RISK OF HEMATOPOIETIC CANCER ASSOCIATED MORTALITY AMONG WORKERS IN THE POULTRY SLAUGHTERING AND PROCESSING INDUSTRIES

DISSERTATION

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Abstract

Objectives

Previous occupational cohort studies among poultry workers have revealed an excess risk of cancer-related mortality, including deaths due to hematopoietic malignancies. However, specific occupational and non-occupational exposures contributing to this excess risk have yet to be identified. Poultry workers are particularly at high risk since an average of 175,000 chickens are killed daily in poultry plants in the United States. This brings poultry workers into intimate contact with their blood, organs, and secretions, which may harbor transmissible oncogenic viruses. Moreover, they are exposed to potentially carcinogenic chemicals that are emitted during packaging and preparation. Hence, our study was conducted to provide preliminary evidence of which specific poultry related and non-poultry related occupational tasks increase the risk of mortality from hematopoietic cancer among poultry workers.

Methods

A pilot case-cohort study was conducted using a combined cohort of 30,411 highly exposed poultry workers and 16,408 control subjects. Exposures pertaining to poultry and non-poultry related tasks were self-reported through telephone interviews from controls and next-of-kin for cases. Hematopoietic cancer mortality risk was assessed using logistic regression odds ratios (OR) and proportional hazard ratios (HR).

Results

To assess possible differential recall between responses obtained directly from live study subjects and those from the next-of kin of deceased study subjects, the questionnaire was administered to a small subset of seven pairs of live control study subjects and their next-of-kin. 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. The highest risks for hematopoietic cancer mortality were among poultry workers in stockyards (OR=4.50, 95%CI=0.34-59.88), work as a poultry farmer (OR=2.67, 95%CI=0.78-9.23), working in non-commercial poultry farms (OR=2.53, 95%CI=0.85-7.52), handling of raw eggs in grocery stores (OR= 2.24, 95%CI=0.05-9.78), working in commercial poultry farms (OR=2.41, 95%CI=0.79-7.33), and spreading of chicken wastes (OR=2.00, 95%CI=0.58-6.89). Direct contact with poultry blood (OR=1.40, 95%CI=0.66-2.95) and killing chickens at work or outside of work (OR=1.35, 95%CI=0.26-7.14 and 1.63 (95%CI=0.72-3.65, respectively) were exposures that were also associated with an increased risk. Among non-poultry associated occupational exposures, working in a chemical plant (OR=6.92, 95%CI=0.56-85.23) and spraying insecticides (OR=3.03, 95%CI=0.78-11.83) incurred an increased risk. Work-related exposure to coal tar, naphthalene, or paraffin was associated with a significantly increased risk (OR=5.63, 95%CI=1.72-18.43). An elevated risk was also observed among subjects that worked at a gasoline station (OR=1.89, 95%CI=0.52-6.96). These exposures are known to be associated with increased exposures to PAHs and benzene. There was a statistically significant increased risk among those who sold seafood at work (OR=4.31,

95%CI=1.08-17.16) and among participants who worked on a commercial mixed farm (OR=3.15, 95%CI=1.20-9.92).

Conclusion

This study provides preliminary evidence that exposure to poultry may be associated with increased mortality from hematopoietic cancer. A plausible explanation is that stockyard workers are regularly exposed to the bodily fluids of poultry, including blood and fecal matter, which may harbor oncogenic viruses that are transmissible to humans. The elevated risk estimates among workers exposed to gasoline as well as chemicals such as coal tar corroborate findings from previous studies that have established benzene and PAHs as risk factors for hematopoietic malignancies, respectively. While our findings support evidence from previous studies linking pesticide use and working on farms with mortality due to hematopoietic cancer, selling seafood was a unique risk factor that was discovered in our study, worthy of further investigation. Case-control studies nested within occupational cohorts of highly exposed subjects of sufficient statistical power may provide an efficient and valid method of investigating and confirming these findings.

Chapter 1. Introduction

Statement of the Problem

Risk factors underlying hematopoietic cancer are as numerous and varied as the subtypes of this particular malignancy. Epidemiologic challenges in studying risk factors for hematopoietic cancers include garnering enough cases and identifying high-risk populations that have high prevalence of exposures. Occupational studies provide an opportunity to access these high-risk populations and have offered new leads to our understanding of cancer that could not have been uncovered in the general population due to their lower exposures. One such high-risk group includes poultry and meat workers. Previous studies have revealed an excess mortality risk of hematopoietic cancers among meat industry workers, particularly in tasks related to slaughtering (Gubéran, Usel, Raymond, & Fioretta, 1993; Metayer, Johnson, & Rice, 1998). However, most of these studies were largely exclusive of those working with poultry. Poultry workers come in contact with thousands of chickens daily. In a typical poultry plant, an average of 175,000 chickens are killed each day (E S Johnson, Shorter, Rider, & Jiles, 1997). This brings them into intimate contact with poultry blood, organs, and secretions (Netto & Johnson, 2003). Frequent cuts and injuries from sharp knives and bone splinters provide a portal of entry for microorganisms and potential oncogenic viruses to enter the body (E S Johnson et al., 1997). Viruses such as avian leukosis/sarcoma viruses (ALSV), reticuloendotheliosis virus (REV), and Marek's disease virus (MDV), have been shown to cause hematopoietic cancers in poultry (Payne, 1998). What remains to be clarified is whether these viruses can cause cancer in humans. Preliminary studies have reported the presence of antibodies to all of these viruses in the sera of poultry workers (Choudat, Dambrine, Delemotte,

& Coudert, 1996; E S Johnson, Overby, & Philpot, 1995). Furthermore, *in vitro* experiments have revealed that these viruses can infect and cause malignant transformation in human cells (Choi & Johnson, 2011; E S Johnson, Overby, et al., 1995). While the virus hypothesis is provocative, there are other exposures prevalent in the poultry industry that may explain the excess mortality of hematopoietic cancers among poultry workers. These exposures include the polycyclic aromatic hydrocarbons, benzene, and phthalates released during the wrapping and preparation of meats (Metayer et al., 1998). Part of the smoking and curing process may also constitute another potential carcinogenic exposure for those working in the poultry industry (Felini et al., 2012; Metayer et al., 1998).

The few studies that have been conducted specifically in the poultry industry have been limited by a small sample size and a lack of detailed investigation into occupational task exposures that may explain the excess risk of hematopoietic cancer mortality in poultry workers(Metayer et al., 1998; Moore et al., 2007). In one of the largest poultry mortality studies conducted to date, our group uncovered an excess mortality in hematopoietic cancer, as well as 10 other cancers(E S Johnson et al., 1997; Eric S. Johnson, Ndetan, & Lo, 2010; Eric S Johnson et al., 2010). I served as a graduate research assistant on this project for 5 years, and was intimately involved in collecting data regarding hematopoietic malignancies. I speculate that chemical and virulent agents may be causing this excess risk. I propose to conduct a *pilot* case-cohort study to determine which specific occupational tasks performed by poultry workers may increase the risk of hematopoietic cancer.

Purpose

This study aims to provide preliminary evidence of which specific occupational exposures and non-poultry related occupational tasks may be associated with increase mortality of hematopoietic cancer among those working in the poultry industry. I also anticipate new exposures may be uncovered that can be used to develop additional hypothesis for further study. I will use a pilot-case-cohort study nested within a combined cohort of 3 cohorts, which were followed up from 1990 to 2003. Hence, the results of our study must be viewed in the context of a pilot investigation, a small-scale feasibility and hypothesis generating study, the results of which will serve as the foundation for future larger scale studies (Leon, Davis, & Kraemer, 2011)

Significance

There have been no studies to date as comprehensive as ours in its aim to investigate the increased risk of mortality due to hematopoietic malignancies among workers in the poultry industry. Our study will use data from three separate poultry cohorts across seven U.S. states, classify hematopoietic malignancies by histologic subtype, and examine over 130 exposures in a task-specific manner. A smaller study conducted by Metayer et al in 1998 used a less exhaustive questionnaire, and focused solely on a single cohort with a significantly smaller source population (Metayer et al., 1998).

This work will be significant to the growing population of poultry workers. Risk factors observed, though preliminary, can be used to instruct Policies specific to poultry plants that can promote safer work environments and proper workplace regulatory controls. This is critical in

protecting the health of this occupational group, one that has largely become marginalized in keeping with their distinction as one of the lowest paid groups of workers in the United States.

In addition, there is also public health significance to the general population should the viral hypothesis prove in future studies to be relevant. In a survey of eggs displayed for sale in a random sample of supermarkets in the New Orleans metropolitan area, 14% were positive for ALSV (Pham, Spencer, & Johnson, 1999). In addition, large stocks of measles and mumps vaccinations, for which chicken embryos are used as a growth substrate, are contaminated with poultry oncogenic viruses, and pose yet another potential risk to the general population(Tsang et al., 1999). Hence, the pervasiveness of this potential threat to those outside of the industrial setting adds an additional layer of significance to our study.

Specific Aims

Aim 1. To identify specific occupational task exposures within the poultry industry associated with increased risk of hematopoietic cancer mortality among poultry workers.

Aim 2. To identify specific non-poultry related occupational tasks associated with increased risk of hematopoietic cancer mortality among poultry workers.

Aim 3. To determine whether risk of mortality differs by histologic subtype among poultry workers.

Chapter 2. Literature Review

Classification and Biology

Hematological malignancies encompass a heterogeneous collection of cancers that originate from the bone marrow, from which the myeloid cell line is derived, and lymphatic system, which gives rise to the lymphoid cell line (Rodriguez-Abreu, Bordoni, & Zucca, 2007). Broadly speaking, malignant transformation of these two major blood cell lineages results in leukemia, lymphoma, and myeloma (Lichtman, 2008; Rodriguez-Abreu et al., 2007). In its native state, the myeloid cell line is responsible for producing granulocytes, erythrocytes, thrombocytes, macrophages and mast cells. Acute and chronic myelogenous leukemia, myelodysplastic syndromes, and myeloproliferative diseases arise consequent to neoplastic changes of this cell line. Cancerous aberration of the lymphoid cell line, which normally produces B, T, NK and plasma cells, results in lymphomas, lymphocytic leukemias, and myelomas.

With a view to incorporate morphologic, biologic, and genetic information into a working nomenclature that has clinical relevance, the World Health Organization put forth their WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissue in 2008. This classification broadly groups malignant blood cancers into two main categories: myeloid neoplasms and lymphoid neoplasms (Vardiman et al., 2009). The distinction between the historical mode of classifying hematologic malignancies, which is based on whether it is located in the blood (leukemia) or lymph nodes (lymphoma), and WHO's classification system, which is

premised on cell lineage, is depicted in Table 1. Moving forward, our study will employ the historic classification system.

Table 1. Classification of Hematologic Malignancies

Classifications Hematologic Malignancies			**2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue**	
Leukemias	**Lymphomas**	**Myelomas**	**Myeloid Neoplasms**	**Lymphoid Neoplasms**
Acute lymphoblastic leukemia	Hodgkin's lymphomas (all 4 subtypes)	Multiple myeloma	Myeloproliferative neoplasms	Precursor lymphoid neoplasms
Acute myelogenous leukemia	Non-Hodgkin's lymphomas (all subtypes)		Myeloid and lymphoid disorders with eosinophilia	Mature B-cell neoplasms
Chronic lymphocytic leukemia*			Myeloproliferative, myelodysplastic neoplasms	Mature T-cell neoplasms
Chronic myelogenous leukemia			Myelodysplastic syndromes	Hodgkin lymphoma
Acute monocytic leukemia			Acute myeloid leukemia and relat neoplasms	Immunodeficiency associated lymphoproliferative disorders
Other leukemias			Acute leukemia of ambiguous lineage	

*Categorized under *lymphomas* according to current WHO classification [referred to as *small lymphocytic lymphoma (SLL)* when leukemic cells are absent]

Leukemia. Leukemia is an overproduction of leukocytes that develop from immature cells called *blasts*. Whereas blasts typically constitute 5% or less of healthy bone marrow, they remain immature in leukemia and continuously proliferate, eventually constituting between 30 - 100% of the bone marrow. Ultimately, these malignant blast cells tend to overpopulate the

bone marrow and inhibit the production of healthy red cells, platelets, and mature white cells (Pui, Robison, & Look, 2008). While numerous pioneering studies explored causative factors underlying leukemia, perhaps the most relevant to our present study was a landmark investigation conducted by Ellerman and Bang in 1908 suggesting that a viral vector in poultry may transmit leukemia, a disease process that had yet to be linked with cancer.

The classification of leukemias is complex and has undergone numerous changes over the years. Leukemias are currently classified into two general categories: *acute*, which progress rapidly and are characterized by the presence of many immature white cells, and *chronic*, which progress insidiously, with the distinctive finding of a greater number of mature white cells. Leukemias can be further classified by the origin of the blast cell that is affected, lymphoid versus myeloid. Lymphoid or lymphocytic leukemia affects circulating lymphocytes (a type of leukocyte) cells, whereas myeloid leukemia arises from abnormal growth in the blood-forming tissue of the bone marrow (Surveillance, Epidemiology, and End Results Program, 2015). Taken together, the traditional classification of leukemias, utilized in both descriptive and analytical epidemiological literature, categorizes leukemia into four groups (1) *acute myeloid leukemia* (AML); (2) *chronic myeloid leukemia* (CML); (3) *acute lymphoid leukemia* (ALL); and (4) *chronic lymphoid leukemia* (CLL), which, as previously noted in the footnote of Table. 1, has been reclassified as a type of non-Hodgkin's lymphoma by the World Health Organization (Alexander, Mink, Adami, Chang, et al., 2007).

Multiple Myeloma. In this disease, plasma cells in the bone marrow become neoplastic and accumulate in the bone marrow, interfering with the production of normal blood cells.

They release a pathognomonic antibody protein, called M protein, which has no immunologic benefit. Multiple myeloma is clinically characterized by lytic bone lesions, renal dysfunction, and hypercalcemia (Raab, Podar, Breitkreutz, Richardson, & Anderson, 2009).

Lymphomas. Non-Hodgkin's lymphomas are uniquely distinct from Hodgkin's lymphomas by their lack of a Reed-Sternberg cell on microscopy. Non-Hodgkin's lymphomas are a heterogeneous group of malignancies that also have their origin in the lymphatic system, a complex network of lymphatic vessels, lymph nodes, and immunoprotective organs including the spleen, tonsils, and thymus gland (Alexander, Mink, Adami, Chang, et al., 2007). T or B lymphocytes produced from lymphoid stem cells undergo malignant transformation, with resulting diverse biological and clinical manifestations (Boffetta, 2011). Non-Hodgkin's lymphomas can develop from these T cells and B cells at almost any stage of their development. Numerous subtypes of non-Hodgkin's lymphoma have been classified according to whether they are B-cell lymphomas or T-cell lymphomas by the WHO System of classification, making the dichotomous categorization of lymphomas into Hodgkin's and non-Hodgkin's lymphomas an antiquated distinction (Vardiman, Harris, & Brunning, 2002). For the purpose of this proposed study, my focus will be restricted to NHL, as no deaths due to Hodgkin's lymphoma were identified in the parent study.

Descriptive Epidemiology

Hematologic malignancies constituted nearly 9% of all incident cancer cases diagnosed in the U.S. in 2013. Rates for new leukemia, non-Hodgkin's lymphoma, and multiple myeloma cases have been rising by 0.2%, 0.5%, and 0.7% on average every year over the past 10 years,

respectively. Death rates have been falling on average 1.3% each year over 2002-2011 (Surveillance, Epidemiology, and End Results Program, 2015). While leukemias and multiple myeloma are sometimes referred to as *liquid tumors*, lymphomas fall under the category of *solid organ tumors*. Of the three histologic subtypes, NHL carries the distinction of having the highest prevalence in the United States, followed, in descending order, by leukemia and multiple myeloma. A predilection for the male gender is consistent across the three histologic subtypes. In 2013, NHL had the highest incidence, and mortality was highest among those suffering from leukemia. Multiple myeloma most commonly affected African-Americans over Caucasians, whereas the converse was true for leukemia and NHL. The median age of diagnosis for all subtypes ranges from 65 years to 69 years. Of note, acute lymphoblastic leukemia (ALL) has a bimodal age distribution. However, since the first peak occurs during early childhood, it is not relevant to the present study, as my focus is on adults working in the poultry industry. The highest survival rate is found among those with NHL, with the lowest found in those with multiple myeloma. The impact of socioeconomic status (SES) on these three subtypes is also a consideration, given that our study is focusing on a group of workers who constitute one of the lowest paid groups of workers in the United States, typically belonging to the lowest socioeconomic stratum. No association has been reported in the literature between SES and NHL and adult leukemia, and findings regarding multiple myeloma are largely inconclusive.

Table 2. Descriptive epidemiology for leukemia, multiple myeloma, and non-Hodgkin's lymphoma

	Leukemia	Multiple Myeloma	Non-Hodgkin's Lymphoma
Prevalence in the U.S.	287,963	77,617	530,919
Estimated new cases (U.S.), 2013	48,610	22,350	69,740
Estimated deaths (U.S.), 2013	23,720	10,710	19,020
Age of diagnosis (median)	65 years	69 years	66 years
Ethnic/racial predilection	Caucasians	African-Americans	Caucasians
Gender predilection (cases/100,000)	Males: 16.3 Females: 10	Males: 7.5 Females: 4.8	Males: 23.9 Females: 16.9
5-year survival rate	56.2%	43.2%	69.0%

Risk Factors

Leukemia: established risk factors. Ionizing radiation is one of the few established causes of leukemia, specifically AML, ALL, and CML (Adami, Hunter, & Trichopoulos, 2008). CML was thought to be most similar to atomic bomb radiation induced leukemia. In fact, studies by Ichimaru et al have revealed a peak in the incidence of CML in Hiroshima victims 6 years after the accident (Ichimaru, Tomonaga, Amenomori, & Matsuo, 1991). A straight line can estimate the exposure-response curve for leukemia in relation to ionizing radiation, except at high levels of exposure, wherein cell killing distorts the linear pattern.

Smoking is an established risk factor specifically for myeloid leukemia (Adami et al., 2008). The most recent update by the International Agency for Research on Cancer (IARC) indicates that there does not seem to be any evidence to support an association between tobacco smoking and lymphoid leukemia (Cogliano et al., 2011). Among older persons (> 60 years), the risk of acute myeloid leukemia increased with amount and duration of smoking (Sandler et al., 1993).

Human T-cell lymphotropic virus type 1 (HTLV-1) has been deemed a risk factor for leukemia, responsible for a small fraction of cases (Adami et al., 2008). The prior use of chemotherapeutic drugs for the treatment of cancer, such as cyclophosphamide and melphalane, has been reported to induce secondary leukemia.

Leukemia: possible risk factors. There is growing evidence that diagnostic radiation, such as prenatal diagnostic X-rays during the last trimester of pregnancy, could be possibly responsible for a small proportion of leukemia cases that occur worldwide (Evans, Wennberg, & McNeil, 1986). It is estimated that 1-2 rad of ionizing radiation in utero may increase the risk of leukemia by a factor of 1.5-2 (Brent, 1989). Studies of patients who have undergone X-rays for ankylosing spondylitis have shown increased risks of acute myeloid, acute lymphatic, and chronic myeloid leukemia. The relative risk appeared to be greatest for acute myeloid leukemia (Darby, Doll, Gill, & Smith, 1987).

Leukemia: occupational risk factors. One of the chemicals that have been conclusively linked to leukemia is benzene, supported by the most recent review by IARC (Cogliano et al., 2011). Benzene exposure is primarily from cigarette smoking, automobile exhaust, and

gasoline. Occupations in which benzene exposure is high are those in the leather industry, rubber refineries, and printing and painting industries (Yaris, Dikici, Akbulut, Yaris, & Sabuncu, 2004) .

Occupational exposure to ionizing radiation has long been deemed as a risk factor for leukemia. In the early twentieth century, radiologists and X-ray technicians were found to be at increased risk for developing leukemia (Matanoski, Seltser, Sartwell, Diamond, & Elliott, 1975). Nuclear workers, particularly those who do not adhere to the necessary protective measures, are at increased risk for gamma-ray induced leukemia (Cardis et al., 2005).

The IARC recently reclassified formaldehyde as a human carcinogen, with "sufficient evidence" to consider a causal association with leukemia. The highest risks were associated with myeloid leukemia (Cogliano et al., 2011). Formaldehyde is used to manufacture numerous products, such as consumer appliances, porcelain-like dishware, and insulation, and is best known as a tissue preservative or bactericide in embalming fluid and medical laboratories (Zhang, Steinmaus, Eastmond, Xin, & Smith).

There is some evidence that the occupational use of hair dyes among beauticians is associated with elevated risk for developing acute leukemia (Rauscher, Shore, & Sandler, 2004); however, the results are inconclusive (Adami et al., 2008).

Farmers have also been shown to be at an increased risk for acquiring leukemia; but there is insufficient evidence to distinguish between viral exposure and exposure to fungicides/herbicides as the potential causative agent (Adami et al., 2008).

Multiple myeloma: established risk factors. Genetic factors play a role in the development of multiple myeloma. A positive family history of monoclonal gammopathy of undetermined significance (MGUS) in a first degree relative is associated with at least a two-fold risk of developing multiple myeloma (Kristinsson et al., 2009). Moreover, patients positive for MGUS have close to 25 times the risk of developing multiple myeloma compared to those that are MGUS negative. With regard to contributing lifestyle factors, a meta-analyses of studies revealed that obesity (BMI>30) was associated with a two-fold risk of developing multiple myeloma (Becker, 2011).

Multiple myeloma: possible risk factors. A diet that is low in the consumption of fish and vegetables could be associated with the development of multiple myeloma (Becker, 2011; Alexander, Mink, Adami, Cole, et al., 2007).

Although HIV/AIDS is not classified as a risk factor for multiple myeloma by the IARC, a recent meta-analysis reported that it was 2.6 times more common among HIV-infected people compared to the general population (Shiels, Cole, Kirk, & Poole, 2009). Other viruses, such as herpes zoster and hepatitis C have been implicated as potential risk factors, but the epidemiologic data remains inconsistent (Becker, 2011; Alexander, Mink, Adami, Cole, et al., 2007).

Multiple myeloma: occupational risk factors. The EPILYMPH study, a large multi-center case-control study conducted in six European countries, analyzed the association between occupational exposures and multiple myeloma (Perrotta et al., 2012). An increased risk of multiple myeloma was found among cases exposed to pesticides for more than 10 years. These

results confirm an association between farming and multiple myeloma as described in a recent systematic review of 30 years of research, which showed a similar elevation in risk estimates for working on a farm for more than ten years (Perrotta, Staines, & Cocco, 2008). Occupational exposure to DDT, chlorophenols, and phenoxy-acetic acids were all associated with an excess risk in case-control studies of patients diagnosed with multiple myeloma. On the other hand, both the EPILYMPH study (Perrotta et al., 2012) as well as a recent review of the carcinogenic potential of more than 100 chemicals conducted by the IARC did not confirm an excess risk due to prolonged exposure to organic solvents such as benzene and ethylene oxide (Cogliano et al., 2011).

There remains an ongoing debate regarding the effects of exposure to low levels of radiation in certain workplaces (e.g., nuclear plants), and certain medical procedures (e.g. X-rays) (Darby et al., 1987) . A recent review concluded that the results do not support an association between such exposures and the development of myeloma, whereas the IARC states there is limited proof for an association (Cogliano et al., 2011).

Non-Hodgkin's lymphoma: established risk factors. Viruses are established risk factors of NHL. The relationship between HIV/AIDS and NHL has consistently shown a strong positive association (Alexander, Mink, Adami, Chang, et al., 2007; Engels et al., 2006). It is believed that chronic antigenic stimulation and immune deficiency may be the causative factor underlying the increased risk of NHL among HIV-infected individuals (Engels et al., 2006). Yet another infectious agent, Epstein-Barr virus (EBV), is an established risk factor for NHL (Cogliano et al., 2011). In fact, a recent review revealed that patients with a self-reported history of infectious

mononucleosis, caused by EBV, showed an increased risk for acquiring NHL (Becker et al., 2012). There is a substantial amount of evidence implicating HTLV1 (human T-cell lymphotropic virus type 1) in the development of NHL (Brant, Cawley, Davison, & Taylor, 2011). The human T-cell leukemia/lymphoma virus (HTLV-1) and EBV directly affect the DNA of lymphocytes, helping to transform them into cancer cells. The hepatitis C virus (HCV) had been previously implicated in the development of hepatocellular carcinoma, and its role in the pathogenesis of NHL has recently been established (Cogliano et al., 2011) (Alexander, Mink, Adami, Chang, et al., 2007). In a meta-analysis of 7 member studies from the International Lymphoma Epidemiology Consortium (InterLymph), the results confirmed this association between HCV and NHL (de Sanjose et al., 2008). With regard to bacterial infections, a recent review conducted by the IARC demonstrated that Helicobacter pylori has been causally associated with NHL (Cogliano et al., 2011).

There also appears to be a genetic component associated with the development of NHL (Alexander, Mink, Adami, Chang, et al., 2007), as NHL in a first-degree relative is associated with an increased risk of developing this disease (Boffetta, 2011). That being said, genetics are hypothesized to account for only a small percentage of NHLs that occur worldwide (Alexander, Mink, Adami, Chang, et al., 2007). Numerous autoimmune conditions have been associated with an increased risk of subsequent NHL development (Alexander, Mink, Adami, Chang, et al., 2007). In a meta-analysis of 20 studies, the risk of NHL is increased by roughly 19-fold in patients with primary Sjögren's syndrome; 7-fold with systemic lupus erythematous (SLE); and 2- to 4-fold with rheumatoid arthritis (RA) (Zintzaras, Voulgarelis, & Moutsopoulos, 2005).

Non-Hodgkin's lymphoma: possible risk factors. Borrelia burgdorferi, a tick-borne spirochete responsible for spreading Lyme disease, has been inconsistently implicated as a risk factor for NHL (Boffetta, 2011). Hepatitis B (HBV) has also been considered as a potential risk factor for NHL (Nath, Agarwal, Malhotra, & Varma, 2010).

Smoking has not shown to be causally associated with NHL; but there are few exceptions. In a pooled analysis of 9 datasets, Morton et al evaluated the associations between cigarette smoking and risk of NHL. The results showed that current smoking was significantly associated with follicular lymphoma, the second most common type of NHL (L. M. Morton et al., 2005).

No consistent associations have been observed with regard to diet and NHL, with few possible exceptions. Although results have not been consistent insofar as types of red meat or preparation methods, studies have reported positive association between red meat consumption and NHL. Conversely, fish intake has been associated with a non-significant decreased risk of NHL in several studies, although intake of omega-3 fatty acids from fish was not associated with reduced risk of NHL.(Alexander, Mink, Adami, Chang, et al., 2007; Boffetta, 2011)

Non-Hodgkin's lymphoma: occupational risk factors. IARC classified benzene as a carcinogen with "limited evidence" of an association with NHL (Cogliano et al., 2011). Animal studies support an association between benzene and lymphomas, but occupational studies are more mixed. Because benzene is similar to alkylating drugs and radiation in producing leukemia, it might be responsible for causing lymphomatous diseases by similar mechanisms

(Yin et al., 1996). In a study of 74,828 chemical workers in China exposed to benzene and 35,805 unexposed workers, a non-significant positive association was reported with regard to NHL mortality, showing a four-fold risk of mortality among workers who were exposed to petroleum for more than ten years. However, there was no dose–response pattern for average or cumulative benzene exposure (Yin et al., 1996). In contradistinction to these findings, a pooled analysis of 26 cohorts of petroleum workers in the USA, UK, Canada, Australia, Italy, and Finland revealed no association between NHL mortality exposure to benzene (Wong & Raabe, 2000).

Solvents, as a general category, have been inconsistently associated with NHL (Vineis, Miligi, & Costantini, 2007). Results from studies specifically examining trichloroethylene (TCE) have been varied; although some studies reported positive associations, there was no consistent exposure–response pattern within or across the studies (Boffetta, 2011).

Occupational and wartime exposure to ionizing radiation has not been associated with an increased risk of NHL. Several studies have reported positive associations with therapeutic or diagnostic radiation exposure, but results are inconsistent, and, in general, dose–response patterns have not been detected (Alexander, Mink, Adami, Chang, et al., 2007; Boffetta, 2011)

A large number of studies on occupational risk factors of NHL were based on occupation or job title. The most consistent finding has been an association between the occupation of schoolteacher and risk for NHL, reported in findings from a meta-analysis of 14 studies. Purportedly, teachers frequently come into contact with children and may consequently have higher rates of exposure to infectious agents, which we know are established risk factors to

NHL (Chia, Wong, & Tai, 2012). However, the main limitations of using job titles as proxies of exposure are the paucity of exposure information at the individual level and the lack of information regarding potential confounders. These results should be interpreted with caution, as publication bias may be present (Baker, Inskip, & Coggon, 1999).

Potential Hazardous Exposures in the Meat and Poultry Industries

Studies have shown that poultry workers are subjected to several hazardous occupational exposures that are potentially carcinogenic (Felini et al., 2011, 2012; Eric S Johnson et al., 2010; Metayer et al., 1998). Primary exposures include contact with fresh blood, inhalation of chemicals released from meat wrapping, nitrosamines that develop from curing and preservation of meats, and polycyclic amines from smoking meats.

Contact with blood in the poultry and meat industry. Potential hazardous exposures in the poultry and meat industry include blood borne transmissible agents, such as prions, bacteria, viruses, and protozoa that have been shown to cause cancer and other diseases in animals (Netto & Johnson, 2003). Numerous studies have shown that bovine leukemia virus (BLV), which is prevalent in cattle and sheep, can induce lymphosarcoma as well as other cancers in these animals. BLV is found in the tissue of cattle and sheep. Whether it can be transmitted to humans remains controversial. Epidemiological and serological studies conducted among agricultural and meat industry personnel suggest that BLV can cross xenographic barriers under experimental conditions, but does not appear to infect humans.

In contrast to meat workers, avian retroviruses viruses, such as avian in sarcoma virus (ALSV), reticuloendotheliosis virus (REV), and lymphoproliferative disease virus (LPDV) are

specific to poultry. Within this animal group, these viruses are markedly more prevalent among chickens and turkeys, and are known to naturally induce cancers in these species (E S Johnson, 1994b; Payne, 1998). Another highly contagious virus found in chickens with significant oncogenic potential is an avian herpes virus known as Marek's disease virus (MDV)(Payne, 1998; Yao et al., 2007). ALSV and REV are some of the most virulent oncogenic viruses that carry the potential to cause cancer among chickens in the span of a few days (Eric S. Johnson et al., 2010; Pham et al., 1999). Of interest to public health investigators is whether these viruses can cause cancer in humans and the route by which humans may be exposed.

Poultry oncogenic viruses have commonly been found in raw or undercooked poultry products, and in eggs meant for human consumption (Pham et al., 1999). These viruses can also contaminate vaccines that are grown in chicken embryo cells. A significant proportion of measles and mumps vaccines that are currently being used in the United States have been contaminated with the ALSV virus (Eric S. Johnson et al., 2010; Tsang et al., 1999). The significance of this exposure is underscored by studies (E S Johnson, Nicholson, & Durack, 1995; E S Johnson, Overby, et al., 1995) that revealed a 31% prevalence of anti-avian leucosis/sarcoma viruses p15 antibodies in the sera of the general population who had no history of occupational exposure to poultry. Yet another study (Choudat et al., 1996) reported a 35% prevalence of anti-avian leucosis/sarcoma viruses antibodies and up to 32% of anti-Marek's disease virus antibodies in white collar workers without a prior history of exposure to poultry. A survey conducted in New Orleans among a random sample of supermarkets reported that 14% of eggs tested positive for exogenous and endogenous ALSV viruses (Pham et al., 1999).

Workers in the poultry slaughtering and processing plants have one of the highest exposures to these viruses (E S Johnson et al., 1997; Netto & Johnson, 2003). In a typical poultry plant, an average of 175,000 chickens are killed per day, placing workers in intimate contact with blood, secretions, and internal organs. Penetrating wounds from contaminated sharp knives and bone splinters, and dermal abrasions caused by abrasive enzymes create a port of entry for these agents to enter the body. Particulate matter that becomes aerosolized with the use of mincing and cutting machines can be inhaled as another route of infection (E S Johnson et al., 1997). Antibody titers to Marek's virus have been shown to be higher among those with these types of exposures to chickens compared to those who are unexposed (Choudat et al., 1996). A review of previous virological studies (E S Johnson, 1994b) clearly described their ability to infect human cells in vitro and in vivo. Hence, it would follow that if these viruses do cause cancer in humans, poultry workers should be among those suffering from the highest rates. Although poultry workers routinely experience a high exposure to these potentially oncogenic viruses, there is limited epidemiological literature examining cancer mortality among this vulnerable group (Felini et al., 2011, 2012; Fritschi, Fenwick, & Bulsara, 2003; E S Johnson et al., 1997; Eric S. Johnson et al., 2010; Moore et al., 2007).

Meat and poultry wrapping. Studies have demonstrated an association between exposure to wrapping machines in the poultry industry and risk of cancer (Fritschi et al., 2003; E S Johnson et al., 1997; Metayer et al., 1998). Fumes are emitted when heat is applied to the plastic film that is used to wrap meat or poultry (Vandervort & Brooks, 1977). Polyvinyl chloride (PVC) plastic films are widely used throughout the meat industry to wrap and label meat products using hot wire and cold rod wrapping machines. Fumes emitted from the

thermal decomposition of these plastic films contain hydrogen chloride, hydrocarbons (chiefly, benzene and polycyclic aromatic hydrocarbons), plasticizers phthalates, and adipates, as well as their breakdown products (E S Johnson S Halabi G Netto G Lucier W Bechtold R Henderson, 1999; O'Mara, 1970; Vandervort & Brooks, 1977)hydrocarbons and phthalates are established carcinogens (Cogliano et al., 2011). The most recent review put forth by the IARC (Cogliano et al., 2011) classified benzene as a carcinogen with "sufficient evidence" to suggest an association with leukemia. Similarly, a study examining the occurrence of cancer in women in the meat industry, chiefly tasked with wrapping and labeling meat and poultry, (E S Johnson, Fischman, Matanoski, & Diamond, 1986b) revealed that they had an almost three-fold risk of death from myeloid leukemia and non-Hodgkins lymphoma. Another study conducted among workers in the meat industry (Metayer et al., 1998) showed an elevated risk of tumors of the myeloid stem cell (including myeloid leukemia) among workers tasked with wrapping meat.

Curing and preservation of meat and poultry. There are three groups of compounds – nitrosamines, heterocyclic amines (HAs), and polycyclic aromatic hydrocarbons (PAHs) – that do not occur naturally in foods, but may be used or may develop during preservation of or while cooking certain foods (Jakszyn et al., 2004). Nitrosocompounds are formed in foods during curing of meat (Sen, Donaldson, Charbonneau, & Miles). Carcinogenic nitrosamines are generated from the interaction of nitrates with amines during the cooking and storage of meat ("IARC Monographs-1987). These compounds are known to be carcinogenic in animals, with some studies showing carcinogenic potential in humans (Jakszyn et al., 2004; Tricker & Preussmann). Hence, poultry workers involved in the commercial preservation and curing process are potentially exposed to these nitrosamines ("IARC Monographs- Monographs

available in PDF format," n.d.). The antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxtoluene (BHT), which are used as preservatives in meat (E S Johnson et al., 1986b) are known carcinogens (Williams, Maeura, & Weisburger, 1983)(Ito, Fukushima, Hagiwara, Shibata, & Ogiso, 1983). A few studies have suggested that meat workers who are involved in the preservation process may be potentially exposed to carcinogenic nitrosamines through inhalation, increasing the risk of lung cancer (E S Johnson, Dalmas, Noss, & Matanoski, 1995; Sen, Miles, Donaldson, Panalaks, & Iyengar, 1973). However, other studies (Baker, Inskip, & Coggon, 1999; Lynge, Andersen, & Kristensen, 1983) have countered this hypothesis, citing insufficient empiric evidence.

Smoking of meat and poultry. Poultry workers in smokehouses are exposed to combustion products from smoking meat, especially polycyclic aromatic hydrocarbons (PAHs) (Colmsjö, Zebühr, & Ostman, 1984; Hansen, Olsen, & Poulsen, 1992; Nordholm, Espensen, Jensen, & Holst, 1986). Exposure to PAHs has been cited as an occupational exposure exclusive to meatpacking and poultry plants that may be related to an increased risk of developing lung cancer (Gustavsson, Fellenius, & Hogstedt, 1987; E S Johnson, Dalmas, et al., 1995; E S Johnson et al., 1986b)The IARC recently classified PAHs as a human carcinogen, with "sufficient evidence" to consider a causal association with lung cancer (Cogliano et al., 2011). In contradistinction to this assertion, a previous study involving butchers and slaughterhouse workers found that exposure to smokehouse fumes was not associated with the excess lung cancer (Gustavsson, Fellenius, & Hogstedt, 1987). However, this lack of association may be attributed to a low proportion of exposed workers, an occupational subgroup of the meat industry that is traditionally not involved in the smoking of meat (Kristensen & Lynge, 1993).

Hematopoietic Cancer Investigations in the Meat Industry

Prior studies investigating occupational risks that give rise to hematopoietic malignancies in the meat industry often included poultry workers as part of their cohort of meat workers, without making a distinction. Hence, in order to provide a comprehensive overview, a summary of these findings is necessary.

Proportional mortality and cohort studies. One of the earliest cohort mortality studies to explore the risk of cancer among meat workers was conducted by Johnson and Fischman (E S Johnson & Fischman, 1982). This study among male members of the meat-cutters union in Baltimore, Maryland, revealed a possible association with hematopoietic malignancies, albeit with a sample size that was limited (PMR=3.75 for myeloid leukemia, with 3 observed deaths; PMR=2.74, with 2 observed deaths for multiple myeloma). A series of similar studies followed, with supporting observations. For example, evidence of an excess risk of developing non-lymphatic leukemia among meat cutters was reported in a Canadian study that included 1678 cases of leukemia. (W. Morton & Marjanovic, 1984). A study examining data from white males who worked in butchering and packing sections of grocery stores did not reveal an excess risk of death from cancers of the hematopoietic and lymphatic systems (E S Johnson, Fischman, Matanoski, & Diamond, 1986a). However, a study conducted among women who worked in the meat industry reported contrasting results (E S Johnson et al., 1986a). This retrospective cohort mortality study, with a follow-up period from 1949-1979, included women working in abattoirs, meatpacking plants, supermarkets, and chicken slaughtering and processing plants. A nearly threefold risk of mortality from myeloid leukemia and NHL was detected among females

working in grocery stores and supermarkets, with an SMR of 1.8 for all hematopoietic/lymphatic cancers. This excess risk observed among women compared to men was attributed to their skewed exposure to fumes that emanate during the wrapping and labeling of meat a task chiefly tasked to women, with men spending less than 15% of their time engaged in this activity. The task of handling of meat, on the other hand, did not seem to be preferentially assigned to a specific gender. Hence, since wrapping of meat was the only distinguishing exposure between the sexes, engaging in this duty seemed to be culpable. As previously detailed, benzene, which is an established risk factor for leukemia (Cogliano et al., 2011) and linked to NHL (Cogliano et al., 2011; Yin et al., 1996)has the highest concentration in the hydrocarbon fraction emitted during the thermal decomposition of polyvinyl chloride plastic film that is utilized in the wrapping and labeling of meat (O'Mara, 1970; Vandervort & Brooks, 1977) A follow up study from 1949-1989 conducted among a subset of the previously studied cohort of local meat cutters union in Baltimore, Maryland reported similar findings, namely an excess risk of deaths from hematopoietic and lymphatic tumors in women compared to men (E S Johnson, 1994b). The results showed an SMR of 1.4 in females, compared to 0.6 in males. Compared to what was seen in the previous study, however, this study showed a decrease in SMR among women for hematopoietic cancers as well as for lung cancers. A significant reduction in exposure to fumes, specifically benzene, emitted during the wrapping of meat occurred after 1975 in the United States, at which time the hot wire was replaced with the *cold rod*. In a biomarker study among meat wrappers, muconic acid (a metabolite of benzene) levels in the urine were compatible with exposure to 1-2 ppm of benzene (E S Johnson, S Halabi, G Netto, G Lucier, W Bechtold, R Henderson, 1999). Risk estimates indicate

that exposure to 1 ppm of benzene for 15 years can potentially increase the risk of mortality from hematopoietic cancers by twofold (Wong, 1987). This may provide an explanation for the ostensible fall in the SMR between the two studies. A mortality study conducted among black males in the meat and poultry industries (E S Johnson, 1989) reported SMRs of 1.9 and 2.5 for leukemias and lymphoid tumors, respectively; but caution should be exercised when interpreting these results, as they were based on one death each. A small Swiss cohort mortality study of 552 cattle and sheep butchers and 310 pork butchers working in Geneva during the period of 1901 to 1969, and followed to 1990, reported an eight-fold excess risk of death from leukemia (5 deaths compared to 0.6 expected) among those butchers born before 1900 (Gubéran et al., 1993). The authors hypothesized that these findings were due to the fact that older butchers slaughtered cattle and meat until 1949, and this intimate contact with cattle blood potentially increased their exposure to Bovine Leukemia Virus (BLV). Mortality results from a cohort of workers in abattoirs and meat packing plants (E S Johnson, Dalmas, et al., 1995) showed a slightly elevated risk for myeloma and NHL, but the sample size was too small for meaningful interpretation. A cohort study among Australian meat industry employees (Fritschi et al., 2003) reported an increased risk of hematopoietic cancer incidence among those with high exposure to animal blood; however, the results were not significant with very wide confidence intervals (OR=2.16, 95%CI=0.5-9) but did not find an increased risk of deaths from hematopoietic cancers among poultry workers . A follow-up study to the previously conducted mortality studies conducted by Johnson et al (E S Johnson et al., 1986a, 1986b; E S Johnson, Overby, et al., 1995) examining the risk of cancer mortality among meat workers revealed the SMRs (standardized mortality ratio) for NHL were significantly lower in females [SMR=0.4 (95%

CI, 0.1–1.0)] and in whites [SMR=0.6 (95% CI, 0.4–0.9)], (E S Johnson, 2011) Although not significant, decreased SMRs for NHL were observed in all race/sex subgroups in abattoirs and meat processing plants, except in the case of non-white males in abattoirs [SMR= 1.2 (95% CI, 0.2–3.4)]. The proportionate mortality ratio (PMR) for lymphoid leukemia was elevated only in non-white males in processing plants, [PMR=3.8 (95% CI, 1.5–9.5)].

The retrospective cohort mortality studies enumerated thus far merely report standardized mortality ratios (SMRs) as their measure of effect, speaking only to the overall excess of cancer-related mortality among poultry workers compared to the general population without acknowledging the factors contributing to this excess. These studies reported SMRs without a detailed investigation of occupational task exposures. Fritchi et al's study was slightly more comprehensive in that it reported standardized incidence ratios and odds ratios for cancer incidence in addition to SMRs (Fritschi et al., 2003). However, exposure assessment was based on job title without any individual job specific data, suggesting that assigned tasks were exclusive to certain job titles without any overlap. An additional deficiency with regard to retrospective cohort mortality studies in this context is that, unlike prospective cohort studies, they rely on past records, a crude measure of exposure assessment as they are often incomplete and of poor quality. Moreover, information regarding potential confounding factors was often missing.

Case-control studies. A series of New Zealand registry based case-control studies that examined the risk of hematopoietic malignancies in association with agricultural occupations consistently found that meat workers were at excess risk, most notably for acute myeloid

leukemia (Pearce, Sheppard, Howard, Fraser, & Lilley, 1986) and NHL (Reif, Pearce, & Fraser, 1989). A series of case-referent studies derived from the New Zealand Cancer Register including 19,904 male cancer patients (Reif et al., 1989) revealed a moderately elevated risk for developing all types of leukemia (OR 1.45, 95% CI 0.90-2.31). Cell type-specific analyses revealed a greater effect with regard to acute myeloid leukemia (OR 2.12, 95% CI 1.09-4.12), corroborating findings from previous studies regarding the probable association between myeloid leukemia and working in the meat industry. Exposure to meat packaging and processing may increase the risk of follicular lymphomas, as is suggested by an elevated odds ratio and positive duration-response relation noted in a study conducted by Tatham et al (Tatham, Tolbert, & Kjeldsberg, 1997). To be specific, after controlling for several confounders, including smoking, a significant positive association was found between working in the meat packaging or processing industries and follicular lymphomas, albeit confined to those with greater than 2 years of exposure. A study conducted to investigate occupational risk and mortality due to leukemia among men in 16 states showed that meat workers (butchers and meat cutters) were at increased risk of death from acute lymphocytic leukemia (OR = 2.2, 95% CI = 0.7-7.0) (Loomis & Savitz, 1991). A nested case control study of hematopoietic tumors among workers in the meat industry (Metayer et al., 1998) reported an excess risk of death from lymphomas in all departments of the meat industry, including slaughtering and working with raw meat, with the exception of meat packing plants. Among butchers in the supermarket setting, multiple myeloma was the most common histologic sub-type of hematopoietic malignancy that was found to be in excess. When categorized by type of exposure, butchers who consistently came into contact with blood and organs when cutting meat (OR = 18.0, 95%

CI = 1.6-207.75) had an elevated risk of death from multiple myeloma compared to those tasked with simply packaging meat (OR = 0.08, 95% CI = 0.7-7.0). However, the sample size was limited, generating odds ratios that were unstable. A study conducted in New Zealand found an increased risk of developing leukemia was associated with employment in the meat industry (Bethwaite, McLean, Kennedy, & Pearce, 2001). These were confined to abattoir (slaughterhouse) workers with over 2 years employment in the industry (OR = 4.9, 95% CI 1.5-15.6), and to persons whose jobs involved contact with animals or animal tissue, implying that biological exposures may be responsible (OR = 5.2 95% CI 1.2-22.2). Work as a butcher was also associated with increased risk, but it was once again confined to butchers working in abattoirs and those who butchered stock on a farm. No increased risk was found for work as retail or wholesale butcher or meatpacker. Moore et al (Moore et al., 2007) conducted a multicenter case control study in Europe, and observed an excess risk of lymphomas (OR=2.00, 95%CI=0.87-4.61), chronic lymphocytic leukemia (OR=2.51, 95% CI=1.162-5.66), and multiple myeloma (OR=2.75, 95%CI=0,60-12.6) among workers exposed to raw beef meat for more than 16 years. In yet another study, McLean et al (McLean & Pearce, 2004) studied 6647 meat workers in New Zealand. The results revealed that there was evidence of a dose-response relation between the incidence of hematopoietic malignancies and duration of employment in jobs that involved jobs with potential exposure to blood.

The majority of the case-control and cohort studies listed above assessed exposure based on interviews or questionnaires that elicited detailed occupational exposure histories. The remaining studies utilized Industrial Hygienists to categorize exposure (Fritschi et al., 2003; Loomis & Savitz, 1991; W. Morton & Marjanovic, 1984; Pearce et al., 1986). Irrespective of the

method of exposure assessment and study design, an elevated risk of at least one histologic subtype of hematopoietic cancer was revealed in all studies.

Hematopoietic Cancer Investigations in the Poultry Industry

The limited number of studies to date specifically examining the risk of hematopoietic malignancies in the poultry industry (Fritschi et al., 2003; E S Johnson et al., 1997; Eric S. Johnson et al., 2010; Eric S Johnson et al., 2010; Metayer et al., 1998; Moore et al., 2007; Netto & Johnson, 2003)argues for further investigation into this topic. Studies have shown that poultry workers are subjected to several hazardous occupational exposures, including chemicals used for processing and wrapping as well as virulent biological agents found in poultry, which may potentially increase their risk of hematopoietic cancer-related mortality (E S Johnson, 1994b; Netto & Johnson, 2003; Priester & Mason, 1974)

Proportional mortality and cohort studies. Johnson et al's (1997) study focused solely on poultry workers from the aforementioned cohort, which included 2639 poultry workers who were compared to 6081 members of the same union never been employed by the meat or poultry industries. Statistically significant results were reported with regard to tumors of the hematopoietic and lymphatic systems (E S Johnson et al., 1997). This study was the first of its kind to examine mortality from cancer and other diseases specific to poultry workers. A risk ratio of 2.9 (1-8.1) and an SMR of 1.2 (0.5-2.3) were reported for all hematopoietic cancers. Although not significant, the SMR for multiple myeloma was 2.1(0.4-6.1). This excess risk of hematopoietic malignancies is consistent with the observation that similar types of tumors have been previously linked to avian oncogenic viruses found in chickens and turkeys ((E S

Johnson, 1994b; Payne, 1998) This limited data suggests that multiple myeloma was one of the tumor types that was involved, and corroborates findings from previous studies that have linked this sub-type with exposure to poultry in the contexts of butchering and farming (E S Johnson, 1994a; Priester & Mason, 1974) A retrospective cohort study in Australia (Fritschi et al., 2003) did not find an increased risk of deaths from hematopoietic cancers among poultry workers. A study conducted specifically among workers from the Missouri Poultry Union (Netto & Johnson, 2003), who were involved in deboning or processing chickens or turkeys, showed no risk for hematopoietic cancers (PMR=1.0, 95%CI=0.5-1.8). An update on the mortality study of the Baltimore poultry union (Eric S Johnson et al., 2010 (a)) among workers who worked exclusively in poultry slaughtering and processing plants revealed an elevated risk of lymphoid leukemia confined to non-white females (SMR=5.9, 95%CI=0.7-21.5). Multiple myeloma did not seem to show the same gender/racial predilection, and was observed to be in excess among both sexes: white males (SMR=5.3, 95%CI=0.6-19.1), and white females (SMR=2.2, 95%CI=0.1-12.5). A cohort mortality study (Eric S. Johnson et al., 2010 (a)) involving poultry workers from five states who worked in poultry slaughtering/processing plants showed an excess risk of many cancers, including tumors of the hematopoietic system. *Killing of chickens* was associated with a significantly elevated risk of lymphoid leukemia (SMR=7.7, 95%CI (1.6-22.5)). The risk of mortality from multiple myeloma was observed to be restricted to non-whites, and monocytic leukemia to females. An update (Eric S Johnson et al., 2010 (b)) of the previously studied mortality study in the Missouri poultry cohort (Netto & Johnson, 2003) reported an excess rate of deaths from leukemia of unspecified cell type (SMR=245, 95%CI=112-465).

As was the case with meat workers, all of the cohort studies described above were retrospective mortality studies that were useful in determining whether there was an overall excess cancer risk in these workers, but not suitable for identifying specific occupational as well as non-occupational cause(s) contributing to this excess risk. The cohort mortality studies conducted by Johnson et al used job titles and departments as surrogate measures of exposure, except in the case of one exposure – *killing chickens*. Another limitation imposed by employing a retrospective cohort design, noted especially in those studies conducted by Johnson et al, is that they were unable to take into account duration of exposure because they relied on incomplete information derived from past records.

Case-control studies. A nested case control study conducted by Metayer et al (1998) revealed a nearly threefold risk of mortality from all hematopoietic cancers among poultry workers exposed to raw poultry meat (OR=3, 95%CI=0.7-13.5) or involved in the killing of chickens (OR=2.8, 95%CI=0.4-21.5). The highest risk of lymphomas was observed among workers in the slaughtering plants; a lower risk of lymphomas was observed among meat cutters who did not engage in the specific activities of killing and dressing. In fact, killing and dressing are the only two activities that are exclusive to slaughtering plants. These activities are known to impose the highest exposure to oncogenic viruses, such as avian leukosis/sarcoma virus. Taken together with the findings of the studies that follow, it may be suggested that oncogenic viruses potentially play a role in the risk of developing lymphomas. Lymphomas were previously found to be the most common cancer among those workers who were involved in killing (E S Johnson et al., 1986b). A multicenter case control study conducted in Europe (Moore et al., 2007) investigated the risk of lymphoma among workers exposed to meat

and poultry. Exposure to chicken meat was associated with significant risk of multiple myeloma – OR=2.05, (95%CI=1.14-3.69) that increased to OR=2.43,(95%CI=1-5.91) after 16 years of exposure. The second most common cancer reported among workers exposed to chicken meat was chronic lymphocytic leukemia, with an OR=1.55, 95%CI=1.01-3.67 that increased to OR=2.06, 95%CI=1.17-3.63 following 16 or more years of exposure.

The case-control studies described above have been limited by either small sample size, or, in the case of Moore et al, by examining only one histologic sub-type. In addition, almost all studies have employed either a cohort or a case-control design to examine this association. This is with the exception of a very small study that focused primarily on meat workers and not poultry workers (Metayer et al., 1998) that employed a nested case-control design. An important benefit that the case-cohort design offers over the traditional cohort study is the efficiency it provides, since covariate information needs to be obtained only among a random sample of the baseline cohort and those individuals who experience the outcome of interest (cases). This is in contrast to a cohort study, wherein covariate information is collected on every individual of the cohort (many of whom do not experience the outcome, especially when the disease is rare) (Wacholder, Silverman, McLaughlin, & Mandel, 1992). The other advantage of utilizing this design versus a basic case-control study is that selection bias is minimized since controls are randomly selected from the same population that gives rise to the cases. Moreover, the case-cohort approach allows efficient testing of associations with multiple health outcomes. In the conventional case-control approach, a control group would have to be selected for each case group, whereas the case-cohort design allows the investigator to use one comparison group repeatedly (Checkoway, Pearce, & Kriebel, 2007). Finally, the design of this

study as a case-cohort also allows for a direct estimation of the risk ratio in the base population without having to employ a full cohort investigation, thereby conserving resources and time (Wacholder et al., 1992).

CHAPTER 3. METHODOLOGY

The present study used a subset of the data acquired as part of a parent study, which employed a retrospective cohort mortality design. The parent study revealed an excess of cancers deaths at 11 different anatomical sites, including hematopoietic malignancies. These studies were conducted in cooperation with the United Food and Commercial Workers International Union (UFCW). Occupational exposures were investigated in workers formerly employed in poultry slaughtering/processing plants.

Over the five years during which I was immersed in this project, I interviewed the next-of-kin of those who lost a family member to hematopoietic cancer as well as other malignancies that were found to be in excess in the parent study. Exposure information gathered pertaining to lung, liver, and pancreatic cancers culminated in two publications (Felini et al., 2011, 2012), with information pertaining to hematopoietic malignancies pending the same level of investigation. What follows is a condensed version of the parent study to provide the necessary context, as well as information regarding the base cohort and the construction of the sub-cohort.

Parent Study: Retrospective Cohort Mortality Study Methods

The source population consisted of 47,400 individuals who were members of UFCW local unions at any time between July 1, 1949 and December 31, 1989. The start date of follow-

up was the date of receipt of the first union dues payment for each individual or 1949, whichever came first. The study population was derived from the three cohorts of workers employed in poultry slaughtering/processing plants: 1) The Baltimore cohort; 2) the Missouri cohort; and 3) the Pension Fund cohort. All three cohorts belong to the United Food & Commercial Workers (UFCW) International Union, which is headquartered in Washington, DC.

The Baltimore Cohort consisted of 2,580 subjects who worked in six poultry slaughtering/processing plants between 1954 and 1979, and were members of a local union in Baltimore, Maryland known as the Baltimore Meatcutters' Union - Local 27. The Missouri cohort consists of 7,700 workers from five poultry slaughtering/processing plants who were members of a local poultry union in Missouri. The Pension Fund cohort, which drew their membership from a geographically wide area of the United States, consisted of 20,712 poultry workers from 11 plants belonging to six UFCW local unions. These plants were located in six states distributed as follows: Three from Louisiana, three from Maine, three from Arkansas, and one each from Missouri, Arizona, and Texas.

For comparative purposes, mortality was also investigated in a group of 16,408 non-poultry workers belonging to two of the union cohorts (6,052, Baltimore; 10,356 Pension Fund). This heterogeneous group of workers was employed exclusively by companies that were involved in the processing and packaging of items other than meat products, such as soft drinks, fish, eggs, milk, and fertilizer.

It was the practice for these unions to keep records even for subjects who were members for only a few days. These records were saved, and it was found that all persons who

completed an application slip also had a record of dues payment. Thus, for the cohort study, a total of 30,992 poultry slaughtering/processing plant workers and 16,408 subjects who worked in non-poultry companies, providing a total study population of 47,400 subjects, constituted the study population.

Deceased members of the cohort were identified by searches of: (1) current union records, (2) Social Security Administration Mortality Files, (3) State Department of Vital Records, (4) motor vehicle registration records, (5) US Postal Service records, (6) Credit Bureaus, (7) direct contact by letter or telephone, (8) Pensions Benefit Information (PBI), (9) the National Death Index (NDI), (10) Veterans Administration (VA), (11), Internet Tracing Services (Public Eye and Ancestory.com), and (12) the Health Care Financing Administration (HCFA).

Vital status was also determined matching the 47,400 union members with records in PBI and NDI. PBI is a private research company that provides death audit information from a combination of public and private data such as the Social Security Administration, Civil Service Commission, Retirement Boards, and state agencies ("Pension Benefit Information Participant Research Service", 2007). NDI, a branch of the National Center for Health Statistics, is a computerized index of death record information submitted by state vital statistics offices for all recorded deaths occurring in the US, beginning with deaths occurring in 1979 (What is NDI?, 2007). The method of matching in PBI relies chiefly on the social security number as the matching criteria, whereas NDI uses a twelve criteria algorithm. NDI matching is a modification of probabilistic approaches developed by Fellegi and Sunter (1969) that assumes the matching algorithm is conservative and will result in limited false non-matches. Of the 47,400 subjects

from the parent study, there were 5,656 deaths identified by PBI and NDI from January 1, 1990 through December 31, 2003, with the cause of death being unknown for 399 of the deceased. To obtain information on the reliability of responses from proxies, the questionnaire was administered to a small subset of seven pairs of live control study subjects and their next-of-kin. The next-of-kin of deceased subjects in the subcohort were interviewed while live subjects were interviewed directly.

Based on the previous mortality findings derived from studies conducted within the Baltimore (E. S. Johnson, Fischman, Matanoski, & Diamond, 1986a) and Missouri cohorts (Netto & Johnson, 2003), cancers of the lung, esophagus, colon, rectum, liver, pancreas, brain, kidney, bladder, bone, lymphoid & hematopoietic systems, and buccal cavity and pharynx occurred in excess in these cohorts. Subsequently, case cohort studies were conducted among lung, pancreatic, liver, and brain deaths to acquire detailed information on individual exposures and possible confounding factors among deceased subjects. I conducted a case-cohort study to provide insight into which specific occupational exposures and non-poultry related occupational tasks may be associated with increased mortality from hematopoietic cancer.

Current Study: Case Cohort Study Methods

Study population. The base population from which cases and controls (the subcohort) will be derived consists of a subset of the total of 47,400 subjects who were studied in the cohort mortality study described above. This subset consists of N= 43,904 subjects out of the 47,400 who were alive as of 01/01/1990, constituting the base population of this study that was followed up from January 1, 1990 until December 31, 2003. Since no new subjects were

added after January 1, 1990, and all the 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.

There were a total of 1,218 cases of death from cancers identified from the case cohort study, which occurred between 01/01/1990 and 12/31/2003; however, attempts were made to trace only 1,126 who had death certificate information. Since all cases were deceased, their next-of-kin provided the interviews for the cases.

The control group, henceforth referred to as the subcohort, was a random sample of all subjects alive on 01/01/1990. Two random samples of 1,000 each were selected about one year apart, making a total of 2,000 subjects randomly chosen. When duplicates were removed, the number reduced to 1,525, consisting of both live and dead persons. The next-of-kin of deceased study subjects were traced by death certificates, internet methods such as Public Records Now (Private Eye), Ancestry.Com, using the computerized Power Finder telephone directory, and other methods, such as Polk Directory and Equifax Credit Bureau records.

Each study subject was assigned a unique identification number that was entered into a computer file along with demographic information obtained from the subject's death certificate. The subject's next-of-kin, as listed on the death certificate, was then traced using a wide ranging system of tracing techniques including searches of: Union Medical & Pension Fund Records, State Departments of Motor Vehicles, Social Security Administration, Credit Card Bureaus, Telephone Directories, ProPhone & PhoneDisc, (computerized data bases of names, telephone numbers and address of telephone subscribers nation-wide) and Private Eye &

Ancestory.com (web-based databases). If the next-of-kin listed on the death certificate did not want to participate or was untraceable, other relatives or acquaintances listed on the death certificate were traced and asked to participate.

Exposure assessment. Information regarding exposure was collected from next-of-kin via telephone interviews conducted previously. The questionnaire was administered to the next-of-kin using a computer-assisted telephone software, Questionnaire Development System (NOVA Research Company, Bethesda, Maryland), containing over 600 comprehensive questions regarding the subject's work in the poultry industry, their history of exposures at work, medical history, and history of allergies, history of cancer, ionizing radiation, drug intake, diet history, and occupational history other than in the poultry industry. Oral consent was obtained prior to beginning the questionnaire. The questionnaire was detailed, and had 600 questions that took an average of 40–60 minutes to administer over the phone. It included demographic variables, including race, gender, date of birth, and date of death. A detailed list of questions (selected questions shown in the tables) regarding occupations and industries within each of the following major headings were asked in the questionnaire: (1) Occupational poultry-specific exposures, including unloading chickens from trucks, hanging chickens on conveyor lines, killing chickens, cutting carcasses, and packing chickens. Workers may be assigned to perform one task, or may perform different tasks over the course of their employment; (2) Mixed occupational poultry- and meat-related exposures; (3) Working on a farm; (4) Working in a seafood harvesting or processing plant; (5) Killing animals other than poultry for the purpose of consumption; (6) Applying agricultural chemicals at work (pesticides, herbicides); and (7)

Working in occupations and industries outside the poultry and meat industries. The risk associated with each job exposure was calculated for ever/never responses.

Outcome assessment. Cases were defined as deaths from all types of hematopoietic cancers (*International Classification of Diseases*, Ninth Revision, code 200, 202-208 or *International Classification of Diseases*, Tenth Revision, codes C82-C96) that occurred in the base population between January 1, 1990 and December 31, 2003. Over the course of two years, death certificates were collected to confirm that the primary cause of death was, in fact, a hematopoietic malignancy. The information provided on the death certificates were used to trace next-of-kin. Death certificates for the cancer cases were retrieved from various state departments of vital records to confirm cancer as the cause of death and to ascertain next-of-kin information. Controls, a sub-cohort that consisted of 1516 live subjects were randomly sampled from the base population, some of whom later died during the study period, were defined as the comparison group. The sub-cohort consisted of live and dead subjects at the time of sampling. The union distribution of the sub-cohort was as follows:

Table 3. Distribution of Sub-cohort by Union

Pension Fund	Baltimore	Missouri
1409	283	308

From the two random samples, 24 individuals happened to be sampled twice. The demographic variables for the sub-cohort group were restricted to information included in the union record (date of birth, gender, start date, end date) and gathered during the interview (race and smoking status). Age was calculated by subtracting the end of the study period,

December 31, 2003, from the date of birth. Survival since last employment was calculated by subtracting the end of study period from the end date of employment. All of the poultry worker comparison group members were alive at the time of interview, which was after the end of the study period. Of the 214 subjects in the sub-cohort (n=1516) who 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.

The demographic variables – date of birth, date of death, gender, race, highest grade completed, marital status, and state in which the death occurred – were extracted from the death certificates.

Statistical Analyses

Descriptive statistics (mean, frequency and percentages) of the sample were calculated to describe the characteristics of the cases and controls. Univariate analyses were also conducted to determine prevalence and missingness of all occupational task exposures. Baseline data from cases and controls were compared using chi-square for categorical variables to determine if there was a statistically significant difference for each of the variables between the two groups. Fisher's exact test was performed instead of the chi-square test, when 25% of the cells had an expected count of less than 5. Variables that were deemed significant were further assed for potential confounding. Bivariable and multivariable analyses were conducted to examine the relationship between specified a priori occupational task exposures and hematopoietic cancer mortality, with consideration given to confounding variables for the multivariable analysis. Based on *a priori* knowledge, age and union site were assessed as

potential confounders in the bivariate analyses. We did consider cigarette smoking as a potential confounder, but we did not have adequate data to assess for confounding. In the bivariate analysis, both variables (age and union site) were significantly different between cases and controls. Age was not found to be linear in the logit; hence, we used categorical age as a potential confounder. The categories of age were chosen based on a-priori knowledge. Confounding was evaluated using stratified analysis and by comparing the change in the main exposure effect (β estimate) between a model containing the confounder and one without the confounder (OR crude - OR adjusted/OR crude). Stratified analyses were conducted to explore stratum-specific risks and to determine if the crude risks were confounded and/or modified by covariates. In the stratified analysis, both age and union site had an impact on the main exposure disease measure of effect of greater than 10%. To simultaneously control for both the variables, model fitting was conducted to test for confounding.

Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression using the SAS LOGISTIC procedure (SAS 9.1, SAS Institute, Cary, NC). Because the control group was a random sample of the base population, the ORs obtained will be direct estimates of the risk ratio (RR) without the need for the rare disease assumption (Wacholder, Silverman, McLaughlin, & Mandel, 1992).

Since time to event information was available, I also used the Cox regression analysis to estimate hazard ratios (HR) and 95% CI. In the Cox regression analysis, hazard ratios (HRs) were estimated using the SAS PHREG procedure. Subjects entered the study at their age on January 1, 1990, (time variable) and the failure time for formation of a risk set was the

difference between their ages at this point in time and their ages at the time of a hematopoietic cancer related death. At failure time, a risk set was formed consisting of the *case and all available controls at risk at that time*. All failures were included, regardless of whether they occurred in the sub-cohort or not. A case outside of the subcohort was not at risk until just before its failure, and therefore was not included in the earlier risk sets. All variables were tested to determine whether they satisfy the proportional hazards assumptions. I tested this assumption by checking the significance of the interaction term between the covariate and time. A significant interaction would imply that the hazard function was not met.

Methodological Considerations

Missing information. I had anticipated missingness to be a challenge. However, when I began my analysis, I found that less than 5% of data was missing for my main exposures. Thus, I did not have to utilize complete strategies, such as weighted complete case analysis or imputation, which would have been necessary if more than 20% of the data were missing (Armijo-Olivo, Warren, & Magee, 2009; Horton & Kleinman, 2007).

Multiple comparisons. The Bonferroni correction was initially considered in my analysis to reduce type 1 errors. Bonferroni corrections are employed to reduce Type I errors (i.e., rejecting H_o when H_o is true) when multiple tests or comparisons are conducted (Bland & Altman, 1995). In order to avoid an inordinate number of spurious positives, the α value is lowered to account for the number of comparisons being performed. The simplest and most conservative approach is the Bonferroni correction, which will set the α value for the entire set of *n* comparisons equal to α by making the α value for each comparison equal to α /*n*.

For a priori comparisons, which are chosen before the data are analyzed, the Fishers protected approach may be utilized to protect against the issue of type 1 errors from multiple comparisons (Carmer, S. G., & Swanson, M. R. (1973). In regards to specific aim 1, since all eleven of my poultry-related occupational exposures for my primary aim were stated a priori, I utilized this approach. For my second specific aim, the specific exposures were not stated a-priori, thus a Bonferroni correction was utilized, generating an alpha value of 0.9965 {1- (0.05 / (7*2)) =0.9965}. With an alpha value 0.9965, none of the exposures from specific aim 2 were deemed statistically significant.

Chapter 4. Results

One hundred fifty-two deaths (cases) from hematopoietic cancer occurred in this cohort between January 1, 1990 and December 31, 2003. We were able to contact the next-of-kin in 61 out of 94 cases for whom next-of-kin information was listed on the death certificates. We report here on the first 48 of the 61 cases whose next-of-kin were traced. Because this was a pilot study, exhaustive attempts were not made to trace individuals. We relied mainly on telephone directories, death certificate information, and web-based methods of tracing to locate individuals. Of the 61 next of kin traced, 48 agreed to participate in the phone interview, yielding a next-of-kin participation rate of 79% (48/61).

Descriptive Analyses

Cases Demographics. Table 1 displays the frequency and proportion of the 48 hematopoietic cancer cases. The average age of death was 65 years, ranging from 36-90 years old at the time of death. Among the cases, there were an equal number of males as well as females (50%). The majority of cases were white (88%). We did not have information pertaining to race for three of the cases. The majority of the cases that were interviewed came from the Chicago Pension Fund cohort (75%), followed by the Missouri and Baltimore cohorts (10% and 15%, respectively). Sixty-seven percent of cases were reported to have previously worked in poultry plants.

Control Demographics. In the sub-cohort, a total of 152 workers were interviewed. They were included in the analysis as a comparison group to the hematopoietic cancer cases. The average age at the time of interview was 57 years, ranging from 38 to 96 years old. The respondents were primarily female (57%). The highest response rate was from whites (71%). Information on race was not available for 17% of the controls. The majority of interviewed controls came from Chicago Pension fund (75%), followed by the Baltimore and Missouri cohorts (24 and 1%, respectively). Of the interviewed controls, 0.78% had previously worked in poultry plants. There were 7 controls that had died before they were interviewed. Next-of-kin were interviewed instead.

Cases versus Controls Characteristics. Cases were compared to controls using chi-square tests on demographic characteristics as well as employment and union status. A significant difference was observed between cases and controls for age and union status. With regard to race, the majority of respondents were white, 88% for cases and 71% for controls (χ^2=

2.67, $p > 0.05$). There was a significant difference in age between cases and controls. Controls tended to be younger than cases, with 40% of them being ≤50 years compared to only 19% among cases ($\chi^2 = 7.99$, $p = <0.005$). The response rate among males was marginally higher than among females (50% and 42%, respectively) ($\chi^2 = 1.67$, $p > 0.05$). Insofar as poultry status, a greater number of controls had worked in the poultry industry compared to cases ($\chi^2 = 2.19$, $p > 0.05$). There was a significant difference in union status between cases and controls ($\chi^2 = 10.75$, $p <0.05$). The majority of cases and controls were from the Chicago cohort (75% and 78%, respectively).

Table 4. Baseline demographic distribution of hematopoietic cancer cases and controls in the combined cohort of poultry and non-poultry United Food & Commercial Workers Union Workers, 1990-2003

Characteristic	Cases, *N*(%)	Controls, *N*(%)	χ^2
Race			2.67
White (%)	42 (88)	108(71)	
Black (%)	3(6)	27(18)	
Unknown (%)	3	17(11)	
Total	48	152	
Gender			1.67
Female (%)	24(50)	87(57)	
Male (%)	24(50)	64(42)	
Unknown (%)	0	1 (0.7)	
Total	48	152	
Age[£]			7.99*
≤ 50 yr (%)	9 (19)	61(40)	
≥ 50 yr (%)	3 9 (81)	87(57)	
Unknown	0	4(3)	
Total	48	152	
Type of Worker			2.19
Poultry (%)	32 (67)	118 (78)	
Non-poultry (%)	16 (33)	34 (22)	
Total	48	152	
Union Status			10.79*
Chicago (%)	35 (75)	113 (78)	
Missouri (%)	5 (10)	2 (1)	
Baltimore (%)	7 (15)	36 (24)	
Unknown (%)	1 (0)	1 (1)	
Total	48	152	

*$p < .05$; [£]Cases (age at death); Control (age at time of interview)

Specific Aim 1

To identify specific occupational task exposures within the poultry industry associated with increased risk of hematopoietic cancer mortality among poultry workers.

Crude Odds Ratios. In the crude analyses (Table 4), the highest risk for hematopoietic cancer among poultry workers was among those who worked in stockyards (OR= 4.04, 95%CI: 0.54, 30.10). Working as a poultry farmer (OR=2.67, CI: 0.78, 9.23) and spreading chicken waste

as manure (OR= 2.50, CI: 0.83, 7.43) were associated with more than a twofold risk of dying from hematopoietic cancer. Handling raw eggs at a grocery store (OR=1.47, CI: 0.36, 5.93), working in a place where feathers were handled (OR= 1.30, CI: 0.51, 3.24), and having direct contact with poultry blood (OR= 1.20, CI: 0.60, 2.40) were all tasks associated with an elevated risk of hematopoietic cancer mortality. Other poultry related tasks, such as killing chickens, handling raw poultry at work, and the use of a wrapping machine, were not associated with an excess risk of hematopoietic cancer mortality.

Adjusted Odds Ratios. After controlling for the two confounders, age and union status, the greatest change in the measure of effect was for the following two exposures: killed chickens at work (OR= 1.35, CI: 0.26, 7.14), and handling raw eggs at a supermarket (OR= 2.24, CI: 0.05, 9.78, Table 4). For both of these exposures, the difference in the adjusted and crude estimates was greater than 40%. For the other exposures, the effect estimate changed by approximately 20%, except for handling raw poultry at work (OR= 0.61, CI: 0.31, 1.22) and working in a place where feathers were handled (OR= 1.38, CI: 0.50, 3.76), where adjustment did not have much bearing on the effect estimates. It is noted that estimates crossed the null when adjusted for age and union status for killing chickens and working in a plant where poultry was slaughtered.

Table 5. Crude and Adjusted Odds Ratios for Occupational Task Exposures and Hematopoietic Cancer Mortality for Poultry Associated Occupational Task Exposures, 1990-2003

Exposure	Crude OR (95% CI)	Adjusted OR (95% CI)*
Worked in a stockyard	4.04 (0.54-30.10)	4.50 (0.34-59.88)
Smoking meat at work	3.42 (0.47-24.98)	3.10 (0.40-22.27)
Worked as a poultry farmer	2.67 (0.78-9.23)	3.06 (0.97-9.63)
Spread chicken/bird wastes as manure	2.50 (0.83-7.43)	2.00 (0.58-6.89)
Handle raw eggs in grocery stores or supermarkets plant	1.47 (0.36-5.93)	2.24 (0.05-9.78)
Work in a place where chicken/bird feathers were handled	1.30 (0.51-3.24)	1.38 (0.50-3.76)
Had direct contact with poultry blood	1.20 (0.60-2.40)	1.40 (0.66-2.95)
Work in a plant where poultry was slaughtered	0.94 (0.37-2.41)	1.13 (0.36-3.45)
Killed chickens/birds at work	0.94 (0.18-4.67)	1.35 (0.26-7.14)
Contact or handle raw poultry at work	0.61 (0.31-1.22)	0.63 (0.30-1.30)
Wrap raw chicken/bird using wrapping machine	0.46(0.13-1.64)	0.58 (0.24-1.40)

* Adjusted for categorical age and union site

To account for time exposed to each occupational task, additional analyses were conducted using hazard ratios. In the crude analyses, poultry workers that worked in stockyards had the highest rate of dying from hematopoietic cancer (HR= 3.15, CI: 0.74, 13.38, Table 5). Poultry workers who smoked meat (HR= 3.42, CI: 0.60, 10.2), worked as a poultry farmer (HR= 2.29, CI: 0.96, 5.48), and spread chicken waste as manure (HR= 2.46, CI: 1.03, 5.84) had more than a twofold rate of mortality from hematopoietic cancer. Working in a place where feathers were handled (HR= 1.54, CI: 0.65, 3.62), handling raw eggs at a grocery store (HR= 1.35, CI: 0.42, 4.36), working in a place where poultry was slaughtered (HR= 1.09, CI: 0.95 – 2.62), and direct contact with poultry blood (HR= 1.06, CI: 0.56, 1.97) were tasks associated with a more

modest increase in rate of mortality from hematopoietic cancer. Spreading bird waste as manure was the only exposure that was statistically significant at the 0.05 level. Other poultry related tasks, such as killing chickens, handling raw poultry at work and using the wrapping machine, were not associated with an increased rate of hematopoietic cancer mortality.

After adjustment for age and union status, highest risks remained for working in stockyard, smoking meats at work, and working as poultry farmer compared to crude estimates. The greatest change in the measure of effect was for the following two exposures: killed chickens at work (HR= 1.11, CI: 0.27, 4.61) and handling raw eggs at a supermarket (HR= 1.66, CI: 0.51, 5.42). For both exposures, the difference in the adjusted and crude estimates was greater than 20%. The exposures for which the effect estimates had less than a 10% change after adjustment were direct contact with poultry blood (HR= 1.10, CI: 0.58, 2.05), working in a plant where poultry was slaughtered (HR= 1.10, CI: 0.58, 2.05), and working in a stockyard (HR= 3.10, CI: 0.94, 10.13).

Table 6. Crude and Adjusted Hazard Ratios for Occupational Task Exposures and Hematopoietic Cancer Mortality for Poultry Associated Occupational Task Exposures, 1990-2003

Exposure	Crude HR (95% CI)	Adjusted HR (95% CI)*
Smoking meat at work	3.42 (0.46-24.99)	3.10 (0.40-24.27)
Worked in a stockyard	3.15 (0.74-13.38)	3.10 (0.94-10.13)
Spread chicken/bird wastes as manure	2.46 (1.03-5.84)£	2.56 (1.10-6.11)£
Worked as a poultry farmer	2.29 (0.96-5.48)	2.36 (0.98-5.64)
Work in a place where chicken/bird feathers were handled	1.54 (0.65-3.62)	1.57 (0.65-3.79)
Handle raw eggs in grocery stores HR supermarkets plant	1.35 (0.42-4.36)	1.66 (0.51-5.42)
Worked in a plant where poultry was slaughtered	1.09 (0.95-2.62)	1.10 (0.58-2.05)
Had direct contact with poultry blood at work	1.06 (0.56-1.97)	1.10 (0.58-2.05)
Killed chickens/birds at work	0.95 (0.23-3.90)	1.11 (0.27-4.61)
Contact HR handle raw poultry at work	0.57 (0.31-1.06)	0.56 (0.30-1.05)
Wrap raw chicken/bird using wrapping machine	0.51 (0.16-1.65)	0.56 (0.17-1.85)

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

Specific Aim 2

To identify specific non-poultry related occupational tasks associated with increased risk of hematopoietic cancer mortality among poultry workers.

Crude odds ratio. In the crude analyses, workers who sold seafood had the highest risk of hematopoietic cancer mortality (OR= 5.58, CI: 1.50 – 20.74). Exposure to coal tar and other gases was associated with more than a fourfold risk of dying from hematopoietic cancer (OR= 4.48, CI: 1.52, 13.16). Slaughtering pigs was associated with nearly a fourfold risk of hematopoietic cancer mortality (OR= 3.74, CI: 1.31, 10.61). Workers who sprayed insecticides

on a farm had greater than a twofold risk of mortality from hematopoietic cancer (OR= 2.68, CI: 0.80, 8.94). Working on a dairy farm (OR= 1.91, CI: 0.66, 5.48) and working on a farm where animals other than poultry were raised for commercial purposes (OR= 1.91, CI: 0.79, 4.59) were associated with an elevated risk of hematopoietic cancer mortality. Working at a gasoline station was another occupational task associated with increased cancer mortality (OR= 1.19, CI: 0.51, 3.24) (Table 6).

Adjusted odds ratios. After controlling for the two confounders, age and union status, the greatest change in the measure of effect was for the following exposure: worked at a gas station (OR= 1.89, CI: 0.52, 6.96). There was a 59% change between the crude and adjusted estimates. Selling seafood showed a 33% change in effect estimate (OR= 4.31, CI: 1.08, 17.16). After adjustment, the change in effect estimate was approximately 25% for exposure to coal tar and other gases (OR= 5.63, CI: 0.61, 10.53), and slaughtering pigs (OR= 2.95, CI: 0.96, 9.11). Working on a dairy farm had the least change in effect estimate after controlling for age and union status (OR= 1.89, CI: 0.61, 5.67) (Table 6).

Table 7. Crude and Adjusted Odds Ratios for Non-Poultry Related Occupational Task Exposures and Hematopoietic Cancer Mortality, 1990-2003.

Exposure	Crude OR (95% CI)	Adjusted OR (95% CI)*
Sold seafood at work	5.58 (1.50-20.74)	4.31 (1.08-17.16)
Exposure to coal tar, turpentine, naphthalene, natural gas, paraffin, smoke	4.48 (1.52-13.16)£	5.63 (1.72-18.43)£
Killed pigs	3.74 (1.31-10.61)	2.95 (0.96-9.11)
Sprayed insecticides on a farm	2.68 (0.80-8.94)	3.03 (0.77-20.16)
Worked on a farm where animals other than poultry were raised for commercial purposes	1.91 (0.79-4.59)	2.21 (0.87-5.63)
Worked on a dairy farm	1.91 (0.66-5.48)	1.89 (0.61-5.67)
Worked at gasoline station, gasoline storage facility	1.19 (0.36-3.92)	1.89 (0.52-6.96)

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

Crude hazard ratios. In the crude analyses, workers who sold seafood had the highest rate of hematopoietic cancer mortality (HR= 3.49, CI: 1.47, 8.30). Slaughtering pigs was associated with a nearly a threefold increased rate of hematopoietic cancer mortality (HR= 2.94, CI: 1.37, 6.35). Exposure to coal tar and other gases as well as spraying insecticides were associated with greater than a twofold rate of dying from hematopoietic cancer [(HR= 2.52, CI: 1.12, 5.67) and (HR= 2.28, CI: 0.89, 5.81), respectively]. Working on a dairy farm as well as working on farms where animals other than poultry are raised was associated with an increased rate of hematopoietic cancer mortality as well. The three exposures that were associated with a statistically significantly elevated rate of hematopoietic cancer mortality were exposure to coal tar, slaughtering pigs, and selling seafood (Table 7).

Adjusted hazard ratios. After controlling for the two confounders, age and union status, the greatest change in the measure of effect was for the following exposure: worked at a gas station (HR= 1.68, CI: 0.58, 4.89). There was a 35% change between the crude and adjusted estimates. For those tasked with spraying insecticides on a farm, the association was statistically significant (HR= 2.79, CI: 1.07, 7.26). Working on a farm where animals other than poultry were raised (HR= 1.96, CI: 0.93, 4.12) and slaughtering of pigs (HR= 2.71, CI: 1.26, 5.86) showed the least change between crude and adjusted estimates (Table 7).

Table 8. Crude and Adjusted Hazard Ratios for Non-Poultry Related Occupational Task Exposures and Hematopoietic Cancer Mortality, 1990-2003

Exposure	Crude HR (95% CI)	Adjusted HR (95% CI)*
Sold seafood at work	3.49 (1.47-8.30)	2.93 (1.26-5.86)
Killed pigs	2.94 (1.37-6.35)	2.71 (1.26-5.86)
Exposure to coal tar, turpentine, naphthalene, natural gas, paraffin, smoke	2.52 (1.12-5.67)	2.85 (1.26-6.46)
Sprayed insecticides on a farm	2.28 (0.89-5.81)	2.79 (1.07-7.26)
Worked on a dairy farm	1.81 (0.76-4.27)	1.70 (0.72-4.04)
Worked on a farm where animals other than poultry were raised for commercial purposes	1.76 (0.84-3.96)	1.96 (0.93-4.12)
Worked at gasoline station, gasoline storage facility	1.24 (0.44-3.46)	1.68 (0.58-4.89)

* Adjusted for categorical age and union site

Specific Aim 3

To determine whether risk of mortality differs by histologic subtype for poultry related occupational tasks. Only crude estimates were calculated due to small numbers.

Crude odds ratio. The crude odds ratios observed in Table 8 for specific poultry related tasks have been stratified by histologic subtype. There were a total of 23 leukemia cases, 16 lymphoma cases, and 9 multiple myeloma cases. *Killing chickens* was associated with leukemia (OR= 1.12, CI: 0.13, 9.38). All three subtypes show a slightly elevated risk of mortality associated with contact with blood. Contact with poultry blood, working in plants where poultry were slaughtered, and spreading chicken waste as manure were associated with higher risks of death from lymphoma compared to leukemia and multiple myeloma. Conversely, working in place where feathers were handled was associated with death from multiple myeloma compared to the other two subtypes.

Working as a poultry farmer was significantly associated with a nearly 11-fold risk of mortality from lymphomas (OR= 10.82, CI: 2.98, 39.13). Working in a plant where poultry was slaughtered showed an estimate below the null for combined hematopoietic cancer mortality (OR= 0.94, CI: 0.37, 2.41). However, when stratified by subtype, lymphomas were the only subtype associated with an elevated risk (OR= 1.37, CI: 0.26, 7.12). Handling of raw eggs was associated with an increased risk in leukemias (OR= 4.26, CI: 1.01, 18.00). Smoking meat at work was found to be associated with both leukemias (OR= 3.00, CI: 0.30, 30.29) and lymphomas (OR= 4.19, CI: 0.41, 42.97).

Table 9. Crude Odds Ratios for Poultry-Related Occupational Task Exposures and Hematopoietic Cancer Mortality by Histologic Subtype, 1990-2003

	Leukemia	*Lymphoma*	*Multiple Myeloma*
	OR (95% CI) N=23	*OR (95% CI) N=16*	*OR (95% CI) N=9*
Killed chickens/birds at work	1.12 (0.13-9.38)		
Had direct contact with poultry blood	1.03 (0.38-2.74)	1.41 (0.50-3.96)	1.06 (0.24-4.56)
Worked as a poultry farmer		10.82 (2.98-39.13)	1.83 (0.21-15.80)
Worked in a plant where poultry was slaughtered	0.65 (0.17-2.45)	1.37 (0.26-7.12)	0.89 (0.58-1.84)
Contacted or handled raw poultry at work	0.58 (0.22-1.53)	0.80 (0.28-2.23)	0.61 (0.14-2.64)
Worked in a stockyard	3.48 (0.33-36.40)	5.67 (0.52-61.72)	
Spread chicken/bird wastes as manure	0.61 (0.07-4.86)	5.59 (1.53-20.43)	1.54 (0.18-13.17)
Worked in a place where chicken/bird feathers were handled	0.67 (0.16-2.71)	1.66 (0.39-6.97)	2.50 (0.40-15.54)
Wrapped raw chicken/bird using wrapping machine	0.41 (0.05-3.22)	0.47 (0.05-3.76)	0.86 (0.10-7.18)
Handled raw eggs in grocery stores or supermarkets plant	4.26 (1.01-18.00)		
Smoked meat at work	3.00 (0.30-30.29)	4.19 (0.41-42.97)	

Crude hazard ratios. In the crude analyses, killing chickens was increased rate of mortality from leukemia (HR= 1.11, CI: 0.15, 8.28), which was different from the crude hazard ratio when the subtypes were combined (HR= 0.95, CI: 0.23, 3.90), showing a slightly protective effect. Poultry farmers had 6.71 times the rate of dying from lymphomas (HR= 6.71, CI: 2.21, 20.74), compared to 2.01 times the rate of dying from multiple myeloma (HR= 2.01, CI: 0.26,

16.71). We saw an increased risk in mortality from lymphomas associated with slaughtering of poultry (HR= 1.36, CI: 0.28, 6.76). Handling of raw eggs was shown to have an increased rate of mortality from leukemias (HR= 3.37, CI: 0.98, 11.56). Smoking meat at work was associated with a nearly fourfold rate of mortality from lymphomas compared to a nearly threefold rate of mortality from leukemias. The only associations significant at the 0.05 level was that between lymphoma and working as a poultry farmer (HR= 6.71, CI: 2.21 –20.33) and between lymphomas and spreading bird waste as manure (HR= 5.75, CI: 1.79 – 18.37).

Table 10. Crude Hazard Ratios for Poultry-Related Occupational Task Exposures and Hematopoietic Cancer Mortality by Histologic Subtype, 1990-2003.

	Leukemia HR (95% CI) n=23	Lymphoma HR (95% CI) n=16	Multiple Myeloma HR (95% CI) n=9
Killed chickens/birds at work	1.11 (0.15-8.28)		
Had direct contact with poultry blood	0.88 (0.33-2.34)	1.28 (0.47-3.47)	1.07 (0.26-4.46)
Worked as a poultry farmer		6.71 (2.21-20.33)	2.01 (0.26-16.71)
Worked in a plant where poultry was slaughtered	0.89 (0.22-3.55)	1.36 (0.28-6.76)	0.88 (0.16-4.82)
Contacted or handled raw poultry at work	0.46 (0.17-1.22)	0.72 (0.27-1.94)	0.54 (0.13-2.27)
Worked in a stockyard	3.71 (0.47-29.02)	5.75 (0.69-47.84)	
Spread chicken/bird wastes as manure	0.82 (0.11-6.13)	5.75 (1.79-18.37)	1.94 (0.24-15.56)
Worked in a place where chicken/bird feathers were handled	0.85 (0.21-3.40)	2.23 (0.50-9.98)	2.53 (0.42-15.16)
Wrapped raw chicken/bird using wrapping machine	0.41 (0.05-3.12)	0.50 (0.07-3.82)	0.78 (0.10-6.12)
Handled raw eggs in grocery stores or supermarkets plant	3.37 (0.98-11.56)		
Smoked meat at work	2.84 (0.38-21.32)	3.75 (0.49-28.64)	

Chapter 5. Discussion

The first aim of this study was to identify specific occupational task exposures within the poultry industry associated with increased risk of hematopoietic cancer mortality. The eleven task-specific exposures on which we focused were selected based on their established carcinogenic potential in the context of hematopoietic cancer mortality. We did, in fact, find an increased risk of hematopoietic cancer mortality associated with nine of the eleven task-specific exposures that we investigated. We compartmentalized our questions into three main subheadings due to the heterogeneous nature of these exposures, and informed by previous studies that have shown them to be the main categories of carcinogenic exposure in the poultry industry (Felini et al., 2012; Eric S. Johnson, Ndetan, & Lo, 2010; Metayer, Johnson, & Rice, 1998): (1) oncogenic viruses, (2) polycyclic aromatic hydrocarbons (PAHs) emitted during the smoking of poultry, and (3) benzene, phthalate, and PAH fumes emanated during the wrapping of poultry.

Exposure to Oncogenic Viruses

Our previous cohort mortality study observed excess mortality rates for hematopoietic cancers in this poultry population (E S Johnson et al., 1997; Netto & Johnson, 2003). Considering their job exposure tasks, I hypothesized that exposure to oncogenic viruses might explain this excess. The most plausible and direct route of transmission for oncogenic viruses is through blood related exposures. Forty percent of our study population had been exposed to poultry blood.

Poultry workers who had *direct exposure to poultry blood* were at higher risk of death due to hematologic cancer (adjusted OR = 1.40), but not significantly so. Our findings are in line with a case-control study conducted by Fritschi et al (2003), which reported that the risk for acquiring hematopoietic cancers was twice as high in 24 workers exposed to high levels of animal blood, inclusive of poultry and red meat, after adjustment for age. However, with regard to histologic subtypes, we discovered that the increased risk of mortality among poultry workers exposed to blood was largely attributable to lymphomas, supporting findings by Metayer et al (1998), the only other study that examined this association by subtype.

In this investigation, *working in a poultry slaughtering plant* resulted in a crude odds ratio of 0.94. However, when adjusted for age and union status, it crossed the null (OR = 1.13). This estimate differed from a previous nested case-control study of 16 workers that observed more than a threefold risk (OR = 3.3) of hematopoietic cancer mortality associated with working in the same setting after matching for race, gender, and age (Metayer et al, 1998). One of the contributing factors to the lower risk estimates in our study was the relatively higher proportion of controls that were involved in this activity (27%) compared to 1% in Metayer et al's study (1998).

We did not observe any risk associated with *killing chickens* in our crude estimate (0.94). However, after adjusting for confounders, we noted a 35% non-significant increased risk of hematopoietic cancer mortality, (OR = 1.35). Less than 10% of cases engaged in this activity. Of the three histologic subtypes, leukemia was the only one for which there was enough to data to assess for this association, which showed a moderate elevated risk (crude OR = 1.12).

Considering that poultry workers come into contact with several hundreds or even thousands of poultry species that are slaughtered daily (E S Johnson et al., 1997), exposure to animal blood increases their risk of infection from virulent oncogenic agents, (E S Johnson et al., 1997). The only three studies to date that have investigated occupational exposure risks in the poultry industry and their association with hematologic malignancy mortality only examined contact with poultry meat rather than the slaughtering process (Fritschi et al., 2003; Metayer et al., 1998; Moore et al., 2007). Moreover, Metayer et al (1998) focused primarily on non-poultry meat workers, and used a far less exhaustive questionnaire. In addition, the case-control studies conducted by Fritschi and Moore have been limited by both a small sample size, and singular focus on only one histologic subtype of hematopoietic cancer. Thus, we have no firm basis for comparison.

Oncogenic viruses can also be transmitted through additional secretory and excretory exposures. In our study, the occupational task exposure associated with the highest risk of hematopoietic tumor mortality was *working in a stockyard*. This task was associated with non-significant increased risk of mortality, even after controlling for confounding factors (OR = 4.50). Stockyard workers are constantly exposed to the bodily fluids of poultry and other animals, including blood and fecal matter, secondary to their regular interaction with livestock and employment in kill/dress areas of the stockyard. These activities are believed to be associated with high exposure to zoonotic microbial agents, including oncogenic poultry, cattle, pig and sheep viruses (Metayer et al., 1998). This may explain the twofold increased risk of hematopoietic cancer mortality among poultry workers who *spread chicken waste as manure*. When time to event was taken into consideration, a statistically significant hazard ratio was

observed for *spreading chicken waste,* even after controlling for confounders (HR= 2.56).

After stratifying by histologic subtype, *working in a stockyard* was associated with an increased risk of mortality from leukemia and lymphomas. We lacked sufficient data to assess for an association with multiple myeloma. These results support the findings of a nested case control study that reported an excess mortality risk of leukemia among meat and poultry workers working in a stockyard (Metayer et al., 1998). Other case-cohort studies of lung, liver, and pancreatic cancer using our cohort have observed a similar increased risk of cancer mortality among poultry workers employed in stockyards (Felini et al., 2011, 2012).

One of the unique findings of our study was the increased risk observed between *handling of raw eggs* and hematopoietic cancer mortality (adjusted OR = 2.24). Previous case-cohort studies conducted by our group of liver and brain cancer mortality (Felini et al., 2011; Gandhi et al., 2014) did not have sufficient data to investigate this association. In our previous case-cohort study of lung cancer and pancreatic cancer, however, occupational exposure to raw eggs seemed to be associated with only a slightly increased risk of lung cancer (OR=1.2), and no risk of pancreatic cancer (OR = 0.4). It is well established that some oncogenic viruses are present in raw eggs destined for human consumption (E S Johnson, 1994), and, in fact, have been discovered in supermarkets in the New Orleans metropolitan area (Pham, Spencer, & Johnson, 1999). However, these viruses have not been linked to human cancers to date. With regard to histologic subtype, we observed handling of raw eggs was significantly associated with an elevated risk of leukemias. We did not have sufficient data to assess this association with lymphomas and multiple myeloma.

Finally, the finding of a moderately increased risk with *handling feathers* (adjusted OR = 1.38) ties in with two previous studies that have shown that Marek's disease virus is excreted and carried in high concentrations in the feather follicles of infected poultry (Choudat, Dambrine, Delemotte, & Coudert, 1996; Yao et al., 2007).

We suspect, therefore, that the high risks associated with these occupational tasks may result from exposure to the oncogenic viruses of food animals in general, including those of poultry (ALSV, REV and MDV), since no other known potentially carcinogenic occupational exposures are associated with these specific occupational tasks (Felini et al., 2011).

Smoking of Poultry

We found that the *smoking of poultry* was associated with more than a threefold risk of hematopoietic cancer mortality (OR = 3.10). When stratified by histologic subtype, there was a slightly higher risk associated with mortality from lymphomas compared to leukemias (OR = 4.19 and 3.00, respectively). We lacked sufficient data to examine the risk of multiple myeloma. Caution should be exercised when interpreting sub-type specific estimates as they were generated from very few exposed cases (n =7).

A plausible explanation underlying this overall risk of hematopoietic cancer mortality may be that poultry workers employed in smokehouses are exposed to combustion products emitted during the smoking process, specifically polycyclic aromatic hydrocarbons (PAHs) (Colmsjö et al., 1984; Hansen et al., 1992; Nordholm et al., 1986). There is a paucity of studies that have examined this relationship specifically among poultry workers, and those that have done so using our cohort did not find an association (Felini et al., 2011; Gandhi et al., 2014).

The only other study that investigated this exposure was in the context of lung cancer conducted by Felini et al (2012), which reported a slightly elevated risk (OR=1.2). However, this estimate was adjusted for cigarette smoking in addition to age and union status. We lacked sufficient data on cigarette smoking to control for it as a potential confounder. If cigarette smoking had been a positive confounder in the association between smoking meat and hematopoietic mortality, it may serve as a plausible explanation as to why we noted a higher risk estimate in our study. However, it is difficult to arrive at any definitive conclusions when this data is sparse.

Wrapping of Poultry

Contrary to what we hypothesized, we not find any risk of hematologic malignancy mortality associated with the *wrapping of poultry* (OR = 0.60). Wrapping machines produce fumes that contain PAH, benzene, and phthalates, strong environmental exposures consistently observed to increase risk of hematopoietic cancer in previous literature of the general population. The only three studies to date that have specifically investigated the carcinogenic effects of wrapping machine fumes have shown an increased risk of hematopoietic cancer mortality (E S Johnson & Fischman, 1982; Eric S. Johnson et al., 2010; Metayer et al., 1998). However, the exception to this was the study conducted by Johnson et al in 2010, whose source population was a mix of poultry and meat workers. This is significant, since the probability of exposure to wrapping machine fumes is very low in poultry slaughtering plants compared to supermarkets and meatpacking plants (Metayer et al., 1998). This was also true in the case of our other case-cohort studies investigating mortality due to brain and pancreatic cancer

mortality in the poultry industry, with only 0 to 2 cases reporting exposure to wrapping machine fumes (Felini et al., 2011; Gandhi et al., 2014). A plausible explanation for the absence of an association between wrapping fumes and hematopoietic cancer mortality may be how the question was asked: '*Did you ever use a wrapping machine?*' This question had the least agreement (40%) between the responses of live workers and their next-of-kin. Since all of these responses for cases were from proxies while information for controls was mainly provided by the study subjects themselves, proxies for cases may have not have been aware if their deceased relatives had ever used a wrapping machine or complained of fumes from a wrapping machine.

In sum, I conclude that the poultry related occupational exposures investigated in this study do increase the risk of hematologic malignancies. This conclusion endorses findings from previous studies. Although the risk of hematopoietic cancer mortality associated with slaughtering of poultry was not as high as we have seen for other cancers, such as brain, pancreatic, and lung cancer, it warrants attention for the possible role biological agents may have in hematopoietic cancer occurrence. Moreover, our findings have biologic precedence. ALSV and REV cause cancer in poultry, and antibodies to these viruses have been detected in humans. However, there is a lack of evidence to ascertain whether or not these viruses are oncogenic in humans (E. S. Johnson, 1994b). If these viruses are oncogenic to humans, then further research collaborating with an industrial hygienist to construct job exposure matrices that can quantify which specific tasks are at highest risk of exposure would be warranted. Given that occupational tasks are complex and are rarely done in isolation, groups of tasks with interacting exposures are more likely to be productive areas of research. With regard to

smoking and wrapping of poultry, the chief issue insofar as arriving at a conclusive statement is that we lacked a sufficient number of exposed cases. This may be attributed to the fact that the questions pertaining to these two exposures are very specific, making it difficult for next-of-kin to accurately recall.

Non-Poultry Occupational Exposures

The second aim of our study was to identify non-poultry related occupational tasks associated with an increased risk of hematopoietic malignancy mortality among poultry workers. The primary purpose of this aim was to determine whether known risk factors of hematopoietic cancers could readily be observed in our analysis. If so, such findings would further support that our study population was a representative sample that could be used in larger studies. Both chemicals as well as farming were found in our study to be risk factors and have been well cited as occupational risk factors for hematopoietic (’t Mannetje, Eng, & Pearce, 2012; Cogliano et al., 2011).

Chemical exposures. The elevated risk estimates that we found in our study among workers *exposed to gasoline* (OR = 1.89) and *exposed to chemicals* such as coal tar (OR = 5.63) corroborate findings from previous studies that have established benzene and PAHs as risk factors for hematopoietic malignancies, respectively (Smith, Jones, & Smith, 2007; Wong, 1987; Yaris, Dikici, Akbulut, Yaris, & Sabuncu, 2004). *Exposure to coal tar* was one of the few statistically significant estimates associated with an elevated risk of hematopoietic cancer in our study. The biological mechanism by which coal tar incurs carcinogenesis is by way of polycyclic aromatic hydrocarbons intercalating into human DNA (Melendez-Colon, Luch, Seidel, & Baird,

1999). Benzene, primarily from cigarette smoke, automobile exhaust, and gasoline, has been conclusively linked to leukemia in the most recent review by IARC (Cogliano et al., 2011). Animal studies support an association between benzene and lymphomas (Regev, Wu, Zlotolow, & Brautbar, 2012), but occupational studies are mixed (Wong, 1987; Yin et al., 1996).

We observed a threefold risk of hematopoietic mortality from *spraying insecticides on a farm* (OR = 3.03). Occupational exposure to DDT, chlorophenols, and phenoxy-acetic acids were all associated with an excess risk in previous case-control studies of patients diagnosed with multiple myeloma(Perrotta et al., 2008). A recent review focusing on cancer burden among pesticide applicators revealed sufficient evidence linking both NHL and leukemia to pesticide exposure (Alavanja, Ross, & Bonner, 2013).

Non-poultry animals and farming. We noted a nearly threefold risk of hematopoietic mortality associated with the *slaughtering of pigs*. This is consistent with previous studies of our same cohort that revealed an increased risk of lung, liver, and pancreatic cancer mortality associated with killing pigs (Felini et al., 2011, 2012), and other studies that have shown an excess risk of cancer mortality specifically among pork butchers (Gubéran, Usel, Raymond, & Fioretta, 1993; E S Johnson, Dalmas, Noss, & Matanoski, 1995; Eric S Johnson et al., 2011). However, the risk of cancer associated with the handling of pigs among butchers may not be due to the exposure to blood alone. Exposure to PAHs during the smoking of meat is highest in pork-packing plants compared to any other meatpacking industry (Metayer et al, 1998). Gubéran et al's study (1993) reported that the higher risk of lung cancer among Geneva pork

butchers was thought to be consequent to fumes rich in PAHs that the smoking process emanates.

As anticipated, we observed a nearly twofold risk of hematopoietic cancer mortality among *dairy farmers* (adjusted OR = 1.89) as well as farmers that *worked with animals other than poultry* (adjusted OR = 2.21). There have been numerous studies that have shown a link between animal and crop farming and the increased risk of hematopoietic mortality (’t Mannetje et al., 2012; Blair & Thomas, 1979; Milham, Samuel, 1971; Pearce, Sheppard, Howard, Fraser, & Lilley, 1986; Perrotta et al., 2012). However, there is insufficient evidence to distinguish between viral exposure and exposure to fungicides/herbicides as the potential causative agent among farmers.

One of the unique findings in our study was a nearly fourfold risk of hematopoietic mortality observed among *workers selling seafood* (adjusted OR = 4.31). This association was statistically significant. There have been no studies to date linking this occupational task to increased hematopoietic mortality. The literature reports the presence of numerous viruses in shrimp, but none so far have been deemed oncogenic in humans (Lightner et al., 1997; Tan et al., 2009). Also, it is difficult to sift out the effects of other established carcinogens that are part of seafood aquaculture, such as disinfectants and pesticides, contributing to hematopoietic cancer mortality (Tu, Silvestre, Phuong, & Kestemont, 2010).

In sum, our findings for non-poultry exposures identified the same strong risk factors identified by previous other studies. As an indirect benefit, some new risk factors may have been uncovered that can be used to generate future hypothesis.

Conclusion

With regard to our first and second specific aims, we observed an elevated risk of hematopoietic cancer mortality for both poultry related and non-poultry-related occupational exposures, with the exception of *using a wrapping machine*, and *contact with raw poultry.* Insofar as our third specific aim, we often lacked sufficient data to examine the association between each of the exposures and the three histologic subtypes of hematologic malignancies.

While our focus for all three aims was on the odds ratio, the hazard ratios observed did not change any of our conclusions for this analysis. Since we had information on time to event, we took the opportunity to calculate hazard ratios. In a Cox proportional model, time to occurrence of each event as well as censoring of participants is taken into consideration. However, in a logistic regression model, the odds ratio computed is a cumulative incidence odds ratio, which does not take into consideration censoring of individuals or time to event. This is particularly important in occupational studies, as issues with follow-up often arise due to workers routinely exiting and reentering the workforce. As expected, in nearly all instances, the point estimates obtained by Cox regression were consistently more precise and conservative compared to the estimates obtain by logistic regression. A study conducted by Symons et al (2002) showed that the divergence between a hazard ratio and an odds ratio is dependent on the product of three factors, which are the length of follow up, the frequency of outcome, and the strength of the association (Symons & Moore, 2002). The study goes on to explain that the numerical value of a hazard ratio exists as an intermediate between the relative risk and the odds ratio, wherein the odds ratio is the farthest away from unity and the relative risk is the

closest to unity. Thus, the greater the risks, the more divergent are the estimates that we see in our results. There were only two estimates for which this was not the case (*spreading chicken waste as manure*, and *handling feathers*), which may simply be due to a function of sparse data leading to unstable estimates.

We considered other explanations that may alter our confidence in the findings observed for all three specific aims. Differential misclassification of exposure information could potentially occur since responders for all cases were next-of-kin proxies, while responders for controls were themselves the study subjects. To determine the impact, if any, on risk estimates when using proxies, an additional analysis was conducted previously to compare responses from 7 pairs of live control study subjects and their next of kin. 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.

Though possible, selection bias should be less of an issue in this study. All the cases that occurred in the cohort were included in the study, and the controls were a random sample of the baseline cohort. Therefore controls were chosen from the same source population that gave rise to cases. There did not appear to be a differential motivation to participate between the case proxies and the controls; the underlying issue for lack of participation was positively identifying a match. Identifying a match was also limited by the completeness of union records. If the name, date of birth, social security number or other identifying information listed in the union record was incorrect, it was difficult to locate the actual individual. If a match was located, the individual generally agreed to participate in the study. The fact that the

participation rate after a match was found was 79% among cases and 71% among controls indicates that non-participation bias should not be a major source of concern. The major reason for non-participation of the matches was they did not want to commit to the length of time that it would take to complete the questionnaire, which was approximately 45 minutes to an hour.

We lacked sufficient information regarding the duration of time involved in a specific occupational task. Hence, we were unable to determine whether there was a dose-response pattern.

The occupational task exposures were not mutually exclusive. Some employees had multiple jobs and therefore multiple exposures within this industry. In this case, effect estimates may have been incorrectly estimated because of overlapping exposures.

It is important to note that the proportion of poultry workers among interviewed cases was lower than it was in interviewed controls (67% versus 78%). Thus, for each assessment of risk for a given poultry task, the comparison group had a higher proportion of poultry workers. Hence, the risk estimates given in this study for poultry related tasks are conservative.

The diagnosis of hematopoietic cases was based on underlying cause of death as coded in the death certificates. Percy et al conducted a study to determine the accuracy of cancer mortality data in death certificates and found (Percy & Gloeckler, 1971). Death certificates with an underlying cause of death of cancer were compared to the hospital diagnosis for 48,826 resident cases of single primary cancers. The detection and confirmation rates for hematopoietic cancers as the underlying cause of death were very high (~96%) compared to other cancers such as brain, colon, and oral. Thus, misclassification of disease should be less of

a concern in our study.

Representativeness and generalizability may have been compromised by two factors: First, the study was limited to union members, for whom safety and health regulations may differ from their non-union counterparts. Second, the lack of racial diversity in our cohorts, which were predominantly comprised of Caucasians, is in contradistinction to the current poultry workforce, which is dominated by racial and ethnic minorities. Moreover, the response rate for racial and ethnic minorities in the case cohort study was extremely low considering the amount of racial and ethnic cancer cases in the cohort, thus limiting the generalizability of the case cohort results to Caucasians.

In summary, these findings should be interpreted thoughtfully and in the context of the design of this study, a feasibility study. That being said, despite our study's low statistical power, we succeeded in confirming established risk factors associated with hematopoietic cancer. Our study distinguishes itself from other studies to date with regard to its methodological approach as a case-cohort study, despite its preliminary nature as a pilot study. Its uniqueness lies in its singular focus on poultry workers, a group that carries the distinction of having the highest known exposure to oncogenic viruses. Moreover, it is the only study of its kind to provide information regarding task-specific mortality consequent to hematologic malignancies among this specific cohort of only poultry workers. While preliminary, our findings provide some evidence that exposure to poultry and raw poultry products may underlie the observed excess risk of hematopoietic cancer mortality among workers in the poultry slaughtering and processing plants.

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