Occupation and Breast Cancer

A Canadian Case–Control Study

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ABSTRACT: A local collaborative process was launched in Windsor, Ontario, Canada to explore the role of occupation as a risk factor for cancer. An initial hypothesis-generating study found an increased risk for breast cancer among women aged 55 years or younger who had ever worked in farming. On the basis of this result, a 2-year case–control study was undertaken to evaluate the lifetime occupational histories of women with breast cancer. The results indicate that women with breast cancer were nearly three times more likely to have worked in agriculture when compared to the controls (OR = 2.80 [95% CI, 1.6–4.8]). The risk for those who worked in agriculture and subsequently worked in automotive-related manufacturing was further elevated (OR = 4.0 [95% CI, 1.7–9.9]). The risk for those employed in agriculture and subsequently employed in health care was also elevated (OR = 2.3 [95% CI, 1.1–4.6]). Farming tended to be among the earlier jobs worked, often during adolescence. While this article has limitations including the small sample size and the lack of information regarding specific exposures, it does provide evidence of a possible association between farming and breast cancer. The findings indicate the need for further study to determine which aspects of farming may be of biological importance and

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to better understand the significance of timing of exposure in terms of cancer risk.

KEYWORDS: **breast cancer; occupation; environment; farming; Canada**

INTRODUCTION

The lifetime risk for breast cancer among Canadian women is approximately 1 in 9. Over the past 30 years, there has been a 25% increase. The majority of cases cannot be explained by the currently known or suspected risk factors. Family history of breast cancer, particularly with respect to having two or more relatives with breast cancer and mutation of the *BRCA1* and *BRCA2* gene, can explain less than 10% of breast cancer cases.[1] Factors that increase cumulative estrogen load have been found to increase risk. There is evidence of an association with diet, alcohol use, body mass index, reproductive history, age, physical activity, and socioeconomic status.[2] The recent increase in incidence may be linked to the combination of identified risk factors and those requiring further study, such as occupational and environmental exposures.[3] Increasing evidence suggests that synthetic chemicals, particularly those that mimic estrogen (xenoestrogens), may increase risk by acting as endocrine disruptors.[4] Such exogenous chemicals include organochlorine pesticides, polycyclic aromatic hydrocarbons, organic solvents, and plastics.[5–8] Animal bioassays have identified over 200 chemical substances that trigger breast cancer.[9] Another factor that has implications for research into the possible role of occupational and environmental exposures is the multistage developmental process that characterizes cancer. Toxic insults, either singular or in combination, may influence the initiation, promotion, and progression of carcinogenesis. Both dose and timing of exposure may be important in terms of risk. It has been suggested that there are critical moments in breast development when the emerging cells may be more susceptible to tumor initiation and progression.[1,4] There may be particular vulnerability during periods of morphological and biochemical change, that is, beginning during gestation and continuing through puberty to time of first pregnancy and possibly throughout the reproductive years.[9] There may also be a combined impact from exposure to carcinogens and hormonally active substances. It has been suggested that genotoxic agents, in conjunction with estrogen, can affect cell repair mechanisms thereby allowing damaged cells to reproduce.[1]

There is a significant gap in our understanding of work-related exposures and breast cancer risk.[10] Many substances shown to induce breast cancer in experimental mammals exist in high concentrations in occupational settings.[11] In spite of the continuing increase in the incidence of cancer in Canada and the existence of carcinogens in occupational environments, there remain no registries or systematic methods to record the occupational histories of cancer patients in general, nor breast cancer patients in particular.

The failure to document lifetime occupational histories and corresponding workplace exposures results in an underestimation of occupationally related cancers and a corresponding lack of substantive prevention-related activity.[12]

METHODS

A hypothesis-generating study, entitled Computerized Recording of Occupations Made Easy (CROME), was conducted between 1995 and 1999 through a collaborative effort of the Windsor Regional Cancer Centre (WRCC), the Ontario Occupational Disease Panel (ODP), and the Occupational Health Clinics for Ontario Workers (OHCOW). The study area, Windsor-Essex, Ontario, Canada, has extensive manufacturing and agricultural activity. The CROME study gathered the occupational histories of 299 breast cancer cases, which were then compared to 237 women with cancers other than breast or ovary. It found an elevated risk for breast cancer among women 55 years of age or younger who had ever worked in farming (OR = 9.05 [95% CI, 1.06–77.43]).[13] There were a number of important limitations to the study including: small sample size; the use of hospital-based controls; and the failure to adequately capture data regarding potential confounders beyond those of age, socioeconomic status, and body mass index. Moreover, detailed occupational descriptions were absent.

On the basis of the results from CROME, a second population-based case–control study, entitled Lifetime Occupational Histories Record (LOHR), was undertaken in 2000 in the same geographical study area to further explore possible associations between breast cancer and occupation in general and farming in particular. LOHR had several improvements over the previous study: it used randomly selected community controls rather than hospital controls; it captured more detailed occupational descriptions; and it collected data for a broader range of potential confounders. Over a 2.5-year period, all female patients treated at the Windsor Regional Cancer Centre (WRCC) with histologically confirmed new incident primary breast cancer were invited to participate. None of the cases had participated in the previous study. The medical records department screened breast cancer patients to confirm pathology and date of diagnosis. A letter was mailed to each eligible patient outlining the study and was followed up by a telephone call. Five hundred sixty-four eligible breast cancer patients participated in the study. Three patients declined participation, resulting in a 99% plus response rate. Community controls were chosen at random using city directory software[14] and were recruited by letter and a scripted follow-up telephone call to improve response rate among the less literate. The information provided to potential controls about the research did not specify a particular focus on occupational or environmental risk factors for breast cancer; the research was simply referred to as a "Risk History

Study." The controls were approximately matched by age and by geographical area. Five hundred ninety-nine eligible community controls participated out of 1146 contacted representing a response rate of 52.2%. All subjects, signed informed consents and each was offered a $20 stipend as compensation for their time.

A comprehensive lifetime history questionnaire was administered to each subject by a trained interviewer. The questionnaire gathered data regarding height and weight (body mass index), marital status, income, education, age of menarche, menstrual history, pregnancy and breast-feeding history, menopausal status, hormone use, family breast cancer history, residential history by three-digit postal code, hobbies, and complete occupational history including age at the start and end of each job. The questionnaire also included questions about a range of occupational exposures: asbestos, man-made mineral fibers, dusts, second-hand tobacco smoke, engine exhaust, other smoke or particulate, metal-working fluids, solvents, paints, strippers, and pesticides. Agricultural workers were also asked about chemical exposures. Subjects' recall regarding specific agents proved to be limited and much of the exposure information was deemed unreliable or was missing. As a result, data regarding exposure to specific agents was not included in the analysis. Jobs were categorized by coders, who were blind as to the case–control status of the subject data, using National Occupational Classification (NOC)[15] codes and the North American Industrial Classification System (NAICS).[16] The NOC codes, which provided more specificity than the NAICS, were included in the analysis. Similar or related occupations were grouped together to provide adequate statistical power.

FINDINGS

Included in the LOHR analysis were data from 564 female breast cancer cases and 599 female controls. The statistical program SPSS Version 10 was used to conduct a three-step multivariate analysis to test the hypothesis of a possible association between breast cancer risk and occupation. Logistic regression analysis was used to calculate odds ratios and their 95% confidence intervals.[17] In the initial step, cases and controls who had ever been employed in agriculture were compared while controlling for duration of employment using five ordinal variables: none, 0.5–5 years, 6–10 years, 11–20 years, and 21 or more years. Due to small sample size duration did not reach statistical significance for any of the specific periods.

In the next step, the odds ratios for the independent variables (e.g., farming) indicate the effect of each variable, after adjusting for covariates, on the probability of developing breast cancer. The following ordinal covariates were included in the model: age at diagnosis (mean age of cases = 60.33, mean

TABLE 1. Descriptive profile of 564 female breast cancer cases and 599 female community controls

	Breast cancer cases		Community controls	
	Yes %	No %	Yes %	No %
Ever pregnant[1]	495 (43%)	65 (5.6%)	527 (45.8%)	64 (5.6)
Ever use hormone replacement	261 (22.4%)	303 (26.1%)	263 (22.6%)	336 (28.9%)
Ever smoke tobacco	249 (21.4%)	315 (27.1%)	273 (23.5%)	326 (28%)
Ever breast feed	378 (32.5%)	186 (16%)	370 (31.8%)	229 (19.7%)
Ever used oral contraceptives[2]	289 (25%)	273 (23.6%)	339 (29.3%)	256 (22.1%)
Mother ever had cancer[3]	125 (10.9%)	431 (37.5%)	146 (12.7%)	447 (38.9%)
Ever reside on a farm or live within a mile of a farm[4]	253 (22.2%)	305 (26.7%)	247 (21.6%)	337 (29.5%)

[1]Missing cases = 12 (1%).
[2]Missing cases = 6 (.5%).
[3]Missing cases = 14 (1.2%).
[4]Missing cases = 21 (1.8%).

age of controls = 58.64); education level; annual household income; body mass index; number of pregnancies; years of oral contraceptive use; months of breast feeding; years of cigarette smoking; alcohol use and marital status. This step also included the following dichotomous covariates (TABLE 1): ever pregnant; ever used hormones; ever smoked tobacco; ever breast feed; ever used oral contraceptives; mother ever had cancer; and ever reside on a farm or live within a mile of a farm. Number of years of residence in Essex County was included as a continuous variable within the model.

The final step in the conditional logistic model included the major occupational groups: automotive-related manufacturing; clerical; communications; dry cleaning; education or library; petrochemical; finance or insurance; food processing; food service; hair dressing; manufacturing or engineering managers; office professionals; skilled sales; health care; janitorial; other manufacturing; plastics; printing, painting, or construction; retail; social service; textile; transportation or security; animal care; sports or arts; pest control; postal; mining or logging; landscaping; home care; and unemployed outside the home. In the final step of the model all the occupations interacted with age, but only four occupations remained within the model (agriculture, retail, and the interactions of agriculture with automotive-related manufacturing and of agriculture with health care).

At this stage there were 1026 subjects (cases = 506; controls = 520) with 137 missing (11.8%). As shown in TABLE 2, the results indicate that women with breast cancer were nearly three times more likely to have worked in agriculture ($n = 154$) when compared to the controls ($n = 133$) (OR= 2.80 [95% CI, 1.6–4.8]). Although the individual contribution of automotive-related

TABLE 2. Logistic regression-estimated odds ratios (OR) of women ever employed in agriculture, automotive-related manufacturing, or health care

	Odds ratio (OR)	95.0% C.I.	
		Lower	Upper
Ever worked in agriculture	2.8[a]	1.6	4.8
Worked in agriculture and then in automotive-related manufacturing	4.1[b]	1.7	9.9
Worked in agriculture and then in health care	2.3[c]	1.1	4.6
Worked in automotive-related manufacturing (but never agriculture)	0.76	0.59	1.10
Worked in health care (but never agriculture)	0.85	0.62	1.17
Ever worked in retail	1.0	1.0	1.05
Age	1.0	1.0	1.02

[a]Sig. = 0.0002
[b]Sig. = 0.002
[c]Sig. = 0 .02

manufacturing alone was not significant (OR = 0.76 [95% CI, 0.59–1.10]), the risk for those who worked in agriculture and subsequently worked in automotive-related manufacturing was further elevated (OR = 4.0 [95% CI, 1.7–9.9]). The individual contribution of health care alone was not significant (OR = 0.85 [95% CI, 0.62–1.17]), however, the risk for those employed in agriculture and subsequently employed in health care was elevated (OR = 2.3 [95% CI, 1.1–4.6]). Agricultural jobs tended to be among the first worked, often during adolescence.

There is a modest body of literature regarding breast cancer risk in agriculture, health care, and the automotive industry.

FARMING OCCUPATIONS AND BREAST CANCER RISK

While some studies of farming populations have shown an elevated risk for breast cancer, as well as other cancers,[18–20] several large cohort studies found no elevated risk for breast cancer.[21–23] Female farmers and laborers have not been as extensively studied as their male counterparts. While most studies did not indicate specific exposures, it is plausible that agricultural chemicals may play a role. There is evidence of an association between breast cancer and some pesticides, such as dichlorodiphenyltrichloroethane (DDT), its metabolite dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), hexachlorobenzene, hexachlorocyclohexane, heptachlor epoxide, and triazine herbicides; others are under review.[24–26] A large number of pesticides are also hormonally active.[27] The herbicide, atrazine, for example, is one of the most widely used agricultural chemicals. The triazine pesticides are considered endocrine disruptors and are suspected human carcinogens.[28] Some agricultural chemicals, such as organochlorine pesticides,

are persistent and bioaccumulate in the adipose tissue.[29] A case–control study that controlled for both traditional breast cancer risk factors as well as exposures among women engaged in farming, found that women who reported being present in the fields during or shortly after pesticide application had an increased risk of developing breast cancer (OR= 1.8 [95% CI, 1.1–2.8]).[30] Among those who reported using pesticides without protective clothing, an increased risk of breast cancer was identified (OR = 2.0 [95% CI, 1.0–4.3]); while women with protective clothing did not have an elevated breast cancer risk (OR = 0.8 [95% CI, 0.4–1.8]). The researchers concluded that, while farming may not present an elevated risk *per se*, farming women who were not adequately protected from exposure to pesticides might have an elevated risk.

A Canadian study found that, among the combined pre- and postmenopausal group, there was an increased breast cancer risk among women who had ever been employed in fruit and vegetable farming (OR = 3.11, 90% [CI 1.24–7.81]).[31]

A recent study examining the breast cancer risk of Hispanic agricultural workers in California associated three specific pesticide exposures—chlordane, malathion, and 2,4-dichlorophenoxyacetic acid (2,4-D)—with elevated breast cancer risk.[32]

HEALTHCARE OCCUPATIONS AND BREAST CANCER RISK

A number of known or suspected carcinogens are present in the healthcare setting. Nurses and other healthcare workers are potentially exposed to ionizing radiation, antineoplastic drugs, anesthetic waste gases, and viruses possibly associated with cancer risk.[33] A number of hormonally active chemicals are, or have been, used in medicine and laboratory work.[34] These include: nonylphenol (used in detergents and plastics); ethylene oxide (a sterilant); bisphenol A (used in polycarbonate plastics); butyl benzyl phthalate; and polychlorinated biphenyls (PCBs). These substances have been shown to display estrogenic activity in human breast cell bioassays.[35] Studies of shift work involving nurses have found statistically significant increases in breast cancer (OR = 1.6 (95% CI, 1.0–2.5)) and a relative risk (RR = 1.36 (95% CI, 1.04–1.78)), respectively.[36,37] These elevations occurred among women who worked night shifts over long periods. It is hypothesized that melatonin is disrupted, thereby affecting estrogen levels. Breast cancer risk among nurses and other healthcare workers was examined in administrative, cohort, and case-controls studies.[38] Of 10 administrative and cohort studies, 8 found a positive association with breast cancer[39–46] while 2 did not.[47,48] Among six case–control studies[31,49–53] there were mixed results. Elevated risk is generally noted in several studies that examined breast cancer among registered hospital nurses but these studies shared methodological limitations; most did not control for known or suspected risk factors. Some of the findings varied depending on

which comparison group was used or whether menopausal status was examined. None controlled for specific exposures and all nurses were grouped into one occupational category assuming that this broad title would be an appropriate surrogate for their exposures. In one case–control study an elevated breast cancer risk was revealed only when the study population was separated into occupational subgroups.[53] None of the existing studies assess timing of exposure.

AUTOMOTIVE-RELATED MANUFACTURING OCCUPATIONS AND BREAST CANCER RISK

A few reports have addressed women autoworkers and risk of breast cancer. A cohort study published in 1994 found no association between female breast cancer and automotive manufacturing.[54] A recent study, however, found a weak association (OR = 1.18 [95% CI, 1.02–1.35]) with soluble metal working fluid (MWF) exposure.[55] There is wide use of chlorinated solvents in the automotive industry and growing evidence that these chemicals may increase breast cancer risk, possibly through endocrine disruption.[9,56] Organic solvents have produced mammary tumors in animal studies. Organic solvents have been detected in breast milk, subjecting the ducts to constant exposure. Interestingly, the majority of breast tumors reside in the ductular system.[57]

DISCUSSION

The LOHR study primarily found and then tested associations with specific occupations. It provides evidence of an association between farming and breast cancer risk as well as an interactive effect between occupational farming exposures and subsequent exposures in other occupational environments. It might be hypothesized that agents or conditions present in agricultural settings initiate the breast cancer process at a vulnerable period (adolescence) and that subsequent exposures to agents or conditions (e.g., shift work) in automotive-related industry, health care, or other industries may act as promotors.

The LOHR study had some limitations. While it attempted to gather information through the interview process about exposures, it was not able to accurately identify specific causative agents. Unfortunately, many of the patients and community controls were not aware of or could not reliably recall their exposures. It is possible that the actual breast cancer risk for some of the women in the LOHR cohort, that is, those who had exposure to specific pesticides, is even higher because the aggregation of the unexposed with the exposed in the analysis may have diluted the findings. Such nondifferential misclassification decreases the probability of detecting associations and tends

to underestimate the actual risks.[58] Another limitation of the LOHR study was the small sample size, which necessitated the grouping of occupational categories thereby increasing the risk of misclassification. There was a significant percentage difference in the response rate of cases (99%) versus controls (52%) raising the issue of possible recruitment or selection bias. Steps had been taken, however, to minimize the risk of such bias. Selection of controls was made independent of the exposures of interest. Information provided about the research did not specify a particular focus on occupational or environmental risk factors (the independent variable) for breast cancer (the dependant variable) in order to reduce the likelihood that those interested in specific exposures would respond.

The results of the LOHR study call for research to determine which aspects of farming may be of biological importance. The further development of our understanding regarding breast cancer risk and farming is an important public health concern given the prevalence of potential pesticide exposure and disease in rural communities. Moreover, the interaction between early and subsequent exposures requires further study and consideration. A clearer understanding is needed regarding the effects of farming exposures during the early periods of life when breast tissue is most vulnerable.

A third study, entitled, Lifetime Histories Breast Cancer Research (LHBCR)[59,60] was initiated in 2004 to evaluate more specific exposures among agricultural and other workers. Open-ended job description questions will provide comprehensive data for expert exposure assessment.[61–63] Estrogen and progesterone receptor status of the tumor will be obtained from pathology reports and included in the analysis. A larger sample size—1000 cases and 1000 controls—will provide added statistical power.[64] Such occupational and environmental breast cancer research may ultimately serve to inform the formulation of breast cancer prevention and early detection strategies. This may be accomplished through the identification of current work practices or exposures that can be modified to minimize breast cancer risk; and through the identification of specific populations at potentially higher risk for breast cancer from past exposures who can be then encouraged to pursue more diligent early detection efforts. It may also encourage previously exposed women to avoid further potentially harmful exposures. The results may also serve to shape public health and regulatory policy regarding prevention strategies.

CONCLUSION

The LOHR study indicates that women who have a history of work in agriculture have an elevated risk for breast cancer. The risk for those who worked in agriculture and were subsequently employed in health care or the automotive industry is further elevated. While occupational categories in this study serve as surrogates for exposure, it is plausible that exposure to agricultural

chemicals is a causative factor. Because many women who worked in farming began during adolescence, it is plausible that the timing of exposure is of significance in terms of risk.

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