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Metalworking Fluids and Colon Cancer Risk

Longitudinal Targeted Minimum Loss-based Estimation

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Background: Metalworking fluids (MWFs) are a class of complex mixtures of chemicals and oils, including several known carcinogens that may pose a cancer hazard to millions of workers. Reports on the relation between MWFs and incident colon cancer have been mixed.

Methods: We investigated the relation between exposure to straight, soluble, and synthetic MWFs and the incidence of colon cancer in a cohort of automobile manufacturing industry workers, adjusting for time-varying confounding affected by prior exposure to reduce healthy worker survivor bias. We used longitudinal targeted minimum loss-based estimation (TMLE) to estimate the difference in the cumulative incidence of colon cancer comparing counterfactual outcomes if always exposed above to always exposed below an exposure cutoff while at work. Exposure concentration cutoffs were selected a priori at the 90th percentile of total particulate matter for each fluid type: 0.034, 0.400, and 0.003 $\frac{mg}{m^3}$ for straight, soluble, and synthetic MWFs, respectively.

Results: The estimated 25-year risk differences were 3.8% (95% confidence interval [CI] = 0.7, 7.0) for straight, 1.3% (95% CI = −2.3, 4.8) for soluble, and 0.2% (95% CI = −3.3, 3.7) for synthetic MWFs, respectively. The corresponding risk ratios were 2.39 (1.12, 5.08), 1.43 (0.67, 3.04), and 1.08 (0.51, 2.30) for straight, soluble, and synthetic MWFs, respectively.

Conclusions: By controlling for time-varying confounding affected by prior exposure, a key feature of occupational cohorts, we were able to provide evidence for a causal effect of straight MWF exposure on colon cancer risk that was not found using standard analytical techniques in previous reports.

Keywords: Colon cancer incidence; Metalworking fluids; Occupational cohorts; Survival analyses; Healthy worker survivor effect; Targeted maximum likelihood estimation

Despite increased screening and improved treatment, colorectal cancer remains the second most fatal cancer worldwide.[1] The rapid increase in the rates of colorectal cancer among migrants from low- to high-risk areas indicates that much of the disease burden is due to environmental causes. Many environmental carcinogens were initially identified in populations of highly exposed workers. Metalworking fluids (MWFs) are a class of complex mixtures used as coolants, lubricants, and anticorrosives during the fabrication of metal products in manufacturing industries that perform machining operations.[2] MWFs are aerosolized when sprayed, generating airborne particulate matter (PM) that has been linked to a number of cancers. With an estimated 4.4 million US workers exposed in 1997,[3] and many more worldwide, MWF exposure poses a potential cancer hazard to workers in electronics manufacturing, new technologies, and alternative energy, as well as in more traditional industries that involve metal machining.

The potentially carcinogenic nature of MWFs and their additives has long been noted.[4] Straight MWFs are mineral oil based; soluble MWFs are water based but contain a small amount of oil; synthetic fluids are water based and contain no oil at all. Ethanolamines and nitrites are added to soluble and synthetic MWFs to inhibit corrosion and adjust pH; the interaction of these chemicals can form nitrosamines, such as *N*-nitrosodiethanolamine (NDELA). The International Agency for Research on Cancer (IARC) has classified polycyclic aromatic hydrocarbons (PAHs), such as benzo(a)pyrene, in the oil-based fluids as a group 1 carcinogen, and nitrosamines in the water-based fluids, as group 2B.[5] MWFs have been linked to excess prostate cancer mortality,[6] as well as excess incidence of laryngeal cancer,[7,8] bladder cancer,[9] malignant melanoma,[10] and breast cancer.[11] The few studies of MWFs in relation to

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What this study adds

Our analysis is the first to assess the association of metalworking fluids with incident colon cancer after adjusting for time-varying confounding affected by prior exposure, a key feature of healthy worker survivor effect in observational studies of occupational cohorts. In doing so, we were able to provide evidence that straight oil-based metalworking fluids may increase colon cancer risk, evidence that was not found using standard methods in previous analyses.

incident colon cancer have reported conflicting findings.[12,13] A previous analysis of the United Autoworkers-General Motors (UAW-GM) cohort reported no evidence of an association between straight, soluble, and synthetic MWFs and incident colon cancer.[14] An important limitation of those studies is the use of standard statistical methods that fail to account for the healthy worker survivor effect, a potential bias due in part to time-varying confounding affected by prior exposure.[15] In many occupational studies, leaving work predicts both future exposure and the outcome of interest (a proportion of workers likely terminates employment due to underlying illness), making it a confounder, and it is also affected by past exposure.[16] This can make it difficult to detect that an exposure is harmful, as the healthiest workers accumulate the most exposure by remaining at work the longest. A directed acyclic graph illustrating the structure of this bias is presented in eFigure 1; http://links.lww.com/EE/A28.

In this study, we used longitudinal targeted minimum loss-based estimation (TMLE) to estimate the difference in the cumulative incidence of colon cancer under hypothetical interventions on the average time-weighted daily exposure to straight, soluble, and synthetic metalworking fluids in each year of employment.[17] TMLE uses the efficient estimating equation framework[18–20] to produce an estimator that adjusts for time-varying confounding. Although TMLE has recently been applied in cancer epidemiology[21], to our knowledge, this is the first application of longitudinal TMLE in the field.

Methods

Study population

The UAW-GM cohort study was initiated in 1984, jointly funded by the United Auto Workers together with General Motors to address workers' health concerns. The cohort includes 46,316 workers from three automobile manufacturing plants in Michigan.[4] All hourly employees who had worked at least 3 years between 1 January 1938 and 1 January 1985 were included, with the exception of employees who had ever worked in a large forge operation and may have been exposed to a variety of known carcinogenic agents.[4] Cohort members alive on 1 January 1985 (N = 33,063), the year in which the Michigan Cancer Registry was established, constitute the cancer incidence subcohort, the study population for this analysis. Date of birth, sex, race, as well as the complete work history, including job title, department, and dates worked, were abstracted from employment records. Information on race was recorded for most workers but remains unknown for approximately 10% of participants.[22] The institutional review board at the University of California, Berkeley approved this study.

Outcome

The outcome for this study is incidence of colon cancer. The cancer incidence subcohort was linked with the Michigan Cancer Registry to obtain incident cancer cases diagnosed between 1 January 1985 and 31 December 2009. The diagnoses were classified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). While findings from previous analyses suggest that the effects of MWFs and their components may vary across the different regions of the large bowel,[14,23] the analyses presented here are based simply on the first primary diagnosis of incident colon cancers (ICD-O-3 codes C18.0–C18.9), because the small number of rectal cancers (n = 144) did not permit the evaluation of this subsite. Workers who died without a diagnosis for colon cancer were censored at death. Follow-up for mortality began in 1941 and ended in 2009. Vital status was obtained through the Social Security Administration, the National Death Index, as well as plant records and copies of state mortality files provided by the United Autoworkers Union.[22]

Exposure assessment

Workers at the three plants in this study could experience exposure to three broad MWF classes: straight mineral oil, soluble, and synthetic fluids. Quantitative exposure estimates for each study participant in each year were calculated on the basis of detailed employment records, available from hire through 31 December 1994. An extensive retrospective exposure assessment was conducted to develop a job–exposure matrix that indicates MWF concentration for each time period, plant, department, and job.[24,25] MWF concentrations, measured in milligrams per cubic meter $\left(\frac{\text{mg}}{\text{m}^3}\right)$ were estimated as an 8-hour time-weighted average based on several hundred personal and area airborne-exposure measurements of total particulate matter (TPM) collected by the research team in 1986–1987.[25] To adjust for temporal trends in MWF concentrations, a set of multipliers (scale factors) was developed based on 394 air measurements collected by the company between 1958 and 1987, review of historical records, and interviews with plant personnel.[25] Scale factors for the 1985–1995 time period were updated based on additional field visits in 1994.[26]

The job–exposure matrix was combined with company employment records to estimate time-varying annual average daily exposure to each MWF throughout the participants' entire employment. Twenty-two percent of the UAW-GM cancer incidence subcohort members were missing some work history (median, 1.9 years missing).[14] Subjects missing more than 50% were excluded from this analysis (2.4%). Among the rest, intermittent missing work history information was interpolated by averaging the exposures from the previous and subsequent jobs, as is the standard approach in occupational cohort studies that rely on employment records.[27] We computed quantitative measures of annual exposure to each fluid type, as measured by TPM. Cumulative exposure, measured in milligrams per cubic meter-years $\left(\frac{\text{mg}}{\text{m}^3}\text{years}\right)$, was estimated by summing across years of employment. To account for colon cancer latency, exposures were lagged by 15 years. This lag period coincides with the gap between the end of the employment data (31 December 1994) and the end of follow-up. The lagged approach assumes that exposure accumulated in the 15 years preceding a diagnosis did not affect cancer risk.

In the statistical analysis described below, we used a dichotomous definition of the observed exposure in which annual average daily MWF levels above a cutoff were defined as "exposed," while MWF levels less than or equal to the cutoff were defined as "unexposed." The cutoffs were determined a priori at the 90th percentile of TPM exposure for each fluid type. Cutoffs were 0.034, 0.400, and 0.003 $\frac{\text{mg}}{\text{m}^3}$ for straight, soluble, and synthetic MWFs, respectively.

Statistical analysis

To address time-varying confounding affected by prior exposure, we applied a targeted minimum loss-based estimation (TMLE) approach to estimate the 25-year cumulative incidence of colon cancer in this cohort. To do this, we followed hypothetical exposure regimens that set exposure above or below the specific cutoffs described above while at work, preventing right censoring by death.[28] The "exposed" interventions are equivalent to assigning workers to a random exposure drawn from the distribution of observed exposures above the cutoff; the "unexposed" interventions are equivalent to assigning workers to a random exposure drawn from the distribution of observed exposures below the cutoff.[29]

The description and the derivation of the statistical properties of the TMLE for multiple time point interventions are provided elsewhere,[30] and a more detailed explanation of the assumed data structure, statistical models, and identifiability assumptions are provided in eAppendix 1; http://links.lww.com/EE/A28. Briefly, TMLE is a semiparametric substitution estimator that uses the efficient estimating equation framework,[18–20] adjusts for time-varying confounding, is consistent under partial model misspecification (double robustness property), and is efficient when models for exposure/censoring mechanism and outcome are correctly specified (local efficiency). It involves estimation of two components: (1) the probability of being exposed (exposure mechanism) and remaining uncensored by death (censoring mechanism) conditional on covariates, and (2) the average outcome conditional on exposure and covariates (outcome model).

Models for exposures in each year t were fit for all actively employed workers in that year. In addition to year of hire, sex, race, and year of follow-up, exposure models included a set of time-varying covariates consisting of age and duration of employment at the start of year t, as well as the proportion of the year spent on leave, an indicator of the plant at which the worker was employed, and cumulative exposures to straight, soluble, and synthetic metalworking fluids in the previous year (year $t-1$). Censoring models for remaining alive in year t included year of hire, sex, race, age, year of follow-up, lagged duration of employment, the proportion of the year spent on leave, a plant indicator, cumulative exposure to each of the three fluid types, and active employment status, all measured in year t. Both the exposure and censoring models were estimated using the main term logistic regression. For each year, model-based predicted exposure and censoring probabilities were used to estimate weights defined by inverse propensity scores of remaining uncensored and following the exposure of interest. Weights greater than 100 were set to 100. The truncation of the weights affected approximately 1.5%, 1.3%, and 1.2% of the observations in the analyses of the effects of straight, soluble, and synthetic MWFs, respectively.

Outcome models were also estimated using the main term logistic regression. While current exposure to each MWF was considered separately, models were adjusted for cumulative exposure to the other two by the end of the previous year. The result is a series of estimates of the cumulative incidence of colon cancer in each year t for each exposure regimen. These estimates were used to calculate risk differences (RDs) and risk ratios (RRs) comparing what the estimated cumulative incidence of colon cancer would have been if the entire worker population had been exposed while actively employed, to the estimated cumulative incidence if the same worker population had been unexposed while at work. The cumulative incidence estimates were then used to estimate the adjusted survival in each year when exposed and when unexposed. In addition to the adjusted survival, we report the crude survival estimated using a Kaplan–Meier analog for dynamic regimens.[31]

While we focus on our parameters of interest, 25-year exposure effect estimates, additional estimates of colon cancer cumulative incidence and corresponding risk differences and ratios in each year of follow-up are provided for all three fluid types in the eTables 1–3; http://links.lww.com/EE/A28. TMLE provides estimates of cumulative incidence at each time point considering all the past. Because the estimated cumulative incidence at year $t+1$ is not constrained to be greater than it was at year t, the TMLE-derived discrete survival function is not necessarily a monotonically decreasing function.

The analysis was performed using the *stremr* package,[32] in R.[33]

Results

Our analytic cohort consisted of 33,063 workers. During the 25-year follow-up, we identified 466 incident colon cancers. Colon cancer cases were more likely to be women, black, and older at the time of their hire than noncases (Table 1). Approximately 8% of the cases were actively employed at the time of their diagnosis. The mean age at diagnosis was 68.2 years. Cases had a shorter mean follow-up and longer mean

Table 1

Characteristics of the UAW-GM subcohort still alive in 1985 when the Michigan Cancer Registry began

	All workers	Incident colon cancer cases	Noncases
N	33,063	466	32,597
Person-year contribution, 1985–2009	692,035	6,185	685,850
Censored (death), n (%)	11,492 (34.76)	—[a]	11,492 (35.25)
Duration of follow-up, mean (SD)	20.93 (6.87)	13.27 (6.91)	21.04 (6.81)
Age at hire, mean (SD)	25.77 (8.02)	29.23 (9.14)	25.72 (7.99)
Female, n (%)	4,493 (13.59)	66 (14.16)	4,427 (13.58)
Black, n (%)	6,237 (18.86)	117 (25.11)	6,120 (18.77)
Age at diagnosis, mean (SD)	68.21 (10.3)	68.21 (10.30)	—[a]
Actively employed at diagnosis, n (%)	36 (7.73)	36 (7.73)	—[a]
Covariates at baseline, in 1985			
Age, mean (SD)	46.38 (14.09)	55.94 (11.63)	46.24 (14.07)
Duration of employment, mean (SD)	14.09 (8.72)	18.19 (10.08)	14.03 (8.69)
Active at work, n (%)	19,356 (58.54)	218 (46.78)	19,138 (58.71)
Ever exposed, n (%)			
Straight	9,778 (29.57)	197 (42.27)	9,581 (29.39)
Soluble	16,593 (50.19)	329 (70.60)	16,264 (49.89)
Synthetic	4,616 (13.96)	87 (18.67)	4,529 (13.89)
Cumulative TPM exposure $\left(\frac{mg}{m^3}\text{years}\right)$, median (IQR)[b]			
Straight	0.91 (0.26–3.71)	1.18 (0.41–6.17)	0.90 (0.26–3.68)
Soluble	5.76 (1.99–14.53)	8.45 (2.74–18.32)	5.73 (1.97–14.41)
Synthetic	0.86 (0.23–2.39)	1.39 (0.23–2.96)	0.85 (0.23–2.38)
Annual TPM exposure $\left(\frac{mg}{m^3}\right)$ during follow-up, median (IQR)[c]			
Straight	0.07 (0.03–0.32)	0.10 (0.04–0.36)	0.07 (0.03–0.32)
Soluble	0.27 (0.17–0.47)	0.37 (0.18–0.6)	0.27 (0.17–0.47)
Synthetic	0.04 (0.02–0.12)	0.04 (0.02–0.13)	0.04 (0.02–0.12)

[a]Variable does not apply to group.
[b]Computed among exposed workers.
[c]Computed among exposed person-years.
IQR indicates interquartile range.

Table 2

Estimated 25-year cumulative incidence (95% CI) of colon cancer for cohorts of workers always exposed above and below the indicated cutoff while at work, and corresponding risk differences and ratios

	Straight MWFs Estimate (95% CI)	Soluble MWFs Estimate (95% CI)	Synthetic MWFs Estimate (95% CI)
Cumulative incidence if exposed[a]	0.066 (0.045, 0.087)	0.042 (0.019, 0.065)	0.028 (0.009, 0.046)
Cumulative incidence if unexposed	0.028 (0.004, 0.051)	0.029 (0.003, 0.056)	0.026 (0.004, 0.056)
Risk difference	0.038 (0.007, 0.070)	0.013 (−0.023, 0.048)	0.002 (−0.033, 0.037)
Risk ratio	2.386 (1.119, 5.084)	1.429 (0.670, 3.045)	1.081 (0.507, 2.304)

[a]Cutoffs were set at the 90th percentile of annual average daily TPM exposure for each fluid type at 0.034, 0.400, and 0.003 $\frac{mg}{m^3}$ for straight, soluble, and synthetic metalworking fluids, respectively.

duration of employment than noncases. In addition, cases had higher lagged cumulative exposure to all three fluid types, and were more likely to have ever been exposed (assuming a lag) to each of the three fluids at baseline (1985) (Table 1).

In Table 2, we present estimates of the 25-year cumulative incidence of colon cancer under hypothetical interventions in which workers were (1) always exposed above the 90th percentile cutoff ("exposed"), (2) and always exposed at or below the 90th percentile ("unexposed") of each fluid type, while at work. The annual worker population and incident colon cancer counts, annual estimates of cumulative incidence for these interventions, and corresponding exposure effect estimates in each year of follow-up, are provided in the eTables 1–3; http://links.lww.com/EE/A28 for straight, soluble, and synthetic MWFs, respectively. For all three fluids, the estimated 25-year cumulative incidence of colon cancer was higher if workers were always exposed (Table 2).

The differences were largest for straight MWFs: we estimated that the 25-year cumulative incidence of colon cancer would be approximately 3.8% higher if workers were always exposed above the 90th percentile than if exposed below while at work (RD = 3.8%, 95% CI = 0.7, 7.0). The 25-year risk would have more than doubled if all workers had been exposed compared with all workers having been unexposed (RR = 2.39, 95% CI = 1.12, 5.08). Crude and adjusted (TMLE) survival curves comparing workers under the two exposure regimens for straight MWFs are presented in the Figure. Crude survival estimates indicate similar survival among exposed and unexposed workers during the first few years of follow-up (Figure A). Adjustment for time-varying confounding via TMLE resulted in greater survival differences for straight MWFs (Figure B).

We found an elevated 25-year risk of incident colon cancer for workers exposed to soluble MWFs, with wide confidence interval for both estimates (RD = 1.3%, 95% CI = −2.3, 4.8; RR = 1.43, 95% CI = 0.67, 3.04). The 25-year cumulative incidence of colon cancer was similar for workers always exposed (2.8%, 95% CI = 0.9, 4.6) and always unexposed (2.6%, 95% CI = 0.4, 5.6) to synthetic MWFs while at work. We estimated a 25-year risk difference of 0.2% (95% CI = −3.3, 3.7) and risk ratio of 1.08 (95% CI = 0.51, 2.30). Crude and adjusted survival estimates for soluble and synthetic MWFs are not shown.

Discussion

In an analysis of 33,063 autoworkers from the UAW-GM cohort study, we examined the relation between exposures to straight, soluble, and synthetic MWFs and incident colon cancer. Having accounted for possible time-varying confounders on the causal pathway, our results provide evidence that occupational exposure to oil-based straight MWFs may increase the risk of incident colon cancer. In addition, our findings suggest a possible link between exposure to soluble MWFs (oil emulsified in water) and colon cancer risk.

The National Institute for Occupational Safety and Health (NIOSH) recommends a TPM exposure limit of 0.5 $\frac{mg}{m^3}$ for metalworking fluids[34]. Metalworking fluid exposures, however, are regulated by OSHA as "particles not otherwise specified" with

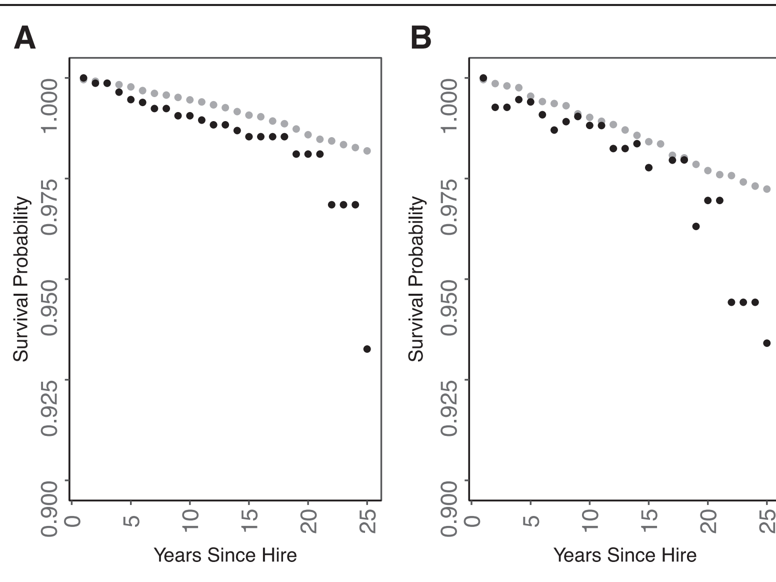

Figure. Straight metalworking fluids: crude (A) and TMLE (B) survival curves for workers in the UAW-GM subcohort always exposed above (black) and below (grey) the cutoff.

a permissible exposure limit of 15 $\frac{\text{mg}}{\text{m}^3}$ for TMP[35]—30 times the recommendation. A recent risk assessment for metalworking fluids based largely on this cohort concludes that after 30 years of exposure to 0.033 $\frac{\text{mg}}{\text{m}^3}$ total particulate matter (described as a typical concentration of daily exposure to mostly soluble fluids), the predicted attributable cancer risk was 0.48 per 1,000 person-years.[36] At 0.02 $\frac{\text{mg}}{\text{m}^3}$, the excess lifetime cancer risk was 7 per 1,000.[36] Park[36] describes the primary affected areas to be the beginning and end of the digestive tract (esophagus and rectum), but did not evaluate colon cancer.

An aerospace cohort study that examined colon and rectal cancer incidence combined in relation to mineral oil exposure reported weak evidence for an inverse association; water-based MWF were not examined.[12] The reasons for the inconsistencies between our findings and those in the aerospace cohort are not clear but suggest that our adjustment for time-varying confounding affected by prior exposure using TMLE may have allowed us to detect an effect otherwise hidden by healthy worker survivor bias. There may also be important differences in the formulation of MWF types, processes, or work practices. Our results are, however, consistent with a Swedish population-based case–control study that reported an elevated risk of incident colon cancer among male petrol station/automobile repair workers exposed to cutting fluids/oils.

While earlier mortality studies of the UAW-GM cohort found no associations with colon cancer mortality and MWF exposure,[26] a later analysis reported that soluble and synthetic MWF exposure was associated with a modest increase in colon cancer risk.[14] However, when known carcinogenic components of soluble and synthetic MWFs were individually examined, both biocides (hazard ratio [HR] = 1.04, 95% CI = 1.02, 1.07) and nitrosamines (HR = 1.02, 95% CI = 1.00, 1.04) were found to increase the risk of colon cancer.[14] Thus, the presence of biocides and nitrosamines in soluble MWFs could explain the elevated risk of colon cancer among workers exposed to these MWFs in our analyses. The increased risk of colon cancer among workers exposed to straight MWFs is likely due to exposure to PAHs, which are formed when oils are heated during machining processes.

A number of potential limitations should be considered in the interpretation of our findings. Since cancers diagnosed before the start of the Michigan Cancer Registry were unknown, colon cancers diagnosed before 1985 were misclassified in our analyses, biasing our estimates toward the null. Our analyses assumed unique latency periods for all workers, when in fact they may vary across individuals.[37] The time-varying job–exposure matrix is the hallmark strength of the UAW-GM cohort study. However, the possibility for exposure misclassification exists, particularly because our analysis had to dichotomize the quantitative exposures, data on the use of protective equipment is not available, and workers' MWF exposure before hire or after employment termination is unknown and assumed to be zero. Furthermore, the assessment of the shape of continuous exposure–response curves through the estimation of marginal structural models is deserving of future research.[38] Finally, few individual-level covariates were available for this cohort, raising concerns about residual unmeasured confounding. Dietary factors, physical inactivity, and excess body weight are important risk factors for colon cancer and would be confounders in this study if they were also associated with exposure. However, there is no a priori reason to expect that any of these factors are likely to vary with exposure, and the *E* value for straight metalworking fluids was 4.2, indicating that the observed association could only be explained by an unmeasured confounder associated with both the treatment and the outcome with a risk ratio of at least 4.2, conditional on measured confounders.[39] The *E* values for soluble and synthetic MWFs were 2.2 and 1.4, respectively.

This study has several strengths. Follow-up continues past employment termination in the UAW-GM cohort. As unemployed workers cannot be exposed, the data contain subject-times in which the probability of exposure is zero, resulting in a structural violation of the positivity assumption. Rather than estimating an unrealistic parameter corresponding to what would have happened if we had intervened to assign high exposure to everyone at all times (even after they had left work), we estimated causal parameters of dynamic interventions[40,41] that assign exposure in response to a subject's employment status. In addition, the outcome is well characterized based on cancer registry data, enabling us to study cancer incidence rather than mortality. Another strength is the availability of data on intermittent time off work, which was used as a time-varying health surrogate. Our statistical methods were able to adjust for this time-varying confounding, reducing healthy worker survivor bias.

Our analysis is the first to provide evidence for a possible relation between MWFs, particularly straight fluids, and incident colon cancer. Given the ubiquity of exposure to these oils and chemicals, lowering occupational limits may prevent a large number of colon cancers worldwide. By estimating the risk reduction associated with lowering occupational exposure limits for specific types of MWFs, we provide a public health framework for our findings.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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