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# Excess lung cancer occurrence in poultry plants. Occupational risk factors: Findings for oncogenic viruses exposure and other occupational exposures

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ABSTRACT

Certain viruses naturally infect and cause cancer in chickens and turkeys. Humans are widely exposed. The viruses cause cancer in primates, and transform human cells in vitro, but it is not known if they cause cancer in humans, mainly because of the lack of epidemiologic evidence. We conducted cohort mortality studies of workers in poultry slaughtering/processing plants across the United States, because they have the highest human exposures. An excess of lung cancer and other deaths was recorded in the poultry workers. Here, we report on a case-cohort study of the lung cancer deaths nested within these cohorts, that was conducted to provide epidemiologic evidence linking these viruses with human cancer occurrence, while adjusting for possible confounders, including workplace chemical carcinogens. We obtained interviews for 339 lung cancer deaths and 457 controls, selected from our combined cohorts of 30,411 poultry plant workers and 16,405 non-poultry workers, belonging to United Food & Commercial Workers unions. Data was analyzed by both logistic regression and Cox regression, adjusting for smoking and other confounders. Lung cancer risk was independently associated with tasks or work areas indicative of exposure to both poultry oncogenic viruses and to workplace chemical carcinogens. The study provides an incremental piece of evidence (epidemiologic), indirectly linking the oncogenic viruses of poultry with the occurrence of cancer in humans, and thus may have public health implications, but the limitations highlighted must be considered. Confirmatory studies, particularly molecular studies providing definitive proof of poultry oncogenic retrovirus integration in human DNA are needed, before the findings observed in this study can be put into proper perspective.

## 1. Introduction

Avian leukosis sarcoma viruses (ALSV), reticuloendotheliosis viruses (REV) and Marek's disease virus (MDV) naturally infect and cause cancer (including lung cancer) in chickens, turkeys, and other birds, and some subtypes can induce cancer within a week of exposure (Saif et al., 2003; Johnson, 1994a). ALSV and REV are enveloped RNA viruses, with ALSV belonging to the genus alpharetrovirus, and REV to the genus mammalian C-type, while MDV is a DNA virus belonging to the alphaherpesvirus genus. The viruses can be transmitted horizontally by contact between birds (exogenous infection), or vertically through congenital infection, in the case of ALSV and REV. In addition, ALSV are naturally present in most chicken genomes (endogenous infection), and are transmitted from generation to generation in a Mendelian fashion, and occasionally expressed as an exogenous infection (Saif et al., 2003). The viruses induce brain cancer and other tumors in primates, and transform human cells in vitro (Johnson, 1994a). Humans are commonly exposed to them occupationally (poultry workers, veterinarians, laboratory workers, cooks, restaurant workers, etc.), and in the general population. Workers in poultry slaughtering and processing plants are exposed, virtually through all the major routes: contaminated hand-to-mouth; inhalation of contaminated air; dermally, through cuts, wounds, scrapes, and breaches in the skin caused by dermatitis from irritating enzymes; and parenterally, through penetrating injuries from sharp knives and bone splinters (Encyclopedia of Occupational Health and Safety, 1972). Exposure is usually significant - workers come into contact daily with large numbers of birds, and as many as 175,000–300,000 chickens can be slaughtered and/or processed in a day in large plants. They also come into direct contact with the blood, secretions, and internal organs of the animals. The general population is exposed from inoculation with ALSV-contaminated vaccines grown in eggs (Tsang et al., 1999). It has been reported that measles, mumps and

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yellow fever vaccines in use in the US are contaminated with endogenous ALSV (Tsang et al., 1999; Victoria et al., 2010). General population exposure also occurs from contact with live or dead chickens and raw products; and eating raw or inadequately cooked poultry products, including eggs. In a survey of eggs displayed for sale in supermarkets in the New Orleans metropolitan area, 14% of eggs were positive for endogenous and exogenous ALSV (i.e., at least one egg in a carton of a dozen eggs) (Pham et al., 1999). Thus, the potential for exposure in humans is widespread.

The viruses are present in the litters of pens, and blood-sucking insects including ticks and mosquitoes can be infected with REV and able to transmit infection between chickens (Saif et al., 2003; Motha et al., 1984). The half-lives in blood, tissue, or the environment, vary from a few hours at 37 °C, less than 2 days at 25 °C, and 45 days at − 22 °C for ALSV, and are not much different for REV, while MDV can be shed for the life of the bird and can maintain its infectivity for up to 8 months at room temperature, and more than 10 years if stored at 4 °C (Saif et al., 2003; Johnson, 1994a). Search for antibodies against these viruses in human sera were mostly negative in early studies, with few exceptions; however these studies used assays that were not sensitive (Johnson, 1994a). Very sensitive tests such as ELISA, Western blot, and polymerase chain reaction (PCR) assays, are now available and have been used with mixed results. Some studies reported a high prevalence of antibodies to ALSV, REV, and MDV not only in poultry workers but also in the general population, while others reported negative findings (Johnson et al., 1995a, 1995b; Choudat et al., 1996; Hussain et al., 2001, 2003). Possible reasons for the discrepancy include: 1) studies that were negative for antibodies tested blood that had been collected and stored for several years (Hussain et al., 2001, 2003), while the positive studies used fresh blood (Johnson et al., 1995a, 1995b; Choudat et al., 1996). It is known that antibody levels even in natural infections in chickens are transient, and more so in mammals, in which levels become undetectable within weeks (Johnson, 1994a). Also, the negative serological studies used much higher dilutions of secondary antibodies than were used in the positive studies. Similarly, the half-lives of normal human peripheral blood leukocytes used in PCR assays are usually less than 3 days for monocytes, less than a week for neutrophils, a few months for B-lymphocytes, and only T-lymphocytes have half-lives measured in years. Notwithstanding, the half-lives of infected cells would be expected to be considerably less, as they are rapidly killed by the immune system. Also, for MDV, the positive study (Choudat et al., 1996) used a nested PCR assay, which was shown to be 100–1000 times more sensitive than the single-round PCR used in the negative studies (Hussain et al., 2001, 2003). Finally, the primers used were different, and may not have been as sensitive as those used in the positive studies. Whether infection with these viruses is transmitted between humans is not known. It is important therefore to obtain epidemiologic evidence as to whether subjects exposed to these viruses have increased risks of cancer.

We conducted mortality studies in 3 cohorts of workers in poultry slaughtering and processing plants located in eight states in the US (Johnson et al., 1986, 1997, 2010, 2011a, 2011b; Netto and Johnson, 2003). As mentioned above, workers in these plants have one of the highest known human exposures to these viruses. We reasoned therefore, if these viruses cause cancer in humans, it would be readily evident in this highly exposed group. The results from these studies indicated that deaths from cancer at 11 different sites, including deaths from cancer of the trachea, bronchus and lung (ICD 162, 9th Revision), (henceforth referred to as lung cancer) occurred in excess in the poultry workers.

However, workers in poultry plants are also exposed to chemical carcinogens in the workplace. These include (1) fumes containing polycyclic aromatic hydrocarbons (PAH), benzene and phthalates that are emitted from the wrapping machines (Pauli et al., 1980; Vandervort and Brooks, 1977; Johnson et al., 1999). It has been shown that meat wrappers using the machine could be exposed to as much as 1–2 ppm benzene, that is, a level of exposure associated with the occurrence of myeloid leukemia in humans (Johnson et al., 1999; Boettner and Ball, 1980; Cook, 1980; Glass et al., 2003); (2) PAH in smokehouses – total PAH concentrations of 2.2–2472 μg/m$^3$ have been recorded in fish smokehouses, compared to the OSHA Permissible Exposure Limit (PEL) of 0.2 μg/m$^3$ (Nordholm et al., 1986), and these levels include PAHs that are carcinogenic in humans, and are comparable to those recorded in aluminum and coke plants (IARC, 1973, 1985; Hansen et al., 1992). Similarly, PAHs including carcinogenic PAH have been recorded at levels of up to 25.52 μg/m$^3$ in the air of meat smokehouses where temperatures are much lower than in fish smokehouses (Nordholm et al., 1986; Hansen et al., 1992; Colmsjo et al., 1984); (3) heterocyclic amines and PAH emitted during the frying or cooking of poultry (Vainiotalo and Matveinen, 1993; Jakszyn et al., 2004); (4) nitrosamines formed during the curing of poultry - Sen et al., reported levels of up to 25 ppm nitrosamines in curing mixtures used by meat workers (Sen et al., 1973, 1974); and possibly (5) airborne aflatoxin produced by the aspergillus fungus – aflatoxin levels of up to 4.8 μg/m$^3$ have been recorded during harvesting in farms (IARC, 2012a), and levels of up to 5800 CFU/m$^3$ in the air of poultry farms (Viegas et al., 2014), although not studied in poultry plants. They are also exposed to bacterial endotoxins that may be risk factors (Paba et al., 2014). In addition, warts are highly prevalent in poultry workers, and human papilloma viruses may also need to be considered (Taylor, 1980). Thus, these exposures together with non-occupational exposures need to be considered before the observed excess occurrence of lung cancer can be incontrovertibly linked to the oncogenic viruses of poultry.

Accordingly, we first conducted pilot case-cohort studies of five of the 11 cancers that were in excess in the poultry cohorts, one of which was lung cancer, using a short questionnaire (Felini et al., 2012). In the lung cancer pilot study, the only oncogenic virus occupational risk factors identified for lung cancer were 1) killing of chickens at work (OR = 4.2; 95% CI, 1.2–14.7) and contact with chicken blood at work (OR = 1.9; 95% CI, 1.0–3.8). Other occupational exposures that were statistically significant were (1) use of chemicals to kill mold (OR = 7.3; 95%CI, 1.1–50.0) and work in a chemical plant (HR = 2.6; 95% CI, 1.1–6.5) (Felini et al., 2012).

Here we present an expanded large case-cohort study of all the lung cancer deaths in the combined cohort that occurred between 1950 and 2010.

## 2. Methods

The source population was identified from the rosters of (1) the United Food and Commercial Workers (UFCW) Meatcutters' Union in Baltimore, Maryland (6 poultry plants), (2) the UFCW Poultry Union in Marshall, Missouri (6 poultry plants) and (3) the UFCW Union Pension Fund in Chicago, Illinois, covering 11 poultry plants in six states. The subjects consisted of 30,411 workers who were exposed to poultry through employment in these 23 poultry slaughtering and processing plants located in eight states (Maryland, Delaware, Virginia, Missouri, Arkansas, Louisiana, Maine and Texas). In addition, a heterogeneous group of 16,405 non-poultry plant workers from ten states (Maryland, West Virginia, Florida, Illinois, Indiana, Massachusetts, New Jersey, Ohio, Pennsylvania and Texas) who were also members of the UFCW Baltimore union or the Chicago Pension Fund, and worked in companies that handled seafood, soft drinks, cheese or oriental food, or manufactured metal containers, etc., was also studied (Johnson et al., 1986, 1997, 2010, 2011a, 2011b; Netto and Johnson, 2003). The combined cohort of 46,816 poultry and non-poultry individuals worked anytime between January 1, 1950 and 31 December 1989, and were followed up from January 1, 1950 to 31 December 2010. Follow-up and tracing methods have been described, and included the National Death Index, tracing companies, etc (Johnson et al., 1986, 1997, 2010, 2011a, 2011b; Netto and Johnson, 2003).

In the study reported here, cases consisted of all 1026 subjects in the combined cohort of 46,816 workers who died of lung cancer (ICD-9 162, and ICD-10 C34) between January 1, 1950 and December 31, 2010. The comparison group was a subcohort that consisted of 2667 subjects randomly sampled from the combined cohort. All cases and 15% of the controls (N = 67) were deceased. For deceased cases and controls, their next-of-kin provided the interview on them through an administered telephone questionnaire, while live control subjects provided the information on themselves. The next of-kin of 38 cases, and 3 controls themselves who had participated in the previous pilot study (Felini et al., 2012), were re-interviewed blindly 4–7 years later, and included in the study.

### 2.1. Questionnaire

#### 2.1.1. Assessment of possible occupational exposures to oncogenic viruses

For each animal conceivably used for food (chickens, turkeys, ducks, doves, partridges, pheasants, quails, geese, grouses, crows/ravens, cattle, pigs, sheep, goats, horses, bison, game animals), subjects were asked the following questions: 1) If they ever worked in a plant where hundreds or thousands of the animal were slaughtered; 2) if they ever worked in a plant where the animal was not killed, but the plant processed hundreds of already-killed animal brought in from elsewhere; 3) if they ever worked in a plant where less than 20 of the animal were killed; 4) if they ever worked in commercial farms handling the animal; 5) if they ever at any time in life worked in a place, or worked for a business, where the eggs of the animal (where appropriate) were handled; 6) if they ever worked in places such as a zoo, pet store, laboratory or other similar places where the animal was handled. If the answer is "Yes", for each animal, and for each of these 6 animal facilities, they were asked the questions listed in Table 1 (using chicken as an example). Table 1 includes a listing of the major tasks carried out in a typical poultry slaughtering/processing plant. Similar but slightly modified tasks in slaughterhouses or processing plants for large animals like cattle and pigs were used. In addition, subjects were asked if they worked in other places or professions where exposure to these viruses could conceivably had occurred such as, the meat and deli departments of supermarkets; restaurants, cafeterias, kitchens; canned food and soup manufacturing plants; places where animals and crops were present; butchers who slaughtered animals, meat cutters (no killing), meat wrappers, veterinarians, meat inspector, gamekeeper, trapper, rancher; work as hunters of game birds (pigeons, pheasants, guinea fowl, etc.) and other game animals (squirrels, rabbits, moose, elk, antelope, deer, etc.), and questions on working in pet stores handling a wide variety of pets (mammals, reptiles, birds, water animals). Information on occupational exposures outside the poultry and meat industries was also collected.

#### 2.1.2. Other assessments

The questionnaire also sought information on life- style; medical history; diet; medication use; substance abuse; family history of medical conditions; radiation exposures; immunizations; hobbies; and the environment; but these non-occupational exposures are not considered here, and their results will be published separately. The questionnaire had 609 primary questions that every subject was asked; if the answer was in the affirmative, secondary questions were asked. On average the questionnaire took 84 min to complete.

### 2.2. Validation study of next-of-kin responses

To examine the reliability of the information provided by the next-of-kin on deceased study subjects, we compared the agreement between the information provided by live study subjects themselves with that on the study subject provided by his/her next-of-kin in a sample of 119 selected pairs of interviews. The comparison was restricted to the 609 primary "Yes/No" questions that everyone was asked, since data was insufficient for analysis for most of the secondary questions. Among pairs, the agreement on 294 questions on which data was available, was 90–100% for 62% of the responses; at least 80% for 81% of the responses, and at least 70% for 96% of the responses. The agreement for killing chickens or turkeys in poultry plants, one of the main indicators of oncogenic virus exposure was 100%.

### 2.3. Statistical analyses

We carried out several analyses:

#### 2.3.1. Model 1

We estimated odds ratios and their associated 95% confidence intervals (CI) by logistic regression, and adjusted for age at employment, gender, race, tobacco smoking, and year of employment, using the SAS PROC LOGISTIC procedure (SAS 9.1, SAS Institute, Cary, NC). These results tend to give more conservative estimates of risk. Risk associated with each job exposure was calculated for ever/never responses.

#### 2.3.2. Model 2

We estimated hazard ratios by the Cox regression (SAS PHREG) and adjusted for age at employment, gender, race, tobacco smoking, duration of employment, using year of entry into follow-up as the baseline hazard.

Both results are presented, and were very similar when data was ample. In virtually every analysis in which there was a significant difference between the two results, the data was observed to be sparse and the number of exposed cases observed to be 10 or less. It should be noted also that the tendency for Cox and logistic results to diverge depends on other factors such as duration of follow-up strength of association, and frequency of the outcome (Symons and Moore, 2002).

In the analyses by histologic types, we present only the more conservative logistic results. Tobacco smoking was adjusted for never smokers vs. ever smokers, and race for whites vs. non-whites – the tremendous increase in Hispanic employment in poultry plants to the point where they now account for over half of the workforce, occurred after assembly of our study population was completed in 1989, hence there are very few Hispanics in our study.

We also examined the effect of including in the logistic model a) the source of the cohort (Baltimore, Chicago, Marshall), b) including or excluding the 38 cases and 3 controls that had participated in the previous pilot case-cohort study of lung cancer (Felini et al., 2012). Only marginal changes in the results were evident in a few instances, and they are highlighted in the tables, otherwise the results of these additional analyses are not presented. Analyses by histologic type of lung cancer in which adjustment was made for age and tobacco smoking only, were also carried out.

Finally, since the two main potentially carcinogenic occupational exposures in poultry plants are poultry oncogenic viruses, and chemical carcinogens associated with cooking, frying, smoking, curing, and wrapping of poultry meat, and are the occupational candidate exposures that could explain the observed increased risk of lung cancer deaths in poultry workers in the cohort studies, limited adjustments for exposure to chemical carcinogens were conducted when risks from exposure to poultry oncogenic viruses were being evaluated, and vice versa. Thus the main potential occupational confounders were investigated.

All exposures where applicable, were quantified as exposure for 5 or more years vs. less than 5 years. In other places, quantification was by framing the question as "Was the subject exposed for many years (Yes or No)". Two major changes in the level of exposure occurred around the late 1970's: 1) exposure to fumes from the wrapping machine that caused asthma and chronic bronchitis in meat wrappers (Pauli et al., 1980; Vandervort and Brooks, 1977) was drastically reduced; 2) direct formation of nitrosamines in curing pre-mixes was eliminated by the removal of spices from the pre-mixes, but nitrosamine exposure continued to occur during the curing process (Sen et al., 1973, 1974).

**Table 1**
Jobs/tasks and areas of work (CHICKEN as an example).

| **CHICKEN slaughtering plants** | | | | | |
|---|---|---|---|---|---|
| **1. Jobs associated with exposure to oncogenic viruses** | | | | | |
| Q0017 | Ever work in a plant where they killed or slaughtered hundreds or thousands of chickens? | Q0033 | Ever involved in washing/rinsing chicken carcasses *before* the insides were removed? | Q0047 | Ever work in a refrigeration room/cold room/chiller where chicken meat was kept at the plant |
| Q0020 | Ever load/unload live chickens from trucks | Q0035 | Ever engaged in re-hanging chickens in chicken slaughtering plants? | Q0090 | Did ever come into direct contact with the blood of chickens at work? |
| Q0022 | Was job to hang the live chickens ready for slaughter | Q0037 | Ever involved in washing the chicken carcasses *after* the insides had been removed? | Q0091 | Ever had any penetrating injury from sharp knives or bone splinters |
| Q0024 | Did kill chickens | Q0039 | Did ever chill chicken meat at a slaughtering plant? | Q0092 | Ever work as an assistant to the poultry meat inspector |
| Q0027 | Did ever work at pulling out the insides of chickens? | Q0041 | Did ever weigh or grade chicken meat | Q0093 | Did ever work in more than one job |
| Q0029 | Did cut out the heart and liver of chickens? | Q0043 | Did ever perform the deboning of chicken carcasses at a slaughtering plant? | Q0094 | Was he/she a maintenance worker |
| Q0031 | Did ever remove the feathers of chickens in slaughtering plant | Q0045 | Ever involved in cutting chicken carcasses into halves or smaller parts (wings, breast, thighs, legs, etc.) | Q0095 | Was his/her job to clean the equipment or clean the floors |
| **2. Jobs associated with exposure to PAH and heterocyclic amines during COOKING AND FRYING** | | | | | |
| Q0049 | Did ever cook chicken meat at the plant (but not sausages or bacon)? | Q0075 | Did ever work in a room or area where chicken meat was fried? | Q0078 | Did job involve frying chicken meat? |
| **3. Jobs associated with exposure to nitrosamines during CURING poultry meat** | | | | | |
| Q0051 | Ever involved in curing Chicken meat or in applying spices, edible compounds or chemicals to the chicken meat (salts, seasonings, brine, etc.)? | Q0054 | Ever involved in making chicken sausages | Q0060 | Did ever work in a room or area where chicken meat was cured? |
| | | Q0057 | Ever involved in making chicken bacon | | |
| **4. Jobs Associated with exposure to PAH and heterocyclic amines during SMOKING and BOILING of poultry meat** | | | | | |
| Q0063 | Did ever work in a room or area where chicken meat was treated with smoke? | Q0069 | Did ever work in a room or area where chicken meat was steamed or boiled? | | |
| Q0066 | Did job involve smoking chicken meat | Q0072 | Did job involve boiling chicken meat? | | |
| **5. Jobs associated with exposure to PAH, benzene, phthalic anhydride during WRAPPING of poultry meat** | | | | | |
| Q0081 | Did ever wrap chicken in plastic film or put it into plastic bags? | Q0082 | Did ever use a wrapping machine to wrap chicken in plastic film or seal it in plastic bags? | Q0087 | Did ever complain of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work? |
| **6. No or negligible carcinogenic exposure** | | | | | |
| Q0085 | Did ever pack chicken meat or raw chickens into boxes? | Q0086 | Did only work in a white-collar job at the slaughtering plant (clerk, secretary, office worker)? | | |

**Table 2**
Demographic and baseline characteristics of cases and controls.

| | | Cohort of 46,816 | | | |
|---|---|---|---|---|---|
| | | Lung cancer cases | | Controls (Subcohort) | |
| | | Total = 1026 | Interviewed = 339 | Total sampled = 2667 | Interviewed = 457 |
| Race | | | | | |
| | White | 757 (74%) | 259 (76%) | NA | 326 (72%) |
| | Non-white | 269 (26%) | 80 (24%) | NA | 129 (28%) |
| | Unknown | 0 | 0 | NA | 2 |
| | Total | 1026 | 339 | 2667 | 457 |
| Gender | | | | | |
| | Females | 449 (44% | 152 (45%) | 1333 (50%) | 244 (54%) |
| | Males | 569 (55%) | 187 (55%) | 1283 (48%) | 207 (45%) |
| | Unknown | 8 (1%) | 0 | 51 (2%) | 6 |
| | Total | 1026 | 339 | 2667 | 457 |
| Age | | | | | |
| | ≤ 50 yrs | 140 (13.36%) | 28 (8.26%) | 554 (20.77%) | 89 (19.47%) |
| | > 50 yrs | 886 (86.35%) | 311(91.74%) | 2113 (79.23%) | 368 (80.53%) |
| | Total | 1026 | 339 | 2667 | 457 |
| Type of Worker | | | | | |
| | Poultry | 587 (57.21%) | 231 (68%) | 1753 (66%) | 352 (77%) |
| | Non-Poultry | 439 (42.79%) | 108 (32%) | 914 (34%) | 103 (23%) |
| | Total | 1026 | 339 | 2667 | 457 |
| Tobacco Smoking Status | | | | | |
| | Ever Smoked | NA | 302 (89%) | NA | 299 (66%) |
| | Never Smoked | NA | 37 (11%) | NA | 154 (34%) |
| | NA or DK | NA | 0 | NA | 0 |
| | Unknown | | | NA | 4 (0008) |
| | Total | 1026 | 339 | 2667 | 457 |
| Source of Cohort | | | | | |
| | Chicago P. Fund | 576 (56%) | 219 (65%) | 1776 (67%) | 348 (76%) |
| | Marshall Union | 151 (15%) | 59 (17%) | 432 (16%) | 70 (15%) |
| | Baltimore Union | 299 (29%) | 61 (18%) | 459 (17%) | 37 (8%) |
| | Total | 1026 | 339 | 2667 | 457 |

## 3. Results

It took between 45 and 115 min (84 min average) to complete the questionnaire. Telephone interviewing was halted after the first 339 of the 1026 lung cancer cases (33%), and the first 457 (17%) of the 2667 controls were interviewed, in order to permit interviewing of adequate numbers of the other rarer cancer cases in the overall case-cohort study of 7 cancers, within the time available. In the overall case-cohort study of the 7 cancer sites, 90.7% (1358) of the first 1498 study subjects or next-of-kin contacted, gave an interview. Of the 140 (9.3%) who refused to give an interview, only 12 (8.6%), 0.8% overall, cited the length of the questionnaire as the reason for refusing. We have already attained 64%, 60%, and 60% overall response rates (interviews completed) for all of the liver, brain, and ovarian cancer cases, respectively, and response rates for the remaining 3 cancer sites are currently over 40%. A comparison of the distribution of baseline characteristics of interviewed subjects with that of subjects in the entire or randomly sampled cohort is given in Table 2.

### 3.1. Tobacco smoking

For all lung cancers combined, the odds ratio (OR) for "ever smoking more than 100 cigarettes during one's entire life" was 3.0 (95% CI, 1.2–7.6), and the hazard ratio (HR) was 2.8 (95% CI, 1.5–6.2). The OR for smoking 5 or more cigarettes a day vs. less than 5 a day was 3.0 (95% CI, 1.4–6.8) for all lung cancers, and 6.7 (95% CI, 1.5–30.0) for non-small cell carcinomas, 2.8 (95% CI, 0.4–21.7) for small cell carcinoma, and 2.2 (95% CI, 0.5–9.5) for adenocarcinoma. The HR for smoking 5 or more cigarettes a day vs. less than 5 a day was 4.4 (95% CI, 2.5–8.3) for all lung cancers. For all lung cancers, the OR for smoking cigarettes for 5 or more years vs. less than 5 years was 3.8 (95% CI, 1.2–12.5), and the HR was 3.9 (95% CI, 1.7–12.7). The OR for having lived for 10 or more years in the same house as someone who smoked was 1.2 (95% CI, 0.8–1.8), and the HR was 1.3 (95% CI, 0.99–1.7). Those who stopped smoking cigarettes for good were significantly at decreased risk of lung cancer and all histologic types, compared to those who did not, except squamous cell carcinoma for which the OR was not significant (not shown).

### 3.2. Main findings

The main findings are for all 339 lung cancer deaths as a group.

Ninety-one percent (308 of 339) of the lung cancer deaths occurred in 8 states that responded to our request for reports: Maryland (27%), Arkansas (21%), Missouri (15%), Maine (7%), Pennsylvania (7%), Massachusetts (6%), Ohio (6%), Texas (2%). The 8 cancer registries in these states were able to provide histology reports for only 58% (N = 195) of all lung cancer deaths (2 states provided histology reports only from the 1980's onwards and 6 states from the 1990's onwards). We did not obtain histology reports for the remaining 31 cases that occurred in Louisiana, Florida, Virginia, North Carolina, California, and Delaware, either because of difficulty in getting the information, or because no request was made when the number of cases involved was less than 2. There were: 126 non-small cell carcinomas (NSCC) classified as adenocarcinomas (N = 54), squamous cell carcinomas (N = 38), large cell carcinomas (N = 17), and 'non-small cell carcinomas' (N = 17); 30 small cell carcinomas; 19 benign neoplasms; and a miscellaneous category (N = 20) consisting of 10 carcinomas NOS, 3 papillary carcinomas, 3 sarcomas, and 1 each of signet ring cell carcinoma, malignant mesothelioma, plasmacytoma, and lymphoma – results for this category are not presented.

**Table 3**
Hazard ratios (HR) and odds ratios (OR) for exposure to oncogenic viruses in chicken slaughtering & processing plants, farms and egg facilities – all lung cancers combined.

| Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls) | | No. of exposed cases | HR[a] | 95% CI | OR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Q0017 | Did ever work in a plant where they killed or slaughtered hundreds or thousands of chickens? | 88 | 0.9 | 0.7–1.1 | 1.0 | 0.6–1.4 |
| Q0019 | First start work at chicken slaughtering plant after 1980 vs. before 1980 | 4 | **6.1** | **2.2–21.7** | 1.2 | 0.1–9.5 |
| Q0024 | Did kill chickens at the plant | 18 | 1.8 | 0.9–3.1 | 2.0 | 0.7–5.7 |
| Q0026 | First start killing chickens at chicken slaughtering plant | 2 | **128.5** | **9.0–2305** | 0.1 | 0.1–8.5 |
| Q0027 | Did ever work at pulling out the insides of chickens? | 36 | **2.1** | **1.3–3.5** | 1.6 | 0.7–3. |
| Q0029 | Ever cut out the heart or liver of chickens at slaughtering plant | 24 | **3.2** | **1.8–5.6** | 1.6 | 0.7–3.8 |
| Q0033 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? | 23 | **29.2** | **12.7–71.0** | **4.1** | **1.5–11.2** |
| Q0037 | Ever involved in washing the chicken carcasses after the insides had been removed? | 17 | **5.1** | **2.4–10.6** | **1.5** | 0.6–3.9 |
| Q0038 | Involved in washing the chicken carcasses after the insides had been removed for 5 or more years vs. less than 5 years | 8 | **16.1** | **1.4–207.4** | 0.9 | 0.0–34.8 |
| Q0043 | Did ever perform the deboning of chicken carcasses at the plant? | 33 | **8.6** | **4.4–17.7** | **2.6** | **1.2–5.8** |
| Q0045 | Did ever cut chickens into halves/parts in chicken slaughtering plants | 35 | **1.7** | **1.0–3.0** | 1.0 | 0.4–2.1 |
| Q0094 | Was he/she a maintenance worker | 7 | **0.4** | **0.1–0.8** | **0.2** | **0.1–0.8** |
| **Exposures within large chicken processing plants (no killing) (Yes: N = 124 cases, N = 190 controls)** | | | | | | |
| Q0096 | Did ever work in a plant where they did not kill or slaughter chickens, but processed hundreds of already-killed chickens brought in from elsewhere? | 124 | 0.8 | 0.6–1.04 | 1.1 | 0.8–1.6 |
| Q0097 | Worked 5 or more yrs. in a processing plant vs. less than 5 yrs. | 36 | **1.6** | **1.1–2.5** | **1.9** | **1.0–3.4** |
| | | | | | 1.7[c] | 0.9–3.0[c] |
| Q0098 | First start work in chicken processing plant in 1980 or after vs. before 1980 | 10 | **4.9** | **2.2–11.5** | 0.3 | 0.9–1.1 |
| Q0099 | Did ever load and unload trucks at the plant? | 19 | 1.6 | 0.9–2.6 | 1.2 | 0.5–2.7 |
| Q0100 | Loaded and unloaded trucks at the plant for 5 or more years vs. less than 5 years | 7 | 0.5 | 0.1–2.2 | 2.9 | 0.4–20.2 |
| Q0101 | Did ever work at pulling out the insides of chickens? | 40 | **2.4** | **1.6–3.6** | **1.8** | **1.0–3.5** |
| Q0102 | Worked at pulling out the insides of chickens for 5 or more years vs. less than 5 years | 12 | 0.6 | 0.2–1.4 | 1.4 | 0.4–5.0 |
| Q0104 | Cut chicken wings/legs/breast at chicken processing plant | 14 | **2.1** | **1.1–4.2** | 2.2 | 0.8–5.8 |
| Q0105 | Did cut out the heart and liver of chickens? | 32 | 1.2 | 0.8–1.9 | 1.7 | 0.9–3.3 |
| Q0106 | Did cut out the heart and liver of chickens for 5 or more years vs. less than 5 yrs.? | 5 | **5.3** | **2.1–15.9** | **5.4** | **1.1–25.8** |
| Q0107 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? | 25 | **3.3** | **2.0–5.4** | **2.0** | **1.0–4.2** |
| Q0109 | Ever washed/rinsed chicken carcasses after the insides were removed | 22 | **1.8** | **1.0–2.9** | **1.3** | **0.6–2.7** |
| Q0110 | Washed/rinsed chicken carcasses after the insides were removed for 5 or more years vs. less than 5 years | 5 | 1.6 | 0.5–6.4 | **11.5** | **1.3–102.2** |
| Q0116 | Deboned chicken carcasses for 5 or more years vs. less than 5 years | 7 | **4.7** | **2.0–12.1** | 2.1 | 0.5–9.0 |
| Q0117 | Did ever cut chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc.)? | 45 | 1.2 | 0.8–1.8 | 1.3 | 0.7–2.5 |
| Q0118 | Cut chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc., for 5 or more years vs. less than 5 years. | 11 | **2.4** | **1.1–5.5** | 1.8 | 0.6–5.7 |
| Q0119 | Ever worked in the refrigerator or cold room/chiller where chicken meat was kept at the plant | 35 | 0.7 | 0.4–1.04 | 1.0 | 0.5–1.8 |
| Q0120 | Did ever work in a refrigeration room/cold room/chiller where chicken meat was kept at the plant for 5 or more yrs. vs. less than 5 years | 9 | **3.3** | **1.4–8.4** | **3.8** | **1.1–13.5** |
| Q0158 | Did ever come into direct contact with the blood of chickens at work? | 76 | 1.4 | 0.9–2.1 | **1.7** | **1.0–3.2** |
| **Exposures within small chicken slaughtering plants (Yes: N = 3 cases, N = 4 controls)** | | | | | | |
| Q0167 | Did ever work in a small chicken slaughtering plant where < 20 chickens were killed daily? | 3 | 0.3 | 0.1–1.0 | 0.2 | 0.0–1.4 |
| Q0170 | Did ever kill chickens at the small plant (Yes: N = 1 Case, N = 1 Control) Unadjusted OR = 3.5 | 1 | 34.4 | 0.6–1962.7 | ∞ | 0.0–∞ |
| **Exposures within a chicken commercial farm (Yes: N = 11 cases, N = 19 controls)** | | | | | | |
| Q0173 | Did ever work in a commercial farm where chickens were raised? | 11 | 1.4 | 0.7–2.6 | 0.8 | 0.3–2.1 |
| Q0176 | Did ever catch live chickens at a farm | 5 | **11.3** | **1.1–542.1** | 0.4 | 0.0–10.8 |
| Q0177 | Did ever clean chicken coops at farm | 5 | **615.0** | **5.0–113491** | 1.5 | 0.1–34.9 |
| Q0178 | Did ever load/unload chickens at farm | 6 | **94.5** | **8.8–3929.1** | 0.5 | 0.0–13.0 |
| Q0179 | Was ever a maintenance worker at chicken farm | 3 | **6037.3** | **55.4–762721** | 2.9 | 0.1–95.2 |
| Q0180 | Did ever drive vehicle transporting chickens at farm | 3 | **39.3** | **3.5–718.2** | 0.2 | 0.0–41.6 |
| Q0181 | Did ever clean floors/equipment at chicken farm | 7 | **663.6** | **40.4–25599.3** | 3.0 | 0.2–47.4 |
| Q0184 | Ever work in more than one job at chicken farm | 5 | **94.6** | **7.2–4154.8** | 1.3 | 0.1–30.7 |
| Q0185 | Ever spread chicken waste as manure at chicken farm | 4 | **80.6** | **2.6–23032** | 1.0 | 0.0–28.0 |
| Q0186 | Did ever breed chickens at chicken farm | 3 | 90.9 | **3.3–6254.8** | 0.8 | 0.0–823.6 |
| **Exposures related to chicken eggs (Yes: N = 4 cases, N = 13 controls)** | | | | | | |
| Q0187 | Did ever at any time work in a place, or work for a business where the eggs of chickens were handled? | 4 | 0.7 | 0.2–1.6 | 0.7 | 0.2–2.3 |
| Q0188 | Worked in a place, or work for a business where the eggs of chickens were handled for 5 of more years vs. less than 5 years | 4 | 0.5 | 0.0–3.9 | 0.5 | 0.0–9.8 |
| **Exposures in zoos, pet stores, laboratories, etc.** | | | | | | |
| Q0203 | Did ever work in zoos, pet stores, laboratories or similar places where chickens were handled | 0 | – | – | – | – |

[a] Cox regression hazard ratios for "All Lung Cancers" were adjusted for age at employment, gender, race, smoking, and duration of employment.
[b] Odds ratios for "All Lung Cancers" were adjusted for age at employment, gender, race, smoking, and year of employment.
[c] Odds ratios and 95% confidence intervals that changed when cohort site was included in the model.

### 3.2.1. *Exposure to poultry oncogenic viruses (Tables 3–5)*

In general, significantly increased risks of lung cancer overall were not observed for a history of simply ever having worked in a poultry facility per se. On the other hand, elevated risks were consistently observed for performing specific tasks or working in areas, associated with potential oncogenic virus exposures.

**Table 4**
Hazard ratios (HR) and odds ratios (OR) for exposure to oncogenic viruses in turkey slaughtering & processing plants, farms and to miscellaneous birds – all lung cancers combined.

| Exposures within large turkey processing plants (Yes: N = 12 cases, N = 20 controls) | | No. of exposed cases | HR[a] | 95% CI | OR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Q0214 | Did ever work in a plant where they killed or slaughtered hundreds or thousands of turkeys? | 7 | 0.5 | 0.2–1.01 | 0.4 | 0.2–1.2 |
| Q0221 | Did ever kill turkeys at turkey slaughtering plant | 3 | **166.5** | **3.3–64138.5** | 201.1 | 0.4–107724 |
| Q0240 | Did ever debone turkey carcasses at slaughtering plant | 2 | **69.2** | **2.0–4672.6** | 3.2 | 0.1–121.6 |
| Q0242 | Was ever involved in cutting turkey carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc.)? | 4 | **79.0** | **4.7–1450.6** | 3.1 | 0.3–31.9 |
| Q0290 | Did ever have more than one job at turkey slaughtering plant | 3 | **36.8** | **2.1–2731.9** | 11.5 | 0.1–1131.5 |
| **Exposures within large turkey processing plants (Yes: N = 12 cases, N = 20 controls)** | | | | | | |
| Q0293 | Did ever work in a plant where they did not kill or slaughter turkeys, but processed hundreds of already-killed turkeys brought in from elsewhere? | 12 | 1.2 | 0.6–2.1 | 0.9 | 0.4–2.2 |
| Q0296 | Ever unload trucks at turkey processing plant | 3 | **93.3** | **5.7–1521.1** | 0.1 | 0.0–18.8 |
| Q0300 | Did ever cut turkeys into wings/legs/breast at turkey processing plant | 6 | **4.7** | **1.2–18.4** | 2.3 | 0.2–32.3 |
| Q0304 | Ever involved in washing/rinsing turkey carcasses before the insides were removed? | 5 | 1.6 | 0.4–5.6 | 1.6 | 0.2–14.0 |
| Q0306 | Ever involved in washing the turkey carcasses after the insides had been removed? | 4 | 1.0 | 0.3–3.7 | 1.3 | 0.1–11.8 |
| Q0312 | Did ever debone turkey carcasses at turkey processing plant | **5** | **5.3** | **1.2–23.1** | 0.7 | 0.1–7.8 |
| Q0314 | Did ever cut turkeys into halves/parts at processing plant | 5 | **5.3** | **1.3–21.5** | 1.8 | 0.1–26.3 |
| Q0316 | Did ever work in the refrigerator/cold room/chiller at turkey processing plant | 5 | **12.5** | **2.6–73.3** | 4.7 | 0.2–107.1 |
| Q0363 | Was job to clean equipment at turkey processing plant | 4 | **10.7** | **1.8–73.5** | 5.3 | 0.2–142.1 |
| **Exposures in small turkey slaughtering plant (Yes: N = 2 cases, N = 1 controls)** | | | | | | |
| Q0364 | Did ever work in a small turkey plant | 2 | **0.1** | **0.0–0.5** | 0.1 | 0.0–1.6 |
| **Exposures in turkey farms** | | | | | | |
| Q0370 | Ever work in a commercial farm where hundreds or thousands of turkeys were raised or bred? | 3 | 1.7 | 0.4–4.6 | 1.5 | 0.3–8.7 |
| **Miscellaneous birds** | | | | | | |
| Q3434 | Worked as a hunter of game birds such as guinea fowl, partridge, geese, pheasant, quail, etc. | 36 | NA | NA | 0.7 | 0.4–1.2 |

[a] Cox regression hazard ratios for "All Lung Cancers" were adjusted for age at employment, gender, race, smoking, and duration of employment.
[b] Odds ratios for "All Lung Cancers" were adjusted for age at employment, gender, race, smoking, and year of employment.

*3.2.1.1. Chicken facilities – all lung cancers (Table 3).* Table 3 gives the results for the 6 main types of facilities investigated. For chicken slaughtering and processing plants, the risks were elevated for nearly all the questions on whether the individual ever performed a given task or worked in a given area with potential for oncogenic virus exposure, and both the logistic and Cox results agree closely, except that the Cox tends to give more statistically significant results. As seen, the data were too sparse for meaningful interpretation of the other results for commercial farms, etc.

*3.2.1.2. Turkey facilities - all lung cancers (Table 4).* The pattern of results obtained for turkey slaughtering and processing plants is similar to that obtained for chicken plants, except that the results tend to be based on fewer subjects, hence more unstable – Table 4.

*3.2.1.3. Chicken and turkey facilities – histologic types (Table 5).* Data were only available for assessing risk from poultry oncogenic viruses in large chicken slaughtering and processing plants. As seen, statistically significantly increased risks were recorded for various histologic types associated with poultry oncogenic virus exposure, and all of the histologic types except benign tumors, were involved – Table 5.

We also estimated risks separately for tobacco smokers and non-smokers for oncogenic virus exposures that were initially significant. In most instances, no differences were observed, and when there were differences, they were not consistent (not shown).

*3.2.1.4. Miscellaneous poultry oncogenic virus occupations (not shown).* The OR for "Did he/she ever work as a butcher who killed any kind of animal was 0.6 (95% CI, 0.1–2.1) for all lung cancers, and for benign tumors the OR = 5.0 (95% CI, 1.1–22.5). Similarly, for working in any kind of pet house, or animal care house for stray animals, or pet shop, the OR for all lung cancer was 1.8 (95% CI, 0.1–30.1), and for benign tumors OR = 31.7 (95% CI, 1.7–596). For occupational hunter of game birds, the OR for all lung cancers was 0.7 (95% CI, 0.4–1.2) and for benign tumors it was 2.9 (95% CI, 1.0–8.7). The risk estimates for working as meat inspector, veterinarian, gamekeeper, trapper, rancher, working in a zoo, or biotech company, were not significantly elevated.

*3.2.2. Exposure to chemicals during cooking/frying, curing, smoking/boiling and wrapping of poultry products (Table 6)*

Data were available for assessing risk in chicken slaughtering and processing plants only. Consistently elevated risks for all lung cancers were recorded for tasks or work areas related to smoking and boiling of poultry meat both in slaughtering and processing plants, with the HR giving more statistically significant results. Significantly elevated risks were seen for tasks or work areas associated with cooking and frying, in processing plants but not in slaughtering plants – Table 6. Significantly increased risks were not initially seen for difficulty in breathing because of fumes from the wrapping machine, but as shown later in Table 10, risks were elevated after adjustment for oncogenic virus exposures, and even significantly so. It is noted that all the different types of chemical carcinogenic exposures were statistically significantly associated with at least one histologic type of lung cancer – Table 5.

*3.2.3. No exposure or minimal exposure to poultry oncogenic viruses (Table 6)*

The odds ratios for office (white collar) workers in chicken slaughtering and processing plants for all lung cancers were 0.1 (95% CI, 0.0–3.4) and 0.8 (95% CI, 0.1–4.6), respectively; the respective hazard ratios were 0.1 (95% CI, 0.0–1.9) and 0.7 (95% CI, 0.2–1.7). There was no office worker who was a case, and one only who was, in turkey slaughter and processing plant plants, respectively.

The OR for packing chickens or chicken meat into boxes in chicken slaughtering plant was 0.6 (95% CI, 0.3–1.4) for all lung cancers, and 0.4 (95% CI, 0.2–0.9) for non-small-cell carcinoma; in chicken processing plants, the OR was 1.2 (95% CI, 0.6–2.1) for all lung cancers. The respective HRs for all lung cancers in slaughtering and processing plants were 0.5 (95% CI, 0.3–0.9) and 0.7 (95% CI, 0.5–1.1).

*3.2.4. Exposures in food canning and soup manufacturing plants*

The odds ratio (OR) for working in a food canning or soup

**Table 5**
Odds ratios (OR) for exposure to oncogenic viruses and chemical carcinogens in poultry/bird-related workplaces (statistically significant results by histologic types).

**Oncogenic virus exposures**

| | | All lung cancers | | Small cell carcinoma | | Non-Small-Cell Carcinoma (NSCC)[c] | | Adenocarcinoma | | Squamous cell carcinoma | | Large cell carcinoma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls)** | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0024 | Did kill chickens at the plant (Exp. Cases = 18; Exp. Controls = 14) | 2.0 | 0.7–5.7 | **7.0** | **1.8–27.2** | | | | | | | | |
| Q0033 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? (Exp. Cases = 23; Exp. Controls = 13) | **4.1** | **1.5–11.2** | **7.7** | **1.6–35.6** | | | | | **16.5** | **2.1–129.0** | | |
| Q0043 | Did ever perform the deboning of chicken carcasses at the plant? | **2.6** | **1.2–5.8** | | | | | **3.0** | **1.0–9.3** | | | | |
| | **Exposures within large chicken processing plants (no killing) (Yes: N = 124 cases, N = 190 controls)** | | | | | | | | | | | | |
| Q0097 | Worked 5 or more yrs. in a processing plant vs. less than 5 yrs. | **1.9**<br>1.7[d] | **1.0–3.4**<br>0.9–3.0[d] | **8.8** | **1.1–71.1** | **2.8** | **1.3–5.6** | **5.3** | **1.4–19.2** | | | | |
| Q0099 | Did ever load and unload trucks at the plant? | 1.2 | 0.5–2.7 | | | | | **1.0** | **0.3–3.7** | | | **7.2** | **1.3–39.8** |
| Q0101 | Did ever work at pulling out the insides of chickens? | **1.8** | **1.0–3.5** | | | **2.5** | **1.2–4.9** | | | **3.0** | **1.0–9.1** | | |
| Q0107 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? | **2.0** | **1.0–4.2** | | | | **1.0–4.9** | | | | | | |
| Q0117 | Did ever cut chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc.)? | 1.3 | 0.7–2.5 | | | | | | | **3.5** | **1.2–10.4** | | |
| Q0120 | Did ever work in a refrigeration room/cold room/chiller where chicken meat was kept at the plant for 5 or more yrs. vs. less than 5 years | **3.8** | **1.1–13.5** | | | **4.5** | **1.0–20.3** | | | | | | |
| Q0158 | Did ever come into direct contact with the blood of chickens at work? | **1.7** | **1.0–3.2** | | | **2.2** | **1.1–4.4** | **3.0** | **1.0–9.1** | **3.9** | **1.1–14.0** | | |
| | **Exposures within large turkey processing plants (Yes: N = 12 cases, N = 20 controls)** | | | | | | | | | | | | |
| Q0293 | Did ever work in a plant where they did not kill or slaughter turkeys, but processed hundreds of already-killed turkeys brought in from elsewhere? | 0.9 | 0.4–2.2 | | | | | **3.5** | **1.3–9.2** | | | | |
| | **Other poultry/bird-related work** | | | | | | | | | | | | |
| Q3434 | Worked as a hunter of game birds such as guinea fowl, partridge, geese, pheasant, quail, etc. | | | | | | | | | | | | |

**Chemical carcinogenic exposures**

| | | All lung cancers | | Small cell carcinoma | | Non-Small-Cell Carcinoma (NSCC)[a] | | Adenocarcinoma | | Squamous cell carcinoma | | Large cell carcinoma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls)** | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| | **1. Exposure to Nitrosamines During CURING Poultry Meat** | | | | | | | | | | | | |
| Q0054 | Ever made chicken sausages | 1.9 | 0.1-27.6 | | | | | | | **21.0** | **1.1–404.1** | | |
| | **2. Exposure to PAH During SMOKING and BOILING of Poultry Meat** | | | | | | | | | | | | |
| Q0069 | Did ever work in a room or area where chicken meat was steamed or boiled? | 1.4 | 0.3–6.9 | | | | | | | **8.9** | **1.1–71.4** | | |

(*continued on next page*)

**Table 5** (*continued*)

| Chemical carcinogenic exposures | | All lung cancers | | Small cell carcinoma | | Non-Small-Cell Carcinoma (NSCC)[a] | | Adenocarcinoma | | Squamous cell carcinoma | | Large cell carcinoma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls)** | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| | **3. Exposure to PAH, Benzene, Phthalic Anhydride During WRAPPING of Poultry Meat** | | | | | | | | | | | | |
| Q0087 | Did ever complain of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work? | 1.1 | 0.3–3.9 | **9.9** | **2.2–45.4** | | | | | | | | |
| Q0085 | Did ever pack chicken meat into boxes | 0.7 | 0.3–1.4 | | | **0.4** | **0.2–0.9** | | | | | | |
| **Exposures within large chicken processing plants (Yes: N = 124 cases, N = 190 controls)** | | | | | | | | | | | | | |
| | **1. Exposure to PAH and Heterocyclic Amines During COOKING AND FRYING** | | | | | | | | | | | | |
| Q0149 | Did job involve frying chicken meat? | **5.2** | **1.3–20.4** | **17.7** | **3.3–95.0** | | | | | **11.5** | **2.2–59.6** | | |
| Q0121 | Did ever cook chicken meat at the plant (but not sausages or bacon)? | **3.6** **(3.0)[d]** | **1.0–12.2** **(0.9–10.4)[d]** | **7.3** | **1.2–43.9** | **4.7** | **1.3–16.4** | | | **9.1** | **2.1–40.5** | | |
| Q0146 | Did ever work in a room or area where chicken meat was fried? | 2.1 | 0.7–6.3 | **9.0** | **1.9–41.9** | | | | | **7.2** | **1.7–30.1** | | |
| | **2. Exposure to PAH During SMOKING and BOILING of Poultry Meat** | | | | | | | | | | | | |
| Q0140 | Did ever work in a room or area where chicken meat was steamed or boiled? | 2.5 | 0.8–7.9 | | | | | | | **7.8** | **1.8–33.0** | | |

The OR for exposure to nitrosamines during making chicken bacon in a chicken processing plant was 25.8 (95% CI, 1.0–726) for benign tumors
The OR for work as a hunter of game birds was 2.9 (95% CI, 1.0–8.7) for benign tumors.

[a] Odds ratios for "All Lung Cancers" were adjusted for age, gender, race, smoking, and year of employment.
[b] Odds ratios for histologic types adjusted for age and tobacco smoking.
[c] NSCC = Adenocarcinoma, Squamous Cell Carcinoma and Large Cell Carcinoma combined.
[d] Odds ratios and 95% confidence intervals that changed when cohort site was included in the model.

**Table 6**
Hazard ratios (HR) and odds ratios (OR) for exposure to chemicals during cooking/frying, curing, smoking/boiling and wrapping of poultry products in chicken slaughtering and processing plants – all lung cancers combined.

| | | No. of exposed cases | All lung cancers | | | |
|---|---|---|---|---|---|---|
| | | | HR[a] | 95% CI | OR[b] | 95% CI |
| **Exposures within chicken slaughtering plants** | | | | | | |
| *A. Exposure to Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines During Cooking and Frying* | | | | | | |
| Q0049 | Did ever cook chicken meat at the plant (but not sausages or bacon)? | 1 | 1.5 | 0.1–7.3 | 0.4 | 0.0–6.9 |
| *B. Exposure to Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines during Smoking and Boiling of Poultry* meat | | | | | | |
| Q0063 | Did ever work in a room or area where chicken meat was treated with smoke? | 2 | **23.2** | **3.6–84.0** | 5.3 | 0.1–270.2 |
| Q0069 | Did ever work in a room or area where chicken meat was steamed or boiled? | 7 | **9.2** | **2.9–24.3** | 1.6 | 0.3–8.9 |
| Q0072 | Did job involve boiling chicken meat | 6 | **13.0** | **3.7–35.5** | 2.6 | 0.4–18.7 |
| *C. Exposure to Polycyclic Aromatic Hydrocarbons, Benzene, Phthalic Anhydride During Wrapping of Poultry Meat* | | | | | | |
| Q0087 | Did ever complain of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work? | 7 | 0.4 | 0.2–0.9 | 0.7 | 0.2–2.8 |
| Q0088 | Complained of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work for 5 years vs. less than 5 years | 3 | 0.02 | 0.0–1.4 | 1.1 | 0.0–39.9 |
| *D. Exposure to Nitrosamines During Curing Poultry Meat* | | | | | | |
| Q0054 | Did ever make chicken sausages | 3 | **11.4** | **1.8–41.3** | 1.9 | 0.1–27.6 |
| *E. No or Low Carcinogenic Virus or Chemical Exposures* | | | | | | |
| Q0085 | Did ever pack chicken meat into boxes | 32 | **0.5** | **0.3–0.9** | 0.6 | 0.3–1.4 |
| Q0086 | Did only work in a white-collar job at the slaughtering plant (clerk, secretary, office worker)? | 1 | 0.1 | 0.0–1.9 | 0.1 | 0.0–3.4 |
| **Exposures within chicken processing plants** | | | | | | |
| *A. Exposure to Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines During Cooking and Frying* | | | | | | |
| Q0149 | Did job involve frying chicken meat? | 8 | **7.7** | **3.3–15.6** | **4.9** | **1.3–18.7** |
| Q0121 | Did ever cook chicken meat at the plant (but not sausages or bacon)? | 9 | **3.8** | **1.7–7.3** | **4.2** | **1.1–16.0** |
| Q0146 | Did ever work in a room or area where chicken meat was fried? | 9 | 1.5 | 0.7–2.9 | 2.3 | 0.7–7.0 |
| Q0147 | Worked in the room where chicken meat was fried for 5 or more years compared to less than 5 years | 4 | **37.9** | **3.8–1062.7** | 5.6 | 0.1–280.0 |
| *B. Exposure to Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines during Smoking and Boiling of Poultry* meat | | | | | | |
| Q0137 | Did job involve smoking meat | 1 | **18.2** | **1.0–101.1** | 4.7 | 0.0–474.9 |
| Q0140 | Did ever work in the room or area where chicken meat was steamed or boiled? | 9 | **4.4** | **2.0–8.5** | 2.1 | 0.6–7.4 |
| Q0143 | Did ever work boiling chicken meat | 3 | 2.8 | 0.7–7.6 | 1.3 | 0.1–13.1 |
| *C. Exposure to Polycyclic Aromatic Hydrocarbons, Benzene, Phthalic Anhydride During Wrapping of Poultry Meat* | | | | | | |
| Q0159 | Did ever complain of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work? | 10 | 0.9 | 0.5–1.8 | 1.5 | 0.5–4.4 |
| Q0160 | Complained of difficulty in breathing because of fumes or smoke while using the wrapping machine to wrap chicken meat at work for 5 years vs. less than 5 years | 1 | **8.7** | **1.6–161.7** | 6.6 | 0.2–210.3 |
| *D. Exposure to Nitrosamines During Curing Poultry Meat* | | | | | | |
| No data | | | | | | |
| *E. No or Low Carcinogenic Virus or Chemical Exposures* | | | | | | |
| Q0156 | Did ever pack chicken meat into boxes | 39 | 0.7 | 0.5–1.1 | 1.2 | 0.6–2.1 |
| Q0157 | Did only work in a white-collar job at the slaughtering plant (clerk, secretary, office worker)? | 4 | 0.7 | 0.2–1.7 | 0.8 | 0.1–4.6 |

[a] Cox hazard ratios for “All Lung Cancers” were adjusted for age at employment, gender, race, smoking, and duration of employment.
[b] Odds ratios for “All Lung Cancers” were adjusted for age at employment, gender, race, smoking, and year of employment

manufacturing plant was 0.7 (95% CI, 0.4–1.2), and the HR was 1.0 (95% CI, 0.7–1.3) for all lung cancers. However, the OR for working there for 5 or more years vs. less than 5 years was 4.6 (95% CI, 1.5–14.5) and the HR was 6.3 (95% CI, 2.7–16.9); the OR for non-small cell carcinoma was 9.8 (95% CI, 1.0–92.1). The OR for working in a room or area in a soup manufacturing plant where meat was steamed or boiled was 0.7 (95% CI, 0.1–7.0), and the HR 1.2 (95% CI, 0.2–4.2) for all lung cancers, while the OR was 47.0 (95% CI, 1.2–1766) for squamous cell carcinoma. In several instances (not shown) odds ratios for some of the exposures observed to be in excess for oncogenic virus

**Table 7**
List of occupational exposures outside the poultry and meat industries.

| Profession | Industries | Industries | Other exposures |
|---|---|---|---|
| Carpenter | Electronics, TV/radio repair | Textile manufacturing | Machine oils |
| Painter | Chemical manufacturing | Forestry | Sand/Silica |
| Brick maker | Formaldehyde manufacturing | Granary | Ionizing radiation |
| Dentist/dental assistant | Lumbar manufacturing | Lawn maintenance | Asbestos |
| Nurse | Pesticide manufacturing | Mining | Gasoline/kerosene/heating fuel |
| Electrician | Construction | Oil/petroleum | PCBs |
| Mechanic | Pharmaceutical drug manufacturing | Uranium mining | Hospital x-ray department |
| Hair dresser/barber | Dye manufacturing | Incinerator plant | Coal/coal tar, naphthalene, natural gas, paraffin, smoke |
| Embalmer in funeral home | Leather tannery | Waste treatment plant | Vinyl chloride |
| Chemical/pesticide applicator | Dry cleaning | Smelter (iron, copper, aluminum, chromium, Arsenic, nickel, cadmium, beryllium) | Dust |
| Plumber | Quarry | Plastics manufacturing | Hair dyes at work |
| Trash collector | Rubber Plant | Gas station, gasoline storage facility | |
| Welder | Fertilizer plant | | |

**Table 8**
Hazard ratios (HR) and odds ratios (OR) for occupational exposures outside the meat & poultry industries for all lung cancers and by histologic type.

| | | No. of exposed cases | All lung cancer | | All lung cancer | | Small cell carcinoma | | Non-small Cell Carcinoma (NSCC)[d] | | Adenocarcinoma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cox regression | | Logistic regression | | Logistic regression | | Logistic regression | | Logistic regression | |
| | | | HR[a] | 95% CI | OR[b] | 95% CI | OR[c] | 95% CI | OR[c] | 95% CI | OR[c] | 95% CI |
| Q4348 | Worked for many years as an auto mechanic | **17** | **2.6** | **1.4–4.3** | **3.0** | **1.2–7.8** | **4.9** | **1.1–21.0** | | | | |
| Q4349 | Worked as auto mechanic for 5 or more years vs. less than 5 years | **6** | **4.2** | **1.2–18.5** | 7.4 | 0.8–71.4 | | | | | | |
| Q4368 | Worked for many years in brick making | **5** | **13.2** | **4.5–30.7** | 5.4 | 0.8–35.6 | | | | | | |
| Q4424 | Worked for many years spraying or applying chemicals to kill mold | **2** | **8.2** | **1.3–27.1** | 1.0 | 0.1–15.0 | | | | | | |
| Q4432 | Worked for many years using chemicals to kill pests, rats, etc. | **3** | **6.7** | **1.6–18.6** | 1.5 | 0.3–8.8 | | | | | | |
| Q4444 | Worked for many years in a petroleum/oil refinery | **4** | **11.2** | **2.7–31.7** | 4.6 | 0.5–43.2 | | | | | | |
| Q4484 | Worked for many years exposed to machine oil | **25** | **1.5** | **0.9–2.3** | 1.5 | 0.7–3.0 | | | | | | |
| Q4485 | Worked at any time at a place with exposure to machine oils for 5 or more yrs. vs. less than 5 yrs. | **3** | **5.4** | **1.8–24.1** | 3.0 | 0.6–14.0 | | | | | | |
| Q4508 | Worked for many years at any time at a smelter where metals such as iron, steel, copper, aluminum, chromium etc. was smelted | **9** | **2.5** | **1.1–4.7** | 2.2 | 0.8–6.6 | | | **3.3** | **1.1–10.4** | **4.9** | **1.2–19.8** |
| Q4536 | Worked for many years at any time at a place where asbestos was handled | **12** | **2.6** | **1.3–4.7** | 2.1 | 0.8–5.9 | | | | | | |
| Q4537 | Worked at a place where asbestos was handled for 5 or more yrs. vs. less than 5 yrs. | **1** | **10.9** | **1.6–224.3** | 24,621 | 0.1–∞ | | | | | | |
| Q4564 | Work with PCBs | **7** | **3.0** | **1.3–6.0** | 0.9 | 0.2–3.7 | | | | | | |
| Q4600 | Ever exposed at work for several years to coal/coal tar | **16** | **2.7** | **1.6–4.4** | 2.4 | 0.7–8.4 | | | | | | |
| Q4604 | Worked in a job where was exposed to smoke for many years | **43** | **1.5** | **1.1–2.2** | 1.3 | 0.8–2.2 | | | | | | |
| Q4605 | Worked in a job where was exposed to smoke for 5 or more years vs. < 5 years | 3 | 1.8 | 0.6–7.5 | 4.4 | 0.8–22.8 | | | | | | |
| Q4608 | Worked for many years exposed to lots of dust | 74 | **1.4** | **1.0–1.8** | 1.0 | 0.6–1.5 | | | | | | |
| Q4629 | Worked for many years as a motor mechanic | **25** | **1.6** | **1.0–2.4** | 1.4 | 0.7–3.0 | | | | | | |
| Q4630 | Worked as a motor mechanic for 5 or more yrs. vs. less than 5 yrs. | **6** | **11.9** | **3.3–55.5** | **5.3** | **1.1–24.7** | | | | | | |

[a] Hazard ratios for "All Lung Cancers" were adjusted for age, gender, race, and duration of employment.
[b] Odds ratios for "All Lung Cancers" were adjusted for age, gender, race, smoking, year of employment.
[c] Odds ratios for histologic types adjusted for age and tobacco smoking.
[d] NSCC = Adenocarcinoma, Squamous Cell Carcinoma and Large Cell Carcinoma combined.

**Table 9**
Exposure to oncogenic viruses in chicken slaughtering and processing plants adjusting for chemical carcinogenic exposures.

| Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls) | | All lung cancers | | Adjusting for cooking chicken meat in chicken slaughterhouse (Q0049) | | Adjusting for working in room where chicken meat was steamed or boiled (Q0069) | | Adjusting for complaining of difficulty in breathing from wrapping machine fumes (Q0087) | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0024 | Did kill chickens | 2.0 | 0.7–5.7 | **2.2** | **1.0–4.8** | **2.3** | **1.0–5.4** | **2.3** | **1.0–5.** |
| Q0027 | Did ever work at pulling out the insides of chickens? | 1.6 | 0.7–3.4 | 1.4 | 0.8–2.6 | 1.4 | 0.7–2.6 | 1.3 | 0.7–2.4 |
| Q0033 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? | **4.1** | **1.5–11.2** | **4.3** | **1.8–9.8** | **3.4** | **1.5–7.6** | **3.1** | **1.4–7.1** |
| Q0037 | Ever involved in washing the chicken carcasses after the insides had been removed? | 1.5 | 0.6–3.9 | 1.8 | 0.9–3.9 | 1.6 | 0.810–3.5 | 1.7 | 0.8–3.6 |
| Q0043 | Did ever perform the deboning of chicken carcasses at a slaughtering plant? | **2.6** | **1.2–5.8** | 1.5 | 0.8–2.8 | 1.6 | 0.9–3.0 | 1.5 | 0.8–2.8 |

| Exposures within large chicken processing plants (no killing) (Yes: N = 124 cases, N = 190 controls) | | All lung cancers | | Adjusting for cooking chicken meat in chicken processing plant (Q0121) | | Adjusting for working in room where chicken meat was steamed or boiled (Q0140) | | Adjusting for working in room where chicken meat was fried (Q0146) | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0097 | Worked 5 or more yrs. in a processing plant vs. less than 5 yrs. | **1.9** | **1.0–3.5** | | | | | | |
| Q0099 | Did load/unload live chickens from trucks? | 1.2 | 0.5–2.7 | 1.1 | 0.5–2.1 | 1.1 | 0.6–2.3 | 1.2 | 0.6–2.3 |
| Q0101 | Did ever work at pulling out the insides of chickens? | **1.8** | **1.0–3.5** | **1.9** | **1.1–3.3** | **2.1** | **1.2–3.6** | **2.1** | **1.2–3.7** |
| Q0105 | Did cut out the heart and liver of chickens? | 1.7 | 0.9–3.3 | **1.8** | **1.0–3.1** | **2.0** | **1.1–3.5** | **1.9** | **1.1–3.4** |
| Q0106 | Did cut out the heart and liver of chickens for 5 or more years vs. less than 5 yrs.? | **5.4** | **1.1–25.8** | **5.5** | **1.3–24.2** | **4.6** | **1.0–20.4** | **5.5** | **1.3–23.6** |
| Q0107 | Ever involved in washing/rinsing chicken carcasses before the insides were removed? | **2.0** | **1.0–4.2** | **2.2** | **1.2–4.3** | **2.1** | **1.1–4.2** | **2.1** | **1.1–4.0** |
| Q0108 | Involved in washing/rinsing chicken carcasses before the insides were removed for 5 or more years vs. less than 5 years | 9.4 | 0.8–109.9 | | | | | | |
| Q0109 | Did wash/rinse chicken carcasses after the insides were removed | 1.3 | 0.6–2.7 | | | | | | |
| Q0110 | Did wash/rinse chicken carcasses after the insides were removed for 5 or more years vs. less than 5 yrs? | **7.5** | **1.3–42.8** | | | | | | |
| Q0111 | Was involved in chilling chicken meat | 1.2 | 0.6–2.4 | | | | | | |
| Q0112 | Was involved in chilling chicken meat for 5 or more years vs. less than 5 yrs? | 4.3 | 0.8–21.8 | 3.5 | 0.7–16.3 | 3.0 | 0.6–14.3 | 3.2 | 0.7–15.2 |
| Q0113 | Weighed or graded chicken meat | 1.2 | 0.6–2.6 | | | | | | |
| Q0114 | Weighed or graded chicken meat for 5 or more years vs. less than 5 years | 2.5 | 0.3–17.9 | | | | | | |
| Q0115 | Did ever debone chicken carcasses for 5 or more years vs. less than 5 years | 1.0 | 0.5–1.9 | | | | | | |
| Q0116 | Did ever debone chicken carcasses for 5 or more years vs. less than 5 years | 2.1 | 0.5–9.0 | | | | | | |
| Q0117 | Did ever cut chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc.)? | 1.3 | 0.7–2.5 | 1.5 | 0.9–2.5 | 1.6 | 0.9–2.7 | 1.6 | 0.9–2.7 |
| Q0118 | Did ever cut chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc. for | 1.8 | 0.6–5.7 | | | | | | |
| Q0119 | Did ever work in a refrigeration room/cold room/chiller where chicken meat was kept at the plant | 1.0 | 0.5–1.8 | | | | | | |
| Q0120 | Did ever work in a refrigeration room/cold room/chiller where chicken meat was kept at the plant for 5 or more yrs. vs. less than 5 yrs | **3.8** | **1.1–13.5** | **4.7** | **1.5–14.1** | **5.1** | **1.6–16.4** | **4.2** | **1.4–12.9** |
| Q0158 | Did ever come into direct contact with the blood of chickens at work? | **1.7** | **1.0–3.2** | **1.0** | **0.6–1.7** | 1.1 | 0.6–1.8 | 1.1 | 0.6–1.8 |

[a] Odds ratios for "All Lung Cancers" were adjusted for age, gender, race, tobacco smoking and date of employment.
[b] Odds ratios adjusted for tobacco smoking and chemical exposure only.

exposure or chemical exposure in Tables 3–6 were also elevated, but they were not significant.

*3.2.5. Exposures in restaurants, cafeterias, kitchens*

For “Did ever work in a Kitchen or as a Cook, Chef, or Chef's Assistant for 5 or more years vs. less than 5 years”, for all lung cancer the OR was 0.8 (95% CI, 0.3–2.4) and the HR 0.3 (95% CI, 0.1–0.9), while the OR for NSCC was 3.4 (95% CI, 1.0–11.0). For “Did ever cook meat in kitchens, cafeterias, restaurants, and other eating places, for 5 or more years vs. less than 5 years” the OR for all lung cancer was 2.0 (95% CI, 0.7–5.9), and the HR was 1.4 (95% CI, 0.6–3.2), while the OR for NSCC was 4.0 (95% CI, 1.2–13.0).

*3.2.6. Occupations outside the poultry industries (Tables 7, 8)*

Data was too sparse to give results for exposures in slaughter and processing plants that handled cattle, pigs, sheep, goats, horses, bison, game animals, hence no results are presented. Table 7 gives the list of occupational exposures outside the poultry and meat industries – results are not presented for most of them because there were no associations. Table 8 gives the results for established occupational causes of, or frequently reported associations with, lung cancer.

*3.2.7. Additional analyses (oncogenic virus and chemical exposures as independent risk factors) – Tables 9, 10*

For each of the oncogenic virus exposure for which a significantly increased risk was observed, we estimated odds ratios adjusting in turn for each of the chemical carcinogenic exposures that was associated with an increased risk (tobacco smoking was also included in the model) – Table 9. The results unequivocally indicate that the odds ratios for tasks or areas of work indicative of oncogenic virus exposures in chicken slaughtering and processing plants remained elevated after the adjustments, thus suggesting that these tasks or areas of work are independent risk factors for lung cancer.

In limited unadjusted analyses, we compared risks for study subjects in chicken slaughtering plants who answered “Yes” to the five statistically significant oncogenic virus exposures (Q0024, Q0027, Q0033, Q0037, Q0043) in Table 3 (exposed), vs. white-collar workers (unexposed). The odds ratios obtained were 6.4 (95% CI, 0.7–61.5), 3.5 (95% CI, 0.4–30.9), 8.8 (95% CI, 0.9–84.1), 3.9 (95% CI, 0.4–36.2), and 3.9 (95% CI, 0.4–35.3), respectively.

Odds ratios were also estimated for tasks or areas of work associated with chemical exposures adjusting for oncogenic virus exposures – Table 10. Elevated risks were still evident, or were even stronger, for these exposures after the adjustments, except for complaining of difficulty in breathing because of fumes from the wrapping machine adjusting for washing/rinsing chicken carcasses, and contact with blood in chicken processing plants.

Unfortunately, because of small numbers it was not possible to examine trends in risks over time either for oncogenic virus or chemical exposures, except for the single result in Table 3 that showed that subjects who first start work in chicken processing plant in 1980 and after were at higher risk of lung cancer than those who started prior to 1980.

## 4. Discussion

### 4.1. General

We studied all cases, and controls were a random sample of all subjects in the cohort. The distributions of demographic variables in cases and controls interviewed were similar to those for all subjects selected for study. Thus selection bias is unlikely to be a serious problem in this study. Some amount of recall or interviewer bias arising from obtaining information from next-of-kin in some instances and from live subjects directly in others, is likely to have unavoidably persisted. However, the validation study showed good agreement overall between information provided by the next-of-kin and that provided by the study subject. There was 100% agreement between the two sources for the questions on killing chickens and turkeys, which are among the most important indicators of oncogenic virus exposures, and the agreement was 70% or higher for all the questions that were significantly increased for oncogenic virus exposure in large chicken slaughtering plants (not shown). The use of tasks as surrogates for exposure to oncogenic viruses has limitations. These tasks are associated with exposure to a multitude of infectious agents that include not only poultry oncogenic viruses, but also other infectious agents such as other viruses, bacteria, fungi, protozoa, and heminths. All of these organisms have different survival/half-lives in various environmental media, varying from hours to many years, and their concentrations change on a day-to-day basis, and their infectivity for humans vary not only with dose but also with the immune status of the subject. All of these factors are unknown, and difficult to take into account in exposure measurement, considering the long study period and the fact that cases are all deceased. In fact it turns out, none of the traditional industrial hygiene assessments of biological agents would have been suitable for characterizing and quantifying exposure adequately, given these circumstances. Thus, use of tasks and areas of work as was done here is the practical way of characterizing exposure to oncogenic viruses. Histology reports were not available prior to the 1980's, however this is not a serious disadvantage, since only 6.5% of lung cancer interviews were from subjects who died before 1990.

The two main occupational exposures of interest that are candidates to explain the excess occurrence of lung cancer deaths in poultry plant workers in the cohort studies are poultry oncogenic viruses and chemical carcinogens, and each is the main occupational confounding exposure for the other. In limited analyses, we were able to obtain risk estimates for one independent of the other. It was not possible to adjust further for occupational exposures outside the meat and poultry industries because of sparse data. Similarly, adjustments for non-occupational confounding factors were incomplete in this round of analyses. Complete adjustments await the identification of non-occupational risk factors (which is not part of this manuscript). These factors will then be candidates for the non-occupational confounding exposures. Once identified, this will permit obtaining risk estimates for occupationally identified risk factors after adjusting for these non-occupational factors as well, and the findings published separately. It is to be noted that the study population was a homogeneous group belonging to the low socioeconomic stratum and consisted of members of the same unions. These characteristics may have conferred some adjustment for unknown confounders. In the statistical models used, adjustments for tobacco smoking was carried out based on the response to the question “Did he/she ever smoke more than 100 cigarettes during their entire life”. It is likely therefore that residual confounding for tobacco smoking remains for some of the risk estimates given. The results for known and established occupational risk factors of lung cancer including tobacco smoking, are consistent with those reported in the literature (Boffetta et al., 1999; Pesch et al., 2012), thus providing assurance that no serious bias has occurred in the study.

A very extensive questionnaire, and a robust nested study design were employed in this study, and the broad objective was to discover occupational risk factors that could explain the occurrence of excess risk of lung cancer deaths observed among workers in poultry slaughtering and processing plants, while adjusting for occupational and non-occupational confounding factors. Absence of a statistically significantly increased risk for a given exposure could be due to chance, lack of statistical power, bias, or a true absence of risk. Similarly, an observed excess of risk could be due to chance from multiple comparisons, bias, or could be a real finding.

Risks presented for each of the various exposures within poultry plants were in relation to workers within the same plants, who would have been classified as exposed if they performed that task or worked in that area of the plant, and “unexposed” if they did not (even though

**Table 10**
Exposure to chemical carcinogens in chicken slaughtering and processing plants adjusting for oncogenic virus carcinogenic exposures – all lung cancers.

**Exposures within large chicken slaughtering plants (Yes: N = 88 cases, N = 146 controls)**

| | | No adjustment for any oncogenic virus exposure | | Adjusting for killing chickens (Q0024) | | Adjusting for pulling out the inside of chickens (Q0027) | | Adjusting for cut out the heart or liver of chickens (Q0029) | | Adjusting for washing/rinsing carcasses before insides removed of chickens (Q0033) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0054 | Did ever make chicken sausages | 1.9 | 0.1–27.6 | 2.1 | 0.9–4.6 | 1.2 | 0.7–2.2 | 1.8 | 0.9–3.5 | **3.6** | **1.7–7.9** |
| Q0063 | Did ever work in a room or area where chicken meat was treated with smoke? | 5.3 | 0.1–270.2 | **2.8** | **1.2–6.3** | 1.5 | 0.8–2.7 | **2.2** | **1.1–4.3** | **3.5** | **1.6–7.7** |
| Q0069 | Did ever work in a room or area where chicken meat was steamed or boiled? | 1.6 | 0.3–8.9 | **2.4** | **1.0–5.6** | 1.4 | 0.7–2.5 | **1.9** | **1.0–3.8** | **3.8** | **1.7–8.3** |
| Q0072 | Did job involve boiling chicken meat | 2.6 | 0.4–18.7 | – | | – | | – | | – | |
| Q0087 | Did complain of difficulty in breathing because of fumes from the wrapping machine | 0.7 | 0.2–2.8 | **2.4** | **1.1–5.5** | 1.3 | 0.7–2.3 | 1.9 | 0.9–3.7 | **3.3** | **1.5–7.5** |
| | | **All Lung Cancers** | | **Adjusting for washing/rinsing carcasses after insides removed of chickens (Q0037)** | | **Adjusting for deboning of chickens (Q0043)** | | **Adjusting for cutting chickens into halves/parts (Q0045)** | | | |
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | | |
| Q0054 | Did ever make chicken sausages | 1.9 | 0.1–27.6 | 1.5 | 0.7–3.0 | 1.4 | 0.8–2.6 | 1.2 | 0.7–2.2 | | |
| Q0063 | Did ever work in a room or area where chicken meat was treated with smoke? | 5.3 | 0.1–270.2 | 1.4 | 0.7–3.0 | 1.5 | 0.8–2.9 | 1.5 | 0.8–2.8 | | |
| Q0069 | Did ever work in a room or area where chicken meat was steamed or boiled? | 1.6 | 0.3–8.9 | 1.4 | 0.7–3.0 | 1.6 | 0.9–3.0 | 1.4 | 0.8–2.6 | | |
| Q0072 | Did job involve boiling chicken meat | 2.6 | 0.4–18.7 | – | – | – | – | – | – | | |
| Q0087 | Did complain of difficulty in breathing because of fumes from the wrapping machine | 0.7 | 0.2–2.8 | 1.5 | 0.7–3.1 | 1.5 | 0.8–2.7 | 1.4 | 0.7–2.5 | | |

**Exposures within large chicken processing plants (Yes: N = 124 cases, N = 190 controls)**

| | | No adjustment for any oncogenic virus exposure | | Adjusting for pulling out the insides of chickens (Q0101) | | Adjusting for cut chicken wings/legs/breast (Q0104) | | Adjusting for washing/rinsing carcasses before insides removed of chickens (Q0107)) | | Adjusting for washing/rinsing carcasses after insides removed of chickens (Q0109) | | Adjusting for direct contact with blood of chickens (Q0158) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0121 | Did ever cook chicken meat at the plant (but not sausages or bacon)? | **4.2** | **1.1–16.0** | **1.6** | **1.0–2.7** | 1.1<br>**2.7** | 0.2–4.9<br>**1.2–6.2** | **2.1** | **1.2–3.8** | 1.4 | 0.7–2.5 | 1.05 | 0.6–1.7 |
| Q0137 | Did job involve smoking meat | 4.7 | 0.0–474.9 | **1.7** | **1.0–2.8** | 1.1<br>**2.6** | 0.3–5.0<br>**1.1–5.9** | **1.9** | **1.0–3.4** | 1.2 | 0.6–2.2 | 1.1 | 0.7–1.7 |
| Q0140 | Did ever work in the room or area where chicken meat was steamed or boiled? | 2.1 | 0.6–7.4 | **1.8** | **1.1–3.0** | 0.6<br>**2.4** | 0.1–3.5<br>**1.0–5.5** | **2.1** | **1.1–3.9** | 1.3 | 0.7–2.4 | 1.1 | 0.7–1.8 |
| Q0149 | Did job involve frying chicken meat? | **4.9** | **1.3–18.7** | **1.7** | **1.0–2.8** | 1.3<br>**2.9** | 0.3–5.9<br>**1.2–6.7** | **2.0** | **1.1–3.7** | 1.3 | 0.7–2.4 | 1.02 | 0.6–1.6 |

(continued on next page)

**Table 10** (*continued*)

| Exposures within large chicken processing plants (Yes: N = 124 cases, N = 190 controls) | | No adjustment for any oncogenic virus exposure | | Adjusting for pulling out the insides of chickens (Q0101) | | Adjusting for cut chicken wings/legs/breast (Q0104) | | Adjusting for washing/rinsing carcasses before insides removed of chickens (Q0107)) | | Adjusting for washing/rinsing carcasses after insides removed of chickens (Q0109) | | Adjusting for direct contact with blood of chickens (Q0158) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR[a] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Q0159 | Did complain of difficulty in breathing because of fumes from the wrapping machine | 6.6 | 0.2–210.3 | 1.5 | 0.9–2.5 | 1.2 | 0.3–5.1 | 1.5 | 0.8–2.8 | 0.9 | 0.5–1.7 | 1.0 | 0.6–1.6 |

[a] Odds ratios for "No adjustment for any oncogenic virus exposure" were adjusted for age, gender, race, tobacco smoking and date of employment.
[b] Odds ratios adjusted for tobacco smoking and specific oncogenic virus exposure only.

nearly all of these "unexposed" subjects would have been exposed to oncogenic viruses from performing other tasks or working in other areas of the same plant). Also, interviewed controls had a higher proportion of poultry workers (77%) than the subcohort or study population (66%). Interviewed cases similarly had a higher proportion of poultry workers (68%) than all cases (57%). Finally, the validation study indicated that the agreement between the study subject's response and that reported by his/her next-of-kin was at least 80% for 81% of the responses, or at least 70% for 96% of the responses, indicating some amount of misclassification of exposure could have occurred. Because of these issues, the estimates of risks given are attenuated, and would likely have been higher in the absence of misclassification. Complementing this, no significantly increased risk was recorded for subjects who were unexposed to poultry oncogenic viruses who worked in white-collar jobs in the offices of chicken and turkey slaughter and processing plants, or who packed chicken products into boxes at the end of the line, who have lower exposures to microorganisms than other production line workers in poultry plants (You et al., 2016). Furthermore, as shown above, when "white-collar" office workers were used as the unexposed group, the risks associated with oncogenic virus exposure were even higher. Likewise, risks reported for various occupational groups with potential for exposure to poultry and other food animal oncogenic viruses are in relation to subjects who do not belong to that specific occupation but some of whom may belong to other high-risk occupations. Finally, we investigated increased risk of death, and not lung cancer incidence. This may not be a serious disadvantage given that the disease has a poor survival (http://www.lung.org/). In spite of the lower power associated with the results for histologic types, it is generally observed that the strength of the association was greater for specific types than for all lung cancers combined, indicating a certain amount of specificity for subtypes. Experience from occupational studies in which benzene is proven to be a cause of myeloid leukemia, and vinyl chloride a cause of hemangiosarcoma of the liver, but not other histologic types of these sites (IARC, 2012b), makes it prudent and important to perform these subtype analyses here also.

Given these caveats, important observations include the following:

### 4.2. *Exposure to oncogenic viruses*

Most of the activities in large slaughtering plants are actually processing activities. The designation of processing plants as used in this study refers to facilities that received carcasses from slaughter plants for further processing but no slaughter was carried out within the premises. Thus, it is possible that the distinction between slaughtering and processing plants to a large extent may be artificial for the exposures of interest, as the results in this study seem to suggest.

The results indicate that in spite of the extensive information that was attempted to collect on occupational exposure to other animals, only performing tasks associated with, or working in areas in which poultry oncogenic virus exposure occurred in chicken and turkey slaughtering and processing plants, was associated with increased risks of lung cancer, and it was independent of any risk associated with exposure to chemical carcinogens, and there was no evidence of interaction with tobacco smoking. These increased risks were even more strongly manifested when histologic types were considered. Working in offices or in the packing area was not associated with any increased risk in these plants. These findings are consistent with various industrial hygiene assessments of exposure to microorganisms, including oncogenic viruses, such as: carcass sampling, human nasal swab sampling, surface sampling, or airborne microorganism concentrations (Paba et al., 2014; You et al., 2016; Goksoy et al., 2004; Kotula and Kinner, 1964; Walker and Ayres, 1959) that indicate that all areas of slaughter and processing plants, and workers, have above-background levels of exposure to microorganisms, and with industrial hygiene assessments that indicated that mean antibody levels to two avian oncogenic viruses (ALSV and REV) were higher in individuals engaged in all tasks in a chicken slaughtering plant, than mean levels in control subjects who never worked in poultry plants (Johnson et al., 1995a, 1995b; Choi and Johnson, 2011a, 2011b). The highest risks were recorded for tasks that involve killing, washing, deboning, pulling out the inside of chickens, cutting the heart and liver out, cutting carcasses into halves or smaller parts, and contact with blood, with higher risks observed for those engaged in these tasks for five or more years. It appears that virtually all histologic types were involved in these observed increased risks, similar to what is observed for tobacco smoking and lung cancer (Khuder et al., 1998). This could be because there are different viruses and strains involved, just as different carcinogens are involved in tobacco smoking, or because as is well known, even a given virus strain may induce different types of tumors in chickens depending on the dose and age at exposure (Saif et al., 2003). The associations observed for "killing of chickens" and "contact with blood" and lung cancer risk in the pilot study (Felini et al., 2012), were also confirmed – the odds ratios for killing in chicken and turkey slaughtering plants were both elevated. The only other study of poultry slaughter plant workers in the literature was not large enough to record any occurrence of a case of lung cancer (Fritschi et al., 2003). Of note also, is that occupational hunting of game birds was significantly associated with benign tumors – Table 5.

It is interesting that an association between killing, or exposure to freshly killed animals or with exposure to meat aerosols and lung cancer has also been reported for workers in cattle, pigs and sheep slaughter plants (Johnson, 1991; Durusoy et al., 2006; Coggon et al., 1989; McLean and Pearce, 2004). In a systematic review of 60 studies, Johnson and Choi (2012) concluded that the overwhelming majority of studies reported a definite excess of lung cancer in workers in meat and poultry slaughter and processing plants.

Some exposure to oncogenic viruses could conceivably have occurred in food and soup manufacturing plants and in restaurants, cafeterias and kitchens, but this study was unable to assess this because of sparseness of data. But, the results for these places suggest that the role of exposure to chemical carcinogens in the occurrence of lung cancer in these places may likely be of importance.

### 4.3. Exposure to chemicals during curing, smoking, cooking, frying, boiling and wrapping of poultry meat

The results provide a strong and fairly consistent evidence that workers with potential exposure to polycyclic aromatic hydrocarbons (PAH) and heterocyclic amines (HCA) during cooking, frying, steaming, boiling, and smoking of meat in poultry slaughtering and processing plants were at increased risk of lung cancer, particularly specific histologic types. Squamous cell carcinoma was invariably involved, although excess risk was also seen for small cell carcinoma. It is noted that the consistency of the association between these chemicals and lung cancer seen for poultry plants, was also evident in related industries such as food and soup manufacturing, and in restaurants, cafeterias and kitchens. PAH and HCA are established causes of cancer including lung cancer in animals or humans (IARC, 1985; Jakszyn et al., 2004; Armstrong et al., 2004), and workers involved in smoking and boiling meat in poultry plants can have above background exposures to PAH and HCA (Nordholm et al., 1986; Colmsjo et al., 1984; Yao et al., 2013). In limited analyses, there was indication that these chemical exposures were risk factors for lung cancer independent of oncogenic virus exposures.

There was a suggestion that potential exposure to nitrosamines during curing of sausage was associated with squamous cell carcinoma, but the low prevalence of curing exposure does not allow for this to be confirmed in other similar settings in the study, or to examine risk by calendar period of exposure.

No significantly increased risk of lung cancer was observed for workers who wrapped meat or used the wrapping machine. However, those who complained of difficulty in breathing because of fumes or smoke emitted from the wrapping machine while using it in poultry slaughter and processing plants, had increased risk of the disease, especially small cell carcinoma, and as shown these risks appear independent of oncogenic virus exposure as well, and as expected, tended to be higher in females than in males (not shown), though not statistically significant. These results are explained by the fact that workers (predominantly women in supermarkets), were known to be exposed to fumes emitted when an electrical heated "hot wire" in the wrapping machine was used to cut the polyvinyl chloride plastic film used to wrap meat. These fumes contained PAH that are known to cause lung cancer in humans (IARC, 1985). Exposure to the fumes during use of the wrapping machine resulted in acute pulmonary effects in workers referred to as "meat wrappers' asthma" and also chronic bronchitis (Pauli et al., 1980). Similar exposures occurred in meat and poultry plants, although the adverse effects were not as well documented in these plants as in supermarkets. This exposure was drastically reduced or eliminated in the mid-1970's with the replacement of the hot wire with a cool rod in these machines, although we found that it was still in use in 1990 in some supermarkets during our muconic acid biomarker study in New Mexico (Johnson et al., 1999). We showed in our cohort studies of supermarket workers that women who wrapped meat in supermarkets had increased risk of lung cancer, and the risk was seen for those employed before 1980 but not in those employed in 1980 or after (Johnson, 1994b). The findings in the current study could be explained by the fact that while some of the wrapping machines used a heated wire or rod to cut plastic, others did not, and cutting was purely mechanical, and no exposure occurred. The question on use of the wrapping machine did not distinguish mechanical from 'hot wire' cutting of the plastic film. Also the reduced exposure after 1979 could have contributed to the overall findings. Unfortunately there were not enough cases to reliably separately analyze risk by period of exposure or by duration of exposure, but the results for difficulty in breathing due to fumes from the wrapping machine do tend to incriminate this exposure, and are similar to the finding that individuals who complained of eye/throat irritation had significantly increased risk of lung cancer from exposure to cooking fumes than those who did not (Metayer et al., 2002).

### 4.4. Occupational exposures outside the poultry industry

The limited data available for work in food canning and soup manufacturing plants, restaurants, or as a cook, etc. only allowed ascribing the observed excess lung cancer occurrence in these groups to exposure to chemical carcinogens during cooking, or steaming and boiling meat, which is consistent with the results for these exposures in poultry plants.

It is not known whether the increased risks of benign tumors associated with hunting, exposure to pets, being a butcher that killed animals, represent risks for truly benign tumors, or pre-malignant tumors. Also, the potential mixed exposure to both birds and other animals for that particular question, further complicates interpretation of the results.

The results for other occupational exposures outside the poultry industry were presented because of the importance of examining if known established occupational risk factors for lung cancer in the literature (IARC, 1985, 2012c, 2014; http://www.lung.org/) were replicated in this study. As seen in Table 8, although the Cox model is not directly comparable to the logistic model since smoking was not adjusted for because of sparse data, the results were not very different, and suggest that the findings for these risk factors were to a large extent replicated in this study, which is one of the most reliable indicators of the overall validity of the findings in this study.

This study has identified tasks and areas of work that are surrogates for exposure to carcinogenic agents in the work environment of poultry slaughtering and processing plants. Of significance is the observation that the findings are consistent with the results obtained in a systematic review of 60 studies that investigated the occurrence of lung cancer in poultry and meat workers. The review found that about 80% of the studies reported at least a 30% increased in risk of lung cancer in meat and poultry workers, even after adjusting for tobacco smoking, and that the evidence pointed to food animal oncogenic viruses as one of the main causes (Johnson and Choi, 2012).

There is sufficient information presented that warrants the need for steps to be taken to protect workers. Education of workers, unions and employers about the potential risks and how to reduce them should be given priority. Other measures include intervention programs to reduce eczema and injury to the skin through wearing of gloves; improved engineering in ventilation systems to reduce the concentration of air-borne infectious agents, or water-borne infectious agents in rinsing water; better enforcement of personal protective measures, and personal hygiene, etc., including but not limited to, measures to reduce or eliminate the occurrence of microorganisms (particularly oncogenic viruses) in birds before they arrive at the plants.

The study has highlighted the need for multidisciplinary research in areas such as 1) epidemiologic research in which studies of different designs with sufficient statistical power can further expand on the findings reported here; 2) laboratory molecular studies to detect ASLV and REV integration in DNA of workers and other humans – demonstration of this, combined with supporting epidemiologic evidence will constitute the definitive proof that these viruses cause cancer in humans; 3) industrial hygiene assessment of exposure to biological agents, especially the oncogenic viruses of poultry in the workplace; 4) serological studies; 5) better designed studies to detect evidence of oncogenic virus contamination in vaccines; 6) more sensitive diagnostic polymerase chain reaction assays that use better-designed primers; and 7) continuous monitoring by health agencies through the conduct of surveys to determine the prevalence of infection of poultry oncogenic viruses in poultry used for food; at the moment it appears only the poultry industry has been engaged in such surveys, and regrettably, their data has not been made open to the general public or research community.

## 5. Conclusion

Workers in poultry slaughtering and processing plants have the highest known human exposure to the oncogenic viruses of poultry. The general population is widely exposed to these viruses. It is not yet established that these viruses cause cancer in humans. This is therefore an important study. It provides critical epidemiologic evidence for the first time that occupational tasks or areas of work associated with exposure to chickens and turkeys that may be infected with poultry oncogenic viruses, are independently associated with increased risks of death from lung cancer, even after adjusting for tobacco smoking, other confounders, and chemical carcinogenic exposures in slaughtering and processing plants, and with risks estimated conservatively. This has important public health implications, as it suggests that these viruses may be associated with cancer occurrence in humans just as they do in chickens and turkeys. The study also provides evidence that exposure to carcinogenic chemicals during curing, smoking, cooking, frying, boiling and wrapping of poultry meat may also independently contribute to the observed excess occurrence of lung cancer in poultry plants. To this end, the study has identified possible carcinogenic hazards in the workplace for this occupational group. Further studies are needed to expand on these findings. In the meantime as mentioned above, steps should be taken to look into minimizing or eliminating these exposures in the workplace in order to protect the workers.

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## Human subjects research

The protocols for both the original cohort study and this case-cohort study were reviewed and approved by the Human Subjects Committee (Institutional Review Board) of the University of North Texas Health Science Center, in accordance with the Helsinki Declaration.

## Conflict of interest

The authors have no conflict of interest.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.07.037.

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