

NIOSH STUDY OF FIREFIGHTERS FINDS INCREASED RATES OF CANCER

A combined population of 30,000 firefighters from three large cities had higher rates of several types of cancers, and of all cancers combined, than the U.S. population as a whole, researchers from the National Institute for Occupational Safety and Health (NIOSH) and colleagues found in a new study.

The new findings are generally consistent with the results of several previous, smaller studies. Because the new study had a larger study population followed for a longer period of time, the results strengthen the scientific evidence for a relation between firefighting and cancer, the researchers said.

The findings were reported in an article posted on-line on Oct. 14, 2013, by the peer-reviewed journal Occupational and Environmental Medicine. The article is available online at <http://oem.bmj.com/content/early/2013/10/14/oemed-2013-101662.full>

The researchers found that:

- Cancers of the respiratory, digestive, and urinary systems accounted mostly for the higher rates of cancer seen in the study population. The higher rates suggest that firefighters are more likely to develop those cancers.
- The population of firefighters in the study had a rate of mesothelioma two times greater than the rate in the U.S. population as a whole. This was the first study ever to identify an excess of mesothelioma in U.S. firefighters. The researchers said it was likely that the findings were associated with exposure to asbestos, a known cause of mesothelioma.

The study analyzed cancers and cancer deaths through 2009 among 29,993 firefighters from the Chicago, Philadelphia, and San Francisco fire departments who were employed since 1950. The study was led by NIOSH in collaboration with the National Cancer Institute and the Department of Public Health Sciences in the University of California at Davis. The study was supported in part by funding from the U.S. Fire Administration.

Firefighters can be exposed to contaminants from fires that are known or suspected to cause cancer. These contaminants include combustion by-products such as benzene and formaldehyde, and materials in debris such as asbestos from older structures.

The findings of the new study do not address other factors that can influence risk for cancer, such as smoking, diet, and alcohol consumption. In addition, few women and minorities were in the study population, limiting the ability to draw statistical conclusions about their risk for cancer.

In a second phase of the study, the researchers will further examine employment records from the three fire departments, to derive information on occupational exposures, and to look at exposures in relation to cancer incidence and mortality. Those findings, when completed, will be published in a future article.



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Occup Environ Med published online October 14, 2013
doi: 10.1136/oemed-2013-101662

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ORIGINAL ARTICLE

Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950–2009)

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/oemed-2013-101662>).

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Received 12 June 2013

Revised 10 September 2013

Accepted 23 September 2013



► <http://dx.doi.org/10.1136/oemed-2013-101803>

To cite: Daniels RD, Kubale TL, Yiin JH, *et al.* *Occup Environ Med* Published Online First: [please include Day Month Year] doi:10.1136/oemed-2013-101662

ABSTRACT

Objectives To examine mortality patterns and cancer incidence in a pooled cohort of 29 993 US career firefighters employed since 1950 and followed through 2009.

Methods Mortality and cancer incidence were evaluated by life table methods with the US population referent. Standardised mortality (SMR) and incidence (SIR) ratios were determined for 92 causes of death and 41 cancer incidence groupings. Analyses focused on 15 outcomes of a priori interest. Sensitivity analyses were conducted to examine the potential for significant bias.

Results Person-years at risk totalled 858 938 and 403 152 for mortality and incidence analyses, respectively. All-cause mortality was at expectation (SMR=0.99, 95% CI 0.97 to 1.01, n=12 028). There was excess cancer mortality (SMR=1.14, 95% CI 1.10 to 1.18, n=3285) and incidence (SIR=1.09, 95% CI 1.06 to 1.12, n=4461) comprised mainly of digestive (SMR=1.26, 95% CI 1.18 to 1.34, n=928; SIR=1.17, 95% CI 1.10 to 1.25, n=930) and respiratory (SMR=1.10, 95% CI 1.04 to 1.17, n=1096; SIR=1.16, 95% CI 1.08 to 1.24, n=813) cancers. Consistent with previous reports, modest elevations were observed in several solid cancers; however, evidence of excess lymphatic or haematopoietic cancers was lacking. This study is the first to report excess malignant mesothelioma (SMR=2.00, 95% CI 1.03 to 3.49, n=12; SIR=2.29, 95% CI 1.60 to 3.19, n=35) among US firefighters. Results appeared robust under differing assumptions and analytic techniques.

Conclusions Our results provide evidence of a relation between firefighting and cancer. The new finding of excess malignant mesothelioma is noteworthy, given that asbestos exposure is a known hazard of firefighting.

INTRODUCTION

There are approximately 1.1 million volunteer and career firefighters in the US.¹ During firefighting activities, these workers may be exposed to many known carcinogens (eg, polycyclic aromatic hydrocarbons (PAHs), formaldehyde, benzene, 1,3-butadiene, asbestos and arsenic) in volatilised combustion and pyrolysis products or debris.² These exposures have raised concerns of increased cancer among firefighters and have prompted a number of exposure assessment and epidemiologic investigations. Some studies have found excess

What this paper adds

- From previous studies, there is limited epidemiological evidence of increased risk of cancer from firefighting.
- We examined cancer in 30 000 career firefighters by pooling information from urban fire departments in three large US cities. The large sample size and long follow-up period improved risk estimates compared with previous studies.
- We report that firefighting may be associated with increased risk of solid cancers. Furthermore, we report a new finding of excess malignant mesothelioma among firefighters, suggesting the presence of an occupational disease from asbestos hazards in the workplace.

cancers of the brain,^{3–8} digestive tract,^{4 5 7–10} genitourinary tract^{5 7 11 12} and lymphohematopoietic organs.^{6 8 13} In a recent meta-analysis of 32 studies, significant excess risk was reported for brain, stomach, colon, rectum, prostate, testes, multiple myeloma and non-Hodgkin lymphoma (NHL).¹⁴ Similarly, the International Agency for Research on Cancer (IARC) reviewed 42 studies and reported significant summary risks for prostatic and testicular cancers and NHL.² Given limited evidence, however, IARC concluded that firefighter exposures were only possibly carcinogenic to humans (Group 2B).

Most studies have examined mortality, but not cancer incidence, among relatively few firefighters recruited from one fire department. The current study examines mortality and cancer incidence in a pooled cohort of firefighters employed in three major US cities. Malignancies of the brain, stomach, oesophagus, intestines, rectum, kidney, bladder, prostate, testes, leukaemia, multiple myeloma and NHL were of a priori interest in the current study, based on possible sites identified in previous reviews.^{2 14} Lung cancer and chronic obstructive pulmonary disease (COPD) were also of interest because inhalation is a major pathway for firefighter exposures, and there is evidence of

chronic and acute inflammatory respiratory effects in firefighters, which may be linked to cancer.² Breast cancer was included as a result of interests shared in researcher discussions with firefighters.

METHODS

Data collection methods

This research was approved by the Institutional Review Boards of the National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI). Personnel records and previous study data were used to assemble the study roster, which comprised male and female career firefighters of all races employed for at least 1 day in fire departments serving San Francisco, Chicago, or Philadelphia, from 1 January 1950, through 31 December 2009. Fire departments were selected based on size, location, work experience, records availability and the willingness of labour and city management to participate. 'Career firefighter' status was determined from job titles categorised by researchers and vetted by each fire department. Selected job titles included general classifications of firefighters, firefighter paramedics, and fire department arson investigators. Persons of known race were mostly Caucasian (81%) and those missing race (2.5%) were hired in earlier periods of lower minority hiring (median year at hire=1955). Therefore, persons missing race were assumed Caucasian and retained in main analyses to maximise study size. Analyses were also conducted excluding persons of unknown race.

Vital status was ascertained from the National Death Index-Plus (NDI-Plus), the Social Security Administration Death Master File (SSA-DMF), personnel and pension board records, and records from the previous studies.^{9 10} Firefighters not found to be deceased were confirmed alive by matches to employment records, Internal Revenue Service (IRS) records, and data accessible through LexisNexis (a private vendor of residential information).

Causes of death were obtained from previous studies,^{9 10} NDI-Plus, and death certificates collected from state vital records and retirement boards. Deaths of Philadelphia firefighters through 1986 were previously determined by Baris *et al.*,⁹ who retrieved and coded death certificates to the ninth revision of the International Classification of Diseases (ICD-9). San Francisco firefighter deaths were determined through 1982 by Beaumont *et al.*¹⁰ In that and the current study, causes of death were coded to the ICD revision in effect at the time of death. The underlying cause of death determined by a trained nosologist was used for all mortality analyses.

Incident cases were defined as all primary invasive cancers, and in situ bladder cancers among firefighters matched to state cancer registries on name, gender, race, date of birth and Social Security number. The last known residence and the state of death were used to narrow inclusion of registries for case ascertainment to 11 states (ie, Arizona, California, Florida, Illinois, Indiana, Michigan, Nevada, New Jersey, Oregon, Pennsylvania and Washington) where nearly 95% of all deaths in known states occurred (see online supplementary table S1). The site and histology of each tumour were used to classify cancers in one of 41 diagnostic groups using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3).¹⁵ The conversion from ICD-O-3 to ICD-10 used the Surveillance, Epidemiology and End Results Program (SEER) recodes (dated 27 January 2003) following slight modification to align with mortality groupings and to account for recent classification changes. Diagnosis dates were assigned as of 1 July of the year of diagnosis if only the diagnosis year was

known, and on the 15th of the month of diagnosis if only the diagnosis month and year were known. The death date was used when death preceded the estimated date.

Statistical methods

The NIOSH Life Table Analysis System (LTAS.NET) was used to examine mortality and cancer incidence.¹⁶ Main analyses used the US population as referent. In all analyses, person-years at risk (PYAR) were stratified by gender, race (Caucasian, other races), age (age 15–85+ years in 5-year categories), and calendar year (in 5-year categories). Confidence limits for risk measures were estimated based on a Poisson distribution for the observed outcome, with exact limits for outcomes with 10 or fewer occurrences.

For mortality analyses, PYAR began on the latest of 1 January 1950 or the date of cohort inclusion, and ended the earliest of the date of death (DOD), the date last observed (DLO), or 31 December 2009. US mortality rates (1950–2009) were used to estimate the expected numbers of deaths for all causes, all cancers and 92 categories of underlying cause of death.¹⁷ Additional mortality rates were developed to separately report on cancers of the small intestine, large intestine and testes to coincide with incidence rates; however, these rates were limited to time periods after 1959. In both cases, the subsites of interest (ie, colon and testes) account for the largest proportion of the deaths in the respective aggregate site (ie, intestine or male genital organs excluding prostate); therefore, the aggregate site reasonably approximates the subsite. The standardised mortality ratio (SMR) was calculated as the ratio of the observed to the total number of expected deaths.

Two approaches were used to examine cancer incidence. The main analyses included first and later primary cancers (ie, multiple-cancer approach) occurring within the risk period. PYAR accrued from the date of statewide ascertainment by the respective fire department's state cancer registry (eg, 1 January 1988 for San Francisco firefighters (see online supplementary table S1)) or cohort inclusion, whichever was latest, and ended at the earliest of the DOD, DLO, or 31 December 2009. Secondary analyses were restricted to the first occurrence of invasive cancer (ie, first-cancer approach). In these analyses, PYAR for cases ended on the date of first diagnosis. In both approaches, the standardised incidence ratio (SIR) was calculated as the ratio of observed malignancies to the expected number of cases estimated using US incidence rates (1985–2009) calculated from SEER data.¹⁸ Additional steps required for first-cancer analyses were: selecting the most common cancer when diagnoses included multiple primary tumours on the same day (n=21), excluding firefighters known to have a cancer diagnosis prior to the start of the risk date (n=55), and adjusting US rates for cancer prevalence using methods described by Merrill *et al.*¹⁹

Heterogeneity in fire department-specific SMRs and SIRs was examined using Poisson regression modelling. To control for gender, age, calendar year and race, an offset term was set to the expected number of deaths or cases in each stratum of the classification table. To address differences between fire departments, a mixed model was used that specified a random intercept term. Thus, the model intercept is the log of the pooled SMR, adjusted for heterogeneity among the fire departments. The significance of heterogeneity was assessed by likelihood ratio test (significance level of 0.05).

Several sensitivity analyses were conducted. First, we examined the effects of including prevalent hires (workers employed before 1950) and short-term workers (those employed <1 year)

in mortality analyses. Prevalent hires must be employed long enough to be recruited into the study; thus, these workers may have a survival advantage compared with persons hired during the follow-up period (ie, incident hires).²⁰ Short-term workers include temporary hires and probationary firefighters whose health and lifestyle patterns may differ from those employed one or more years. Short-term workers may also have had substantial occupational histories other than as firefighters, possibly in jobs with hazardous exposures. Second, we examined age effects on risk estimates in two age-at-risk categories (17–64, 65+ years). Testing of an effect across all 5-year age groups was accomplished using mixed models adjusted for age-at-risk groups. Third, we conducted SMR analyses restricting observation to age 84 years or less. Including PYAR for ages 85+ years could bias results from: rates used in analyses that are open-ended, more uncertainty in underlying cause of death at later ages, and subjects who are incorrectly traced as alive having a disproportionate effect in the open-ended age group.²¹ Fourth, we calculated SMRs using California, Illinois and Pennsylvania State populations as referent for firefighters from San Francisco, Chicago and Philadelphia, respectively. Last, SMRs and standardised rate ratios (SRRs) were calculated for categories of employment duration (<10, 10–<20, 20–<30, 30+ years). Trend slopes with Wald-based two-sided p values (significance level of 0.05) were calculated for the change in SRRs with increasing duration.

RESULTS

There were 29 993 firefighters available for study, contributing 858 938 PYAR (table 1). The cohort was largely male (97%), with mean age at first employment and total years employed of 29 and 21 years, respectively. Fewer than 5% of firefighters

were short-term workers and approximately 30% were first employed prior to 1950. A higher percentage of women (9.4%) were short-term workers compared with men (4.3%) (see online supplementary table S2). Prevalent hires, on average, tended to be employed longer (+7.9 years, t test $p < 0.001$) and had a greater attained age (+17.0 years, t test $p < 0.001$) than incident hires. Persons eligible for incidence analyses using the multiple-cancer approach ($n = 24\,453$) contributed 403 152 PYAR. The first-cancer approach included 24 398 persons contributing 383 577 PYAR. There were 4461 malignant tumours distributed among 3903 firefighters with cancer. Among these, 488 reported cancers at multiple primary sites. Mortality and cancer incidence results are summarised in table 2 and in online supplementary tables S3–S5. To aid in comparisons with previous studies, table 2 also shows summary risk estimates (SREs) reported by LeMasters *et al*¹⁴, whose meta-analysis included studies published through 2003.

Mortality

With the US population referent, all-cause mortality was at expectation (SMR=0.99, 95% CI 0.97 to 1.01, $n = 12\,028$). Ischaemic heart disease was the leading cause of death (SMR=1.01, 95% CI 0.98 to 1.04, $n = 3619$). There was significantly decreased mortality in other outcomes that may be related to healthy worker selection and survivor effects (HWE), such as non-malignant respiratory diseases (SMR=0.80, 95% CI 0.74 to 0.86, $n = 796$), cerebrovascular disease (SMR=0.91, 95% CI 0.84 to 0.98, $n = 636$), diabetes mellitus (SMR=0.72, 95% CI 0.62 to 0.83, $n = 175$), nervous system disorders (SMR=0.80, 95% CI 0.69 to 0.93, $n = 187$), and alcoholism (SMR=0.61, 95% CI, 0.41 to 0.86, $n = 31$). In particular, there was a strong decrease in COPD mortality (SMR=0.72, 95% CI

Table 1 Demographic characteristics of the cohort by fire department and combined (1950–2009)

Description	All fire departments	San Francisco	Chicago	Philadelphia
Study cohort:				
Eligible for mortality analysis	29 993	5313	15 185	9495
PYAR	858 938	154 317	419 414	285 207
Years of follow-up; avg. (SD)	29 (16)	29 (16)	28 (16)	30 (16)
Race (%):				
White	24 244 (80.8)	4254 (80.1)	11 736 (77.3)	8254 (86.9)
Other	5008 (16.7)	986 (18.6)	2808 (18.5)	1214 (12.8)
Unknown	741 (2.5)	73 (1.4)	641 (4.2)	27 (<1.0)
Gender (%):				
Male	29 002 (96.7)	5009 (94.3)	14 694 (96.8)	9299 (97.9)
Female	991 (3.3)	304 (5.7)	491 (3.2)	196 (2.1)
Vital status:				
Alive (%)	17 965 (59.9)	3239 (61.0)	9241 (60.9)	5485 (57.8)
Deceased (%)	12 028 (40.1)	2074 (39.0)	5944 (39.1)	4010 (42.2)
Unknown cause of death	144	9	91	44
Attained age*; avg. (SD)	60 (16)	62 (16)	59 (16)	61 (16)
LTFU	175	1	32	142
PYAR potentially LTFU (%)	8809 (1.0)	59 (<1.0)	1483 (<1.0)	7267 (2.5)
Employment:				
Avg. hire year	1968	1967	1970	1965
Age at hire; avg. (SD)	29 (5)	29 (5)	29 (5)	27 (5)
Employment years; avg. (SD)	21 (11)	22 (11)	21 (11)	21 (11)
Hired before 1950 (%)	8085 (27)	1682 (32)	3294 (22)	3109 (33)
Employed <1 year (%)	1328 (4.4)	194 (3.7)	891 (5.9)	243 (2.6)

*Age attained at earliest of the date of death, date LTFU or 31 December 2009.
Avg., average; LTFU, lost to follow-up; PYAR, person-years at risk.

Table 2 Standardised mortality and incidence ratios in firefighters for select outcomes compared to results from a recent meta-analysis

Underlying cause (ICD-10 codes)	Current study results (US population referent)					Meta-analysis of LeMasters <i>et al</i> ^{14*}		
	Mortality (1950–2009)†		Cancer incidence (1985–2009)			Studies	SRE (95% CI), Likelihood rating	
	Obs	SMR (95% CI)	All cancers	First cancer	Obs			SIR (95% CI)
All cancers (C00–C97)	3285	1.14 (1.10 to 1.18)	4461	1.09 (1.06 to 1.12)	3890	1.09 (1.06 to 1.12)	25	1.05 (1.00 to 1.09), 3
MN oesophagus (C15)	113	1.39 (1.14 to 1.67)	90	1.62 (1.31 to 2.00)	80	1.71 (1.36 to 2.13)	8	1.16 (0.86 to 1.57), 3
MN stomach (C16)	110	1.10 (0.91 to 1.33)	93	1.15 (0.93 to 1.40)	72	1.02 (0.80 to 1.28)	13	1.22 (1.04 to 1.44), 2
MN intestine (C17–C18)	326	1.30 (1.16 to 1.44)	398	1.21 (1.09 to 1.33)	351	1.29 (1.16 to 1.43)	NA	NA
MN large intestine (C18)	264	1.31 (1.16 to 1.48)	381	1.21 (1.09 to 1.34)	335	1.28 (1.15 to 1.43)	25	1.21 (1.03 to 1.54), 2
MN small intestine (C17)	8	1.66 (0.72 to 3.27)	17	1.15 (0.67 to 1.85)	16	1.43 (0.82 to 2.33)	NA	NA
MN rectum (C19–C21)	89	1.45 (1.16 to 1.78)	166	1.11 (0.95 to 1.30)	140	1.09 (0.91 to 1.28)	13	1.29 (1.10 to 1.51), 2
MN lung (C33–C34)	1046	1.10 (1.04 to 1.17)	716	1.12 (1.04 to 1.21)	602	1.13 (1.04 to 1.22)	19	1.03 (0.97 to 1.08), 3
MN breast (C50)	8	1.39 (0.60 to 2.73)	26	1.26 (0.82 to 1.85)	24	1.32 (0.84 to 1.96)	NA	NA
MN prostate (C61)	282	1.09 (0.96 to 1.22)	1261	1.03 (0.98 to 1.09)	1176	1.03 (0.97 to 1.09)	13	1.28 (1.15 to 1.43), 1
MN other male genital (C60, C62–C63)	<5	0.47 (0.13 to 1.20)	17	0.62 (0.36 to 0.99)	17	0.67 (0.39 to 1.07)	NA	NA
MN testes (C62)	<5	0.73 (0.15 to 2.14)	15	0.75 (0.42 to 1.24)	15	0.79 (0.44 to 1.30)	4	2.02 (1.30 to 3.13), 2
MN kidney (C64–C66)	94	1.29 (1.05 to 1.58)	166	1.27 (1.09 to 1.48)	129	1.24 (1.04 to 1.48)	12	1.07 (0.78 to 1.46), 3
MN bladder (C67–C68)‡	84	0.99 (0.79 to 1.22)	316	1.12 (1.00 to 1.25)	272	1.18 (1.05 to 1.33)	11	1.20 (0.97 to 1.48), 3
MN brain (C47, C70–C72)	73	1.01 (0.79 to 1.27)	51	1.02 (0.76 to 1.34)	48	1.06 (0.78 to 1.41)	19	1.32 (1.12 to 1.54), 2
NHL (C46.3, C82–C85, C88.0, C88.3, C91.4, C96)§	123	1.17 (0.97 to 1.40)	170	0.99 (0.85 to 1.15)	145	0.99 (0.83 to 1.16)	8	1.51 (1.31 to 1.73), 1
Leukaemia (C91.0–C91.3, C91.5–C91.9, C92–C95)	122	1.10 (0.91 to 1.31)	100	0.94 (0.77 to 1.15)	85	0.93 (0.74 to 1.15)	8	1.14 (0.98 to 1.31), 2
Multiple myeloma (C88.7, C88.9, C90)	42	0.89 (0.64 to 1.20)	36	0.72 (0.50 to 0.99)	33	0.75 (0.52 to 1.06)	10	1.53 (1.21 to 1.94), 1
Other cancers:¶								
Mesothelioma (C45)	12	2.00 (1.03 to 3.49)	35	2.29 (1.60 to 3.19)	26	2.00 (1.31 to 2.93)	NA	NA
MN buccal and pharynx (C00–C14)	94	1.40 (1.13 to 1.72)	174	1.39 (1.19 to 1.62)	148	1.41 (1.20 to 1.66)	9	1.23 (0.96 to 1.55), 2

*Results from Table 5 of LeMasters *et al*¹⁴; likelihood of cancer risk by meta-analysis criteria: 1=probable, 2=possible, 3=unlikely.

†SMRs restricted to 1960–2009 for MN large intestine, MN small intestine, and MN testes and 2000–2009 for mesothelioma.

‡Urinary bladder incidence included in situ (D09.0) and invasive cases as per SEER protocol.

§NHL incidence data exclude Kaposi sarcoma (C46.3).

¶Sites not listed among cancers of a priori interest but reporting statistically significant excess mortality and cancer incidence.

ICD-10, International Classification of Diseases, 10th Revision; MN, malignancy; NA, not applicable; NHL, non-Hodgkin lymphoma; Obs, observed; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio; SMR, standardised mortality ratio; SRE, summary risk estimate.

0.65 to 0.80, $n=367$). Few non-malignant outcomes were elevated, although statistically significant excess mortality was observed for cirrhosis and other chronic liver disease (SMR=1.26, 95% CI 1.12 to 1.41, $n=299$) and acute glomerulonephritis with renal failure (SMR=1.56, 95% CI 1.07 to 2.20, $n=32$). Deaths from falls (SMR=1.31, 95% CI 1.08 to 1.58, $n=113$) and other accidents (SMR=1.17, 95% CI 1.01 to 1.34, $n=197$) were also elevated.

By contrast with non-malignant outcomes, we observed excess overall cancer mortality (SMR=1.14, 95% CI 1.10 to 1.18, $n=3285$) (table 2). The elevation was largely attributable to excess cancers of the lung (SMR=1.10, 95% CI 1.04 to 1.17, $n=1046$), oesophagus (SMR=1.39, 95% CI 1.14 to 1.67, $n=113$), intestine (SMR=1.30, 95% CI 1.16 to 1.44, $n=326$), rectum (SMR=1.45, 95% CI 1.16 to 1.78, $n=89$) and kidney (SMR=1.29, 95% CI 1.05 to 1.58, $n=94$). There was little evidence of excess mortality from the remaining cancers of a priori interest; however, statistically significant SMRs were apparent for buccal and pharynx cancers (SMR=1.40, 95% CI 1.13 to 1.72, $n=94$), malignancies of the liver, gall bladder and biliary tract (SMR=1.30, 95% CI 1.06 to 1.57, $n=107$), and malignant mesothelioma (SMR=2.00, 95% CI 1.03 to 3.49, $n=12$).

Women and non-Caucasians

All-cause mortality among women was near expectation (SMR=0.91, 95% CI 0.59 to 1.33, $n=26$). Accidental death was the leading cause (SMR=2.79, 95% CI 1.21 to 5.50, $n=8$) resulting in 31% of the total deaths among women. While there was little evidence of excess overall cancer mortality among women (SMR=0.74, 95% CI 0.27 to 1.61, $n=6$), most cancer deaths were from breast cancer (SMR=1.46, 95% CI 0.30 to 4.26, $n<5$). Bladder cancer mortality was statistically significant (SMR=33.51, 95% CI 4.06 to 121.05, $n<5$) based on few cases. Non-Caucasian males were characterised by decreased all-cause mortality (SMR=0.68, 95% CI 0.62 to 0.74, $n=453$) and all-cancers (SMR=0.80, 95% CI 0.65 to 0.97, $n=104$). They had few observed deaths in any a priori outcome, and lung cancer mortality was below expectation (SMR=0.67, 95% CI 0.44 to 0.97, $n=27$). Only prostate cancer mortality showed an excess approaching statistical significance (SMR=1.64, 95% CI 0.95 to 2.63, $n=17$) among non-Caucasian males (table 3).

Cancer incidence

There was little difference in SIRs when comparing analysis approaches; therefore, reporting focused on results from the multiple-cancer approach (table 2). All-cancer incidence was slightly above expectation (SIR=1.09, 95% CI 1.06 to 1.12, $n=4461$). Observed elevations in cancers of a priori interest were generally consistent with mortality data as evidenced by significant excess cancers of the oesophagus (SIR=1.62, 95% CI 1.31 to 2.00, $n=90$); large intestine (SIR=1.21, 95% CI 1.09 to 1.34, $n=381$); kidney (SIR=1.27, 95% CI 1.09 to 1.48, $n=166$) and lung (SIR=1.12, 95% CI 1.04 to 1.21, $n=716$). As in mortality analyses, there were excess buccal and pharynx cancers (SIR=1.39, 95% CI 1.19 to 1.62, $n=174$) and malignant mesothelioma (SIR=2.29, 95% CI 1.60 to 3.19, $n=35$). Of those diagnosed with mesothelioma, 31 (88.6%) were pleural. Excess laryngeal cancer incidence was also observed (SIR=1.50, 95% CI 1.19 to 1.85, $n=84$). The incidence of most remaining cancer sites was near expectation; however, multiple myeloma was significantly decreased (SIR=0.72, 95% CI 0.50 to 0.99, $n=36$).

Women and non-Caucasians

Overall cancer incidence among women was elevated, but not significantly (SIR=1.24, 95% CI 0.89 to 1.69, $n=40$). Consistent with mortality, female bladder cancer incidence was statistically significant but based on few cases (SIR=12.53, 95% CI 3.41 to 32.08, $n<5$). Nearly half of all cases were breast cancer (SIR=1.45, 95% CI 0.86 to 2.29, $n=18$). Nearly all breast cancers were diagnosed prior to the attained age of 55 years, with the highest SIR between the ages of 50 and 54 years (SIR=2.66, 95% CI 0.86 to 6.21, $n=5$). Left-sided disease appeared more frequent (61%, $n=11$). Overall cancer incidence among non-Caucasian male firefighters was near expectation (SIR=0.92, 95% CI 0.81 to 1.05, $n=240$). There was excess prostate cancer (SIR=1.26, 95% CI 1.02 to 1.54, $n=94$) but decreased lung cancer (SIR=0.67, 95% CI 0.43 to 1.00, $n=24$) (tables 3 and 4).

Sensitivity analyses

Except for COPD and cancers of the lung, prostate and brain, there was little evidence of heterogeneity in SMRs (see online supplementary table S6) or SIRs (see online supplementary table S7) across fire departments for outcomes of a priori interest. For mortality, the between-department variance was largely attributable to outlying decreased lung cancer (SMR=0.76, 95% CI 0.64 to 0.89, $n=142$) and COPD (SMR=0.53, 95% CI 0.40 to 0.69, $n=57$) in San Francisco firefighters, and excess cancers of the prostate (SMR=1.28, 95% CI 1.08 to 1.50, $n=152$) and lung (SMR=1.23, 95% CI 1.13 to 1.34, $n=566$) in Chicago firefighters. The between-department variance in mortality persisted when using state populations as referent (see online supplementary table S8). Similarly, heterogeneous lung cancer incidence stemmed from decreased cases among San Francisco firefighters (SIR=0.70, 95% CI 0.56 to 0.87, $n=81$); however, there was outlying excess prostate cancer incidence among San Francisco firefighters (SIR=1.22, 95% CI 1.08 to 1.37, $n=276$). Brain cancer SIRs varied widely across fire departments; excess cancer was observed in San Francisco firefighters (SIR=1.95, 95% CI 1.14 to 3.12, $n=17$), while decreased cancer was reported for Chicago (SIR=0.53, 95% CI 0.28 to 0.91, $n=13$).

Restricting analyses to firefighters with one or more years of employment had negligible effects (see online supplementary table S9). Slight increases in SMRs were observed for most a priori outcomes when restricting the cohort to incident hires, although these differences were not statistically significant. Age-at-risk differences in mortality also lacked statistical significance, but SMRs generally appeared greater at older ages. SMRs for cancers of the breast (SMR=1.42, 95% CI 0.46 to 3.32, $n=5$), oesophagus (SMR=1.41, 95% CI 1.05 to 1.86, $n=51$), and kidney (SMR=1.47, 95% CI 1.09 to 1.95, $n=48$) were highest among workers less than 65 years of age (see online supplementary table S10). Significant age-at-risk differences in SIRs were evident for prostate ($p<0.001$) and bladder ($p=0.002$) cancers (see online supplementary table S11). The heterogeneity was largely attributable to significant increases in prostate (SIR=1.21, 95% CI 1.10 to 1.33, $n=426$) and bladder (SIR=1.33, 95% CI 1.08 to 1.62, $n=97$) cancer risks among firefighter aged 64 years or less. Excess prostate cancer was limited to ages 45–59 years (SIR=1.45, 95% CI 1.28 to 1.64, $n=249$), while the age pattern of excess bladder cancer incidence was unclear. The effects of restricting PYAR to age-at-risk <85 were inconsequential (see online supplementary table S12). Excluding firefighters without race information also had little

Table 3 Standardised mortality and incidence ratios among men compared with the US population for causes of a priori interest

Underlying cause (ICD-10 codes)	Mortality (1950–2009)				Cancer incidence (1985–2009)*			
	Caucasian		Other		Caucasian		Other	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
All causes	11 549	1.01 (0.99 to 1.03)	453	0.68 (0.62 to 0.74)	NA	NA	NA	NA
All cancers (C00-C97)	3175	1.16 (1.12 to 1.20)	104	0.80 (0.65 to 0.97)	4181	1.10 (1.07 to 1.13)	240	0.92 (0.81 to 1.05)
MN oesophagus (C15)	110	1.46 (1.20 to 1.75)	<5	0.51 (0.11 to 1.49)	87	1.70 (1.36 to 2.09)	<5	0.73 (0.15 to 2.15)
MN stomach (C16)	105	1.12 (0.92 to 1.36)	5	0.81 (0.26 to 1.89)	87	1.19 (0.96 to 1.47)	6	0.76 (0.28 to 1.66)
MN intestine (C17-C18)	319	1.32 (1.18 to 1.48)	7	0.68 (0.27 to 1.40)	379	1.23 (1.11 to 1.36)	18	0.90 (0.53 to 1.42)
MN rectum (C19-C21)	86	1.46 (1.17 to 1.81)	<5	1.21 (0.25 to 3.53)	159	1.16 (0.99 to 1.36)	7	0.62 (0.25 to 1.28)
MN lung (C33-C34)	1019	1.12 (1.05 to 1.19)	27	0.67 (0.44 to 0.97)	689	1.15 (1.07 to 1.24)	24	0.67 (0.43 to 1.00)
MN breast (C50)	5	1.43 (0.46 to 3.34)	0	NC	6	0.79 (0.29 to 1.72)	<5	3.32 (0.40 to 12.00)
MN prostate (C61)	265	1.06 (0.94 to 1.20)	17	1.64 (0.95 to 2.63)	1167	1.02 (0.96 to 1.08)	94	1.26 (1.02 to 1.54)
MN other male genital (C60, C62-C63)	<5	0.49 (0.13 to 1.26)	0	NC	16	0.64 (0.37 to 1.04)	<5	0.38 (0.01 to 2.13)
MN kidney (C64-C66)	91	1.31 (1.05 to 1.60)	<5	1.05 (0.22 to 3.07)	151	1.26 (1.06 to 1.47)	14	1.46 (0.80 to 2.45)
MN bladder (C67-C68)†	80	0.96 (0.76 to 1.19)	<5	1.19 (0.14 to 4.30)	305	1.11 (0.99 to 1.24)	7	0.92 (0.37 to 1.91)
MN brain (C47, C70-C72)	72	1.03 (0.81 to 1.30)	<5	0.44 (0.01 to 2.47)	49	1.05 (0.78 to 1.39)	<5	0.67 (0.08 to 2.42)
NHL (C46.3, C82-C85, C88.0, C88.3, C91.4, C96)‡	119	1.18 (0.98 to 1.41)	<5	1.01 (0.28 to 2.60)	161	1.02 (0.87 to 1.19)	7	0.56 (0.23 to 1.16)
Leukaemia (C91.0-C91.3, C91.5-C91.9, C92-C95)	117	1.10 (0.91 to 1.32)	5	1.28 (0.41 to 2.98)	88	0.88 (0.71 to 1.09)	11	1.90 (0.95 to 3.40)
Multiple myeloma (C88.7, C88.9, C90)	41	0.92 (0.66 to 1.25)	<5	0.35 (0.01 to 1.97)	35	0.76 (0.53 to 1.06)	<5	0.24 (0.01 to 1.32)
COPD (J40-J44)	362	0.73 (0.65 to 0.81)	5	0.50 (0.16 to 1.16)	NA	NA	NA	NA

*Incidence results based on analysis of all invasive primary cancers (ie, multiple-cancer approach).

†Urinary bladder incidence included in situ (D09.0) and invasive cases as per SEER protocol.

‡NHL incidence data exclude Kaposi sarcoma (C46.3).

COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases, 10th Revision; MN, malignancy; NA, not applicable; NC, not calculated; NHL, non-Hodgkin lymphoma; Obs, observed; SIR, standardised incidence ratio; SEER, Surveillance, Epidemiology, and End Results; SMR, standardised mortality ratio.

Table 4 Standardised mortality ratios (US population referent) and rate ratios for select outcomes* by employment duration (lagged 10 years)

Underlying cause (ICD-10 codes)	Employment duration (years)								Trend slope†, p Value
	0-<10		10-<20		20-<30		30+		
	Obs	SMR (95% CI) SRR (95% CI)	Obs	SMR (95% CI) SRR (95% CI)	Obs	SMR (95% CI) SRR (95% CI)	Obs	SMR (95% CI) SRR (95% CI)	
MN oesophagus (C15)	13	1.17 (0.62 to 2.00) (Reference)	28	1.72 (1.14 to 2.48) 2.43 (1.07 to 5.50)	53	1.40 (1.05 to 1.83) 1.17 (0.56 to 2.41)	19	1.18 (0.71 to 1.84) 0.60 (0.27 to 1.35)	-2.14×10 ⁻⁶ , 0.141
MN stomach (C16)	12	0.80 (0.41 to 1.40) (Reference)	18	0.92 (0.54 to 1.45) 0.33 (0.08 to 1.43)	47	1.07 (0.79 to 1.43) 0.39 (0.10 to 1.55)	33	1.53 (1.06 to 2.15) 0.40 (0.10 to 1.58)	3.06×10 ⁻⁷ , 0.822
MN intestine (C17-C18)	27	0.86 (0.57 to 1.26) (Reference)	52	1.27 (0.95 to 1.67) 1.16 (0.38 to 3.54)	171	1.42 (1.22 to 1.65) 0.62 (0.27 to 1.44)	76	1.28 (1.01 to 1.60) 0.40 (0.17 to 0.94)	-7.54×10 ⁻⁶ , <0.001
MN rectum (C19-C21)	13	1.48 (0.79 to 2.54) (Reference)	19	1.58 (0.95 to 2.46) 0.99 (0.33 to 2.97)	37	1.35 (0.95 to 1.86) 0.61 (0.24 to 1.52)	20	1.52 (0.93 to 2.34) 0.43 (0.16 to 1.14)	-1.61×10 ⁻⁶ , 0.001
MN lung (C33-C34)	123	1.02 (0.85 to 1.22) (Reference)	184	1.03 (0.88 to 1.19) 1.32 (0.97 to 1.80)	523	1.14 (1.05 to 1.24) 1.24 (0.91 to 1.68)	216	1.12 (0.98 to 1.28) 0.80 (0.59 to 1.08)	-8.83×10 ⁻⁶ , 0.216
MN prostate (C61)	24	1.39 (0.89 to 2.07) (Reference)	23	1.08 (0.68 to 1.62) 0.66 (0.31 to 1.41)	148	1.10 (0.93 to 1.29) 0.84 (0.47 to 1.50)	87	1.01 (0.81 to 1.25) 0.69 (0.39 to 1.22)	-2.03×10 ⁻⁶ , 0.192
MN kidney (C64-C66)	12	1.10 (0.57 to 1.92) (Reference)	18	1.24 (0.73 to 1.95) 0.61 (0.26 to 1.48)	47	1.43 (1.05 to 1.90) 1.25 (0.58 to 2.69)	17	1.19 (0.69 to 1.91) 0.70 (0.29 to 1.67)	-1.05×10 ⁻⁷ , 0.924
MN bladder and other urinary (C67-C68)	8	1.05 (0.45 to 2.08) (Reference)	7	0.65 (0.26 to 1.34) 0.25 (0.08 to 0.79)	46	1.08 (0.79 to 1.45) 1.15 (0.49 to 2.70)	23	0.94 (0.60 to 1.41) 1.03 (0.38 to 2.83)	2.58×10 ⁻⁶ , 0.258
MN brain and other nervous (C47, C70-C72)	12	0.65 (0.34 to 1.13) (Reference)	15	0.88 (0.49 to 1.46) 0.80 (0.30 to 2.19)	32	1.17 (0.80 to 1.65) 1.48 (0.60 to 3.68)	14	1.47 (0.80 to 2.46) 1.52 (0.53 to 4.34)	1.01×10 ⁻⁶ , 0.118
NHL (C46.3, C82-C85, C88.0, C88.3, C91.4, C96)	18	0.98 (0.58 to 1.55) (Reference)	9	0.51 (0.23 to 0.96) 1.18 (0.41 to 3.45)	63	1.35 (1.04 to 1.73) 1.15 (0.60 to 2.22)	33	1.47 (1.01 to 2.06) 1.04 (0.51 to 2.15)	-7.39×10 ⁻⁸ , 0.849
Leukaemia (C91.0-C91.3, C91.5-C91.9, C92-C95)	18	0.91 (0.54 to 1.44) (Reference)	23	1.36 (0.86 to 2.05) 2.24 (0.92 to 5.50)	54	1.11 (0.83 to 1.45) 1.36 (0.65 to 2.87)	27	1.06 (0.70 to 1.54) 1.13 (0.48 to 2.67)	-5.10×10 ⁻⁹ , 0.997
Multiple myeloma (C88.7, C88.9, C90)	5	0.84 (0.27 to 1.96) (Reference)	<5	0.52 (0.14 to 1.34) 0.56 (0.11 to 2.82)	22	0.97 (0.61 to 1.47) 1.59 (0.47 to 5.41)	11	0.99 (0.49 to 1.77) 1.25 (0.33 to 4.75)	5.27×10 ⁻⁷ , 0.407
COPD (J40-J44)	33	0.78 (0.54 to 1.10) (Reference)	38	0.69 (0.49 to 0.94) 1.07 (0.60 to 1.91)	185	0.70 (0.60 to 0.81) 1.03 (0.67 to 1.60)	111	0.75 (0.62 to 0.91) 0.83 (0.53 to 1.31)	-2.80×10 ⁻⁶ , 0.005

*Excluding a priori causes with total observations <20.

†Cause-specific deaths per year of employment-person-year.

COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases, 10th Revision; MN, malignancy; NHL, non-Hodgkin lymphoma; Obs, observed; SMR, standardised mortality ratio; SRR, standardised rate ratio.

effect on a priori outcomes (results not shown). Finally, there was no apparent trend in increasing risk with employment duration; however, negative trends in COPD and colorectal cancer SRRs were evident (table 4). Subsequent sensitivity analyses revealed that SRRs were largely dependent on selection of cut-points and lag periods (results not shown).

DISCUSSION

This study is among the largest examining cancer risk in career firefighters. The pooled approach and long follow-up period improved risk estimates relative to previous studies. With few exceptions, there was little evidence of significant cancer risk heterogeneity across fire departments or age groups. Furthermore, sensitivity analyses did not suggest the potential for significant bias from including short-term workers, prevalent hires, or person-time in the open-ended age-group (85+ years). Despite notable differences in the analytical approaches, we observed remarkable similarities between mortality and incidence analyses. Additionally, the results of incidence analyses were not significantly affected by the choice of including multiple primaries or only the first cancer diagnosis. The lack of significant differences in results between fire departments, end-points, and analytic techniques suggest that the pooled study findings are robust and generalisable to similar firefighter populations.

We observed decreases in many non-malignant diseases that suggest improved health in these firefighters compared with the general population. This finding is not surprising given health requirements for entering and remaining in the fire service. Nevertheless, there was a modest excess in overall cancer mortality and incidence brought about by excess solid cancers at several sites of a priori interest. With few exceptions, our results are consistent with those previously reported and similar to SREs presented in the meta-analysis by LeMasters *et al.*¹⁴ Nevertheless, we found little evidence of excess cancers of the testes, brain and lymphohematopoietic systems, which is contrary to the synthesis by LeMasters *et al.*¹⁴ and subsequently published studies.^{8 11}

We observed about a twofold increase in malignant mesothelioma mortality and incidence compared with the US population. Malignant mesothelioma is largely attributable to asbestos exposure, with sparse evidence of other causes.²² Excess malignant mesothelioma in US firefighters was not previously described; however, excess incidence was recently observed in Nordic firefighters aged 70+ years,²³ and increased risk of asbestos-induced pulmonary and pleural fibrosis was reported in a study of New York City firefighters.²⁴ Although firefighter exposures to asbestos are known, the absence of previous reports of malignant mesothelioma is not surprising given the rarity and extremely long latency (20–40 years) of the disease. The average time between the date first employed and the date of diagnosis in the current study was 45 years; therefore, firefighting exposure-induced disease may be discernible only after lengthy follow-up. Also, previous studies have been hindered by the lack of specific codes for mesothelioma deaths before ICD-10.

We observed excess digestive cancers, mainly of oesophageal and colorectal sites. Information on occupational causes is sparse, although there is limited evidence suggesting asbestos and diesel exhaust exposures may be weakly associated with gastrointestinal cancers.^{25 26} Still, the relation between these hazardous exposures and digestive cancers appears small compared to the effects of other factors such as diet, obesity, physical activity, tobacco use and alcohol consumption.^{22 27} We also

found increased risk of oral, pharyngeal and laryngeal cancers, compared with the US population. Similar to digestive cancers, important risk factors for these sites are tobacco and alcohol consumption, with lesser evidence that exposures to wood dusts, smoke, asbestos, PAHs and acid mists may also increase risk.^{22 28 29}

Some insight into the degree of a potential bias from the lack of controlling for lifestyle factors can be gained from previous surveillance of firefighter behaviours. For example, the prevalence of smoking among current firefighters appears less than the general population, and is decreasing,^{30–33} a trend that is consistent with observed decreases in non-malignant smoking-related diseases (eg, COPD, stroke) but contradictory to excess digestive, oral and respiratory cancers. As another example, previous studies suggest there is increased obesity among firefighters compared with the general population.^{34–36} Obesity, or a dietary intake that is high in meat, fat, or overall caloric intake could contribute increased gastric or colorectal cancer risk, although concomitant elevations in health outcomes that are more strongly related to these factors (eg, ischaemic heart disease, diabetes mellitus, hypertension and stroke) were not found. Last, information on alcohol consumption within the fire service is sparse and inconsistent.^{37–40} Some studies suggest that firefighter behaviours may differ from the general population, although it is not clear that any perceived behavioural difference is sufficient to explain disparities in alcohol-related health outcomes. In the current study, the information on non-malignant and potentially alcohol-related mortality was at conflict; there was excess mortality from cirrhosis and other chronic liver disease, but fewer than expected alcoholism deaths. Alternate explanations for increased cirrhosis mortality may be exposures to chemical toxins or infectious disease,^{41–43} which may also account for excess acute renal dysfunction, a disease that is more common among those with chronic liver disease.

Fewer than 4% of firefighters in our study were women. There was evidence of excess female bladder and breast cancers; however, only bladder cancer mortality and incidence reached statistical significance. Modest excess bladder cancer has been observed in some occupations involving known or suspected bladder carcinogens (eg, PAHs, and diesel exhaust), yet contrary to our findings, risk patterns by occupation tend not to differ by gender.²² There is little evidence linking female breast cancer to workplace exposures; however, prolonged shift work may be a risk factor (and to a lesser extent a risk factor for prostate, colon and endometrial cancers).² Moreover, similar findings had not been reported previously, although increased risk of Hodgkin lymphoma and cancers of the cervix and thyroid among women firefighters (n=2017) was recently described.¹¹ Given the small sample and the lack of confirmatory results, our findings on female outcomes merit cautious interpretation.

Excess bladder and prostate cancer incidence was found among firefighters less than 65 years of age. Interestingly, the prostate cancer excess was limited to ages between 45 years and 59 years, which was consistent with recent observations in Nordic firefighters.²³ Similar mortality patterns were not observed. These cancers have relatively high survival; therefore, the underlying cause of death may be an inferior risk measure compared to cancer diagnoses. The early onset of these cancers suggests an association with firefighting. Prostate and bladder cancer diagnoses can occur following routine screening.^{44 45} As an alternative explanation, differences in medical screening (eg, prostate-specific antigen tests) among firefighters compared to the general population could have contributed to the observed excess. Data on cancer screening practices are lacking; however,

it is plausible that screening may be more frequent among firefighters with improved healthcare availability and heightened cancer awareness.

There was little evidence of increasing cancer risk with increasing employment; however, there were notable analytical shortcomings that merit discussion. First, rather than specifying cut-points and an exposure lag period specific to each outcome, we applied cut-points (10, 20 and 30 years) used in earlier studies^{5 9 46} and a common exposure lag period (10 years) to all outcomes; these choices were found to be influential in subsequent sensitivity analyses. Second, our methods have limited capability to account for HWE or other sources of bias that may have masked a dose response. Last, employment duration may poorly represent exposure potential given that some jobs are prone to lower exposures compared with others. For these reasons, a detailed exposure assessment is underway to support multivariable regression modelling for improved dose-response analyses.

Death certificates and registry data used in the current study are imperfect measures of cancer risk. In the absence of a national cancer registry, coverage is limited geographically; therefore, cases occurring outside catchment areas would be missed. Cases occurring before the registries attained comprehensive coverage have also been missed. Mortality analyses have the advantage of broader temporal and spatial coverage, but may poorly characterise cancers with relatively high survival (eg, cancers of the breast, bladder, testes and larynx). Finally, there may have been errors in tracing which can also bias study results. Although errors in ascertainment cannot be ruled out, our use of multiple information sources and end points, and the low numbers of participants lost to follow-up or moving out of catchment areas, act to minimise these errors.

CONCLUSION

In this first phase of examining health effects in career firefighters, we report on mortality and cancer incidence among nearly 30 000 career firefighters followed from 1950 through 2009. Compared with the US population, we found small to moderate increases in risk for several cancer sites and for all cancers combined, stemming mostly from excess malignancies of the respiratory, digestive and urinary systems in otherwise healthy individuals. Our findings are consistent with previous studies and strengthen evidence of a relation between firefighters' occupational exposure and cancer. We found a previously unreported twofold excess of malignant mesothelioma among firefighters. Given that asbestos is the only known causal agent for malignant mesothelioma, and firefighter exposures are probable, the excess is likely to be a causal association.

This report provides the foundation for subsequent analyses of firefighter risks, some of which are ongoing. In upcoming research, detailed employment histories (eg, number and types of fire runs) and institutional knowledge (eg, use of respiratory protection and source capture ventilation of diesel exhaust) will be used to derive exposure metrics to more accurately examine dose response. Future regression modelling will also enable examination of temporal effects that are poorly suited to life-table analyses, such as time since first exposure. Expansion and continued follow-up of this cohort would enhance future analyses, particularly among women and non-Caucasian firefighters.

Acknowledgements This study was made possible through the continued cooperation of the men and women serving the Chicago, Philadelphia and San Francisco fire departments. We especially wish to acknowledge those who provided key assistance: Chicago (José Santiago, Tom Ryan, John McNalis, Mark Edingburg, Hugh Russell and Richard Edgeworth); Philadelphia (Lloyd Ayers, Henry

Costo, William Gault and Thomas Garrity); San Francisco (Joanne Hayes-White, Ginny Franklin, Tom O'Connor, Rhab Boughn and Tony Stefani); and within the US Fire Administration (William Troup and Glenn Gains). We acknowledge NIOSH staff and their contractors for contributing to the collection, coding and management of study data. We also wish to thank Grace LeMasters and Paul Demers for their valued counsel during manuscript development.

Contributors RDD participated in design, data collection, analysis and manuscript development. TLK conceived the study and participated in design and data collection. JHY participated in design, data collection and analysis. MMD, TRH, DB, SHZ, JJB and KMW participated in design and data collection. LEP participated in design and critical appraisal. All authors participated in the interpretation and presentation of results and have read and approved the final manuscript.

Funding Research funding was provided by the National Institute for Occupational Safety and Health (NIOSH) by intramural award under the National Occupational Research Agenda (NORA), and by the US Fire Administration (USFA). This research was also supported, in part, by the intramural research programme of the National Institutes of Health (NIH), National Cancer Institute (NCI).

Competing interests None.

Ethics approval This research was approved by the Institutional Review Boards of the National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI). Approvals for cancer registry access were granted by 11 states (ie, Arizona, California, Florida, Illinois, Indiana, Michigan, Nevada, New Jersey, Oregon, Pennsylvania and Washington). Approvals were also granted by vital records centres for death certificates maintained in 25 states (Alaska, Arizona, Arkansas, California, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Massachusetts, Michigan, Minnesota, Mississippi, New Jersey, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Virginia, Washington and Wisconsin). The state public health entities provided vital status information in accordance with state policies, and disclaim responsibility for any analyses, interpretations, or conclusions herein.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data were supplied by the Illinois Department of Public Health and the Bureau of Health Statistics and Research, Pennsylvania Department of Health. These public health entities specifically disclaim responsibility for any analyses, interpretations, or conclusions. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDS) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDS or FDOH. The collection of cancer incidence data used in this study was also supported by the California Department of Public Health as part of the statewide cancer reporting programme mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centres for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centres for Disease Control and Prevention or their contractors and subcontractors is neither intended nor to be inferred.

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