All Cancer Incidence – GM Manuscript

**Introduction**

Metalworking fluids (MWF) are complex mixtures of oils and chemicals used in machining operations as coolants and lubricants during cutting or grinding operations. Exposure can occur from inhalation of aerosolized metalworking fluid when sprayed generating airborne particulate matter (PM) or dermal exposure from splashes, dipping 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), MWF continue to pose a hazard to millions of workers in automobile manufacturing and other metal machining-related jobs.2 Driven primarily by the automobile industry, the workforce exposed to MWF will continue to expand, especially in Asia and Central and South America. The global MWF market size is projected to reach 15.85 billion by 2027, exhibiting a revenue-based compound annual growth rate of 4.4%. In 2019, synthetic MWFs were the second-largest product segment in the market and corrosive preventive oils, additives used in soluble and synthetic MWFs, are anticipated to increase at a compound annual growth rate of 3.8% (2020-2027).

Occupational exposure to metalworking fluids (MWF) has been linked to increased cancer risk for several cancer sites, including cancers of the bladder, larynx, lung, prostate, pancreas, rectum, and skin.3-11 Potential carcinogens in MWF include hydrocarbons, chlorinated paraffins, aliphatic amins, nitrosamines, polycyclic aromatic hydrocarbons (PAH), formaldehyde-releasing agents, diethanolamine, and many other specialty additives.12 Straight and some soluble MWFs are complex mixtures of paraffinic, naphthenic, and aromatic compounds refined from mineral oil. The properties of mineral oil classified as carcinogenic to humans are thought to be due primarily to PAHs content.13 To adjust pH and prevent corrosion, ethanolamines and nitrites are added to soluble and synthetic MWFs; however, these chemicals can interact to form nitrosamines, such as N-nitrosodiethanolamines (NDELA), which are also possible human carcinogens.14 Evidence of the carcinogenicity of other additives to soluble and synthetic MWFs has been shown in animals,15-17 but their carcinogenic effect on humans18 has not been established.

Following the release of the 1988 National Institute of Occupational Safety and Health (NIOSH) Criteria Document, which recommended exposure limit (REL) for occupational exposure to MWF be 0.5 mg/m3 for total PM (TPM) and 0.4 for respirable PM, multiple reviews concluded cancer-specific risks associated with at least some MWF based largely on the United Autoworkers – General Motors cohort study (UAW-GM).19 This work was jointly funded by General Motors Corporation and the United Auto Workers union in an effort to conduct an extensive exposure assessment and understand cancer risk. The UAW-GM cohort is an occupational cohort of 46,316 hourly workers in automotive manufacturing and is considered to be the most comprehensive cohort study of MWF-exposed workers. Results from this large cohort have been mixed, with evidence that exposure to straight, oil-based MWF moderately increases the incidence of laryngeal,20, 21 bladder,3 melanoma,5 breast,22 and colon14 cancers. Although the literature is sparse, increased risk of cervical cancer and breast cancer in younger women has also been identified.22, 23 Furthermore, prior UAW-GM analyses have demonstrated the presence of the healthy worker survivor effect (HWSE),24, 25 although these studies did not include a wide range of cancers in their case ascertainment.

The UAW-GM cohort has recently extended vital status follow-up from 1985-2015, providing the opportunity to broadly examine the risk of incident cancers with quantitative exposure measures for the three MWF classes and expand our knowledge of which relationships may be at risk of bias from the HWSE.

**Methods**

Study population

The UAW-GM cohort has been described in detail previously.19, 26 Briefly, the UAW-GM cohort includes all hourly workers identified through company records at 3 automobile manufacturing plants in Michigan who worked for ≥3 yrs.19 The manufacturing facilities were selected to produce a pool of workers almost exclusively exposed to MWFs and to reduce the likelihood of exposure to a variety of known toxic and carcinogenic agents.19 The present study excluded subjects missing more than half of their employment history (4%). Follow-up for cancer incidence now extends from 1973 to 2015; the final study population was comprised of 39,132 workers.

Covariates

Subject characteristics, including year of birth, sex (male, female), race (white, black, unknown), and worksite (plant 1, 2, 3) were obtained from company records. Multiple imputation of subjects with unknown race (18%) was used. The imputed data sets (n= 50) were created by full conditional specification in R, with models including all exposures, outcomes, and covariates.

Exposure

Exposure assessment has been described previously.27-29 Quantitative exposure estimates for each MWF were calculated for each subject stemmed from detailed employment records and a time-varying job-exposure matrix (JEM). The JEM was based on several hundred personal and area size-selective samples for PM (mg/m3) collected across jobs and departments by the research team, in combination with historical industrial hygiene records. Scale factors were applied to estimate historical levels of exposure relative to baseline measurements made by the research industrial hygienists (mid-1980s).27 These scale factors reflect the dramatic decreases in exposure concentrations over the second half of the 20th century, particularly in the early 1970s with the passage of the Occupational Safety and Health Act.

MWF exposures were assigned to individuals according to job and department and calendar time, weighted by work time. For those missing less than half their work history, gaps in employment history information were interpolated by averaging exposures from previous and subsequent jobs. The exposure-response models considered exposure to straight, soluble, and synthetic MWF measured as cumulative exposure to total PM (TPM). The work history records were initially collected in 1985 and extended up to 1995. To account for cancer latency and as necessitated by the available data, exposure-response models for this analysis are based on cumulative MWF exposure (mg/m3-years) lagged by 21 years.

Outcome

At the start of follow-up, 39,132 subjects were alive and eligible to be included. Data on vital status was obtained through linkage with the Social Security Administration, the National Death Index, plant records, death certificates, and state mortality files. The outcome of interest was cancer incidence. The UAW-GM incidence cohort was linked with the Michigan Cancer Registry to identify incident cancer cases diagnosed between January 1, 1985, and December 31, 2015. Data are collected by the Michigan Department of Community Health as part of the Michigan Cancer Surveillance Program, which began in 1985 and participates in the National Program of Cancer Registries of the Centers for Disease Control and Prevention. We obtained data on first diagnosis of all cancers (International Classification of Disease for Oncology, revisions 9 and 10 (ICD-9 and ICD-10) codes), colon (xxx), rectal (xxx), pancreatic (xxx), esophageal (xxx), stomach (xxx), laryngeal (xxx), lung and bronchial (xxx), breast (xxx), prostate (xxx), kidney and renal pelvic (xxx), and bladder (xxx) cancers; melanoma (xxx), leukemia (xxx), and non-Hodgkin lymphoma (xxx). Site-specific cancers were selected based on having at least 100 identified incident cases during the follow-up period.

Analytic methods

In all of our analyses, follow-up began 3 years after hire and no earlier than 1973 for plants 1 and 2 or 1985 for plant 3. Follow-up ended at first primary cancer incidence, age 108 (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 LTF, meaning that <0.5% of the participants were LTF.

We estimated associations between cumulative exposure to straight, soluble, and synthetic MWF and each cancer outcome as adjusted hazard ratios (HR) in Cox proportional hazards models with age as the timescale. In addition to age, all models included year of hire, race, sex, and plant, calendar year and the other MWF exposures to adjust for potential confounding. Cumulative exposures to the three MWF were categorized with a pre-determined reference group. The distribution of exposure to each fluid type among the cases of each cancer were used to determine the cut points for the exposed categories in order to maximize statistical efficiency. Cumulative straight and synthetic exposures had referent groups of zero exposure. For soluble exposures, a more ubiquitous exposure in this cohort, the upper bound of the reference group was set to 0.05 mg/m3·years to avoid extremely small numbers of cancer cases in the reference group and thereby increase stability of the HR estimates. This cut-off is approximately 1% of what cumulative exposure would be after ten years at the NIOSH REL.

The presence of HWSE depends on three underlying conditions: (1) leaving work predicts future exposure, (2) leaving work is associated with disease outcome, and (3) prior exposure increases the probability of leaving work. As occupational exposure falls to zero after leaving work, this study assessed conditions (2) and (3). We assessed the presence of two conditions necessary for the HWSE by estimating HRs using Cox proportional hazards models to predict cancer incidence and employment terminations, following an approach similar to Naimi et al.30 Age was used a timescale and all models were adjusted for cumulative MWF exposure (lagged 1 year), race (multiply imputed), plant, sex (not included in sex-specific models – prostate and breast cancer), and calendar year. For condition (2), cancer outcomes were modeled as a function of employment termination (=1 if subject left work). Follow-up began on the same dates for each of the plants as with the primary analysis and ended on either the date of first cancer diagnosis (any or site-specific), date of death, or December 31, 1994 (the last date for which we have employment data), whichever occurred first.

**Results**

Characteristics of the final study population are presented in Table 1. This predominantly white (64%) and male (88%) comprised of 39,132 employees who contributed over 1 million person-years overall and xxxxxx during employment. Workers were more likely to be exposed to soluble MWFs (87%), slightly over half were exposed to straight fluids, and approximately a third to synthetic fluids, while working. Over a max of 42 years of follow-up, over half the cohort had died and 20% had been diagnosed with cancer. The median age at first primary cancer diagnosis was 67 years (interquartile range (IQR), 59-74) and the median years at work among those with a known worker exit was 15.73 (7.65-27.06).

Straight exposure

As seen in Figure 1, there were 7,809 incident cancer cases of a first cancer diagnosed at any site with the highest exposure category demonstrating a HR of 1.13 (95% CI: 1.06-1.21). The estimated exposure-response for cumulative straight fluid exhibited a monotonic pattern for colon, rectal, laryngeal, and lung and bronchial cancers. In the highest cumulative straight fluid exposure category, stomach cancer rose to a HR of 1.54 (1.01-2.35), kidney and renal pelvic cancer to 1.59 (1.09-2.31), and bladder cancer to 1.28 (0.99-1.65). Modestly elevated HRs were found for rectal, esophageal, breast cancers and melanoma in response to straight fluid exposure. Results were generally below or closely surrounding the null for colon, pancreatic, prostate, and lung and bronchial cancers, leukemia, and non-Hodgkin lymphoma.

Soluble exposure

Exposure to cumulative soluble MWFs exhibited a slight dose-response gradient with a significantly elevated HR in the highest exposure category (HR: 1.14; 95% CI: 1.05-1.24). Esophageal cancer, bladder cancer, melanoma, and non-Hodgkin lymphoma HRs increased with increasing exposure; contrastingly, a negative dose-response gradient was found for kidney and renal pelvic cancers. All other cancers demonstrate non-monotonic exposure-response patterns. Non-Hodgkin lymphoma HRs were significantly elevated in categories with the greatest exposures, with the highest exposure category rising to 1.70 (1.13-2.54). A significantly elevated HR was also found in the highest exposure category for prostate cancer (HR: 1.28; 1.10-1.49).

Synthetic exposure

All-cancer incidence associated with cumulative exposure to synthetic fluids hovered close to the null in all exposure categories. A negative exposure-response gradient with increasing cumulative synthetic MWF exposure was found for breast cancer, kidney and renal pelvic cancer, and melanoma; positive monotonic exposure-response patterns were found for rectal cancer, lung and bronchial cancer, and non-Hodgkin lymphoma. The HR in the highest exposure category was 1.52 (1.01-2.29) for rectal cancer, 1.47 (0.90-2.40) for esophageal cancer, and 1.16 (1.00-1.35) for prostate cancer. HRs were close to or below the null for the other cancers at any level of exposure.

Cancer incidence in association with leaving work

Results for the assessment of condition (2) were not entirely consistent across the fourteen incident cancer outcomes examined (figure 4). Based on the main model adjusted for covariates, we found that the hazard of lung and bronchial () and pancreatic () cancers among those who left work were approximately twofold the hazard of those who were still at work at the time of cancer incidence. The association between leaving work and cancer incidence was slightly elevated for rectal cancer and non-Hodgkin lymphoma. Cancers with results below the null were kidney and renal pelvic, melanoma, stomach, and leukemia and statistical significance below the null was found for prostate, and bladder cancers.

Prior exposure in association with probability of leaving work

MWF exposure was associated with leaving work in at least one category of MWF exposure. Those in the second quartile of cumulative exposure to oil-based straight and soluble MWFs were at a higher risk for leaving work. In contrast, only those in the highest exposure category of synthetic MWFs were at a higher risk for leaving work.

**Discussion**

This is the first study to investigate the association of exposure to MWFs and the incidence of cancer across fourteen cancer sites using follow-up extended to the end of 2015 in this large cohort of automobile manufacturing workers. We observed strong associations between all-site cancer incidence and the highest category of straight and soluble MWF exposure, and modest but non-significant relationships with water-based synthetic fluids, which contain no oil. Over 42 years of follow-up, the incidence of several types of cancers among UAW-GM autoworkers were significantly elevated with at least one MWF. Risks for stomach, breast, kidney and renal pelvic, and bladder cancers were more elevated with straight MWFs as compared to soluble or synthetic fluids, suggesting that PAHs may influence the etiology of these cancers similarly to what has been observed in other PAH-exposed industries.31-34 In addition, risk for rectal, pancreatic, and prostate cancer and non-Hodgkin lymphoma were most elevated with soluble or synthetic MWFs, indicating that potential causative agents in soluble and synthetic fluids, such as nitrosamines, may play a role in specific cancer etiologies.

Recently, Costello and colleagues conducted a UAW-GM mortality study extending follow-up through 2015. Increased stomach cancer mortality was reported in the highest straight fluid exposure category (HR: 1.86; 95% CI: 1.17-2.97) and no trend was observed in exposure-response patterns for stomach cancer and any of the MWF types, in contrast to a previous study using incidence which found no evidence of excess risk.20 Several other mortality studies of MWF-exposed working populations have also reported excess risk of stomach cancer among machinists,35, 36 engine manufacturers,37 and workers exposed to grinding with water-based cutting fluids,38 precision grinding,39 or to oil mists.40 The present research is consistent with results from the mortality studies, as we found no clear associations between stomach cancer incidence and MWF exposure, with the exception of the highest straight fluid exposure category, wherein the HR rose to 1.54 (95% CI: 1.01-2.35). Similar results can be found for kidney and renal pelvic cancers, in which the HR rose to 1.59 (95% CI: 1.09-2.31) in the highest straight fluid exposure category. These results may suggest threshold effects, which can be further explored through targeted exposure-response analyses.

The findings of this study are concordant with several other UAW-GM cohort studies as moderately elevated associations with straight MWFs have been found for laryngeal,4 bladder,3 melanoma,5 breast,22 and rectal7 cancers. For example, Eisen and colleagues21 found a monotonic exposure-response gradient with laryngeal cancer and straight fluid leading to a twofold increase risk for the highest category of exposure. This conclusion was generally supported by Zeka et al.’s20 follow-up study of aerodigestive cancers in the UAW-GM cohort. The present work tempers the magnitude of the association; however, an increasing dose-response gradient for laryngeal cancer continued to be observed, ultimately rising to 1.34 (95% CI: 0.89, 2.02) in the highest straight fluid exposure category. Akin to a previous analysis of the UAW-GM cohort,4 our research did not find evidence of an association between any MWF type and incident colon cancer; however, we did not control for time-varying confounding affected by prior exposure which has since provided evidence of a causal effect of straight MWF exposure on colon cancer.14 The moderate increases in site-specific cancer incidence among workers exposed to straight MWFs is likely due to PAHs, which are formed when oils are heated during machining processes.

Synthetic MWFs have been modestly linked with increased risk of several cancers, including esophageal, liver, prostate, and rectal (refs). Results for lung cancer have been inconsistent with a recent analysis suggesting a positive association for synthetic MWF and lung cancer mortality (refs). Our cancer incidence results largely reflect these previous findings. Pancreatic cancer was elevated in the second and third highest exposure categories, a monotonic exposure-response pattern was observed for rectal cancer and non-Hodgkin lymphoma, and prostate cancer risk rose to 1.16 (95% CI: 1.00-1.35) with the highest category of synthetic fluid exposure. One possible explanation for null results in other cancers is that synthetic MWF were introduced later; therefore, exposed persons had to have remained employed longer, introducing some survivor bias among the older cases. The cancers which have shown elevated incidences or a positive exposure-response patterns generally exhibit a latency of approximately 5-10 years, giving them time to become clinically detectable between exposure to synthetic fluids and the end of the study period. The presence of biocides and nitrosamines in soluble and synthetic MWFs could explain the elevated risk of several cancers among workers exposed to these MWFs in our analysis. Understanding the relationship between cancers with elevated incidence and synthetic fluids and their additives should be a priority to explore further given the growing market for these fluid products.

The secondary aim of this study was to assess the potential for bias due to the HWSE in a longitudinal study of cancer incidence and MWF exposure in order to guide our future analytical approach. Evidence of a higher risk of cancer for those who left work was approximately twofold for pancreatic (HR: 2.02; 95% CI: 0.94-4.35) and lung and bronchial cancers (HR: 1.91; 95% CI: 1.47-2.48). As these cancers are often aggressive with regard to case fatality and survival time, worker’s symptoms may cause them to leave work earlier. In addition, we found evidence for the third condition required for HWSE among all workers: (3) prior MWF exposure increases probability of leaving work. Our results are consistent with a previous UAW-GM study which found evidence that leaving work was a strong predictor of lung and prostate cancer, further supporting evidence against claims that the HSWSE is unlikely to impact cancers with late-stage symptoms or poor survival.41 There is no information available providing reasons that subjects in this cohort left work; therefore, we assume employment termination was voluntary and serves as an indicator of underlying health status. These results provide evidence that employment status is a time-varying confounder (conditions (1) and (2)) affected by prior exposure (condition (3)).42 G-methods30 should be used to address the HWSE and avoid bias in exposure-response analyses for pancreatic and lung and bronchial cancers.

The strength of this study lies in the statistical power for relatively rare cancers and the quantitative exposure assessment of MWF by type.43, 44 In addition, this study boasts of a large sample size, long follow-up, and specifically pinpoints cancers at risk of the HWSE that may need causal inference methods, such as g-methods, to avoid unnecessary underestimation. By follow-up the longitudinal all-cancer mortality study from Costello and colleagues, this research provides the opportunity to examine cancer’s with high 5-year survival rates that are better served to use incidence as their outcome rather than mortality, such as cancers of the bladder, breast, prostate, kidney and renal pelvic, melanoma, and non-Hodgkin lymphoma.

Our main limitation in this resource is unmeasured potential confounders. Although we controlled for age and race, we did not account for several other risk factors that may affect cancer incidence and MWF exposure, such as socioeconomic status, smoking, and alcohol consumption. However, since the cohort was autoworkers employed at the same 3 plants, we did not expect large differences in socioeconomic status. In addition, prior studies of this cohort found no association between MWF exposure and cirrhosis death, a proxy for alcohol consumption (ref). Although unmeasured confounding may account for some portion of the results observed, this study contributes to the literature as it is the first to present a comprehensive view of cancer incidence in relation to MWF exposure.

Underreporting of certain cancers to the Michigan state cancer registry is a potential source of outcome misclassification in our cohort population. Previous studies have found that the most commonly underreported cancer types have been melanomas, prostate, and hematologic malignancies, which are cancers often diagnosed and treated outside of the hospital setting.45, 46 Not sure what to say about counteracting this potential issue. Due to the quantitative exposure assessment of MWF being based on a job-exposure matrix, there will be some non-differential misclassification of exposure as well; however, this would likely attenuate our results. In addition, our results may be at risk of the HWSE because workers who are least susceptible to occupational exposures’ adverse effects may stay at work the longest and accrue the most exposure. Our use of 21-year lag may diminish this issue, but not account for self-selection out of the workforce that occurred 21 years prior to cancer incidence. The lag may also lead to attenuation of our results, especially for cancers with shorter latency, and our pathway analysis identifies which cancers are most susceptible to the bias.

We report elevations in several the incidences of several cancers, including rectal, stomach, kidney and renal pelvic, breast, and non-Hodgkin lymphoma, from long-term occupational exposure to MWF. Our analysis is the first to provide a broad overview of cancer incidence in the UAW-GM cohort, and supports evidence of the relationships between site-specific cancers and MWFs found in previous work. Furthermore, our pathway analysis offers knowledge of specific cancers where attenuation by the HWSE should be excluded.

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