Cancer incidence and mortality among firefighters

Hamed Jalilian[1], Mansour Ziaei[2], Elisabete Weiderpass[3,4,5,6], Corina Silvia Rueegg[7], Yahya Khosravi[8]*, Kristina Kjaerheim[4]

[1] Department of Occupational Health and Safety, Faculty of Health, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2] School of Health and Nutrition, Bushehr University of Medical Sciences, Bushehr, Iran
[3] Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
[4] Department of Research, Cancer Registry of Norway - Institute of Population-Based Cancer Research, Oslo, Norway
[5] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[6] Genetic Epidemiology Group, Folkhälsan Research Center, and Faculty of Medicine, Helsinki University, Helsinki, Finland
[7] Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital and Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway
[8] Department of Occupational Health and Safety, Research Center for Health, Safety and Environment, Alborz University of Medical Sciences, Karaj, Iran

Corresponding author at:
Department of Occupational Health and Safety, Research Center for Health, Safety and Environment, Alborz University of Medical Sciences, Karaj, Iran.
E-Mail: yakhosravi@yahoo.com, Tel & Fax: +98 26 34643922

Word count body of the text from Introduction to Discussion/Conclusions): 3550
Keyword: firefighter, firefighting, cancer, review, meta-analysis

Mean text abbreviations:
95% confidence intervals (CI)
International classification of disease (ICD-9)
Meta-relative risks (MRR)
Newcastle-Ottawa Scale (NOS)
Non-Hodgkin lymphoma (NHL)
Odds ratio (OR)
Personal protective equipment (PPE)
Polycyclic aromatic hydrocarbons (PAHs)
Proportional mortality ratio (PMR)
Relative risk (RR)
Standardized incidence ratio (SIR)
Standardized mortality ratio (SMR)
Summary incidence risk estimates (SIRE)
Summary mortality risk estimates (SMRE)
Summary risk estimates (SRE)
The International Agency for Research on Cancer (IARC)

Article category: Cancer epidemiology

Novelty and impact

Firefighters are exposed to high levels of carcinogens during their work. Results regarding the impact of these exposures on cancer risk and mortality have been inconsistent, however. In this meta-analysis, the authors found that firefighters have a significantly elevated risk of developing a number of cancers (colorectal, prostate, testicular, bladder, thyroid, and pleural cancers and malignant melanoma), while mortality rates are increased for rectal cancer and non-Hodgkin's lymphoma. These results suggest that improved preventive measures and medical attention are needed for this group worldwide..

Abstract

Firefighters are exposed to both known and suspected carcinogens. This study aims to systematically review the literature on the association of firefighting occupation and cancer incidence and mortality, overall and for specific cancer sites. A systematic review using PubMed, Embase, and Web of Science was performed up to January 1, 2018. We extracted risk estimates of cancers and calculated summary incidence risk estimates (SIRE), summary mortality risk estimates (SMRE), and their 95% confidence intervals (CI). Publication bias and risk of bias in individual studies were assessed using Begg's and Egger's tests and the Newcastle-Ottawa scale (NOS), respectively. We included 50 papers in the review and 48 in the meta-analysis. We found significantly elevated SIREs for cancer of the colon (1.14; CI 1.06 to 1.21), rectum (1.09; CI 1.00 to 1.20), prostate (1.15; CI 1.05 to 1.27), testis (1.34; CI 1.08 to 1.68), bladder (1.12; CI 1.04 to 1.21), thyroid (1.22; CI 1.01 to 1.48), pleura (1.60; CI 1.09 to 2.34), and for malignant melanoma (1.21; CI 1.02 to 1.45). We found significant SMREs of 1.36 (1.18 to 1.57) and 1.42 (1.05 to 1.90) for rectal cancer and Non-Hodgkin's lymphoma, respectively. Considering the significantly elevated risk of some cancers in this occupational group, we suggest improving preventive measures and securing adequate and relevant medical attention for this group. Further studies with more accurate and in-depth exposure assessments are indicated.

1. Introduction

Firefighters are exposed to both known and suspected carcinogens during their work. Although exposure is often for short periods of time, exposure levels can be high [1]. Studies on the chemistry of fire showed toxic levels of hazardous substances, such as acetaldehyde, formaldehyde, sulfur dioxide, benzene, toluene, and ethylbenzene amongst other substances in the smoke during the knockdown and overhaul firefighting phases [2-5], and in structural fires [6] as well as in vehicle fires [7]. In addition to direct exposure to the carcinogenic smoke, firefighters' personal protective equipment (PPE) and other work equipment can be a source of occupational hazardous substances exposures. Studies reported accumulation of plasticizers [8], metals [9], and polycyclic aromatic hydrocarbons (PAHs) [1] on firefighter's PPE and other work equipment.

The exposure of firefighters to these carcinogens was supported by analysis of their blood and urine profiles. Studies reported high levels of dioxin-like compounds in the blood of firefighters compared to those of the general population [10, 11]. Urine analyses have found elevated levels of 1-hydroxynaphthalene and 1-hydroxyacenaphthene (the predominant metabolites of PAHs) [5], and indicators of exposure to benzophenone-3, bisphenol-A, triclosan, and methylparaben [12] in active firefighters.

A number of studies have examined cancer incidence and mortality among firefighters [13]. Results have been inconsistent, but generally indicating elevated risk at least of some cancer types. The most recent meta-analysis by LeMasters et al. (2006) reported elevated summary risk estimates (SRE,- pooled cancer incidence and cancer mortality risk estimates), for multiple myeloma, non-Hodgkin lymphoma (NHL), prostate cancer, and testicular cancer [14]. Another review of selected malignancies reported an increased summary relative risk for kidney, brain, and bladder cancer as well as NHL [15].

The International Agency for Research on Cancer (IARC) evaluated the scientific literature in 2010, and concluded in classifying the firefighting occupation as possibly carcinogenic to humans (Group 2B) [16].

Some quantitative reviews have been carried out since 2010 [16, 17], but, to the best of the authors' knowledge, no complete peer-reviewed meta-analysis has been published since the systematic review of LeMasters et al. in 2006. Furthermore, none of the previous meta-analyses has stratified their results by cancer incidence and cancer mortality, even though risk factors for these different measures of disease burden might differ. We, therefore, aimed to systematically review the literature on the association between firefighting occupation and cancer incidence and mortality and estimate the effect of firefighting occupation on cancer incidence and mortality, overall and stratified by type of cancer.

2. Methods

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines (Table S1, supplementary file) [18].

2.1. Eligibility criteria

We included original articles published in English by 01.01.2018 in peer-reviewed journals that investigated the association of firefighting occupation with any type of cancer risk or cancer mortality in humans. The studies needed to report a relative risk (RR), odds ratio (OR), standardized incidence ratio (SIR), or standardized mortality ratio (SMR) with 95% confidence intervals (CI) or provide sufficient data to calculate them. We only included studies where the exposure clearly preceded the outcome and firefighting occupation was compared to the general population, other occupations or internal comparison was done. We excluded studies on volunteer or trainee firefighters, and those reporting effect size on cancers in organ systems of the body only, such as respiratory, urinary, or genital system. Furthermore, studies reporting the proportional mortality ratio (PMR) only were included in the qualitative synthesis but not the quantitative [19].

2.2. Search strategy

We searched the electronic databases Web of Science, PubMed, and Embase with adapted search terms for each database. The search term included two categories of words: 1) keywords for the target occupation (firefighter) and 2) keywords for the outcome (cancer risk or cancer mortality) (Table S2, Supplementary material). To ensure literature saturation, the investigators manually searched through Google Scholar and screened the references of relevant original studies or review articles.

2.3. Study selection

Study selection was performed by two independent researchers (HJ and MZ) by first screening the titles, abstracts, and keywords, and then screening the full texts. The proportion of agreement between the two researchers was calculated for each selection process. A third researcher (YKH) was included in the decision-making process, whenever HJ and MZ were not able to reach an agreement.

2.4. Data extraction

Data extraction was performed by one researcher (HJ) and double-checked by another researcher (MZ). For each study, a risk estimate on the association of firefighting occupation and cancer incidence and/or cancer mortality and its 95% CIs was obtained from the maximally adjusted model (overall and for individual cancer sites, if reported): ORs, SIRs, RRs, or SMRs. In addition we extracted the following variables: authors' names, year of publication, country, time period of case ascertainment, sample size, number of cases, level of adjustment, study design, type of effect estimate, cancer classification code (outcome), source of outcome data, studied occupation (i.e. whether the study investigated only firefighters or several occupations), source of occupational information, occupational coding system, source of control population, and information assessed on exposure to carcinogenic agents.

Classification of the cancer types was adapted to the ninth revision of the version of the international classification of disease (ICD-9) (Appendix I, Supplementary material). In addition, we extracted estimates on colorectal cancers and malignant melanoma and other skin cancer combined. We aggregated risk estimates on single cancer sites using the method from Hamling et al. [20].

If the data was overlapping between publications, the publication with more complete or more extensive data was included in the systematic review and meta-analysis.

Due to a limited number of female firefighters, effect sizes of male firefighters were extracted or effect sizes of both sexes combined if not reported for men individually.

2.5. Risk of bias in individual studies

Two researchers (HJ and MZ) independently assessed the quality of case-control and cohort studies using the Newcastle-Ottawa scale (NOS) [21]. This scale contains eight items within three categories: selection (four items, one point each), comparability (one item, up to two points), and exposure/outcome (three items, one point each). The sum of points indicates the methodologic quality of each individual study included, with nine points representing the highest quality and zero points the lowest quality, respectively. In the case of disagreement between two researchers, a third party (YKH) settled the case by discussion among the researchers until an agreement was reached.

2.6. Statistical analysis

We performed random-effects meta-analyses overall and stratified by cancer type for the risk estimate on the association between firefighter occupation and cancer incidence and cancer mortality. Summary incidence risk estimates (SIREs) and summary mortality risk estimates (SMREs) were calculated for each cancer outcome by pooling risk estimates (SIRs, ORs, and RRs) and mortality estimates (SMRs, ORs, RRs), respectively. The logarithm of SMR, SIR, RR, and OR and their standard errors were used for these analyses. Heterogeneity between studies was tested with the Q-test [22]. The I^2-index was used to quantify the extent of heterogeneity and we interpreted a value between 25-49% as low heterogeneity, a value between 50-74% as moderate and a value ≥75% as high heterogeneity. [23].

We used the forest plot to display the summary estimates overall and stratified by cancer type. Publication bias was assessed by the Begg's test and the Egger's test for each type of cancer. All analyses were conducted using the STATA 14 (Stata Corp, College Station, TX).

We used a modified method described by LeMasters et al. [14] for the overall evaluation of the association of firefighting on cancer incidence and mortality. The strength of the association was classified into "probable", "possible", or "unlikely" for each cancer, based on the two criteria: pattern of meta-relative risks (MRR: i.e. SIREs and SMREs), and consistency between studies (Appendix II, Supplementary material).

3. Results

3.1. Study selection

We identified 2,635 articles with our research of which 947 were duplicates (Figure 1). We excluded 1,580 records by screening titles and abstracts (agreement = 85%) and another 58 (agreement = 95%) when looking at the full-texts. Two studies only reported PMR risk estimate

[24, 25], resulting in 50 [13, 24-72] studies included in the qualitative synthesis and 48 studies in the quantitative (Table S3 and S4, Supplementary material).

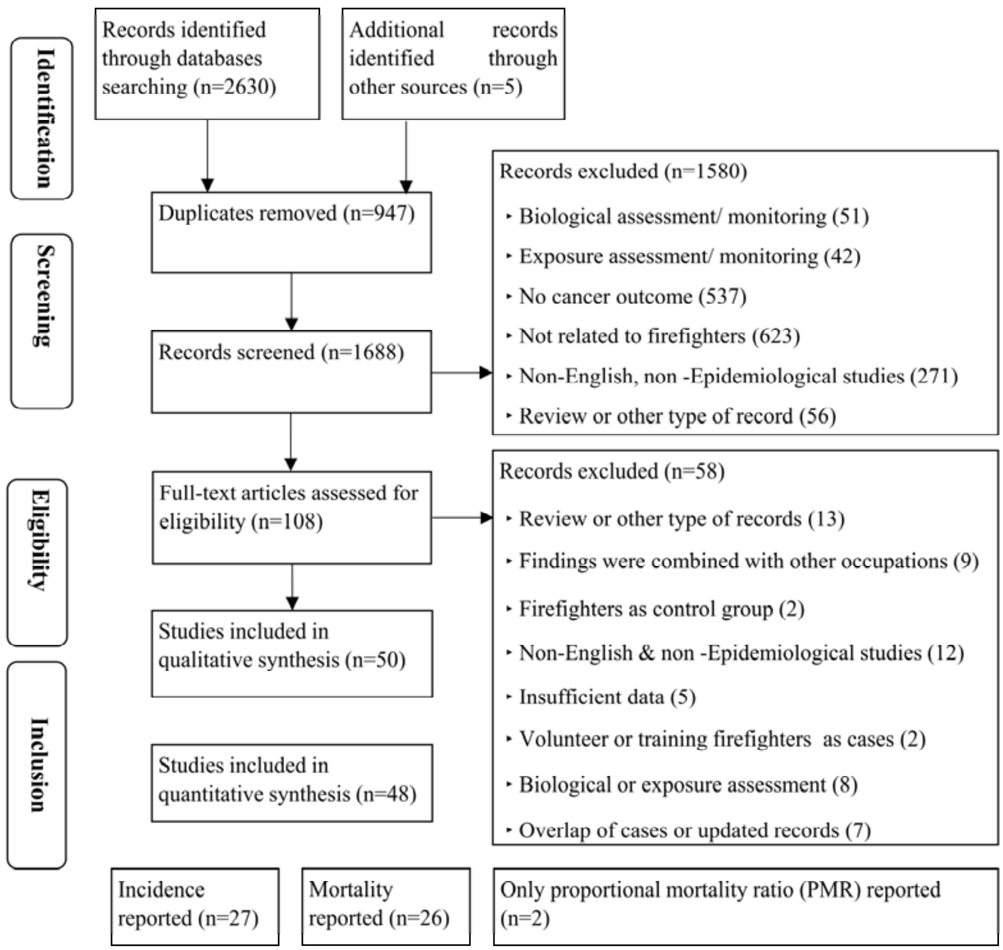

Figure 1. PRISMA flow diagram of article screening and selection in the qualitative and quantitative sections

3.2. Characteristics of studies reporting cancer incidence

A total of 27 studies have investigated the association between cancer incidence and firefighting occupation (Table 1). Of these, 13 were case-control (48%), and 14 were cohort (52%) studies. The studies were conducted in 11 countries, dominantly in the USA (41%). Time period of case ascertainment was between 1950 and 2014 with a maximum of 30057 firefighters included.

Several studies have used more than one source to collect information on cancer incidence but the most dominant source was cancer registries (21 studies). Classification of cancer disease was based on the ICD (44%), ICD for oncology (30%) and the surveillance, epidemiology, and end results (SEER) programme (4%). The studies on cancer incidence have used interviews/questionnaires, censuses, civil registration system, employment records, tumor registry database, and hospital records to collect occupational information. Firefighting was the target occupation in 15 studies while 12 studies have studied several occupations. Studies considered the duration of employment (42%), calendar periods (15%), age (18%), task or activity within employment (7%), and time since employment (7%) as exposure categories. The studies have dominantly used national, regional, or local populations as comparison groups. Different confounders were considered in the maximally adjusted models as presented in Table 1. It should be noted that a minor overlap between study subjects was observed among three Nordic cohort studies between 2014 and 2017.

Table 1. Characteristics of studies reporting on firefighting and cancer incidence

First author, Year (Ref)	**Country**	**Time period**	**Sample size (case)**	**Study design**	**Source of cancer data**	**Cancer classification**	**Source of occupation data**	**Studied occupation**	**Exposure categories**	**Occupation identifier**	**Comparison group**
Sama, 1990 [33]	USA	1982–1986	29990 (321)	Case-control	Tumor registry	ICD for oncology	Tumor registry	Firefighters	OT, AS	CCP	Regional employees, policemen
Delahunt, 1995 [42]	New Zealand	1978-1986	13467 (710)	Case-control	Tumor registry	ICD	Tumor registry	Multi occupations	OT	NSCO	Other diseases and cancers
Krstev, 1998 [47]	USA	1986-1989	2296 (981)	Case-control	Tumor registry	NR	Interview/ questionnaire	Multi occupations	OT, DoE	SOC	LP
Elci,	Turkey	1979-1984	2873	Case-	Hospital records	ICD for	Interview/	Multi	OT	SOC	Other cancers

2003 [51]			(1354)	control		oncology	questionnaire	occupations			
Krishnan, 2003 [52]	USA	1991-1994 & 1997-1999	1743 (879)	Case-control	Tumor registry	ICD for oncology	Interview/ questionnaire	Multi occupations	OT	SOC	Other cancers
Stang, 2003 [53]	German	1995-1997	1066 (269)	Case-control	Department(s) information, A reference pathologist	NR	Interview/ questionnaire	Firefighters	OT, DoE	ISCO	LP, internal
Gaertner, 2004 [54]	Canada	1994-1997	3734 (887)	Case-control	Tumor registry	NR	Interview/ questionnaire	Multi occupations	OT, DoE	SOC	RP
Kang, 2008 [58]	USA	1987-2003	161778 (2125)	Case-control	Tumor registry	ICD for oncology	Tumor registry	Firefighters	OT, AS	Tumor registry	Policemen, Other cancers
Corbin, 2011 [59]	New Zealand	2007-2008	1249 (457)	Case-control	Tumor registry	NR	Interview/ questionnaire	Multi occupations	OT	NSCO	NP
Karimi, 2012 [62]	USA	2002-2007	2452 (1217)	Case-control	Tumor registry	ICD for oncology	Interview/ questionnaire	Multi occupations	OT, DoE	SOC	NP
Paget-bailly, 2013 [63]	France	2001-2007	4580 (1833)	Case-control	Tumor registry	ICD for oncology	Interview/ questionnaire	Multi occupations	OT, DoE	ISCO	LP
Tsai, 2015 [68]	USA	1988–2007	678132 (3996)	Case-control	Tumor registry	SEER	Tumor registry	Firefighters	OT	CCP	Other cancers
Sritharan, 2017 [72]	Canada	1994-1997	3540 (1737)	Case-control	Tumor registry	ICD for oncology	Interview/ questionnaire	Multi occupations	OT, DoE	NSCO	RP
Morton, 1984 [29]	USA	1963-1977	1678	Cohort	Hospital records, DC	NR	Hospital records, DC	Multi occupations	OT	CCP	LP
Giles, 1993 [37]	Australia	1980-1989	2865	Cohort	Tumor registry	ICD	ERs	Firefighters	OT, DoE, AS, TSE	ERs	RP
Demers, 1994 [40]	USA	1974-1989	4325 (2447)	Cohort	Tumor registry	ICD	ERs	Firefighters	OT, DoE, TSE	ERs	LP, policemen
Firth, 1996 [46]	New Zealand	1972-1984	26207	Cohort	Tumor registry	ICD	Tumor registry	Multi occupations	OT	NSCO	NED
Bates*,	New	1977-1995	8040	Cohort	Health information	ICD	ERs	Firefighters	OT, CP	ERs	NP

2001 [50]	Zealand		(4305)		services						
Zeegers, 2004 [55]	Netherlands	1986-1993	2355 (830)	Cohort	Tumor registry	NR	Interview/ questionnaire	Multi occupations	OT, DoE	NSCO	NP
Ma, 2006 [57]	USA	1981-1999	36813 (1022)	Cohort	Department(s) information	ICD	ERs	Firefighters	OT	ERs	RP
Zeig-Owens, 2011 [60]	USA	1996-2001	9853	Cohort	Tumor registry, Health information services	ICD for oncology	ERs	Firefighters	OT	ERs	NP
Ahn, 2012 [61]	South Korea	1980-2007	33416 (29438)	Cohort	Tumor registry	ICD	ERs	Firefighters	OT, DoE	Organizational Classification	Organizational employees
Daniels*, 2014 [64]	USA	1950-2009	29993	Cohort	DC, ERs	ICD	ERs	Firefighters	OT, DoE	ERs	NP
Pukkala, 2014	Nordic countries	1961–2005	16422	Cohort	Tumor registry	ICD	Census	Firefighters	OT, AS, CP	ISCO	NP
Glass*, 2016 [69]	Australia	1976-2011	30057	Cohort	Tumor registry, DC	ICD	ERs	Firefighters	OT, DoE, TADE	ERs	NP
Kullberg, 2017 [70]	Sweden	1951-1983	1080	Cohort	Tumor registry	ICD	ERs	Firefighters	OT, DoE, AS, CP	ERs	RP
Petersen, 2017 [71]	Denmark	1968-2014	9061	Cohort	Tumor registry	ICD	Civil Registration System	Firefighters	OT, DoE, CP, TADE	Registration systems	NP, Regional employees, military

*reported cancer incidence and mortality estimates.

Abbreviations: AS, age-specific; CCP, codes of census population; CP, calendar periods; DC, death certificate; DoE, duration of employment; ERs, employment records (including pension records, enrolment records, fire department records, Employee Service Record, payroll records); ICD, international calcification of disease; ICD-O, international classification of disease for oncology; ISCO, international standard classification of occupations (ILO codes); LP, local population; NED, national employment database; NP, national population; NR, not reported; NSCO, national standard classification of occupations; OR, odds ratio; OT, occupational title; RP, regional population; RR, rate ratio (relative risk); SEER, the surveillance, epidemiology, and end results (program); SIR, standardized incidence ratio; SmOR, standardized morbidity odds ratio; SOC, U.S. department of commerce codes -standard occupational classification; TADE, task or activity during of employment; TSE, time since employment; USA, United States of America

3.3. Characteristics of studies reporting cancer mortality

A total of 26 articles investigated the association between firefighting and cancer mortality (Table 2). Of these, 21 were based on cohorts (81%), three were case-control (11%), and two were PMR studies (8%) studies. The studies were carried out in 14 countries, with the majority in the USA (54%). Time-period of case ascertainment was between 1921 and 2011 with a maximum of 30057 firefighters. All studies except one completely or partly extracted the outcome data from death certificates, and all (except four who did not report on this) of them used the ICD (version 7 to 10 and oncology version) to classify the cancer outcome. In addition, in 19% of studies, the death certificates also were used as a source of occupational data. Most of the remaining studies have extracted this information from employment records (73%). Of the 26 studies, 21 have investigated only firefighters and five have studied several occupations including firefighters. In addition, they analyzed the data based on the duration of employment (48%), calendar periods (15%), age (15%), task or activity within the employment (12%), time since employment (11%), and status of employment (4%). The studies used dominantly national, regional, or local populations as comparison groups. Again, different covariates were considered in the maximally adjusted model as presented in Table 2.

Table 2. Characteristics studies reporting on firefighting and cancer mortality

First author, Year (Ref)	**Country**	**Time period**	**Sample size (cases)**	**Study design**	**Source of cancer data**	**Cancer classification**	**Source of occupation data**	**Studied occupation**	**Exposure categories**	**Occupation identifier**	**Comparison group**
Feuer, 1986 [24]	USA	1974-1980	901 (271)	PMR	DC -nosologist	ICD	ERs	Multi occupations	OT, DoE	ERs	RP, NP, policemen
Burnett, 1994 [25]	USA	1984–1990	5744	PMR	DC	ICD	DC	Firefighters	OT	DC	internal

Figgs, 1995 [44]	USA	1984-1989	143340 (23890)	Case-control	DC	ICD	DC	Multi occupations	OT	SOC	Other disea
Finkelstein, 1995 [45]	Canada	1979-1988	3788 (967)	Case-control	DC	NR	DC	Multi occupations	OT	SOC	Other disea and cancer
Ma, 1998 [48]	USA	1984-1993	6607 (1883)	Case-control	DC	NR	DC	Firefighters	OT	CCP	internal, O diseases an cancers
Mastromatteo, 1959 [13]	Canada	1921-1953	1039	Cohort	DC	NR	ERs	Firefighters	OT	ERs	RP
Berg, 1975 [26]	USA, UK	1949-1953, 1959-1963	NR	Cohort	DC	NR	DC	Multi occupations	OT	CCP	NP
Musk, 1978 [27]	USA	1915-1975	5655	Cohort	DC	ICD	ERs	Firefighters	OT, SoE	ERs	RP, NP
Eliopulos, 1984 [28]	Australia	1939-1978	990	Cohort	DC	ICD	ERs	Firefighters	OT	DC	RP
Blair, 1985 [30]	USA	1954-1970	293958	Cohort	DC	ICD	Interview/ questionnaire	Multi occupations	OT	CCP	Internal
Vena, 1987 [31]	USA	1950-1979	1867	Cohort	DC -nosologist	ICD	ERs	Firefighters	OT, DoE, CP	ERs	NP
Hansen, 1990 [32]	Denmark	1970-1980	48580 (886)	Cohort	DC	ICD	census	Firefighters	OT, AS	Census	Internal, N
Beaumont, 1991 [34]	USA	1940-1970	3066	Cohort	DC -nosologist	ICD	ERs	Firefighters	OT, DoE, TSE	ERs	NP
Grimes, 1991 [35]	USA	1969-1988	205	Cohort	DC	ICD	ERs	Firefighters	OT	DC	RP
Demers, 1992 [36]	USA	1945-1989	8077 (4401)	Cohort	DC	ICD	ERs	Firefighters	OT, DoE, AS, TSE	ERs	NP, policer
Guidotti, 1993 [38]	Canada	1927-1987	3328	Cohort	DC -nosologist	ICD	ERs	Firefighters	OT, DoE, CP	ERs	RP
Aronson, 1994 [39]	Canada	1950-1989	5414	Cohort	DC- nosologist	ICD	ERs	Firefighters	OT, DoE, TSE, AS	ERs	LP

Tornling, 1994 [41]	Sweden	1931-1983	1116	Cohort	Tumor registry, DC	ICD	ERs	Firefighters	OT, DoE, AS, TADE	ERs	RP
Deschamps, 1995 [43]	France	1977-1991	830	Cohort	DC - nosologist	ICD	ERs	Firefighters	OT	ERs	NP
Baris, 2001 [49]	USA	1925-1986	7789	Cohort	DC	ICD	ERs	Firefighters	OT, DoE, CP, TADE	ERs	NP, interna NED
Bates*, 2001 [50]	New Zealand	1977-1995	8040 (4305)	Cohort	Health information services	ICD	ERs	Firefighters	OT, CP	ERs	NP
Ma, 2005 [56]	USA	1972-1999	36813	Cohort	Department(s) information, DC	ICD	ERs	Firefighters	OT	ERs	RP
Daniels*, 2014 [64]	USA	1950-2009	29993	Cohort	DC	ICD	ERs	Firefighters	OT, DoE	ERs	NP
Ahn, 2015 [66]	South Korea	1980-2007	33442 (29453)	Cohort	DC	ICD	ERs	Firefighters	OT, DoE	Organizational Classification	NP
Amadeo, 2015 [67]	France	1979–2008	10829	Cohort	DC	ICD	ERs	Firefighters	OT	ERs	NP
Glass*, 2016 [69]	Australia	1976-2011	30057	Cohort	Tumor registry, DC	ICD	ERs	Firefighters	OT, DoE, TADE	ERs	NP

*reported cancer mortality and morbidity estimates.

Abbreviations: AS, age-specific; CCP, codes of census population; CP, calendar periods; DC, death certificate; DoE, duration of employment; ERs, employment records (including pension records, enrolment records, fire department records, Employee Service Record, payroll records); ICD, international calcification of disease; ICD-O, international classification of disease for oncology; ISCO, international standard classification of occupations (ILO codes); NED, national employment database; NR, not reported; OR, odds ratio; OT, occupational title; PMR, proportional mortality ratio; RR, rate ratio (relative risk); SEER, the surveillance, epidemiology, and end results (program); SIR, standardized incidence ratio; SMR, standardized mortality ratio; SOC, U.S. department of commerce codes -standard occupational classification; SoE, status of employment; TADE, task or activity during of employments; TSE, time since employment; UK, United Kingdom; USA, United States of America.

3.4. Risk of bias in individual studies

Except for one case-control study on cancer incidence, all studies included were of good quality with at least 6 points (Table S5, Supplementary material). However, only 15% of the studies reporting on incidence and 7% of the studies on mortality obtained the nine points.

3.5. Cancer incidence and mortality among firefighters

Figure 2 displays the SIRE of firefighters for all cancers and individual cancer sites. The findings showed an increased cancer incidence among firefighters for colon, rectal, prostate, testicular, bladder and thyroid cancers as well as mesothelioma, and malignant melanoma. There was no overall increased risk for all cancers among firefighters. Overall, heterogeneity was statistically significant among all cancers as well as for eleven cancer sites.

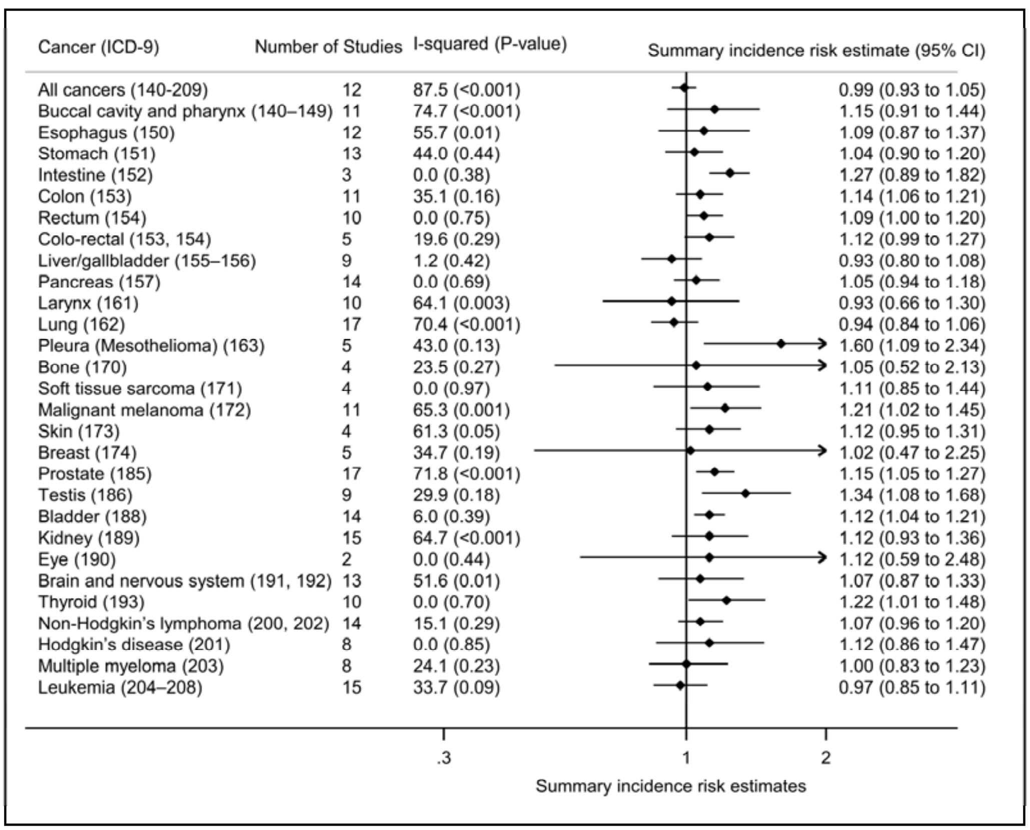

Figure 2. Forest plot of summary incidence risk estimates (SIRE) for firefighters overall and by individual

Figure 3 shows the SMRE for firefighters from all cancers and individual cancer sites. The results indicated a significantly increased mortality from rectal cancer and NHL. There was no overall increased mortality from all cancers in firefighters. However, heterogeneity was observed among 12 out of 23 cancers site and all cancers, too.

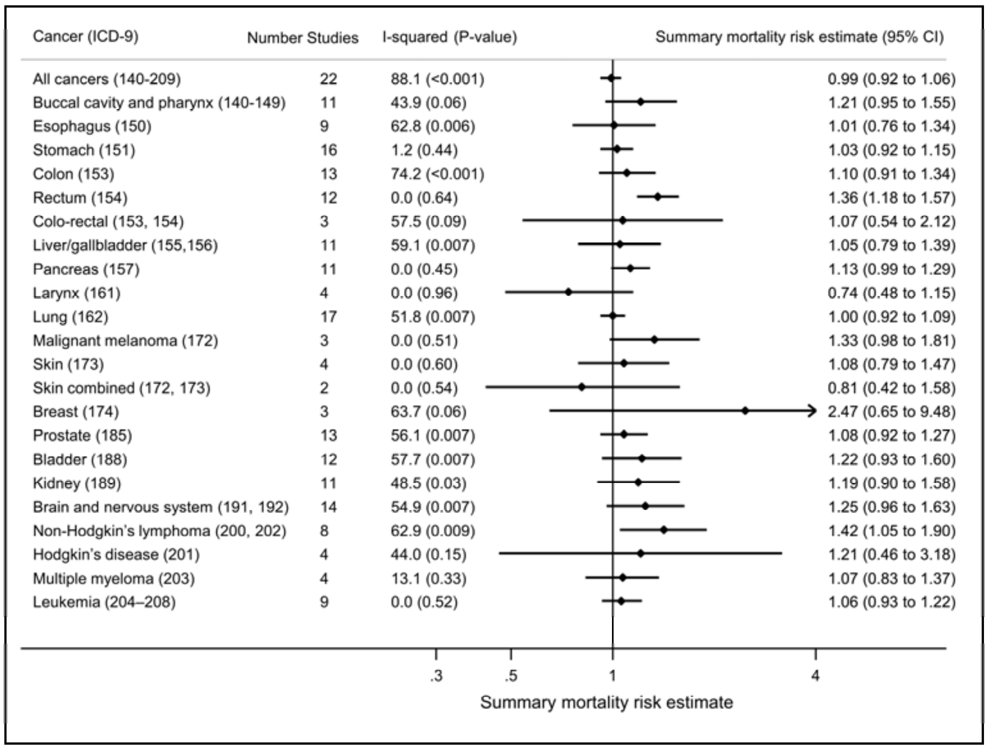

Figure 3. Forest plot of summary mortality risk estimates (SMRE) for firefighters overall and by individual cancer site

The overall likelihood of the observed cancer incidence and mortality among firefighters, considering quality indicators, is presented in Table 3. There is probable cause for an increased incidence of colon, pleural, testicular, and thyroid cancers among firefighters, as well as possible cause for the increased incidence of the intestine, rectal, colorectal, prostate, bladder, and eye cancers, soft tissue sarcoma, malignant melanoma, and Hodgkin's lymphoma. Increased cancer mortality among firefighters is probable for rectal cancer, and possible for pancreatic and pleural cancers, as well as Hodgkin's disease and NHL.

Table 3. Likelihood of increased cancer incidence and mortality in firefighters

Cancer (ICD-9)	**Incidence**			**Mortality**		
	Criterion† 1	**Criterion 2**	**Likelihood**	**Criterion 1**	**Criterion 2**	**Likelihood**
All cancers (140-209)	No star	No star	Unlikely	No star	No star	Unlikely
Buccal cavity and pharynx (140–149)	*	No star	Unlikely	*	No star	Unlikely
Esophagus (150)	No star	No star	Unlikely	No star	No star	Unlikely
stomach (151)	No star	No star	Unlikely	No star	No star	Unlikely
Intestine (152)	*	*	Possible	Missing	Missing	Missing
Colon (153)	**	**	Probable	No star	No star	Unlikely
Rectum (154)	*	*	Possible	**	**	Probable
Colo-rectal (153, 154)	*	*	Possible	No star	No star	Unlikely
Liver/gallbladder (155–156)	No star	No star	Unlikely	No star	No star	Unlikely
Pancreas (157)	No star	No star	Unlikely	*	*	Possible
Larynx (161)	No star	No star	Unlikely	No star	No star	Unlikely
Lung (162)	No star	No star	Unlikely	No star	No star	Unlikely
Pleura (Mesothelioma) (163)	**	**	Probable	*	*	Possible
Bone (170)	No star	No star	Unlikely	Missing	Missing	Missing
Soft tissue sarcoma (171)	*	*	Possible	Missing	Missing	Missing
Malignant melanoma (172)	**	*	Possible	Missing	Missing	Missing
Skin (173)	*	No star	Unlikely	No star	No star	Unlikely
Skin combined (172, 173)	Missing	Missing	Missing	No star	No star	Unlikely
Breast (174)	No star	No star	Unlikely	*	No star	Unlikely
Prostate (185)	**	*	Possible	No star	No star	Unlikely

Testis (186)	**	**	Probable	Missing	Missing	Missing
Bladder (188)	*	*	Possible	*	No star	Unlikely
Kidney (189)	*	No star	Unlikely	*	No star	Unlikely
Eye (190)	*	*	Possible	Missing	Missing	Missing
Brain and nervous system (191, 192)	No star	No star	Unlikely	*	No star	Unlikely
Thyroid (193)	**	**	Probable	Missing	Missing	Missing
Non-Hodgkin's lymphoma (200, 202)	No star	No star	Unlikely	**	*	Possible
Hodgkin's disease (201)	*	*	Possible	*	*	Possible
Multiple myeloma (203)	No star	No star	Unlikely	No star	No star	Unlikely
Leukemia (204–208)	No star	No star	Unlikely	No star	No star	Unlikely

† Criterion 1: pattern of summary risk estimate association; criterion 2: consistency (Appendix II, Supplementary material)

†† Probable: Meta-relative risk (MRR) was significantly ($p<0.05$) increased > 1.10 (**), with no heterogeneity; Possible: MRR was significantly ($p<0.05$) increased > 1.10 (**), but with a significant heterogeneity or MRR value was > 1.10 but this was not significant (or vice versa) (*), with no significant heterogeneity; Unlikely: other conditions (Appendix II, Supplementary material)

3.6. Publication bias

Table S6 (Supplementary material) shows the results of Egger's and Begg's tests. We found no significant indication of publication bias in any study (incidence and mortality), except in those reporting on Hodgkin's Lymphoma mortality (P_{Egger}=0.03).

4. Discussion

In the present study, we systematically reviewed the literature on the association between firefighting occupation and cancer incidence and mortality. We found a significantly increased incidence for colon (14%), rectal (9%), prostate (15%), testicular (34%), bladder (12%), and thyroid (22%) cancers as well as mesothelioma (60%) and malignant melanoma (21%) in firefighters. Of these, only the increased incidence of colon, pleural, testicular, and thyroid cancers were considered probable to be true associations when assessed by the specified criteria.

We found a significantly elevated mortality from rectal (36%) cancer as well as NHL (42%). Increased mortality from rectal cancer was considered probable and increased mortality from NHL, pancreatic and pleural cancers possibly related to the occupation. We found high levels of heterogeneity across all studies of incidence and mortality in all cancer sites (87.5% and 88.1%, respectively). We found no indication of publication bias, except in the studies reporting on Hodgkin's Lymphoma mortality, but these results should be interpreted with caution because these tests are known to have low power to detect bias when there are less than 10 studies.

Comparison to previous meta-analyses

Totally, four peer-reviewed meta-analyses including Howe and Burch (1990) [73], Youakim (2006) [15], LeMasters et al. (2006) [14], and Sritharan et al. (2017) [74] have studied the association of firefighting occupation and some selected malignancies. We compared the current study findings with the recent and comprehensive studies conducted by Sritharan et al. (2017) and LeMasters et al. (2006).

All cancers combined

In accordance with LeMasters et al. (2006), who observed no statistically significant association between firefighting occupation and incidence or mortality risks of overall cancers, we found an incidence and mortality risk of 0.99. However a high level of heterogeneity (88%) was seen in both types of studies. Some recent large cohort studies have found a moderately elevated (5-10%) overall cancer incidence [65, 69]. However, additional epidmiological studies are needed to meet a consistent and more reliable conclusion.

Digestive system

The current results on colon and rectal cancer were in accordance with what has been reported previously. LeMasters et al. (2006) found the pooled risk of 1.21 (1.03 to 1.41) and 1.29 (1.10 to

1.51), for colon and rectum cancers, and a pooled SMR of 0.92 (0.73 to 1.16) for stomach cancer. Finally, we found a non-significant 27% elevation of risk for cancer of the small intestine, based on three studies. However, this cancer is rare and has not previously been included in any meta-analysis and more investigations would be needed to assess its association to the firefighting occupation. Limited evidence suggests asbestos, diesel exhaust and dust [75-77], smoke, PAHs, and acid mists [78, 79] to be related to the risk of digestive system cancer. A large part of studies on the firefighter's exposures has revealed that this occupational group is exposed to all these agents during their working life [7, 80-82]. Therefore, the current results on digestive system cancers might be explained by these exposures. However, the investigations indicate that these occupational exposures have smaller effects than lifestyles factors such as diet, physical activity, smoking and alcohol consumption on digestive cancers [78, 83].

Mesothelioma

Risk of mesothelioma was significantly elevated with SIRE of 1.60 and SMRE of 1.33. Mesothelioma might be expected among firefighters since asbestos can be found in many structures and buildings falling apart during/after fires [82]. This cancer is rare and requires long follow-up in cohort studies, and has not been included in any previous meta-analysis.

Malignant melanoma

The SRE of 1.32 (1.10 to 1.57) was reported by the LeMasters et al., and in agreement with this, we found a 21% increase in incidence and 33% increase in mortality risks for malignant melanoma. While exposure of skin to UV radiation is the most important risk factor for malignant melanoma, exposure to PAHs, arsenic and other carcinogenic substances covering and penetrating the PPE and the skin may also contribute to the elevated risk [1, 9].

Prostate cancer

Overall, night-shift working [84], experience of stressful conditions [85], exposure to endocrine disruptors (e.g. polychlorinated biphenyls [PCBs] and polyhalogenated aromatic hydrocarbons (including bisphenol A, dioxin, and dibenzofurans) and heavy metals (e.g. arsenic and cadmium) [86], are the most relevant risk factors for prostate cancer in firefighters [10, 87, 88]. LeMasters et al. (2006) found a pooled SIR of 1.29 (1.09 to 1.51) and concluded that prostate cancer was probably linked to firefighter occupation. In another recent investigation, Sritharan et al. (2017) reported the pooled risk of 1.17 (1.08 to 1.28; I^2:72%) and 1.12 (0.92 to 1.36; I^2: 50%) for incidence and mortality, respectively [74]. We found similar results for prostate cancer, with significantly elevated incidence, and non-significantly elevated mortality.

Lymphohaematopoietic malignancies

The elevated risk of NHL among firefighters may be explained by exposure to benzene, other organic solvents [6, 11, 89] and bio-persistent agents (polychlorinated/-brominated substances) [90, 91]. In line with the current findings, LeMasters et al. (2006) categorized this disease as probable cancers among firefighting occupation (SRE: 1.51; 1.31 to 1.73) [14]. Moreover, the IARC Working Group meta-analysis [16] stated that NHL probably is related to occupational exposure cancers among firefighters.

In agreement with LeMasters et al. (2006), no statistically significant elevated risk was observed for Hodgkin lymphoma or leukemia. For multiple myeloma, LeMasters et al. (2006) suggested an SRE of 1.53 (1.21 to 1.94), but in the current meta-study, we observed no elevated incidence or mortality risk.

Bladder and kidney cancers

LeMasters et al. (2006) reported an SER of 1.20 (0.97 to 1.48), while we found 12% elevated statistically significant risk for bladder cancer incidence. A significantly elevated risk of bladder cancer in this occupational group may be related to exposure to known bladder carcinogens, including aromatic amines and PAHs [4, 6, 81, 92], combustion products [93], heavy metals (cadmium and arsenic) [86, 94], heat [95], and high concentration of carcinogens in urine [6]. In line with the previous meta-studies result [14, 15] on kidney cancer among firefighters, no elevated statistically significant risk was found in the current study.

Testicular cancer

In line with the current findings on testicular cancer incidence (SIRE: 1.34; CI 1.08, 1.68), LeMasters et al. (2006) found pooled SIR of 1.83 (1.13 to 2.79) and SRE of 2.02 (1.30 to 3.13) for testicular cancers. Additionally, they suggested this cancer as probable occupational cancer among firefighters. The literature on occupational causes of testicular cancer is sparse, but firefighters are exposed to potential risk factors, such as endocrine disruptors, cadmium, combustion product, and night shiftwork as the occupational risk factors to onset testicular cancer [96]. The IARC Working Group meta-analysis [16] stated that testicular is a probable occupational cancer among firefighters.

Thyroid cancer

Thyroid cancer has not previously been included in any meta-analysis. The body of evidence suggests ionizing radiation and pesticides exposure as the main occupational risk factors [97], but firefighters are not very likely to be exposed to these risk factors. However, iron, cobalt, and lead may affect thyroid function by inducing over-secretion of the thyroid stimulating hormone and this can be a trigger to cancer progression [98]. Some studies have also revealed that exposure to chemicals such as dioxins may alter thyroid hormone levels [98]. So far, no well-documented records are available to link firefighters' exposures and thyroid cancer.

Strengths and weaknesses of the study

Exposure information was not well-defined in the underlying articles and due to the small number of studies in most of cancers we could not further stratify our meta-analysis by different types of exposure surrogates (for example duration of exposure, start age of exposure, etc.). This is the first comprehensive meta-analysis on firefighters and cancer that stratifies the outcomes by cancer incidence and cancer mortality. This is important because the predictors for the two outcomes may differ.

Implications of our study

An increased risk of some cancers indicated that firefighters might not be adequately protected against carcinogenic hazards. To ensure a safer work environment we need technological development on the protective gear and educational efforts towards safer practices in fire extinguishing. Occupational health services should be available for all firefighters, and medical surveillance considered for selected cancers. Studies with better exposure assessment are urgently needed to identify specific etiologic factors.

Conclusions

We found an increased risk for incidence and mortality of certain cancers in firefighters. Especially worth mentioning are the newly identified thyroid cancers and mesothelioma. We suggest improving technologies and education of firefighters to decrease their carcinogenic exposure and recommend special attention towards early detection of the respective cancers in this population at risk.

Founding

This work was supported by Alborz University of Medical Sciences (grant No. 1396-02-22-1579); and the European Union Seventh Framework Programme (FP7-PEOPLE-2013-COFUND) under grant agreement n° 609020 - Scientia Fellows.

Reference

1. Fabian TZ, Borgerson JL, Gandhi PD, Baxter CS, Ross CS, Lockey JE, Dalton JM. Characterization of firefighter smoke exposure. *Fire Technology* 2014;50: 993-1019.

2. Bolstad-Johnson DM, Burgess JL, Crutchfield CD, Storment S, Gerkin R, Wilson JR. Characterization of firefighter exposures during fire overhaul. *Am Ind Hyg Assoc J* 2000;61: 636-41.

3. Baxter CS, Hoffman JD, Knipp MJ, Reponen T, Haynes EN. Exposure of Firefighters to Particulates and Polycyclic Aromatic Hydrocarbons. *J Occup Environ Hyg* 2014;11: D85-D91.

4. Jones L, Burgess JL, Evans H, Lutz EA. Respiratory protection for firefighters—Evaluation of CBRN canisters for use during overhaul II: In mask analyte sampling with integrated dynamic breathing machine. *J Occup Environ Hyg* 2016;13: 177-84.

5. Oliveira M, Slezakova K, Alves MJ, Fernandes A, Teixeira JP, Delerue-Matos C, Pereira MdC, Morais S. Polycyclic aromatic hydrocarbons at fire stations: firefighters' exposure monitoring and biomonitoring, and assessment of the contribution to total internal dose. *J Hazard Mater* 2017;323: 184-94.

6. Fent KW, Eisenberg J, Snawder J, Sammons D, Pleil JD, Stiegel MA, Mueller C, Horn GP, Dalton J. Systemic Exposure to PAHs and Benzene in Firefighters Suppressing Controlled Structure Fires. *Ann Occup Hyg* 2014;58: 830-45.

7. Fent KW, Evans DE. Assessing the risk to firefighters from chemical vapors and gases during vehicle fire suppression. *J Environ Monit* 2011;13: 536-43.

8. Alexander BM, Baxter CS. Flame-retardant contamination of firefighter personal protective clothing A potential health risk for firefighters. *J Occup Environ Hyg* 2016;13: D148-D55.

9. Easter E, Lander D, Huston T. Risk assessment of soils identified on firefighter turnout gear. *J Occup Environ Hyg* 2016;13: 647-57.

10. Shaw SD, Berger ML, Harris JH, Yun SH, Wu Q, Liao C, Blum A, Stefani A, Kannan K. Persistent organic pollutants including polychlorinated and polybrominated dibenzo-p-dioxins and dibenzofurans in firefighters from Northern California. *Chemosphere* 2013;91: 1386-94.

11. T Mannetje A, Eng A, Walls C, Dryson E, McLean D, Kogevinas M, Fowles J, Borman B, O'Connor P, Cheng S, Brooks C, Smith AH, et al. Serum concentrations of chlorinated dibenzo-p-dioxins, furans and PCBs, among former phenoxy herbicide production workers and firefighters in New Zealand. *Int Arch Occup Environ Health* 2016;89: 307-18.

12. Waldman JM, Gavin Q, Anderson M, Hoover S, Alvaran J, Ip HSS, Fenster L, Wu NT, Krowech G, Plummer L. Exposures to environmental phenols in Southern California firefighters and findings of elevated urinary benzophenone-3 levels. *Environ Int* 2016;88: 281-7.

13. Mastromatteo E. Mortality in city firemen. 2. A study of mortality in firemen of a city fire department. *Arch Indust Health* 1959;20: 227-33.

14. LeMasters GK, Genaidy AM, Succop P, Deddens J, Sobeih T, Barriera-Viruet H, Dunning K, Lockey J. Cancer risk among firefighters: A review and meta-analysis of 32 studies. *J Occup Environ Med* 2006;48: 1189-202.

15. Youakim S. Risk of cancer among firefighters: A quantitative review of selected malignancies. *Arch Environ Occup Health* 2006;61: 223-31.

16. International Agency for Research on Cancer. *Volume 98-Painting, firefighting, and shiftwork*ed., vol. 98: IARC Press, International Agency for Research on Cancer, 2010.

17. Crawford JO, Winski T, McElvenny D, Graveling R, Dixon K. *Firefighters and cancer: the epidemiological evidence*. Research Report TM/17/01. Research Avenue North, Riccarton, Edinburgh, EH14 4AP, Institute Of Occupational Medicine 2017.

18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6: e1000097.

19. Roman E, Beral V, Inskip H, McDowall M, Adelstein A. A comparison of standardized and proportional mortality ratios. *Stat Med* 1984;3: 7-14.

20. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;27: 954-70.

21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses Ottawa: *Ottawa Health Research Institute*, 2007.

22. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10: 101-29.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327: 557.

24. Feuer E, Rosenman K. Mortality in police and firefighters in New Jersey. *Am J Ind Med* 1986;9: 517-27.

25. Burnett CA, Halperin WE, Lalich NR, Sestito JP. Mortality among fire fighters: A 27 state survey. *Am J Ind Med* 1994;26: 831-3.

26. Berg JW, Howell MA. Occupation and bowel cancer. *J Toxicol Env Heal A* 1975;1: 75-89.

27. Musk AW, Monson RR, Peters JM, Peters RK. Mortality among Boston firefighters, 1915-1975. *Br J Ind Med* 1978;35: 104-8.

28. Eliopulos E, Armstrong BK, Spickett JT, Heyworth F. Mortality of fire fighters in western-australia. *Br J Ind Med* 1984;41: 183-7.

29. Morton W, Marjanovic D. Leukemia incidence by occupation in the Portland-Vancouver metropolitan area. *Am J Ind Med* 1984;6: 185-205.

30. Blair A, Walrath J, Rogot E. Mortality patterns among US veterans by occupation. I. Cancer. *J Natl Cancer Inst* 1985;75: 1039-47.

31. Vena JE, Fiedler RC. Mortality of a municipal-worker cohort: IV. Fire fighters. *Am J Ind Med* 1987;11: 671-84.

32. Hansen ES. A cohort study on the mortality of firefighters. *Br J Ind Med* 1990;47: 805-9.

33. Sama SR, Martin TR, Davis LK, Kriebel D. Cancer incidence among massachusetts firefighters, 1982-1986. *Am J Ind Med* 1990;18: 47-54.

34. Beaumont JJ, Chu GS, Jones JR, Schenker MB, Singleton JA, Piantanida LG, Reiterman M. An epidemiologic study of cancer and other causes of mortality in San Francisco firefighters. *Am J Ind Med* 1991;19: 357-72.

35. Grimes G, Hirsch D, Borgeson D. Risk of death among Honolulu fire fighters. *Hawaii Med J* 1991;50: 82-5.

36. Demers PA, Heyer NJ, Rosenstock L. Mortality among firefighters from three northwestern United States cities. *Br J Ind Med* 1992;49: 664-70.

37. Giles G, Staples M, Berry J. Cancer incidence in Melbourne Metropolitan Fire Brigade members, 1980-1989. *Health Rep* 1993;5: 33-8.

38. Guidotti TL. Mortality of urban firefighters in Alberta, 1927-1987. *Am J Ind Med* 1993;23: 921-40.

39. Aronson KJ, Tomlinson GA, Smith L. Mortality among fire fighters in metropolitan toronto. *Am J Ind Med* 1994;26: 89-101.

40. Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L. Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). *Cancer Causes Control* 1994;5: 129-35.

41. Tornling G, Gustavsson P, Hogstedt C. Mortality and cancer incidence in stockholm fire fighters. *Am J Ind Med* 1994;25: 219-28.

42. Delahunt B, Bethwaite PB, Nacey JN. Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry. *Br J Urol* 1995;75: 578-82.

43. Deschamps S, Momas I, Festy B. Mortality amongst Paris fire-fighters. *Eur J Epidemiol* 1995;11: 643-6.

44. Figgs LW, Dosemeci M, Blair A. United States non-Hodgkin's lymphoma surveillance by occupation 1984- 1989: A twenty-four state death certificate study. *Am J Ind Med* 1995;27: 817-35.

45. Finkelstein MM. Occupational associations with lung cancer in two Ontario cities. *Am J Ind Med* 1995;27: 127-36.

46. Firth HM, Cooke KR, Herbison GP. Male cancer incidence by occupation: New Zealand, 1972-1984. *Int J Epidemiol* 1996;25: 14-21.

47. Krstev S, Baris D, Stewart P, Dosemeci M, Swanson GM, Greenberg RS, Schoenberg JB, Schwartz AG, Liff JM, Hayes RB. Occupational risk factors and prostate cancer in US blacks and whites. *Am J Ind Med* 1998;34: 421-30.

48. Ma F, Lee DJ, Fleming LE, Dosemeci M. Race-specific cancer mortality in US firefighters: 1984-1993. *J Occup Environ Med* 1998;40: 1134-8.

49. Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A, Zahm SH. Cohort mortality study of Philadelphia firefighters. *Am J Ind Med* 2001;39: 463-76.

50. Bates MN, Fawcett J, Garrett N, Arnold R, Pearce N, Woodward A. Is testicular cancer an occupational disease of fire fighters? *Am J Ind Med* 2001;40: 263-70.

51. Elci OC, Akpinar-Elci M, Alavanja M, Dosemeci M. Occupation and the risk of lung cancer by histologic types and morphologic distribution: A case control study in Turkey. *Monaldi Arch Chest Dis* 2003;59: 183-8.

52. Krishnan G, Felini M, Carozza SE, Miike R, Chew T, Wrensch M. Occupation and adult gliomas in the San Francisco Bay Area. *J Occup Environ Med* 2003;45: 639-47.

53. Stang A, Jöckel KH, Baumgardt-Elms C, Ahrens W. Firefighting and risk of testicular cancer: Results from a German population-based case-control study. *Am J Ind Med* 2003;43: 291-4.

54. Gaertner RRW, Trpeski L, Johnson KC, Paulse B, Dewar R, Dryer D, Kreiger N, Liewer E, Robson D, Fincham S, Le N. A case-control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control* 2004;15: 1007-19.

55. Zeegers MP, Friesema IH, Goldbohm RA, van den Brandt PA. A prospective study of occupation and prostate cancer risk. *J Occup Environ Med* 2004;46: 271-9.

56. Ma FC, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H, Lai SH. Mortality in Florida professional firefighters, 1972 to 1999. *Am J Ind Med* 2005;47: 509-17.

57. Ma FC, Fleming LE, Lee DJ, Trapido E, Gerace TA. Cancer incidence in Florida professional firefighters, 1981 to 1999. *J Occup Environ Med* 2006;48: 883-8.

58. Kang D, Davis LK, Hunt P, Kriebel D. Cancer incidence among male Massachusetts firefighters, 1987-2003. *Am J Ind Med* 2008;51: 329-35.

59. Corbin M, McLean D, Mannetje At, Dryson E, Walls C, McKenzie F, Maule M, Cheng S, Cunningham C, Kromhout H. Lung cancer and occupation: A new zealand cancer registry-based case–control study. *Am J Ind Med* 2011;54: 89-101.

60. Zeig-Owens R, Webber MP, Hall CB, Schwartz T, Jaber N, Weakley J, Rohan TE, Cohen HW, Derman O, Aldrich TK, Kelly K, Prezant DJ. Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study. *Lancet* 2011;378: 898-905.

61. Ahn YS, Jeong KS, Kim KS. Cancer morbidity of professional emergency responders in Korea. *Am J Ind Med* 2012;55: 768-78.

62. Karami S, Colt JS, Schwartz K, Davis FG, Ruterbusch JJ, Munuo SS, Wacholder S, Stewart PA, Graubard BI, Rothman N, Chow WH, Purdue MP. A case-control study of occupation/industry and renal cell carcinoma risk. *Bmc Cancer* 2012;12.

63. Paget-Bailly S, Guida F, Carton M, Menvielle G, Radoï L, Cyr D, Schmaus A, Cénée S, Papadopoulos A, Févotte J, Pilorget C, Velten M, et al. Occupation and head and neck cancer risk in men: Results from the ICARE Study, a French population-based case-control study. *J Occup Environ Med* 2013;55: 1065-73.

64. Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM, Pinkerton LE. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). *Occup Environ Med* 2014;71: 388-97.

65. Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, Sparén P, Demers PA. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med* 2014.

66. Ahn YS, Jeong KS. Mortality Due to Malignant and Non-Malignant Diseases in Korean Professional Emergency Responders. *Plos One* 2015; 10;10:e0120305.

67. Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaëlle C, Simone MP, Lembeye C, Imbernon E, Brochard P. French firefighter mortality: analysis over a 30-year period. *Am J Ind Med* 2015;58: 437-43.

68. Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM. Risk of cancer among firefighters in California, 1988-2007. *Am J Ind Med* 2015;58: 715-29.

69. Glass DC, Pircher S, Del Monaco A, Vander Hoorn S, Sim MR. Mortality and cancer incidence in a cohort of male paid Australian firefighters. *Occup Environ Med* 2016;73: 761-71.

70. Kullberg C, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, Bigert C. Cancer incidence in Stockholm firefighters 1958–2012: an updated cohort study. *Int Arch Occup Environ Health* 2018; 91:285-291.

71. Petersen KKU, Pedersen JE, Bonde JP, Ebbehoej NE, Hansen J. Long-term follow-up for cancer incidence in a cohort of Danish firefighters. *Occup Environ Med* 2017;75:263-269.

72. Sritharan J, Demers PA, Harris SA, Cole DC, Peters CE, Villeneuve PJ. Occupation and risk of prostate cancer in Canadian men: A case-control study across eight Canadian provinces. *Cancer Epidemiol* 2017;48: 96-103.

73. Howe GR, Burch JD. Fire fighters and risk of cancer: an assessment and overview of the epidemiologic evidence. *Am J Epidemiol* 1990;132: 1039-50.

74. Sritharan J, Pahwa M, Demers PA, Harris SA, Cole DC, Parent M-E. Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies. *Environ Health* 2017;16: 124.

75. Boulanger M, Morlais F, Bouvier V, Galateau-Salle F, Guittet L, Marquignon M-F, Paris C, Raffaelli C, Launoy G, Clin B. Digestive cancers and occupational asbestos exposure: incidence study in a cohort of asbestos plant workers. *Occup Environ Med* 2015: 72:792-7.

76. Paris C, Thaon I, Hérin F, Clin B, Lacourt A, Luc A, Coureau G, Brochard P, Chamming's S, Gislard A, Galan P, Hercberg S, et al. Occupational Asbestos Exposure and Incidence of Colon and Rectal Cancers in French Men: The Asbestos-Related Diseases Cohort (ARDCo-Nut). *Environ Health Perspect* 2017;125: 409-15.

77. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum* 2012;100:11-465.

78. Schottenfeld D, Fraumeni Jr JF. *Cancer epidemiology and prevention*, 4th ed. New York, NY: Oxford University Press, 2006.

79. Paget-Bailly S, Cyr D, Luce D. Occupational exposures to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx: a quantitative literature review. *Int Arch Occup Environ Health* 2012;85: 341-51.

80. Froines JR, Hinds WC, Duffy RM, LaFuente EJ, LIU W-CV. Exposure of firefighters to diesel emissions in fire stations. *Am Ind Hyg Assoc J* 1987;48: 202-7.

81. Baxter CS, Hoffman JD, Knipp MJ, Reponen T, Haynes EN. Exposure of Firefighters to Particulates and Polycyclic Aromatic Hydrocarbons. *J Occup Environ Hyg* 2014;11: D85-D91.

82. Markowitz SB, Garibaldi K, Lilis R, Landrigan PJ, Kilburn K, Selikoff IJ, Kipen H, Levin SM, Miller J, Oliver LC, Stigliano J, Fite J, et al. Asbestos exposure and fire fighting. *Ann N Y Acad Sci* 1991;643: 573-81.

83. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal Habits and Indoor Combustions Volume 100e A Review of Human Carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012;100:1-538.

84. Rao D, Yu H, Bai Y, Zheng X, Xie L. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. *Onco Targets Ther* 2015;8: 2817-26.

85. Wirth M, Vena JE, Smith EK, Bauer SE, Violanti J, Burch J. The Epidemiology of Cancer Among Police Officers. *Am J Ind Med* 2013;56: 439-53.

86. Garg T. Environmental and Occupational Exposures and Prostate Cancer. In: Mydlo JH, Godec CJ. *Prostate cancer: Science and clinical practice* ed. London Wall, EC2Y 5AS, UK: Academic Press, 2016: 191-8.

87. Waldman JM, Gavin Q, Anderson M, Hoover S, Alvaran J, Ip HSS, Fenster L, Wu NT, Krowech G, Plummer L, Israel L, Das R, et al. Exposures to environmental phenols in Southern California firefighters and findings of elevated urinary benzophenone-3 levels. *Environ Int* 2016;88: 281-7.

88. Fabian T, Borgerson JL, Kerber SI, Gandhi PD, Baxter CS, Ross CS, Lockey JE, Dalton JM. *Firefighter exposure to smoke particulates*: Underwriters Laboratories, 2010.

89. Smith MT, Jones RM, Smith AH. Benzene Exposure and Risk of Non-Hodgkin Lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007;16: 385-91.

90. Schecter A, Stanley J, Boggess K, Masuda Y, Mes J, Wolff M, Fürst P, Fürst C, Wilson-Yang K, Chisholm B. Polychlorinated biphenyl levels in the tissues of exposed and nonexposed humans. *Environ Health Perspect* 1994;102: 149-58.

91. Edelman P, Osterloh J, Pirkle J, Caudill SP, Grainger J, Jones R, Blount B, Calafat A, Turner W, Feldman D, Baron S, Bernard B, et al. Biomonitoring of chemical exposure among New York City firefighters responding to the World Trade Center fire and collapse. *Environ Health Perspect* 2003;111: 1906-11.

92. Pesch B, Taeger D, Johnen G, Gawrych K, Bonberg N, Schwentner C, Wellhäußer H, Kluckert M, Leng G, Nasterlack M. Screening for bladder cancer with urinary tumor markers in chemical workers with exposure to aromatic amines. *Int Arch Occup Environ Health* 2014;87: 715-24.

93. Golka K, Weistenhöfer W. Fire fighters, combustion products, and urothelial cancer. *J Toxicol Environ Health B Crit Rev* 2008;11: 32-44.

94. Järup L. Hazards of heavy metal contamination. *Br Med Bull* 2003;68: 167-82.

95. Snider III JW, Datta NR, Vujaskovic Z. Hyperthermia and radiotherapy in bladder cancer. *Int J Hyperthermia* 2016;32: 398-406.

96. Mester B, Behrens T, Dreger S, Hense S, Fritschi L. Occupational causes of testicular cancer in adults. *The international J Occup Environ Med* 2010;1: 160-70.

97. Aschebrook-Kilfoy B, Ward MH, Valle CTD, Friesen MC. Occupation and Thyroid Cancer. *Occup Environ Med* 2014;71: 366-80.

98. Baxter PJ, Aw T-C, Cockcroft A, Durrington P, Harrington JM. *Hunter's diseases of occupations*: 10th ed. London: Arnold: CRC Press, 2010.