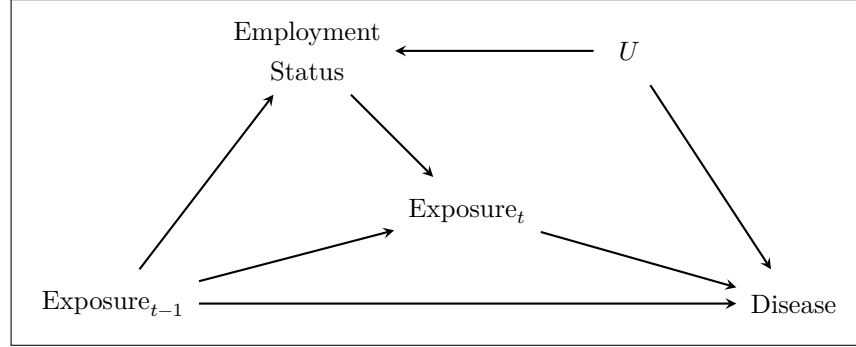# HWSE path analysis

Stomach cancer, bladder cancer, and non-Hodgkin Lymphoma

October 22, 2020

The presence of the healthy worker survivor effect (HWSE) implies the presence of the following three conditions:

1. Leaving work predicts (future) exposure
2. Leaving work is associated with the disease
3. Prior exposure predicts predicts leaving work

In occupational cohort studies investigating occupational exposure, the first condition readily satisfied. To assess the presence of conditions 2 and 3, we fit Cox proportional hazards models. Associations between prior exposure and disease are also presented here. In particular, the outcomes under consideration are incidences of stomach cancer, bladder cancer, and non-Hodgkin lymphoma.

Data. The analytic data constitute a subset of the UAW-GM Cohort. Person-time is accrued starting in 1941, or three years after hire, whichever came later. Cancer incidence follow-up begins in 1985 for plant 3 and 1973 for plants 1 and 2. Individuals were considered lost to follow-up if they were still alive and cancer-free at age 108 or greater (the maximum observed age at death). For now, those of unknown race were considered to be white.

Metalworking fluid exposure and cancer incidence.

- Person-time starts in 1985 for plant 3 and 1973 for plants 1 and 2 (since we have SEER data for plants 1 and 2).
- Follow-up ends at time of cancer incidence, death, loss to follow-up, or December 31, 2015, whichever comes earlier.
- Cumulative exposure to the three metal working fluid types lagged 21 years are the main exposures of interest.

- Exposure was categorized into 4 levels including the referent group where possible, and 3 or 2 levels otherwise.
  - The referent group for straight and synthetic metalworking fluids is 0 mg/m^3·years
  - that for soluble metalworking fluids is 0–0.05 mg/m^3·years.
- Covariates included in the model are splined calendar year, splined year of hire, race, plant, and sex.
- Risk sets were indexed by age.

Leaving work and cancer incidence.

- As in the metalworking fluid-cancer incidence models, follow-up starts starts in 1985 or 1973, depending on the plant.
- Follow-up ends at time of cancer incidence, death, reaching 80 years of age, censoring due to end of employment records, or December 31, 2015, whichever comes earlier.
  - Ending follow-up at 80 years of age is meant to exclude cases that are *not* thought to be linked to employment status.
- The main exposure of interest is employment status with no lag and with a lag of 21 years; the levels are:
  - employed,
  - left work under the age of 50, and
  - left work over the age of 50.
- When employment status *was not* lagged, those who will still at work on January 1, 1995 were censored on that day
- When employment status *was* lagged, the censor date was lagged by the same amount.
- Covariates included in the model are cumulative metalworking fluid exposure (lagged 1 and 22 years) splined calendar year, splined yer of hire, race, plant, and sex.
- Risk sets were indexed by age.

Prior exposure and leaving work.

- For consistency, follow-up for these models *also* begins in 1985 or 1973, depending on the plant.
- The outcome of interest is binary employment status, lagged 21 years.
  - Those who will still at work on January 1, 1995 were censored on January 1, 2016.
- The exposures of interest are cumulative metalworking fluid exposure, lagged 22 years.
- Follow-up ends at time of leaving work, death, reaching 80 years of age, censoring due to end of employment records, or December 31, 2015, whichever comes earlier.
- Other covariates included in the model are splined calendar year, splined year of hire, race, plant, and sex.
- Risk sets were indexed by age.

Table 1: Summary of population characteristics. Follow-up starts in 1973 for plants 1 and 2, and 1985 for plant 3. Follow-up ends in 2015.

	n	p	
Study population size (N)	39 132	100%	
Race			
White	25 119	64%	
Black	6 862	18%	
Unknown	7 151	18%	
Sex			
Male	34 498	88%	
Female	4 634	12%	
Plant♮			
Plant 1	11 467	29%	
Plant 2	15 910	41%	
Plant 3	11 755	30%	
Ever exposed to MWFs			
Straight	21 294	54%	
Soluble	34 055	87%	
Synthetic	12 530	32%	
Diagnosed with cancer by end of follow-up	7 894	20%	
	Median	25th %tile	75th %tile
Years of follow-up	39.5	34.3	46.98
Years at work*	15.73	7.65	27.06
Year of hire	1965	1952	1973
Age at hire (years)	24	20	31
Year of birth	1937	1921	1949
Year of first cancer diagnosis	1999	1991	2007
Age at first cancer diagnosis (years)	67	59	74
Cumulative exposure♯ to MWFs (mg/m^3·y)			
Straight	0.69	0.21	2.53
Soluble	4.93	1.93	13.31
Synthetic	0.44	0.15	1.56

♮ Some individuals worked at several sites; plant indicates the site of longest work record time.

* Among those with known date of worker exit.

♯ Summary statistics calculated for ever-exposed individuals at end of follow-up only. Exposures were lagged 21 years.

Table 2: Adjusted HR estimates for cancer incidence and employment status.

	n	HR	(95% CI)	p
Stomach cancer (142 events)				
Still employed	19	1.00	–	
Not employed	123	1.04	(0.57, 1.90)	0.89
Left work (under 50)	57	0.88	(0.46, 1.68)	0.70
Left work (50 or older)	66	1.50	(0.78, 2.90)	0.23
Left work (under 55)	77	0.96	(0.52, 1.80)	0.91
Left work (55 or older)	46	1.22	(0.62, 2.40)	0.56
Left work (under 60)	97	1.03	(0.56, 1.91)	0.91
Left work (60 or older)	26	1.08	(0.52, 2.22)	0.84
Bladder cancer (296 events)				
Still employed	27	1.00	–	
Not employed	269	0.82	(0.50, 1.34)	0.43
Left work (under 50)	115	0.68	(0.40, 1.14)	0.14
Left work (50 or older)	154	0.98	(0.58, 1.63)	0.93
Left work (under 55)	151	0.72	(0.43, 1.20)	0.20
Left work (55 or older)	118	0.98	(0.58, 1.66)	0.94
Left work (under 60)	197	0.76	(0.46, 1.26)	0.29
Left work (60 or older)	72	0.96	(0.55, 1.65)	0.87
Non-Hodgkin's lymphoma (210 events)				
Still employed	22	1.00	–	
Not employed	188	1.05	(0.60, 1.85)	0.86
Left work (under 50)	104	1.05	(0.59, 1.89)	0.86
Left work (50 or older)	84	1.05	(0.57, 1.93)	0.89
Left work (under 55)	119	0.94	(0.53, 1.70)	0.85
Left work (55 or older)	69	1.33	(0.71, 2.50)	0.38
Left work (under 60)	149	0.98	(0.55, 1.76)	0.95
Left work (60 or older)	39	1.31	(0.67, 2.55)	0.43

Table 3: Adjusted HR estimates for cancer incidence and employment status lagged by 21 years.

	n	HR	(95% CI)	p
Stomach cancer (166 events)				
Still employed	123	1.00	–	
Not employed	43	0.81	(0.55, 1.20)	0.30
Left work (under 50)	17	0.99	(0.56, 1.74)	0.97
Left work (50 or older)	26	0.73	(0.46, 1.16)	0.19
Left work (under 55)	26	0.88	(0.54, 1.41)	0.59
Left work (55 or older)	17	0.74	(0.43, 1.27)	0.27
Left work (under 60)	35	0.92	(0.60, 1.41)	0.71
Left work (60 or older)	8	0.55	(0.26, 1.16)	0.12
Bladder cancer (394 events)				
Still employed	284	1.00	–	
Not employed	110	0.86	(0.68, 1.11)	0.24
Left work (under 50)	39	0.90	(0.62, 1.29)	0.56
Left work (50 or older)	71	0.85	(0.64, 1.12)	0.25
Left work (under 55)	68	0.96	(0.71, 1.29)	0.78
Left work (55 or older)	42	0.76	(0.54, 1.06)	0.11
Left work (under 60)	83	0.91	(0.69, 1.20)	0.50
Left work (60 or older)	27	0.76	(0.50, 1.15)	0.19
Non-Hodgkin's lymphoma (295 events)				
Still employed	211	1.00	–	
Not employed	84	0.88	(0.66, 1.17)	0.39
Left work (under 50)	30	0.83	(0.54, 1.26)	0.37
Left work (50 or older)	54	0.91	(0.66, 1.27)	0.58
Left work (under 55)	50	0.87	(0.61, 1.23)	0.42
Left work (55 or older)	34	0.90	(0.61, 1.33)	0.60
Left work (under 60)	61	0.85	(0.62, 1.17)	0.32
Left work (60 or older)	23	0.97	(0.61, 1.55)	0.90

Table 4: Adjusted HR estimates for **leaving work**. Leaving work was lagged 21 years.

Covariate	level	n	HR	(95% CI)	p	
Cumulative straight	0	9407	1.00	–		
	> 0 to 0.238	1226	1.12	(1.03, 1.21)	0.01	*
	> 0.238 to 1.19	1226	0.97	(0.90, 1.05)	0.51	
	> 1.19	1226	1.02	(0.94, 1.09)	0.69	
Cumulative soluble	0 to 0.05	7399	1.00	–		
	> 0.05 to 1.8	1817	1.37	(1.27, 1.48)	< 0.005	*
	> 1.8 to 6.75	1934	1.24	(1.15, 1.35)	< 0.005	*
	> 6.75	1935	1.14	(1.05, 1.24)	< 0.005	*
Cumulative synthetic	0	10674	1.00	–		
	> 0 to 0.138	804	0.89	(0.81, 0.98)	0.02	*
	> 0.138 to 0.583	803	0.82	(0.75, 0.90)	< 0.005	*
	> 0.583	804	0.78	(0.71, 0.84)	< 0.005	*
Race	White	10857	1.00	–		
	Black	2228	0.62	(0.59, 0.66)	< 0.005	*
Plant	1	3848	1.00	–		
	2	5788	0.70	(0.66, 0.73)	< 0.005	*
	3	3449	0.50	(0.47, 0.53)	< 0.005	*
Sex	Male	11388	1.00	–		
	Female	1697	1.44	(1.36, 1.52)	< 0.005	*
P-spline of calendar year ($df = 17$)		13085		–	< 0.005	*
P-spline of year of hire ($df = 15.72$)		13085		–	< 0.005	*

Table 5: Adjusted HR estimates for incidence of **stomach cancer** ($n = 214$).

Covariate	level	n	HR	(95% CI)	p	
Cumulative straight	0	108	1.00	–		
	> 0 to 0.347	36	1.13	(0.72, 1.78)	0.60	
	> 0.347 to 3.28	35	0.73	(0.46, 1.14)	0.16	
	> 3.28	35	1.54	(1.01, 2.36)	0.05	
Cumulative soluble	0 to 0.05	50	1.00	–		
	> 0.05 to 4.02	54	0.64	(0.41, 0.99)	0.04	*
	> 4.02 to 13.1	55	0.78	(0.50, 1.24)	0.30	
	> 13.1	55	0.80	(0.49, 1.30)	0.37	
Cumulative synthetic	0	158	1.00	–		
	> 0 to 0.64	28	0.98	(0.59, 1.63)	0.95	
	> 0.64	28	1.12	(0.70, 1.80)	0.63	
Race	White	159	1.00	–		
	Black	55	1.70	(1.18, 2.45)	< 0.005	*
Plant	1	73	1.00	–		
	2	91	1.18	(0.76, 1.84)	0.46	
	3	50	0.78	(0.49, 1.23)	0.28	
Sex	Male	198	1.00	–		
	Female	16	0.49	(0.28, 0.83)	0.01	*
P-spline of calendar year ($df = 8.19$)		214		–	0.84	
P-spline of year of hire ($df = 11.35$)		214		–	0.81	

Table 6: Adjusted HR estimates for incidence of **bladder cancer** ($n = 533$).

Covariate	level	n	HR	(95% CI)	p	
Cumulative straight	0	236	1.00	–		
	> 0 to 0.388	99	1.32	(1.00, 1.74)	0.05	
	> 0.388 to 2.71	99	1.03	(0.78, 1.35)	0.84	
	> 2.71	99	1.29	(1.00, 1.67)	0.05	
Cumulative soluble	0 to 0.05	88	1.00	–		
	> 0.05 to 3.86	146	0.85	(0.64, 1.13)	0.27	
	> 3.86 to 13	149	0.98	(0.73, 1.33)	0.92	
	> 13	150	1.15	(0.84, 1.58)	0.39	
Cumulative synthetic	0	393	1.00	–		
	> 0 to 0.255	47	0.85	(0.59, 1.21)	0.36	
	> 0.255 to 1.28	46	0.89	(0.63, 1.27)	0.54	
	> 1.28	47	0.80	(0.57, 1.11)	0.18	
Race	White	479	1.00	–		
	Black	54	0.56	(0.41, 0.76)	< 0.005	∗
Plant	1	144	1.00	–		
	2	186	0.94	(0.70, 1.26)	0.69	
	3	203	1.13	(0.87, 1.47)	0.35	
Sex	Male	510	1.00	–		
	Female	23	0.30	(0.20, 0.47)	< 0.005	∗
P-spline of calendar year ($df = 9.01$)		533		–	0.53	
P-spline of year of hire ($df = 7.93$)		533		–	< 0.005	∗

Table 7: Adjusted HR estimates for incidence of **non-hodgkin's lymphoma** ($n = 393$).

Covariate	level	n	HR	(95% CI)	p	
Cumulative straight	0	172	1.00	–		
	> 0 to 0.34	74	1.17	(0.84, 1.61)	0.35	
	> 0.34 to 2.19	73	0.90	(0.65, 1.23)	0.51	
	> 2.19	74	1.21	(0.90, 1.64)	0.21	
Cumulative soluble	0 to 0.05	54	1.00	–		
	> 0.05 to 3.04	111	1.37	(0.96, 1.96)	0.08	
	> 3.04 to 11.1	114	1.42	(0.97, 2.07)	0.07	
	> 11.1	114	1.64	(1.09, 2.45)	0.02	*
Cumulative synthetic	0	273	1.00	–		
	> 0 to 0.245	40	0.91	(0.61, 1.37)	0.66	
	> 0.245 to 1.46	40	0.99	(0.67, 1.46)	0.95	
	> 1.46	40	1.07	(0.74, 1.55)	0.72	
Race	White	347	1.00	–		
	Black	46	0.64	(0.46, 0.90)	0.01	*
Plant	1	99	1.00	–		
	2	156	1.10	(0.78, 1.56)	0.60	
	3	138	1.01	(0.73, 1.38)	0.96	
Sex	Male	348	1.00	–		
	Female	45	0.93	(0.66, 1.29)	0.65	
P-spline of calendar year ($df = 10.4$)		393		–	0.02	*
P-spline of year of hire ($df = 9$)		393		–	0.41	