had probable/definite exposure to straight and/or soluble MWFs. Similarly, 64% of the controls with probable/definite exposure to straight MWFs, and 42% of the controls with probable/definite exposure to soluble MWFs, also had probable/definite exposure to at least one other type of MWF. Exposure to two or three of the MWFs was also common among cases. In a model that adjusted exposure to each MWF type for exposure to the others (Table 4), the risk estimates were generally lower than in the MWF-specific models. However, straight MWFs continued to display a pattern of monotonically increasing risk with increasing cumulative exposure ($p=0.075$), with a two-fold risk in the highest category (OR=2.2, CI=0.9–5.2). Risk was no longer elevated for soluble MWFs. The risk pattern for synthetic MWFs was unchanged.

Table 5 shows ORs for probable/definite exposure to MWFs and bladder cancer risk stratified by smoking status. Because the study population was dominated by smokers (87% of cases, 70% of controls ever smoked), the number of never smokers exposed to MWFs was small. Among never smokers, we observed nonsignificantly elevated ORs for possible exposure to mineral oil (OR=1.5, CI=0.9–2.5) and for probable/definite exposure to straight MWFs (OR=1.4, CI=0.4–4.2). Compared to former smokers who were unexposed, those with possible exposure to mineral oil had a significant increase in risk (OR=1.5, CI=1.1–2.1); ORs for the three types of MWFs were nonsignificantly elevated. Compared to current smokers unexposed to MWFs, those exposed to straight fluids had a two-fold risk, and those exposed to synthetic fluids had a three-fold risk, but neither association was significant. We also analyzed smoking and MWF exposure as a joint variable where the referent group comprised nonsmokers who were not exposed to MWFs (not shown). ORs for current smokers with probable/definite exposure to MWF were quite high and statistically significant (straight MWFs: OR=10.8, CI=3.9–29; soluble MWFs: OR=6.5, CI=3.0–13.9; synthetic MWFs: OR=17.3, CI=4.7–64), but confidence intervals were wide. The interactions between smoking and MWF exposure were not significant ($p=0.61$ for straight

MWFs, $p=0.65$ for soluble MWFs, $p=0.56$ for synthetic MWFs), although ORs for straight and synthetic MWFs were greater than those expected under the additive model.

Discussion

To our knowledge, this is the first population-based case-control study to estimate bladder cancer risk for individual types of MWFs based on quantitative exposure metrics. Occupational exposure to straight MWFs, which are composed of mineral oil plus additives, was associated with an increased bladder cancer risk among men, and the risk rose with increasing cumulative exposure. There was a significantly elevated risk of bladder cancer among non-metalworkers who were possibly exposed to mineral oil in other types of jobs. Exposure to soluble MWFs, which contain mineral oil emulsified in water, was associated with a modestly elevated risk at the highest cumulative exposure level, but the association was not significant and dissipated after adjustment for exposure to the other MWF types. Although there was a suggestion of a possible association with synthetic/semi-synthetic MWFs, small numbers hampered our ability to conduct a meaningful analysis for this category. Indirect exposure to any MWF was associated with a marginally significant 50% increase in bladder cancer risk, indicating that men who do not work directly with MWFs, but may work near metal machining operations, also may have an elevated bladder cancer risk.

Our findings are generally consistent with those of the United Auto Workers-General Motors (UAW-GM) cohort study. In that study, researchers developed quantitative measures of exposure to the three types of MWFs for each of (34)(34)(34) 21,999 cohort members, who were then followed for cancer incidence over time (1985–2004).(22;28) An increased hazard rate ratio for bladder cancer was observed for straight, but not for soluble or synthetic, MWFs. Hazard ratios increased significantly as cumulative exposure to straight MWFs increased ($p\text{-trend}=0.02$), reaching a significant twofold ratio in the highest exposure category, similar to the magnitude of association observed in our study.(28) Incident bladder cancer risk was also examined in a retrospective cohort study of 55,000 aerospace workers in California.(31) Exposure to mineral oils used in machining was associated with nonsignificantly elevated bladder cancer incidence rate ratios of 1.75 and 1.42 for workers assessed as having medium and high cumulative exposures, respectively, with no trend with duration of exposure; the other types of MWFs were not examined. In an earlier study, bladder cancer mortality increased significantly with cumulative exposures to straight oil in grinding (mortality odds ratio [MOR]=3.0, 7 bladder cancer deaths) and machining/heat treat (MOR=2.9, 4 bladder cancer deaths) operations among workers in two Detroit-area engine plants.(29) Other studies have examined MWFs without differentiating by fluid type. A Canadian population-based case-control study reported a marginally significant, 20% increased bladder cancer risk among people occupationally exposed to MWFs, with a 50% increase at the highest exposure level.(30) Bladder cancer incidence was not elevated in a Swedish cohort of men exposed to MWFs, but the number of cases was small.(32) Bladder cancer mortality was not elevated in a study of automobile plant workers exposed to MWFs. (33) Because bladder cancer has a high survival rate, with many more incident cases than deaths each year, mortality studies of this disease do not reflect incidence and consequently often suffer from small numbers of deaths and null findings.

Mineral oil has historically contained PAHs,(18;34) which are suspected of being among the carcinogenic components of straight MWFs. In 1984, IARC classified mineral oil as a human carcinogen, largely because of its PAH content and increased risk of skin and scrotal cancers.(23;24) Exposure to PAHs has been associated with an increased risk of bladder cancer in industries using PAH-containing coal tar pitch.(28;39;40) PAH removal from mineral oils began in the 1950s (41) and levels were drastically reduced by the mid-1980s.(42;43) We attempted to stratify the cumulative exposure analysis for straight MWFs on calendar year of first exposure to ascertain whether risks were lower among men who were first exposed in the 1980s, but too few subjects were available for meaningful analysis. Straight MWFs may also contain additives such as polar lubricants and, occasionally, sulfur-, chlorine-, or phosphorous-based lubricants.(44)

The small number of men exposed to synthetic/semi-synthetic MWFs made it difficult to interpret the elevated ORs in the lowest and highest levels of cumulative exposure that persisted after adjustment for exposure to the other MWF types. The associations were not significant and there was no trend with increasing cumulative exposure. An association is conceivable since these fluids have contained nitrosamines, predominantly n-nitrosodiethanolamine, which has been classified by IARC as an animal carcinogen and a possible human carcinogen (Group 2B),(25) as well as biocides, surfactants, borates, and other additives and contaminants.(45) Our finding warrants further study in a population with a higher prevalence of exposure to synthetic and semi-synthetic MWFs and a way to distinguish between them.

In our earlier, job-title-based analysis of data from this study, the elevated risk of bladder cancer for male precision metalworkers and metalworking/plasticworking machine operators was evident only among smokers,(21) and the interaction between smoking and precision metalworking was significant. In the current study, limiting the probability analysis to never smokers did lower the risk estimates, although modestly elevated ORs remained for probable/definite exposure to straight MWFs and for exposure to mineral oils. Small numbers of non-smoking, MWF-exposed men limited our ability to examine the cumulative exposure metric among nonsmokers. We did not observe a significant interaction between smoking and MWF exposure in the current study, although the joint effect between smoking and exposure to straight MWFs or synthetic MWFs was stronger than that expected under an additive model.

The most important strength of this study is the state-of-the-art exposure assessment, yielding quantitative measures of exposure to specific types of MWFs and demonstrating the level of detail with which occupational exposures can be assessed in a case-control study. The occupational data included a lifetime work history and job- and industry-specific questionnaire modules administered to elicit specific information on MWF exposure. This information, combined with an extensive literature review,(37;38) a detailed exposure intensity model,(35) and a method for deriving exposure estimates at the job-group level when subject-specific information was unavailable,(35;36) led to the most comprehensive study of MWF exposure ever performed in a case-control study, and a confirmation of the associations suggested by occupational cohort studies after adjustment for smoking and other confounders. Moreover, the decision rules for deriving the exposure estimates are

transparent and can be applied in other studies. In addition, because our study was population-based, the MWF-exposed group included a large number of men working in a wide variety of small machine shops, filling an important gap left by occupational cohort studies. Another strength inherent to the study design is the inclusion of both active and inactive workers in the study population, minimizing possible bias due to the healthy worker survivor effect in cohort studies. Another strength is the large number of bladder cancer cases included.

A limitation of the exposure assessment was the relatively small number of potentially exposed men who responded to direct questions about MWF exposure. Of the 493 men assessed as having a non-zero probability of exposure to MWFs, only 119 (24%) had responded to questions about MWF use, and there was substantial variability among their responses; the exposure metrics for the remaining men assessed as exposed were based on extrapolation from those who had answered the questions along with other information sources. This likely led to nondifferential exposure misclassification among the men for whom exposure was inferred, which typically biases the risk estimates towards the null.⁽⁴⁶⁾ Another potential source of exposure misclassification is that dermal exposure was not considered; this potentially important route of exposure was not evaluated because of the difficulties associated with retrospective assessment of dermal exposure ⁽⁴⁷⁾ and the expectation that it would be correlated with inhalation exposure. In addition, the small number of men assessed as having probable or definite exposure to any MWF (n=204) limited our ability to analyze trends by duration and cumulative exposure, and to rigorously analyze possible effect modification by smoking. The 65% participation rate for cases and controls, while typical for case-control studies in this time period, can be viewed as a limitation. We do not have information on occupational exposures for nonrespondents and cannot evaluate whether this led to bias in the risk estimates, but we believe that participation is unlikely to have differed between cases and controls in an exposure-dependent manner. Another limitation is biased reporting of occupational histories and MWF use, potentially leading to inflated risk estimates if cases had better recall of exposures than controls. That bladder cancer risk increased with increasing expert-assessed cumulative exposure to straight MWF suggests that this finding is unlikely to be attributable to differential recall by case-control status. Finally, we were unable to evaluate associations between MWF exposure and bladder cancer risk among women because few women in our study population held machining jobs.

In conclusion, exposure to straight MWFs was associated with a significantly increased bladder cancer risk, as was employment in non-metalworking jobs with possible exposure to mineral oil. These findings strengthen prior evidence for mineral oil as a bladder carcinogen.

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What this paper adds

- Metalworking has been associated with an increased risk of bladder cancer in over 20 studies, with metalworking fluids (MWFs) suspected as the responsible exposure.
- Previous studies of MWFs and bladder cancer are limited by a lack of information on smoking and other confounders, a focus on large plants that are not representative of other settings in which MWF exposure is prevalent, and/or an inability to distinguish between different types of MWFs.
- We used state-of-the-art, quantitative exposure assessment methods to investigate bladder cancer risk for three types of MWFs among men in the population-based New England Bladder Cancer Study, adjusting for smoking and other factors.
- Exposure to straight MWFs (composed of mineral oils plus additives) was associated with a significantly increased bladder cancer risk, as was employment in non-metalworking jobs with possible exposure to mineral oil, strengthening prior evidence for mineral oil as a bladder carcinogen while addressing limitations of earlier studies.
- Our study demonstrates the level of detail with which occupational exposures can be assessed in a case-control study.

Table 1

Selected characteristics of men in the metalworking fluid analysis, New England Bladder Cancer Study

Characteristic	Cases (%) (n=895)		Controls (%) (n=1,031)	
Age (years)				
<55	144	(16.1)	168	(16.3)
55–64	232	(25.9)	248	(24.1)
65–74	339	(37.9)	408	(39.6)
75+	180	(20.1)	207	(20.1)
Race				
White	843	(94.2)	977	(94.8)
Native American/White	45	(5.0)	40	(3.9)
Other	7	(0.8)	14	(1.4)
Hispanic Status				
Yes	17	(1.9)	17	(1.7)
No	878	(98.1)	1,014	(98.3)
State				
Maine	447	(49.9)	554	(53.7)
Vermont	162	(18.1)	173	(16.8)
New Hampshire	286	(32.0)	304	(29.5)
Smoking Status				
Never	114	(12.7)	305	(30.0)
Former	483	(54.0)	555	(53.8)
Current	279	(31.2)	147	(14.3)
Occasional	19	(2.1)	24	(2.3)
Metalworking Fluid Exposure				
None	622	(69.5)	720	(69.8)
No mineral oil	258	(28.8)	362	(35.1)
Possible mineral oil	364	(40.7)	358	(34.7)
Indirect only	48	(5.4)	43	(4.2)
Possible	121	(13.5)	168	(16.3)
Probable	39	(4.4)	46	(4.5)
Definite	65	(7.3)	54	(5.2)

Table 2

Probability of occupational exposure to metalworking fluids (MWFs) and risk of bladder cancer within the New England Bladder Cancer Study¹

	Cases	Controls	OR (95% CI)
No exposure to MWFs or mineral oil (referent)	258	362	1.0
Possible exposure to mineral oil	364	358	1.4 (1.1–1.8)
Any MWF			
Only indirect exposure	48	43	1.5 (0.95–2.4)
Possible direct exposure ²	121	168	1.0 (0.8–1.4)
Probable direct exposure ³	39	46	1.1 (0.7–1.9)
Definite direct exposure ⁴	65	54	1.6 (1.03–2.4)
Straight MWFs⁵			
Only indirect exposure to straight MWFs	57	57	1.3 (0.8–2.0)
Possible direct exposure to straight MWFs ²	159	208	1.1 (0.8–1.4)
Probable direct exposure to straight MWFs ³	8	7	1.6 (0.6–4.9)
Definite direct exposure to straight MWFs ⁴	49	37	1.7 (1.1–2.8)
Soluble MWFs⁶			
Only indirect exposure to soluble MWFs	64	58	1.5 (0.97–2.2)
Possible direct exposure to soluble MWFs ²	132	174	1.1 (0.8–1.5)
Probable direct exposure to soluble MWFs ³	29	38	1.0 (0.6–1.7)
Definite direct exposure to soluble MWFs ⁴	47	41	1.5 (0.96–2.5)
Synthetic MWFs⁷			
Only indirect exposure to synthetic MWFs	65	72	1.2 (0.8–1.8)
Possible direct exposure to synthetic MWFs ²	166	200	1.2 (0.9–1.6)
Probable direct exposure to synthetic MWFs ³	17	10	2.0 (0.8–4.6)
Definite direct exposure to synthetic MWFs ⁴	8	7	1.8 (0.6–5.1)

¹ From logistic regression models with adjustment for age (<55 years, 55–64 years, 65–74 years, 75+ years), race (white only, Native American/white, other races), state, smoking status (never, occasional [<100 cigarettes over the lifetime], former, current), and employment in a high-risk occupation for bladder cancer (other than those involving MWF or mineral oil exposure, ever/never).

² Probability of exposure >0 and <0.5

³ Probability of exposure 0.5 and <1

⁴ Probability of exposure =1

⁵ Excludes 2 controls unexposed to straight MWF but exposed to other MWF

⁶ Excludes 1 case unexposed to soluble MWF but exposed to other MWF

⁷ Excludes 17 cases and 23 controls unexposed to synthetic MWF but exposed to other MWF

Table 3

Hours of exposure and cumulative exposure to metalworking fluids (MWFs) and risk of bladder cancer among men assessed as having definite or probable exposure to each MWF within the New England Bladder Cancer Study¹

	Cases	Controls	OR (95% CI)
No exposure to MWFs or mineral oil (referent)	258	362	1.0
Straight MWFs			
Hours of exposure			
1,000	17	19	1.2 (0.6–2.4)
>1,000–6,000	22	13	2.5 (1.2–5.3)
>6,000	18	12	1.8 (0.8–3.9)
			p=0.076
Cumulative exposure (mg/m ³ *hours)			
64	18	16	1.5 (0.7–3.2)
>64–389	18	16	1.7 (0.7–3.1)
>389	21	12	2.2 (1.02–4.8)
			p=0.041
Soluble MWFs			
Hours of exposure			
2,000	26	33	1.1 (0.6–1.9)
>2,000–6,480	23	22	1.5 (0.8–2.9)
>6,480	27	24	1.6 (0.9–2.9)
			p=0.104
Cumulative exposure (mg/m ³ *hours)			
136	24	28	1.1 (0.6–2.0)
>136–362	25	28	1.5 (0.8–2.7)
>362	27	23	1.5 (0.8–2.8)
			p=0.133
Synthetic MWFs			
Hours of exposure			
2,250	13	9	1.9 (0.7–4.8)
>2,250	12	8	1.7 (0.6–4.7)
			p=0.268
Cumulative exposure (mg/m ³ *hours)			
38	13	8	2.3 (0.9–6.0)
>38	12	9	1.4 (0.5–3.7)
			p=0.483

¹ From logistic regression models with adjustment for age (<55 years, 55–64 years, 65–74 years, 75+ years), race (white only, Native American/white, other races), state, smoking status (never, occasional [<100 cigarettes over the lifetime], former, current), and employment in a high-risk occupation for bladder cancer (other than those involving MWF or mineral oil exposure, ever/never).

Table 4

Bladder cancer risk associated with cumulative exposure to straight, soluble, and synthetic metalworking fluids (MWFs) among men assessed as having definite or probable exposure to MWF within the New England Bladder Cancer Study, with all three MWF types in one model ¹

	Cases	Controls	OR (95% CI)
Straight MWFs			
Unexposed to straight MWFs	838	987	1.0
64 mg/m ³ *hours	18	16	1.5 (0.7–3.3)
>64–389 mg/m ³ *hours	18	16	1.3 (0.6–2.9)
>389 mg/m ³ *hours	21	12	2.2 (0.9–5.2)
			p=0.075
Soluble MWFs			
Unexposed to soluble MWFs	819	952	1.0
136 mg/m ³ *hours	24	28	0.8 (0.4–1.5)
>136–362 mg/m ³ *hours	25	28	1.1 (0.6–2.0)
>362 mg/m ³ *hours	27	23	1.0 (0.5–2.1)
			p=0.759
Synthetic MWF			
Unexposed to synthetic MWF	870	1,014	1.0
38 mg/m ³ *hours	13	8	2.1 (0.8–5.7)
>38 mg/m ³ *hours	12	9	1.1 (0.4–3.0)
			p=0.838

¹ From logistic regression models with adjustment for age (<55 years, 55–64 years, 65–74 years, 75+ years), race (white only, Native American/white, other races), state, smoking status (never, occasional [<100 cigarettes over the lifetime], former, current), and employment in a high-risk occupation for bladder cancer (other than those involving MWF or mineral oil exposure, ever/never).

Table 5

Bladder cancer risk associated with probable/definite exposure to straight, soluble, and synthetic metalworking fluids (MWFs), by smoking status, within the New England Bladder Cancer Study¹

	Cases	Controls	OR (95% CI)
Never Smokers			
No exposure to MWFs or mineral oil (referent)	43	119	1.0
Possible exposure to mineral oil	46	98	1.5 (0.9–2.5)
Probable/definite exposure to:			
Straight MWFs	7	13	1.4 (0.4–4.2)
Soluble MWFs	7	23	0.8 (0.3–2.3)
Synthetic MWFs	0	5	–
Former Smokers			
No exposure to MWFs or mineral oil (referent)	138	195	1.0
Possible exposure to mineral oil	193	192	1.5 (1.1–2.1)
Probable/definite exposure to:			
Straight MWFs	29	23	1.8 (0.96–3.2)
Soluble MWFs	42	39	1.5 (0.9–2.5)
Synthetic MWFs	11	8	2.2 (0.8–5.7)
Current Smokers			
No exposure to MWFs or mineral oil (referent)	70	43	1.0
Possible exposure to mineral oil	116	60	1.2 (0.7–2.0)
Probable/definite exposure to:			
Straight MWFs	20	6	2.0 (0.7–5.6)
Soluble MWFs	26	14	1.2 (0.6–2.7)
Synthetic MWFs	14	3	3.1 (0.8–12)

¹From logistic regression models with adjustment for age (<55 years, 55–64 years, 65–74 years, 75+ years), race (white only, Native American/white, other races), state, and employment in a high-risk occupation for bladder cancer (other than those involving MWF or mineral oil exposure, ever/never).