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Cancer mortality in poultry slaughtering/processing plant workers belonging to a union pension fund

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ABSTRACT

Background: The role of zoonotic biological agents in human cancer occurrence has been little studied. Humans are commonly exposed to viruses that naturally infect and cause cancer in food animals such as poultry that constitute part of the biological environment. It is not known if these viruses cause cancer in humans.
Objective: To study cancer mortality in the largest cohort to date, of 20,132 workers in poultry slaughtering and processing plants, a group with the highest human exposures to these viruses.
Methods: Mortality in poultry workers was compared with that in the US general population through the estimation of standardized mortality ratios.
Results: Significantly increased risks were observed in the cohort as a whole or in subgroups, for several cancer sites, viz: cancers of the buccal cavity and pharynx; pancreas; trachea/bronchus/lung; brain; cervix; lymphoid leukemia; monocytic leukemia; and tumors of the hemopoietic and lymphatic systems. Elevated SMRs that were not statistically significant were observed for cancers of the liver, nasopharynx, myelofibrosis, and myeloma. New sites observed to be significantly in excess in this study were cancers of the cervix and penis.
Conclusion: This large study provides evidence that a human group with high exposure to poultry oncogenic viruses has increased risk of dying from several cancers. Other occupational carcinogenic exposures could be of importance in explaining some of the findings, such as fumes from wrapping machines. These findings may have implications for public health amongst persons in the general population who may also be exposed to these viruses. What is needed now are epidemiologic studies that can demonstrate whether the excess of specific cancers can be attributed to specific occupational exposures while adequately controlling for other potential occupational and non-occupational carcinogenic exposures.

1. Introduction

Certain viruses commonly infect and cause a wide variety of cancers in chickens and turkeys destined for human consumption. They include the avian leukosis/sarcoma viruses, reticuloendotheliosis viruses, and Marek's disease virus. The avian leukosis/sarcoma viruses and reticuloendotheliosis viruses are among the most potent cancer-causing agents known, and can induce cancer in poultry in a matter of a few days (Johnson, 1994; Saif et al., 2003). These agents are found present in raw poultry products, including raw or inadequately cooked poultry meat and eggs meant for human consumption (Pham et al., 1999), and in vaccines grown in eggs (Tsang et al., 1999). In a survey of eggs displayed for sale in a random sample of supermarkets in the New Orleans metropolitan area, 14% of eggs were positive for endogenous and exogenous avian leukosis/sarcoma viruses (i.e. at least one egg in a carton of a dozen eggs (Pham et al., 1999). Similarly, it has been reported that virtually all stocks of measles and mumps vaccines (these vaccines are grown in eggs) currently in use in the United States are contaminated with the endogenous variety of avian leukosis/sarcoma viruses (Tsang et al., 1999). Thus the general population is commonly exposed. This is evident from the Johnson et al. (1995a, 1995b) studies that recorded at least a 31% prevalence of anti-avian leukosis/sarcoma viruses p15 antibodies in sera of general population subjects without occupational exposure to poultry. Similarly, Choudat et al. (1996) reported a prevalence of anti-avian leukosis/sarcoma viruses antibodies of up to 35% and anti-Marek's disease virus antibodies of up to 32% in white collar workers without exposure to poultry. It is therefore of great interest whether these agents also cause cancer in humans.

To answer this question we conducted mortality studies of two separate cohorts of workers who were employed in poultry slaughtering/processing plants, one identified from a union in

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Baltimore, Maryland ($N=2580$) (Johnson, 1989; Johnson et al., 1986a, 1986b, 1997, 2010a), and the other from a union in Marshall, Missouri ($N=7700$) (Johnson et al,. 2010b; Netto and Johnson, 2003). This occupational group has one of the highest human exposures to these agents. In a typical large plant that may kill more than 75,000 chickens per day, workers may have intimate contact with blood, secretions, and internal organs. Moreover, frequent cuts and injury from sharp knives and bone splinters (Cai et al., 2005), and dermatitis from irritant enzymes and secretions make it easy for microorganisms to penetrate the skin and enter the body. In addition, exposure can also occur via the airborne route (Harris et al., 1962). No other human group *en masse* has such a high potential for exposure. Thus, if these viruses cause cancer in humans, we reason this will be most readily evident in this highly exposed group of workers.

Results from these two cohorts thus far indicate that several cancers were significantly occurring in excess. These were cancers of the lung, base of the tongue, palate and other unspecified mouth, tonsil and oropharynx, nasal cavity/middle ear/accessory sinus, esophagus, recto-sigmoid/rectum/anus, pancreas, liver and intrabiliary system, thyroid, thymus/heart/mediastinum/pleura, the adrenals and other endocrine organs, cervix, myelofibrosis, lymphoid leukemia, monocytic leukemia, multiple myeloma, and other specified type/unspecified type of leukemia (Johnson et al., 1986b, 1997, 2010a, 2010b; Netto and Johnson, 2003). To investigate further if these findings can be replicated, we studied mortality in a new cohort of 20,132 workers which is the largest cohort thus far studied, and the findings are presented below.

While we hypothesize that poultry oncogenic viruses are the primary suspect for any observed excess cancer occurrence, they are not the only potentially carcinogenic exposures in poultry slaughtering/processing plants. Polyvinyl chloride plastic films were introduced in 1963 for wrapping meat (Pauli et al., 1980; Vandervort and Brooks, 1977). Fumes emitted from the wrapping machines contain known carcinogens such as benzene, polycyclic aromatic hydrocarbons, and phthalates (Vandervort and Brooks, 1977). Other potentially carcinogenic exposures are smoke or aerosol emitted during smoking or cooking of poultry products that contain polycyclic aromatic hydrocarbons and heterocyclic amines, and exposure to nitrosamines during the curing of poultry (Jakszyn et al., 2004; Nordholm et al., 1986; Sen et al., 1974; Vainiotalo and Matveinen, 1993). Thus, these other exposures are also candidates for explaining any excess occurrence of cancers in these workers.

2. Materials and methods

The study population consists of all 20,132 workers who were ever employed anytime between 1972 and 1990 in 11 poultry slaughtering/processing plants located in five States in the US (Arkansas, Louisiana, Maine, Missouri, Texas). They were identified from the roster of a Pension Fund administered by the United Food & Commercial Workers International Union. Mortality was studied for the period January 1, 1972 to December 31, 2003, during which time a total 2454 workers had died. The cause of death was coded according to the 9th Revision of the International Classification of Diseases (ICD). The ICD codes were not available for 40 of the 2,454 deceased subjects (1.6%).

Methods of follow-up include the National Death Index, Social Security Administration, State Departments of Vital Records, State Departments of Motor Vehicles, US Post Office, personal contact by telephone and mail, and internet tracing methods. The Pension Benefit Information Inc., a private company, was also used to identify deceased persons. This company matches subjects against US death records for all years from the 1800s to the present, using information received from Social Security Administration, State Departments of Vital Records, Health Care Financing Administration, as well as the Civil Service Commission, Railroad Retirement Board, and the Department of Defense. Because of the extensive follow-up methods employed, subjects whose vital status was unknown after the end of follow-up were assumed to be alive at the end of study.

Date of birth information was missing for 156 subjects, i.e., 0.8% of the entire cohort; however, it was available for all deceased workers. Rather than excluding the 156 persons from the analysis, these subjects had their date of birth imputed based on the median year of birth of workers with known date of birth who joined the union in a particular year—thus if a member without date of birth joined the union in 1975, he/she was assigned as his/her year of birth, the median year of birth for all persons with known date of birth who joined the union that particular year. This measure was deemed to be associated with negligible bias, since the total person-years will be little affected.

Statistical analyses involved estimation of standardized mortality ratios (SMR), stratifying on age, calendar time, gender, race and plant, using the US general population as the comparison group. Analysis was conducted using the OCMAP Plus software from the University of Pittsburgh, USA. Information on race was available only for deceased individuals with a death certificate/known cause of death. Therefore to perform the SMR analyses, race was artificially assigned at random to each of the 17,641 individuals in the study without a death certificate/known cause of death, based on the racial distribution of deceased persons with known race. In a similar study of workers in the meat industry, the racial distribution of deceased subjects was found to be no different from that of a sample of current workers representing more than half of the union membership (Johnson et al., 1986a). The cohort was stratified by plant, and then stratified into four subgroups by race and sex (black males, black females, white males, white females), and each of these groups stratified according to age (5-year intervals) and calendar year at entry into the cohort (5-year intervals). Person-years were accumulated from January 1972 for those who were already members of the union before that date. For those who became members later, person-years commenced on the date of union membership. Membership in the union was compulsory from the first day of employment, thus the date of hire was virtually the same as the date of membership for persons who were hired after the plant had been unionized. Person-years were enumerated up to the date of death, or date of termination of the study on December 31, 2003, whichever was earlier. Expected deaths were derived by multiplying the person-years in each cell by the corresponding gender-, calendar year-, age-specific mortality rate for the United States general population. Observed and expected deaths for each cell were summed over all ages and calendar years, and over all strata, and the SMR estimated as the total observed number of deaths divided by the total expected. The 95% confidence intervals for the SMR were calculated according to a simple exact method that links both the Poisson and chi-square distributions (Liddell, 1984).

Because we artificially assigned date of birth and race information that was missing for some individuals in the SMR analyses, we also estimated cause-specific proportional mortality ratios (PMR) in similar fashion, as date of birth and race information was available for all subjects in the PMR analyses. A limited sensitivity analysis for race was also conducted.

A questionnaire was sent by the United Food & Commercial Workers International Union to individual plants requesting them to indicate (yes/no) whether chickens and turkeys had ever been slaughtered, cooked/fried, smoked, or cured in the plant, whether the 'hot' wire or 'cool rod' wrapping machine was ever used, and whether workers ever complained of being bothered by fumes from the wrapping machine. Based on the responses, plants were further classified according to these activities.

3. Results

The year of birth distribution is given in Table 1. More than two-thirds of the cohort were born in 1950 or later, and the average duration of follow-up was 23.8 years. A description of the location and demographic make-up of the plants is given in Table 2. The PMR results were almost identical to the SMR results, and are therefore presented as an Appendix A. In Table 3, are presented the SMR results for causes of death for which a statistically significant or greater than 2-fold risk was observed in

Table 1
The distribution of year of birth of pension fund poultry workers.

Interval	No. of subjects	Percentage	Cumulative percentage
1900–1910	29	0.14	0.14
1910–1920	358	1.78	1.92
1920–1930	1044	5.19	7.11
1930–1940	1813	9.01	16.11
1940–1950	3499	17.38	33.49
1950–1960	8849	43.95	77.45
1960–1970	4536	22.53	99.98
1970+	4	0.02	100.00
Total	20,132	100.00	100.00

Table 2
Location and demographic make-up of poultry plants.

Plant	Located	State	No. of subjects	No. of deceased whites (%)	No. of Deceased Females (%)
1 (12018)	Natchitoches	Louisiana	737	13 (15.5)	45 (53.6)
2 (12030)	Alexandria	Louisiana	419	0 (0)	27 (38.6)
3 (13019)	Carthage	Missouri	523	56 (88.9)	30 (47.6)
4 (21055)	Arcadia	Louisiana	7	2 (100)	0 (0)
5 (24010)	Lewiston	Maine	1296	151 (93.8)	54 (33.5)
6 (24011)	Belfast	Maine	803	124 (96.1)	52 (40.3)
7 (24012)	Belfast	Maine	1658	236 (97.5)	110 (45.5)
8 (32710)	El Dorado	Arkansas	3319	74 (17.7)	201 (48.1)
9 (32830)	Russellville	Arkansas	10227	953 (82.9)	526 (45.7)
10 (35045)	Lufkin	Texas	943	45 (41.3)	53 (48.6)
11 (44220)	El Dorado	Arkansas	200	7 (26.9)	5 (19.2)
Total			**20132**	1661 (67.7)	1103 (44.95)

the cohort as a whole, or in particular race/sex subgroups. Previous software for analyzing occupational studies have typically grouped cancers of the buccal cavity and pharynx as a single group (ICD 140–149). For the first time, we recently were able to examine risk for individual subtypes in the group, in the Baltimore poultry study (Johnson et al., 2010a). In Table 3, we present the results for individual subtypes of the group ($N=15$) even though some may involve only a single death, because these subtypes have not been investigated before, and for comparison with the Baltimore and Missouri cohorts.

The main findings of significantly elevated SMRs were for cancers of the buccal cavity and pharynx, pancreas, lung, cervix, penis, brain, lymphoid leukemia, monocytic leukemia, and benign neoplasms of the lip, oral cavity, pharynx, etc. Elevated SMRs that were not statistically significant were observed for cancers of the liver, nasopharynx, myelofibrosis, and myeloma.

The overall SMR for the 15 deaths from cancer of the buccal cavity and pharynx was 2.94 (95% CI 1.64–4.85) (not shown) and in Table 3 this group is broken down into subtypes. Markedly elevated SMRs for the various subtypes in particular race/sex subgroups are seen, with no consistent race/sex pattern. The excess of lung cancer is confined to white males and females, SMRs of 1.9, 95% CI 1.5–2.3, and 1.5, 95% CI 1.2–1.9, respectively. The observed excess of lymphoid leukemia (SMR=5.9, 95% CI 1.6–15.2 and SMR=3.3, 95% CI 0.4–12.1), seemed confined to non-white males and females, respectively, as also appears to be the case for multiple myeloma. The excess of monocytic leukemia is confined to females of both races (overall SMRs=17.7, 95% CI 2.1–64.1), while myelofibrosis occurred in white males only. The excess of cancer of the penis occurred in both races (overall SMR=8.6, 95% CI, 1.0–31.1), as also that for uterine cervix (overall SMR=2.2, 95% CI 1.3–3.5) and benign neoplasms of the lip, oral cavity, pharynx, etc., (overall SMR=104.2, 95% CI 52.0–186.5). For cancers of the liver and pancreas, the pattern is less clear. A two-fold excess of brain cancer appears to be occurring in almost all race/sex subgroups. The SMR of 0.6 (95% CI 0.4–0.9) for breast cancer was significantly depressed in white women, but not in non-white women 1.1 (95% CI 0.7–1.7).

In Table 4 are given the results for cancers observed to be occurring in excess by type of activity carried out in the poultry plants.

The results for the sensitivity analyses are given in Table 5. When the entire cohort was analyzed assuming all study subjects were white, instead of the 68% used in the SMR analyses, the SMRs for cancers of the lung, breast, cervix, lymphoid and hemopoietic systems, lymphoid leukemia, and myelofibrosis were unchanged. For the remaining cancer sites, the change was less than 10%, except for cancers of the penis (15%), liver (20%), and cancers of the buccal cavity and pharynx (palate and unspecified mouth) (19%), pyriform sinus (29%), other ill-defined oropharynx (33%), and nasopharynx (44%). Similarly, assuming all the study subjects were black did not change the SMRs by more than 44%.

4. Discussion

4.1. Specific findings

Several cancers were observed to be occurring in excess in this cohort study. Except for cancer of the penis, the risks for all the major cancer sites for which a statistically significant elevated SMR was recorded in this study, were also elevated in at least one of the two other cohort studies, and in most instances in both (Johnson et al., 1986b, 1997, 2010a, 2010b; Netto and Johnson, 2003). Thus this study supports previous reports of excess occurrence of cancer deaths in workers in poultry slaughtering and processing plants. Since all of the plants carried out killing (the activity associated with among the highest exposures to oncogenic viruses) exposure to oncogenic viruses cannot be ruled out in explaining the excess for any of these cancers. The only clear finding is the association of lymphoid leukemia, and possibly liver and cervical cancers with killing. It is to be noted that killing activities were also observed to be associated with excess of cancers of the lung, liver, pancreas, and tumors of the hemopoietic and lymphatic systems after adjusting for tobacco smoking, in a pilot case-cohort study conducted within this same cohort (Felini et al., 2009; Preacely et al., unpublished), and in nested case-control studies within a cohort of meat workers who handled cattle, pigs, and sheep (Johnson, 1991; Metayer et al., 1998).

Avian leukosis/sarcoma viruses are known to induce a wide variety of tumors in chickens (Saif et al., 2003). Similarly, the excess occurrence of warts caused by human papilloma viruses is well known in poultry workers (Stehr-Green et al., 1993). Cancers of the buccal cavity and pharynx, cervix, and penis, and benign neoplasms of the lip, oral cavity, and pharynx that are observed in the present study to be in excess, are known to be caused by, or associated with human papilloma viruses (de Araujo Souza et al., 2009; Dillner et al., 2000; Scully, 2002). Hence papilloma viruses and the other poultry oncogenic viruses are suspects for the cause of the possible excess of these cancers in this cohort, although the role of exposures associated with wrapping and cooking cannot be also completely ruled out.

In the Baltimore cohort (Johnson et al., 2010a) the SMR for cervical cancer was 2.5 each for white and non-white women, although not statistically significant (unpublished). In the Missouri cohort (Johnson et al., 2010b; Netto and Johnson, 2003), the

Table 3
Standardized mortality ratios for selected cancers for the period 1972 to 2003.

Cause of death	Poultry workers								
	Non-white males	White males	All males	Non-white females	White females	All females	All non-whites	All whites	All groups
	N=2849	*N*=6782	*N*=9631	*N*=3550	*N*=6951	*N*=10,501	*N*=6399	*N*=13,733	*N*=20,132
	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)	Obs. SMR (95% CI)
Death from all malignant neoplasms	90 1.0 (0.8–1.3)	216 1.4 (1.2–1.6)	306 1.3 (1.1–1.4)	109 1.2 (1.0–1.4)	220 1.1 (1.0–1.3)	329 1.1 (1.0–1.3)	199 1.1 (1.0–1.3)	436 1.2 (1.1–1.3)	635 1.2 (1.1–1.3)
Gum	0 –(0.0–146)	1 26.7 (0.7–149)	1 15.9 (0.4–88.9)	0 –(0.0–269)	0 –(0.0–11.5)	0 –(0.0–80.5)	0 (0.0–94.6)	1 14.4 (0.4–80.1)	1 9.2 (0.2–51.3)
Palate/other unspec. mouth	1 2.5 (0.1–14.1)	3 6.6 (1.4–19.3)	4 4.7 (1.3–12.0)	0 –(0.0–28.3)	0 –(0.0–12.1)	0 –(0.0–8.5)	1 1.9 (0.0–10.6)	3 3.9 (0.8–11.5)	4 3.1 (0.8–8.0)
Pyriform sinus; hypopharynx	0 –(0.0–15.5)	1 4.3 (0.1–24.1)	1 2.1 (0.1–11.9)	0 –(0.0–92.7)	0 –(0.0–40.2)	0 – (0.0–28.1)	0 –(0.0–13.3)	1 3.1 (0.1–17.2)	1 1.7 (0.0–9.3)
Other, ill-defined oropharynx	3 4.1 (0.8–11.8)	0 –(0.0–5.4)	3 2.1 (0.4–6.1)	1 6.5 (0.2–36.5)	3 8.7 (1.8–25.5)	4 8.0 (2.2–20.6)	4 4.5 (1.2–11.5)	3 2.9 (0.6–8.5)	7 3.6 (1.5–7.5)
Nasopharynx	0 –(0.0–7.5)	0 –(0.0–11.3)	0 –(0.0–4.5)	1 10.7 (0.3–59.6)	1 5.0 (0.1–27.9)	2 6.8 (0.8–24.6)	1 1.7 (0.0–9.5)	1 1.9 (0.0–10.6)	2 1.8 (0.2–6.5)
Liver, intrabiliary	5 1.3 (0.4–3.0)	4 1.0 (0.3–2.6)	9 1.1 (0.5–2.2)	3 2.5 (0.5–7.4)	5 1.9 (0.6–4.5)	8 2.1 (0.9–4.2)	8 1.6 (0.7–3.1)	9 1.4 (0.6–2.6	17 1.5 (0.8–2.3)
Pancreas	5 1.2 (0.4–2.8)	15 1.9 (1.1–3.2)	20 1.7 (1.0–2.6)	5 1.3 (0.4–3.1)	2 0.2 (0.0–0.8)	7 0.6 (0.2–1.2)	10 1.3 (0.6–2.3)	17 1.0 (0.6–1.7)	27 1.1 (0.7–1.6)
Trachea, bronchus, lung	31 1.1 (0.7–1.6)	96 1.9 (1.5–2.3)	127 1.6 (1.3–1.9)	20 0.09 (0.6–1.4)	70 1.5 (1.2–1.9)	90 1.3 (1.1–1.6)	51 1.0 (0.8–1.4)	166 1.7 (1.4–2.0)	217 1.5 (1.3–1.7)
Breast	0 –(0.0–29.3)	0 –(0.0–19.0)	0 (0.0–11.5)	22 1.1 (0.7–1.7)	27 0.6 (0.4–0.9)	49 0.8 (0.6–1.0)	22 1.1 (0.7–1.7)	27 0.6 (0.4–0.9)	49 0.8 (0.6–1.0)
Cervix uteri	–	–	–	8 2.9 (1.3–5.8)	10 1.8 (0.9–3.3)	18 2.2 (1.3–3.5)	8 2.9 (1.3–5.8)	10 1.8 (0.9–3.3)	18 2.2 (1.3–3.5)
Penis	1 11.2 (0.3–62.3)	1 7.0 (0.2–39.0)	2 8.6 (1.0–31.1)	–	–	–	1 11.2 (0.3–62.3)	1 7.0 (0.2–39.0)	2 8.6 (1.0–31.1)
Brain/meninges/Cord/CN/CNS/PNS/ ANS	3 2.0 (0.4–6.0)	8 1.2 (0.5–2.3)	11 1.3 (0.7–2.4)	6 2.1 (0.8–4.5)	12 2.0 (1.0–3.5)	18 2.0 (1.2–3.2)	9 2.1 (0.9–3.9)	20 1.6 (1.0–2.4)	29 1.7 (1.1–2.4)
Lymphoid and hemopoietic	14 1.8 (1.0–3.1)	18 1.0 (0.6–1.5)	32 1.2 (0.8–1.7)	10 1.3 (0.6–2.4)	18 1.0 (0.6–1.7)	28 1.1 (0.7–1.6)	24 1.6 (1.0–2.3)	36 1.0 (0.7–1.4)	60 1.2 (0.9–1.5)
Malig. immun, myeloma, plasma cell	5 2.7 (0.9–6.4)	2 0.8 (0.1–3.0)	7 1.6 (0.7–3.4)	2 1.7 (0.2–6.0)	3 1.1 (0.2–3.2)	5 1.3 (0.4–2.9)	7 2.3 (0.9–4.8)	5 1.0 (0.3–2.2)	12 1.5 (0.8–2.5)
Lymphoid leukemia	4 5.9 (1.6–15.2)	3 1.6 (0.3–4.8)	7 2.8 (1.1–5.9)	2 3.3 (0.4–12.1)	1 0.7 (0.0–4.1)	3 1.5 (0.3–4.5)	6 4.7 (1.7–10.2)	4 1.3 (0.3–3.2)	10 2.2 (1.1–4.1)
Monocytic leukemia	0 –(0.0–157)	0 –(0.0–46.0)	0 –(0.0–35.6)	1 28.9 (0.7–161)	1 12.8 (0.3–71.3)	2 17.7 (2.1–64.1)	1 17.2 (0.4–95.9)	1 6.3 (0.2–35.2)	2 9.2 (1.1–33.4)
Myelofibrosis	0 –(0.0–23.6)	2 4.4 (0.5–15.9)	2 3.3 (0.4–11.8)	0 –(0.0–20.2)	0 –(0.0–8.5)	0 –(0.0–6.0)	0 (0.0–10.9)	2 2.2 (0.3–8.1)	2 1.6 (0.2–5.9)
Benign neoplasm of lip, oral cavity, pharynx, other dig	0 –(0.0–175)	4 127.9 (34.9–327.5)	4 76.4 (20.8–195.6)	2 122.6 (14.8–443.0)	5 135.8 (44.0 –316.8)	7 131.7 (52.9–271.3)	2 53.5 (6.5–193.4)	9 132.1 (60.4–250.7)	11 104.2 (52.0–186.5)
All deaths	424 0.9 (0.8–1.0)	927 1.3 (1.2–1.4)	1351 1.2 (1.1–1.2)	369 1.4 (1.3–1.6)	734 1.3 (1.2–1.4)	1103 1.3 (1.2–1.4)	793 1.1 (1.0–1.2)	1661 1.3 (1.2–1.4)	2454 1.2 (1.2–1.3)

Figures in parentheses are 95% confidence intervals.

Table 4
SMRs for Cancers observed to be occurring in excess by type of activity in the poultry plant.

Disease	Killing only	Killing and use of wrapping machine	Killing, use of wrapping machine, complaints about fumes from wrapping machine	Killing, wrapping, cooking
	$N=219$ deaths (95% CI)	$N=553$ deaths (95% CI)	$N=532$ deaths (95% CI)	$N=1150$ deaths (95% CI)
Gum	$N=0$	$N=0$	$N=1$ SMR=46.2 (1.2–258)	$N=0$
Palate, etc.	$N=0$	$N=0$	$N=2$ SMR=7.9 (1.0–28.5)	$N=2$ SMR=3.3 (0.4–11.9)
Tonsil, etc.	$N=0$	$N=0$	$N=1$ SMR=3.2 (0.1–18.0)	$N=0$
Pyriform sinus	$N=0$	$N=0$	$N=0$	$N=1$ SMR=3.7 (0.1–20.7)
Ill-defined oropharynx	$N=0$	$N=2$ SMR=3.6 (0.4–13.1)	$N=2$ SMR=5.5 (0.7–19.8)	$N=3$ SMR =3.5 (0.7–101)
Nasopharynx	$N=0$	$N=0$	$N=1$ SMR=5.3 (0.1–29.7)	$N=1$ SMR=2.0 (0.1–112)
Liver	$N=4$ SMR=2.7 (0.7–6.9)	$N=3$ SMR=0.9 (0.2–2.6)	$N=2$ SMR=0.9 (0.1–3.2)	$N=8$ SMR=1.5 (0.6–2.9)
Pancreas	$N=3$ SMR=1.1 (0.2–3.4)	$N=5$ SMR=0.9 0.3–2.2)	$N=7$ SMR=1.4 0.6–2.9)	$N=12$ SMR=1.0 (0.5–1.7)
Trachea, bronchus, lung	$N=17$ SMR=1.1 (0.7–1.8)	$N=37$ SMR=1.3 (0.9–1.7)	$N=49$ SMR=1.6 (1.2–2.1)	$N=114$ SMR=1.6 (1.3–1.9)
Cervix	$N=2$ SMR=1.6 (0.2–5.9)	$N=7$ SMR=2.2 (0.9–4.6)	$N=0$	$N=9$ SMR=1.8 (0.8–3.3)
Penis	$N=0$	$N=1$ SMR=19.5 (0.5–109)	$N=0$	$N=1$ SMR=9.8 (0.2–54.5)
Brain, etc.	$N=0$	$N=8$ SMR=3.3 (1.4–6.5)	$N=7$ SMR=1.9 (0.8–3.8)	$N=14$ SMR=1.7 (0.9–2.8)
Myeloma	$N=1$ SMR=0.9 (0.0–5.0)	$N=4$ SMR=1.7 (0.5–4.4)	$N=0$	$N=$ 7 SMR=1.6 (0.6–3.3)
Lymphoid leukemia	$N=3$ SMR=7.7 (1.6–22.5)	$N=2$ SMR=2.4 (0.3–8.8)	$N=1$ SMR=1.1 (0.0–5.9)	$N=4$ SMR=1.7 (0.5–4.5)
Myelofibrosis	$N=0$	$N=0$	$N=0$	$N=2$ SMR=3.2 (0.4–11.4)
Benign neoplasm of lip, oral cavity, pharynx	$N=0$	$N=1$ SMR=35.9 (0.9–200.3)	$N=2$ SMR=101.2 (12.2–365.5)	$N=8$ SMR =139.7 (60.3–275.2)

Figures in parentheses are 95% confidence intervals.

SMR was 1.5 in white women and 5.2 in non-white women, although not statistically significant (Johnson et al., 2010b).

With regards to lung cancer, the excess of this disease has been reported in cohort (Fritschi et al., 2003; Johnson et al., 1986b; Johnson, 1994; Johnson and Choi, 2009; Johnson et al., 2010a) and nested case-control (Johnson, 1991; Preacely et al., unpublished) studies to be related to exposure to oncogenic viruses and wrapping of meat and poultry, even when tobacco smoking was adjusted for (Johnson, 1991; Preacely et al., unpublished). However, these studies have not had sufficient statistical power to investigate the smoking and curing of meat and poultry products as risk factors for the lung cancer excess. In the present study, the lung cancer excess seems greatest in plants with a history of problems with fumes from the wrapping machine, and plants in which smoking or cooking of poultry was carried out. Thus these other exposures could be contributory to the excess.

The excess of brain cancer seems to affect almost all race/sex subgroups equally. All types of plants also seem to be affected, except those that performed only killing, but this is may be due to the small sample size of this group of workers. The highest risk observed in plants that kill and use the wrapping machine, suggest that either or both of these exposures are candidates that should be considered for explaining the excess.

Esophageal and rectal cancers are the only two cancers reported to be in excess in the Baltimore poultry cohort (Johnson et al., 2010a), but not in this study or the Missouri poultry study (Netto and Johnson, 2003; Johnson et al., 2010b). Thus the Baltimore results for these two sites could be chance findings, or it is possible that the Missouri cohort and this Pension Fund cohort do not as yet have sufficient aging or latency to record excess deaths from these diseases.

4.2. General considerations

Overall, this study confirms the findings of three other cohort studies that workers in poultry slaughtering and processing plants have increased risk of dying from certain cancers (Fritschi et al., 2003; Johnson et al., 2010a, 2010b). New findings were for cancers of the cervix and penis. Since lost persons were assumed to be alive, the SMR estimates given for the main findings are unlikely to have been exaggerated. This cohort is a well-defined and complete cohort, being derived from a pension fund, and the investigators independently checked and confirmed the completeness of the cohort by cross-checking application records with union dues payment records, and extensive methods of follow-up were employed, hence selection bias is unlikely. Also, artificially assigning date of birth or race to subjects in the SMR analyses, as expected, did not appear to have biased the SMR results to any significant degree. From theory, when all deaths are completely ascertained, and the all-causes SMR=1, cause-specific PMRs are expected to be exactly the same as the corresponding SMRs. When the all-causes SMR >1 or <1 the cause-specific PMRs are expected to underestimate or overestimate the corresponding SMRs, respectively, to a degree related to how much the all-causes SMR exceed unity (Decoufle et al.,1980; Johnson, 1986; Wong and Decoufle, 1982). This predicted pattern was realized in this study also, and the cause-specific PMRs were close to the SMRs—see Appendix A. Hence, the PMR results provide a readily available valid check for the missing data in the SMR analyses. Also, the sensitivity analyses indicate that whether the entire cohort was assumed to be all white or all non-white, the change in cause-specific SMRs in every case was less than 45%. This should be viewed in relation to the statistically significant cause-specific SMRs reported, nearly all of which were increased at least 2-fold, or were substantially higher.

For some of the cancers (brain, other ill-defined oropharynx, and lymphoid leukemia) and benign neoplasms of the lip etc., the increased risks appeared generalized, affecting all or three of the four race/sex groups, with both races affected for cancers of the cervix and penis. For the rest, the increased risks appear restricted to certain race or sex subgroups (palate, etc. in males; nasopharynx, liver, monocytic leukemia in females; lung in whites, myeloma in non-whites). It has been observed in our previous studies of workers in the meat and poultry industries that killing activities tended to be carried out by men, and wrapping by women. In supermarkets, meatcutters are typically men and meatwrappers are typically women. Up to the 1970s, meatcutters in supermarkets were almost exclusively white, and in meatpacking plants killing activities were assigned to blacks. Thus these exposure patterns could explain why increased risks seemed confined to particular race/sex subgroups. On the other

Table 5
Sensitivity analyses for cancers in excess.

Cause of death	All groups $N=20,132$ Race randomly assigned to non-deceased. (Main analysis) Obs. SMR (95% CI)	All groups $N=20,132$ Entire cohort assumed to be white Obs. SMR (95% CI)	All groups $N=20,132$ Entire cohort assumed to be non-white Obs. SMR (95% CI)
Death from all malignant neoplasms	635 1.2 (1.1–1.3)	635 1.2 (1.1–1.3)	635 1.1 (1.0–1.2)
Gum	1 9.2 (0.2–51.3)	1 10.1 (0.3–56.5)	1 7.6 (0.2–42.3)
Palate/other unspec. mouth	4 3.1 (0.8–8.0)	4 3.7 (1.0–9.5)	4 2.3 (0.6–5.8)
Pyriform sinus; hypopharynx	1 1.7 (0.0–9.3)	1 2.2 (0.1–12.1)	1 1.1 (0.0–5.9)
Other, ill-defined oropharynx	7 3.6 (1.5–7.5)	7 4.8 (1.9–9.8)	7 2.3 (0.9–4.8)
Nasopharynx	2 1.8 (0.2–6.5)	2 2.6 (0.3–9.5)	2 1.0 (0.1–3.7)
Liver, intrabiliary	17 1.5 (0.8–2.3)	17 1.8 (1.1–2.9)	17 1.0 (0.6–1.6)
Pancreas	27 1.1 (0.7–1.6)	27 1.2 (0.8–1.7)	27 1.0 (0.7–1.5)
Trachea, bronchus, lung	217 1.5 (1.3–1.7)	217 1.5 (1.3–1.8)	217 1.3 (1.2–1.5)
Breast	49 0.8 (0.6–1.0)	49 0.8 (0.6–1.0)	49 0.8 (0.6–1.0)
Cervix uteri	18 2.2 (1.3–3.5)	18 2.2 (1.3–3.5)	18 2.2 (1.3–3.5)
Penis	2 8.6 (1.0–31.1)	2 9.9 (1.2–35.8)	2 6.5 (0.8–23.6)
Brain/meninges/Cord/CN/CNS/PNS/ANS	29 1.7 (1.1–2.4)	29 1.6 (1.1–2.3)	29 2.1 (1.4–3.0)
Lymphoid and hemopoietic	60 1.2 (0.9–1.5)	60 1.2 (0.9–1.5)	60 1.2 (0.9–1.5)
Malig. Immun, myeloma, plasma cell	12 1.5 (0.8–2.5)	12 1.6 (0.8–2.8)	12 1.2 (0.6–2.1)
Lymphoid leukemia	10 2.2 (1.1–4.1)	10 2.2 (1.1–4.0)	10 2.3 (1.1–4.3)
Monocytic leukemia	2 9.2 (1.1–33.4)	2 8.9 (1.1–32.0)	2 10.3 (1.2–37.2)
Myelofibrosis	2 1.6 (0.2–5.9)	2 1.6 (0.2–5.7)	2 1.7(0.2–6.3)
Benign neoplasm of lip, oral cavity, pharynx, other dig	11 104.2 (52.0–186.5)	11 113.2 (56.5–202.5)	11 87.8 (43.8–157.1)
All deaths	2454 1.2 (1.2–1.3)	2454 1.3 (1.3–1.4)	2454 1.0 (1.0–1.1)

Figures in parentheses are 95% confidence intervals.

hand differences in sample size could also partly explain these differences. Nested case-control studies are needed to investigate these risk patterns in greater detail.

Although the retrospective cohort design employed in the study is useful in indicating whether there is increased cancer risk in these workers overall, it is not however suitable for investigating the specific occupational cause(s) responsible for the excess. Also, it is unlikely that the effects of the other potentially carcinogenic exposures such as curing and smoking of meat that are associated with low prevalence (1–4%) can be detected in this study. Similarly, it is not possible from this type of study to investigate the role of non-occupational factors. Although we have shown from pilot nested case-control studies that the excess of cancers of the lung, pancreas, and liver persisted after adjusting for tobacco smoking, this has not been investigated yet for several of the other cancers observed to be in excess, and for other confounding exposures. For example, the role of non-occupational exposures such as alcohol intake has not been taken into account in the excess occurrence of liver or pancreatic cancer, and may well be contributory. Cancer of the cervix, penis, buccal/nasal/pharyngeal cavity/passages are all known to be associated with tobacco smoking or alcohol intake, as well as with human papilloma viruses. Thus, non-occupational factors could wholly or partly be responsible for the excess of some of these cancers in poultry workers. Another limitation is that we were not able to present results by duration of exposure, because although dates of union membership were accurate indications of dates of employment for workers who started working after the plants had been unionized, they were not good surrogates of employment dates for those workers who started working in these plants before the plants were unionized. At the moment a case can be made that oncogenic viruses and fumes from the wrapping machine are candidates for more detailed investigation as to their role in the occurrence of some of these cancers, because they are common exposures (12–100% prevalence).

The public health implication that the excess occurrence of some of these cancers in these workers may be associated with exposure to oncogenic viruses is not trivial. Although the intensity of exposure to these viruses in the general population cannot be expected to be as high as those experienced by poultry workers in this study, the general population is nevertheless widely exposed to them through contact with live poultry, blood or secretions and

raw meat, through ingestion of raw or inadequately cooked poultry meat or eggs, and through inoculation with live vaccines such as measles, mumps, and yellow fever vaccines that are grown in eggs (Hussain et al., 2003; Johnson, 1994; Tsang et al., 1999). This potential for widespread exposure is evident from, (1) serological studies (Choudat et al., 1996; Johnson et al. 1995a, 1995b), and could be life-long for many; (2) the demonstrated presence of these viruses in eggs sampled from supermarkets (Pham et al., 1999).

5. Conclusion

The major importance of this study is that it is a new study of workers assembled from several states covering a wide area of the United States, and it is the largest cohort study of workers in poultry slaughtering and processing plants conducted to date, and it confirmed nearly all the findings of studies of previous poultry cohorts. However, significant limitations remain, and include: (1) that even this large study was not large enough to investigate the role of some of the less frequent candidate occupational exposures; (2) it was not suitable for investigating the role of non-occupational confounding exposures; (3) occupational exposures were not well defined or fully measured. These limitations can be overcome with the conduct of large nested case-control studies with sufficient statistical power, and this should be given due consideration in future, so that measures can be taken to reduce exposures and protect workers, where indicated. Also, the role of food animal transmissible agents in the etiology of human cancers warrants attention.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2010.05.010.

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