Literature Review and Meta-analysis on Colorectal Cancer Risk and Firefighting

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INTRODUCTION

Occupational health and safety for firefighters have received increasing attention over the last two decades, due to the growing concern of potential health risks for firefighters. These workers not only face severe physical and psychological demands, but also face potential risks of chronic adverse health consequences such as cancer [1-32]. Only a few studies were conducted before 1980 in this area [33-36]. Fire fighters are exposed to a wide variety of toxic chemicals including known and unknown suspected carcinogens, such as benzene in wood smoke, polycylic aromatic hydrocarbons (PAHs) in soots and tars, arsenic in wood preservatives, asbestos in building insulation, diesel engine exhaust, and dioxins. The widespread introduction of synthetic building materials in the late 1950s increased the complexity of the firefighters exposure. The combustion of the common plastic polyvinyl chloride (PVC), for example, has estimated to produce dozens of different chemicals including cyanide. A substantial body of literature now exists on the carcinogenic hazards of firefighting. [35,37-45].

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The mortality experience of firefighters has been an active topic of epidemiological investigations, while incidence studies are rare. Results suggest that certain causes of death are likely to be associated with firefighting including heart disease, obstructive pulmonary disease, and certain cancers such as lung cancer, genitourinary cancer, leukemia, lymphomas, and melanoma. Colorectal cancer (cancer of colon and rectum) has been also one of these cancer sites that are found likely to be associated with firefighting [2,6-13,15-18,24,34].

However, the findings of possible association between firefighting and colorectal cancer have been inconsistent. Several review papers on cancer including colorectal cancer and firefighting have been published during last 15 years [1-3,14,46]. The most recent review paper was published in 2003, which was focused on latent health effects in firefighters but did not analyze the colorectal cancer as a group [3]. The most comprehensive review on colorectal cancer and firefighting was done by Guidotti [2]. The reviewers concluded that "there is less strong suggestion in the literature for colon and rectal cancer" associated with firefighting. A few of new studies involving colorectal cancer and firefighting have been published [7,10,16]. A recent study was a retrospective cohort study among 7789 Philadelphia firefighters employed between 1925-1986 and showed significant association results for colon cancer but not rectal cancer [7]. The most recent study, the largest cohort study among firefighters so far, did not show any significant association for either colon or rectum in that cohort.[65]

A systematic review is needed to determine if firefighting is associated with the risk of colorectal cancer by including the newly published papers. There is another question, which is even more important: If firefighting is proved to be associated with colorectal cancer risk at certain level, how should we attribute colorectal cancer cases or deaths among firefighters to the firefighting activities?

The difficulty of answering above question is that colorectal cancer is also a common cancer in general population. Based on Canadian Cancer Statistics 2005, an estimated 19,600 Canadians will be diagnosed with colorectal cancer and 8,400 will die of it in 2005. On average, 377 Canadians will be diagnosed with colorectal cancer and162 Canadians will die of it every week. One in 14 men is expected to develop colorectal cancer during their lifetime and one in 28 will die of it. One in 16 women is expected to develop colorectal cancer during their lifetime and one in 31 will die of it. Overall, colorectal cancer is the second leading cause of death from cancer [47].

General causes of colorectal cancer include a family history of colorectal cancer and familial colorectal cancer syndromes (familial adenomatous polyposis), black race, ethnic background: Jews of Eastern European descent (Ashkenazi Jews), a personal history of colorectal polyps, a personal history of chronic inflammatory bowel disease, aging, a diet mostly from animal sources, physical inactivity, obesity, diabetes, smoking and alcohol intake [48].

The primary goal of this paper is to conduct a systematic review focusing on firefighting and colorectal cancer risk based published literatures in scientific journals to determine any association and possible “exposure-response” relationships between firefighting and colorectal cancer risk. The secondary goal of this paper is to estimate probability of colorectal cancer risk attributable to firefighting activities among firefighters. All analyses will be done for the colon, rectal, and colorectal cancer combined, respectively.

METHOD

Literature Search and Review

A systematic literature review was conducted according to acceptable guidelines of performing a scientific systematic literature review [49]. The intent of the literature search is to be as comprehensive as possible initially to avoid omission of potentially relevant databases.

Literature Source

Primary source and search terms: Medline/Pubmed, Cancerlit, and Embase search was performed using the following strategy: (fire OR firemen OR firefighter OR firefighters OR firefighting) AND (colon OR rectum OR rectal OR colorectal) AND (cancer OR cancers OR tumors OR tumor OR carcinoma OR carcinomas OR neoplasm OR neoplasms OR polyps). The search was conducted on September 1, 2005 covering the period from 1950 to 2005 among peer-reviewed publications.

Secondary source: References of retrieved papers based on the first search were checked and the relevant papers, which were not identified in the first search, were retrieved.

Additional source: References which were mentioned by peer-reviewers of the draft version this report but not identified by the literature search were also included as candidates of the literature review.

Study inclusion and exclusion

Only officially published original studies in scientific journals (in English) which provided risk estimates and significance test results (confidence intervals, standard errors, or p values) or parameters that could be used to obtain the risk estimates and significance test results on colon, rectum, or colorectal cancer among firefighters, were included in the literature review. For instance, in some studies confidence intervals (CIs) of Standard Mortality Ratio (SMR) were not provided. However, if observed number of deaths were available, the confidence intervals of the SMR could be calculated.

If multiple papers for the same study population were identified, the latest or most complete study would be used. For instance, The Seattle firefighter population was first included in the Heyer et al's 1990 paper[15] then was included in a later expanded study in Demers et al 1992 paper. [11] Thus Heyer's paper was excluded in the literature review. If multiple models were presented in a paper, the best model with the most confounding variables adjusted or longer period covered would be used in the analysis. However, if a study involved both incidence and mortality analyses, both were included in literature review. For instance, Demers et al's 1994 paper reported incidence study result for the same population of their 1992 paper on mortality [10]. This later paper was also included in the review but was analyzed separately.

Exclusion: If cancer of interest was not specified or the firefighting was not specified in the study, the paper was excluded. Female and non-white populations were excluded in the analysis, since the Canadian fire service was dominated historically, and is currently, by white, non-Jewish men of northern European origin.

Review and abstraction

All studies identified as relevant for answering the research question were reviewed. The items to be extracted during review included general information about the study (authors, year of publication, journal of publication, volume, pages, population size, data covering period, etc), exposure measures and grouping (overall firefighting, duration of employment, etc), outcome measures (point estimates, CI, p-values, etc), and study quality measures (method for case ascertainment, study design, method of data collection, analysis method, etc).

Comparability of risk measures

The combination of results from observational studies is a difficult process, due to the use of different methods across studies. Fortunately, there was more uniformity in major studies of firefighters than in most studies in occupational epidemiology. They are almost all historical cohort studies. This makes comparability a much more reasonable assumption.

Standardized mortality ratio (SMR), mortality odds ratio (MOR), and Odds Ratio (OR) were assumed as valid estimations of relative risks (RR) and as comparable to each other with a little adjustment. For instance, a SMR of 200 is comparable to an OR of 2.00. One often noted shortcoming of SMR analysis is that, the comparisons of SMRs between groups will not be appropriate if their confounder, such as age, distribution differs. [50] Thus an assumption would be needed that common confounder distribution among firefighter populations should be similar to each other.

Proportionate mortality ratio (PMR) was considered as not really comparable to the other measures in this review, since it compared only distributions of causes of deaths. It is just as possible that firefighters had a deficit of non-cancer causes of death as that they had an excess of cancer causes, a situation on which the PMR might shed no light. PMRs was considered good approximations to SMRs obtained from cohort studies when cohort's all-causes combined SMR is equal to 1.0 (i.e. , observed is equal to expected). [50]However, SMRs were analyzed with and without PMRs in the meta-analysis to examine the impact of the inclusion of PMR studies as a part of sensitivity analysis.

Standard incidence ratio (SIR) was assumed to be comparable to Standard mobidity odds ratio (SMOR). Separate analysis was conducted for incidence studies including SIR and SMOR from mortality studies. We believed that incidence measures were more relevant to the risk of obtain colorectal cancer among firefighters and the cancer registry based incidence studies might have less misclassification in sub-sites of cancer than death certificate based mortality studies.

Data for each cancer site

Colon and rectal cancers were reviewed separately. Only papers with colon or/and rectal cancer result were included in the analysis for each of the two sites. As to colorectal cancer, the analysis included studies that reported the data for colorectal cancer directly. In addition, if colorectal cancer site was not specified in the original paper but colon and rectal cancers were reported as separate sites, the cancer of colon and rectum were combined as colorectal cancer. The sum of observed colon and rectal cancer cases divided by the sum of expected colon and rectal cancer cases would be the SMR for colorectal cancer combined. The colorectal cancer combination was done only when both colon and rectal cancers were available. If only colon or rectum cancer was reported, the colorectal cancer SMR would not be generated.

Although separate analysis was done for colon and rectal cancers when examining mortality data, there was a reasonably high probability that these two cancers were misclassified, particularly in data arising from death certificates. In addition, a few studies specified only colorectal combined result without any specification on either colon or rectal cancers. Thus, colorectal cancer combined analysis was considered as more valid because it might have less misclassification and more studies could be included in the colorectal cancer combined analysis.

Colorectal cancer in Canada

Geographical distribution and incidence and mortality trend of colorectal cancer data in Canada were based on data from "Canadian Cancer Statistics 2005". The data period covered was for 1976-2005. The data for 2002-2005 was projected by Canadian Cancer Society. [47] Maps for projected 2005 data and trend figures for 1976-2005 were recreated for the presentation in this paper. This information on geographical and period patterns of colorectal cancer would be helpful in estimation of risk of colorectal cancer that could be attributable to background risk factors in the general population for a particular area or a period. For instance, a firefighter colorectal cancer case occurred in an area with very low background incidence might have higher probability to be associated with occupational exposures than in an area with very high background incidence in the general population.

Common Risk factors of Colorectal Cancer

Reviewing for other risk factors than firefighting was not within the scope of this literature review. This paper, however, briefly introduced other risk factors accepted by American Cancer Society. The common risk factors for colorectal cancer have been listed in its recent publication "Colorectal Cancer Facts & Figures Special Edition 2005" [48].

Meta-analysis

Cancer Sites and Risk Measures Grouping

Meta-analysis was performed in different combinations of cancer sites and risk measures. Analyses on SIR, SMR, PMR, and SMR-PMR combined were done for each of the three cancer sites including colon cancer, rectal cancer, and colorectal cancers combined, respectively, as long as the data was available.

Overall risk of firefighting

Meta-analysis was performed to calculate a summarized risk estimate based on results of overall risk of firefighting from selected eligible literatures using a random effect model [51-53]. This method used as weights the inverse of the sum of the between-study variance and each study's variance, and results in more conservative (wider) confidence intervals compared to the fixed effects methods. The main product of the analysis will be a point estimate of the odds ratio for the association between the overall firefighting and colorectal cancers, its 95% confidence interval. In addition, the results of individual studies and the combined estimates were plotted in forest plots, ordering studies by publication year. In the forest plot the weights for which the result of each study was assigned based on sample size were also presented in addition to the point estimates and 95% CIs.

For analysis on overall risk of firefighting, the odd ratio (*OR)* (or other risk measures) could usually be derived from the paper directly, since all papers reported a risk estimate for firefighting. The primary outcome of meta-analysis is the summary estimate of log(*OR*), combined across studies. If the estimate of log(*OR*) in study *i* is $\log(OR)_i$, then the inverse-variance weighted pooled estimate will be denoted by $\log(OR)_P$, where:

$$\log(OR)_P = \frac{\sum w_i \times \log(OR)_i}{\sum w_i}$$

The weight w_i for study *i* equals the inverse of the variance of $\log(OR)_i$:

$$w_i = 1/(se_{\log(OR)})^2$$

The standard error of the summary estimate = $\sqrt{\frac{1}{\sum w_i}}$

This can be used to derive a confidence interval for log(*OR*) in the usual way.

“Exposure-response” between duration of employment and colorectal cancer

Some of the studies looked at duration of employment and the risk of firefighting, which allowed us to examine the possible “exposure-response” between duration of employment in firefighting and colorectal cancer. The analyses were based on estimates of the average effect per unit of exposure (duration in each 10 years). These measures were calculated under a rather strong assumption of a log-linear dose response effect, since it was difficult to address more complicated exposure-response relationships due to the limitation in data. Because the duration category system in each of the papers varied from study to study, a direct combination of different studies would face problem of inconsistent exposure categories. It is hard to combine a study with duration category in 1-14, 15-29, …… with a study with duration category in 1-9, 10-19,20-29, …… for instance. We estimated the increase in log-odds ratio (and its standard error) associated with one unit of change in the duration using the method of Chêne and Thompson [52], then we pooled these studies together [51-53].

The following steps were taken to summarize the “exposure-response” relationship for all eligible studies.

1) To derive $\log(OR)_i$ from each study with multiple categories in duration

As explained above, the aim was to estimate the increase in the log odds of the outcome *D* per unit increase in *X* (duration in years) for each study with multiple duration categories. Formally, we wish to estimate β, the coefficient of X in the logistic regression model:

$$\log(OR)_i \text{ of } D = \alpha + \beta X$$

2) Once a log $(OR)_i$ and standard error were generated for each study, then a pooled log(O*R*) could be generated using regular meta-analysis tool described in the section of “Analysis on overall risk of firefighting”.

Evaluation of heterogeneity and sensitivity analysis

Heterogeneity is often the norm rather than the exception in meta-analysis of observational studies. Heterogeneity tests were performed to examine the heterogeneity of studies which were pooled [54]. Ideally, this method would permit us to identify heterogeneity in study results. However, the small number of studies would limit the evaluation of study heterogeneity and we considered it likely that some combined measures of effect would still present some unexplained heterogeneity. Once heterogeneity became a concern, sensitivity analysis would be performed by including and excluding the paper of concern in the separate meta-analysis and examine the impact of the particular study to the summarized risk outcomes. For instance, the highest risk estimate for colorectal cancer among all studies was reported by Berg and Howell [32]. The SMR for colorectal cancer was 279 (198.1-380.8) and caused significant heterogeneity if included in summarized risk estimate. In this study, however, the occupation for deaths was “usual occupation” from death certificate and the occupation for population was “current occupation” from census. This difference might have resulted in over-reporting of occupation on death certificate so that a sensitivity analysis was conducted to examine the impact of inclusion or exclusion of this study on the summarized risk estimate.

<u>Estimation of Probability of a Firefighting-related Colorectal Cancer</u>

Colorectal cancer is a common cancer in general population and may be associated with many non-firefighting factors. It is not a realistic to identify a firefighting related colorectal cancer because, among other drawbacks, it fails on the two most likely contingencies. If firefighting is one among many factors and occupational as a firefighter tips the balance in a general mechanism of cancer causation, then it is unlikely that a marker for firefighting-induced colorectal cancers can be identified because each case more or less follows a common final pathway. It is more realistic to think that the probability of a specific colon, rectal or colorectal cancer being occupational can be estimated.

The attributable risk fraction (ARF) is usually used to estimate attributable risk to an exposure among people who are exposed using the following formula from Kelsey et al: Methods in

Observational Epidemiology [55]: Attributable risk fraction for exposed = (Risk Ratio-1) / Risk Ratio. This indicator is very helpful to estimate the percentage of cases that can be attributed to a particular exposure such as firefighting among the exposed people. For instance, if the OR of colon cancer for firefighting was 2.5 then the ARF wouldl be (2.5-1)/2.5=60%, meaning that among firefighters 60% of colon cancer cases could be attributed to firefighting or a colon cancer case would have 60% of probability of getting the cancer from firefighting or 40% of probability of getting cancer from other risk factors. The limitation of this indicator is that this estimation is aggregated measure assuming other risk factors are all at an average level even if the risk estimate for firefighting has been adjusted for all confounding. Thus it does not reflect the risk attribution change due to the change in status of other risk factors of an individual case from a population average. Thus it is very important that individual information on other risk factors needs to be considered in examining individual cases.

<u>Software</u>

Microsoft Excel was used for data abstraction and data preparation. Cancer incidence and mortality maps were created using ArcMap 8.2 [56] . The calculation of SMR and 95% CIs was done using PAMCOMP v1.41 [57]. Stata 8.0 was used to perform meta-analysis, generate the plot, and evaluate the heterogeneity [58] .

RESULT

<u>Geographic distribution of colorectal cancer in Canada</u>

Based on Canadian Cancer Statistics 2005 [47], colorectal cancer incidence and mortality maps were created by sex (Figure 1 to 4). All rates were adjusted against 1991 Canada population. Generally speaking, cancer incidences and mortalities were higher in provinces in the east than those in the west of Canada. Newfoundland /Labrador and Nova Scotia were provinces with highest incidences and mortality, while British Columbia, Alberta, and Saskatchewan were provinces with lower incidence and mortality rates.

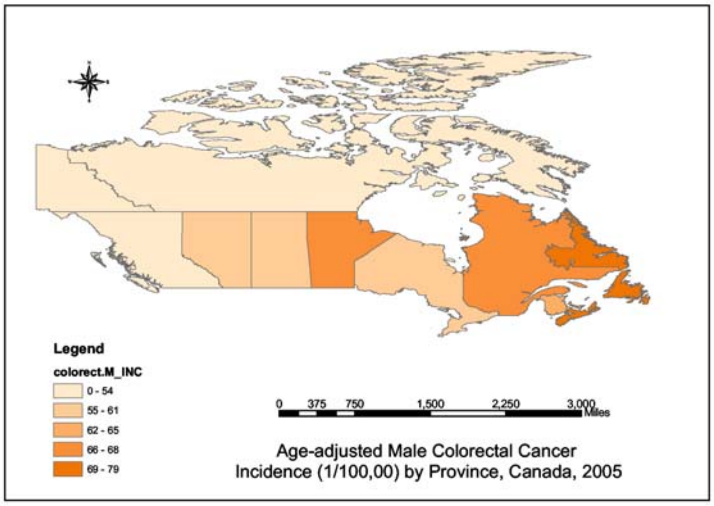


Figure 1. Age adjusted male colorectal cancer incidence by province, Canada, 2005 [47]

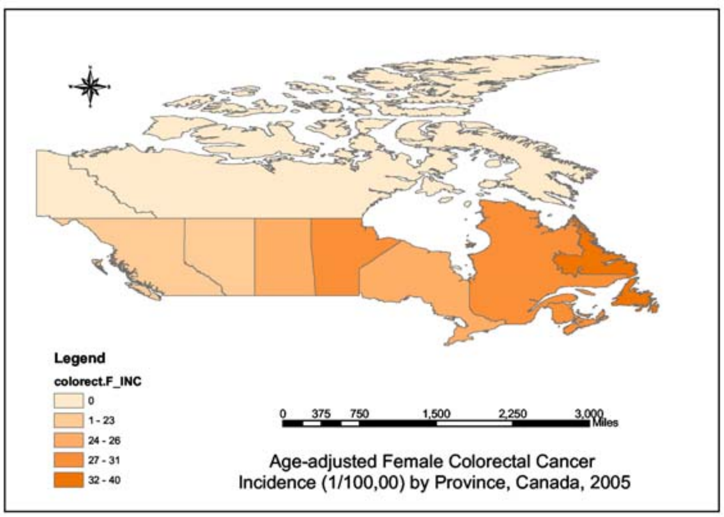


Figure 2. Age-adjusted female colorectal cancer incidence by province, Canada, 2005[47]

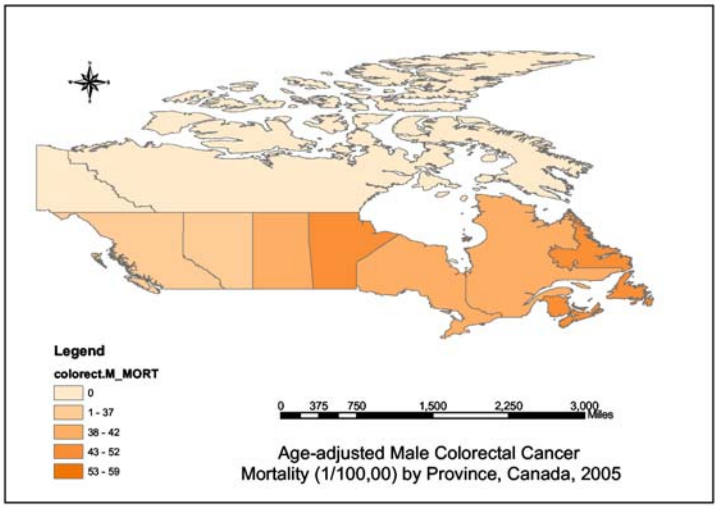


Figure 3. Age-adjusted male colorectal cancer mortality by province, Canada, 2005 [47]

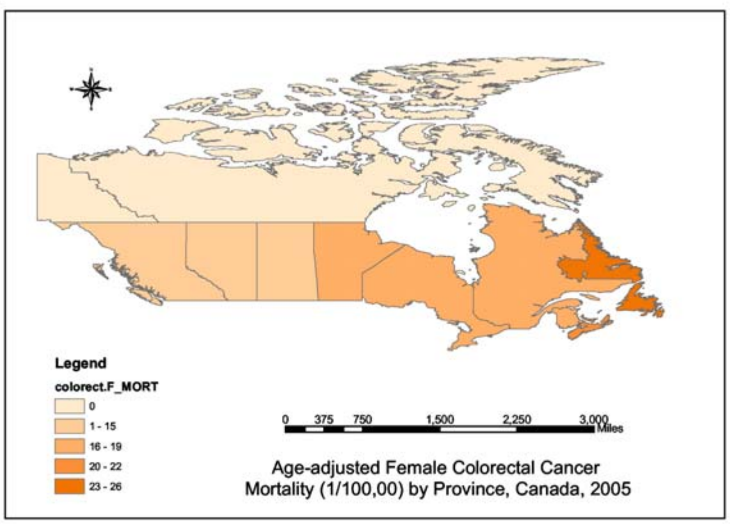


Figure 4. Age-adjusted female colorectal cancer mortality by province, Canada, 2005 [47]

Colorectal cancer trend in Canada

Although the recent trend had been for decreasing incidence and mortality associated with colorectal cancer and the projections were made on longer time trends, there has been an actual slight increase in incidence among both men and women annually since 1997. Mortality has continued to decline for both sexes but more so among women. Consensus is emerging internationally about the benefits of population-based screening for colorectal cancer. This is under consideration in Canada at both provincial and national levels. However, some screening is already occurring in Canada and may have contributed to the most recent increased incidence and decreased mortality rates. The establishment and evaluation of organized screening programs can best evaluate this effect. Figure 5 shows the trend of incidence and mortality by sex from 1976 to 2005. The data for 2002-2005 were projected by Canadian Cancer Society [47] .

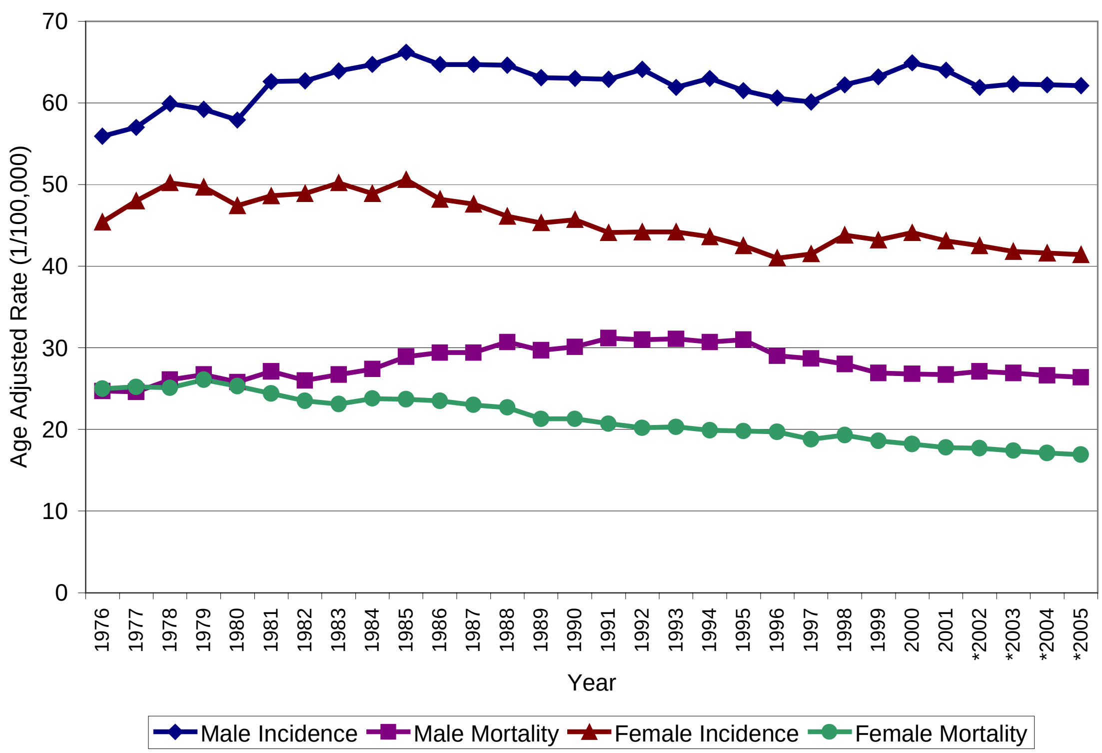


Figure 5. Age-adjusted Incidence and Mortality Rates by Sex, 1976-2005, Canada

Common Risk Factors of Colorectal Cancer

According to American Cancer Society [48], general causes of colorectal cancer include the following factors:

A family history of colorectal cancer: If you have a first-degree relative (parent, sibling, or offspring) who has had colorectal cancer, your risk for developing this disease is increased. People who have 2 or more close relatives with colorectal cancer make up about 20% of all people with colorectal cancer. The risk increases even further if the relatives are affected before the age of 60. About 5% to 10% of patients with colorectal cancer have an inherited genetic abnormality that causes the cancer. One abnormality is called *familial adenomatous polyposis (FAP)* and a second is called *hereditary nonpolyposis colorectal cancer (HNPCC)*, also known as Lynch syndrome. These abnormalities are described later in this document. No other clearly identified genetic abnormalities have been described at this time.

Familial colorectal cancer syndromes: Familial adenomatous polyposis is a disease where people typically develop hundreds of polyps in their colon and rectum. Usually this occurs between the ages of 5 and 40. Cancer usually develops in 1 or more of these polyps beginning at age 20. By age 40 almost all people with this disorder will have developed cancer if preventive surgery is not done. Hereditary nonpolyposis colon cancer (HNPCC) is the other clearly defined genetic syndrome. It accounts for 3% to 4% of all colorectal cancers. This also develops when people are relatively young. These people also have polyps, but they only have a few, not hundreds. Women with this condition also have a very high risk of developing cancer of the endometrium (lining of the upper part of the uterus).

Race/Ethnic background: Colorectal cancer incidence and mortality rates are highest in black man and women. Incidence rates among Asian Americans/pacific islanders, Hispanics/Latinos, American Indians/Alaska natives are low than those among whites. Jews of Eastern European descents (Ashkenazi Jews) have a higher rate of colorectal cancer.

A personal history of colorectal polyps: If you have had an adenomatous polyp, you are at increased risk for colorectal cancer. This is especially true if the polyps are large or if there are many of them.

A personal history of chronic inflammatory bowel disease: Chronic inflammatory bowel disease (IBD), including *ulcerative colitis* and *Crohn's disease*, is a condition in which the colon is inflamed over a long period of time. If you have chronic inflammatory bowel disease, your risk of developing colorectal cancer is increased.

Aging: Your chances of developing colorectal cancer increase markedly after age 50. More than 90% of people diagnosed with colorectal cancer are older than 50.

A diet mostly from animal sources: A diet that is high in fat, especially fats from animal sources, can increase your risk of colorectal cancer. Over time, eating a lot of red meats and processed meats can increase colorectal cancer risk.

Physical inactivity: If you are not physically active, you have an increased risk of developing colorectal cancer.

Obesity: If you are very overweight, your risk of dying of colorectal cancer is increased.

Diabetes: People with diabetes have a 30% to 40% increased chance of developing colorectal cancer. They also tend to have a higher death rate after diagnosis.

Smoking: Recent studies indicate that smokers are 30% to 40% more likely than nonsmokers to die from colorectal cancer. Smoking may be responsible for causing about 12% of fatal colorectal cancers. Almost everyone knows that smoking causes cancers in sites in the body that come in direct contact with the smoke, such as the mouth, larynx, and lungs. However, some of the cancer-causing substances are swallowed and can cause digestive system cancers, such as esophageal and colorectal cancer. Some of these substances are also absorbed into the bloodstream and can increase the risk of developing cancers of the kidneys, bladder, cervix, and other organs.

Alcohol intake: Colorectal cancer has been linked to the heavy use of alcohol. While some of this may be due to the effects of alcohol on folic acid in the body, it still would be wise to avoid heavy alcohol use.

Other occupational exposure: Some studies examined association of colorectal cancer risk with occupational exposures to asbestos, benzene, electromagnetic fields, formaldehyde, lead, and solvents. The results were inconsistent.

According to American Cancer Society [48], the point estimates of selected risk factors for colorectal cancer are summarized in Table 1.

Table 1. Summary of Selected Risk Factors for Colorectal Cancer

Risk Factor	Value	Relative Risks
Race/ethnicity	Black	1.15
	Asian	0.89
	Hispanic/Latinos	0.78
Family history of colon cancer	Yes	1.80
Physical activity	30 min moderate activity, 5 days a week	0.60
Obesity	Body mass index>=30	1.75
Diet	Red meat>=7 servings/week	1.50
	Vegetable and fruit >=5 serving/day	0.70
Smoking	Ever	1.50
Alcohol intake	>=4 drinks/week	1.40

<u>Additional Risk factors for Rectal Cancer</u>

It is important to recognize that colon cancer and rectal cancer share almost all known risk factors for colon cancer. There are additional risk factors for rectal cancer, alone, which relate to lifestyle and which appear to be relatively small in overall population effect but which are elevated among certain subgroups defined by sexual preference and practice.[59-64]. These practices would have to be more frequent among firefighters than in the general population for there to be confounding. There is no evidence or reason to believe so. If they are less, then overall colorectal rates would be less, because rectal cancer would then be less frequent.

Potential Carcinogenic Hazards of Firefighting

Many literatures now exist on the carcinogenic hazards of firefighting. [35,37-45]. The widespread introduction of synthetic building materials in the late 1950s increased the complexity of the firefighters exposure. Fire fighters would likely be exposed to carcinogens such as:

- Benzene
- Polycylic aromatic hydrocarbons (PAHs)
- Arsenic in wood preservatives,
- Asbestos in building insulation,
- Diesel engine exhaust
- Dioxins.
- Vinyl chloride
- Chloroform
- Coal tar
- Asphalt
- Polychlorinated dibenzofurans
- Dibenzo-p-dioxins
- Formaldehyde
- Metals (chromium, cadmium)
- Aromatic amines
- Chlorinated hydrocarbons

These and other potential hazards were also summarized in detail in the review paper by Guidotti and Clough [14].

Firefighting and Colorectal Cancer

Included studies

Based on inclusion criteria listed above, 17 studies included in the meta-analysis. The relative risk measures and their 95% CIs are listed in Table 2. The earliest paper included was published in 1975 and the latest one was in 2005. Most of these studies used an occupational cohort design.

Table 2. Result of Risk Measures and 95% Confidence Intervals for Studies Included in Meta-analysis

Authors	Year	Population	Design	Indicator	Colorectal		Colon		Rectal	
					Obs.	Risk (95% CI)	Obs.	Risk (95% CI)	Obs.	Risk (95% CI)
Berg and Howell	1975	1949-53, 1959-63, US	Surveillance	SMR	39	279 (198.1-380.8)				
Decoufle et al	1977	1967, us	Cohort	PMR	40	149.8 (107.2-204)	23	119 (75.5-178.8)	17	229.7 (133.8-367.8)
Howe and Londsay	1983	1965-73, Canada	Cohort	SMR			2	154 (19-556)		
Eliopulos et al	1984	1939-78, Western Australian	Cohort	SMR			4	159 (43-407)		
California HSD	1987	California	Surveillance	SMR			6	131 (48-284)		
Vena and Fiedler	1987	1950-79, Buffalo	Cohort	SMR	23	190.1 (120.5-285.2)	16	183 (105-297)	7	208 (84-428)
Sama et al	1990	1982-86, Massachusetts	Surveillance	SMOR*	55	125.6 (94.6-163.4)	33	120 (80-182)	22	135 (84-219)
Beaumont et al	1991	1970-82, San Francisco FD	Cohort	SMR	37	111.4 (78.5-153.6)	24	99 (63-147)	13	145 (77-249)
Demers et al	1992	1945-89, 4 cities, US	Cohort	SMR	32	87.2 (59.6-123.1)	24	85 (54-126)	8	95 (41-187)
Guidotti	1993	1927-87, Alberta, Canada	Cohort	SMR	14	161 (88-271)				
Aronson et al	1994	1950-89, Toronto	Cohort	SMR	24	93 (59.6-138.4)	11	60 (30-108)	13	171 (91-293)
Burnett et al	1994	1984-90, 27 states, US	Cohort	PMR					37	148 (105-205)
Demers et al	1994	1974-89, Washington, US	Cohort	SIR	35	106.7 (74.3-148.4)	23	110 (70-160)	12	100 (50-180)
Tornling et al	1994	1931-83, Stockholm	Cohort	SMR	14	127.3 (69.6-213.5)	6	85 (31-185)	8	207 (89-408)
Tornling et al	1994	1931-83, Stockholm	Cohort	SIR	18	121.6 (72.1-192.2)	8	90 (29-177)	10	170 (81-312)
Ma et al	1998	1984-93, 24 States, US (white)	Cohort	MOR	176	101.4 (87-117.6)	149	100 (90-120)	27	110 (80-160)
Baris et al	2001	1925-86, Philadelphia, PA	Cohort	SMR	78	138.1 (109.1-172.3)	64	151 (118-193)	14	99 (59-168)
Bates et al	2001	1977-96, New Zealand	Cohort	SMR	10	120.5 (57.8-221.6)	7	119 (40-260)	4	121 (30-310)
Bates et al	2001	1977-96, New Zealand	Cohort	SIR	16	81.6 (46.7-132.6)		60(20-120)	9	115(50-220)
Ma et al	2005	1972-99, Florida	Cohort	SMR	45	110.3 (80.5-147.7)	38	114 (81-156)	7	94 (38-193)

* SMOR: standardized morbidity odds ratio, treated as SIR.

Overall risk of firefighting and heterogeneity test

The Summarized relative risk of firefighting with colorectal cancer and heterogeneity test results are shown in Table 3. The Forest plots with individual studies and summarized relative risk for firefighting and each cancer are presented in figure 6-16.

SIR: Based on SIR, the result suggested the summarized relative risk for colon, rectal, and colorectal cancer is at 1.08, 1.29, and 1.13 respectively and none of them were statistically significant since the lower boundaries of 95% CI were all below 1. Chi-squared tests showed that there were no heterogeneity in the pooled studies (table 3, figure 6-8).

SMR: Colon cancer did not show a significant association with overall firefighting, although there were two studies demonstrated significant associations (figure 9). Rectal cancer (RR: 1.23; 95% CI: 1.00-1.51) and colorectal cancer combined (1.16 (1.01-1.33) showed significant associations with overall firefighting, respectively. If Berg and Howell's paper was included in the study, the risk estimates for colorectal cancer was at 1.29 (95% CI: 1.05-1.59) but the heterogeneity test became very significant suggesting this particular study was very different from other studies in the pooled analysis (table 3, figure 9-12).

PMR: Only one study for colon and colorectal cancer and two studies for rectal cancer were identified. Basically PMRs were higher than SMRs since it compared only distributions of causes of deaths. Other than the magnitude, rectal and colorectal cancers were found consistently significant as SMR studies (table 3). .

SMR and PMR: Although PMR was considered as not a comparable risk measure to SMR. In order to estimate the risk estimates for colorectal cancer in the worst scenario, PMR studies were pooled with SMR studies to produce summarized risk estimates. Again Berg and Howell's paper was tested for sensitivity. Please note that Berg and Howell's study only reported colorectal cancer with subsite information for colon or rectal caner, so that it only influenced the colorectal cancer analysis. The results showed that colon cancer still did not appear to be associated with overall firefighting. However, rectal cancer showed an elevated risk estimate at 1.37 (95% CI: 1.15-1.64. Due to the dilution of colon cancer, colorectal risk estimated was at 1.19 but still significant (95% CI: 1.04-1.37) without the inclusion of Berg and Howell's study. The heterogeneity test was almost significant (p=0.09). Once Berg and Howell's study being included the summarized the risk estimate reached 1.31 (95% CI: 1.08-1.59) (table 3, figure 13-16).

Table 3. Summarized relative risk of firefighting with colorectal cancer and heterogeneity test

Cancer	Number of Studies	Original Risk Measures	RR	95% CI		Heterogeneity	
						Chi-squared test p value	I-squared
Colon cancer	4	SIR	1.08	0.82	1.42	0.6710	0.0%
Rectal cancer	4	SIR	1.29	0.94	1.78	0.7630	0.0%
Colorectal cancer	4	SIR	1.13	0.94	1.38	0.5700	0.0%
Colon cancer	12	SMR	1.12	0.95	1.32	0.0960	36.9%
Rectal cancer	9	SMR	1.23	1.00	1.51	0.657	0.0%
Colorectal cancer	10	SMR	1.16	1.01	1.33	0.1320	34.5%
Colorectal cancer	*11	SMR	1.29	1.05	1.59	0.0000	74.1%
Colon cancer	1	PMR	1.19	0.76	1.88	n/a	0.0%
Rectal cancer	2	PMR	1.75	1.15	2.66	0.1780	44.8%
Colorectal cancer	1	PMR	1.50	1.07	2.09	n/a	0.0%
Colon cancer	13	SMR or PMR	1.12	0.97	1.31	0.1270	32.0%
Rectal cancer	11	SMR or PMR	1.37	1.15	1.64	0.381	6.6%
Colorectal cancer	11	SMR or PMR	1.19	1.04	1.37	0.0910	38.6%
Colorectal cancer	*12	SMR or PMR	1.31	1.08	1.59	0.0000	72.5%

Note: p value>0.05 suggests there is no significant heterogeneity among pooled studies

I-squared indicator is a variation in pooled relative risk attributable to heterogeneity

* Berg and Howell study was included

n/a: only one study in the cell so that the heterogeneity was not performed

Figure 6. Forest Plot For Firefighting And Colon Cancer in SIR Studies

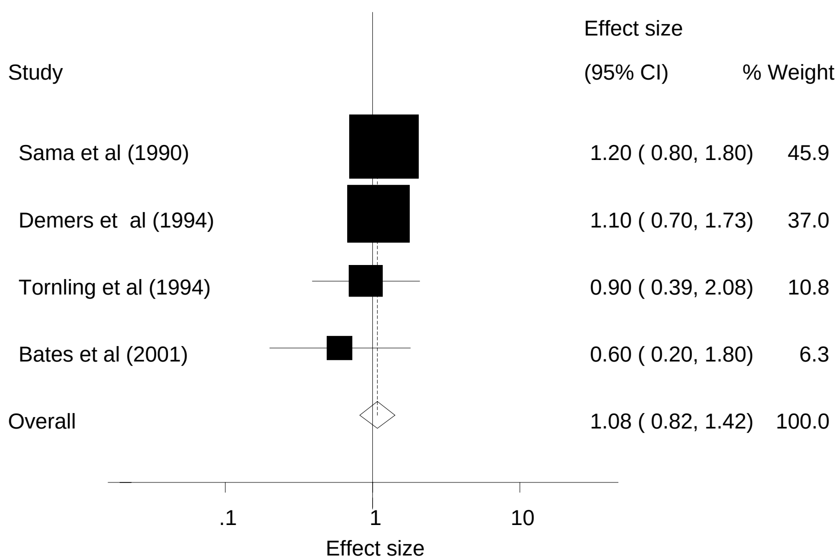


Figure 7. Forest Plot For Firefighting And Rectal Cancer in SIR Studies

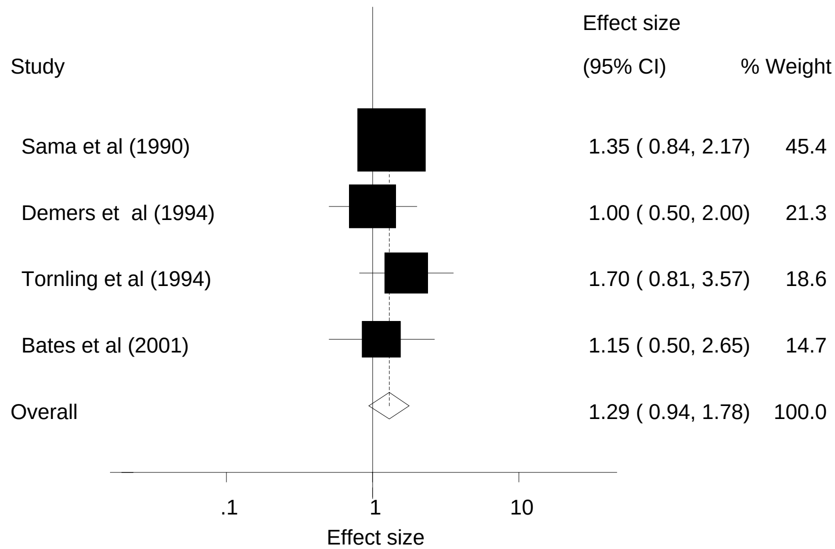


Figure 8. Forest Plot For Firefighting And Colorectal Cancer in SIR Studies

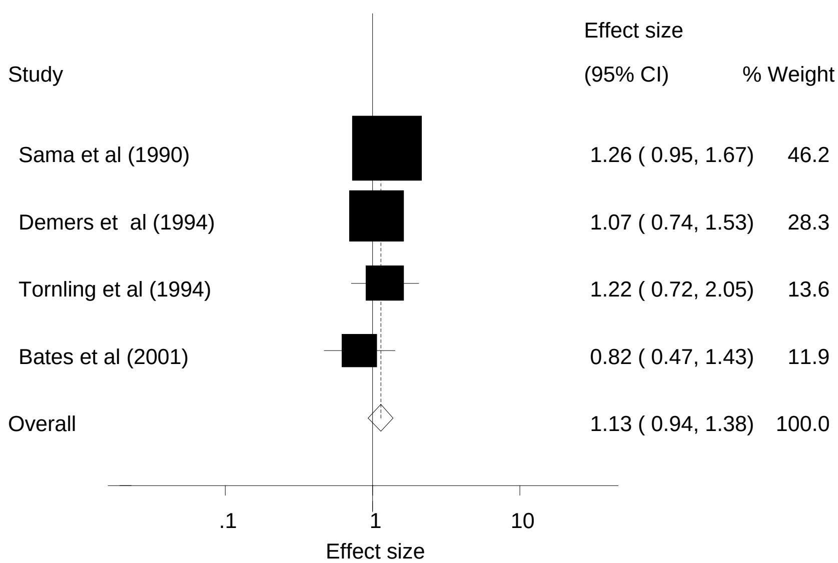


Figure 9. Forest Plot For Firefighting And Colon Cancer in SMR Studies

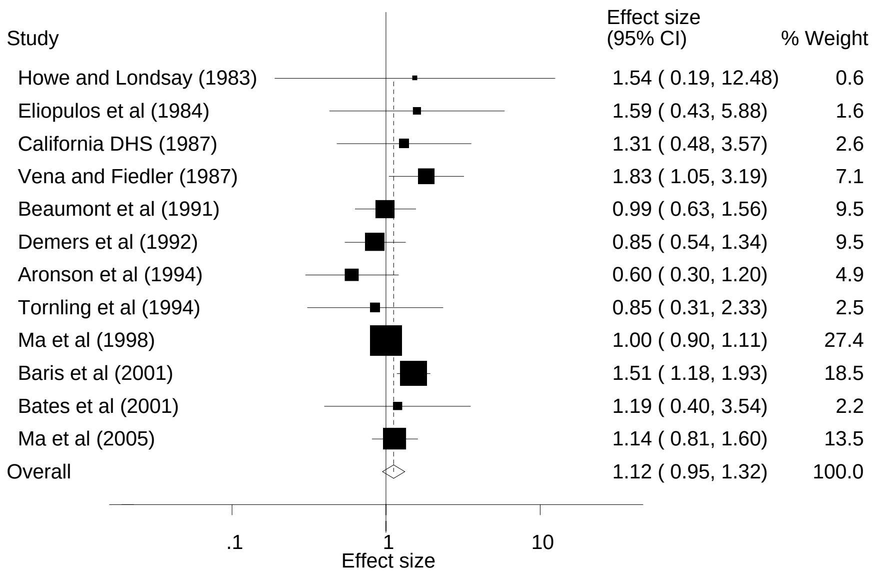


Figure 10. Forest Plot For Firefighting And Rectal Cancer in SMR Studies

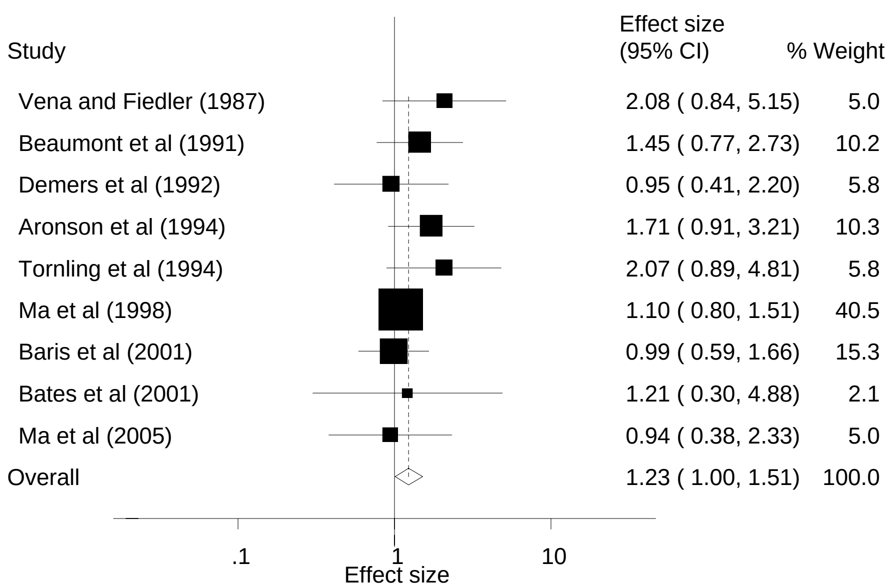


Figure 11. Forest Plot For Firefighting And Colorectal Cancer in SMR Studies (excluding Berg and Howell's Study)

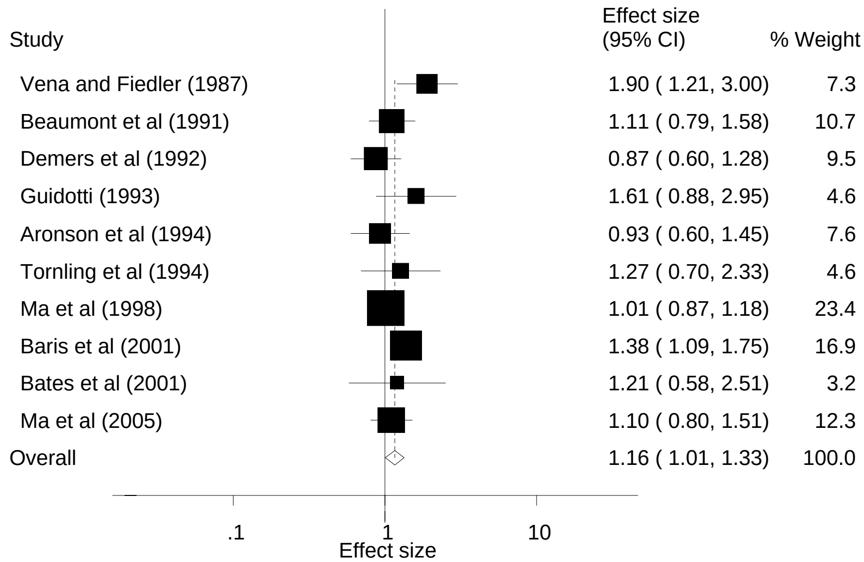


Figure 12. Forest Plot For Firefighting And Colorectal Cancer in SMR Studies (Including Berg and Howell's Study)

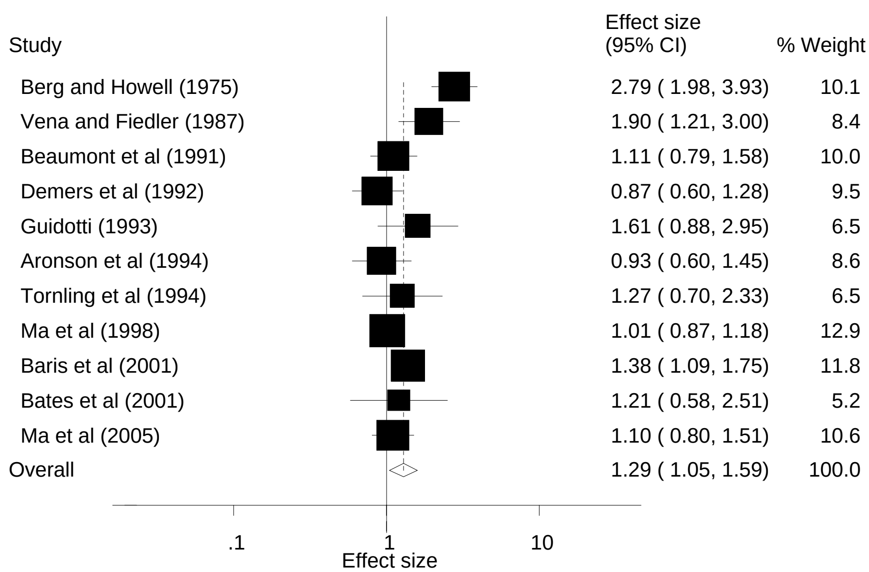


Figure 13. Forest Plot For Firefighting And Colon Cancer in SMR and PMR Studies

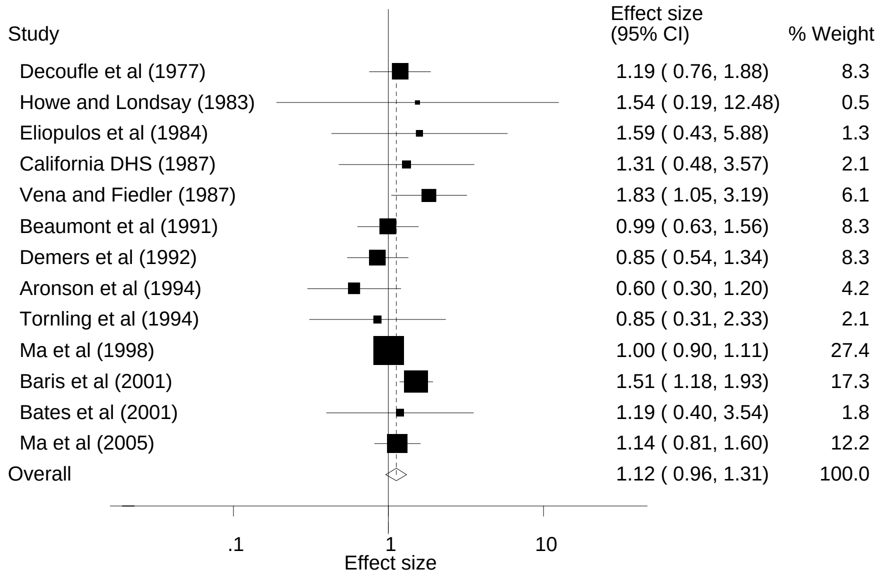


Figure 14. Forest Plot For Firefighting And Rectal Cancer in SMR and PMR Studies

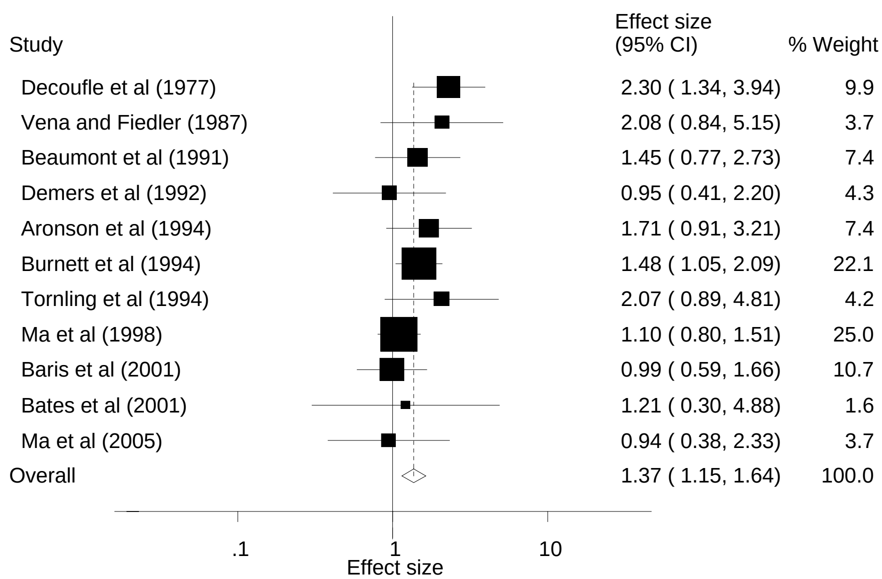


Figure 15. Forest Plot For Firefighting And Colorectal Cancer in SMR and PMR Studies (Excluding Berg and Howell's Study)

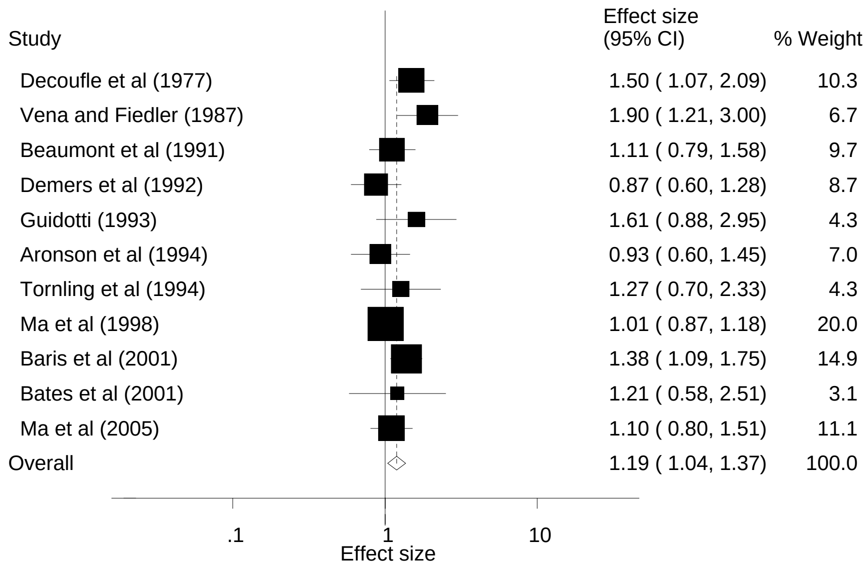
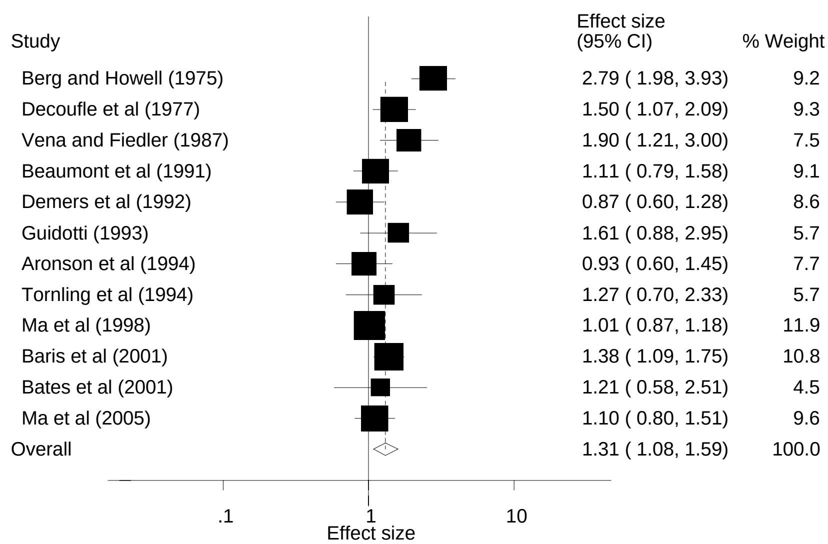


Figure 16. Forest Plot For Firefighting And Colorectal Cancer in SMR and PMR Studies (Including Berg and Howell's Study)



“Exposure-response” between duration of employment in firefighting and colorectal cancer

Four mortality studies analyzed the “exposure-response” between duration of employment and the risk for colon cancer, three for rectal cancer, and only two for colorectal combined, because observed case numbers were not available to combine colon and rectal cancer (Table 4). Two incidence studies examined duration and colon, rectal, and colorectal cancer. The result showed that all summarized “exposure-response” were not statistically significant. Two studies, however, Vena and Fielder’s (RR: 1.35; 95% CI: 1.16-1.56) and Baris et al’s (RR: 1.128; 95% CI: 1.01-1.26) studies, demonstrated strong “exposure-response” between duration of employment and the risk for colon cancer (table 4). When pooled with other two studies, the association was borderline significant with a RR of 1.12 (95% CI: 0.99-1.26), suggesting that with each 10 years of increase in firefighting duration the risk of colon cancer would increase 12%.

Table 4. "Exposure-response" for Each 10 Years' Increase in Firefighting for Each Study and Pooled Relative Risk Estimates

Original Risk Measures	Cancer	Authors	Year	RR	95% CI		Weight (%)
SMR	Colon						
		Vena and Fiedler	1987	1.35	1.16	1.56	23.77
		Beaumont et al	1991	1.02	0.89	1.18	24.48
		Demers et al	1992	1.00	0.87	1.16	23.84
		Baris et al	2001	1.13	1.01	1.26	27.91
		Overall		1.12	0.99	1.26	100.00
	Rectal						
		Beaumont et al	1991	1.07	0.83	1.37	26.84
		Aronson et al	1994	1.11	0.93	1.34	49.33
		Baris et al	2001	1.00	0.77	1.31	23.83
		Overall		1.07	0.94	1.22	100.00
	Colorectal						
		Beaumont et al	1991	1.03	0.92	1.16	51.89
		Baris et al	2001	1.10	0.98	1.24	48.11
		Overall		1.07	0.98	1.16	100.00
SIR	Colon						
		Demers et al	1994	1.09	0.90	1.32	77.86
		Bates et al	2001	1.18	0.82	1.69	22.14
		Overall		1.11	0.93	1.31	100.00
	Rectal						
		Demers et al	1994	0.94	0.64	1.37	54.49
		Bates et al	2001	1.16	0.76	1.77	45.51
		Overall		1.03	0.78	1.37	100.00
	Colorectal						
		Demers et al	1994	0.99	0.96	1.02	74.31
		Bates et al	2001	1.17	0.93	1.48	25.69
		Overall		1.03	0.89	1.20	100.00

Estimation of probability of a Firefighting-related Colorectal Cancer risk

Calculating ARF for firefighting:

Table 6 showed the ARF%s for overall firefighting activities based on the result of Table 3. PMR studies were not calculated separately but with SMR studies due to the small numbers.

Table 5.Attributable Risk Fraction (%) for Summarized Relative Risk Estimates from firefighting

Cancer	Number of Studies	Original Risk Measures	RR	APR%
Colon cancer	4	SIR	1.08	7.3
Rectal cancer	4	SIR	1.29	22.5
Colorectal cancer	4	SIR	1.13	11.8
Colon cancer	12	SMR	1.12	10.6
Rectal cancer	10	SMR	1.23	18.7
Colorectal cancer	11	SMR	1.16	13.8
Colorectal cancer	*12	SMR	1.29	22.5
Colon cancer	13	SMR or PMR	1.12	11.0
Rectal cancer	12	SMR or PMR	1.37	27.1
Colorectal cancer	12	SMR or PMR	1.19	16.2
Colorectal cancer	*13	SMR or PMR	1.31	23.6

* Berg and Howell study was included

The results showed that depending on different scenarios ARF% to firefighting ranged from 7.2 to11% for colon cancer; 18.7-27.1% for rectal cancer; and 11.8- 23.6%. In other word, the probability of getting colorectal cancer from firefighting related risk factors for a colorectal cancer case among firefighters was at 11.8 - 23.6%

Summarized Relative Risk and Attributable Risk Fraction by Duration:

Although the duration did not show significant association with colorectal cancer risk, to be conservative we provided another approach, which allow you to determine ARFs by duration of firefighting. Tables 6 were created based the result of table 4. The results showed that on average the RR of dieing from or suffering from colorectal cancer would increase with duration of employment and reach 1.6 level at highest after 40 years of exposure. The attributable risk fraction to firefighting would reach 36% at highest after 40 years of exposure.

Table 6. Summarized Relative Risk and Attributable Risk Fraction by Duration

Original Risk Measures	Cancer	RR				ARF%			
		10Y	20Y	30Y	40Y	10Y	20Y	30Y	40Y
SMR	Colon	1.117	1.248	1.394	1.557	10.47	19.85	28.25	35.76
	Rectal	1.074	1.153	1.239	1.331	6.89	13.31	19.28	24.84
	Colorectal	1.066	1.136	1.211	1.291	6.19	12.00	17.45	22.56
SIR	Colon	1.106	1.223	1.353	1.496	9.58	18.25	26.08	33.17
	Rectal	1.030	1.061	1.093	1.126	2.91	5.74	8.49	11.15
	Colorectal	1.033	1.067	1.102	1.139	3.19	6.29	9.28	12.18

CONCLUSION

Based on the above literature review and meta-analysis results, summary estimates were generated by pooling eligible studies together. The following are the findings of this review. However, any future publications on colorectal cancer risk among firefighters would likely change these findings.

1) All of the incidence studies published so far did not show any significant association between firefighting and cancer of colon and rectum, or colorectal cancer combined and the pooled analysis also failed to reach a level of a statistical significance;

2) In mortality studies, rectal cancer and colorectal cancer combined were found associated with overall firefighting exposure with statistical significance. The relative risk was below 1.5 in the worst scenario. Colon cancer did not show significant association with firefighting. Although two early studies did show elevated colon cancer risks among firefighters, this effect was diluted by a few later large-scale studies.

3) The attributable risk fraction analysis suggested that colorectal cancer in firefighters might have at most a 24% probability of being associated with firefighting;

4) The duration analysis results showed that, on average, the RR of dying from or suffering from colon cancer would slightly increase with duration of employment and reach 1.6 level at highest after 40 years of exposure, although this increasing trend was not statistically significant. The attributable risk fraction for firefighting would reach its highest at 36% after 40 years of exposure. Rectal cancer and colorectal cancer would also slightly increase with duration of employment without statistical significance and the slope of increase were even smaller than colon cancer.

5) The above conclusion was based on a pooled analysis of eligible studies and reflects the average risk level for colorectal cancer for the entire firefighter population. It should not be applied directly to individual firefighter cases.

6) For individual cases, information on other risk factors such as age, family history, smoking, etc. need to be obtained. In addition to the information on other risk factors, it is important to be aware of background levels of colorectal cancer risk in the area of residence. For instance, the probability of a work relationship with firefighting would also be increased in the individual who is young, not a smoker, without a family history of colorectal cancer, is not obese, and resides in a geographical area with a low rate of colorectal cancer.

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