Occupational Histories of Cancer Patients in a Canadian Cancer Treatment Center and the Generated Hypothesis Regarding Breast Cancer and Farming

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Occupational exposures increase cancer risks. The Windsor Regional Cancer Centre in Windsor, Ontario, was the first Canadian cancer treatment center to collect the work histories of its patients, which were recorded using a computer-based questionnaire. Breast cancer cases represented the largest respondent group. The lifetime occupational histories of 299 women with newly diagnosed breast cancers were compared with those of 237 women with other cancers. Odds ratios (ORs) were calculated using logistic regression, adjusting for age, social class, and education. The OR for women ≤ 55 years of age with breast cancer who had ever farmed, compared with women of the same age with other cancers, was 9.05 (95% CI 1.06, 77.43). Patients' occupational histories can help to inform understanding of cancer etiology and prevention. This effort points to a need for investigation of the possible association between breast cancer and agricultural hazards such as pesticides. *Key words*: breast cancer; Canada; cancer registry; epidemiology; farming; occupational history.

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The scientific literature[1–13] and Ontario government commissions[14–17] recognize the excess risk borne by workers exposed to carcinogens in their work environments. In spite of these increased risks, there has been little effort to document the occupational histories of cancer patients in Canada, or to develop a preventive strategy to reduce workers' risks.

Cancer treatment centers in Ontario, Canada, do not routinely collect occupational histories of cancer patients. Occupational cancer research has been constrained by the limited occupational history data obtained from death certificates or records, which indicate only predominant occupation. According to Marrett and Weir,[18] ". . . Ontario has no systemic means for generating hypotheses linking cancer incidence and employment, industry, occupation or workplace exposures. This fact stands in the way of reliably estimating the burden of occupational cancers in this province."

This lack of attention to the possible association between lifetime workplace exposures and cancer contributes to the under-reporting and minimal recognition of occupational risk factors in the etiology of carcinogenesis.[19]

Leigh et al.[20] published estimates of the extents and costs of occupational diseases in the United States. Occupationally related cancer was determined to be the leading cause of death due to workplace exposures, responsible for between 31,025 to 51,708 deaths in 1992. The researchers further attributed the greatest economic loss, of approximately $9.4 billion, to occupationally related cancer.

Kraut[5] estimates there are 4,000 to 10,100 cases of occupationally related cancer in Canada each year, based on 1989 incidence data. He further states that cancer mortality ranges from 2,052 to 5,130 deaths per year.

In spite of the magnitude of this public health problem and the social–human costs, the lack of a standardized occupational-data-collection system in North America remains virtually the same as it was 20 years ago, when Doll and Peto[1] wrote:

> On present knowledge, therefore, it is impossible to make any precise estimate of the proportion of the cancers today that are attributable to hazards at work. . . . It is, therefore, odd that despite the passionate debates that have taken place about the likely magnitude of the number of U.S. cancer deaths that are or

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will be attributable to occupation, no routine system has been adopted in the U.S. for generating reliable information.

The current lack of interest in collecting occupational histories has raised questions about a systemic "social class" bias[6,10,22] among the medical, employer, and government policymakers. Dr. Infante told the U.S. President's Cancer Panel that

> . . . disproportionate death from cancer among blue-collar workers is a social class issue and that the problem is neglected because it is a potentially explosive issue. It raises questions about the control of production and cost of production.

The study described herein took place in Windsor–Essex County, Ontario, Canada. The Windsor-Essex area, which has a both urban and rural population of approximately 350,000 within a small land area in the Great Lakes Basin, is located on the American–Canadian border across from the city of Detroit. Windsor– Essex is the center of the Canadian auto industry, with operations of all three major North American auto makers, as well as over 800 other manufacturers, many of them auto-related. The community is located within a day's travel of 90% of North America's vehicle assembly plants, giving the Windsor–Detroit corridor the highest volume of international trade in the world. Agriculture is also a significant economic activity with over 325,000 acres producing as much as any one of the Atlantic provinces.[22]

This Windsor–Essex community manifests cancer incidence and mortality rates exceeding the provincial rates. These rates were identified in a 1995 Health Profile produced by the local District Health Council.[23] Higher rates of leukemia, lung cancers, and colorectal cancers among males and elevated rates of breast, lung, and uterine cancers in females were cited.

Gilberston and Brophy [24] published an analysis of data for Windsor–Essex, provided by Health Canada, for the period between 1986 and 1992. Windsor was the only location among 17 Great Lakes Areas of Concern in Canada in which the overall cancer incidence rate was elevated in either males or females. There were elevated rates of morbidity and mortality from cancers of the digestive organs, respiratory tract, genitourinary organs, and lymphatic and hematopoietic tissues.

METHODS

In 1994, the Industrial Disease Standards Panel (later renamed the Ontario Occupational Disease Panel), the Occupational Health Clinics for Ontario Workers (OHCOW) in Windsor, and the Windsor Occupational Health Information Service (WOHIS) approached the Windsor Regional Cancer Centre (WRCC) about the need to document the occupational histories of local cancer patients.

A year later these groups launched a computerized data-collection project, Computerized Recording of Occupations Made Easy (CROME), to collect occupational histories at the WRCC. CROME was developed through a process that involved occupational health professionals, medical specialists, including a respirologist and oncologist, a researcher familiar with farming methods in Essex County, and a panel of trade union health and safety representatives from the auto and related industries.

The design of CROME was not based upon any previously developed occupational-history-gathering measure. Rather, it was designed to fulfill a broad research mandate—to screen for possible associations between any occupations and any cancers without a priori hypotheses.

The consulting panel composed an abbreviated list of industrial and occupational categories using their own knowledge of the most locally prevalent industries and occupations. Sixteen major industries and 300 occupational categories were included in the list. These categories were then matched to Health Canada's Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes.[25] Rather than attempt to create a questionnaire to capture a detailed exposure history that would adequately address all potential exposures in every possible occupation, occupation was treated as a "surrogate" for exposure within the CROME construct.[26] Exposure within recorded industries and occupations were assumed based on available industrial hygiene literature. CROME captured length of employment (i.e., duration) and time from employment to onset of disease (i.e., latency), but not intensity of exposure. The CROME database also captured age and such key socioeconomic status (SES) variables as residence area, income level, and educational status.

A computer programmer produced the basic CROME database, and it was then enhanced with graphics and menus. It was intended that cancer patients would use this user-friendly, touch-screen data-collection tool to enter their full chronologic work histories with little or no support from cancer treatment center staff. After an initial pilot, however, it was apparent that most patients required at least some staff support to adequately record their work histories.

Following the pilot phase, an evaluation was initiated to test the reliability of the data collected. An occupational health nurse and an occupational hygienist interviewed 50 cancer patients who had completed recording their occupational histories utilizing CROME. The pilot and evaluation helped refine the computer system, and modifications were made.

For the next three years trained clinic staff conducted computer-assisted interviews with cancer patients who volunteered to participate in the project. Interviews took, on average, between 20 to 30 minutes to complete and were conducted whenever the staff

TABLE 1. Descriptive Profiles of 299 Breast Cancer Cases and 237 Other Cancer Controls

	Breast Cancer		Other Cancer	
	No.	%	No.	%
Age at diagnosis (years)				
25–46	22	7.4	28	11.8
46–55	58	19.4	42	17.7
56–65	84	28.1	60	25.3
66–75	101	33.8	72	30.4
75 and older	34	11.4	35	14.8
Education*				
Less than high school diploma	45	27.4	43	29.7
High school diploma	44	26.8	39	26.9
Some post–high school education	44	26.8	37	25.5
University degree	31	18.9	26	17.9
Median annual household income†				
$15,000–37,999	72	24.1	68	28.7
$38,000–45,999	79	26.4	56	23.6
$46,000–59,999	68	22.7	58	24.5
$60,000–89,999	80	26.8	55	23.2
Smoking pack-years				
None	208	69.6	157	66.2
1–24	52	17.4	46	19.4
25 or more	39	13.0	34	14.3
Farming Person-Years ‡				
None	257	86.0	212	89.5
1–9	24	8.0	15	6.3
20 or more	18	6.0	10	4.2

*Proportion of missing data did not differ significantly between cases and controls (c2 test).
†Ecological measure; based on 70 Essex County, Ontario census tracts in 1996.
‡Includes field crop production,crop spraying and dusting,vineyard or fruit farming, greenhouse or nursery operations, livestock farming,other agricultural jobs, and other farm services.

could accommodate them in their clinic schedules. Patients who were awaiting treatment would be invited to document their occupational histories. No attempt was made to select one group of cancer patients over another. However, due to such circumstances as treatment availability and waiting times, the largest group of cases recorded in CROME was that of women with breast cancer. This group slightly exceeded the category of women with cancers other than breast cancer.

This selection method is likely to have yielded a random sample. Since the generation of the hypothesis followed the data collection process, the specific hypothesis of the case–control study did not: 1) influence the manner in which the data were collected, or 2) influence the decisions of the clinic staff regarding which cases were selected for recording occupational histories.

The structured interviews completed by the cancer patients included a detailed occupational history of the following: major industry; occupational category; duration; age; level of education; and years starting and ending each job during the course of the patients' entire adult working life. CROME was matched with the patients' medical charts, which provided additional data regarding potential key covariates such as age at time of diagnosis, and lifetime cigarette smoking pack-years.

Because socioeconomic status (SES) is such a centrally important variable in breast cancer research, itself a significant predictor of breast cancer, as well as of other known determinants of breast cancer, and because this study's personal-level SES proxy—educational achievement—was not available for nearly half of the study sample (this did not differ significantly between cases and controls), an ecological measure of SES was also included (see Table 1).[27–29] A census-tract–based ecologic measure of income status—median annual household income—that was based on residence at the time of diagnosis was geographically coded for each study participant.[30]

RESULTS

In 1999, the data collected using CROME were analyzed and a breast cancer-farming hypothesis was explored. Women with breast cancer were compared with women with cancers other than breast cancer.

The cases were composed of the 299 primary malignant female breast cancer cases, selected by convenience from the WRCC patient treatment roster between January 1, 1995, and December 31, 1998 (International Classification of Diseases, 9th edition, ICD-9 code = 174).[31]

TABLE 2. Logistic-regression-estimated Odds Ratios (ORs) of the Ever Potentially Pesticide Exposed–Breast Cancer Association by Age Group

	Estimates Adjusted for the Following Variables								
	Age			Age and Education			Age and Income		
	No.	OR	(95% CI)	No.	OR	(95% CI)	No.	OR	(95% CI)
Ever farmed									
All ages	536	1.34	(0.81,2.34)	309	1.38	(0.67, 2.83)	536	1.36	(0.74,2.51)
≤ 55 years old	150	2.57	(0.75,8.85)	89	9.05	(1.06,77.43)	150	2.81	(0.94,8.40)*
≥ 56 years old	386	1.18	(0.65,2.13)	220	0.88	(0.44, 1.92)	386	1.14	(0.57,2.28)

*90% confidence interval 1.12,7.05.

The comparison group, i.e., control group, consisted of 237 women with cancers other than breast cancer who were receiving treatment at the WRCC during the same time period. The control group was composed of women who had 28 different types of cancer; none of which accounted for more than 15% of the sample. Because of their consistently observed associations with pesticide exposures, lymphoma cases were excluded.[32,33] The controls, with variability in age and residence, allowed for the construction of a stable logistic regression model.

Table 1 shows that a substantial proportion of the women in this study's aggregate sample had farmed (13%) for at least a year of their adult working lives.

The calculation of descriptive statistics among cases and controls, including stratification and adjustment, employed standard epidemiologic and biostatistics techniques.[32] Logistic regression odds ratios (ORs) were created. The logistic model regressed the key dependent variable (breast cancer [women 55 years old or younger]) on the key occupational independent variable (farming) adjusting for key confounders.[34] Covariates included age, education, and smoking history. Because cigarette smoking was not shown to be a confounder of this study's hypothesis (i.e., in this study's database smoking pack-years was not significantly associated with farming, or with breast cancer), in the interest of both parsimony and statistical power, it was removed from all of the logistic regression models.

Associations with breast cancer are displayed in Table 2. The table's left column lists hypothesized farming–breast cancer OR point estimates and their associated 95% confidence intervals that were age-adjusted. These three models systematically replicated null findings across the following different samples: all ages; women 55 years of age or younger; and women 56 years of age or older, who had ever farmed. These null associations are consistent with most other of this field's studies that have not accounted for critical confounders such as SES. Of greater interest are the table's center and right columns, which show socioeconomic-status–adjusted models adjusted, respectively, for personal (educational achievement) and ecologic (census tract median household income) measures of SES.

The point estimates of increased breast cancer risk among farmers ranged from three- to ninefold, albeit within rather broad confidence intervals. Even granting its limitations, the consistency and size of this preliminary study's breast cancer—farming association strongly suggests that this relationship ought to be treated as a successfully tested hypothesis that warrants future testing with more rigorous epidemiologic methods.

DISCUSSION

The initial CROME case–control study had a number of strengths. It used data regarding lifetime occupational histories of study participants. It controlled for-the potentially confounding influences of such socioeconomic factors as education and income status. As shown in Table 2, for women 55 years old or younger who had ever engaged in farming, there was an OR = 9.05, 95% CI 1.06, 77.43, albeit with a wide confidence interval. The wide confidence interval was the result of missing SES data that reduced the power of the sample. Among all such women, the age- and socioeconomic-status–adjusted rate of breast cancer was tentatively observed to be an almost threefold excess (OR = 2.81; 95% CI 0.94,8.40).

There are many epidemiologic studies of the association of pesticides and breast cancer.[35–71] Studies that adjusted for potentially important confounders generally produced stronger aggregate findings of the exposure–cancer associations than did those based on unadjusted estimates. Population-based studies that provided any adjustment for the "healthy worker" effect found evidence of a pesticide–breast cancer association. Several studies concluded that the results were not definitive and that uncertainty still exists about the association between specific pesticide exposures and breast cancer. The CROME findings, which controlled for two different measures of SES—one personal (education) and the other ecologic (consensus tract-level income)—seemed to offer some convergent validation of the general tendency.

The CROME study had a number of limitations. It was not able to control for known breast cancer risk factors such as family history, and estrogen-related factors such as use of oral contraceptives and reproductive history. Because "occupation" was used as a surrogate for actual exposure, there was no information about specific exposures, or their intensities or durations. On the other hand, this approach captured the effect of real-life mixed exposures. The sample was small, and the use of a comparison group made up of women with cancers other than breast cancer raises potential confounding issues. For example, while the lymphoma cases were eliminated because they share possible common etiologic risk factors with breast cancer, there may be other cancers that are similarly influenced.

FUTURE DIRECTIONS

The limitations of this preliminary study have been addressed in a follow-up study designed to test the breast cancer–farming hypothesis. A detailed questionnaire, entitled the Lifetime Occupational History Registry (LOHR), has replaced CROME. LOHR captures such covariates as age, socioeconomic status, parity, family history, obesity and BMI, age of menopause, oral contraceptives, pregnancies, number of children, lactation, menopausal status, age of menarche, hormone-replacement therapy, and marital status.[29,72–74] Community controls are randomly selected from the population rather than using hospital-based controls. The SIC and SOC codes have been replaced with the updated North American Industrial Classification System[75] and National Occupational Codes.[76] Specific pesticide-exposure questions and the recording of data regarding key confounders will serve to strengthen the validity of any findings.

The steady increase in the incidence of breast cancer in Canada suggests exposures to occupational– environmental agents play a role in the genesis of this disease.[77] The National Cancer Institute of Canada[78] estimated that 19,200 Canadian women would contract breast cancer in the year 2000. Almost 29% would die from it. It is currently projected that the lifetime risk of breast cancer is 1 in 9.5 women. Over the last 30 years there has been an almost 1% annual increase of breast cancer incidence in Canada. Only lung cancer has a slightly greater impact of lost years of life for Canadian women.

The majority of breast cancer cases cannot be explained by the current list of attributable risks.[79–82] Therefore, there is a need to test for other potential risk factors. There is evidence that exogenous chemicals are contributing to the overall incidence.[40,83,84] One area that has received particular attention is the family of synthetic substances that "mimic" estrogens (xenoestrogens). It has been suggested that they have the ability to disrupt the endocrine system and contribute to the neoplastic process. This group includes organochlorine pesticides, polycyclic aromatic hydrocarbons, organic solvents, and plastics.[82,83,85–92]

It is hypothesized that farming as an occupation is a proxy for direct or indirect pesticide exposure (e.g., exposure to pesticide residues through handling agricultural products). Duell et al [64] found that women who reported being present in the fields during or shortly after pesticide application had a 80% increased risk (OR = 1.8, 95% CI 1,1.28 of developing breast cancer.

While 2,3,7,8-tetrachlorodibenzo-*p*-dioxin has anti-estrogenic properties and is protective of adult animals for breast cancer from carcinogen exposures, there is evidence from animal testing that prenatal exposure to dioxin may increase the susceptibility to mammary cancer.[93] This research poses a new hypothesis that may help to further clarify the possible biological dimension of prenatal exposure to endocrine disruptors and the occurrence of breast cancer in humans.

Carcinogenesis is postulated to be a complex interaction between genetics and the environment.[29] But younger women, between the age of menarche and the time of first pregnancy, appeared to be particularly vulnerable to genetic damage from exogenous carcinogens. The cells in the immature, developing breast are not yet differentiated and cells are dividing at a greater rate than later in life.[94] The susceptibility of cell mutation, coupled with the greater propensity of undifferentiated cells to bind with carcinogens, and thus trigger DNA damage, means the exposure of younger women to exogenous toxins can be crucial.[95] Furthermore, later reproductive factors, which will influence estrogenic load, can influence this risk.

As is indicated by the literature, female breast tissue may be more susceptible to tumor initiation and progression during periods of great morphologic and biochemical change, that is, beginning at puberty to time of first pregnancy and possibly continuing throughout the reproductive years. This study reveals the importance of understanding more about the effects of farming exposures during this younger period of a women's life.

The populations with the highest levels of chlorinated pesticide concentrations, outside the pesticide industry, have been identified in agricultural areas.[96,97] Over 1,500 pesticides are available worldwide. Some of these substances are known human carcinogens, possible human carcinogens, and animal carcinogens, while others are without toxicologic data.[98] Farming populations bear an elevated risk of cancers of the brain and of the breast, leukemia, lip cancer, lymphomas, multiple myelomas, prostate cancer, skin cancer, soft tissue sarcomas, and cancer of the stomach.[99–102] Among women engaged in farming, excess risks of non-Hodgkin's lymphoma, leukemia, multiple myeloma, soft tissue sarcoma, and cancers of the breast, ovary, lung, bladder, cervix, and sinonasal cavities have been observed.[102] This excess cancer burden occurs within a population that has generally been viewed as "healthier" given their reported lower rates of smoking, greater levels of physical activity, and possibly healthier diets. Their lower rates of total mortality, heart disease, and several cancers, including cancers of the lung, esophagus, colon, and bladder, have suggested that the etiologic triggers of these excess cancers may be exposures to pesticides (insecticides, herbicides, fumigants, fungicides), solvents, engine exhaust fumes, welding fumes, viruses, and microbes.[77,102,103]

CONCLUSION

The CROME project represents a step in the development of a standardized occupational history questionnaire that could be employed at cancer centers across Ontario. If such data were to be collected, the resulting data set would provide many opportunities to investigate cancer–occupation–exposure hypotheses, such as the breast cancer–farming hypothesis. Findings of elevated risks and the identification of causal agents would encourage occupational cancer prevention strategies to emerge.

The Windsor Regional Cancer Centre is committed to the continuing investigation of occupational and environmental risks. It is supporting new research proposals, while discussing how to incorporate occupational histories into its patient intake process.

Watterson,[98] Davis et al.,[77] and Steingraber[103] have argued that public policy continues to lag behind in the area of occupational and environmental cancer research and prevention. Furthering our understanding of cancer risks and occupational and environmental exposures is an important public health pursuit considering the prevalences of both the disease and exposures. The development of a standardized occupational history questionnaire and its adoption throughout cancer treatment center networks, nationally and internationally, would begin to address the neglected challenge Doll and Peto[1] made two decades ago, when they encouraged public health officials to aggressively pursue new knowledge and understanding through the systematic collection of relevant occupational data.

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