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A Pilot Case-Cohort Study of Brain Cancer in Poultry and Control Workers

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We conducted an exploratory study to investigate which exposures (including poultry oncogenic viruses) are associated with brain cancer in poultry workers. A total of 46,819 workers in poultry and nonpoultry plants from the same union were initially followed for mortality. Brain cancer was observed to be in excess among poultry workers. Here we report on a pilot case-cohort study with cases consisting of 26 (55%) of the 47 brain cancer deaths recorded in the cohort, and controls consisting of a random sample of the cohort ($n = 124$). Exposure information was obtained from telephone interviews, and brain cancer mortality risk estimated by odds ratios. Increased risk of brain cancer was associated with killing chickens, odds ratio (OR) = 5.8 (95% confidence interval, 1.2–28.3); working in a shell-fish farm, OR = 13.0 (95% CI, 1.9–84.2); and eating uncooked fish, OR = 8.2 (95% CI, 1.8–37.0). Decreased risks were observed for chicken pox illness, OR = 0.2 (95% CI, 0.1–0.6), and measles vaccination, OR = 0.2 (95% CI, 0.1–0.6). Killing chickens, an activity associated with the highest occupational exposure to poultry oncogenic viruses, was associated with brain cancer mortality, as were occupational and dietary shellfish exposures. These findings are novel.

INTRODUCTION

Certain viruses commonly infect and cause cancer in poultry. They include the avian leukosis/sarcoma viruses (ALSV) that cause leukemia and a wide variety of cancers in chickens and turkeys; and the reticuloendotheliosis virus (REV) and Marek's disease virus (MDV) that cause lymphoid leukosis and neurolymphomatosis in chickens (1–4). Subgroup-A ALSV naturally cause gliomas in chickens (4). Brain cancer has also been experimentally induced in primates from ALSV inoculation (5). ALSV and REV can infect and/or transform human cells in vitro (1,6), and some, but not all studies, have reported the presence of antibodies against ALSV, REV, and MDV in the blood of poultry workers and the general population (7–9). It is not known if these viruses cause cancer in humans.

To determine whether poultry oncogenic viruses may play a role in human cancer occurrence, we sought occupational groups that typically have among the highest known human exposures to poultry and raw poultry products (10–12). Workers in poultry slaughtering and processing plants have such an exposure, as they handle thousands of chickens daily. They also have direct contact not only with live chickens but also with raw poultry meat and blood products, and the internal organs during slaughtering and processing (13,14). Injuries from sharp knives, bone splinters, and dermatitis (15,16) that allow viruses and other microbial agents to gain easy access into the body through breaches in the skin, are frequent among them. They also work in enclosed spaces for prolonged periods of time and are exposed via inhalation to airborne organisms (13). Thus, if these oncogenic viruses cause cancer in humans, it should be readily evident in this occupational group that is so highly predisposed to infection with these agents. In our previous mortality analyses of 3 separate cohorts of poultry workers (10–12), several cancer sites, including brain cancer, were observed to be occurring in excess. Brain cancer was significantly elevated

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in one of the cohorts, and the excess appeared to occur in all race/sex subgroups (10). In each of the two other cohorts, excess risk was observed in females but was not statistically significant (11,12).

The only other published cohort study of poultry workers in slaughtering and processing plants was by Fritschi et al. (2003), but no information was provided on brain cancer (17).

Here we report the findings of a pilot case-cohort study nested within a combined cohort of the 3 poultry cohorts we reported on previously and a nonpoultry comparison group (10–12), to provide preliminary evidence of which occupational and nonoccupational exposures may explain the excess occurrence of brain cancer deaths observed in poultry workers in the cohort.

METHODS

The source population for this case-cohort study consisted of the 30,411 poultry workers and 16,408 nonpoultry workers, for a total of 46,819 subjects who were members of the United Food & Commercial Workers (UFCW) unions between 1949 and 1989. Among this group, 2915 died during follow-up. The remaining 43,904 subjects that were alive as of January 1, 1990 constitute the base population that was followed up from January 1, 1990 until December 31, 2003. Because no new subjects were added after January 1, 1990, and all subjects lost to follow-up were assumed to be alive at the end of the study, the group of subjects alive as of January 1, 1990 was essentially a closed cohort (See Fig. 1).

Cases were defined as all 47 deaths from brain cancer (ICD-O 191, 9th revision) that occurred in the base population between January 1, 1990 and December 31, 2003. The comparison group for the brain cancer cases was a subcohort that consisted of 1516 live subjects randomly sampled from the base population, some of whom later died during the study period (see Fig. 1).

Because this was a pilot study, exhaustive attempts were not made to trace study subjects or their next-of-kin. Thus, we report here on the first 26 of the 47 (55%) brain cancer deaths whose next-of-kin were traced and provided information over the phone on the deceased cases, within the limited time available to do the study. Similarly, of the first 214 subjects in the subcohort ($n = 1516$) that were traced during the time available, 152 (71%) completed phone interviews with the same questionnaire either directly (if alive), or through their next-of-kin if deceased (see Fig. 1). None of the interviewed cases were members of the control group.

The questionnaire consisted of 646 questions that took an average of 40 to 60 min to administer over the phone. It included demographic variables on race, gender, date of birth, and date of death. A detailed list of questions (selected questions shown in the tables) on occupations and industries within each of the following major headings were asked in the questionnaire: 1) occupational poultry-specific exposures. These tasks included unloading chickens from trucks, hanging chickens on conveyor lines, killing chickens, cutting carcasses, and so on. The tendency was to assign workers to perform one main task, but they could perform different tasks over the course of their employment at a poultry plant; 2) mixed occupational poultry- and meat-related exposures; 3) working or living on a farm; 4) occupational exposure to seafood; 5) killing food animals other than poultry; 6) applying chemicals at work; and 7) working in occupations and industries outside the poultry and meat industries. Risk associated with each job exposure was calculated for ever/never responses. Dates and duration of working each task are not presented because of sparse data. There were also detailed nonoccupational questions on lifestyle, medical history, diet, medication use, family medical history, radiation exposures, and immunizations.

Baseline data between cases and controls were compared using t-tests and chi-square tests. The main analyses consisted of unconditional logistic regression and Cox proportional hazards regression. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated using the SAS PROC LOGISTIC procedure (SAS 9.1, SAS Institute, Cary, NC). Because the control group was a random sample of the base population, the ORs obtained were direct estimates of the risk ratio without need for the rare disease assumption (18). In the Cox regression analysis, hazard ratios were estimated using the SAS PHREG procedure. Subjects entered the study at the age attained on January 1, 1990 (time variable) and the failure time for formation of a risk set was the age at death of a brain cancer case. At failure time, a risk set was formed consisting of the case and all available controls at risk at that time. Risk estimates were adjusted for age and cohort (union) status. With few exceptions the results from both the Cox and logistic regression analyses were closely similar. Thus, we present only the ORs in the tables. Both ORs and hazard ratios are given in the text when there is divergence. The divergent results are consistent with the generally recognized observation that risk estimates given by the 2 measures tend to diverge when relative risks are very high (19).

RESULTS

Table 1 demonstrates the baseline characteristics of interviewed and non-interviewed cases and subcohort controls. Both interviewed cases and controls were similar to the underlying populations they were sampled from. The only exception was that interviewed subjects in the subcohort were more likely to be poultry workers (78%) than all subjects in the subcohort (59%).

Occupational Poultry and Nonpoultry Exposures

Table 2 demonstrates the risk estimates in decreasing order for occupational poultry and nonpoultry exposures. For occupational poultry exposures, the only statistically significant result was that workers who killed chickens were approximately 6 times more likely to die from brain cancer compared to workers that did not kill poultry (OR = 5.8, 95% CI: 1.2–28.3). Nonsignificant but slightly elevated risks were observed for other

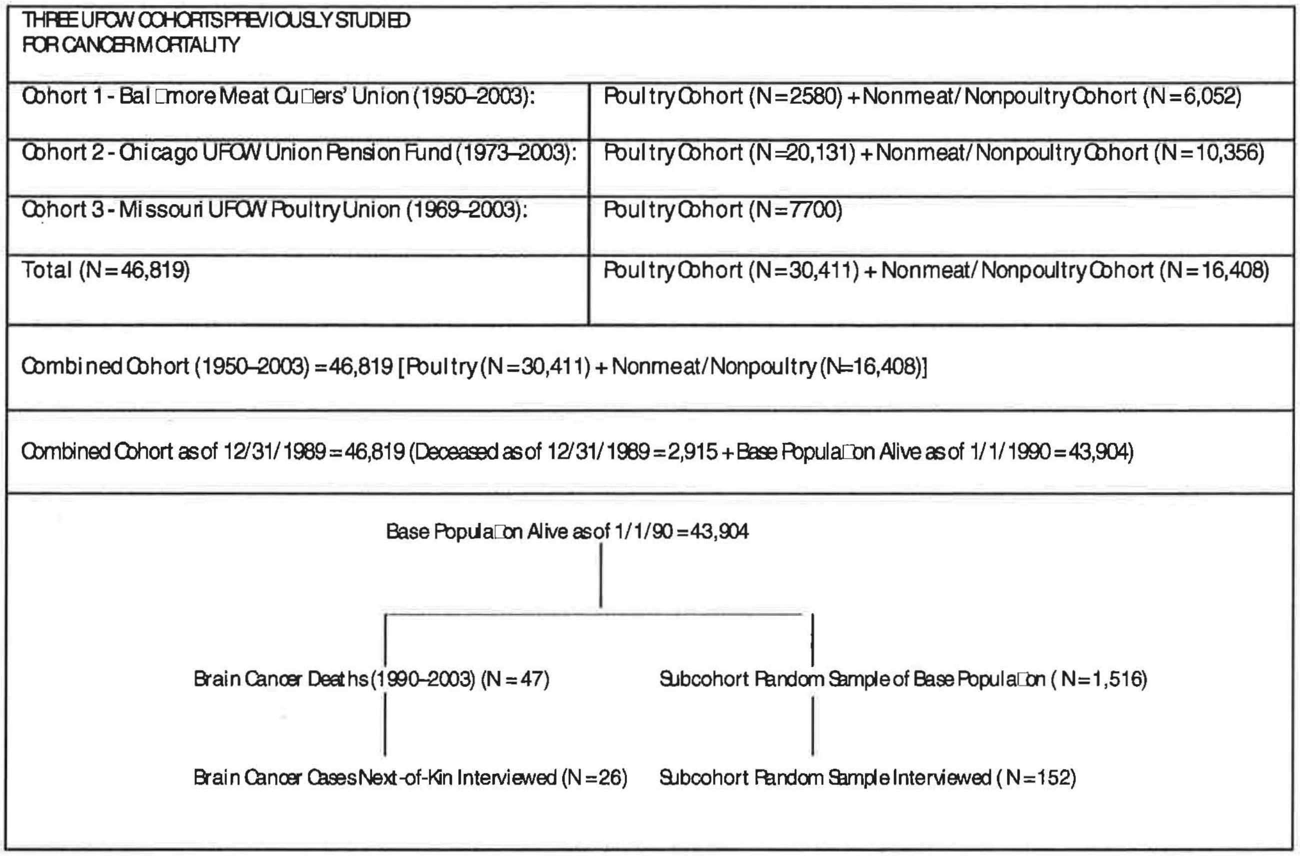

FIG. 1. Description of 3 cohorts originally studied and flow chart of selection of study subjects in the Brain Cancer Case-Cohort Study of United Food & Commercial Workers (UFCW) Union Workers, USA, 1990–2003.

poultry-related exposures. The highest risk for nonpoultry exposures was obtained for working in a shell-fish farm (OR = 13.0, 95% CI: 1.9–84.2; HR = 4.0, 95% CI: 1.0–15.7). Elevated risks that were not statistically significant were also observed for working as a fisherman (OR = 3.0), and selling seafood (OR = 2.7). The only other statistically significant result was for working in smelters OR = 4.8 (95% CI: 1.0–24.2).

Other Exposures: Lifestyle, Behavioral, and Medical History

For medical history, elevated risks were obtained for non-specified treatment with radiation, history of migraine, head injury, and epilepsy (Table 3). The results were significant for only history of radiation treatment (OR = 12.7, 95% CI: 3.9–41.2; HR = 7.1, 95% CI: 2.9–17.6); and history of migraine (OR = 3.7, 95% CI: 1.3–10.5). Significant decreased risks were observed for history of chicken pox illness and history of measles vaccination. History of cold sores and allergic conditions appear protective, but neither was statistically significant.

For dietary history, statistically significant results were recorded for usually eating uncooked fish or shellfish (OR = 8.2, 95% CI: 1.8–37.0; HR = 4.0, 95% CI: 1.4–11.8); salted meat (OR = 5.5, 95% CI: 2.0–15.0); and barbecued meat (OR = 4.4, 95% CI: 1.5–12.6). The results for eating smoked meat were elevated but not significant (OR = 2.5, 95% CI: 0.9–6.8).

For lifestyle, significantly decreased risks were observed for exercising regularly and for cell phone use.

DISCUSSION

Killing is believed to be one of the jobs associated with the highest risk of exposure to oncogenic viruses of poultry, cattle, pigs, and sheep in poultry and meat slaughtering and processing plants. Our findings in this study with regards to the poultry industry indicate that, only workers engaged in killing chickens were significantly at increased risk of brain cancer. This finding is consistent with previous studies conducted by our group using this same combined cohort of 46,819 subjects to explore cancer mortality of the lung, liver, and pancreas (19,20). It is also consistent with the observation that working in the kill/dress area of abattoirs where cattle, pigs, and sheep were slaughtered, contact with warm meat by butchers or meat workers in abattoirs was significantly associated with lung cancer risk (21–23).

TABLE 1
Baseline demographic distribution of brain cancer cases and controls in the combined cohort of Poultry and Nonpoultry United Food & Commercial Workers Union Workers, USA, 1990–2003

	Brain cancer cases		Controls	
Demographics	Total ($n = 47$)	Interviewed ($n = 26$)	Totals ($n = 1{,}516$)	Interviewed ($n = 152$)
Race*				
White (%)	38 (81)	22 (85)	1,099 (72)	108 (71)
Black (%)	9 (19)	4 (15)	324 (21)	27 (18)
Unknown (%)	0	0	93 (6)	17 (11)
Total	47	26	1,516	152
Gender				
Female (%)	28 (60)	15 (58)	785 (52)	87 (57)
Male (%)	19 (40)	11 (42)	723 (48)	64 (42)
Unknown (%)	0	0	8 (1)	1 (1)
Total	47	26	1,516	152
Age				
≤50 yr (%)	25 (53)	16 (62)	1,061 (70)	103 (68)
> 50 yr (%)	18 (38)	10 (38)	413 (27)	48 (32)
Unknown	4 (9)	0	42 (3)	1 (1)
Total	47	26	1,516	152
Type of worker				
Poultry (%)	26 (55)	15 (58)	898 (59)	118 (78)
Nonpoultry (%)	10 (21)	6 (23)	618 (41)	34 (22)
Unknown (%)	11 (23)	5 (19)	0	0
Total	47	26	1,516	152

*Race information was not available in union records and was obtained only from death certificates for deceased or interviewed subjects. Hispanics were classified as whites.

Hence the preliminary findings in the present study suggest poultry oncogenic viruses may be one of the most likely occupational exposures responsible for the observed excess of brain cancer in workers in poultry plants. This study offers additional evidence to support previous reports of the presence of antibodies against avian leukosis/sarcoma viruses, REVs and MDV in the sera of poultry workers and subjects in the general population (7–9). In our extended study of antibody levels in poultry workers, although the sample was too small to include workers who had specifically been engaged in killing activities, workers who potentially had high exposure tasks, such as cutting hearts and liver, were also found to have significantly higher antibody titers to ALSV and REV (24,25).

The literature for gliomas, in particular, reveals 2 studies that examined occupational exposures to poultry by combining poultry workers with workers exposed to other animals. Hence it was not possible to obtain risks for occupational poultry exposures alone (26,27). In one of them a higher incidence of glioma was recorded among butchers that did not wear gloves during meat handling and who received cuts at least once a month, compared to those who did not (26). To our knowledge, only one study, apart from ours, has specifically reported on brain cancer risk and occupational exposure to poultry (28). Although a protective effect was observed with ever killing chickens in that study, it appeared that virtually all the cases and controls killed poultry (28). Thus the design of the study did not permit a valid assessment of occupational poultry exposure as a risk factor of brain cancer.

One of the novel findings in our study was the 13-fold increased risk observed for working on shellfish farms. Similarly, increased risks of brain cancer mortality were also recorded for fishermen and workers involved in selling seafood. A statistically significant increased risk for brain cancer mortality was also recorded for individuals who consumed uncooked fish or shellfish, indicating that the associations between seafood and brain cancer observed in this study may not be chance findings. The literature supports the presence of numerous viruses in shrimps, although none has been reported to be oncogenic (29,30). Also, the role of other exposures related to seafood aquaculture such as pesticides, antipathogenic agents, and disinfectants (31) and other chemicals cannot be ruled out as possible carcinogens contributing to the excess of brain cancer.

Other exposures for which previous investigators reported similar findings as ours for increased brain cancer risks include rubber (32), electro-magnetic fields (33), chemicals (34), and metals (35–37). Headaches have been reported to be associated

TABLE 2
Adjusted odds ratios (OR) and 95% confidence intervals (CI) for occupational poultry and nonpoultry exposures in the Brain Cancer Case-Cohort Study of United Food & Commercial Workers Union Workers, 1990–2003

Exposure	Adjusted£ OR (95% CI)
Occupational poultry exposures	
Killed chickens/birds at work	5.8 (1.2, 28.3)*
Had contact with poultry blood	1.7 (0.6, 4.7)
Worked in a commercial poultry farm	1.6 (0.4, 6.0)
Handled or used poultry waste	1.4 (0.4, 5.5)
Cooked poultry partly or wholly	1.3 (0.3, 5.5)
Occupational nonpoultry exposures	
Worked in a shellfish farm	13.0 (1.9, 84.2)*
Worked in a chemical plant	8.0 (0.5, 138.4)
Worked in forestry	6.3 (0.4, 94.3)
Worked at smelters	4.8 (1.0, 24.2)*
Worked as a fisherman	3.0 (0.6, 16.2)
Sold seafood at work	2.7 (0.5, 15.3)
Worked in rubber plants	2.7 (0.3, 28.5)
Killed goats	2.3 (0.2, 26.5)
Lived on a horse farm as a child	2.0 (0.6, 6.5)
Worked on a horse farm	1.9 (0.6, 6.7)
Worked on a pig raising farm	1.8 (0.6, 5.6)
Worked on a dairy farm	1.7 (0.4, 7.1)
Worked on a commercial mixed farm (crop and animal)	1.6 (0.3, 8.4)
Worked on a commercial crop farm	1.5 (0.5, 4.7)
Had electrical jobs	1.3 (0.3, 5.2)
Worked in a X-ray department	1.3 (0.0, 40.9)
Worked in a granary where nuts or grains were stored	1.2 (0.1, 18.2)
Handled seafood at work	1.0 (0.3, 3.1)

£Adjusted for age and union site; *statistically significant.

with brain tumors (38) as observed in this study, although they could be the result rather than being related to the cause of the disease. The relationship between head trauma and brain tumor is inconsistent (39,40). Our study demonstrated more than twofold risk of brain tumor mortality among those with prior brain injury. Also, elevated risk due to having a history of epilepsy was observed in our study, which is consistent with prior findings (41–44).

Previous studies have quite consistently reported protective effects of allergic conditions on brain cancer risk (41,44–46). Our findings for history of allergic conditions to dust and pollen appear supportive of these reports. Similarly, a protective role for history of chickenpox (varicella zoster) and herpesvirus infection has frequently been reported (45,47–48), and similar findings were recorded in this study also for chickenpox infection and oral herpes infection (cold sores).

Ionizing radiation is the only known established risk factor for brain tumors (49), and our study found a significant increased risk of brain cancer in patients who received medical treatment with radiation. The decreased association observed with cell phone use may be artifactual as all the cases were deceased before cell phone use became affordable, as compared to controls who lived longer or remained alive.

N-nitroso compounds have been found in a variety of dietary products (50,51). Consistent with the literature, our study showed significantly increased risk for brain tumor mortality when eating salted, smoked, or barbequed meat and cheese for most of their lives.

Although this pilot study succeeded in replicating risk factors observed in larger studies of brain tumors, results should be interpreted with caution. First, this is a pilot study with limited statistical power, and thus did not have the capacity to adequately investigate other potentially carcinogenic occupational exposures such as smoking, curing, cooking, and wrapping of poultry. Positive findings may be due to chance, or influenced by multiple comparisons made. Second, selection bias could also influence our study findings. However, the likelihood of this problem seems significantly reduced because all cases that occurred in the cohort were selected for study and the control was a random sample of the base population. Also, the distributions of race and gender among the interviewed study subjects were similar to those for all study subjects. In addition,

TABLE 3
Adjusted odds ratios (OR) and 95% confidence intervals (CI) for selected health conditions, behavioral and lifestyle factors, and radiation in the pilot Brain Cancer Case-Cohort Study of Poultry and Nonpoultry United Food & Commercial Workers Union Workers, 1990–2003

History	Adjusted[£] OR (95% CI)
Medical history	
Had radiation treatment for a medical condition	12.7 (3.9, 41.2)*
Diagnosed with migraines	3.7 (1.3, 10.5)*
Prior head injury	2.3 (0.7, 7.5)
Diagnosed with epilepsy	2.3 (0.3, 16.1)
Allergic to dust	0.4 (0.1, 1.6)
Allergic to pollen	0.3 (0.1, 1.3)
Had cold sores on the lip	0.3 (0.1, 1.0)
Diagnosed with chickenpox	0.2 (0.1, 0.6)*
Received immunizations against measles	0.2 (0.1, 0.6)*
Dietary history[#]	
Ate uncooked fish/shellfish	8.2 (1.8, 37.0)*
Ate salted meat	5.5 (2.0, 15.0)*
Ate barbequed meat	4.4 (1.5, 12.6)*
Ate nuts	2.7 (1.0, 7.3)*
Ate smoked meat	2.5 (0.9, 6.8)
Ate cheese	1.3 (0.3, 4.8)
Other	
Regularly performed any type of exercise	0.3 (0.1, 0.7)*
Ever owned or used a cell phone	0.2 (0.1, 0.6)*

[£]Adjusted for age and union site; *statistically significant; [#]consumed these food items for most of their lives.

the proportion of poultry workers among interviewed cases was similar to the proportion among the total number of cases. In fact, the controls that were interviewed had a higher proportion of poultry workers compared to the total number of controls. This may have biased the risk estimates toward the null value. Third, response bias is possible because responders for all cases were proxies, whereas responders for controls were mostly the live study subjects themselves. To determine the impact, if any, on risk estimates with using proxies, additional analysis was performed to compare responses from 7 pairs of live control study subjects and their next-of-kin. The responses obtained did not show evidence of severe response bias. Of the 245 direct responses obtained for dichotomous questions, there was an agreement of 80% to 100% between the pairs for nearly 75% of the responses, with less than 60% agreement for only 8% of the responses. Fourth, misclassification for the underlying cause of death may have occurred, because we relied on death certificates for the diagnosis of brain cancer. If misclassification did occur, it is likely to be nondifferential, which would pull the risk estimates toward the null. Fifth, because most of the questions were of the type "were you ever exposed," this study was not able to ascertain temporality or dose-response relationships. Finally, confounding by socioeconomic status, though a consideration, is unlikely because this study used a homogenous occupational group of subjects who earned minimum wage, and all of them belonged to the same international union. Despite the limitations, this study is the first to investigate brain cancer occurrence in relation to poultry oncogenic exposures in a well-defined high-risk poultry worker cohort, and it succeeded in uncovering possible new risk factors.

CONCLUSION

A key contribution of this pilot study was providing new, but preliminary, evidence that exposure to poultry and raw poultry products may explain the observed excess of brain cancer mortality previously observed among workers in poultry slaughtering and processing plants. Killing chickens at work is associated with one of the highest exposures to the oncogenic viruses of poultry within an occupational group that already has high potential for such an exposure. This study adds to the broader evidence of increased oncogenic viral antibodies in the sera of poultry workers, and similar increased risks observed with killing chickens in other cancers. The role of other poultry occupational and nonoccupational exposures need to be adequately assessed in more rigorous studies before a clear a definitive conclusion about the role of poultry oncogenic viruses in the etiology of brain cancer can be clearly elucidated. Similarly, the association of brain cancer mortality with shellfish and seafood exposures is novel and needs to be confirmed in other larger studies.

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