UAW-GM Cohort Study

With additional model terms; exposure lagged 30 years

November 12, 2019

Introduction

In previous survival analyses, hazard ratios associated with exposure to the three metalworking fluid types were estimated simultaneously in the same Cox proportional hazards model. There was a concern that those estimates may have been biased or misleading, as those models assumed independent covariate (statistical) effects e.g. that the effect of exposure to straight metalworking fluids was constant across levels of exposure to other metalworking fluid types. One way we attempted to address this concern was to fit independent models for each exposure-outcome pair of interest with one additional term to capture changes in the log-hazard associated with the combination of zero exposure to one metalworking fluid type and nonzero exposure to some other metalworking fluid type.

Model

Let $\boldsymbol{W}(t)$ represent the vector of potential confounders at time t. Let X_{St}, $X_{\text{So}}(t)$, and $X_{\text{Sy}}(t)$ represent cumulative exposure to straight, soluble, and synthetic metalworking fluids, respectively at time t. If we were interested in straight metalworking fluids, then the log hazard for the outcome could be modeled:

$$
\begin{aligned}
\log\left[h\left(t \mid \boldsymbol{W}(t) = \boldsymbol{w}(t), \boldsymbol{X}(t) = \boldsymbol{x}(t), \hat{\boldsymbol{\beta}}\right)\right] = \; & \log\left[h_0(t)\right] \\
& + \hat{\beta}_1 \mathbb{1}\left[x_{\text{St}}(t) \in (0, \text{St}_{\text{low}}]\right] \\
& + \hat{\beta}_2 \mathbb{1}\left[x_{\text{St}}(t) \in (\text{St}_{\text{low}}, \text{St}_{\text{mid}}]\right] \\
& + \hat{\beta}_3 \mathbb{1}\left[x_{\text{St}}(t) \in (\text{St}_{\text{mid}}, \text{St}_{\text{high}}]\right] \\
& + \hat{\beta}_4 \mathbb{1}\left[x_{\text{So}}(t) \in (0, \text{So}_{\text{low}}]\right] \\
& + \hat{\beta}_5 \mathbb{1}\left[x_{\text{So}}(t) \in (\text{So}_{\text{low}}, \text{So}_{\text{mid}}]\right] \\
& + \hat{\beta}_6 \mathbb{1}\left[x_{\text{So}}(t) \in (\text{So}_{\text{mid}}, \text{So}_{\text{high}}]\right] \\
& + \hat{\beta}_7 \mathbb{1}\left[x_{\text{Sy}}(t) \in (0, \text{Sy}_{\text{low}}]\right] \\
& + \hat{\beta}_8 \mathbb{1}\left[x_{\text{Sy}}(t) \in (\text{Sy}_{\text{low}}, \text{Sy}_{\text{mid}}]\right] \\
& + \hat{\beta}_9 \mathbb{1}\left[x_{\text{Sy}}(t) \in (\text{Sy}_{\text{mid}}, \text{Sy}_{\text{high}}]\right] \\
& + \hat{\beta}_{10} \mathbb{1}\left[x_{\text{St}}(t) = 0\right] \mathbb{1}\left[x_{\text{So}}(t) + x_{\text{Sy}}(t) > 0\right] \\
& + \hat{\beta}_{11} w_1(t) + \hat{\beta}_{12} w_2(t) + \hat{\beta}_{13} w_3(t) + \cdots
\end{aligned}
$$

where St_{low}, So_{low}, and Sy_{low} represent the upper boundaries of low exposure to the three types of metalworking fluids among cases at time of death, respectively; St_{mid}, So_{mid}, and Sy_{mid} represent the upper boundaries of moderate exposure among cases at time of death; and St_{high}, So_{high}, and Sy_{high} represent maximum exposure among cases at time of death. If we were interested in exposure to soluble metalworking fluids, we would replace the 10^{th} covariate with $\mathbb{1}\left[x_{\text{So}}(t) = 0\right] \mathbb{1}\left[x_{\text{St}}(t) + x_{\text{Sy}}(t) > 0\right]$. For synthetic, we would replace with $\mathbb{1}\left[x_{\text{Sy}}(t) = 0\right] \mathbb{1}\left[x_{\text{St}}(t) + x_{\text{So}}(t) > 0\right]$. Note that if all three terms were included simultaneously, we would have a rank-deficient model matrix.

Results

Table 1: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **straight** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
Laryngeal cancer (73 cases)						
0	mg/m^3·years	45				
> 0 to 0.3	mg/m^3·years	14	1.41	0.41	(0.62, 3.21)	
> 0.3	mg/m^3·years	14	0.78	0.53	(0.36, 1.69)	
Trend				0.57		
Lung cancer (1894 cases)						
0	mg/m^3·years	1176				
> 0 to 0.3	mg/m^3·years	240	1.10	0.32	(0.92, 1.31)	
> 0.3 to 1.4	mg/m^3·years	239	0.94	0.53	(0.79, 1.13)	
> 1.4	mg/m^3·years	239	0.89	0.15	(0.75, 1.05)	
Trend				0.29		
Esophageal cancer (176 cases)						
0	mg/m^3·years	106				
> 0 to 0.5	mg/m^3·years	24	0.93	0.82	(0.52, 1.68)	
> 0.5 to 2.2	mg/m^3·years	23	1.23	0.47	(0.70, 2.17)	
> 2.2	mg/m^3·years	23	1.19	0.51	(0.70, 2.03)	
Trend				0.44		
Stomach cancer (194 cases)						
0	mg/m^3·years	125				
> 0 to 0.3	mg/m^3·years	23	1.28	0.41	(0.71, 2.31)	
> 0.3 to 2.6	mg/m^3·years	23	1.01	0.97	(0.57, 1.81)	
> 2.6	mg/m^3·years	23	1.95	0.02	(1.13, 3.34)	*
Trend				0.04		*
Colon cancer (407 cases)						
0	mg/m^3·years	256				
> 0 to 0.3	mg/m^3·years	51	0.91	0.61	(0.62, 1.32)	
> 0.3 to 2.4	mg/m^3·years	50	0.75	0.13	(0.51, 1.09)	
> 2.4	mg/m^3·years	50	0.97	0.86	(0.68, 1.37)	
Trend				0.94		
Rectal cancer (83 cases)						
0	mg/m^3·years	54				
> 0 to 0.6	mg/m^3·years	15	1.26	0.57	(0.57, 2.81)	
> 0.6	mg/m^3·years	14	0.84	0.65	(0.39, 1.81)	
Trend				0.56		
Bladder cancer (138 cases)						
0	mg/m^3·years	83				
> 0 to 0.5	mg/m^3·years	27	1.43	0.22	(0.81, 2.50)	
> 0.5	mg/m^3·years	28	0.78	0.35	(0.46, 1.31)	
Trend				0.57		
Liver cancer (123 cases)						
0	mg/m^3·years	70				
> 0 to 0.9	mg/m^3·years	26	0.90	0.74	(0.49, 1.65)	
> 0.9	mg/m^3·years	27	1.25	0.42	(0.73, 2.17)	

Table 1: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **straight** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
Trend				0.20		
Pancreatic cancer (315 cases)						
0	mg/m^3·years	188				
> 0 to 0.2	mg/m^3·years	43	1.43	0.10	(0.93, 2.19)	
> 0.2 to 0.8	mg/m^3·years	42	1.36	0.17	(0.88, 2.10)	
> 0.8	mg/m^3·years	42	0.73	0.12	(0.49, 1.08)	
Trend				0.38		
Skin cancer (69 cases)						
0	mg/m^3·years	41				
> 0 to 0.9	mg/m^3·years	14	1.24	0.60	(0.55, 2.81)	
> 0.9	mg/m^3·years	14	1.14	0.74	(0.52, 2.53)	
Trend				0.79		
Prostate cancer (418 cases)						
0	mg/m^3·years	225				
> 0 to 0.3	mg/m^3·years	65	1.17	0.39	(0.82, 1.65)	
> 0.3 to 1.5	mg/m^3·years	64	1.05	0.80	(0.74, 1.49)	
> 1.5	mg/m^3·years	64	0.92	0.61	(0.66, 1.27)	
Trend				0.40		
Brain and nervous system cancers (128 cases)						
0	mg/m^3·years	86				
> 0 to 0.9	mg/m^3·years	21	0.54	0.09	(0.27, 1.10)	·
> 0.9	mg/m^3·years	21	0.70	0.27	(0.37, 1.32)	
Trend				0.72		
Leukemia (200 cases)						
0	mg/m^3·years	119				
> 0 to 0.3	mg/m^3·years	27	1.08	0.78	(0.62, 1.87)	
> 0.3 to 1.7	mg/m^3·years	27	0.94	0.84	(0.55, 1.63)	
> 1.7	mg/m^3·years	27	0.92	0.74	(0.55, 1.53)	
Trend				0.36		
Breast cancer (76 cases)						
0	mg/m^3·years	53				
> 0 to 0.7	mg/m^3·years	11	1.27	0.61	(0.51, 3.17)	
> 0.7	mg/m^3·years	12	2.55	0.03	(1.07, 6.11)	*
Trend				0.11		

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI
Laryngeal cancer (73 cases)					
0 to 0.1	mg/m^3·years	28			
> 0.1 to 7.2	mg/m^3·years	23	0.99	0.98	(0.47, 2.08)

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
> 7.2	mg/m^3·years	22	1.45	0.37	(0.65, 3.27)	
Trend				0.03		*
Lung cancer (1894 cases)						
0 to 0.1	mg/m^3·years	735				
> 0.1 to 3	mg/m^3·years	387	0.99	0.93	(0.85, 1.16)	
> 3 to 9.3	mg/m^3·years	386	1.02	0.85	(0.86, 1.19)	
> 9.3	mg/m^3·years	386	1.07	0.45	(0.90, 1.27)	
Trend				0.04		*
Esophageal cancer (176 cases)						
0 to 0.1	mg/m^3·years	65				
> 0.1 to 3	mg/m^3·years	35	1.04	0.88	(0.63, 1.73)	
> 3 to 10.2	mg/m^3·years	38	1.17	0.57	(0.68, 1.99)	
> 10.2	mg/m^3·years	38	1.48	0.19	(0.83, 2.64)	
Trend				0.05		*
Stomach cancer (194 cases)						
0 to 0.1	mg/m^3·years	96				
> 0.1 to 4.3	mg/m^3·years	33	0.51	0.01	(0.31, 0.85)	*
> 4.3 to 11.3	mg/m^3·years	32	0.76	0.30	(0.45, 1.28)	
> 11.3	mg/m^3·years	33	0.74	0.29	(0.43, 1.29)	
Trend				0.95		
Colon cancer (407 cases)						
0 to 0.1	mg/m^3·years	147				
> 0.1 to 3	mg/m^3·years	87	1.04	0.81	(0.76, 1.42)	
> 3 to 11.6	mg/m^3·years	86	0.79	0.15	(0.56, 1.09)	
> 11.6	mg/m^3·years	87	0.95	0.78	(0.67, 1.35)	
Trend				0.99		
Rectal cancer (83 cases)						
0 to 0.1	mg/m^3·years	36				
> 0.1 to 6.5	mg/m^3·years	21	0.74	0.41	(0.37, 1.50)	
> 6.5	mg/m^3·years	26	1.28	0.52	(0.61, 2.66)	
Trend				0.33		
Bladder cancer (138 cases)						
0 to 0.1	mg/m^3·years	46				
> 0.1 to 3.2	mg/m^3·years	30	0.91	0.73	(0.53, 1.56)	
> 3.2 to 8.7	mg/m^3·years	30	1.05	0.85	(0.61, 1.82)	
> 8.7	mg/m^3·years	32	0.89	0.69	(0.50, 1.57)	
Trend				0.36		
Liver cancer (123 cases)						
0 to 0.1	mg/m^3·years	37				
> 0.1 to 2	mg/m^3·years	29	1.53	0.14	(0.86, 2.71)	
> 2 to 6.6	mg/m^3·years	28	1.31	0.36	(0.73, 2.37)	
> 6.6	mg/m^3·years	29	0.98	0.94	(0.52, 1.84)	
Trend				0.43		
Pancreatic cancer (315 cases)						
0 to 0.1	mg/m^3·years	125				

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
> 0.1 to 2.8	mg/m^3·years	64	0.68	0.04	(0.47, 0.98)	*
> 2.8 to 8.3	mg/m^3·years	63	0.73	0.12	(0.50, 1.08)	
> 8.3	mg/m^3·years	63	0.69	0.07	(0.46, 1.04)	·
Trend				0.61		
Skin cancer (69 cases)						
0 to 0.1	mg/m^3·years	28				
> 0.1 to 6.4	mg/m^3·years	21	1.17	0.69	(0.54, 2.53)	
> 6.4	mg/m^3·years	20	1.63	0.28	(0.68, 3.91)	
Trend				0.16		
Prostate cancer (418 cases)						
0 to 0.1	mg/m^3·years	109				
> 0.1 to 4	mg/m^3·years	103	1.00	0.99	(0.73, 1.38)	
> 4 to 11.9	mg/m^3·years	103	1.02	0.89	(0.74, 1.43)	
> 11.9	mg/m^3·years	103	0.97	0.86	(0.68, 1.37)	
Trend				0.14		
Brain and nervous system cancers (128 cases)						
0 to 0.1	mg/m^3·years	54				
> 0.1 to 2.7	mg/m^3·years	25	1.56	0.14	(0.86, 2.84)	
> 2.7 to 8	mg/m^3·years	24	1.91	0.05	(1.01, 3.61)	*
> 8	mg/m^3·years	25	1.81	0.09	(0.92, 3.56)	·
Trend				0.60		
Leukemia (200 cases)						
0 to 0.1	mg/m^3·years	76				
> 0.1 to 2.5	mg/m^3·years	42	1.25	0.36	(0.77, 2.01)	
> 2.5 to 7.3	mg/m^3·years	41	1.11	0.68	(0.67, 1.84)	
> 7.3	mg/m^3·years	41	0.78	0.37	(0.46, 1.34)	
Trend				0.15		
Breast cancer (76 cases)						
0 to 0.1	mg/m^3·years	52				
> 0.1 to 2.2	mg/m^3·years	13	0.52	0.11	(0.23, 1.16)	
> 2.2	mg/m^3·years	11	0.29	0.01	(0.11, 0.77)	*
Trend				0.46		

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

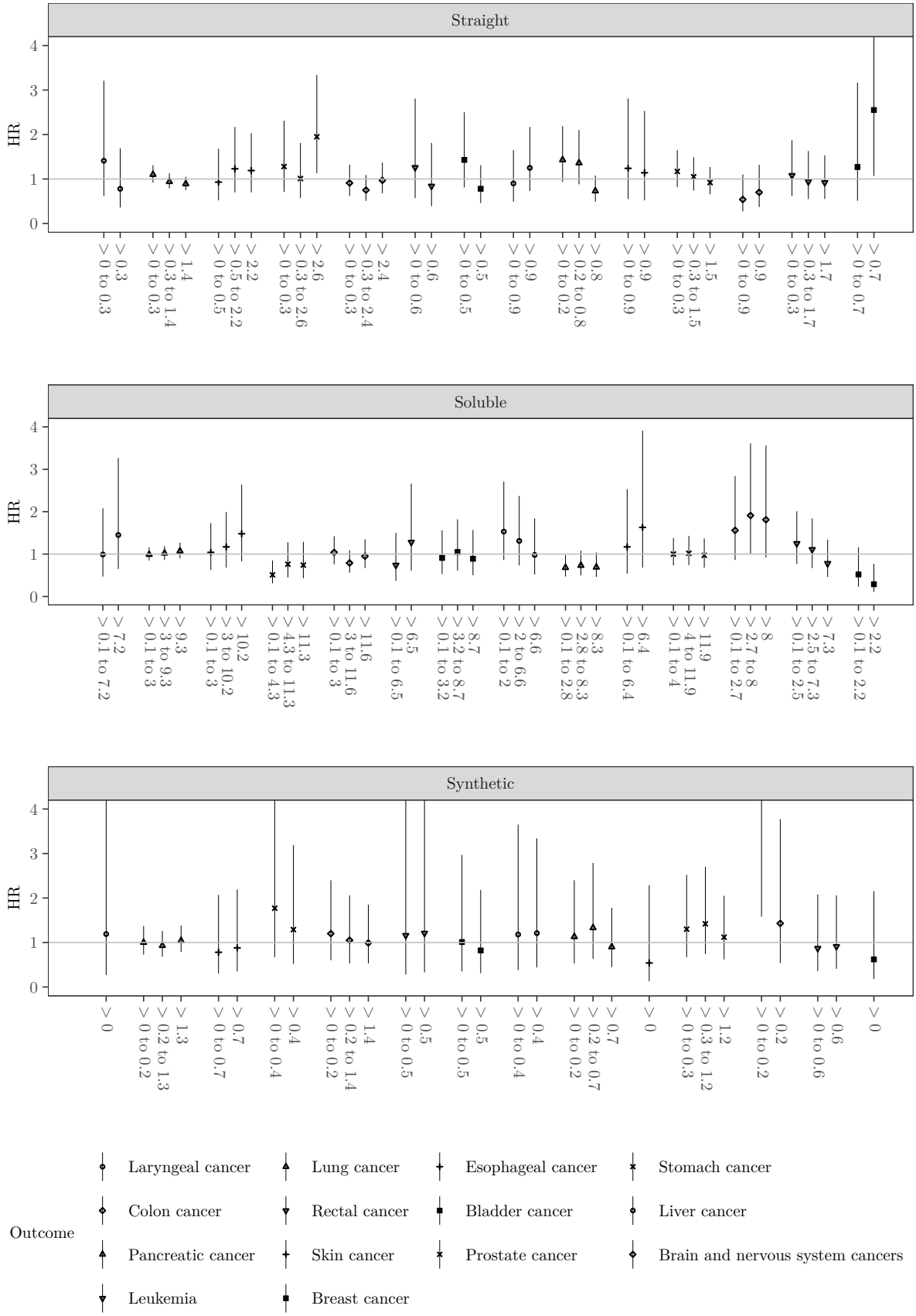
		Number of cases	HR	p	95% CI
Laryngeal cancer (73 cases)					
0	mg/m^3·years	58			
> 0	mg/m^3·years	15	1.19	0.82	(0.27, 5.17)
Lung cancer (1894 cases)					
0	mg/m^3·years	1515			

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
> 0 to 0.2	mg/m^3·years	127	1.00	0.99	(0.73, 1.37)	
> 0.2 to 1.3	mg/m^3·years	126	0.93	0.63	(0.68, 1.26)	
> 1.3	mg/m^3·years	126	1.04	0.79	(0.79, 1.38)	
Trend				0.32		
Esophageal cancer (176 cases)						
0	mg/m^3·years	141				
> 0 to 0.7	mg/m^3·years	18	0.78	0.62	(0.30, 2.07)	
> 0.7	mg/m^3·years	17	0.88	0.79	(0.35, 2.19)	
Trend				0.96		
Stomach cancer (194 cases)						
0	mg/m^3·years	162				
> 0 to 0.4	mg/m^3·years	16	1.77	0.25	(0.67, 4.64)	
> 0.4	mg/m^3·years	16	1.29	0.58	(0.52, 3.19)	
Trend				0.91		
Colon cancer (407 cases)						
0	mg/m^3·years	340				
> 0 to 0.2	mg/m^3·years	23	1.20	0.60	(0.60, 2.40)	
> 0.2 to 1.4	mg/m^3·years	22	1.05	0.90	(0.53, 2.06)	
> 1.4	mg/m^3·years	22	0.99	0.97	(0.53, 1.85)	
Trend				0.53		
Rectal cancer (83 cases)						
0	mg/m^3·years	66				
> 0 to 0.5	mg/m^3·years	8	1.16	0.84	(0.28, 4.89)	
> 0.5	mg/m^3·years	9	1.21	0.77	(0.33, 4.48)	
Trend				0.51		
Bladder cancer (138 cases)						
0	mg/m^3·years	111				
> 0 to 0.5	mg/m^3·years	14	1.01	0.98	(0.35, 2.97)	
> 0.5	mg/m^3·years	13	0.82	0.70	(0.31, 2.18)	
Trend				0.04		*
Liver cancer (123 cases)						
0	mg/m^3·years	97				
> 0 to 0.4	mg/m^3·years	13	1.18	0.77	(0.38, 3.65)	
> 0.4	mg/m^3·years	13	1.21	0.71	(0.44, 3.34)	
Trend				0.57		
Pancreatic cancer (315 cases)						
0	mg/m^3·years	249				
> 0 to 0.2	mg/m^3·years	22	1.13	0.75	(0.53, 2.40)	
> 0.2 to 0.7	mg/m^3·years	22	1.33	0.45	(0.63, 2.79)	
> 0.7	mg/m^3·years	22	0.90	0.76	(0.45, 1.78)	
Trend				0.32		
Skin cancer (69 cases)						
0	mg/m^3·years	56				
> 0	mg/m^3·years	13	0.54	0.40	(0.13, 2.29)	
Prostate cancer (418 cases)						

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
0	mg/m^3·years	316				
> 0 to 0.3	mg/m^3·years	34	1.30	0.44	(0.67, 2.52)	
> 0.3 to 1.2	mg/m^3·years	34	1.42	0.29	(0.74, 2.70)	
> 1.2	mg/m^3·years	34	1.12	0.70	(0.62, 2.05)	
Trend				0.70		
Brain and nervous system cancers (128 cases)						
0	mg/m^3·years	100				
> 0 to 0.2	mg/m^3·years	14	4.54	0.01	(1.58, 13.07)	*
> 0.2	mg/m^3·years	14	1.43	0.47	(0.54, 3.77)	
Trend				0.74		
Leukemia (200 cases)						
0	mg/m^3·years	156				
> 0 to 0.6	mg/m^3·years	22	0.87	0.75	(0.36, 2.08)	
> 0.6	mg/m^3·years	22	0.91	0.83	(0.41, 2.06)	
Trend				0.88		
Breast cancer (76 cases)						
0	mg/m^3·years	66				
> 0	mg/m^3·years	10	0.62	0.45	(0.18, 2.15)	


Straight
HR
0
1
2
3
4
> 0 to 0.3
> 0.3
> 0 to 0.3
> 0.3 to 1.4
> 1.4
> 0 to 0.5
> 0.5 to 2.2
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> 0 to 0.3
> 0.3 to 2.6
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> 0.3 to 2.4
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> 0 to 0.9
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> 0 to 0.2
> 0.2 to 0.8
> 0.8
> 0 to 0.9
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> 0.3 to 1.5
> 1.5
> 0 to 0.9
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> 0 to 0.3
> 0.3 to 1.7
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> 0.7
Soluble
HR
0
1
2
3
4
> 0.1 to 7.2
> 7.2
> 0.1 to 3
> 3 to 9.3
> 9.3
> 0.1 to 3
> 3 to 10.2
> 10.2
> 0.1 to 4.3
> 4.3 to 11.3
> 11.3
> 0.1 to 3
> 3 to 11.6
> 11.6
> 0.1 to 6.5
> 6.5
> 0.1 to 3.2
> 3.2 to 8.7
> 8.7
> 0.1 to 2
> 2 to 6.6
> 6.6
> 0.1 to 2.8
> 2.8 to 8.3
> 8.3
> 0.1 to 6.4
> 6.4
> 0.1 to 4
> 4 to 11.9
> 11.9
> 0.1 to 2.7
> 2.7 to 8
> 8
> 0.1 to 2.5
> 2.5 to 7.3
> 7.3
> 0.1 to 2.2
> 2.2
Synthetic
HR
0
1
2
3
4
> 0
> 0 to 0.2
> 0.2 to 1.3
> 1.3
> 0 to 0.7
> 0.7
> 0 to 0.4
> 0.4
> 0 to 0.2
> 0.2 to 1.4
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> 0 to 0.5
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> 0 to 0.4
> 0.4
> 0 to 0.2
> 0.2 to 0.7
> 0.7
> 0
> 0 to 0.3
> 0.3 to 1.2
> 1.2
> 0 to 0.2
> 0.2
> 0 to 0.6
> 0.6
> 0
Outcome
Laryngeal cancer
Lung cancer
Esophageal cancer
Stomach cancer
Colon cancer
Rectal cancer
Bladder cancer
Liver cancer
Pancreatic cancer
Skin cancer
Prostate cancer
Brain and nervous system cancers
Leukemia
Breast cancer