Introduction

The United Auto Workers-General Motors (UAW-GM) Cohort Study is a longitudinal occupational cohort study established in the early 1980s to study the health effects of metalworking fluids (Eisen et al. 1992, 2001). Metalworking fluids (MWF) are complex mixtures of fluids used in industrial metalworking operations to lubricate and cool machinery and parts. The three major classes of MWF are straight, soluble, and synthetic metalworking fluids (Byers 2006). Possible routes of human exposure include absorption through skin, inhalation or aerosols, and ingestion of droplets.

A central concern in the analysis of occupational cohorts is the potential for the healthy worker survivor effect (HWSE), the phenomenon by which healthy individuals remain at work, while less healthy individuals leave work – possibly in response to exposure-related health decline. In the presence of the HWSE, those with the highest cumulative occupational exposures are also those who are less at risk of disease. Thus, standard measures of association would show an inverse relationship between occupational exposure and poor health outcomes (Arrighi and Hertz-Picciotto 1994). The HWSE is an example of time-varying confounding affected by past exposure. Previous studies have attempted to assess the presence of the HWSE in observed data by assessing so-called path-specific associations using Cox proportional hazards modeling (Naimi et al. 2013; Garcia et al. 2017). However, these measures of associations are themselves subject to the confounding they seek to quantify.

If sequential ignorability of exposure status at each point in follow-up and positivity can be attained conditional on covariates, then causal methods can be applied to account for the HWSE. Past studies have applied causal methods capable of accounting for time-varying confounding affected by past exposure to the study of MWF exposures and cancer mortality outcomes in the UAW-GM Cohort Study (Garcia et al. 2018; Izano et al. 2019), but the study of cancer incidence outcomes is further problematized by incomplete observation of cancer incidence outcomes over the study period. We wish to make inferences about the carcinogenicity of MWF exposure over an individual's lifetime starting three years after they enter the workforce. The UAW-GM cohort includes those hired roughly between 1938 and 1982. However, cancer incidence reporting at the Michigan Cancer Registry did not begin until 1985. In particular, we have the presence of *left filtering* in the UAW-GM Cohort Study when cancer incidence is the outcome of interest: before 1985, both cancer incidence status and time of cancer incidence are unknown. Observation of the complete cancer incidence outcome vector over the study period is conditional on an individual surviving to 1985 cancer-free.

In the presence of the HWSE, left filtering implies outcome misclassification that is informative of true cancer status. As part of her dissertation research, Izano (2017)

Arrighi, H. Michael, and Irva Hertz-Picciotto. 1994. "The Evolving Concept of the Healthy Worker Survivor Effect." *Epidemiology* 5 (2): 189–96. http://www.jstor.org/stable/3702361.

Byers, Jerry P. 2006. *Metalworking Fluids*. CRC Press.

Eisen, Ellen A, Judith Bardin, Rebecca Gore, Susan R Woskie, Marilyn F Hallock, and Richard R Monson. 2001. "Exposure-Response Models Based on Extended Follow-up of a Cohort Mortality Study in the Automobile Industry." *Scandinavian Journal of Work, Environment & Health* 27 (4): 240–49.

Eisen, Ellen A, Paige E Tolbert, Richard R Monson, and Thomas J Smith. 1992. "Mortality Studies of Machining Fluid Exposure in the Automobile Industry I: A Standardized Mortality Ratio Analysis." *American Journal of Industrial Medicine* 22 (6): 809–24.

Garcia, Erika, Sally Picciotto, Sadie Costello, Patrick T Bradshaw, and Ellen A Eisen. 2017. "Assessment of the Healthy Worker Survivor Effect in Cancer Studies of the United Autoworkers-General Motors Cohort." *Occupational and Environmental Medicine* 74 (4): 294–300.

Garcia, Erika, Sally Picciotto, Andreas M Neophytou, Patrick T Bradshaw, John R Balmes, and Ellen A Eisen. 2018. "Lung Cancer Mortality and Exposure to Synthetic Metalworking Fluid and Biocides: Controlling for the Healthy Worker Survivor Effect." *Occupational and Environmental Medicine* 75 (10): 730–35.

Izano, Monika A. 2017. "Estimating Causal Effects of Occupational Exposures." PhD thesis, University of California, Berkeley; University of California, Berkeley.

Izano, Monika A, Oleg A Sofrygin, Sally Picciotto, Patrick T Bradshaw, and Ellen A Eisen. 2019. "Metalworking Fluids and Colon Cancer Risk: Longitudinal Targeted Minimum Loss-Based Estimation." *Environmental Epidemiology* 3 (1): e035.

Naimi, Ashley I, Stephen R Cole, Michael G Hudgens, M Alan Brookhart, and David B Richardson. 2013. "Assessing the Component Associations of the Healthy Worker Survivor Bias: Occupational Asbestos Exposure and Lung Cancer Mortality." *Annals of Epidemiology* 23 (6): 334–41.