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The proportion of cancer attributable to occupational exposures

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Abstract

Purpose—To review the literature on the estimation of the population attributable fraction (PAF) of cancer due to occupational exposures and to describe challenges in the estimation of this metric. To help illustrate the inherent challenges, we also estimate PAFs for selected cancers diagnosed in the United States in 2010 attributable to work as a painter (causally associated with bladder and lung cancer) and shiftwork (possibly associated with breast cancer).

Methods—We reviewed and summarized previous reports providing quantitative estimates of PAF for total cancer due to occupational exposures. We calculated PAF estimates for painters and shiftwork using methodology from a detailed investigation of the occupational cancer burden in Great Britain, with adaptations made for the U.S. population.

Results—The estimated occupation-attributable fraction for total cancer generally ranged between 2% and 8% (men, 3-14%; women, 1-2%) based on previous reports. We calculated that employment as a painter accounted for a very small proportion of cancers of the bladder and lung diagnosed in the United States in 2010, with PAFs of 0.5% for each site. In contrast, our calculations suggest that the potential impact of shiftwork on breast cancer (if causal) could be substantial, with a PAF of 5.7%, translating to 11,777 attributable breast cancers.

Conclusions—Continued efforts to estimate the occupational cancer burden will be important as scientific evidence and economic trends evolve. Such projects should consider the challenges involved in PAF estimation, which we summarize in this report.

Introduction

Occupational exposures, among the first identified carcinogens,[1;2] make up a substantial proportion of established cancer-causing agents identified to date, with at least 45 of the 113 agents classified by the International Agency for Research on Cancer (IARC) as

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carcinogenic to humans (Group 1) involving workplace chemicals or employment in selected occupations and industries.[3-6] Over the past four decades, the proportion of total cancer incidence or mortality attributable to occupational exposures has been estimated using various methods in different populations because of its important implications regarding the development and enforcement of occupational health regulations and their prioritization across different occupational agents.[7-20] However, efforts to calculate the population attributable fraction (PAF) of cancer due to occupation (henceforth referred to as the "occupation-attributable fraction") in the United States and other countries are complicated by many challenges.[12;21;22]

In this article, we will review the published literature on the estimation of the occupation-attributable fraction of cancer and discuss some of the challenges in estimation of this metric. To help illustrate these challenges, we also estimated the PAFs for selected cancers diagnosed in the United States in 2010 attributable to work as a painter (for cancers of the lung and bladder) and shiftwork (breast cancer).

Estimates of the total occupational cancer burden

We have limited our review to reports providing quantitative estimates of the total occupation-attributable fraction of cancer, developed using calculations of PAF or similar statistics based on estimates of exposure prevalence and relative risk;[7-12] these estimates are summarized in Table 1. This list excludes reported PAF estimates that were not based on quantitative methods[13-16] or that were based on previously reported estimates.[17-19] We also excluded one estimate that included only lung cancer, mesothelioma, and leukemia.[20]

The first reported quantitative estimate of the total occupation-attributable fraction was reported in 1978 by Bridbord et al.[7] The report, which considered six occupational exposures and six cancer sites, estimated that "...occupationally related cancer may comprise as much as 20% or more of total cancer mortality in coming decades", with asbestos alone contributing up to 13%-18%, and additional exposures potentially accounting for an additional 10%-20%. The vast majority of projected occupation-attributable cancer deaths involved mesothelioma and cancers of the respiratory tract. However, the calculations had several data limitations and were based on questionable assumptions, such as the application of relative risk estimates obtained from studies of highly exposed workers to the total number of potentially exposed workers (irrespective of exposure level) in order to make cancer projections. For this and other reasons, the estimated occupational cancer burden from Bridbord et al. likely represents an overestimate of the true occupational cancer burden.

In 1981, Doll and Peto assessed the occupational cancer burden as part of a landmark report estimating the proportions of U.S. cancer mortality attributable to different lifestyle and environmental factors.[8] From their assessment, which considered 13 occupational exposures and (primarily) nine cancer sites, they estimated that only about 4% of all U.S. cancer deaths were attributable to occupational factors (approximately 8% for men and 1% for women). Lung cancer accounted for about 70% of occupational cancer mortality, with an estimated occupation-attributable fraction of 15% in men and 5% in women. Some assumptions made in the analysis may have led to an underascertainment of the occupational cancer burden, such as the restriction to cancers diagnosed before age 65, and the low estimated PAF due to asbestos for mesothelioma of the peritoneum (assumed to be 15% for men, 5% for women) and pleural cavity (25% for men, 5% for women). Doll and Peto acknowledged that their overall estimate was tentative, asserting that "...the final conclusion is unlikely to be out in either direction by more than a factor of about two", and likely to change with the discovery of additional occupational carcinogens.

The most recent calculation of occupation-attributable cancer in the United States was reported in 2003 by Steenland et al. as part of a comprehensive assessment of the magnitude of national mortality due to selected causes of death associated with occupational exposures.[9] Through calculations involving agents classified by IARC as established human carcinogens (Group 1) and probably carcinogenic to humans (Group 2A; for bladder cancer and lung cancer only) for nine established occupation-related cancers, the authors estimated the proportion of U.S. cancer deaths attributable to occupation at between 2.4% and 4.8% (3.3-7.3% for men and 0.8-1.0% for women). The three largest contributors were lung cancer (site-specific PAF 8-19% for men, 2% for women), mesothelioma (85-90% for men, 23-90% for women), and bladder cancer (7-19% for men, 3-19% for women). Steenland et al. noted that their total estimate may be conservative given their decision to include only well-established occupation-related cancers.

Estimates of total occupation-attributable fractions for cancer have also been calculated for other populations. In 1997, Dreyer et al. calculated the proportion of total cancer incidence attributable to occupational exposures in the Nordic countries between 1970-84, focusing on nine exposure categories involving IARC Group 1 agents and seven cancer sites linked to occupation.[10] They projected occupation-attributable fractions for total cancer of 2% (3% for men, 0.1% for women) across these populations by the year 2000. In 2001, Nurminen and Karjalainen utilized a Finnish job-exposure matrix and published relative risks for 22 IARC Group 1 and 22 Group 2A agents for 26 cancer sites to estimate the impact of occupational exposures on cancer deaths, as part of a broader project quantifying occupation-related mortality in Finland.[11] Their estimated occupation-attributable fraction of 8% (14% for men, 2% for women) is comparatively high, due at least in part to the larger number of evaluated agents and cancer sites considered, some with limited epidemiologic evidence of association.

In 2012, Rushton et al. reported a detailed examination quantifying the occupational cancer burden in Great Britain, both overall and within selected industrial sectors.[12] The authors considered all relevant IARC Group 1 agents and occupations as well as Group 2A agents for which the epidemiologic evidence was rated as "strong" or "suggestive" in IARC monographs, calculating occupation-related PAF estimates for total cancer and 24 individual sites. Overall, 5.3% of total cancer was estimated to be due to occupational exposures (8.2%, men; 2.3%, women). Of the estimated 13,598 incident cancers registered in Britain in 2004 attributable to occupational exposures, the five leading malignancies were lung cancer (40%), non-melanoma skin cancer (21%), breast cancer (14%), mesothelioma (14%), and bladder cancer (4%). Forty-one percent of the occupation-attributable cancers were attributable to work in the construction industry.[23] Among women, 54% of the occupation-attributable cancers were breast cancers attributable to shift work.

These PAFs across studies are not directly comparable with one another due to differences in the definition of occupational exposure, number of cancer sites considered, national employment patterns, distributions of exposure within at-risk occupations, and other factors. Nonetheless, the majority of published reports suggest that the occupation-attributable fraction for total cancer in developed countries ranges between 2% and 8%. Sex-specific PAF estimates range between 3-14% for men and 1-2% for women, although the latter estimate should be interpreted with caution given the paucity of studies designed to detect occupational cancer risks among women.[24]

Examples: PAFs for cancer due to painting and shiftwork

To help illustrate many of the challenges involved in calculating occupation-attributable fractions for cancer, we estimated the proportion of selected cancers diagnosed in the United States in 2010 attributable to work as a painter (for cancers of the lung and bladder) and shiftwork (breast cancer). These two occupational risk factors were the focus of a comprehensive review of the epidemiologic and toxicological literature for evidence of carcinogenicity conducted at IARC in 2007.[25] Following the review, the IARC working group maintained the previous classification of painting as a Group 1 carcinogenic exposure causing lung cancer, and concluded that there was sufficient epidemiologic evidence that it is also a bladder carcinogen. Shiftwork, evaluated for the first time by IARC, was classified as a Group 2A agent; the epidemiologic evidence informing this classification came mainly from studies of breast cancer.

We have developed estimates of the PAF and the number of incident cancers attributable to painting and shiftwork using the methodology of Rushton et al. for calculating the occupational cancer burden,[12;26] with adaptations made for the U.S. population. For these calculations, we assumed an exposure-cancer latent period of 10-50 years (i.e., a risk exposure period of 1960-2000 for occupation-related cancers diagnosed in 2010).

1) Estimating the proportion of the population exposed—We first developed estimates of n_0, the number of U.S. workers employed as painters or performing shiftwork in 1980, the risk exposure period midpoint, using census and survey data, respectively. The number of workers with a painting-related occupation in 1980 was estimated at approximately 710,000 (586,000 men, 124,000 women) using employment data from the 1980 U.S. Census of Population for job titles including the words "painter" or "painting".[27] By applying an estimate of the prevalence of shiftwork among female full-time and salary workers (13%) from the 1985 Current Population Survey (CPS)[28] to the 1980 Census estimate of the total number of employed women (approximately 41,000,000), we estimated the number of U.S. women who performed shiftwork in 1980 at approximately 5,400,000.

We then calculated the number of people alive in 2010 who were "ever exposed" to employment as a painter or in shiftwork, $N_{e(REP)}$, using an equation described by Hutchings and Rushton.[26]

The equation, in its simplest form, can be expressed as follows:

$$N_{e(REP)} = n_0 + \{n_0 \; * \; TO \; * \; t\}$$

where n_0, defined previously, is the number of workers employed in the midpoint of the risk exposure period (1980), TO is the annual staff turnover (assumed to be 0.10 for men and 0.14 for women, consistent with previous reports[9;26;29]), and t is the number of years in the risk exposure period (40). Thus, the cohort of ever-exposed workers in 2010, $N_{e(REP)}$, represents the sum of the original cohort of exposed workers, approximated by n_0, and a cohort of turnover-recruited workers, n_0 * TO * t. U.S. life table estimates of the proportions of the general population surviving to the target year (2010) were used in the full equation for $N_{e(REP)}$ to take into account survival to the target year so that only the ever-exposed cohort members surviving to 2010 would be counted. We generally used the model parameter values of Rushton et al., with the exception of using life table and population data for the United States, and specifying the retirement age as 65 for both men and women. Our estimates of $N_{e(REP)}$ indicate that approximately 2.7 million Americans in 2010 had ever worked as a painter and 30.4 million women had ever performed night shiftwork.

To estimate the proportion of the population exposed, we divided $N_{e(REP)}$ by the estimated total number of people ever of working age during the risk exposure period and alive in 2010. Our calculated estimates of the proportion of the population exposed were 1.3% for work as a painter (2.2%, men; 0.6%, women) and 29% for shiftwork among women.

2) Estimating the cancer relative risks—Estimates of cancer relative risk (RR) for ever having worked in painting were obtained from recent meta-analyses summarizing results from studies of bladder cancer and lung cancer among painters; the summary RRs calculated from smoking-adjusted results were 1.28 (95% confidence interval [CI] 1.15 to 1.43; 27 studies) and 1.35 (95% CI 1.21-1.51; 27 studies), respectively.[30;31] In a 2013 meta-analysis of shiftwork and breast cancer, the summary RR for having ever performed shiftwork was 1.21 (95% CI 1.00-1.47; 8 studies).[32]

3) Calculating the PAF and number of occupation-attributable cancers—We calculated estimates of PAF due to painting and shiftwork using Levin's equation:

$$PAF = Pr(\mathrm{E}) \; * \; (RR - 1) / \{1 + Pr(\mathrm{E}) \; * \; (RR - 1)\}$$

where Pr(E) is the proportion of the population exposed. The number of attributable incident cancers (AN) was approximated using the following equation:

$$AN = PAF \; * \; \mathrm{D}$$

where D is the number of site-specific incident cancers in 2010.[33] We calculated lower and upper estimates of the PAF and AN using the lower and upper 95% confidence limits of the summary RR.

Our estimates of the PAF and number of attributable cancers for painting and shiftwork are summarized in Table 2. These findings indicate that employment as a painter accounts for a very small proportion of cancers of the bladder and lung diagnosed in the United States, with PAF estimates of 0.5% (lower estimate 0.3%, upper estimate 0.8%) and 0.5% (0.3%, 0.7%) respectively, accounting for 347 (186, 531) and 1,093 (657, 1,588) incident cancers, respectively, in 2010. In contrast, our calculations suggest that the potential impact of shiftwork on breast cancer (if causal) could be substantial, with a PAF of 5.7% (0.0%, 11.9%) and an estimated 11,777 (0, 24,625) potentially attributable incident cases in the United States in 2010.

Issues in calculating and interpreting PAFs

Our examples raise several issues, summarized below, that require consideration when calculating and interpreting national estimates of occupation-attributable cancer burden using data drawn from multiple sources. More detailed discussions have been previously published.[12;21;22]

First, several potential sources of uncertainty are apparent when estimating exposure prevalence for PAF calculation. Such prevalence data for the target population may be unavailable or, if present, limited in detail or quality. For example, our use of Census data for occupational titles including “paint” has likely led to an underestimate in the number of painters in the U.S. workforce, as there is likely to be a substantial number of workers classified under other job titles who paint. Data estimating the distribution in exposure levels in the target population are often non-existent, necessitating either assumptions regarding the distribution or (as we have done) calculations limited to a dichotomized (ever vs. never) definition of exposure. Calculations of PAF using dichotomized exposure estimates, one level consisting exclusively of unexposed individuals, are unbiased when misclassification is nondifferential and the relative risk estimate is applicable to the exposure definition; however, such a crude exposure definition can lead to a loss of precision when the exposed group includes levels of exposure where there is no increased risk.[34] In instances where national exposure data are not available, estimates from external populations are occasionally used, although the representativeness of such data requires careful consideration. Importantly, the prevalence and intensity levels of many occupational exposures have been changing over time; such secular trends, if not accounted for, may introduce substantial error. In the examples of painting and shiftwork, we assumed no secular trend in U.S. exposure prevalence, which is generally supported by data from multiple census and CPS cycles.[28;35] Other necessary assumptions regarding exposure-cancer latency and job employment turnover will also substantially affect PAF calculations.

Similarly, several challenges in estimating RRs for the target population are apparent. The process of identifying a single estimate of RR or a credible range of estimates from the totality of published evidence can be laborious. Published meta-analyses, if available, can greatly simplify this process. In selecting external RR estimates for PAF calculation, the portability of the estimate requires consideration; for example, the application of a RR associated with very high exposure levels to a prevalence estimate of workers with any exposure will result in a biased, inflated PAF. In the case of our estimates for painting and shiftwork, the estimates of exposure prevalence and RR both referred to any painting and shiftwork, and were thus compatible. Other issues affecting the validity of external RR estimates include publication bias, uncontrolled confounding, and whether the RR estimates are based on incidence vs. mortality data. This last point is extremely important when calculating the PAF for less lethal occupation-related malignancies such as bladder cancer. For bladder cancer, mortality studies are often underpowered to identify occupational risk, as in the case of some cohort studies of metalworkers.[36] Thus for less lethal cancers, the PAF is better applied to incident case numbers than deaths in order not to underestimate the attributable numbers.

A particular limitation of the Levin equation for PAF calculation, used in our examples, is that it is strictly valid only under the assumption that there is no confounding of the exposure relative risk.[21;22] In the presence of confounding, the equation produces a biased estimate of PAF, even if the RR estimate used has been adjusted for the confounding factor(s). Ongoing work has shown that the bias from using confounder-adjusted RRs is close to the ratio of adjusted to unadjusted relative risk and generally likely to be small.[26] Methods for calculating overall PAF for a given exposure across strata of confounder levels can minimize such bias.[37-39]

Lastly, from a practical standpoint, PAF estimates are most useful in informing public health regulations when the exposure-disease association is recognized as causal in nature, and when the exposure is preventable. In this context, our PAF estimate for shiftwork should be interpreted with caution, given uncertainty regarding its status in terms of causality. Given the large number of breast cancers potentially attributable to shiftwork, and its uncertain impact on other malignancies, there is a critical need for additional epidemiologic research to resolve whether shiftwork is a human carcinogen.

Conclusions

As we have summarized, past publications have provided estimates of 2% to8% of total cancer as attributable to occupational exposures. The true magnitude of the occupational cancer burden may be greater given the large number of possible carcinogens (IARC Group 2B) with as-yet inconclusive evidence, and the continuing identification of new potentially carcinogenic agents in the workplace. Conversely, levels of exposure to many occupational carcinogens in developed countries are likely to decline with increased regulation and transfer of manufacturing-industry jobs to developing countries. Thus, continued efforts to estimate the total occupation-attributable fraction for cancer will be important in the future as scientific evidence and economic trends evolve. In addition, it will also be important to extend such investigations to developing countries, where the occupational cancer burden may be substantial given increasing industrialization and limited occupational health regulations.[40] All such projects should carefully consider the many challenges involved in PAF estimation, which we and others have discussed.[12;21;22]

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Table 1

Estimates of the proportion of total cancer attributable to occupational exposures in the United States and other countries

Year	Authors	Country	Occupational Agents Considered	Occupationally-Associated Cancers Considered	Estimated Proportion of Total Cancers Attributable to Occupation
1978	Bridbord et al.	United States	Asbestos, arsenic, benzene, chromium, nickel oxides, petroleum fractions	Colon/rectum, esophagus, leukemia, lung, mesothelioma, stomach	20% or more of future cancer mortality, based on then-current exposures
1981	Doll and Peto	United States	Aromatic amines, arsenic, asbestos, benzene, bischloroemethyl ether, cadmium, chromium, ionizing radiation, isopropyl oil, mustard gas, nickel, polycyclic hydrocarbons in soot/tar/oil, vinyl chloride*	Bone, bladder, larynx, leukemia, liver, lung, mesothelioma, non-melanoma skin, prostate, and others**	4% (6.8%, men; 1.2%, women)
1997	Dreyer et al.	Denmark, Finland, Iceland, Norway, Sweden	Arsenic, asbestos, benzene and other solvents, leather dust, metals / metal compounds /pigments, mining, polycyclic aromatic hydrocarbons,wood dust	bladder, kidney, larynx, leukemia, lung, mesothelioma, nasal cavity	2% (3%, men; <0.1%, women)
2001	Nurminen and Karjalainen	Finland	44 agents; 22 IARC Group 1 (carcinogenic to humans) and 22 Group 2A (probable human carcinogens)	26 cancer sites	8% (14%, men; 2%, women)
2003	Steenland et al.	United States	All IARC occupational Group 1 agents and lung/ bladder Group 2A agents (circa 2002)	bladder, kidney, larynx, leukemia, liver, lung, mesotheloima, nasal sinus / nasopharynx, skin	2.4-4.8% (3.3-7.3%, men; 0.8-1.0%, women)
2012	Rushton et al.	Great Britain	41 IARC occupational Group 1 and Group 2A agents	24 cancer sites	5.3% (8.2%, men, 2.3%, women)

* These exposures are listed in the original report as occupational carcinogens established at the time of the report; however, it is unclear how many of these exposures were considered in the estimation of the occupation-attributable fraction.

** Assumed that 1% of male cases and 0.5% of female cases of “cancers that possibly may be produced by occupational hazards” (mouth, esophagus, stomach, colon/rectum, pancreas, connective tissue, kidney, brain, Hodgkin lymphoma, non-Hodgkin lymphoma) are attributable to occupational exposures.

Table 2

Estimated U.S. site-specific cancer burden in 2010 due to occupation as a painter and shiftworker

		People ever exposed	Bladder cancer			Lung cancer			Breast cancer		
Occupation	**Population**	**N (%)**	**RR (LE-UE)**	**PAF% (LE-UE)**	**N_{Attrib} (LE-UE)**	**RR (LE-UE)**	**PAF% (LE-UE)**	**N_{Attrib} (LE-UE)**	**RR (LE-UE)**	**PAF (LE-UE)**	**N_{Attrib} (LE-UE)**
Painter	Men	2,123,441 (2.2)	1.28 (1.15-1.43)	0.6 (0.3-0.9)	318 (171-486)	1.35 (1.21-1.51)	0.8 (0.5-1.1)	877 (528-1,273)			
Painter	Women	617,395 (0.6)	1.28 (1.15-1.43)	0.2 (0.1-0.3)	29 (16-45)	1.35 (1.21-1.51)	0.2 (0.1-0.3)	216 (130-314)			
Painter	Total	2,740,836 (1.3)	1.28 (1.15-1.43)	0.5 (0.3-0.8)	347 (186-531)	1.35 (1.21-1.51)	0.5 (0.3-0.7)	1,093 (657-1,588)			
Shiftworker	Women	30,351,032 (28.7)							1.21 (1.00-1.47)	5.7 (0.0-11.9)	11,777 (0-24,625)

Abbreviations: RR, relative risk; PAF, population attributable risk; N_{Attrib}, number of incident cancers in 2010 attributable to exposure; LE, lower estimate; UE, upper estimate.