

## FOCUS REVIEW

## Does Exposure to Agricultural Chemicals Increase the Risk of Prostate Cancer among Farmers?

Marie-Élise Parent\*, Marie Désy, and Jack Siemiatycki

**ABSTRACT:** Several studies suggest that farmers may be at increased risk of prostate cancer. The present analysis, based on a large population-based case-control study conducted among men in the Montreal area in the early 1980's, aim at identifying occupational chemicals which may be responsible for such increases. The original study enrolled 449 prostate cancer cases, nearly 4,000 patients with other cancers, as well as 533 population controls. Subjects were interviewed about their occupation histories, and a team of industrial hygienists assigned their past exposures using a checklist of some 300 chemicals. The present analysis was restricted to a study base of men who had worked as farmers earlier in their lives. There were a total of 49 men with prostate cancers, 127 with other cancers and 56 population controls. We created a pool of 183 controls combining the patients with cancers at sites other than the prostate and the population controls. We then estimated the odds ratio for prostate cancer associated with exposure to each of 10 agricultural chemicals, i.e., pesticides, arsenic compounds, acetic acid, gasoline engine emissions, diesel engine emissions, polycyclic aromatic hydrocarbons from petroleum, lubricating oils and greases, alkanes with  $\geq 18$  carbons, solvents, and mononuclear aromatic hydrocarbons. Based on a model adjusting for age, ethnicity, education, and respondent status, there was evidence of a two-fold excess risk of prostate cancer among farmers with substantial exposure to pesticides [odds ratio (OR)=2.3, 95% confidence interval (CI) 1.1-5.1], as compared to unexposed farmers. There was some suggestion, based on few subjects, of increased risks among farmers ever exposed to diesel engine emissions (OR=5.7, 95% CI 1.2-26.5). The results for pesticides are particularly noteworthy in the light of findings from previous studies. Suggestions of trends for elevated risks were noted with other agricultural chemicals, but these are largely novel and need further confirmation in larger samples.

### INTRODUCTION

Prostate cancer is the most frequently occurring cancer among Canadian men.(1) Despite extensive research, the etiology of this disease remains poorly understood. Only a few risk factors for prostate cancer have been clearly established to date including age, a positive family history of the disease, and ethnicity. The normal function of the prostate is controlled by testosterone, and androgenic stimulation of the prostate over a prolonged period may promote or initiate carcinogenesis.(2,3) The prostate gland is also sensitive

to estrogens.(4) Administration of estrogens reduces testosterone production, and is used to control disseminated prostate cancer. However, there is epidemiologic and experimental evidence suggesting that estrogenic hormones may cause DNA damage and initiate prostate cancer.(5-9) Taken together, these observations suggest that both androgens and estrogens are associated with the risk of prostate cancer, and that exogenous factors that could influence hormone levels could play an etiological role. The large gradients in risks across ethnic groups, geographical areas and the evidence from migrant studies point out to a strong, as yet undefined, influence of environmental factors.(10) It is thought that prostate cancer could result from a complex interplay between several environmental, lifestyle and genetic factors. (10-13)

The possible etiologic role of environmental factors, such as those encountered in the workplace, has been

\*To whom correspondence should be addressed:

Marie-Élise Parent, Ph.D.  
Associate Professor, Epidemiology and Biostatistics Unit  
INRS-Institut Armand-Frappier  
531, Boul. des Prairies  
Laval, Quebec, Canada. H7V 1B7  
Email: marie-elise.parent@iaf.inrs.ca

reviewed.(12) A large number of studies have assessed the risk of prostate cancer in various occupation groups. Most of them were based exclusively on job titles, providing only indirect evidence of the underlying risk factors. There are some hints that occupational groups potentially exposed to pesticides, which include farmers but also pesticide manufacturers, workers exposed to metalworking-related substances, workers exposed to diesel engine emissions, to polycyclic aromatic hydrocarbons (PAH) and to cadmium might experience excess risks. The evidence is reviewed briefly here.

*Farming, pesticides and herbicides:* One puzzling observation is the generally consistent pattern for an excess risk of prostate cancer among farmers.(12) At least 100 studies have examined the relationship between farming (as a job title) and prostate cancer. Results from meta-analyses based on these are consistent with a weak, positive association.(14-17) However, with a summary relative risk of about 1.1, chance cannot be ruled out with certainty. The association might also reflect some systematic bias, possibly publication bias. Finally the positive association might reflect lifestyle factors or environmental factors such as occupational exposures. The slight excess of prostate cancers contrasts with low risks for most other cancers and non-neoplastic diseases among farmers.(14) The interpretation of this body of evidence remains uncertain.(18)

Very few studies to date have considered, other than in a very crude way, the role of specific chemical agents in the farmers' environment. Because several pesticides are estrogen-like compounds that can modulate hormone levels,(19) these agents are under particular suspicion. Yet the evidence for a putative role of pesticides in prostate cancer etiology is still very limited. Use of pesticides has been associated with prostate cancer in some(20-27) but not all studies.(28-32) Discordant evidence concerning hazards due to pesticides also comes from studies of workers involved in manufacturing or spraying of these compounds(33-42), and pesticide applicators.(4,43-55) Most of these studies were quite small. Early reports from the Agricultural Health Study Cohort regarding chlorinated pesticides are conflicting.(56,57) Finally, in a few studies,(58,59) but not all,(23,25,29,60) elevated risks for workers exposed to fertilisers have been reported. Genetic susceptibility might modify prostate cancer risk from pesticide exposure.(61,62)

Farming can involve a wide range of activities, including equipment operating, mechanical maintenance and repair, soldering, carpentry, livestock handling, pesticide, fertilizer application, etc. These can entail potential exposures to very diverse agents such as solvents, fuels and oils, metal dusts, welding fumes,

engine exhausts, paints, pesticides, herbicides, insecticides, fertilizers, zoonotic viruses, microbes, fungi, organic dusts, and sunlight. For most of these, evidence with regard to prostate cancer is lacking.

*Metalworking-related exposures:* Metal workers such as mechanics, repairmen, and machine operators may be at increased risks of prostate cancer.(63-65) However, in few studies were specific exposures examined. Among those that did, there was some evidence of associations with some metallic dusts and with metalworking chemicals, such as solvents, cutting oils, mineral oils, heating oils, hydraulic fluids, lubricating oils and acids.(64,66-69) These findings were not always replicated, however.(32)

*PAH and engine emissions:* There is some evidence, albeit not entirely consistent,(70) of excess risks in occupational groups with potential exposure to PAHs.(66,71-77) In a few studies that entailed substance-based exposure assessment protocols, one found excess risks in relation to liquid fuel combustion products and PAH as a class,(66) and another(78) found excess risk in relation to diesel fuel and fumes, soot, tar and pitch. Contrasting results, suggesting no association with PAHs or diesel fumes, have been reported as well.(32,67) Diesel engine emissions may induce changes in enzymatic activities in the prostate glands of animals.(78,79) In addition, the anti-estrogenic effects of certain hydrocarbons, such as benzo(a)pyrene, may promote the growth of prostate cancer cells. Several PAHs may interact with estrogen receptor signalling.(80)

*Cadmium:* Cadmium is found in some insecticides and fertilisers, and exposure can occur in several workplaces. Other sources include diet and tobacco smoke.(77) Following some early reports of excess risk of prostate cancer among cadmium-exposed workers, more recent and larger studies failed to confirm these.(81-83) Nevertheless, experimental data suggest that prostatic tumours can be induced experimentally in rodents by oral exposure to cadmium.(84)

Overall, the available evidence on occupational factors remains limited. The vast majority of studies of occupational circumstances and prostate cancer conducted to date were retrospective mortality studies in which job or industry titles as recorded on death certificates were used as indices of exposure. Although such studies are useful in providing leads, what is really needed are studies of occupational factors based on refined exposure assessment protocols.(18,85)

One of the most detailed and in-depth evaluations of the association between occupational exposures and prostate cancer has been carried out by our research group through analyses of our multiple-site, case-control study conducted in Montreal in the

1980s.(86,87) Several occupational substances exhibited moderately strong associations with prostate cancer, including metallic dust, liquid fuel combustion products, lubricating oils and greases, and PAH from coal.(66) Estimates of the proportion of prostate cancer cases in the population that would be attributable to occupational exposures ranged from 12 to 21 percent. These figures may have been somewhat overestimated and precision was low. Still, even if the true attributable fraction were in the range of 5 to 10 %, it would represent an important public health issue. Interestingly, we have recently found a similar pattern of risk in relation to prostate cancer for exposure to some of these substances during leisure-time activities.(88)

In order to further investigate the role of agricultural exposures in prostate cancer, we conducted a new analysis of the aforementioned Montreal-based study, this time focusing on men, both cases and controls, with a history of farming. Results from these analyses are reported here.

## MATERIALS AND METHODS

### Study sample

In the 1980s, our research group undertook a large population-based case-control study in Montreal to explore the relationship between hundreds of occupational exposures and 19 cancer sites. This study has been described in detail elsewhere.(86) Briefly, nearly 4,000 incident cancer cases, all males, were recruited, including 449 prostate cancer patients. A group of 533 population controls, frequency matched on age and residential area to the cancer patients, was also interviewed.

For the purpose of the present analyses, we restricted the case series to those 49 prostate cancer cases who had ever been farmers, and constituted a control series of 183 men who had also been farmers (combining 56 population controls and 127 patients with cancer at a site other than the prostate). No cancer type represented more than 20% of the entire group of 127 cancer patients.

### Data collection

Data were collected as part of face-to-face interviews. Information was collected on socio-demographic factors and lifestyle. A semi-structured questionnaire was used to obtain a detailed description of each job held by each subject over his lifetime. Trained interviewers probed for details about work activities, raw material used, work environment, etc. A team of expert chemists and industrial hygienists then reviewed each reported job and inferred the potential exposure to 294 chemical agents.

For each exposure thought to be present in the worker's environment, the team of chemists had to describe the degree of certainty that the exposure actually occurred (whether it was possible, probable or definite), the frequency of exposure (less than 5% of time in a normal work-week, 5 to 30% of time, or more than 30%), the relative concentration of the exposure (low, medium or high), and the number of years of exposure.

### Data analysis

Unconditional logistic regression was used to model the risk of developing prostate cancer associated with exposure to the selected chemicals during farming. Potential confounders entered into the regression models included age (years), ethnicity (French / Anglo / Italian / Other European / Other), educational level (years), and respondent status (self / proxy).

Ten chemicals were retained for analysis. Firstly, we selected 4 substances which had at least 20% lifetime prevalence of exposure among controls, and which were either of a priori interest based on studies of occupational groups, i.e., pesticides, diesel engine emissions, PAH from petroleum, and lubricating oils and greases. Secondly, we expanded the list of chemicals to be studied to include 6 other substances who had so-called suggestive odds ratios in this database, defined here as 1.3 or more. These were: arsenic compounds, acetic acid, gasoline engine emissions, alkanes with 18 carbons or more, solvents, and MAH.

Only those subjects categorized as "probably" or "definitely" exposed to the selected agricultural chemicals by the expert chemists/hygienists were considered as exposed. Moreover, we excluded from the analyses those subjects who had been exposed only in the 5 years before diagnosis or enrolment in the study.

We first conducted analyses categorizing subjects as never or ever exposed to the agricultural chemicals under study. For pesticides, for which there were sufficient numbers, we further restricted our analysis to a subset of subjects with "substantial" exposure, defined as having a medium or high frequency of exposure, a medium or high concentration of exposure and a duration of exposure greater than 5 years. Finally, we assessed the risk of prostate cancer associated with increasing concentration, frequency, and duration of exposure to pesticides.

## RESULTS

Farmers with prostate cancer were more often of French ancestry than control farmers (Table 1). Cases and controls differed marginally in terms of educational level and respondent status. Seventy nine percent of

Characteristics	Cases	Controls
Mean age (years)	63	61
Ethnicity (%)		
French	78	56
Anglo	2	7
Italian	12	22
Other European	8	13
Other	0	2
Mean educational level (years)	8	7
Proxy respondents (%)	14	17

**Table 1.** Characteristics of the 49 case farmers and 183 control farmers

farming occupations reported in this study population were as farm workers or farm labourers, while 21% were as farm manager, foreman or owner.

Subjects categorized here as exposed had been exposed only during farming, and never in other jobs held by farmers. There were in fact four substances which were exclusive to farming, namely pesticides, arsenic compounds, acetic acid and diesel engine emissions, which means that they were never encountered in other jobs that the farmers had held.

Table 2 shows the risk estimates for prostate cancer associated with ever exposure to the selected substances. Odds ratios were slightly elevated for all 10 chemicals studied, although only diesel engine emissions achieved statistical significance.

For pesticides (Table 3), we also assessed risks associated with exposure at the substantial level, as well as according to the different dimensions of exposure. Farmers with substantial exposure to pesticides had a significant, two-fold excess in risk, compared to unexposed farmers. The risk increased slightly with increasing frequency and duration of exposure. Nearly all exposures to pesticides were rated at the medium concentration level, precluding an evaluation of the risks with increasing concentration levels.

## DISCUSSION

Results from this analysis offer a glimpse at the role of pesticides on the risk of prostate cancer among farmers. One particular characteristic of this study is that it was based on both case and control farmers. Farmers tend to have a specific lifestyle related to their work activities. Nearly all previous studies of farmers and prostate cancer have used non-farmers as controls. Our approach might have made our cases and controls more homogeneous in terms of their lifestyle habits, thereby providing some internal adjustment for potential as yet undefined lifestyle-related risk factors for prostate cancer. However, by doing so, we might have attenuated our chances of observing differences in

risks associated with chemical exposures. For this reason, the odds ratios estimated here possibly represent conservative estimates of risk.

Advantages of the study include the detailed exposure assessment scheme, based on expert judgment, carried out on a case-by-case basis, and based on in-person interviews eliciting detailed job description and work practices. This exposure assessment approach is recognized as the reference method for such as study design.<sup>(89)</sup> Moreover, prostate cancer cases were incident cases, we had access to different control groups, and were able to adjust for some potential confounders.

The main limitation of this analysis is the small number of farmers it is based on, owing to the population-based nature of the study. We had no information on dietary habits. However, because this analysis was restricted to farmers, cases and controls might have been relatively comparable in this respect.

The types of pesticides used were not systematically elicited from the subjects. However, among those who volunteered the information, the most common types were "Paris Green" (a mixture of lead arsenate, acetic acid, and mineral oil), lime (calcium oxide), Dichloro-Diphenyl-Trichloroethane, and "Bouillie Bordelaise" (a mixture of copper sulfate and lime).

Investigating prostate cancer risks in relation to occupational exposures is important because exposure levels in the workplace may be higher than in the general environment and because most workplace substances find their way into the general

Exposure	N <sub>ca</sub>	OR	95%CI
Pesticides	25	1.4	0.7-2.7
Arsenic compounds	15	1.4	0.6-3.0
Acetic acid	12	1.5	0.7-3.4
Gasoline engine emissions	5	1.3	0.4-4.5
Diesel engine emissions	5	5.7	1.2-26.5
Polycyclic aromatic hydrocarbons from petroleum	6	1.4	0.3-5.8
Lubricating oils and greases	9	1.5	0.6-4.0
Alkanes with ≥18 carbons	9	1.8	0.7-5.0
Solvents	7	1.8	0.6-5.6
Mononuclear aromatic hydrocarbons	6	1.7	0.5-5.4

**Table 2.** Odds ratio (OR)\* and 95% confidence interval (CI) for prostate cancer associated with ever exposure to selected chemicals during farming

\*Adjusted for age, ethnicity, education, respondent status

environment.(85) Understanding whether occupational chemicals cause prostate cancer is important not only for prevention, but it can also contribute to an understanding of carcinogenesis. While there is still limited physiologic evidence on the extent to which different exogenous chemicals may affect the prostate gland, it is known that some chemicals (i.e., dioxins, diesel emissions) can alter enzymatic activity in the prostate.(79,90) Exposure to certain chemicals such as cadmium can induce prostate tumours in animals.(91)

A great deal of interest is being directed towards the hypothesis that certain environmental chemicals may act as endocrine disruptors or modulators.(2-4,19,92,93) Exposure during development and adult years could be relevant.(94) The effects may be due to their a) mimicking endogenous hormones such as estrogens and androgens, b) antagonising endogenous hormones, c) altering the pattern of synthesis and metabolism of hormones, and/or d) modifying hormone receptors levels. As hormonal influences are likely related to prostate cancer etiology, hormone-modulating exogenous chemicals are of particular interest.(95) Several industrial chemicals have been associated with endocrine-disrupting effects including some metals (cadmium, lead, mercury, aluminium), phenolic derivatives (phenol, bisphenol-A, pentachlorophenol, resorcinol, PCBs), phthalates (used as plasticizers), variously substituted benzenes (polycyclic aromatic hydrocarbons [PAH], benzo[a]pyrene), styrenes (used in the manufacture of plastics and rubber), carbon disulphide (used in the production of rayon), dioxin, and several organochlorine pesticides, fungicides and herbicides.(93,96-100) Extremely low exposures to some endocrine modulators (plasticizers, alkylphenols) have been found to induce adverse effects on the male reproductive tract of rodents.(100) Considerable

concentrations of chlorinated hydrocarbons can accumulate in the male genital tract, in the reception zone for spermatozoa.(101) Also, endogenous estrogens are bound to the sex hormone-binding globulin while many exogenous estrogens are not, resulting in higher concentrations of free compounds.(19) Taken together, this body of evidence suggests that exposure to a wide variety of exogenous chemicals would modulate hormone levels, which in turn, could influence prostate cancer development.

## CONCLUSION

In conclusion, farmers exposed to high levels of pesticides had a two-fold excess risk of prostate cancer compared to unexposed farmers. Exposure to diesel engine emissions was also associated with elevated risks, but statistical precision was low. Hints of excess risks were noted for other chemicals. Some of these tended to be correlated to one another, which would explain why risk estimates were similar for several of the chemicals studied. For instance, arsenic compounds and acetic acid are common ingredients in some pesticides. Conversely, activities involving agricultural machinery repairs would be expected to entail conjoint exposure to several chemicals such as lubricating oils and greases, solvents and engine emissions.

The results presented here are based on a limited sample. Nevertheless, in light of the accruing epidemiological and experimental evidence, further exploration around these potential associations is warranted. The Agricultural Health Study, a US-based prospective cohort study initiated in 1993, currently follows a large group of pesticides applicators from Iowa and North Carolina. It is hoped that upcoming results from this large study will shed light on the health risks, including prostate cancer, incurred by agricultural workers.

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Pesticides	N <sub>ca</sub>	OR	95%CI
<b>Level of exposure</b>			
Any	25	1.4	0.7-2.7
Substantial	17	2.3	1.1-5.1
<b>Frequency of exposure</b>			
Low	7	0.9	0.3-2.3
Medium or high	18	1.7	0.8-3.6
<b>Duration of exposure</b>			
Up to 10 years	11	1.2	0.5-2.8
More than 10 years	14	1.5	0.7-3.4

**Table 3:** Odds ratio (OR)\* and 95% confidence interval (CI) for prostate cancer associated with exposure to pesticides during farming by level, frequency and duration of exposure

\*Adjusted for age, ethnicity, education, respondent status

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**Marie-Élise Parent** is Associate Professor in Epidemiology at INRS-Institut Armand-Frappier, Université du Québec. She graduated from the University of Toronto (M.Sc. 1988) and from the Université de Montréal (Ph.D. 1994). Her main research interests relate to studying the role of environmental, lifestyle and genetic factors in cancer development. She has held career awards from the Fonds de la recherche en santé du Québec, and receives grant support from the Canadian Cancer Society / National Cancer Institute of Canada, and from the Canadian Institutes of Health Research. She is a member of the Board of Directors of the Canadian Society for Epidemiology and Biostatistics.