Non-Hodgkin Lymphoma (NHL) is the seventh most common cancer type in the United States and has garnered intense research attention because its incidence in the United States doubled between 1973 and 1994, before plateauing at around 19 per 100,000 persons per year (Ekström-Smedby 2006; “SEER cancer statistics review 1973-1994” 1994). The strongest known risk factor of NHL is immunosuppression, both congenital and acquired (Chiu and Hou 2015; Filipovich et al. 1992). Modulation of immune function contributes to the pathogenesis of NHL directly by perturbing lymphocyte function or indirectly by reducing immunosurveillance against neoplasms. Immunodeficiency may also interact with infection with Epstein-Barr Virus, resulting in uncontrolled B-cell proliferation (Oertel and Riess 2002). Acquired immunodeficiency through infection with human immunodeficiency virus (HIV) can lead to genetic lesions and dysregulation while increasing vulnerability to infection by other oncogenic agents (Alexander et al. 2007; Grulich et al. 1999). However, since immunodeficiency and infection with HIV are rare, they cannot fully explain the historic rise or present burden of NHL (Shiels et al. 2013). Since the rise in NHL incidence coincided with a period of rapid and extensive chemicalization in industry, agriculture and warfare, there has been stronger interest in the environmental and occupational epidemiology on NHL (Nelson 2005; Romero 2021). A meta-analysis of 44 articles published between 1980 and 2014 found statistically significant associations between NHL and exposure to pesticides of several classes including carbamate, organophosporus, triazine, and organochlorine (Schinasi and Leon 2014). While this meta-analysis presents striking evidence of the potential explanatory role of occupational exposures, it also highlights the limited breadth of occupational exposures studied.

Studies of NHL and other important occupational exposures including oils, solvents, and lubricants remain inconclusive (Ekström-Smedby 2006). Furthermore, since NHL is relatively rare, nearly all studies of NHL incidence follow a single time-point case-control design (Alexander et al. 2007; Schinasi and Leon 2014). Large multicenter studies including EPILYMPH and InterLymph attained large enough numbers of cases to investigate particular NHL subtypes, but despite their impressive size and comprehensiveness, were limited by the lack of quantitative time-varying exposure information and the lack of adjustment for time-varying confounding affected by past exposure (Besson et al. 2006; Morton et al. 2014). In the case of occupational studies, the healthy worker survivor effect (HWSE) is a key concern. The HWSE is the dynamic selection process by which healthier individuals remain at work, where they accumulate more occupational exposure, and less healthy individuals leave work (Arrighi and Hertz-Picciotto 1994). Standard analyses of occupational cohorts affected by the HWSE result in a downward bias on the exposure-outcome associations of interest, as less healthy workers typically accrue less exposure than healthier workers.

Metalworking fluids (MWF), an important class of occupational exposures, are complex mixtures of oils and chemicals used to lubricate and cool metal during manufacturing processes. During use, MWFs aerosolize and present a potential health hazard to exposed workers. The type of MWF applied depends in part on the particular metalworking operation. Straight MWF, the oldest class of MWF, is comprised mostly of mineral oil. Concerns over the carcinogenicity of MWF began as early as the 1970s, when the International Agency for Research on Cancer (IARC) classified mineral oils as carcinogenic, citing studies of occupational exposures among workers in oil, textile, and metal industries (IARC 1973). The combination of health concerns, the high cost of oil in the 1970s, and the introduction of performance-enhancing water-soluble chemical additives led to the gradual replacement of straight MWF with water-based soluble and synthetic MWFs for many, but not all operations (Childers 2006). The elimination of particular etiologic agents often leads to their replacement with other potentially hazardous chemical compounds, however (Kassotis et al. 2020; Maertens et al. 2021). Although water-based MWF contain little to no mineral oil, they contain a richer cocktail of additives including chromates, cycloalkanes, phenols, organochlorines, nitrites, sulfonates, and triazines: classes of chemicals with known or plausible carcinogenicity (IARC 1987, 2014, 2017). Hence, limits on entire classes of exposures grouped by functional use may result in stronger, more lasting protections for worker health than limits on particular etiologic agents because they will remain in place even as the composition and formulation of complex occupational exposures change (Maertens et al. 2021). More than 20 years after the IARC classification of mineral oils as carcinogenic, the National Institute for Occupational Safety and Health (NIOSH) concluded that there exists substantial evidence linking all MWF exposure to several different cancers and now recommends an exposure limit of 0.5 mg/m3 for total particulate matter derived from any type of MWF (Mirer 2003; Rosenstock 1998).

Here, we assess the effect of hypothetical MWF exposure limits on NHL cumulative incidence in the United Auto Workers-General Motors (UAW-GM) Occupational Cohort Study. The large size of the study population and rich time-varying, quantitative MWF exposure data provide an opportunity to study this relatively rare cancer and evaluate realistic interventions on MWF exposure in a longitudinal cohort setting. A recent study of cancer incidence in this iconic occupational cohort found a monotonic association between NHL and exposure to soluble MWF (Colbeth et al. 2022, in press). This association was based on a traditional Cox proportional hazards regression, a method vulnerable to bias due to confounding by time-varying factors affected by past exposure. We therefore explore this association using an estimator capable of adjusting for time-varying confounding and censoring affected by past exposure: the hazard-extended iterative conditional expectation (ICE) parametric g-formula. Like other causal estimators in statistics, the hazard-extended ICE g-formula yields marginal effect estimates of hypothetical interventions, which are more compatible with a population health framework than conditional measures.

The g-formula is a well-known result in causal inference for the identification of causal effects in the presence of the HWSE or more generally, time-varying confounding affected by past exposure (Robins 1986). The three standard representations of the g-formula include (1) a non-iterated expectation over the joint density of covariates, (2) the ICE over time, and (3) an inverse probability weighted expectation. A parametric g-formula is a plug in estimator for the g-formula under its first, non-iterative, representation. It involves the parametric modeling of the full joint distribution of the outcome, exposure, and covariates under study for each time point (Taubman et al. 2009). Counterfactual quantities under hypothetical interventions of interest are computed from Monte Carlo samples from the fitted parametric models. In longitudinal settings, this approach often requires specifying and fitting large number of models in order to satisfy the exchangeability assumptions necessary for causal identification. Since applications of the parametric g-formula are often context-laden, there are no unified guidelines for model specification.

When researchers or adversarial reviewers are not wholly comfortable with the full set of parametric assumptions required by the parametric g-formula, the ICE g-formula may be preferred. Parametric estimators using the ICE representation of the g-formula only require modeling conditional outcome distributions, so they require fewer parametric assumptions than non-iterative parametric g-formula estimators.

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