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ENDOTOXIN EXPOSURE AND LUNG CANCER MORTALITY BY TYPE OF FARMING: IS THERE A HIDDEN DOSE-RESPONSE RELATIONSHIP?

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Abstract: Previous studies have suggested that those in occupations exposed to endotoxin have a reduced rate of lung/respiratory cancer. An initial investigation found a significantly reduced risk of all sites malignant neoplasms in white male crop and livestock farmers, and black male and female crop farmers. This study provides data on lung/respiratory cancers in the same workers. Data were obtained from occupation and industry-coded US death certificates collected from 26 states for the period 1984–1993. Cause, sex, and race specific proportionate mortality ratios (PMRs) were calculated using a National Institute of Occupational Safety and Health computer program. A pooled relative risk (PRR) was obtained by summing up separately and then dividing the sex-race specific observed and expected cases, separately in crop and livestock farmers. Deaths from respiratory cancer were 12,482 and 2,290, and deaths from lung cancer were 12,091 and 2,201. In each sex and race group respiratory and lung cancer PMRs are generally lower than unity. Lung cancer PRR was 0.80 (0.78-0.81) in crop farmers and 0.70 (0.67-0.73) in livestock farmers, a significant difference ($p<0.0001$). Comparison of our findings with those by Nieuwenhuijsen *et al.* [1999] reporting personal exposure measurements in groups of Californian farmers (endotoxin averaging 132.5 EU/m^3 during livestock farming against 19.9 EU/m^3 during field crop and fruit farming), suggests a decreasing lung cancer risk with increasing endotoxin exposure, and supports a possible dose-response relationship between the two.

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INTRODUCTION

Numerous studies have been published on mortality rates for farmers [2, 3, 12, 28, 30]. These studies generally report lower than expected rates of cancer in farmers, including lung/respiratory cancer. The lower than expected rates of lung cancer in farmers have been attributed to the healthy worker effect (HWE), less exposure to carcinogenic substances, and reduced smoking [2, 30]. A less frequently mentioned reason for lower lung cancer risk is exposure to endotoxin, which has been shown to be a potent stimulator of endogenous antineoplastic mediators [7, 10, 11].

Exposure assessment in agriculture is difficult because of the varied cyclic nature of the farmers' work and the diverse location of the farms. Exposure may vary with

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Table 1. Sex and race specific proportionate mortality ratio (PMR) with 95% confidence interval (CI) and number of deaths observed (N) for respiratory cancer and lung cancer in crop and livestock farmers.

Classification of death (ICD Code)	White Male PMR (CI) N	Black Male PMR (CI) N	White Female PMR (CI) N	Black Female PMR (CI) N	All PRR (CI) N
Crop farmers					
Respiratory system cancer (160-165)	0.79* (0.78-0.81) 10,891	0.80* (0.76-0.85) 1,420	0.71* (0.58-0.86) 107	0.51* (0.39-0.65) 64	0.79* (0.77-0.80) 12,482
Trachea, bronchus and lung cancer (162)	0.80* (0.78-0.82) 10,579	0.80* (0.76-0.85) 1,345	0.71* (0.58-0.86) 104	0.52* (0.40-0.66) 63	0.80* (0.78-0.81) 12,091
Livestock farmers					
Respiratory system cancer (160-165)	0.71* (0.67-0.74) 2,217	1.01 (0.64-1.54) 22	0.76 (0.57-1.01) 50	1.22 (0.03-6.78) 1	0.71* (0.68-0.74) 2,290
Trachea, bronchus and lung cancer (162)	0.70* (0.67-0.74) 2,131	1.02 (0.63-1.56) 21	0.75* (0.55-1.00) 48	1.26 (0.03-7.04) 1	0.70* (0.67-0.73) 2,201

* $p < 0.05$

local farming practices, commodities grown or raised, geography, climate, and other factors.

Occupation and industry coded United States death certificates were collected from 26 States (Colorado, Georgia, Idaho, Indiana, Kansas, Kentucky, Maine, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Utah, Vermont, Washington, West Virginia, and Wisconsin) by the National Occupational Mortality Surveillance (NOMS) data system for the years 1984-1993. Using these data, mortality from several causes has been reported in crop and, separately, livestock farmers by Lee *et al.* [12]. Data on lung and respiratory cancers, which were not included in the initial investigation [12], are here presented in order to provide clues regarding the causes of the low lung cancer risk in agricultural workers.

MATERIALS AND METHODS

Occupation and industry coded United States death certificates were collected from 26 states by NOMS for the years 1984–1993, as previously described in Lee *et al.* [12]. In the absence of denominators, cause-specific proportionate mortality ratios (PMRs) were calculated, by dividing the proportion of deaths due to a specific cause among farmers with the proportion of deaths due to that cause among all decedents in the database, adjusting by 5-year age groups [12]. Sex and race specific PMRs for occupations and industries were calculated by means of a National Institute of Occupational Safety and Health computer program. The data analysed here concern deaths from respiratory system cancer (codes 160-165 according to the International Classification of Diseases, ICD) and lung cancer (ICD code 162). Statistical significance and 95% confidence interval (CI) were determined using the Mantel-Haenszel χ^2 test as reported by Lee *et al.* [12]. PMRs and CI are reported separately for white male (WM), white female (WF), black male (BM) and black female (BF) crop and livestock farmers.

A pooled relative risk (PRR) has been obtained in crop farmers and livestock farmers by summing up separately (and then dividing) observed and expected cases giving rise to PMR for WM, BM, WF, BF. The CI for PRR was obtained on the basis of Poisson distribution of observed cases.

A reasonable approach to proportionate mortality analysis is, according to Checkoway [6], to compute proportionate mortality ratios for a specific disease as a proportion of a broader disease category in which it is included (e.g., lung cancer as a proportion of all cancers). Hence, the Proportionate Cancer Mortality Ratio (PCMR) is the estimate of effect. According to Cassinelli [5], lung cancer PCMR has been calculated by dividing the lung cancer PMR by the all-cancer PMR reported by Lee *et al.* [12]; confidence intervals for this PCMR have been derived based on the Poisson distribution.

The standardized mortality ratios observed in two categories of farmers were compared by using approximate chi square statistics according to Breslow and Day [4] formula 3.7.

Based on the prevalences (1977–1978) of non-smokers, former smokers, moderate and heavy smokers in a random sample of white male US farmers and all occupations combined [13], we calculated the Confounding Risk Ratio (CRR) according to Axelson [1], by assuming that lung cancer relative risk is 5, 10 and 20 in former, moderate and heavy smokers, respectively. Then, an indirect adjustment for smoking was made by dividing the observed PMR (and its lower and upper confidence limit) by CRR.

RESULTS

In crop farmers and in livestock farmers, respectively, deaths from all causes were 229,549 and 44,930 [12], deaths from respiratory cancer were 12,482 and 2,290, and deaths from lung cancer were 12,091 and 2,201.

Table 1 shows that in each sex and race group of crop and livestock farmers respiratory and lung cancer PMRs are generally lower than unity, while groups not showing reduced risk include few (22 or less) cancer cases. It can also be seen that CIs for respiratory and lung cancer PMRs are largely overlapping among sex and race groups.

Although they are both significantly below unity, PRRs for respiratory system cancer and lung cancer are lower in livestock than in crop farmers. As regards lung cancer mortality, the result of the chi square test comparing two PRRs, equal to 29.0, indicates that the risk in livestock farmers is significantly lower ($p < 0.0001$) than that in crop farmers.

In WM, for whom mortality data were available to a larger extent, lung cancer PCMR was 0.91 (CI = 0.89 - 0.93) in crop farmers and 0.75 (0.72-0.79) in livestock farmers. The difference between two PCMRs, wider than that between the corresponding PMRs (Tab. 1), is highly significant at the χ^2 test (result = 63.2; $p < 0.0001$).

A CRR of 0.8454 was estimated from the smoking data of WM farmers reported by Levin [13]. The rough adjustment for smoking resulted in smoking-adjusted lung cancer risks of 0.95 (CI = 0.92 - 0.97) in WM crop farmers and 0.83 (CI = 0.79 - 0.88) in WM livestock farmers. These estimates suggest that smoking habits can not account for the whole reduction in lung cancer risk, particularly among WM livestock farmers.

DISCUSSION

PMRs have the attractive feature of providing results relatively quickly. A short-coming of this approach is that when the PMRs for some diseases are elevated, counterbalancing proportionate mortality deficits will occur for other causes. This occurs because, by definition, the total number of observed deaths from all causes combined will equal the expected number. Proportionate mortality studies can be used with greater confidence when observed and expected distributions of specific diseases are compared within a disease category for which the HWE is weak or non-existent. Since cancer mortality is generally less affected by the HWE than cardiovascular mortality [18], Checkoway [6] suggests comparing observed and expected site-specific cancer proportionate mortality, in which the mortality for a particular cancer site is expressed as PCMR. As reported in Results, the difference between two PCMRs is wider than that between the corresponding PMRs.

Our findings agree with those observed in other similarly exposed populations. A significant reduction of lung cancer mortality was found in the sub-cohort of 1,561 Italian dairy farmers (standardised mortality ratio (SMR) = 0.49; with 95% confidence interval (CI) = 0.31 - 0.74), but not in the sub-cohort of 722 crop/orchard farmers (SMR = 0.81; CI = 0.46 - 1.31) [16]. The lung cancer odds ratio (OR) was 0.66 (CI = 0.48 - 0.92) among New Zealand dairy farmers, while a non-significant decreased risk (OR = 0.87; CI = 0.64 - 1.18) was found among crop and orchard farmers [25]. The relative risk of lung cancer was as low as 0.36 (CI = 0.34 - 0.38) in a cohort of farmers from Sweden [32] where dairy farming is predominant [14]. A standardised incidence rate of 0.50 (CI = 0.35 - 0.68) has been found among pesticide applicators in Swedish agriculture, who are mainly dairy farmers [31]. The lung cancer SMR was 0.53 (CI = 0.30 - 0.87) among Icelandic farmers who mainly raise sheep and/or cattle [24]. Lastly, lung cancer incidence was 0.52 of that expected in males [27], and 0.33 in females [30] in New York State, where farming is predominantly dairy [29].

In a study from Poland, time schedule studies were conducted in selected animal and plant production farms during the whole year. Farmers engaged in animal breeding devoted 50–66% of yearly working time in activities entailing a high exposure to endotoxin (care of animals). On plant production farms, harvesting of vegetables, cleaning of grain, manual loading of grain and manure accounted for less than 20% of the yearly working time [19]. Even though among crop farmers grain/vegetable harvesting [21] and storage [9] entail a high endotoxin exposure, when estimating potential health effects it is important to take into account both parameters, level of exposure and duration of exposure.

Several studies have measured exposure to dust and its constituents such as endotoxin during livestock farming, where the endotoxin level is high because of the presence of organic material (e.g., animal faeces) and environmental conditions allowing bacteria to grow [20, 22, 23, 26].

A recent paper reported on comparative personal exposure levels to organic dusts and endotoxin during livestock farming and during field crop fruit and nut farming in a random sample of California farmers while performing individual farm operations [21]. Using endotoxin values found in handling different materials and performing several tasks, we computed a geometric mean of inhalable endotoxin levels, which was 132.5 EU/m^3 in 35 air samples collected in livestock related operations, against 19.9 EU/m^3 in 107 air samples collected in crop related operations. Relatively high inhalable endotoxin levels were measured during machine harvesting of vegetables (tomatoes) and nuts, and removing of weeds [21]. Since the latter tasks are performed in warm months (June, July, August, September), the frequency of high exposure is approximately 0.33 (= 4/12), and a dose index on a yearly basis is about 6.6 EU/m^3 (= 0.33 × 19.9) in crop farmers. By contrast, since endotoxin exposure occurs 12 months a year in livestock farmers, their dose index is 132.5 EU/m^3 (= 1 × 132.5).

Among our WM livestock and crop farmers, PMRs (CI) are 1.83 (1.47 - 2.26) and 1.33 (1.18 - 2.49) respectively for asthma, 23.38 (13.36 - 37.96) and 5.93 (3.52 - 9.38) respectively for extrinsic allergic alveolitis [12]. Since both diseases are due to organic dust these findings confirm that livestock farmers are exposed to organic dust levels higher than crop farmers.

A recent study reported that in dairy farmers lung cancer OR decreased by 19% per head of cattle (OR = 0.81; CI = 0.68 - 0.97), when the influence of age and smoking habits was controlled [17]. The increasing number of dairy cows, which probably increases the daily hours of exposure in cowsheds, is an indirect indicator of the suggested true protection factor: dust-borne biological agents, such as endotoxin, (1→3)-beta-D-glucans, a major cell wall component in fungi [8], and peptidoglycans, a component of the outer cell membrane of Gram-positive bacteria [9].

In a recent meta-analysis of epidemiologic evidence on cancer risk in textile workers, lung cancer risk was reduced in workers exposed to cotton dust - but not in textile workers using synthetic fibers or silk - especially in the past when dustiness of workplaces was high [15]. Since adjustment for smoking made little difference to the findings, the latter could be attributed to the exposure to cotton dusts containing endotoxin.

CONCLUSION

An increasing trend in endotoxin exposure – lowest in the general population, intermediate in crop farmers, highest in livestock farmers - parallels a decreasing trend in lung cancer risk which reduces from 1.00 (general population) to 0.81 (crop farmers) to 0.71 (livestock farmers). This supports the evidence that the phenomenon of the anti-cancer effects from endotoxin is a real biological event. Since our data are registry based, and exposure data have not been collected among the participants in the study, further studies allowing exposure-response modelling and control of confounders are warranted.

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