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Original Contribution

Exposure to Metalworking Fluids and Cancer Incidence in the United Auto Workers–General Motors Cohort

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In previous studies, investigators have reported increased risks of specific cancers associated with exposure to metalworking fluids (MWFs). In this report we broadly examine the incidence of 14 types of cancer, with a focus on digestive, respiratory, and hormonal cancers, in the United Auto Workers–General Motors (UAW-GM) cohort, a cohort of workers exposed to MWFs (1973–2015). The cohort included 39,132 workers followed for cancer incidence. Cox models yielded estimates of adjusted hazard ratios, with categorical variables for lagged cumulative exposure to 3 types of MWF (straight, soluble, and synthetic). We fitted penalized splines to examine the shape of the exposure-response relationships. There were 7,809 incident cancer cases of interest. Oil-based straight and soluble MWFs were each modestly associated with all cancers combined. Exposure-response patterns were consistent with prior reports from this cohort, and results for splined exposures generally reflected their categorically modeled counterparts. We found significantly increased incidence of stomach and kidney cancer with higher levels of straight MWF exposure and increased rectal and prostate cancer with increasing water-based synthetic MWF exposure. Only non-Hodgkin lymphoma and prostate cancer were associated with soluble MWF. All results for colon and lung cancers were null. Our results provide updated evidence for associations between MWF exposure and incidence of several types of cancer.

cohort studies; incidence; metalworking; metalworking fluids; neoplasms; occupational exposure; occupational health; proportional hazards models

Abbreviations: CI, confidence interval; HR, hazard ratio; MWF, metalworking fluid; SEER, Surveillance, Epidemiology, and End Results; UAW-GM, United Auto Workers–General Motors.

Metalworking fluids (MWFs) are complex mixtures of oils and chemicals used to cool and lubricate metal in metal machining operations in industrial settings. Today, exposure occurs from inhalation of aerosolized MWF; when sprayed, the fluids generate airborne particulate matter. In the past, exposure also occurred from splashes, dipping one's hands into fluids, or handling parts covered in fluids (1). Classified as straight (compounds refined in mineral oils), soluble (oils emulsified in water), or synthetic (water-soluble chemical lubricants without oils), MWFs continue to pose a hazard to millions of workers globally (2). Driven primarily by the automobile industry, the global MWF market size is projected to reach US$15.1 billion by 2030. In 2019, synthetic MWFs were the second-largest product segment in the market, and the use of corrosive preventive oils, which are soluble and synthetic MWF additives, is anticipated to increase over the next decade (3).

Several reviews, based largely on evidence from the United Auto Workers–General Motors (UAW-GM) Study, a cohort study of mortality among US hourly autoworkers, concluded that cancer-specific mortality was associated with some types of MWF (4, 5). An initial 1992 study (6) was jointly funded by General Motors Corporation (Detroit, Michigan) and the United Auto Workers union (Detroit, Michigan) in an effort to conduct an extensive exposure assessment and understand potential digestive and respiratory cancer risks associated with MWFs. Decades of research based on the UAW-GM cohort, comprising 46,316 hourly workers, has since linked occupational MWF exposure to cancer at several sites, such as the breast, bladder, larynx, lung, prostate, pancreas, rectum, and skin (7–15). Multiple mortality follow-ups have been conducted (6, 16, 17), including our recent overview of mortality from 14 types of cancer spanning several body systems (18). However, UAW-GM incidence analyses have targeted specific sites, and the results suggest that exposure to straight, oil-based MWF moderately increases the risks of laryngeal (19), bladder (7), melanoma (9), breast (14), and colon (20) cancer.

Recently, we extended vital status and cancer incidence follow-up to 2015, which provided us with the opportunity to broadly examine incident cancer and the functional form of specific exposure-response relationships by applying semiparametric smoothers. We assessed a breadth of cancers similar to those evaluated in our recent mortality overview (18) with a concentration on incidence, which can better capture the risk of cancers with a high 5-year survival probability.

METHODS

Study population

The UAW-GM cohort has been described previously (6, 17). Briefly, the original cohort included all hourly workers identified through General Motors company records who had ever worked at any of 3 automobile manufacturing plants in Michigan. This subset of participants includes those who worked for ≥3 years, were hired before December 31, 1984, and were alive when the cancer incidence registries were created. The Surveillance, Epidemiology, and End Results (SEER) Program catchment area for plants 1 and 2 was created on January 1, 1973, and the Michigan Cancer Registry, which covers all 3 plants, was started on January 1, 1985 (6). Analyses excluded subjects who were missing information on more than 50% of their General Motors employment history (4%). Follow-up for cancer incidence now extends from 1973, at the earliest, to 2015; the final study population included 39,132 workers. Loss to follow-up has been minimal (<2%) (18).

Covariates

Data on subject characteristics, including year of hire, sex, race, and worksite, were obtained from company records. Multiple imputation was used to address unknown race (18%). The imputed data sets (M = 50 imputed data sets in the main analyses) were created by full conditional specification, with models including all exposures, outcomes, and covariates.

Exposure assessment

Exposure assessment has been described previously (21–23). Quantitative exposure estimates for each MWF were calculated for each subject-year from detailed employment records available through 1994 and a time-varying job-exposure matrix. The job-exposure matrix was based on several hundred personal and particle-size–selective area samples for particulate matter (mg/m^3) collected in the mid-1980s across jobs and departments, in combination with historical industrial hygiene records. Scale factors were applied to estimate levels of exposure relative to 394 historical air sampling measurements and historical record reviews (21).

Cumulative MWF exposures were assigned to individuals by combining the job-exposure matrix with employment records of job, department, plant, and calendar period, weighted by work time. Gaps in work-history information were interpolated from the last known value. Employment histories (exposures incurred) after 1994 were unavailable and were not considered in this analysis. The exposure-response models included exposure to straight, soluble, and synthetic MWFs, each measured as cumulative exposure (mg/m^3 per year) to total particulate matter and lagged by 21 years to account for cancer latency and as necessitated by the available data.

Case ascertainment

At the start of follow-up, 39,132 subjects were alive and eligible for inclusion. The UAW-GM incidence cohort was linked with the Michigan Cancer Registry to identify incident cases of each type of cancer diagnosed between January 1, 1985 (when the Michigan Cancer Surveillance Program began), and December 31, 2015 (24, 25). Workers at plants 1 and 2 were also linked to the Detroit, Michigan, SEER database (https://seer.cancer.gov/), which was created in 1973. We obtained data on first diagnosis of all cancers; site codes conformed to the *International Classification of Diseases for Oncology, Third Edition* (26) (see Web Table 1, available at https://doi.org/10.1093/aje/kwac190, for coding). Site-specific cancers were selected on the basis of having ≥100 incident cases during follow-up. Data on vital status were obtained through linkage with the Social Security Administration, the National Death Index (National Center for Health Statistics, Hyattsville, Maryland), plant records, death certificates, and state mortality files.

Analytical methods

Follow-up began on the latter of 3 years after hire or the start of the relevant cancer registry—1973 for plants 1 and 2 and 1985 for plant 3. Follow-up ended at cancer incidence for each type of cancer, age 108 years (the oldest observed age at death), death, or the end of 2015, whichever occurred first. Upon reaching the oldest observed age at death, subjects were considered lost to follow-up (<0.5%).

We estimated associations between cumulative exposure to straight, soluble, and synthetic MWFs and each cancer outcome using Cox proportional hazards models with age as the time scale. The models included year of hire (10-year bands), race (White, Black), sex (except in the sex-specific breast and prostate cancer analyses), plant (1–3), calendar year (5-year bands), and the other MWF exposures to adjust for potential confounding. Cumulative MWF exposures were categorized into quartiles with a predetermined reference group. Straight and synthetic fluids had referent groups of zero exposure. For soluble fluids, a more ubiquitous exposure in this cohort, the upper bound of the reference group was set to 0.05 mg/m^3 per year to avoid extremely small numbers of cancer cases and thereby increase the stability of the estimates. This cutoff corresponds to 1% of what the cumulative exposure would be after 10 years at the National Institute for Occupational Safety and Health's recommended exposure limit (total particulate matter set to 0.5 mg/m^3 in 1998) (27). To maximize statistical efficiency, we categorized the 3 MWF exposures on the basis of the distribution of cases for each specific cancer outcome, with cutoffs at the 25th, 50th, and 75th percentiles.

We then treated cumulative exposure as a continuous variable and used a flexible smoothing approach to estimate exposure-response curves in Cox models predicting digestive cancers (colon, esophageal, pancreatic, rectal, and stomach) with penalized splines for straight (oil-based) and synthetic (water-based) fluids, respectively (28). Exposure-response models for soluble MWF were not fitted because of their wide variation in biocides and other chemical additives, as well as in the ratios of water to oil (27). More informative exposure-response smoothing results are assumed to generate from oil-based straight fluid and water-based synthetic fluid. The analyses were carried out twice, first treating unknown race as a separate race category and then by multiply imputing race (M = 18 imputed data sets in these secondary analyses). For multiple imputation, point estimates were averaged across the imputed data sets and the variance estimates were calculated as a linear combination of the mean variance and excess variance across the imputations. Degrees of freedom were selected on the basis of the minimum corrected Akaike's information criterion and biological plausibility.

R software, version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. All research protocols were approved by the Office for the Protection of Human Subjects at the University of California, Berkeley.

RESULTS

This predominantly White (64%), male (88%) cohort was comprised of 39,132 employees who contributed over 1 million person-years overall, of which 287,525 preceded the endpoint of our available employment records (1995) (Table 1). Most workers were exposed to soluble MWF at some point during their employment at General Motors (87%). Over a maximum of 43 years of follow-up, more than half the cohort died and 20% were diagnosed with cancer.

Straight fluid exposure

As Figure 1 shows, there were 7,809 incident cancer cases diagnosed at any site, with the highest exposure category demonstrating a hazard ratio (HR) of 1.13 (95% confidence interval (CI): 1.06, 1.21). The estimated exposure response for cumulative straight fluid exhibited a monotonic pattern for colon and rectal cancers. In the highest exposure category, the risk of stomach cancer rose to an HR of 1.54 (95% CI: 1.01, 2.35), that of kidney and renal pelvic cancer to

Table 1. Demographic and Exposure Characteristics of the UAW-GM Cohort, 1973–2015

Characteristic	Study Population (*n* = 39,132)		
	No.	%	Median (IQR)
Race			
White	25,119	64	
Black	6,862	18	
Unknown	7,151	18	
Sex			
Male	34,498	88	
Female	4,634	12	
Plant[a]			
Plant 1	11,467	29	
Plant 2	15,910	41	
Plant 3	11,755	30	
Type of MWF exposure[b]			
Straight	21,294	54	
Soluble	34,055	87	
Synthetic	12,530	32	
Diagnosed with cancer by end of follow-up	7,894	20	
Duration of follow-up, years			39.50 (34.30–46.98)
Duration of employment, years[c]			15.73 (7.65–27.06)
Year of hire			1965 (1952–1973)
Age at hire, years			24 (20–31)
Year of birth			1937 (1921–1949)
Year of first cancer diagnosis			1999 (1991–2007)
Age at first cancer diagnosis, years			67 (59–74)
Type of cumulative MWF exposure, mg/m^3 per year[d]			
Straight			0.69 (0.21–2.53)
Soluble			4.93 (1.93–13.31)
Synthetic			0.44 (0.15–1.56)

Abbreviations: IQR, interquartile range; MWF, metalworking fluid; UAW-GM, United Auto Workers–General Motors.

[a] For individuals who worked at several plants, plant was taken to be the site where they had accrued the most recorded work time.

[b] Individuals could be exposed to 1 or more of the 3 types of MWF over the course of the follow-up period.

[c] Among those with a known date of leaving work.

[d] Summary statistics calculated for ever-exposed individuals at the end of follow-up only. Exposures were lagged by 21 years.

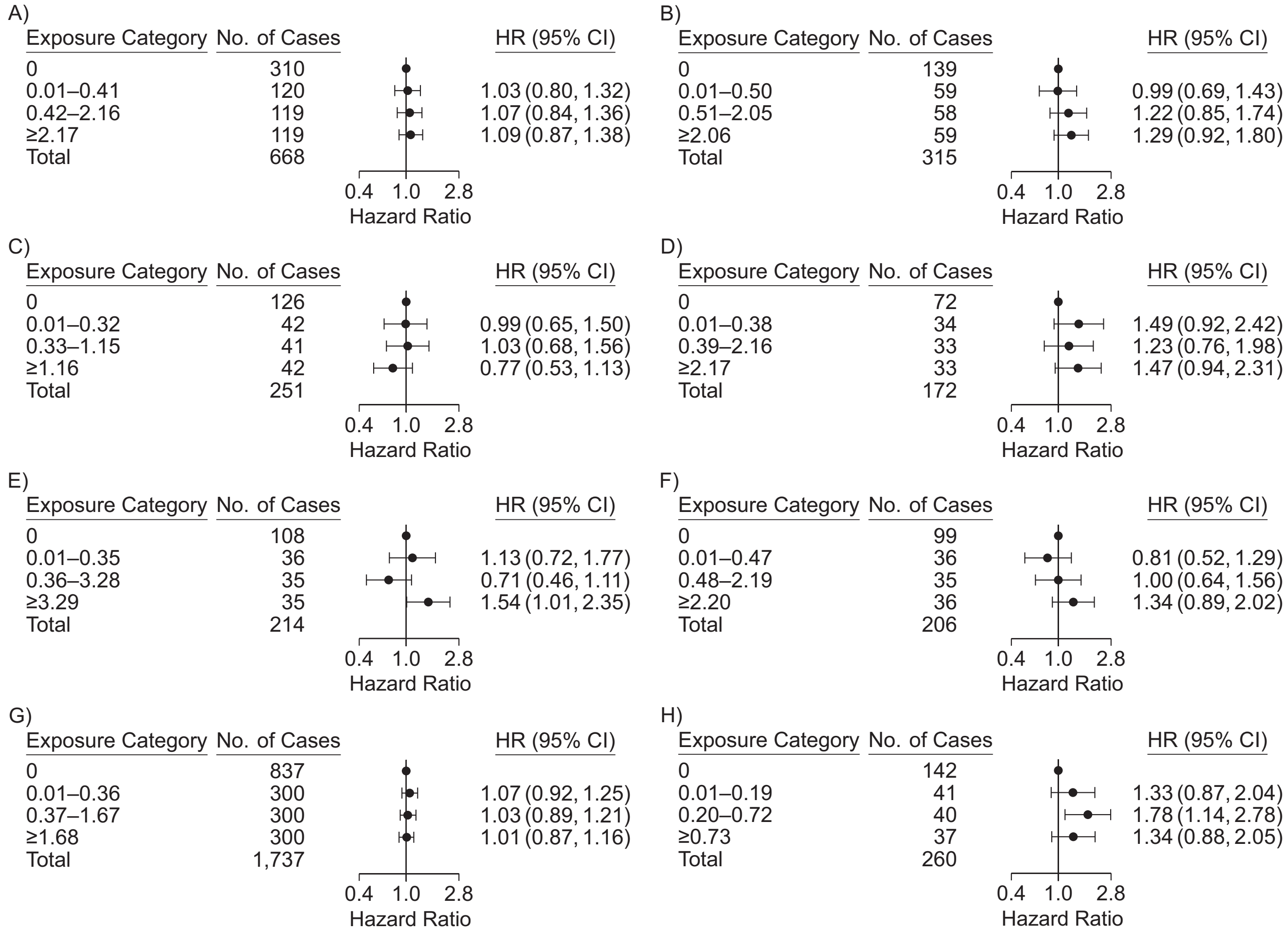

Figure 1 Continues

an HR of 1.59 (95% CI: 1.09, 2.31), and that of bladder cancer to an HR of 1.28 (95% CI: 0.99, 1.65). Modestly elevated HRs were found for melanoma and rectal, bladder, esophageal, and breast cancers in relation to straight fluids in most or all exposed categories.

Soluble fluid exposure

For all cancers combined, exposure to cumulative soluble MWF exhibited a slight exposure-response gradient, with a significantly elevated HR in the highest category (HR = 1.14, 95% CI: 1.05, 1.24) (Figure 2). Prostate cancer, melanoma, and non-Hodgkin lymphoma HRs increased with increasing exposure; by contrast, a negative exposure-response gradient was found for kidney and renal pelvic cancers. All other cancers demonstrated nonmonotonic exposure-response patterns. A significantly elevated HR was found in the highest exposure category for prostate cancer (HR = 1.28, 95% CI: 1.10, 1.49) and all non-Hodgkin lymphoma HRs were significantly elevated, with the HR in the highest exposure category rising to 1.70 (95% CI: 1.13, 2.54).

Synthetic exposure

The HRs for incidence of all cancers combined in relation to cumulative exposure to synthetic fluids hovered close to the null in all exposure categories (Figure 3). Excluding the referent category, HRs decreased with increasing cumulative synthetic MWF exposure for breast cancer, kidney and renal pelvic cancer, and melanoma. Positive monotonic exposure-response patterns were found for rectal and esophageal cancers, with the HRs in the highest exposure categories rising to 1.52 (95% CI: 1.01, 2.29) and 1.47 (95% CI: 0.90, 2.40), respectively. In addition, an elevated HR was found in the highest exposure category for prostate cancer (HR = 1.16, 95% CI: 1.00, 1.35). HRs were close to or below the null value for other cancers at any level of exposure.

Smoothing

Cox models with penalized splines were applied to smooth the exposure response for stomach cancer in relation to straight fluid (Figure 4), as well as for several other

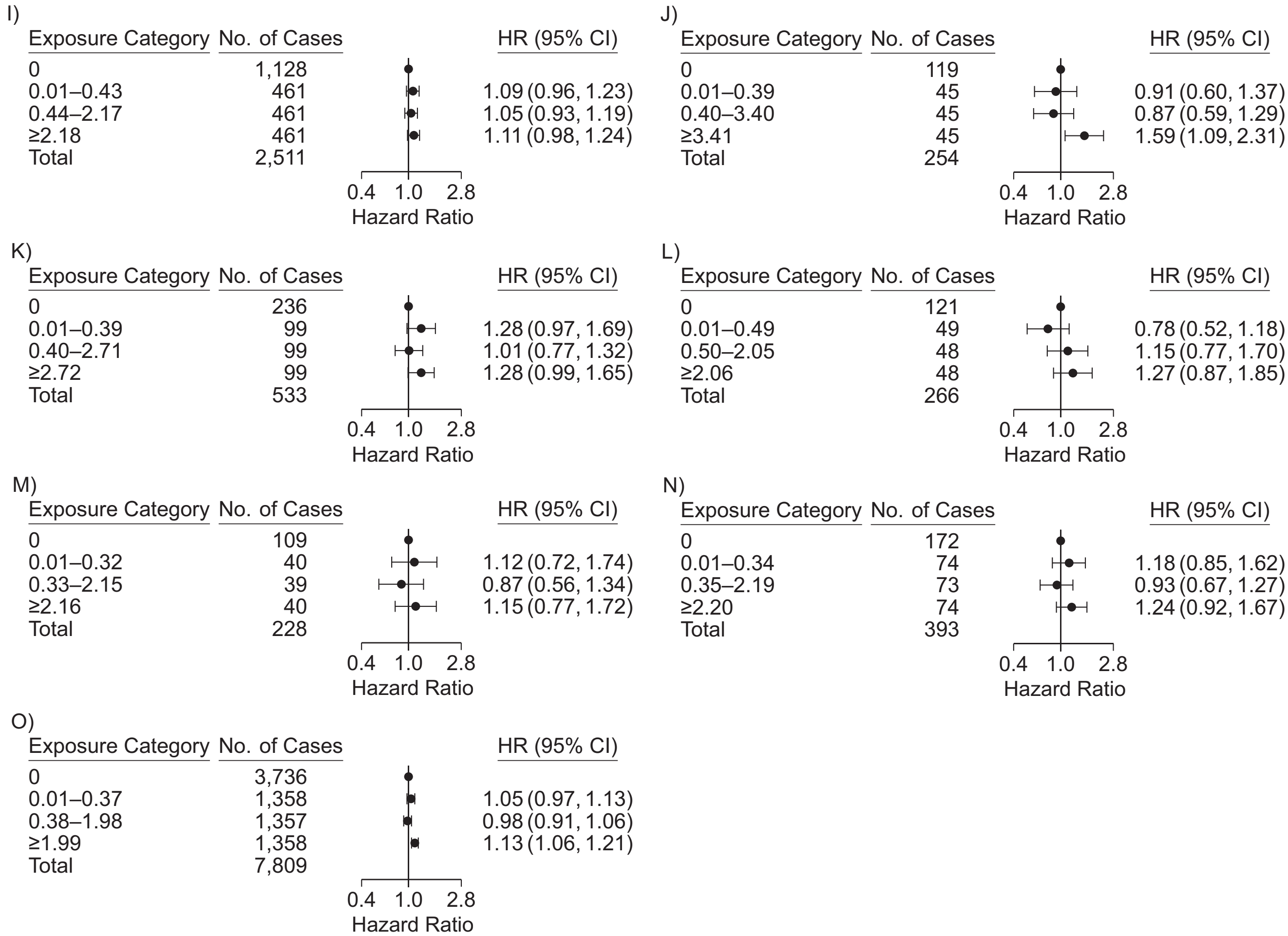

Figure 1. Hazard ratios (HRs) for cancer incidence as a function of cumulative straight metalworking fluid (MWF) exposure, Michigan, 1973–2015. The models used age as the time scale and adjusted for year of hire, race, sex, plant, calendar year, and the other cumulative MWF exposures. Cumulative exposures for all MWFs were lagged by 21 years. To maximize statistical efficiency, cutpoints were based on the empirical distribution of the exposure among the cases. A) Colon cancer; B) rectal cancer; C) pancreatic cancer; D) esophageal cancer; E) stomach cancer; F) laryngeal cancer; G) lung and bronchial cancer; H) breast cancer; I) prostate cancer; J) kidney and renal pelvic cancers; K) bladder cancer; L) melanoma; M) leukemia; N) non-Hodgkin lymphoma; O) all cancers. Bars represent 95% confidence intervals (CIs).

associations (Web Figures 1–6). The HR for stomach cancer increased with increasing cumulative straight fluid exposure, and the smoothed confidence intervals excluded the null for most of the exposure range. The HR rose to 2.0 at 26.4 mg/m^3 per year, which was approximately the 98th percentile of the case exposure distribution.

Results did not change when unknown race was treated as a separate category (data not shown).

DISCUSSION

To our knowledge, this study is the first to have broadly investigated the association between MWF exposure and cancer incidence in this well-established cohort of autoworkers. We observed moderate associations between the incidence of all cancers combined and the highest categories of straight and soluble MWF exposure, and a modest but non-significant relationship with synthetic fluids, which contain no oil. Risks for several types of cancer were significantly elevated among UAW-GM autoworkers with exposure to at least 1 MWF, and results using models with categorical exposures were consistent with continuous exposure analyses using penalized splines. Risks for stomach, breast, kidney and renal pelvic, and bladder cancer were more elevated with straight fluids than with soluble or synthetic fluids, suggesting that polycyclic aromatic hydrocarbons may influence these cancers' etiology, similar to what has been observed in other industries involving exposure to polycyclic aromatic hydrocarbons (29–32). In addition, risks for rectal, pancreatic, and prostate cancer and non-Hodgkin lymphoma were most elevated with exposure to soluble or synthetic MWF, indicating that potential causative agents in these fluids, such as nitrosamines, may play a role in specific cancer etiologies. Associations between all levels of MWF

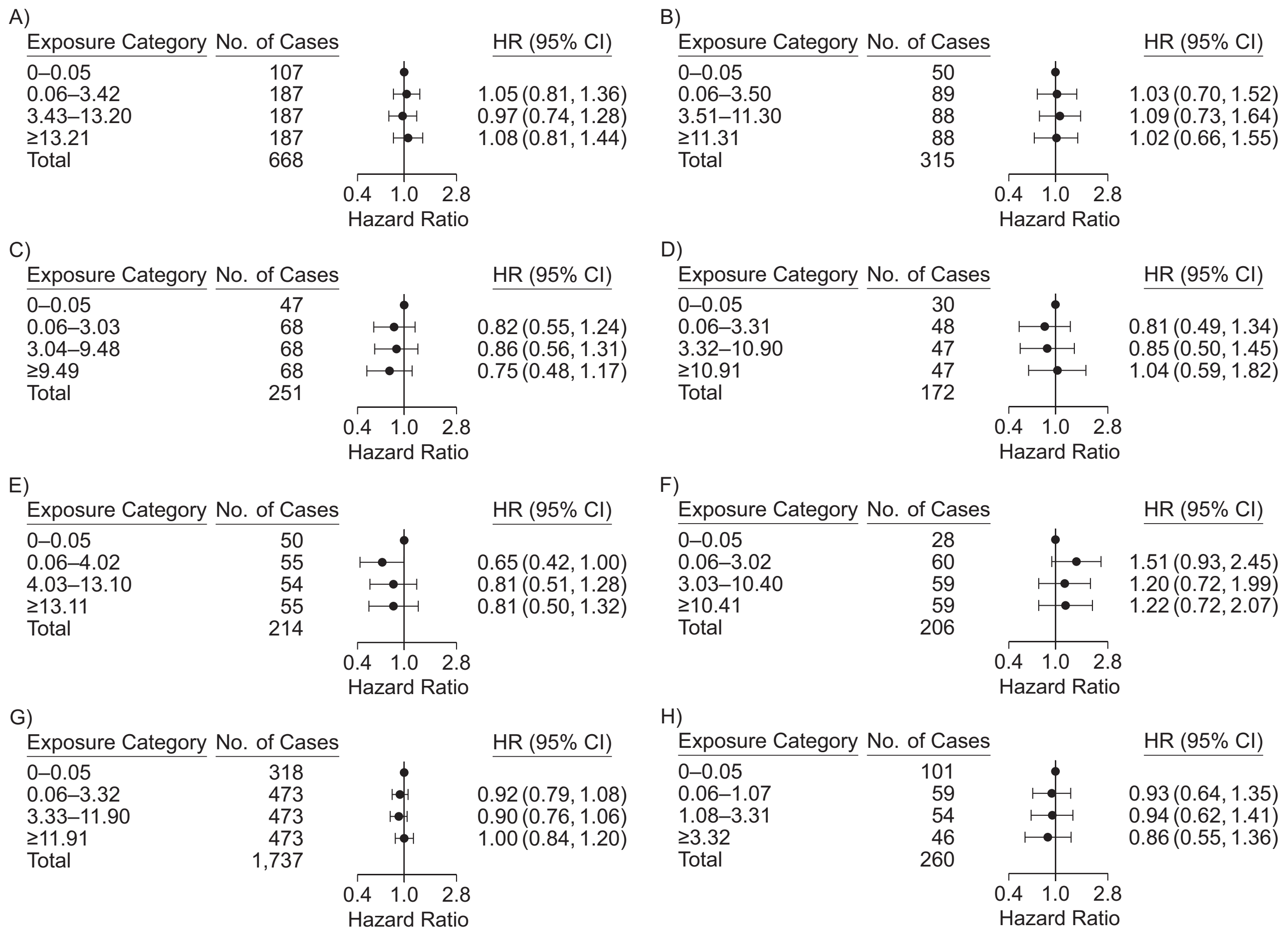

Figure 2 Continues

exposure and incident colon or lung and bronchial cancers were null.

Digestive cancers were of primary interest to General Motors Corporation and the United Auto Workers union when this cohort was created in 1985. Recently, we reported mortality results from this cohort with follow-up through 2015, including an increased risk for stomach cancer mortality in the highest straight fluid exposure category (HR = 1.86, 95% CI: 1.17, 2.97) (18). This result was in contrast to a previous incidence study with follow-up ending in 1994 which found no evidence of excess risk (19). Our present results are consistent with the recent mortality study (18): We found no increasing trends in stomach cancer risk across increasing categories of any MWF exposure, except for the highest straight fluid exposure category, wherein the HR rose to 1.54 (95% CI: 1.01, 2.35). This finding was reinforced by penalized spline regression, in which the hazard with high exposure was twice that of the unexposed. Several other mortality studies of MWF-exposed working populations have also found excess risk of stomach cancer among machinists (33), engine manufacturers (34), and workers exposed to oil mists (35). Similar to our stomach cancer results, the HR for kidney and renal pelvic cancers rose to 1.59 (95% CI: 1.09, 2.31) in the highest straight fluid exposure category. Together, these results suggest threshold effects, which can be further explored through targeted exposure-response analyses.

Our findings are concordant with several other UAW-GM analyses: Moderately elevated associations with straight MWF have been found for laryngeal (8), bladder (7), melanoma (9), breast (14), and rectal (10) cancers. We did not find evidence of an association between any type of MWF and incident colon cancer, akin to an earlier analysis of the UAW-GM cohort (8); however, in a more recent study, Izano et al. (20) adjusted for the healthy worker survivor effect and found evidence of an association with straight MWF exposure. Straight MWFs are a concern because they contain polycyclic aromatic hydrocarbons, which are hypothesized to be the primary carcinogens within straight MWFs (36, 37). The carcinogenicity of polycyclic aromatic hydrocarbons is often attributed to their ability to bind to DNA, thus generating several disorder effects that may drive tumor initiation (38–40).

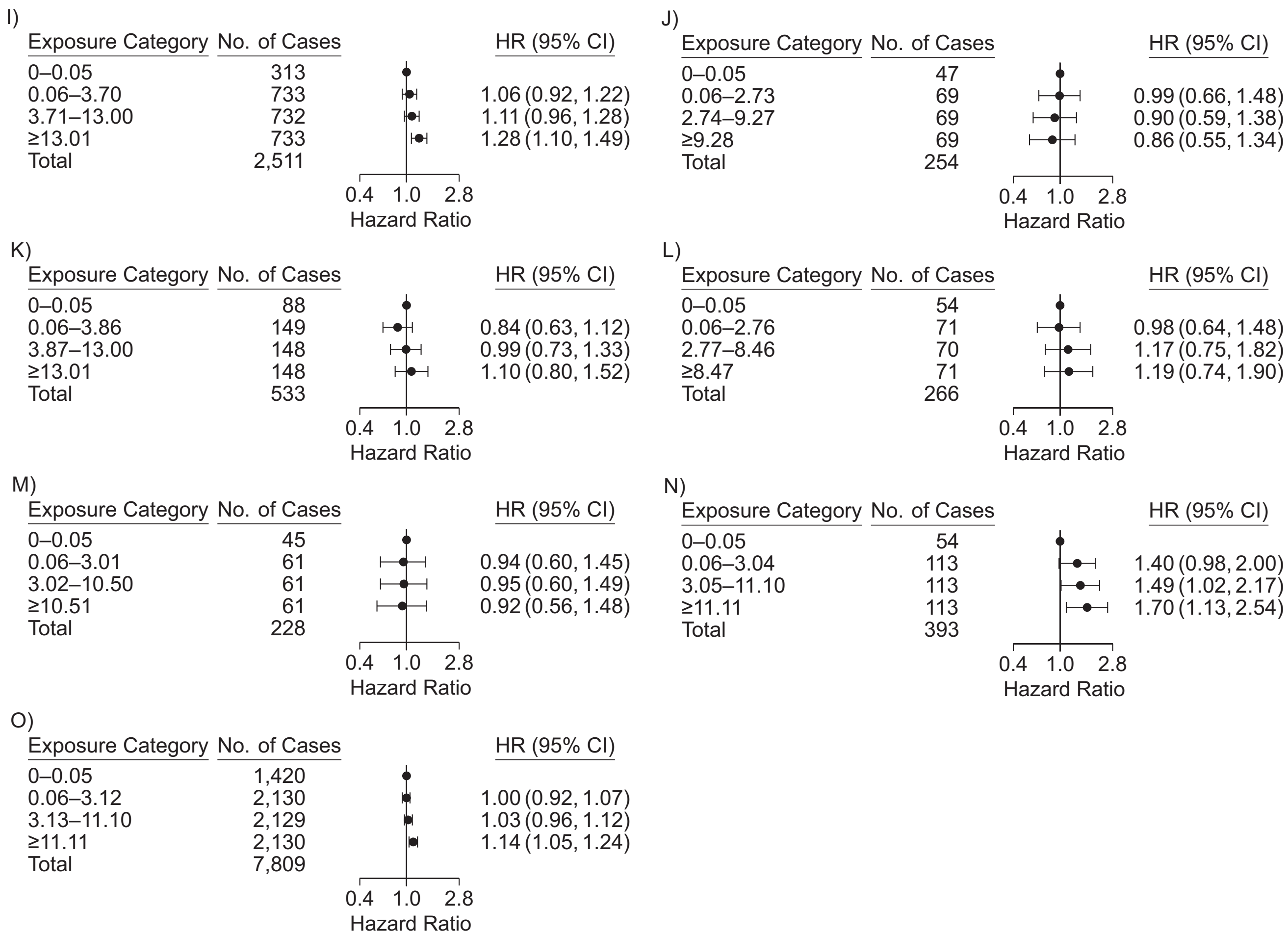

Figure 2. Hazard ratios (HRs) for cancer incidence as a function of cumulative soluble metalworking fluid (MWF) exposure, Michigan, 1973–2015. The models used age as the time scale and adjusted for year of hire, race, sex, plant, calendar year, and the other cumulative MWF exposures. Cumulative exposures for all MWFs were lagged by 21 years. To maximize statistical efficiency, cutpoints were based on the empirical distribution of the exposure among the cases. A) Colon cancer; B) rectal cancer; C) pancreatic cancer; D) esophageal cancer; E) stomach cancer; F) laryngeal cancer; G) lung and bronchial cancer; H) breast cancer; I) prostate cancer; J) kidney and renal pelvic cancers; K) bladder cancer; L) melanoma; M) leukemia; N) non-Hodgkin lymphoma; O) all cancers. Bars represent 95% confidence intervals (CIs).

Previously in this cohort, synthetic MWFs have been modestly linked with increased risk of several cancers, including esophageal, liver, prostate, and rectal cancer (10, 17). Our results generally support these findings, as we observed large increases in the HRs for esophageal, prostate, and rectal cancer in the highest categories of synthetic fluid exposure. In addition, this is the first (to our knowledge) observed association between incident non-Hodgkin lymphoma and soluble fluids, but it is potentially important: The HRs rose steadily to 1.70 (95% CI: 1.13, 2.54) in the highest exposure category. Soluble and synthetic MWFs could be carcinogenic due to the presence of biocides and nitrosamines (20, 41), which are routinely added to the fluids to counteract short-term microbial growth (42, 43). Understanding the relationship between cancer risk and soluble and synthetic fluids is imperative given the growing market (3) for these fluid products and their additives.

Although our results are consistent with previous exposure-response patterns, the current estimates are often smaller in magnitude (7, 9, 14, 19, 20). We consider 3 possible explanations. First, this study's extended follow-up generated more cases in the highest exposure categories, leading to more stable estimates. For example, our bladder cancer and straight fluid results are slightly attenuated from those of Friesen et al. (7), who found an HR of 2.07 as compared with our HR of 1.49 with a similar cutpoint for the highest category (Web Table 2), based on dozens more cases. Second, depletion of susceptible individuals over extended follow-up leads to built-in selection bias from the HR (44). However, this bias would be mildly attenuated in our open cohort, where subjects could enter follow-up until 1985. Finally, our overall estimates may mask stronger exposure-response results within subgroups of age, race, or exposure period (14, 45, 46). For example, the link between synthetic

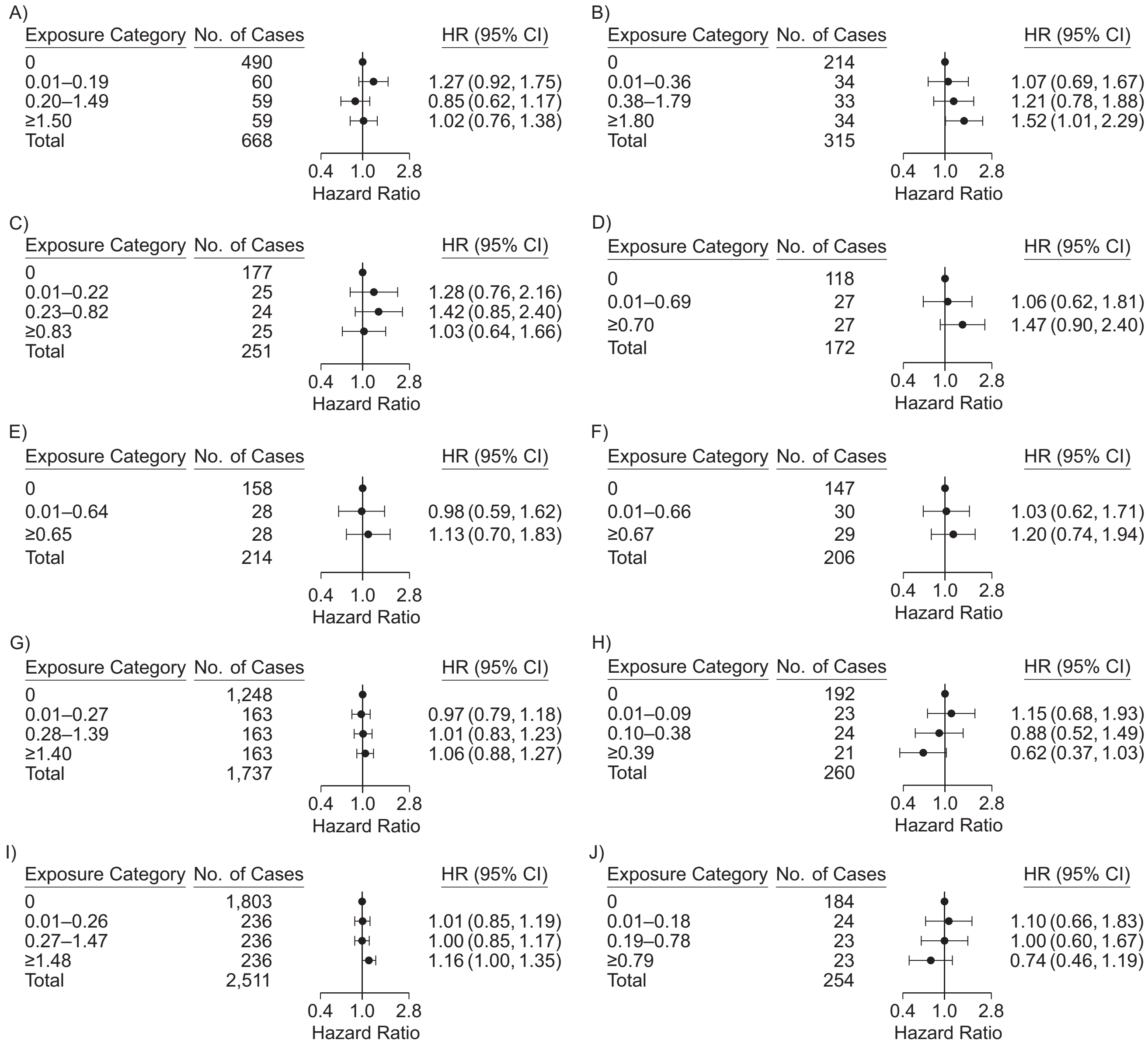

Figure 3 Continues

MWF and elevated breast cancer incidence was previously found to be strongest among younger women (14).

The strength of this study lies in the statistical power to detect relatively rare cancers (because of the large sample size), long follow-up, and quantitative MWF exposure assessment (47, 48). In contrast with our recent mortality study (18), this research provides the opportunity to examine cancers with high 5-year survival rates that are better measured with incidence, such as cancers of the bladder, breast, and prostate, kidney and renal pelvic cancer, melanoma, and non-Hodgkin lymphoma (49). One potential limitation is unmeasured confounding. Although we controlled for age and race, we could not account for potential confounders such as alcohol consumption, socioeconomic status, and smoking. However, prior studies of this cohort found no association between MWF exposure and cirrhosis death, a proxy for alcohol consumption (16, 18). Additionally, this study and our past research (7, 17) have found no association between MWFs and lung cancer incidence, a proxy for smoking. Although the autoworkers were all employed at the same 3 plants, implying similar socioeconomic status, there was a wide range in salary between those working in skilled trades, such as metal machining, and unskilled assembly workers (50).

Subjects diagnosed out of state or diagnosed in state before the registries started were not included in the local registries, introducing potential for outcome misclassification. However, the MWF exposures were similar between

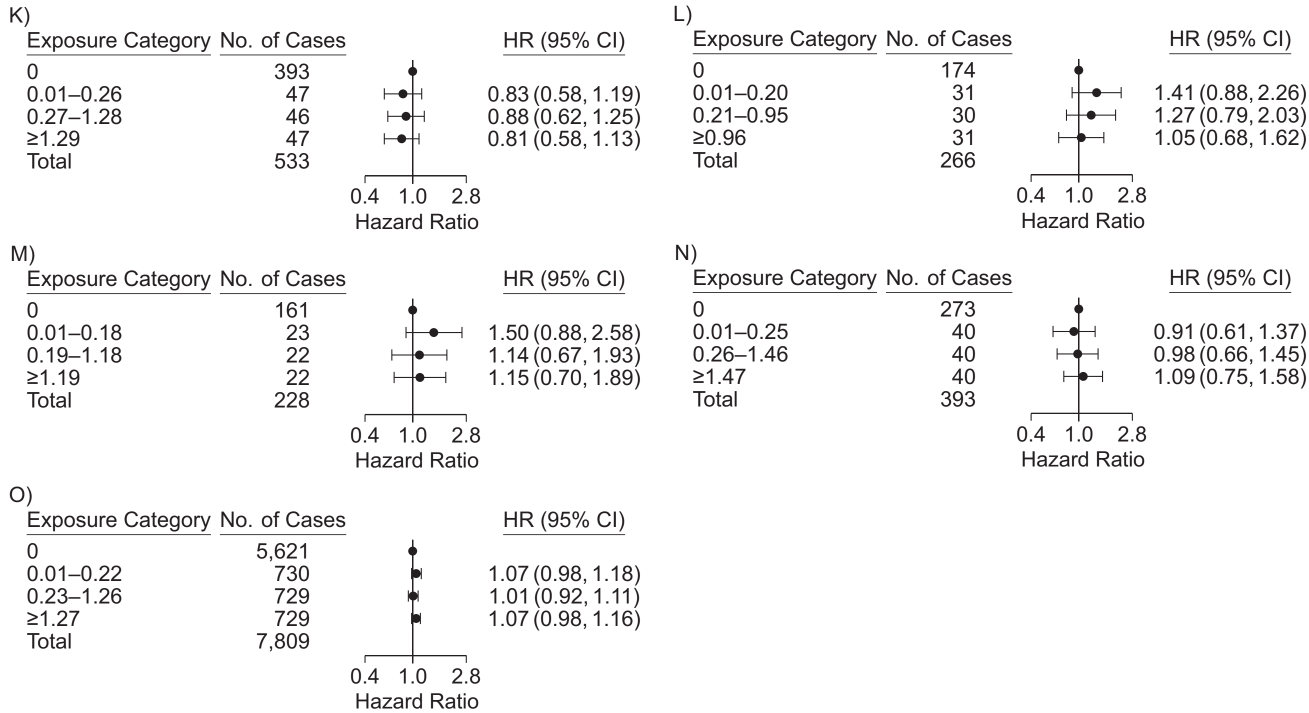

Figure 3. Hazard ratios (HRs) for cancer incidence as a function of cumulative synthetic metalworking fluid (MWF) exposure, Michigan, 1973–2015. The models used age as the time scale and adjusted for year of hire, race, sex, plant, calendar year, and the other cumulative MWF exposures. Cumulative exposures for all MWFs were lagged by 21 years. To maximize statistical efficiency, cutpoints were based on the empirical distribution of the exposure among the cases. A) Colon cancer; B) rectal cancer; C) pancreatic cancer; D) esophageal cancer; E) stomach cancer; F) laryngeal cancer; G) lung and bronchial cancer; H) breast cancer; I) prostate cancer; J) kidney and renal pelvic cancers; K) bladder cancer; L) melanoma; M) leukemia; N) non-Hodgkin lymphoma; O) all cancers. Bars represent 95% confidence intervals (CIs).

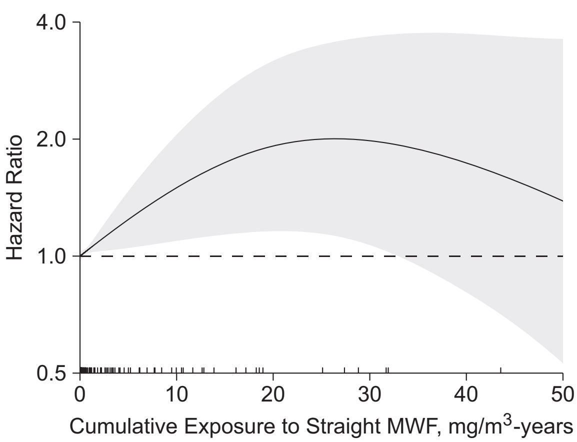

Figure 4. Hazard ratio for stomach cancer incidence as a function of cumulative straight metalworking fluid (MWF) exposure, Michigan, 1973–2015. The spline was estimated from a Cox proportional hazards model using age as the time scale and controlled for year of hire, multiply imputed race (18 imputed data sets), sex, plant, calendar year, and cumulative exposure to soluble and synthetic MWFs. The optimal degree of smoothing (degrees of freedom (df)) was chosen on the basis of the minimum corrected Akaike's information criterion as a measure of goodness of fit (df = 2.24). The spline is presented up to the 99th percentile of observed cumulative exposure. The shaded area shows the 95% pointwise confidence intervals.

the cancer deaths that occurred out of state and those of persons who died in Michigan, suggesting that migration was nondifferential (7). Additionally, our use of SEER data allowed us to capture some cancers diagnosed prior to the start of or overlooked by the Michigan Cancer Registry. Another limitation concerns the lack of employment and exposure data after 1994. While there is a lag between exposure and cancer diagnosis, its length depends on the type of cancer (51). Some cancers have shorter latency than the 21 years required by the available data; therefore, we may have misclassified the relevant exposure in those analyses. The gap between the end of our employment records and the end of follow-up might explain our comparatively lower estimates than prior studies' and may limit our ability to detect associations. Finally, our results may be at risk of attenuation from the healthy worker survivor effect (52). Our use of a 21-year lag may diminish this issue (53–55) but cannot account for self-selection out of the workforce that occurred 21 years prior to cancer incidence. Further analyses targeting specific incident cancers may use G-methods to explore the extent of bias via the healthy worker survivor effect (56).

We report elevations in the incidence of several cancers, including rectal, prostate, and stomach cancer, kidney and renal pelvic cancer, and non-Hodgkin lymphoma, from long-term occupational exposure to MWFs. To our knowledge, our analysis is the first to provide an overview of cancer incidence in the UAW-GM cohort and supports evidence of relationships between site-specific cancers and MWFs found in previous work.

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The data set is available upon request, but with limitations to preserve the autonomy and rights of individual participants.

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Conflict of interest: none declared.

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