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A Case-Cohort Study to Investigate the Excess of Liver Cancer Observed in Workers in Poultry Slaughtering & Processing Plants

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ABSTRACT

This is a case-cohort study to examine whether the excess of liver cancer deaths observed in workers in poultry plants could be explained by oncogenic viruses and chemical carcinogenic exposures within the plants. A detailed telephone questionnaire was administered, and responses were analyzed by logistic regression. Odds ratios for several indicators of high exposure to oncogenic viruses or chemical carcinogens in poultry plants and related industries were elevated, but not statistically significant, except the odds ratio for direct contact with the blood of meat in kitchens, eating places, etc. Established risk factors were replicated, and new ones identified.

The study was unable to unequivocally assess risks due to oncogenic viruses or chemical carcinogenic exposures in poultry plants, mainly because observed elevated risks did not achieve statistical significance. The same also applies to some non-occupational factors. Noteworthy risk factors identified include the *increased* risks for eating cabbage, mussels, blood sausage, meringue, playing football, and *decreased* risks for history of frequent intake of soft drinks, gelatin-based meals, vitamins, frequent use of microwave oven to cook, and history of childhood diseases, and nonspecific symptoms. The significance of these findings is unknown, and they will need to be replicated in studies with adequate statistical power.

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Introduction

Virtually everyone in the general population is exposed to viruses that are known to cause tumors in chickens, turkeys, and other domestic fowls. The viruses include 1) avian leukosis/sarcoma viruses (ALSV); 2) reticuloendotheliosis viruses (REV); 3) Marek's disease virus (MDV); and 4) papilloma viruses (1). However, it is not known if these viruses also cause cancer in humans. Workers in poultry slaughtering and processing plants potentially have the highest known human exposures to these viruses. Thus, they represent a suitable group to investigate if the viruses cause cancer in humans. But the workers are also exposed to chemical carcinogens in the workplace that would need to be considered in such an investigation. The chemicals include 1) polycyclic aromatic hydrocarbons (PAH) during the smoking of poultry meat (2); 2) PAH and heterocyclic amines during the cooking or frying of poultry meat (3); 3) PAH, benzene, and phthalates during the wrapping of poultry products in plastic films (4); 4) nitrosamines during the curing of poultry meat (5); and 5) aflatoxin produced by the fungus Aspergillus that is present in the air of the plants (6).

We initially conducted three separate cohort mortality studies of a total of 30,411 workers employed in poultry slaughtering and processing plants, and 16,405 non-poultry workers, in different parts of the United States, all of whom belonged to the same United Food & Commercial Workers (UFCW) International Union. Several cancers were observed to be occurring in excess in the poultry workers, including liver and lung cancers (7–9). We next conducted a small pilot case-cohort study of 11 liver cancer deaths **(8 expected to be primaries)** and a random sample of 152 controls within the combined cohort of 46,816 poultry and non-poultry subjects. Killing of chickens within poultry plants was the only occupational task that was associated with a statistically significant increased risk of liver cancer in this pilot study (10). We recently provided strong epidemiologic evidence for the first time in a case-cohort study within this

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cohort of 46,816 subjects that occupational and non-occupational exposures to poultry oncogenic viruses were independent risk factors for lung cancer (11,12). Now, we present below the results of a larger liver cancer case-cohort study within this same population of 46,816 UFCW union workers. The primary purpose of this case-cohort study was to investigate whether the excess occurrence of liver cancer deaths among workers in poultry slaughtering and processing plants could also be explained by exposure to poultry oncogenic viruses in the workplace. Hence, great attempts were made in an extensive questionnaire to obtain information on all imaginable potential exposures to oncogenic viruses in workplaces both within and outside of the poultry industry, and on other occupational and non-occupational risk factors.

Methods

A total of 46,816 subjects were followed up from January 1, 1950, until December 31, 2010, during which time 73 deaths from liver cancer (ICD, Ninth Revision, code 155 or ICD Tenth Revision, code C22) (henceforth referred to as cases) were recorded in the cohort. All 73 deaths were listed from death certificates as the underlying cause of death. Here, we report on a case-cohort study of 47 of the 73 deaths (64%) for whom we obtained interview information. Their exposure history was compared with that of 443 out of 2,667 controls (17%) for whom interview information was successfully obtained. A total of 2,667 subjects (subcohort) were randomly selected from the entire cohort. Live subcohort subjects themselves and the next-of-kin of deceased cases and subcohort members were traced using a variety of methods that include the National Death Index, Lexis/Nexis, Intelius, Microbilt, Private Eye, Skip Tracing, Equifax, current and former union members, union records, telephone directories, etc. Once contact was made with the correct person, an extensive questionnaire was administered over the phone. The next-of-kin provided information on the 47 deceased cases and 67 deceased subcohort members, while live subcohort members were interviewed directly.

Questionnaire

Subjects were asked if they had ever worked in plants or facilities where the major animals used for food (chickens, turkeys, ducks, doves, partridges, pheasants, quails, geese, grouses, crows/ravens, cattle, pigs, sheep, goats, horses, bison, game animals) were slaughtered, processed, or handled (including their eggs where applicable). If the answer is in the affirmative, a series of more detailed secondary questions on exposures related to the primary question was asked.

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 vegetables, fruits 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; and questions on working in pet stores handling a wide variety of pets (mammals, reptiles, birds, water animals).

The questionnaire also sought information on exposures such as hunting (rabbits, pigeons, guinea fowl, squirrels); lifestyle; medical history; diet; medication use; substance abuse; family history of medical conditions; radiation exposures; immunizations; hobbies; and the environment. In all, there were 4956 primary and secondary questions, and the questionnaire took on average 84 min to complete.

In order to examine the reliability of the information provided by the next-of-kin on deceased study subjects, in a validation study, 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 119 pairs of interviews. The comparison was restricted to "Yes/No" responses. Among pairs, the agreement 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. Of all possible responses, only 0.6% were "Don't Know" responses by the study subjects, as compared with 3.9% "Don't Know" responses by the next-of-kin.

Statistical Analysis

The main statistical analysis consisted of logistic regression in which the outcome was death from liver cancer. Adjustment was made for sex, source of cohort, years of follow-up, year of employment, and tobacco smoking. Regression models were fitted to the data using the SAS PROC LOGISTIC procedure (SAS 9.1, SAS Institute, Cary, NC), and odds ratios (OR) and their associated 95% confidence intervals (CI) estimated. We also conducted Cox regression analysis as well. The results were very similar when data were ample; hence, the Cox results are not presented.

Table 1. Distribution of baseline characteristics.

	Full cohort ($N = 46,816$)	All liver cancer deaths in the cohort of 46,816 ($N = 73$)	Interviewed liver cancer deaths ($N = 47$)	Subcohort control ($N = 2,667$)	Interviewed subcohort control ($N = 447$)
SEX					
F	50.73	36.99	40.91	49.98	53.83
M	47.54	63.01	59.09	48.11	45.30
Unknown	1.73			1.91	0.88
RACE					
White	73.67	69.86	72.73	73.57	71.77
Black	26.33	30.14	27.27	28.23	26.43
MEAN AGE AT EMPLOYMENT					
	60.68	63.64	65.52	60.29	59.32
MEDIAN AGE AT EMPLOYMENT					
	62.00	60.00	63.50	58.00	58.00
POULTRY					
Yes	64.96	58.90	59.09	65.73	77.46
No	35.04	41.10	40.91	34.27	22.54
LOCATION					
Chicago	65.12	56.16	59.09	66.59	76.37
Missouri	16.45	13.70	18.18	16.20	15.54
Baltimore	18.43	30.14	22.73	17.21	8.10

Results

Distribution of Baseline Characteristics

In Table 1 is given a comparison of the distribution of baseline characteristics of interviewed subjects versus those of subjects initially selected, or the entire cohort.

Tobacco Smoking

None of the tobacco smoking variables (cigarettes, cigar, pipe, etc.) was significantly associated with the risk of liver cancer (not shown), except living 10 or more years in the same house as someone who smoked vs. less than 10 years, OR = 0.4 (95% CI, 0.2–1.0).

Although we asked about facilities handling all the different animals listed above, adequate data were available for only employment in large chicken slaughtering and processing plants, and a few food-related facilities. Results are presented in tables if of interest, irrespective of whether statistically significant or not.

Occupational Exposure to Poultry Oncogenic Viruses and Carcinogenic Chemicals in Chicken Slaughtering & Processing Plants

In Table 2 are listed the results for ORs that were above unity in chicken slaughtering and processing plants. No statistically significant association was observed for either poultry oncogenic viruses or chemical carcinogenic exposures in these plants.

Occupational Exposure to Poultry Oncogenic Viruses and Carcinogenic Chemicals in Farms, Supermarkets, Restaurants, Cafeterias, Kitchens, Food & Soup Canning & Manufacturing Plants

Only the odds ratio for contact with the blood of meat at work in kitchens, cafeterias, restaurants, and other eating places, OR = 21.0 (95% CI, 1.3–331.1) was significant – Table 3. No associations were observed for exposure to chemical carcinogens.

Hunting and Farm Exposures

No **association** was observed for exposures related to hunting and farming. The odds ratio for working many years in a granary where grain or nuts were stored was 4.5 (95% CI, 0.3–74.4). Similarly, **no associations** were recorded for employment outside the meat and poultry industries (not shown).

Non-Occupational Exposures

Certain dietary exposures, notably those related to intake of game animals, mussels, blood sausage, and cabbage, alcohol intake, cirrhosis, hepatitis, and playing football frequently, were significantly associated with increased risk of liver cancer – Table 4. Significantly reduced risks were observed for some medical conditions, frequent intake of vitamins, sodas, and gelatin, frequent use of microwave, and use of a cellphone. No increased risks were observed for any immunization.

Table 2. Oncogenic viruses and chemical carcinogenic exposures in chicken slaughtering and processing plants.

1. Oncogenic Virus Exposures in Chicken Slaughtering Plants						2. Oncogenic Virus Exposures in Chicken Processing Plants					
Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*			Exposed Cases	Exposed Controls	OR*	95% CI*
Q0017	Did ever work in a plant where they killed or slaughtered hundreds or thousands of chickens?	8	145	**0.3**	**0.1–0.9**	Q0096	Did ever work in a plant where they did not slaughter chickens, but processed hundreds of already killed chickens brought in from elsewhere?	16	181	1.4	0.6–3.2
Q0018	Worked 5 or more yrs. in a slaughtering plant vs. less than 5 yrs.	1	70	–	–	Q0097	Worked 5 or more yrs. in a processing plant vs. less than 5 yrs.	10	97	0.8	0.2–3.4
Q0022	Was job to hang the live chickens ready for killing?	1	31	–	–	Q0099	Did load/unload live chickens from trucks?	4	31	2.8	0.4–17.5
Q0024	Did kill chickens	1	13	89.4	Too wide to be meaningful	Q0100	Loaded/unloaded live chickens from trucks for 5 or more years vs. less than 5 yrs.	2	15	2.3	0.1–101.5
Q0029	Did cut out the heart and liver of chickens?	1	28	3.2	0.0–367.5	Q0101	Did ever work at pulling out the insides of chickens?	4	58	3.0	0.6–16.6
Q0033	Ever involved in washing/rinsing chicken carcasses before the insides were removed?	1	13	4.4	0.1–235.4	Q0103	Did ever cut chicken into wings/legs/thighs/breast, etc.	4	96	0.6	0.1–3.4
Q0035	Did ever rehang chicken carcasses at slaughtering plant	1	48	1.2	0.0–62.4	Q0104	Did cut up chickens into different parts such as wings, legs, breast, etc. for 5 or more years vs. less than 5 yrs.	3	53	inestimable	inestimable
Q0039	Did ever chill chicken meat	1	31	3.5	0.1–97.2	Q0105	Did ever cut out the heart or liver of chickens	2	50	1.5	0.2–9.1
Q0045	Was ever involved in cutting chicken carcasses into halves or smaller parts (wings, breasts, thighs, legs, etc.)?	2	52	inestimable	inestimable	Q0107	Did ever wash/rinse chicken carcasses	1	30	2.6	0.2–29.9
Q0047	Did ever work in refrigerator/cold room/chiller	1	49	0.9	0.0–490.1	Q0115	Did ever debone chicken carcasses	2	73	0.6	0.1–6.0
Q0090	Ever had direct contact with blood in chicken slaughter plant	2	91	0.3	0.0–285.7	Q0117	Did ever cut chicken into halves/parts	2	76	0.4	0.0–3.8

(*Continued*)

Table 2. Continued.

1. Oncogenic Virus Exposures in Chicken Slaughtering Plants						2. Oncogenic Virus Exposures in Chicken Processing Plants					
Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*			Exposed Cases	Exposed Controls	OR*	95% CI*
Q0092	Did ever work as an assistant to the meat inspector?	1	11	26.9	Too wide to be meaningful	Q0119	Did ever work in a refrigeration room/ cold room/chiller where chicken meat was kept at the plant	4	77	0.3	0.0–3.1
Q0093	Did work in more than one job in a plant where chickens were killed?	2	80	inestimable	inestimable	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.	2	34	- -	– –
						Q0158	Did ever have direct contact with chicken blood	4	126	0.6	0.1–3.6
						Q0162	Did ever have penetrating injury	3	88	0.6	0.1–3.2
						Q0164	Did ever work in more than one job	3	106	**0.1**	**0.0–0.7**
						Q0165	Was ever a maintenance worker	2	25	0.4	0.0–3.7
						Q0166	Was job to clean the equipment or clean the floors every day?	6	61	0.7	0.1–3.3
3. Chemical Carcinogenic Exposures in Chicken Slaughtering Plants						**4. Chemical Carcinogenic Exposures in Chicken Processing Plants**					
Q0081	Ever wrap chickens in plastic film/plastic bags in chicken slaughterhouse	1	49	1.6	0.0-152.5	Q0152	Ever wrap chickens in plastic film/plastic bags in chicken processing plant	4	78	1.0	0.2-5.7
						Q0153	Ever use the wrapping machine to wrap chickens	3	42	1.2	0.1–12.1
						Q0156	Did ever pack chicken meat into boxes in chicken processing plants	4	90	1.1	0.2–5.5

*Adjusted for sex, cohort source, years of follow-up, year of employment, smoking.

Table 3. Oncogenic viruses and chemical carcinogenic exposures in farms, supermarkets, restaurants, cafeterias, kitchens, food and soup canning, and manufacturing plants.

1. Oncogenic Virus Exposures in Commercial Farms, Supermarkets, Restaurants, Cafeterias, Kitchens						2. Oncogenic Virus Exposures in Food and Soup Canning/ Manufacturing Plants					
		Exposed Cases	Exposed Controls	OR*	95% CI*			Exposed Cases	Exposed Controls	OR*	95% CI*
Q0173	Did ever work in a commercial farm where chickens were raised	1	19	0.9	0.1-7.0	Q3377	Did ever work in a food and soup manufacturing plant where they canned or made processed food products using meat, broth, vegetables etc.?	6	49	0.9	0.3-3.0
Q3475	Lived as child on a poultry farm	14	115	1.7	0.7-4.0	Q3378	Worked in a food and soup manufacturing plant where they canned or made processed food products using meat, broth, vegetables, etc. for 5 or more years vs. less than 5 years	3	20	2.4	0.0-136.0
Q3300	Handled raw meat in a supermarket	3	17	1.7	Too wide to be meaningful	Q3380	Cut or handle raw meat in a food/soup manufacturing plant	1	9	inestimable	inestimable
Q3316	Ever had direct contact with blood in supermarket	2	9	0.6	Too wide to be meaningful	Q3383	Had direct contact with blood in food/soup manufacturing plant	1	7	inestimable	inestimable
Q3317	Ever had penetrating injury in supermarket	0	5	inestimable	inestimable	Q3384	Had penetrating injury at food/soup manufacturing plant	2	7	0.5	0.0-28.7
Q3318	Had frequent entry into the cooler/refrigeration room in supermarket	1	10	0.7	Too wide to be meaningful	Q3426	Job involved frequent entry into the cooler/refrigeration room/chiller	2	17	0.2	0.0-45.7
Q3322	Handled meat in a supermarket	1	5	1.6	0.1-28.5	Q3428	Worked as a maintenance worker at a food and soup manufacturing plant (repaired equipment, fixed plumbing, electrical repairs, etc.)	3	6	inestimable	inestimable
Q3359	Work in restaurant, cafeteria, kitchen jobs	10	145	1.2	0.5-2.7	Q3429	Job involved cleaning equipment, floors	1	11	1.5	Too wide to be meaningful
Q3362	Did ever work in a restaurant, cafeteria, kitchen or as a cook, chef, or chef's Assistant?	8	71	2.0	0.3-14.3	Q3431	Worked as a meat inspector in a food/soup plant	1	6	4.6	0.5-46.2
Q3321	Clean equipment, floors every day in supermarket	1	5	19.9	Too wide to be meaningful						
Q3363	Worked in a in a restaurant, cafeteria, kitchen or as a cook, chef, or chef's Assistant for 5 or more yrs. vs. less than 5 yrs.	3	30	6.5	0.6-72.1						
Q3365	Cut raw meat in restaurants, cafeterias, kitchens,	4	32	inestimable	inestimable						
Q3366	Cut raw meat in restaurants, cafeterias, kitchens, for 5 or more yrs. vs. less than 5 yrs.	2	15	inestimable	inestimable						

(*Continued*)

Table 3. Continued.

	1. Oncogenic Virus Exposures in Commercial Farms, Supermarkets, Restaurants, Cafeterias, Kitchens	Exposed Cases	Exposed Controls	OR*	95% CI*
Q3371	Did ever come into direct contact with the blood of meat at work in kitchens, cafeterias, restaurants, and other eating places?	6	44	**21.0**	**1.3-331.1**
Q3372	Did ever have penetrating injury in restaurants, cafeterias, kitchens	1	23	0.3	0.0-9.3
Q3373	Job involve frequent entry into cooler/refrigeration room in restaurants, cafeterias, kitchens	3	48	1.1	0.2-7.4
Q3375	Was ever a maintenance worker in restaurants, cafeterias, kitchens	0	9	- -	- -
Q3376	Did clean equipment or floors every day in restaurants, cafeterias, kitchens	3	50	0.4	0.0-4.3
	3. Chemical Carcinogenic Exposures in Commercial Farms, Supermarkets, Restaurants, Cafeterias, Kitchens				
Q3306	Was ever a meat wrapper in a supermarket	2	12	inestimable	inestimable
Q3315	Did ever pack chicken meat into boxes in supermarkets	2	3	1.6	Too wide to be meaningful
Q3368	Cooked meat in restaurants, cafeterias, kitchens,	5	78	2.8	0.3-29.0
Q3369	Cooked meat in restaurants, cafeterias, kitchens, for 5 or more yrs. vs. less than 5 yrs.	3	32	9.9	0.4-220.0
	5. Hunting and Farm Exposures				
Q3430	Worked in a place where poultry birds, animals, and crops were present	4	16	1.5	0.3-7.2
Q3434	Hunter for game birds like guinea fowl,	5	53	1.1	0.4-3.1
Q3437	Hunter for game animals like rabbits,	6	81	0.6	0.2-1.8
Q3473	Lived as child on a farm where any kind of animal was raised (poultry, fish,	20	198	1.6	0.7-3.6
Q3475	Lived anytime as child in poultry farm	14	115	1.7	0.7-4.0

	2. Oncogenic Virus Exposures in Food and Soup Canning/ Manufacturing Plants	Exposed Cases	Exposed Controls	OR*	95% CI*
	4. Chemical Carcinogenic Exposures in Food and Soup Canning/Manufacturing Plants				
Q3385	Cooked meat in food/soup manufacturing plant	1	7	2.3	0.0-328.7
Q3391	Applied spices, edible compounds in food/ soup plants	1	4	inestimable	inestimable
Q3418	Wrapped meat in plastic films, plastic bags in food and soup plants	1	5	inestimable	inestimable
Q3419	Used wrapping machine to wrap meat in plastic films in food/soup plants	1	4	inestimable	inestimable
	5. Hunting and Farm Exposures (Contd.)				
Q3477	Lived as child in cattle farm	15	131	1.6	0.7-3.7
Q3479	Lived as child on a pig farm	13	116	1.8	0.8-4.3
Q3481	Lived as child on sheep/ goat farm	1	44	0.4	0.1-3.1
Q3483	Lived as child on a horse farm	4	66	0.9	0.3-2.8
Q3487	Lived as child on fish farm	2	14	2.1	0.4-10.4
Q4488	Worked for many years in a granary where grain or nuts were stored	1	4	4.5	0.3-74.4

* Odds ratios adjusted for sex, cohort source, years of follow-up, year of employment, smoking

Table 4. Non-occupational exposures.

Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*	Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*
	1. Dietary						**3. Environmental Exposures**				
Q3973	Ate beef/veal	44	418	0.9	0.1–7.5	Q4290	Used a microwave oven to cook at home weekly/monthly vs not every month or never?	17	71	**0.3**	**0.1–0.7**
Q3986	Ate fried, sautéed, stir fried beef/veal at least once a month vs. less frequently	7	147	**4.4**	**1.2–15.9**		**4. Medical Conditions**				
Q4032	Ate braised/pot roasted chicken at least once a month vs. less frequently	21	306	**2.3**	**1.0–5.4**	Q4688	Sometimes complained of body numbness	8	208	**0.2**	**0.1–0.7**
Q4095	Ate broiled game animal like deer at least once a month vs. less frequently	17	165	**28.3**	**2.4–339.4**	Q4691	Sometimes suffer from memory loss	2	111	**0.2**	**0.0–0.9**
Q4096	Ate rotisserie game animal like deer at least once a month vs. less frequently	18	167	39.9	Too wide to be meaningful	Q4732	Ever suffered from or being told had hepatitis	6	19	**6.3**	**2.0–20.1**
Q4105	Ate fried, sautéed, stir fried game animal like deer at least once a month vs. less frequently	7	136	**7.2**	**1.5–34.1**	Q4733	Ever suffered from or being told had cirrhosis	11	9	**31.2**	**9.6–101.3**
Q4170	Ate mussels at least once a month vs. less frequently	35	412	**3.9**	**1.1–14.0**	Q4740	Ever suffered from or being told had mumps	8	200	**0.3**	**0.1–0.9**
Q4172	Ate winkles at least once a month vs. less frequently	37	419	4.6	0.7–30.6	Q4741	Ever suffered from or being told had chickenpox	18	294	**0.3**	**0.1–1.0**
Q4210	Ate blood sausage/blood pudding/black pudding at least once a month vs. less frequently	37	423	**13.1**	**2.1–82.5**		**5. Drugs/Medications**				
Q4226	Ate yogurt at least once a month vs. less frequently	37	234	**0.2**	**0.1–0.8**	Q4764	Take vitamins frequently	7	225	**0.3**	**0.1–0.9**
Q4232	Ate meringue at least once a month vs. less frequently	31	395	2.5	0.9–7.3		**6. Immunizations**				
Q4237	Ate dark green leafy vegetables at least once a month vs. less frequently	6	86	2.0	0.6–6.4	Q4778	Vaccination for tuberculosis	13	157	0.7	0.2–2.1
Q4238	Ate cabbage at least once a month vs. less frequently	4	119	**3.5**	**1.0–12.3**	Q4779	Vaccination for smallpox	15	177	0.9	0.3–2.7
Q4254	Did ever drink coffee	42	329	1.5	0.5–4.6	Q4780	Vaccination for diphtheria, whooping cough	13	144	0.9	0.3–3.1
Q4257	Did ever stop drinking coffee for good?	10	44	**3.4**	**1.2–9.5**	Q4781	Vaccination for rubella	14	170	1.7	0.5–6.0
Q4261	Drank soft drinks, sodas, at least once a month vs. less frequently	20	139	**0.3**	**0.2–0.8**	Q4782	Vaccination for tetanus	19	273	0.5	0.1–1.4
Q4266	Ate gelatin or gelatin-based meal such as Jell-O, marshmallows, low fat yogurt weekly/monthly vs not every month or never?	33	253	**0.2**	**0.1–0.8**	Q4783	Vaccination for measles	18	204	1.0	0.3–3.1
	2. Alcohol and Illicit Drug Use					Q4784	Vaccination for mumps	16	191	1.3	0.4–4.1
Q4793	Did ever drink Beer?	34	248	1.5	0.6–3.9	Q4785	Vaccination for yellow fever	8	48	2.0	0.5–8.2

(*Continued*)

Table 4. Continued.

Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*	Question Number		Exposed Cases	Exposed Controls	OR*	95% CI*
Q4794	Drank six or more cans/bottles of beer a week vs. less than six	18	90	2.4	0.9–5.7	Q4786	Vaccination for influenza	21	254	1.0	0.4–2.8
Q4797	Ever drunk wine	11	168	0.6	0.2–1.5	Q4787	Vaccination for typhus	8	52	1.4	0.4–5.6
Q4798	Drank 6 or more glasses of wine a week vs. fewer	3	17	**11.0**	**1.7–69.1**	Q4788	Vaccination for typhoid	11	55	2.4	0.7–8.7
Q4801	Did ever drink liquor?	19	155	1.2	0.5–2.8	Q4789	Vaccination for meningococcal disease	6	34	1.9	0.4–8.3
Q4806	Ever use cocaine	5	30	**3.8**	**1.1–13.2**	Q4790	Vaccination for hepatitis A/B/C	12	120	1.5	0.5–4.5
	7. Other risk factors					Q4791	Vaccination for pneumococcal disease	7	74	1.0	0.3–3.6
Q4673	Play football at least once a month vs. less frequently	43	427	**5.7**	**1.3–25.6**	Q4792	Did ever receive gamma globulin	3	18	4.4	0.4–46.0
Q4851	Did at some time in life own a cell phone?	10	324	**0.2**	**0.1–0.4**						

*Adjusted for sex, cohort source, years of follow-up, year of employment, smoking.

Discussion

General

The distribution of baseline demographic characteristics of the 47 interviewed cases was similar to that of all 73 cases in the cohort. Similarly, the distribution for the 443 interviewed controls was similar to that of the 2,667 subcohort members or the entire cohort of 46,816. The close agreement between the information provided by the live study subjects and that on the live study subjects by the next-of-kin for the vast majority of primary questions indicates that the next-of-kin did provide reliable information on study subjects, while the low frequency of "Don't Know" response indicates that both study subjects and the next-of-kin were able to reliably recall primary events. The diagnosis of liver cancer cases was based on the death certificate listing of underlying cause. Some misclassification could have occurred from secondary tumors, but it has been shown that at least 77 percent would be expected to be true primaries when compared to medical records listing (13).

We studied 64 percent of all liver cancer cases in the cohort and 17 percent of controls. Low or differential response rates between cases and controls may predispose, but do not by themselves giving rise to selection bias. Bias results when response rates differ for exposed and unexposed cases, or for exposed and unexposed controls (14). The distributions of demographic variables in interviewed cases and controls were similar to those for all cases in the cohort and for controls in the subcohort, respectively. Thus, selection bias is unlikely to have been a serious problem in this study. Although it appears that the proportion of controls eventually interviewed was low (17%), we deliberately stopped interviewing more controls because we had already achieved a control:case ratio of almost 10:1; this exceeds the ratio of 4:1 recommended for increasing ratio the precision of a case-control study (15).

Elevated ORs were recorded for ever smoking cigarettes or all types of tobacco, and smoking for five or more years compared to less, but none was statistically significant (not shown). A consistent relationship between tobacco smoking and liver cancer is not firmly established. A meta-analysis reported a small statistically significant increased risk of 1.33 for ever smoking versus never; out of the 7 studies involved in the analysis, 4 showed a significant increased risk, while the other three did not (16). One study showed increased risk in females but not in males (17).

Occupational Exposure to Poultry Oncogenic Viruses and Chemical Carcinogens

In general, above background exposure to microorganisms in poultry slaughter and processing plants (including poultry oncogenic viruses) occurs throughout the plants from the time the birds are unloaded and brought into the plants, until the end of the production line when the poultry products are packed into boxes. Certain tasks or areas of the plants such as killing, washing, deboning, eviscerating, working in the maintenance department are associated with high exposures to microbial agents (including poultry oncogenic viruses), while packing is associated with the least exposure. This pattern of exposure has been well documented in industrial hygiene studies from surface, air, carcass, and personal nasal swab sampling for these agents (18–22). Serological industrial hygiene studies by us for the presence of antibodies against two of the poultry oncogenic viruses in poultry plant workers also recorded similar findings (23,24). As seen in Table 2, within *slaughtering* plants, the ORs for high-exposure jobs, such as killing, cutting the heart and liver out, washing and rinsing chicken carcasses, were clearly elevated, though not statistically significant. Similar nonsignificant elevated risks are seen for several, though not all, of potential poultry oncogenic virus exposures in chicken *processing* plants and other facilities that handle poultry such as restaurants, supermarkets, farm (Table 3). Noteworthy, the ORs for contact with blood (a potential high risk oncogenic virus exposure) in kitchens, eating-places, etc., were statistically significantly elevated. Also, in the small pilot liver cancer case-cohort study, we had conducted the odds ratio obtained for killing chickens was 9.1 (95% CI, 1.9–42.9) (10); in the current study, we also observed an increased risk, but the estimate was imprecise. Also, it is to be noted that a death certificate case-control study in Texas also reported a twofold increased risk for being a butcher as a risk factor for liver cancer that was statistically significant (25).

The failure of the ORs for the high-risk microbial exposures to achieve statistical significance in the current study is possibly due to the following: 1) general lack of statistical power of the study; 2) interviewed controls had a higher percent of poultry workers than the subcohort from which they were sampled. Thus, poultry workers were over-represented in the interviewed controls, and this selection bias would have the effect of underestimating the ORs related to poultry exposures; 3) the proportion of poultry workers among the 2,663 workers in subcohort or among the 46,816 workers in the cohort was very high, 65.7% and 65.0%, respectively; hence, this high rate would have worsened the over-representation of poultry workers among the interviewed control group; 4) the subcohort or interviewed controls contained cancer cases from 10 sites that were observed to be occurring in excess in poultry workers in the original poultry cohorts from which they were selected (7–9). This will also have the effect of attenuating the ORs. 5) While the validation study indicated that the next-of-kin were able to provide reliable information on most of the primary questions, for some questions this was not the case, and significant misclassification of exposure and attenuation of risk may have occurred. For example, 36 percent of the next-of-kin of cases were not first-degree relatives and may have been less able to provide reliable information on some questions. The failure of elevated ORs to achieve statistical significance because of these other issues would have been further aided by the low statistical power.

Similarly, the study did not have sufficient statistical power to adequately investigate occupational chemical carcinogenic exposures, even though elevated ORs were recorded for some of the exposures.

Non-Occupational Exposures

Dietary Exposures

Our results indicate that subjects who frequently ate meat and poultry, prepared in various ways (frying, broiling, etc.) or processed such as blood sausage, were at increased risk of liver cancer than those who did so infrequently. This is consistent with the reported association of red meat with increased liver cancer seen in the large US NIH-AARP cohort study (26), but not with the large European multinational cohort study that did not find any relationship for red meat and poultry (27). A meta-analysis by Luo et al. (28) did not find a relationship between intake of red and processed meats and liver cancer, while an inverse relationship was observed for intake of poultry. A review by Koumbi (29) reported that few studies have investigated the role of diet as a risk factor of liver cancer and that the results are inconsistent for many types of food, including fruits, vegetables, yogurt, crustaceans, soft drinks. The most consistent results are for increased risks associated with high intake of red meat and food with high glycemic index such as sugar.

The mechanism for the role of high glycemic index in carcinogenesis is thought to be via increased insulin concentrations, glucose intolerance and insulin

resistance, even in the absence of diabetes mellitus. Foods, such as sugars, syrups, sweets, white bread and soft drinks, are the main culprits (29). Thus, our findings for a protective effect for intake of gelatin and gelatin-based food, yogurt, soft drinks and sodas, although appear contradictory, may simply result from patients on the advice of their doctor, reducing their sugar intake drastically after the diagnosis of liver cancer has been made. Similarly, the increased risk associated with intake of mussels and cabbage is consistent with some but not all studies indicating increased risks with vegetable intake, although we could not find data on cabbage specifically (30–33).

A pooled analysis of several cohort studies in the United States, and a review of the literature in general indicate that coffee drinking is associated with a reduced risk of liver cancer (34,35). No significant association was observed in the current study. However, subjects who reported to have stopped drinking coffee for good had increased risk of liver cancer. Whether coffee intake has a role in the occurrence of liver cancer is not known, since it is possible that liver cancer patients may likely give up drinking coffee as a result of their illness.

Frequent consumption of nuts was not observed in this study or in the pilot study (10) to be associated with increased liver cancer risk, and neither was working for many years in a granary. Aflatoxin is a known liver carcinogen that is frequently found in nuts and granaries (36). The absence of a significant association for nuts in the current study may be due to the low power of the study, as some of the ORs were >1.

Medical Conditions

As expected, a history of hepatitis and cirrhosis was associated with an increased risk of liver cancer consistent with the literature (37,38). The inverse relationship between history of chickenpox and mumps is consistent with the observed nonsignificant elevated risk of immunization with mumps vaccine, which is known to be contaminated with poultry oncogenic viruses (39). A similar inverse relationship was observed between history of mumps and measles and immunization against them in the lung cancer case-cohort study within this same study population (12).

Alcohol Consumption

Alcohol is a known risk factor for liver cancer (38,40). In the current study, a strong relationship was observed for high frequency of wine intake and weak associations for beer and liquor. Furthermore, alcoholic cirrhosis is a risk factor for the disease (37,38).

Immunizations

We investigated immunization against tuberculosis, smallpox, tetanus, diphtheria/pertussis/tetanus, rubella, measles, mumps, influenza, yellow fever, typhus, typhoid, meningococcal and pneumococcal diseases, viral hepatitis, and immunoglobulin. No statistically significantly elevated odds ratio was observed for any immunization. The ORs for vaccines grown in chicken eggs that may carry poultry oncogenic viruses (measles, mumps, yellow fever, typhus and influenza) were 1.3, 1.3, 2.1, 1.2, and 1.0, respectively. The failure for these somewhat elevated ORs to achieve statistical significance may be due to the reasons given above and may also indicate no association exists. It is worthwhile noting that in the pilot case-cohort study of liver cancer, a significant association was observed for yellow fever and typhoid vaccinations (10). The odds ratio for typhoid vaccination in the current study is 2.4 (95% CI, 0.7–8.7). On the other hand, these nonsignificant elevated risks may be due to chance since an oncogenic effect of a vaccine does not have to affect all organs equally.

Other Risk Factors

There were several other factors that were associated with significantly decreased risks such as taking vitamins frequently, nonspecific complaining of numbness or memory loss, and owning a cellphone. The significance of these findings remains unknown, and while some of them may be of no consequence and due to chance, others may need to be replicated in other studies. The observed decreased risk associated with cellphone use has been seen in all our 5 pilot studies and in the lung cancer case-cohort study (10,12,41–43) and is believed to be an artifact resulting from the cases (all deceased) in these studies who could have died in earlier periods when cellphone use was rare or absent, than controls who were mostly alive and more recently interviewed at a time when cellphone is highly prevalent, and owning a cellphone is related to being interviewed for the study.

The significance of the observed inverse relationship with frequent use of a microwave oven is not known, but it is conceivable that this may be related to this method of food preparation that may be associated with less formation of chemical carcinogens such as PAHs and heterocyclic amines. The significance of the increased risk associated with playing football at least once a month is not known and may

be a chance finding. Use of anabolic steroids is well known in athletes, and these drugs are known to induce adenomas in the liver, and there are anecdotal reports that they cause liver cancer also, but strong scientific evidence is lacking. The association between liver cancer and cocaine use is not clearly established in the literature. Illicit drug use may be associated with other lifestyle factors that predispose to liver cancer risk, or carcinogenic substances may be present in drugs that are illicitly manufactured, http://drugabuse.com/library/drug-and-cancer-risk/, and there have been isolated reports linking cocaine use with cancer, http://usatoday30.usatoday.com/life/health/doctor/lhdoc216.htm. It is possible also that cocaine use is associated with hepatitis B and C infections that are highly prevalent in illicit drug users, and are known causes of liver cancer.

Conclusion

To our knowledge, this is the largest study to explore the relationship of occupational and nonoccupational carcinogenic exposures among poultry workers. The study has provided only weak evidence that occupational exposure to oncogenic viruses or chemical carcinogens in poultry plants may be responsible for the excess occurrence of liver cancer deaths in cohort studies of workers in poultry slaughtering and processing plants, mainly because elevated risks observed for some of these exposures failed to achieve statistical significance. The findings for immunization with vaccines grown in eggs were indeterminate. A primary reason for these types of results is the lack of statistical power, but other limitations outlined above may also be contributory. In spite of these limitations, the study confirmed previous established risk factors for liver cancer such as hepatitis, cirrhosis, alcohol consumption, and other risk factors reported by several but not all studies in the literature for dietary exposures. Apparently new or not frequently specifically reported risk factors identified in this study include the increased risk of eating cabbage, mussels, blood sausage, meringue, playing football, and decreased risks for history of frequent intake of soft drinks, gelatin-based meals, vitamins, frequent use of microwave oven to cook, and history of childhood diseases, and nonspecific symptoms. The significance of these findings is unknown, and they will need to be replicated in studies with adequate statistical power.

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No potential conflict of interest was reported by the authors.

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Human Subjects Research

The protocol for this case-cohort study was approved by the Human Subjects Committee (Institutional Review Board) of the University of North Texas Health Science Center.

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