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Causal and Nonlinear Models of Cancer Risk among Autoworkers
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List of Terms and Abbreviations

Chronic Obstructive Pulmonary Disease (COPD)

Confidence interval (95% CI)

Hazard ratio (HR)

Healthy Worker Survivor Effect (HWSE)

Metalworking fluids (MWF)

Polycyclic Aromatic Hydrocarbons (PAH)

Standardized Incidence Ratio (SIR)

Standardized Mortality Ratio (SMR)

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Abstract

Metalworking fluids (MWF) are complex mixtures of oils and chemicals widely used industry to cool and lubricate metal operations. There are millions of US workers exposed to MWF and their use is increasing internationally despite the presence of known carcinogens, such as polycyclic aromatic hydrocarbons in oil-based fluids, and ethanolamines and nitrosamines in water-based fluids. Our cohort of 46,397 United Autoworkers at General Motors (UAW-GM) is the only existing study with quantitative estimates of lifetime exposure to both water- and oil-based MWF. We have taken advantage of this resource by extending vital status follow-up from 50 to 60 years and linking with the Michigan Cancer Registry to identify incident cancers diagnosed in the cohort over the past 20 years.

Based on the cancer incidence data, we have found new positive associations between straight MWF exposure and bladder cancer and malignant melanoma. For both cancers, the hazard rate ratio rose to 2-fold in the highest quintile of cumulative exposure to straight MWF. We also reported standardized incidence ratios (SIRs) for all cancers in the sub-cohort of female autoworkers. We found an elevated SIR of 2.71 (95% CI: 1.94, 3.69) for cervical cancer incidence, though there was no evidence of any association with MWF exposure.

In a new effort to tease out the common components of oil-and water-based MWF, we developed a set of new exposure metrics and evaluated them with respect to cancer incidence. Laryngeal and bladder cancer were most strongly associated with PAH. Rectal cancer was associated with synthetics as well as straight MWF. Protective effects were observed for biocide exposure and lung and stomach cancer; biocide may be a surrogate for endotoxin contamination of the water-based soluble and synthetic fluids.

Perhaps the paper with the greatest potential impact is the one where we apply g-estimation to reduce healthy worker survivor bias. G-estimation is one of several new causal methods in epidemiology. It was originally developed to address HWE, but until our recent work it had never been applied in an occupational cohort study. Results of our analysis suggest that exposure to straight MWF increases risk of mortality from all causes of death combined, COPD, ischemic heart disease and all cancers combined, as well as lung cancer and prostate cancer in particular. This is the first study to report a positive association between oil-based MWF, COPD ischemic heart disease and lung cancer mortality. By providing a roadmap for the application of g-estimation, we hope to encourage more widespread use of these innovative and critically important new epidemiologic methods for identifying occupational causes of disease.

Section 1

Significant Key findings.

As reported by Friesen et al (2009), this was the first cohort study to examine bladder cancer risk with quantitative measures of exposure to three metalworking fluid classes and their additives. Metal machining and other mineral oil-exposed occupations have been consistently associated with excess risk of bladder cancer in population-based case-control studies. There were no quantitative estimates of risk, however, prior to our recently published paper. The strong quantitative exposure-response we observed in relation to cumulative exposure to straight MWF will substantially strengthen the evidence for mineral oils as a bladder carcinogen. We have also found associations between synthetic fluids and several cancer sites for the first time; positive associations with cancers of the rectum and colon, and protective effect for lung cancer (Friesen et al. AJIM 2011).

The findings for malignant melanoma incidence and straight MWF, as reported by Costello et al (2011) are also new and important. MWF has long been associated with dermatitis and skin cancer mortality, but never before with incidence of this deadlier form of skin cancer. Results provide evidence, based on quantitative measures of MWF, that oil-based MWF, particularly straight mineral oils, are associated with the incidence of malignant melanoma.

Our most significant work, however, in terms of general impact on both the field of occupational epidemiology and on worker health, may be the successful application of g-estimation to adjust for HWSE in occupational studies. We have presented our approach and the results in several international meetings and audiences have been extremely enthusiastic. We submitted a second revision of the manuscript to *Epidemiology* in August. Our recent success in applying this causal approach to reduce HWSE was built on the past efforts of other investigators over many years. It is critical that our recent results and computer programs be subjected to the highest degree of scrutiny and the causal approach applied to other occupational cohort studies. Because the approach eliminates the downward bias caused by HWSE, it allows true hazards to be identified in epidemiologic studies.

On the basis of new results obtained in several different analyses over this project period, we understand more about the complex relations between MWF and lung cancer. In contrast to our original expectation, results for this cancer had been null in relation to all types of MWF. Recent evidence suggested an inverse association for lung cancer with cumulative exposure to synthetic fluids containing biocides. Now we have new evidence, based on g-estimation, that after adjusting for HWSE, years of exposure to straight fluid causes *an increase* in the hazard ratio for all cancers combined, and a significantly elevated hazard ratio for lung cancer (Chevrier et al, SER 2011). Moreover, we also have further evidence that lung (and stomach) cancer may be inversely associated with synthetic MWF (possibly due to the endotoxin contamination

of these water-based fluids). Altogether these results paint a somewhat complicated, but coherent story for lung cancer that warrants still further investigation and synthesis.

Translation of Findings.

Most of the evidence for the carcinogenicity of MWF has been focused on straight mineral oils. Exposure to straight metalworking fluid has been associated with several different cancers – incidence and mortality. Both the prevalence of straight MWF as well as airborne concentrations was substantially reduced in these automobile plants over the 60 year follow-up period of this study. Moreover, the most likely carcinogenic component of straights, polycyclic aromatic hydrocarbons (PAH), was also reduced by the industry wide transition to solvent refining methods during this period. Today water-based MWF are more common than straight. No cancers have been clearly and consistently associated with soluble MWF, although several have a pattern of association that faintly echoes their association with straights, e.g. malignant melanoma and prostate cancer. Rectal cancer is the only cancer that has been positively associated with synthetic MWF in our recent incidence study, raising concern about the carcinogenicity of synthetic MWF for the first time. Inverse associations, however, were also reported between synthetic MWF and both stomach and lung cancer. One explanation for the observed protective effects was microbial contamination of the water based synthetic fluids. In particular, endotoxins that exist in these environments have been found to be protective for lung and stomach cancer in other occupational settings, such as cotton textile mills.

Outcomes/Impact.

We have found significant excess risk of bladder cancer and malignant melanoma in relation to straight MWF using traditional Cox proportional hazards models. We have also reported new evidence, based on g-estimation, that exposure to straight MWF increases risk of mortality due to all causes of death combined, heart disease, chronic obstructive pulmonary disease and all cancers combined, as well as lung cancer and prostate cancer. Taken together, these findings will potentially impact the workplace by reinforcing efforts to reduce exposure to straight MWF via substitution by water-based MWF (soluble or synthetic) in metalworking operations throughout industry.

Moreover, comparing results between g-estimation and traditional methods suggests that g-estimation effectively reduces healthy worker survivor bias. The significant positive results for both ischemic heart and respiratory disease mortality in relation to straight MWF are important new findings. Ischemic heart disease has not generally been considered to be a potential occupational disease. These findings suggest that future occupational health research should be directed towards this chronic disease. The success of g-estimation in addressing this pervasive form of downward bias in occupational studies is of major importance to the field of occupational epidemiology. By providing a roadmap for application, we hope to encourage more widespread use of these innovative and critically important new methods for identifying occupational causes of disease.

Section 2

Scientific Report.

Aim 1: Fit semiparametric models for incidence of selected urinary, gastrointestinal, respiratory and other cancers in relation to cumulative MWF exposures, in time widows to account for disease latency.

The full cancer incidence cohort includes all 34,549 hourly workers at three Michigan automotive plants who had worked a minimum of 3 years pre-1985 and were alive on 1 Jan 1985. All incident cancers were obtained from the Michigan Cancer Registry (1985-2004) and vital status follow-up was also extended to 2005. We have published positive findings for bladder cancer and straight MWF (Freisen et al 2009) and malignant melanoma and straight fluid (Costello et al, 2011). For the bladder cancer study, we identified two PAH relevant time exposure windows. The first time window was pre-1986. In the mid-1980s most oil-containing MWF fluids were reformulated to use highly treated base oils to remove or minimize PAH exposure, thus avoiding the carcinogen label on the Material Safety Data Sheet. The second time window was further restricted to exposures pre-1970, before the transition to more highly refined base oils with lower PAH content began. The strongest association (based on model fit) was found with straight MWF lagged by 20 years. The penalized spline curves for the 20 year lag and the pre-1970 time window metrics were essentially indistinguishable, but the confidence limits were wider for the pre-1970 time window. The 10 year lag and the pre-1986 time window metrics were also indistinguishable.

Based on 76 incident cases of malignant melanoma in the cohort of 14,139 white males, the HR was 1.99 (95% CI: 1.00-3.96) for the highest category of straight MWF (Costello et al 2011). Risk was greatest in the most recent time window. Penalized splines suggested a linear exposure-response over the full range of exposure. The change in HR for malignant melanoma per mg/m^3-year of straight MWF increased monotonically from 1.01 to 1.04, when the date of birth restriction increased from 1925 to 1945 in 5-year intervals. Results for soluble MWF were more modest. There was no association with synthetic MWF.

We have also published exposure-response relationships for selected cancer outcomes (respiratory, urinary, gastrointestinal, reproductive and skin) in relation to constituent-based metrics to account for the common components of the oil- and water-based fractions (Friesen et al, 2011). In Cox regression, we found straight or PAH-containing MWF increased the risk of cancer of the skin, bladder, larynx, prostate and breast. Synthetic or water-based MWF increased the risk of colon and rectal cancers. For stomach cancer, a protective effect was observed with biocides, nitrosamine, and water-based MWF. For lung cancer, a protective effect was observed with biocide-containing MWF. Based on these constituent-based metrics, we demonstrated that soluble MWF contributes to the carcinogenicity of both the oil- and water-based metrics. One unit of soluble MWF, however, was consistently less potent than a unit of straight or synthetic MWF.

We have also estimated SIRs for cancer incidence and updated SMRs for all causes of death, separately for males and females. The SIR for cervical cancer was statistically significantly elevated (40 observed cases) in the sub-cohort of 5700 women and in race specific subgroups; 3.25 and 2.10, respectively for white and black women. (The SMR for cervical cancer was also statistically significantly elevated for white women (3.44) based on 7 observed deaths.) Based on the elevated SIR, we examined cervical cancer in an internal analysis. Results for oil-based straight fluid were null. Relative risks for soluble and synthetic MWFs, and nitrosamines were modestly elevated, but none were statistically significant. This is described in a paper (Betenia et al, SJWEH, In Press). Melissa Friesen is further exploring other types of cancer incidence and mortality in the female sub-cohort, with particular attention to lung cancer, in relation to constituent based exposure metrics she has developed to MWF.

Aim 2: Apply causal models to reduce healthy worker bias by fitting structural nested accelerated failure time models to address leaving work as a time varying confounder and use g-estimation to estimate the overall biologic effect of exposure.

We have made great strides on this Aim and have completed the first successful application of G-estimation to an occupational cohort study. The manuscript has been revised and is now under review at Epidemiology (Chevrier et al 2011). In the paper, we compare results based on g-estimation of accelerated failure time models with results based on standard Cox models with a series of adjustments that have been proposed for dealing with HWSE. These adjustments included: (1) restricting analyses to unemployed individuals with at least 15 years of follow up; (2) adjusting for time since hire; (3) adjusting for employment status; and (4) adjusting for temporary time off work.

G-estimation simulates nested randomized-controlled trials at each time point (calendar year) conditional on prior covariates. The parameter of interest is the ratio of the median survival time if all individuals in the study population were exposed throughout the follow-up period to the median survival time if all individuals were unexposed (i.e. the survival ratio). We compared results obtained using standard Cox models with those obtained by applying g-estimation as described by Robins (1992). We followed the procedure described by Hernan et al. (2005) and Witteman et al. (1998) with some modifications. In addition to the covariates of age, race, gender, and plant, g-estimation models also included a variable for the amount of temporary time off work taken in each person year of active work status, expressed as the proportion of each year. A step-by-step description of the application of the g-estimation method was provided as an Appendix to provide a detailed guide for other investigators interested in applying this method to their own data.

To compare results from g-estimation with results using ordinary methods, we first needed to transform the survival ratios into hazard ratios. To do this we have used a parametric approach where we fit a Cox model to the counterfactual survival times for each subject if always unexposed and if exposed for five years, i.e. two survival times per subject. The hazard ratios derived from g-estimation were striking in

comparison with results from the standard models. In standard models, hazard ratios were below or approximately equal to 1.0 for all causes combined, heart disease, COPD, as well as for several cancers. By contrast, the hazard ratios transformed from the g-estimated survival ratios were all significantly above the null for all causes combined, heart disease, COPD, as well as lung and prostate cancer. In relation to 5 years of exposure to straight MWF, the g-estimated HR was 1.07 (95%CI: 1.05, 1.11) for all causes of death combined, 1.23 (95% CI: 1.13, 1.38) for COPD, 1.15 (95% CI: 1.11, 1.19) for ischemic heart disease, and 1.07 (95% CI: 1.05, 1.12) for all cancers combined. For lung and prostate cancer, the HR was 1.07 (95% CI: 1.04, 1.14) and 1.21 (95% CI: 1.04, 1.34), respectively. Because results suggest that g-estimation actually does reduce downward bias caused by the healthy worker survivor effect, I expect this paper to have a major impact on the field of occupational epidemiology.

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