ORIGINAL ARTICLE

Cancer incidence among workers with blood lead measurements in two countries

Kyle Steenland,[1] Vaughn Barry,[1] Ahti Anttila,[2] Markku Sallmen,[3] William Mueller,[4] Peter Ritchie,[4] Damien Martin McElvenny,[4] Kurt Straif[5]

ABSTRACT

Objective Study carcinogenicity of inorganic lead, classified as 'probably carcinogenic' to humans by the International Agency for Research on Cancer (brain, lung, kidney and stomach).

Methods We conducted internal and external analyses for cancer incidence in two cohorts of 29 874 lead-exposed workers with past blood lead data (Finland, n=20 752, Great Britain=9122), with 6790 incident cancers. Exposure was maximum measured blood lead.

Results The combined cohort had a median maximum blood lead of 29 µg/dL, a mean first blood lead test of 1977, and was 87% male. Significant (p<0.05) positive trends, using the log of maximum blood lead, were found for brain cancer (malignant), Hodgkin's lymphoma, lung cancer and rectal cancer, while a significant negative trend was found for melanoma. Borderline significant positive trends (0.05≤p≤0.10) were found for oesophageal cancer, meningioma and combined malignant/benign brain cancer. Categorical analyses reflected these trends. Significant interactions by country were found for lung, brain and oesophageal cancer, with Finland showing strong positive trends, and Great Britain showing modest or no trends. Larynx cancer in Finland also showed a positive trend (p=0.05). External analyses for high exposure workers (maximum blood lead >40 µg/dL) showed a significant excess for lung cancer in both countries combined, and significant excesses in Finland for brain and lung cancer. The Great Britain data were limited by small numbers for some cancers, and limited variation in exposure.

Conclusions We found strong positive incidence trends with increasing blood lead level, for several outcomes in internal analysis. Two of these, lung and brain cancer, were sites of a priori interest.

Key messages

What is already known about this subject?
► Inorganic lead is considered a probable carcinogen by the International Agency for Research on Cancer, based primarily on findings for brain, stomach, kidney and lung cancer.

What are the new findings?
► We have studied a large two-country cohort of 30000 lead-exposed workers, with documented blood lead levels, who had 7000 incident cancers during the follow-up period.
► We have found significant positive exposure-response relationships for brain and lung cancer, and also for Hodgkin's lymphoma and rectal cancer.
► We found a significant negative trend for melanoma.

How might this impact on policy or clinical practice in the foreseeable future?
► The positive findings for lung and brain cancer confirm earlier findings.
► Our data suggest that permissible standards for blood lead levels, often set to 40 µg/dL, are too high.

INTRODUCTION

With the worldwide elimination of leaded gasoline, lead levels have dropped considerably in world populations.[1 2] However, lead has been and remains a relatively common occupational exposure in many countries. For example, in the UK there were an estimated 250 000 workers exposed to lead in the early 1990s (approximately 1% of the employed population, see https://tradingeconomics.com/united-kingdom/employed-persons), and as of 2005 an estimated 2% of the employed population was estimated to have been exposed to lead occupationally at some point.[3] In Finland in the period 1970–1990, approximately 2% of the workforce was estimated to have had lead exposure, based on a Finnish job-exposure matrix.[4]

The International Agency for Research on Cancer (IARC) and the National Toxicology Programme (NTP) have concluded that inorganic lead compounds are *probably carcinogenic to humans* and *reasonably anticipated to be human carcinogens*, respectively, based primarily on lung and stomach cancers, and some suggestive effects on kidney and brain cancer.[5 6] A 2010 IARC workshop on future research priorities called for more studies of lead-exposed workers.[7]

Since the IARC and NTP reviews, there have been several publications describing cancer incidence in lead-exposed workers. Regarding brain cancer, van Wijngaarden and Dosemeci[8] studied brain cancer using a job-exposure matrix data (JEM) to estimate lead exposure, in a large population-based cohort followed in the USA in the 1980s (n=317 000), using occupation and industry from death certificates. They found an association with presumed lead exposure (18% exposed) and brain cancer mortality (120 deaths), with an HR of 1.5
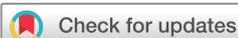
(95% CI 0.9 to 2.3) for exposed versus non-exposed, and indications of an exposure-response trend. Liao et al,[9] using a JEM, studied a large general population (n=135 000) in Shanghai, with about 8% exposed occupationally. These authors found an excess, although non-significant, risk for incident brain cancer (relative risk (RR)=1.8 (95% CI 0.7 to 4.8)). Parent et al[10] found no association with glioma using a JEM in a seven-country population-based case-control study with 1800 incident glioma cases. In an analogous case-control study in the same seven countries using the same JEM, Sadetzki et al[11] likewise found no association between lead and meningioma, with 1906 incident cases. In both these studies, the percentage of exposed cases and controls was between 5% and 10%.

Findings for lung cancer have been mixed. In the study by Liao et al[9] in Shanghai, an excess risk of lung cancer (after controlling for smoking) was found for men (lung RR=1.4 (95% CI 1.0 to 2.0), 35 exposed cases), but not for women. Wynant et al[12] found no elevation of lung cancer in exposed workers in a population-based case-control study (1500 cases, 1500 controls) in Montreal in which exposure was assessed by a JEM. Ilychova and Zaridze[13] found no increased lung cancer among Moscow printing workers, but the number of lung cancers was small (n=40), with no direct measurements of exposure. Regarding other cancers, the studies by Liao et al[9] and Ilychova and Zaridze[13] found little or no excess in stomach cancer, but did find an excess of kidney cancer in the highest exposed workers.

To further investigate possible associations, we have conducted a pooled analysis for cancer incidence among two cohorts of workers with documented blood lead levels (n=29 874), enrolled in surveillance programmes in Finland and Great Britain. The Finnish cohort (n=20 752) has been followed previously for cancer incidence, in the mid-1990s.[14 15] The Finnish cohort also formed part of a more recent mortality analysis of Great Britain, the USA and Finnish cohorts.[16] The Great Britain cohort (n=9122) has not been studied previously for cancer incidence, although it has for mortality.[17]

The documented blood lead levels among these workers avoid some of the uncertainty of whether workers were actually exposed to lead, which occurs when exposure is estimated based on job title or a job-exposure matrix.

Findings for health risk by blood lead levels may have implications for standards. Current regulations in the UK require consultation with a doctor to consider removal from the workplace when levels reach $30\,\mu g/dL$ for pregnant women, $40\,\mu g/dL$ for teenage workers and $50\,\mu g/dL$ for other adult workers (http://www.hse.gov.uk/pubns/priced/l132.pdf). If the doctor recommends removal, the employer must comply, and the worker can return only with the doctor's recommendation. In Finland, workers must be removed when their blood levels exceed $50\,\mu g/dL$ (or $1.9\,\mu g/dL$ for pregnant women) (Markku Sallmen, personal communication). In the USA, the Occupational Safety and Health Administration (OSHA) requires removal of workers from exposure when blood lead levels exceed $50\,\mu g/dL$ (construction) or $60\,\mu g/dL$ (general industry), based on a standard adopted in 1978, motivated by acute lead poisoning.[18] Several authors have called for lowering currently permissible occupational blood lead levels to $20\,\mu g/dL$.[18 19]

METHODS
Cohorts
The Finnish cohort of 20 752 workers (12% women) with documented blood lead was originally followed for cancer incidence through 1988.[16 17] Follow-up has now been extended through 2013. Blood lead levels were measured during the years 1973–1982, as part of a nationwide surveillance programme.

The Great Britain cohort (9122 workers, 15% women) was followed previously for mortality through 2011.[19] The cohort had blood lead levels measured in the period 1975–1979.

The subjects in these cohorts were exposed to lead occupationally; they were exposed in a large number of different occupations and industries in each country.

Exposure data
The exposure data consisted of blood lead tests, conducted under occupational surveillance programmes. Details are available in the original publications.[17 19] Complete work histories were not available, nor were data on any demographic variables beside birth date, death date, emigration date and gender. Half (47%) of the combined cohort had only one blood lead test, while the other half had a median of 3.

For workers with multiple blood measurements, values were available in the Finland cohort, but for Great Britain we had only the maximum lead level, the minimum lead level and the number of measurements. We used the maximum blood lead as the principal exposure metric, motivated by two factors. First, when more than one blood lead measurement was available, they tended to be similar to each other, so the maximum was not far from the mean (see data below). Second, any accurate measure of cumulative exposure being absent, we believed that the maximum blood lead was likely to be a reasonable choice for the most biologically relevant measure to predict future disease risk.[20]

Analyses
Person-time began at time of first blood lead test, and continued until the end of follow-up, death or year of emigration. For persons with an incident cancer, person-time at risk for that cancer ended at time of diagnosis. However, person-time for other cancers continued, starting from time of first blood test until date of death, end of follow-up or an incident cancer of interest (16% of people with cancer had more than one primary cancer). Follow-up for these cohorts matched the original mortality follow-up dates, that is, 31 December 2011 for Great Britain and 31 December 2013 for Finland.

There are some data indicating that those with a primary cancer are more likely to have a second primary cancer.[21] As a sensitivity analysis, we re-ran our internal analyses for malignant brain and lung cancer using 1) only primary cancers and 2) all primary cancers but taking into account the correlation among subjects with more than one cancer[22] via a procedure available in SAS PROC PHREG (https://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_phreg_sect054.htm).

We conducted internal analyses for different incidence outcomes via Cox regression (SAS V.9.22, http://support.sas.com/en/support-home.html), with age as the time variable, while controlling for decade of year of birth, gender and country. We tested the proportional hazard assumption for exposure, which was not violated. We also tested for interaction by country, and by gender. We conducted both categorical and continuous analyses. Categorical analyses used lead exposure categories of <20, 20–29, 30–39 and 40+ $\mu g/dL$. The lower cutpoint of $<20\,\mu g/dL$ was motivated by the scarcity of many workers in the Great Britain cohort with levels $<20\,\mu g/dL$, while the upper bound was motivated by its use by OSHA as the upper bound of a safe level.

Table 1 Descriptive data for cohorts from Finland and Great Britain (GB)

Country	N	Person-years	Deaths	Incident cancers	Mean year first follow-up*	Last year follow-up	Mean year of birth	% female
GB	9122	272 682	3477	1950	1976	2011	1939	15
Finland	20 752	655 766	7109	4840	1977	2013	1943	12
Combined	29 874	928 448	10 586	6790	1977	n.a.	1942	13

*Year of first blood lead test.
n.a., not available.

For brain cancer, we conducted analyses of malignant cancers only, and for malignant and benign combined, given that benign tumours can be as lethal as malignant tumours, and their pathology is not markedly different (www.cancer.org/cancer/brain-spinal-cord-tumors-adults.html). There were 85 malignant brain tumours and 76 benign brain tumours in the combined cohorts. We also analysed gliomas and meningiomas separately.

For Finland, where we had data on multiple tests per person, we also ran analyses using time-dependent maximum blood lead. Results were virtually identical to results based on analyses using time-independent maximum blood lead, and we present only time-independent analyses. We tested for continuous trends using either maximum blood lead or its natural log, and report both for the combined country analyses. For country-specific analyses, we report the better-fitting log term for all sites except larynx cancer in Finland, where the untransformed term fits better, and there we give both results.

We conducted external analyses via SIRs (rate ratio for exposed vs referent), using national incidence rates as the reference, stratified by 5-year age and calendar time categories, via the NIOSH Life Table Analysis System.[23] We used the International Classification of Diseases groupings for disease-specific rates from the NIOSH Life Table categories.[24] Great Britain and Finnish national cancer incidence rates were provided by Dr McElvenny (Great Britain) and Dr Anttila (Finland).

RESULTS

Table 1 provides a summary of cohort statistics. The Finnish cohort is twice as large as the Great Britain cohort; the cohorts are quite similar with regard to year of first follow-up, age and gender.

Table 2 provides summary data on the blood lead tests. Great Britain had much higher median maximum blood lead, with few people under 20 µg/dL, and 58% of workers above 40 µg/dL. Nonetheless, the Finnish cohort also contributed a substantial number to the highest lead category (>40 µg/dL).

Forty-seven per cent of the combined cohort had more than one blood lead test (mean of three for those with >1). The intraclass correlation coefficient (proportion of variance between subjects out of total variance, ie, the sum of between and within variance) for those with multiple measurements was a high 0.93, indicating that the variance within a person's multiple measurements was much less than the variance between the mean blood lead levels of different workers.

Table 3 gives the results for cancer incidence risk among the combined cohort, for all cancers for which there was a trend in continuous log transformed or untransformed maximum blood lead with p≤0.10, as well as for several of a priori interest. There were positive trends (p<0.10) for brain cancer (malignant and malignant+benign), lung cancer, oesophageal cancer, rectal cancer and Hodgkin's lymphoma. There was a negative trend for melanoma. Stomach and kidney cancers, both of a priori interest, showed no evidence of trends.

There were significant (p≤0.05) interactions, using either log or untransformed maximum blood lead, between countries for brain cancer, lung cancer and oesophageal cancer. Most of these interactions were for the untransformed exposure metric (only lung cancer showed an interaction using logged maximum blood lead). Table 4 shows the country-specific data for all cancers with a significant interaction as shown in table 3, using either exposure metric. Table 4 also includes larynx cancer, although the interaction term with country was not significant as shown in table 3, because it was a cancer of a priori interest, and because the trend in Finland using untransformed maximum blood lead was significant. Table 4 shows that in general positive significant trends were largely confined to Finland.

We also conducted a random effects meta-analysis for the trend test using log maximum blood lead, across the two countries, for the results in table 4, given the significant heterogeneity found in table 3.[25] For lung cancer, the meta-analytic random effects rate ratio was 1.26 (95% CI 0.93 to 1.70), slightly lower than the result as shown in table 3 (RR=1.34). Results for malignant brain cancer and all brain cancer were 1.28 (95% CI 0.71 to 2.30) and 1.37 (95% CI 1.00 to 1.87), respectively, while the result for oesophageal cancer was 1.32 (95% CI 0.91 to 1.93). For larynx cancer, we used untransformed maximum blood lead as our metric as it fits appreciably better in Finland; results for the meta-analysis were 1.01 (95% CI 0.99 to 1.02).

We also ran a series of sensitivity analyses. We ran analyses restricting to the first primary cancer, or taking into account possible correlations between multiple primaries. Results differed slightly when using only first primaries, but hardly at all when taking correlations into account (online supplemental table 1). We also calculated HRs for an increase in IQR (75%–25%) for

Table 2 Distribution of maximum blood lead levels (µg/dL) from cohorts in Finland and Great Britain

Country	Total	Max blood lead <10 µg/dL	Max blood lead 10–<20 µg/dL	Max blood lead 20–<30 µg/dL	Max blood lead 30-<40 µg/dL	Max blood lead 40+ µg/dL	Median max blood lead µg/dL	Mean # blood leads per person
Great Britain	9122	1%	9%	17%	16%	58%	48	4
Finland	20 752	16%	41%	22%	9%	11%	19	3
Combined	29 874	11%	31%	21%	11%	26%	23	3

Max, maximum.

Table 3 Results for cancer incidence for sites with either a p value for BL trend <0.10, or of a priori interest, Great Britain and Finland combined*

Cancer site†	Max BL (µg/dL) and cutpoints	N	HR	LCL HR	UCL HR	P for country interaction, log continuous max BL† country	P for country interaction, continuous max BL† country
Brain malignant	<20 (referent)	36	1.00				
Brain malignant	20–29	16	1.02	0.56	1.84		
Brain malignant	30–39	10	1.34	0.66	2.74		
Brain malignant	40+	23	1.71	0.94	3.12		
Brain malignant	Log max BL		1.42	1.01	2.00	0.14	**0.04**
Brain malignant+benign	<20 (referent)	73	1.00				
Brain malignant+benign	20–29	38	1.18	0.73	1.91		
Brain malignant+benign	30–39	17	1.27	0.68	2.37		
Brain malignant+benign	40+	33	1.62	0.96	2.72		
Brain malignant+benign	Log max BL		1.37	1.02	1.83	0.31	**0.06**
Glioma	<20 (referent)	32	1.00				
Glioma	20–29	12	0.87	0.44	1.70		
Glioma	30–39	10	1.31	0.61	2.82		
Glioma	40+	19	1.40	0.71	2.76		
Glioma	Log max BL		1.34	0.92	1.96	0.13	**0.05**
Meningioma	<20 (referent)	25	1.00				
Meningioma	20–29	15	2.14	0.86	5.33		
Meningioma	30–39	4	2.16	0.66	7.07		
Meningioma	40+	9	2.03	0.68	6.09		
Meningioma	Log max BL		1.65	0.92	2.97	0.79	0.35
Oesophagus	<20 (referent)	30	1.00				
Oesophagus	20–29	19	1.20	0.67	2.15		
Oesophagus	30–39	18	2.00	1.08	3.71		
Oesophagus	40+	42	1.81	1.03	3.19		
Oesophagus	Log max BL		1.34	0.98	1.83	0.16	**0.009**
Hodgkin's lymphoma	<20 (referent)	12	1.00				
Hodgkin's lymphoma	20–29	10	1.89	0.81	4.42		
Hodgkin's lymphoma	30–39	6	2.37	0.87	6.43		
Hodgkin's lymphoma	40+	10	2.36	0.93	5.99		
Hodgkin's lymphoma	Log max BL		1.70	1.01	2.84	0.37	0.15
Lung	<20 (referent)	330	1.00				
Lung	20–29	220	1.39	1.17	1.65		
Lung	30–39	128	1.56	1.26	1.93		
Lung	40+	305	1.57	1.30	1.90		
Lung	Log max BL		1.34	1.21	1.48	**0.0002**	**<0.0001**
Melanoma	<20 (referent)	98	1.00				
Melanoma	20–29	85	1.09	0.80	1.48		
Melanoma	30–39	59	1.01	0.71	1.44		
Melanoma	40+	142	0.74	0.54	1.01		
Melanoma	Log max BL		0.84	0.72	0.97	0.79	0.95
Rectum	<20 (referent)	93	1.00				
Rectum	20–29	54	1.25	0.89	1.76		
Rectum	30–39	22	0.98	0.61	1.58		
Rectum	40+	77	1.49	1.03	2.17		
Rectum	Log max BL		1.30	1.06	1.59		
	Max BL		1.005	1.002	1.008	0.39	0.55
Stomach	<20 (referent)	80	1.00				
Stomach	20–29	58	1.55	1.10	2.18		
Stomach	30–39	26	1.39	0.88	2.21		
Stomach	40+	42	1.02	0.66	1.58		
Stomach	Log max BL		1.11	0.89	1.39	0.67	0.84
Kidney	<20 (referent)	109	1.00				
Kidney	20–29	49	1.05	0.75	1.48		
Kidney	30–39	20	0.91	0.56	1.49		

Table 3 continued

Cancer site†	Max BL (µg/dL) and cutpoints	N	HR	LCL HR	UCL HR	P for country interaction, log continuous max BL† country	P for country interaction, continuous max BL† country
Kidney	40+	41	1.00	0.66	1.51		
Kidney	Log max BL		0.99	0.81	1.22	0.70	0.51
Larynx	<20 (referent)	20	1.00				
Larynx	20–29	16	1.61	0.83	3.13		
Larynx	30–39	9	1.73	0.77	3.93		
Larynx	40+	24	1.92	0.94	3.91		
Larynx	Log max BL		0.89	0.62	1.26		
	Max BL		1.004	0.998	1.010	0.24	0.13
Bladder	<20 (referent)	115	1.00				
Bladder	20–29	53	0.94	0.68	1.31		
Bladder	30–39	26	0.90	0.58	1.40		
Bladder	40+	83	1.24	0.87	1.75		
Bladder	Log max BL		1.10	0.91	1.33	0.97	0.38

*Categorical results, trend test and country heterogeneity test for all cancer sites with a trend test <0.10, or cancers of a priori interest elevated in some prior studies (stomach, kidney, larynx). Cox models, with age as the time scale, adjusted for country, gender and year of birth category (year of birth <1920, 1920–1929, 1930–1939, 1940–1949, 1950–1959 and 1960–1969). Trend tests (change in rate ratio for unit BL) reported for log max BL and untransformed BL trend.

†Bladder cancer, ICD-9 188–9, ICD-10 C67–8, brain cancer malignant ICD-9 191–2, ICD-10 C47, C70–2, brain cancer benign ICD-9 225, ICD-10 D32–3, oesophageal cancer ICD-9 150, ICD-10 C15, glioma (malignant or benign) ICD-9 191, 225, ICD-10 C71, D33, Hodgkin's lymphoma ICD-9 201, ICD-10 C81, kidney cancer ICD-9 189, ICD-10 C64–6, larynx cancer ICD-9 161, ICD-10 C32, lung cancer ICD-9 162, ICD-10 C33–4, melanoma ICD-9 173–3, ICD-10 C43–4, meningioma (malignant or benign) ICD-9 192, ICD-10 C70, D32, rectal cancer ICD-9 1544, ICD-10 C19021, stomach cancer ICD-9 151, ICD-10 C16.

BL, blood lead; ICD, International Classification of Diseases; LCL HR, 95% lower confidence limit of HR; max, maximum; UCL HR, 95% upper confidence limit of HR. Values in bold are p-values <0.10.

maximum blood lead for each country (IQR 8.2 in Finland, 20.7 in Great Britain) (for some specific cancer, see online supplemental table 2). Finally, given the small numbers of cancers in some cases in the referent categories for Great Britain as shown in table 4 (cancers with significant heterogeneity by country), we also calculated categorical results for these cancers for Great Britain combining the lowest referent category (<20) with the second category (20–20), making the referent <30. These results show no significant positive trends in the Great Britain data (online supplemental table 3) by increasing categories of blood lead.

We found no suggestion of a trend between blood lead and breast cancer (rate ratios 1.00, 1.04, 1.28 and 1.02 in the combined analyses, by increasing lead category, with no suggestion of effect modification by country). We also tested for interaction between gender and logged maximum blood lead for all specific cancers. For both countries combined, there were no significant (p<0.05) interactions. For Great Britain, there was only one, for larynx cancer, but it was based on only one female case. For Finland, there were two, colon and multiple myeloma, both higher in women but not showing a significant positive trend. Overall, there were 75 analyses for gender interactions, hence about three would have been expected by chance.

Results for SIRs (external comparisons) for both countries combined (using national rates as the referent) are shown in table 5, for those with maximum blood lead ≥40 µg/dL, for causes listed in table 4. Only lung cancer showed a significantly elevated SIR (p<0.05) for both countries combined. For Finland, brain cancer, lung cancer and Hodgkin's lymphoma showed significant excesses.

DISCUSSION

Our study was based on workers with documented lead exposure via blood lead tests. Blood lead reflects short-term exposure, in the last few months,[26] although with high cumulative exposure lead stored in bone can leach into the blood, causing chronically elevated blood lead.[27] This cohort definition has both advantages and disadvantages. Without work history, we do not have data on length of time in a job potentially exposed to lead. On the other hand, for each individual worker we avoid the uncertainty arising from many job-exposure matrices, as to whether workers in specific jobs were actually exposed to lead, by having a measure of an internal dose. A recent study has also shown that maximum past blood lead, for 211 US lead-exposed workers in a lead surveillance programme, was strongly correlated with bone lead, which is a marker of cumulative exposure.[20]

Our strongest findings were for brain and lung cancer. Brain cancer was an outcome of a priori interest, given the prior findings for brain cancer incidence from the Finnish cohort with follow-up through 1990.[16] Brain cancer showed positive trends which were consistent for the two main subtypes, glioma and meningioma, and for the combined malignant and benign brain tumours. Lead is known be able to pass through the blood–brain barrier due its ability to mimic calcium.[28]

Regarding lung cancer, other metals are also well known to cause lung cancer (nickel, chromium, cadmium, beryllium). On the other hand, our lung cancer findings could be confounded by smoking, which might be associated with higher exposure (tobacco smoke also has lead in it, but this would be small percentage compared with the occupational contribution). Two other smoking-related cancers showed significant positive trends (oesophagus, larynx (Finland only)). We had no data on smoking. However, internal analyses comparing workers with workers are generally less subject to confounding by smoking, compared with external analyses comparing workers with the general population.[29 30] In particular, internal comparisons in which the uppermost lead exposure category showed HRs of 1.5 or above (oesophagus, lung, larynx) are unlikely to be due to confounding by smoking under hypothetical or observed smoking differences between low-exposed and high-exposed

Table 4 Results for cancer incidence by country, for sites showing interaction between country and continuous blood lead (p interaction≤0.10)*, with blood lead trend tests

Outcome	Maximum blood lead (µg/dL) and cutpoints	Number of cancers	HR	LCL HR	UCL HR	P trend log continuous maximum blood lead
Brain malignant, Finland	<20 (referent)	35	1.00			
Brain malignant, Finland	20–29	11	0.79	0.40	1.57	
Brain malignant, Finland	30–39	8	1.41	0.65	3.06	
Brain malignant, Finland	40+	14	2.06	1.10	3.85	
Brain malignant, Finland	Log max blood lead		1.59	1.09	2.32	0.02
Brain malignant, Great Britain	<20 (referent)	1	1.00			
Brain malignant, Great Britain	20–29	5	2.86	0.33	24.49	
Brain malignant, Great Britain	30–39	2	1.23	0.11	13.65	
Brain malignant, Great Britain	40+	9	1.50	0.19	12.01	
Brain malignant, Great Britain	Log max blood lead		0.84	0.38	1.85	0.66
Brain malignant+benign, Finland	<20 (referent)	72	1.00			
Brain malignant+benign, Finland	20–29	32	1.04	0.61	1.75	
Brain malignant+benign, Finland	30–39	14	1.44	0.75	2.77	
Brain malignant+benign, Finland	40+	19	1.74	0.99	3.08	
Brain malignant+benign, Finland	Log max blood lead		1.48	1.07	2.03	0.02
Brain malignant+benign, Great Britain	<20 (referent)	1	1.00			
Brain malignant+benign, Great Britain	20–29	6	3.36	0.40	27.92	
Brain malignant+benign, Great Britain	30–39	3	1.22	0.11	13.44	
Brain malignant+benign, Great Britain	40+	14	2.26	0.29	17.33	
Brain malignant+benign, Great Britain	Log max blood lead		0.99	0.49	1.97	0.97
Glioma, Finland	<20 (referent)	31	1.00			
Glioma, Finland	20–29	7	0.59	0.26	1.36	
Glioma, Finland	30–39	7	1.44	0.63	3.30	
Glioma, Finland	40+	10	1.71	0.83	3.54	
Glioma, Finland	Log max blood lead		1.55	1.01	2.37	0.05
Glioma, Great Britain	<20 (referent)	1	1.00			
Glioma, Great Britain	20–29	5	2.87	0.33	24.61	
Glioma, Great Britain	30–39	3	1.23	0.11	13.63	
Glioma, Great Britain	40+	9	1.52	0.19	12.19	
Glioma, Great Britain	Log max blood lead		0.81	0.37	1.77	0.59
Oesophagus, Finland	<20 (referent)	27	1.00			
Oesophagus, Finland	20–29	12	1.08	0.54	2.13	
Oesophagus, Finland	30–39	10	2.25	1.09	4.67	
Oesophagus, Finland	40+	10	1.86	0.90	3.85	
Oesophagus, Finland	Log max blood lead		1.58	1.05	2.38	0.03
Oesophagus, Great Britain	<20 (referent)	3	1.00			
Oesophagus, Great Britain	20–29	7	1.29	0.33	5.00	
Oesophagus, Great Britain	30–39	8	1.56	0.41	5.87	
Oesophagus, Great Britain	40+	32	1.64	0.50	5.37	
Oesophagus, Great Britain	Log max blood lead		1.07	0.66	1.71	0.79
Lung, Finland	<20 (referent)	306	1.00			
Lung, Finland	20–29	159	1.28	1.06	1.56	
Lung, Finland	30–39	78	1.63	1.27	2.09	
Lung, Finland	40+	105	1.77	1.42	2.21	
Lung, Finland	Log max blood lead		1.46	1.29	1.65	<0.0001
Lung, Great Britain	<20 (referent)	24	1.00			
Lung, Great Britain	20–29	61	1.37	0.85	2.19	
Lung, Great Britain	30–39	50	1.19	0.73	1.94	
Lung, Great Britain	40+	200	1.26	0.82	1.93	
Lung, Great Britain	Log max blood lead		1.07	0.89	1.28	0.46
Larynx, Finland	<20 (referent)	19	1.00			
Larynx, Finland	20–29	11	1.38	0.66	2.90	
Larynx, Finland	30–39	4	1.29	0.44	3.79	
Larynx, Finland	40+	9	2.39	1.08	5.28	
Larynx, Finland	Log max blood lead		0.80	0.57	1.12	0.20

Table 4 continued

Outcome	Maximum blood lead (µg/dL) and cutpoints	Number of cancers	HR	LCL HR	UCL HR	P trend log continuous maximum blood lead
Larynx, Finland	Max blood lead		1.02	1.00	1.03	0.05
Larynx, Great Britain	<20 (referent)	1	1.00			
Larynx, Great Britain	20–29	5	2.47	0.29	21.20	
Larynx, Great Britain	30–39	5	2.66	0.31	22.83	
Larynx, Great Britain	40+	15	1.94	0.25	14.70	
Larynx, Great Britain	Log max blood lead		0.80	0.57	1.12	0.55
	Max blood lead		1.001	0.992	1.011	0.76

*Adjusted for gender and year of birth (10-year categories).
LCL HR, 95% lower confidence limit of HR; UCL HR, 95% upper confidence limit of HR.

workers. Earlier work has shown that for diseases which are strongly related to smoking (eg, lung cancer), observed smoking differences between low-exposed and high-exposed workers are likely to account for excesses of only 20%–40%.[31] [32] It might also be noted that in an earlier nested case-control study of lung cancer in the Finnish cohort which has smoking data, smoking was not associated with blood lead level.[17] Also, we found no positive trends for bladder cancer and kidney cancer, both of which are typically associated with smoking. Finally, in a recent study of 211 lead-exposed workers in another lead surveillance system in the USA, no association was found between maximum past blood lead level and pack-years of smoking (correlation 0.01), although this finding is limited by small sample size and by being in a different country.[20]

Socioeconomic status (SES) may be related to cancer risk for some cancers, perhaps mediated by smoking. We matched the Finnish data to 1970, 1975, 1980, 1985 and 1990 census data by broad occupational category; 99% of cohort workers had a match. Using the last available census for each worker, the percentage of workers in the blue-collar category of blood lead (ie, <10, 10–20, 20–30, 30–40 and 40+ µg/dL) were 71%, 77%, 78%, 78% and 81%, respectively, indicating some, but only modest, decrease in SES with higher lead exposure. It seems unlikely that this level of difference in SES between blood levels would have strongly confounded our internal comparison in Finland. We had no data on SES in England.

We found an association between lead and larynx cancer, although only in Finland. Larynx cancer is not known to be associated with lead.[33] A prior association has been seen previously in only one mortality study.[34] On the other hand, larynx cancer is rare and power to detect associations is generally quite low in

lead cohort studies; often no data are presented for this cancer. Furthermore, it is an organ directly impacted by inhaled lead. A recent analysis of a large European case-control study found that several known lung carcinogens were also significantly associated with larynx cancer.[35]

We also found new associations, not previously found in the literature, between lead and Hodgkin's lymphoma and oesophageal cancer. On the other hand, we found no evidence of an association between lead and either stomach or kidney cancer, both sites of a priori concern.

External comparison analysis via SIRs, restricted to the highest category (≥40 µg/dL), showed lower excesses for high-exposed workers than internal analyses, possibly due to a healthy worker effect. On the other hand, when limiting SIR analyses to Finland, we found high SIRs for lung, oesophageal, brain and Hodgkin's lymphoma, which were similar in magnitude to those shown in internal analysis.

Most of the positive cancer trends with higher exposure were found in Finland. The lack of positive findings in Great Britain diminishes the likelihood that the excesses observed predominantly in Finland are causal. However, the scarcity of cancers in Great Britain in the low exposure range, in contrast with Finland, may have limited our ability to observe trends in Great Britain in internal analyses. Most workers in Great Britain were exposed to levels >40 µg/dL, unlike Finland; possibly this reflects a different strategy in choosing which workers to include in lead surveillance. The number of cancers in the reference category in Great Britain is correspondingly frequently sparse.

We made a large number of comparisons, and cannot rule out the possibility that some of country-specific findings on cancers not of a priori interest could be due to random chance, given the

Table 5 SIRs for those with ≥40 µg/dL maximum blood lead*

Cause	Observed combined	SIR combined	Lower 95% CL	Upper 95% CL	Observed Finland†	SIR Finland†	Lower 95% CI	Upper 95% CI
Bladder cancer	83	0.93	0.73	1.10	28	1.27	0.84	1.83
Brain cancer	23	0.97	0.57	1.31	14	2.31	1.26	3.88
Oesophogeal cancer	42	1.14	0.79	1.43	10	1.89	0.91	3.47
Hodgkin's lymphoma	10	1.28	0.49	1.96	7	2.89	1.16	5.96
Kidney cancer	36	0.83	0.56	1.07	15	0.98	0.55	1.61
Larynx cancer	24	1.26	0.76	1.69	9	2.05	0.94	3.89
Lung cancer	306	1.19	1.06	1.31	105	1.71	1.4	2.07
Rectal cancer	78	1.07	0.84	1.28	19	1.17	0.70	1.82
Stomach cancer	42	0.68	0.48	0.86	9	0.56	0.25	1.05

*SIRs calculated using national rates for Great Britain and Finland as the referent rates for each country-specific cohort, then combining observed and expected across countries. Adjusted for age/gender/calendar time. Rates for non-Hodgkin's lymphoma not available consistently for both countries.
†No SIR was significantly elevated in Great Britain.
CL, confidence limit.

multiple comparisons. On the other hand, positive exposure-response trends greatly outnumbered negative ones, suggesting random chance might not be the explanation.

In summary, findings are suggestive of lead effects on several sites of cancer incidence, in particular the a priori sites of lung and brain. Other sites are unexpected, including rectum, oesophagus and Hodgkin's lymphoma. Confounding by smoking and SES may be playing a minor role in some excesses, but are unlikely to explain them entirely. On the other hand, prior sites of interest, kidney and stomach, find no support in our data.

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