

Update of Cancer and Non-Cancer Mortality in the Missouri Poultry Cohort

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Background Workers in poultry slaughtering and processing plants have one of the highest human exposures to transmissible agents that cause cancer and other diseases in chickens and turkeys, and also have other occupational carcinogenic exposures. The general population is also exposed to these transmissible agents.

Methods We investigated mortality in workers who belong to a poultry union in Missouri, and estimated standardized mortality ratios.

Results Significantly increased mortality was observed for some leukemias, benign neoplasms, thyroid diseases, bacterial infections, and schizophrenic disorders. The risk of breast cancer and several non-cancer conditions was significantly depressed.

Conclusion The findings add to the growing evidence suggesting that workers occupationally exposed to transmissible agents and carcinogens in the poultry industry, are at increased risk of dying from certain chronic diseases, including cancer. *Am. J. Ind. Med.* 54:49–54, 2011. © 2010 Wiley-Liss, Inc.

KEY WORDS: *oncogenic viruses; infectious agents; chickens; occupational mortality; neurologic diseases*

INTRODUCTION

Chickens and turkeys are naturally infected with a plethora of transmissible agents that cause a wide variety of acute and chronic diseases (including cancer) in the animals [Diseases of Poultry, 2003]. Coming into contact with live and dead poultry, their blood, and secretions, raw meat

products, eggs, and ingestion of raw or inadequately cooked meat and egg products expose humans to these same agents occupationally and non-occupationally. Human exposure may also occur from vaccination with contaminated vaccines that are grown in eggs carrying these agents, since it is known for example, that virtually all stocks of measles and mumps vaccines currently in use in the United States carry endogenous avian leukosis/sarcoma viruses [Tsang et al., 1999]. Although it is known that some of these agents also infect/cause disease in humans [Hedberg et al., 1989; Johnson et al., 1995a,b; Choudat et al., 1996], the role of the vast majority in the etiology of human diseases has been little studied and remains unknown.

Cohort mortality studies of persons who worked in poultry slaughtering and processing plants have investigated the long-term effects of exposure to these agents in humans [Johnson et al., 1986a,b, 1997, 2010a,b,c; Johnson, 1987a,b, 1989; Fritschi et al., 2003; Netto and Johnson, 2003]. The current study reported here is an update of mortality (cancer and non-cancer) in a cohort of workers in a poultry union in Missouri (Local 410A), which we had

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previously studied for mortality between 1969 and 1990, during which time 459 deaths were recorded [Netto and Johnson, 2003]. This time follow-up has been extended to the end of 2003, and 1,337 deaths were recorded for the period 1969–2003.

MATERIALS AND METHODS

The membership of Local 410A was derived from six poultry plants in the state of Missouri, located in Marshall, Milan, Macon, Carrolton, Moberly, and Colfax. Five of the six plants slaughtered, processed or handled fresh or frozen raw chickens or turkeys at some time in their history, but they also carried out other major activities such as manufacturing fruit, meat, and cream pies, gravy, meat loafs, and Salisbury steak. Four of the five plants also cooked or fried chickens or veal. The sixth plant had only 17 employees and handled mainly feathers, and experienced no deaths. These activities may involve frying, smoking, curing, and wrapping of poultry, which may also be associated with exposure to carcinogens such as polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines, benzene, and phthalates [Sen et al., 1974; Vandervort and Brooks, 1977; Pauli et al., 1980; Nordholm et al., 1986; Vainiotalo and Matveinen, 1993; Jakszyn et al., 2004].

The cohort was defined as all persons who were members of Local 410A between January 1, 1969 and December 31, 1988. A total of 7,700 workers met this cohort definition and were followed up from January 1, 1969 through December 31, 2003, during which time 1,337 deaths (17.4%) were recorded. Methods of follow-up included the National Death Index, Social Security Administration (SSA), State Departments of Vital Records (SDVR), State Departments of Motor Vehicles, personal contact by telephone, 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, also using information received from SSA, SDVR, Health Care Financing Agency, as well as the Civil Service Commission, Railroad Retirement Board, and the Department of Defense. Subjects whose vital status was unknown after the end of follow-up were assumed to be alive at the end of study. Some of the towns in which the poultry plants were located have a high proportion of Hispanics (mainly of Mexican origin). Many of these may have been migrant workers who were temporarily in the United States while they were working, but could have returned to Mexico and died there. We would not know these deaths.

Cause of death was coded to the 9th Revision of the International Classification of Diseases. Of the 1,337 deaths, cause of death information was obtained for all but 45 (3.4%). All persons with a death certificate had complete date of birth

information. However, date of birth information was missing for 325 subjects not known to have died, that is, 4.2% of the entire cohort. Date of joining the union was known. Rather than excluding persons with missing birth dates from the analysis, their date of birth was imputed based on the median year of birth of workers with known date of birth joining 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 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 affected to a negligible degree.

The data management was performed using Statistical Analysis Software (SAS) version 9.1.3, and the data was analyzed using the Occupational Mortality Program (OCMAP) Plus software, from the University of Pittsburgh in the United States. Statistical analyses involved estimation of standardized mortality ratios (SMR) using the US general population as the comparison group. 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 individual in the study without a death certificate/known cause of death, based on the racial distribution of deceased persons with known race (94% of whom were white). The cohort was stratified by plant, and then stratified into four subgroups by race and sex (black males, black females, white males, and 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 1, 1969 for those who were already members of the union before that date. For those who became members after that date, the enumeration of their person-years commenced on the date of their union membership. Person-years were accumulated 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]. Since over 94% of deceased subjects were white, the results are presented for males, females, and the entire cohort only, with race imputed for non-deceased subjects as described above. SMR analyses were also conducted in which the entire study population was classified as white. The protocol for this study was approved by the University of North Texas Health Science Center Institutional Review Board.

TABLE I. Numbers of Study Subjects, Deaths and Person-Years of Observation by Race and Gender

Category	Number of subjects	Number of deaths	Person-years of observation
All males	1,761	257 (19.2)	40,891
All females	5,939	1,080 (80.8)	161,015
All whites	7,288 ^a	1,262 (94.4)	190,925 ^a
All non-whites	412 ^a	75 (5.6)	10,981 ^a
White males	1,701 ^a	245 (18.3)	39,409 ^a
Non-white males	60 ^a	12 (0.9)	1,482 ^a
White females	5,587 ^a	1,017 (76.1)	151,516 ^a
Non-white females	352 ^a	63 (4.7)	9,499 ^a
Total study population	7,700	1,337	201,906

^aRacial distribution estimated from distribution of deaths by race among deceased subjects.

RESULTS

The description of the study population is given in Table I. Nearly all deceased subjects were white. SMR results for which race was imputed is presented in Table II. The SMRs for which the entire cohort was assumed to be white are not presented, since the results by both methods were virtually identical.

The all-causes SMR of 87 for the entire cohort was significantly depressed (mainly in men), as was the overall SMR of 82 for all cancers (mainly in men). The SMR for leukemias of other specified cell type and leukemia of unspecified cell type (ICD 207,208) was similarly elevated in both sexes, though it was significant only among women. The SMR for breast cancer was depressed, SMR = 63. The remaining cancers listed in Table II are those that were significantly elevated in either of our two other cohort

TABLE II. Standardized Mortality Ratios for Cancers and Non-Cancers for the Period 1969–2003

Causes of death (9 th ICD revision)	All males obs. SMR (95% CI)	All females obs. SMR (95% CI)	All groups obs. SMR (95% CI)
Cancers			
All cancers (ICD 140–208)	54, 55 [41–72]	298, 90 [80–101]	352, 82 [74–91]
Breast cancer (ICD 174,175)	0	40, 63 [45–86]	40, 63 [45–86]
Other leukemias of specified cell type; leukemia of unspecified cell type (ICD 207,208)	2, 213 [26–769]	7, 256 [103–528]	9, 245 [112–465]
Cervix (ICD 180)	0	12, 160 [83–279]	12, 160 [83–279]
Brain/meninges/cord/CN/CNS/PNS/ANS (ICD 191–192)	0	13, 158 [84–270]	13, 119 [63–203]
Malig. immunoprolif dis, myeloma, malig. plasma cell (ICD 203)	0	6, 108 (40–236)	6, 83 (30–181)
Rectum, recto-sigmoid, anus (ICD 154)	1	3, 59 (12–172)	4, 59 (16–151)
Liver and biliary system (ICD 155)	2, 93 (11–336)	4, 89 (24–228)	6, 90 (33–197)
Pancreas (ICD 157)	2, 41 (5–149)	16, 96 (55–156)	18, 84 (50–132)
Trachea, bronchus and lung (ICD 162)	23, 67 (42–100)	72, 97 (76–122)	95, 87 (71–107)
Non-cancers			
Benign neoplasm of lip/oral cav/pharynx/oth dig (ICD 210–211)	0	3, 3951 [815–11545]	3, 3111 [642–9093]
Certain zoonotic bacterial diseases (ICD 020–027)	1, 6649 [166–37048]	4, 9296 [2533–23802]	5, 8610 [2795–20093]
Disorders of the thyroid gland (ICD 240–246)	1, 1297 [32–7226]	7, 708 [285–1459]	8, 751 [324–1479]
Schizophrenic disorders (ICD 295)	1, 2255 [56–12564]	3, 1488 [307–4347]	4, 1626 [443–4163]
Diabetes mellitus (ICD 250)	2, 24 [3–87]	40, 120 [86–163]	42, 101 [73–136]
Senile and pre-senile psychotic conditions (ICD 290,331)	2, 84 [10–304]	7, 42 [17–87]	9, 48 [22–90]
Hypertensive heart disease (ICD 401–405)	2, 43 [5–156]	10, 51 [24–93]	12, 49 [25–86]
Ischemic heart disease\ICD 410–414	52, 57 [43–75]	212, 92 [80–102]	264, 82 [72–93]
Subarachnoid hemorrhage (ICD 430)	1, 92 [2–512]	2, 30 [0–105]	3, 35 [7–103]
Intracerebral hemorrhage (ICD 431,432)	3, 80 [17–234]	4, 26 [7–68]	7, 37 [15–76]
Occlusion/stenosis precerebral and cerebral arteries (ICD 433,434)	4, 50 [14–127]	18, 47 [28–74]	22, 47 [30–72]
Pneumonia (ICD 480–486)	6, 75 [27–162]	17, 56 [32–89]	23, 60 [38–89]
Cirrhosis/chronic liver disease/liver abscess/other (ICD 571–573)	2, 24 [3–87]	13, 69 [37–119]	15, 55 [31–91]
Suicide and self-inflicted injury (ICD E950–E959)	1, 9 [0–52]	3, 25 [5–73]	4, 18 [5–45]
All causes of death	257, 67 [59–76]	1080, 93 [87–99]	1337, 87 [82–91]

SMR = RR × 100.

studies, or in both of them [Johnson et al., 1986b, 1997, 2010a,c].

Among non-cancer outcomes, significantly elevated SMRs were observed for benign neoplasms of the lip, oral cavity, pharynx, and other digestive system (ICD 210–211, SMR = 3,111); certain zoonotic bacterial diseases (ICD 020–027, SMR = 8,610); disorders of the thyroid gland (ICD 240–246, SMR = 751); and schizophrenic disorders (ICD 295, SMR = 1,626; Table II).

Significantly depressed SMRs were recorded in both sexes combined for senile and pre-senile psychotic conditions, chronic rheumatic heart disease, hypertensive disease, ischemic heart disease, various types of stroke, pneumonia, liver disease, and suicide/self-inflicted injury. The SMR for diabetes was significantly depressed in men but not in women.

DISCUSSION

Contrary to previous studies of poultry cohorts, where a significant excess of all-cause mortality was observed [Johnson et al., 2010a,b,c], men in the current cohort of poultry workers demonstrated significantly depressed all-causes SMR. The reason for this is not known. A possible reason is that in Milan for example, the proportion of Hispanic workers may have been disproportionately high, since 22% of the population in the town is Hispanic compared to the average of 2% for the State of Missouri (<http://www.epodunk.com/cgi-bin/popInfo.php?locIndex=20493>). Many of these workers were from Mexico and some of them could have been male migrant workers whose deaths occurred outside the United States, and therefore not known to us. Thus our assumption that lost persons were alive at the end of the study could have resulted in underestimating mortality.

Cancers

In the current study, only deaths from other leukemia of other specified cell type and leukemia of unspecified cell type (ICD 207,208), were significantly in excess, SMR = 245 (95% CI, 112–465). In our previous studies of other poultry workers, lymphoid leukemia, monocytic leukemia, and myelofibrosis occurred in significant excess [Johnson et al., 2010a,c]. Although the specific histologic subtypes of leukemia occurring in excess were not identified in the current study, the leukemia findings overall for poultry workers in all these studies, are supported in part by previous studies of poultry farmers. Blair and Thomas [1979] in a study in Nebraska, reported an odds ratio of 2.0 for unspecified acute leukemia among farmers in counties with large numbers of chickens. In a similar study in Iowa by Burmeister et al. [1982], an association was observed

between unspecified lymphatic leukemia and production of egg-laying chickens. In a death certificate study also, Milham [1971] reported an association between poultry farming and leukemia. Finally, Bross et al. [1972] in a case–control study reported a relative risk of 1.26, which was significant at the 99% level of significance in adult leukemics for exposure to chickens.

For cancers that were significantly in excess in other studies of poultry workers [Fritschi et al., 2003; Johnson et al., 1986b, 1997, 2010a,c], but not in this one, the SMRs for cervix and brain/meninges/other nervous system were also elevated in the present study. For eight other cancer sites occurring in excess in any of these other cohorts (palate/other unspecified mouth, tonsil/oropharynx, other ill-defined oropharynx, nasal cavity/middle ear/accessory sinuses, esophagus, penis, lymphoid leukemia, and monocytic leukemia), zero or one death each was observed in the present study. Considering only 17% of the cohort is deceased, the present study did not have adequate statistical power or sufficient follow-up for the occurrence of many cancer sites to be adequately evaluated.

Non-cancers

The observed highly significantly increased SMR of 3,111 for benign neoplasms of the lip and mouthparts in this Missouri cohort was similar to our previous findings in other poultry worker cohorts [Johnson et al., 2010a,c]. These benign tumors may represent misdiagnosed cancers, or were coded as underlying cause when the immediate cause of death was due to other fatal conditions such as pneumonia, which may not infrequently result from these tumors.

The results for zoonotic bacterial diseases indicate increased risks of death from infection. This is expected, as a variety of microorganisms that naturally infect poultry birds are known to infect or cause disease in workers who are exposed to these agents [Johnson et al., 1995a,b; Choudat et al., 1996; Tiong et al., 2007]. Similar results were also obtained in the only other two cohort studies of workers in poultry slaughtering plants [Johnson et al., 2010b].

The excess occurrence of schizophrenic disorders seen in the present study was also seen in the other two poultry cohorts [Johnson et al., 2010b]. These findings are very interesting, and although many causes have been postulated for schizophrenia including an infective origin [Boksa, 2008; Sorensen et al., 2009], its cause is still unknown. The association of schizophrenia with poultry exposure is a new finding originating from our studies only, and should be regarded as a generated hypothesis from these studies that could be worthy of further investigation.

The association of disorders of the thyroid gland with poultry exposure is also interesting and may not be a chance occurrence, since excess was also recorded in the two other poultry cohort studies [Johnson et al., 2010b].

The deficits of deaths from intracerebral hemorrhage, subarachnoid hemorrhage, occlusion/stenosis of the precerebral, and cerebral arteries, hypertensive disease, chronic rheumatic heart disease, ischemic heart disease, and pneumonia, observed in this study were not consistently observed in the other poultry cohorts. In contrast increases were observed in some subgroups, and no clear pattern emerged across these studies for these conditions. The deficits observed here may be partly related to the overall significantly depressed SMR for the all-cause mortality in the cohort, which could be a manifestation of the “healthy worker effect” or possibly may reflect an under-ascertainment of deaths as mentioned above.

Deaths from suicides and self-inflicted injury were significantly depressed in this study. In the two other poultry cohorts, the SMR in either cohort was 70 [Johnson et al., 2010b], but while it was statistically significant in the former it was not in the latter. These findings may be related to non-occupational factors.

Caution should be exercised in interpreting the results of this study because of the small numbers of deaths involved in specific cases, and because many causes of death were investigated (185 altogether). Also, it was not possible to consider or control for occupational and non-occupational confounding factors such as tobacco smoking and alcohol ingestion. The cohort studied is still young with only 17% deceased, and this could contribute to the failure to observe the other associations that were seen in the two other cohorts, but not seen in this one, such as for senile and pre-senile psychotic conditions, anterior horn disease, myasthenia gravis, and certain cancers.

One death from slow virus infection of the central nervous system was recorded in the cohort (SMR = 570, 95% CI 10–3,180). To our knowledge prion disease is not known to occur in poultry. This might be an indication that it does, but has not been hitherto recognized, or it is possible that this subject also worked in plants where cattle or sheep were handled.

While our primary hypothesis is that transmissible agents present in poultry may be the source of chronic human diseases, this study was unable to examine the role of other potentially harmful occupational exposures associated with cooking, curing, and wrapping of poultry in the occurrence of these diseases. Further follow-up of this Missouri cohort and other poultry cohorts, and nested case–control studies within them, may provide clearer insight into the significance of the current findings, especially for infectious and possibly neurologic diseases.

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