Evaluating Exposure Limits for Reducing Non-Hodgkin Lymphoma Incidence

An Application of the Hazard-Extended Iterative Conditional Expectation G-formula

Kevin T. Chen[1,2], Ellen A. Eisen[1]

University of California, Berkeley School of Public Health

[1] Division of Environmental Health Sciences [2] Division of Epidemiology & Biostatistics

Introduction

- Non-Hodgkin lymphoma (NHL) incidence increased 4-fold since 1960
- Rise in NHL followed growing use of industrial chemicals
- Past occupational studies of NHL were limited
  - Crude exposure assessment
  - Conditional estimates of association
  - Unrealistic static interventions
  - Potential bias due to the healthy worker survivor effect (HWSE)
- **We estimate counterfactual cumulative incidence of NHL from 1985 to 2004 under hypothetical limits on average annual occupational exposure to metalworking fluid (MWF)**

Methods

Interventions: g_a on average exposure A_k in year k:

$$g_a: \; A_k \longrightarrow \begin{cases} A_k & \text{if } A_k \leq a \\ a & \text{if } A_k > a \end{cases}$$

- Hypothetical limits: $a = 0.5,\ 0.25,\ 0.05$ mg/m^3
- g_a is a longitudinal stochastic intervention
- No censoring by death

Data: United Auto Workers-General Motors Cohort Study

- *Quantitative exposure* for each person-year of employment from hire to 1995 based on several hundred samples
- *NHL outcome* from 1985 to 2005 via linkage to the Michican Cancer Registry (MCR) and the Surveillance, Epidemiology, and End Results (SEER) Program
- *Covariates* are age, calendar year, employment status, cumulative time off, year of hire, sex, race, and plant

Estimation: Hazard-extended parametric G-formula

- Pooling exposure history over $K = 8$ time periods
- Exposure history at each time summmarized as cumulative exposure

Assumptions for causal inference

- *Conditional exchangeability*
- *Positivity (overlap)*
- *Consistency*
- *Correct model specification*

Results

Table 1: **Population and non-Hodgkin lymphoma (NHL) case characteristics.**

	Study population	NHL cases
N (person-years)	34,734 (596,698)	231 (2,777)
Race		
White	22,789 (66%)	173 (75%)
Black	6,304 (18%)	21 (9%)
Unknown	5,641 (16%)	37 (16%)
Sex		
Male	30,235 (87%)	206 (89%)
Female	4,499 (13%)	25 (11%)
Plant		
Plant 1	8,721 (25%)	68 (29%)
Plant 2	14,258 (41%)	90 (39%)
Plant 3	11,755 (34%)	73 (32%)
Ever exposed[1]	31,044 (89%)	210 (91%)
Deceased by end of follow-up	10,384 (30%)	33 (14%)
Year of birth	1940 (1925, 1950)	1929 (1919, 1940)
Year of hire	1967 (1953, 1976)	1959 (1951, 1969)
Age at hire (years)	23.6 (20.0, 30.1)	25.4 (21.1, 33.6)
Cumulative time off (years)[1]	1.05 (0.30, 1.80)	0.71 (0.14, 1.40)
Years at work[2]	15.3 (7.3, 27.1)	19.2 (8.0, 29.9)
Cumulative exposure (mg/m^2·yr)[1,3]	4.65 (1.85, 12.13)	7.16 (2.86, 20.91)

[1] Lagged 10 years; [2] Among those who left work before 1995;
[3] Among ever-exposed indidivuals.

Figure 1: **Cumulative exposure at end of follow-up under hypothetical limits on average annual exposure. Rug plots mark cumulative exposure accrued by NHL cases at end of follow-up.**

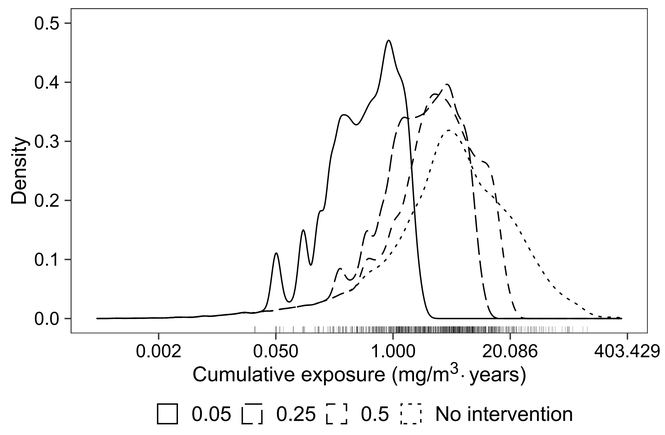

Figure 2: **Counterfactual cumulative incidence ratio estimates comparing hypothetical limits on average annual exposure to no limit.**

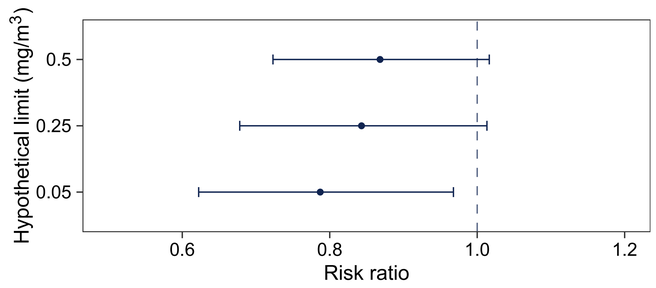

Table 2: **Counterfactual cumulative incidence estimates under hypothetical limits on average annual exposure and no censoring.**

Exposure limit	Person-years intervened (%)	Cases expected	(95% BS CI)
None	0	332	(283, 378)
0.5 mg/m^3	23.8	288	(226, 354)
0.25 mg/m^3	36.2	280	(214, 353)
0.05 mg/m^3	43.9	261	(199, 330)

Discussion and Conclusions

- Limiting average annual MWF exposure reduces NHL incidence
- Longitudinal stochastic interventions represent realistic policies
  - NIOSH Recommended Exposure Limit is 0.5 mg/m^3
- Our method reduced potential bias due to HWSE
- Outcome models were logistic regressions; assumption of correct model specification may be more plausible under machine learning approaches with cross-validation

References

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