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Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987–1991

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Background Nitrate and atrazine are two chemicals that are heavily used in certain sectors of agriculture. They are suspected to be associated with the development of certain types of tumours.

Methods Existing data were obtained on the incidence of specific types of cancers, contamination of drinking water with atrazine and nitrate, and related agricultural practices for the 40 ecodistricts in the province of Ontario. The data were merged into a georelational database for geographical and statistical analyses. Weighted (by population size) least squares regression analyses were conducted while controlling for confounding socioeconomic and lifestyle factors. Maximum likelihood spatial error models were estimated when least square regression error terms were found to be spatially autocorrelated using the Moran's I statistic.

Results Atrazine contamination levels (range 50–649 ng/l, maximum acceptable concentration [MAC] = 60 000 ng/l) were positively associated ($P < 0.05$) with stomach cancer incidence and negatively associated with colon cancer incidence. Nitrate levels, (range 0–91 mg/l, MAC = 10 mg/l) were negatively associated with stomach cancer incidence.

Conclusion The associations found at the ecodistrict level, both positive and negative, if confirmed by other studies, raise serious questions about maximum allowable limits for atrazine, as well as possibilities of complex trade-offs among disease outcomes, and interactions of biophysical and social mechanisms which might explain them. Although the negative associations appear to have no direct biological explanations, such counter-intuitive outcomes may occur in complex systems where social and biological variables interact.

Keywords Colon, stomach, cancer, atrazine, nitrate, agroecosystem, water, spatial

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Spatial variations in health, disease and mortality rates provide investigational opportunities that may yield information on both (a) relationships with spatially distributed social and environmental risk factors, and (b) spatial clustering of the rates or risk factors within geographical areas. Analyses conducted by Walter[1,2] have shown that, in Ontario, there have been regional patterns of cancer incidence along with known variation in relevant risk factors for certain cancers, making Ontario 'a suitable location for the further study of the relationship between environment and cancer'. He goes on to suggest that future efforts might include an extension of the ecologic approach to relate cancer incidence and relevant exposure data.

One important source of exposure to potential carcinogens in agroecosystems is through water contamination by agrichemicals. Modern agriculture has become one of the major contributors to water contamination.[3] Indeed, contamination of groundwater with atrazine and nitrate has been shown to be a problem in Ontario agroecosystems.[4] Elsewhere, studies[5–10] have shown equivocal correlations and/or associations between atrazine and/or nitrate and non-Hodgkin's lymphoma and cancers of the bladder, colon, nervous system, stomach and ovary. Any potential relationships are still inconclusive.

In 1995, an Ecological Regionalization[11] divided Canada, with increasing resolution, into ecozones, ecoregions, ecodistricts

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and soil landscapes using a number of criteria, including: climate, soil type, water drainage patterns, natural flora and fauna, and agricultural practices which were closely related to the previous attributes. In a related paper, ecodistricts, both conceptually and empirically through an analysis of homogeneity of exposure data, were found to be the preferred spatial configuration and scale for aggregate data regression analysis, compared to census divisions, sub-divisions or health units.[12]

The purpose of this observational study was to investigate aggregate level associations among human cancer incidence, atrazine and/or nitrate contamination of drinking water, and related agricultural practices in Ontario agroecosystems for 1987–1991. There were two units of interest for this research, the agroecosystem level—represented by the ecodistrict, the unit of analysis—and the individual human level.

Methodology

Data collection and handling

The dependent variables used in the analyses were age-standardized cancer incidence ratios for 1987–1991; specifically, cancers that have been hypothesized to be associated with either atrazine or nitrate exposure: cancers of the stomach, colon, ovary, bladder, and central nervous system, and non-Hodgkin's lymphoma (ICD-9 codes 151.0–151.9; 153.0–153.9, 159; 183.0–183.9; 188.0–188.9; 191.0–192.9; 200.0–200.9 and 202.0–202.9, respectively[13]). Cancer data were obtained, by census sub-division (CSD), from a cancer surveillance programme of the entire Ontario population, the Ontario Cancer Registry (OCR). The OCR raw data, as well as the other data, were aggregated into ecodistricts utilizing a geographical information systems software package.[14] Cancer incidence rates were calculated for each of the 40 ecodistricts in Ontario as follows: the number of new cases of cancers in each ecodistrict during 1987–1991, divided by the number of person-years of population-at-risk during 1987–1991. The population-at-risk was imputed by summing the 1991 population with the estimated annual populations for the inter-censal years, 1987–1990, assuming proportional population change between 1986 and 1991. The cancer incidence rates were then indirectly age standardized using sex-specific 5-year age groups to ensure stable age-standardized incidence rates for each sex.

Exposure data were sub-divided into (a) water contamination data, (b) agricultural practices data, and (c) other confounding variables data. First, water contamination data were derived from two sources: the Ontario Drinking Water Surveillance Program (ODWSP: a municipal water supplies monitoring system) and the Ontario Farm Groundwater Quality Survey (OFGQS: a 1991–1992 survey of 1300 farm wells[4]). Mean contamination levels were determined for each ecodistrict and data source, and then means were proportionally combined according to the ED population they represented, to create one overall average contamination level for each ecodistrict, using the following formula:

$$COMBINEDlevel = (ODWSPlevel * \frac{ODWSPpopulation}{TOTALpopulation}) + (OFGQSlevel * \frac{1 - ODWSPpopulation}{TOTALpopulation})$$

Table 1 Range and distribution of nitrate and atrazine contamination levels in drinking water, and person-years of observation in Ontario agroecosystems, 1987–1991

Parameter	Nitrate (mg/l)	Atrazine (ng/l)	Person-years of observation
Minimum	0.05	50	96 603
25th percentile	0.7	93.78	293 842
Median	1.52	125.9	629 569
75th percentile	2.63	184.66	1 294 300
Maximum	7.79	649.43	11 212 575
Average	2	162.74	1 207 859

The Ontario Landscape Resource Unit, under the auspices of Agriculture and Agri-food Canada, provided data on landuse and pesticide, fertilizer and manure application from three sources: (a) the 1991 Census of Agriculture; (b) the 1986 Census of Agriculture; and (c) the 1988 and 1983 Surveys of Pesticide Use in Ontario. Each of the variables was divided by the ecodistrict area in square kilometres to account for differing ecodistrict sizes and then included in the multiple variable modelling process to differentiate between agrichemical exposure through drinking water contamination and exposures through other routes such as skin contact or inhalation at time of application.

Data for a number of other potential confounding variables, such as alcohol consumption, smoking, education level, income, and occupational exposures were also obtained from the Ontario Health Survey[15] and the 1991 Census of Canada. Walter and Hayes[16] used many of these potential confounding variables in their investigation of associations of cancer incidence and drinking water quality in Ontario. From the census and survey data, average responses for each ecodistrict were subsequently determined in order to produce average values for the potential confounding variables at the ecodistrict unit of analysis.

Statistical analyses

Descriptive statistics (Table 1) and the omnibus test developed by D'Agostino and Pearson[17] were performed to determine the distributional structure of the data. Various transformations were tested in order to normalize the cancer incidence ratios. The ratio or transformed ratio with the lowest K^2 (most normally distributed) was selected for subsequent regression analyses. Independent variables were normalized in the same manner.

Least squares regression analyses were conducted between each of the cancer incidence ratios and the two independent variables of interest—mean nitrate and mean atrazine contamination levels of drinking water. All regressions were weighted by population size due to large population disparities among ecodistricts.

Cancers which were associated with either of the two independent variables of interest to $P < 0.25$ (Table 2) were further analysed in multiple variable least squares regression analyses with the full complement of independent variables using a forward stepwise procedure with entry and stay criteria set at $P < 0.15$ and $P < 0.05$, respectively. Nitrate and atrazine contamination levels were forced into the models in separate analyses due to *a priori* hypotheses of their relationships with the dependent variables. Two-way interaction terms between

Table 2 *P*-values < 0.25 from regression results for age-standardized incidence ratios of various cancer types by sex in Ontario agroecosystems, 1987–1991

	Nitrate level *P* (coefficient sign)		Atrazine level *P* (coefficient sign)	
Cancer type	Female	Male	Female	Male
Bladder	–	–	–	–
Colon	0.048 (+)	–	0.041 (–)	0.006 (–)
Brain	0.101 (+)	0.072 (+)	–	–
Non-Hodgkin's lymphoma	–	–	–	0.075 (–)
Stomach	0.003 (–)	0.0001 (–)	0.242 (+)	0.046 (+)
Ovary	–	N/A	–	N/A

– *P*-value was > 0.25.

significant independent variables were offered in subsequent analyses.

Goodness of fit of the final models was examined using a number of techniques. First, the residuals of the final models which contained nitrate and/or atrazine contamination of drinking water were tested for spatial autocorrelation with the Moran's I statistic.[18] A binary weighting scheme was adopted, representing adjacency of ecodistrict pairs. The adjusted R^2 and plot of regression residuals versus predicted values were also examined.

Where goodness of fit was poor, regressions and goodness of fit assessments were repeated using an alternate weighting factor, the reciprocal of the square of the studentized residuals (residuals/standard error of the residuals), as suggested by Pocock.[19] Maximum likelihood spatial error models were estimated using the software package[20] SPACESTAT™ when least square regression error terms were found to be spatially autocorrelated, as suggested by Anselin.[21]

Results

The following cancers met the entry criterion ($P < 0.25$) for the multiple variable least squares regression analyses: cancer of the colon, brain and stomach with drinking water nitrate exposure in women; brain and stomach cancers with drinking water nitrate exposure in men; colon and stomach cancer with drinking water atrazine exposure in both men and women; and non-Hodgkin's lymphoma with drinking water atrazine exposure in men.

Of the multiple variable least squares regression analyses of the cancers with $P < 0.25$, only the models with the dependent variables stomach and colon cancer produced significant associations ($P < 0.05$) with atrazine and/or nitrate contamination levels. In the case of stomach cancer in men, age-standardized incidence ratios were found to be positively associated with atrazine levels in drinking water, and negatively associated with nitrate levels in drinking water and education level. Identical results were obtained with and without forcing drinking water nitrate and atrazine exposure.

Goodness of fit diagnostic tests resulted in a Moran's I statistic of –0.2141, an adjusted R^2 of 0.6313 and some coning in the plot of regression residuals versus predicted values. Therefore, the final model was refit, using an alternate weighting factor, the reciprocal of the square of the studentized residuals, producing a model with three variables significantly associated with the square root of the age-standardized stomach cancer incidence ratios for men, as shown in Table 3.

Table 3 Multiple variable regression results for the square root of age-standardized incidence ratios of stomach cancer in men in Ontario agroecosystems, 1987–1991

Variable	Parameter estimate[a]	95% CI
Intercept	1.45	1.20, 1.70
Ln(Atrazine) (ng/l) in water	0.245	0.198, 0.293
Ln(Nitrate) (mg/l) in water	–0.136	–0.151, –0.122
Ln(Population per cent with <Grade 9 education)	–0.05	–0.067, –0.033

[a] Parameter estimates are small due to dependent and independent variable normalization.

The goodness of fit diagnostic tests were much better with the alternate weighting, with an improved adjusted R^2, a non-insignificant Moran's I of 0.0254, and very little coning in the residuals plot. Interpreting the final model, while mathematically holding the other variables constant, for each 100 ng/l increase in atrazine levels found in drinking water, there was an observed increase of 0.6 of a case of stomach cancer per 100 000 person-years at risk, respectively.

Similar results were found for stomach cancer in women. Age-standardized incidence ratios were found to be positively associated with atrazine levels in drinking water, 1990 occupational industrial chemical exposure and fertilizer expenditures in 1991, and negatively associated with nitrate levels in drinking water and per cent of families with low income in 1991. Interaction variables were insignificant for both men and women. Interpreting the final model, while mathematically holding the other variables constant, for each 50 ng increase in atrazine levels found in drinking water, there was an observed increase of 1.0 case of stomach cancer per 100 000 person-years at risk, respectively.

In the case of colon cancer in women, age-standardized incidence ratios were found to be negatively associated with atrazine levels in drinking water, and positively associated with tonnes/km^2 manure applied in 1991 and education levels in 1991. Goodness of fit diagnostic tests again resulted in a moderate adjusted R^2 of only 0.4554, a Moran's I of –0.0642, and a mild diagonal distribution of residuals in a plot of regression residuals versus predicted values. However, refitting the model using the alternate weighting factor did not improve the model fit. The final model results are shown in Table 4.

Similar results were found for colon cancer in men. Age-standardized incidence ratios were found to be negatively associated with atrazine levels in drinking water, and positively

Table 4 Multiple variable regression results for the cube of age-standardized incidence ratios of colon cancer in women in Ontario agroecosystems, 1987–1991

Variable	Parameter estimate[a]	95% CI
Intercept	186 004	95 627, 276 381
Ln(Atrazine) (ng/l) in water	–21 783	–38 927, –4639
Amount (tonnes/km^2) of manure applied in 1991	38	14, 62
Ln(Population per cent with <Grade 9 education)	11 833	3348, 20 318

[a] Parameter estimates are large due to dependent variable normalization.

associated with per cent smokers and per cent of families considered low income. Identical results were obtained with and without forcing drinking water atrazine exposure. Interaction variables were insignificant for both men and women.

Discussion

It was found that, although other relationships were suggested when analysed in isolation, in the presence of potential confounding variables, only cancers of the colon and stomach were significantly associated with one or both of the two variables of interest. It is possible that additional relationships may have been present in the research data but due to the limited number of ecodistricts under analysis, the power of the study was only large enough to detect stronger associations.

With regard to the colon cancer results, it appeared that atrazine levels had a sparing effect on colon cancer incidence, however, there is no biological plausibility for such a conclusion. One plausible explanation is that areas with the climate and soil that were more suitable for corn production (the primary crop for atrazine application), were also more suitable for vegetable production, leading to higher consumption of vegetables, constituents of which are known to have sparing effects on colon cancer.[22] From the 1991 agricultural census, there was a positive correlation ($r = +0.45$, $P = 0.0043$) between grain corn production and vegetable production. Further research may elucidate this relationship.

Other variables in the colon cancer models for men and women were not surprising. Smoking is a known carcinogen for many sites in the body, although for colon cancer, it is, at best, a weak carcinogen.[22] Similarly, socioeconomic variables such as low income and lower education levels are also known indirect risk factors of health and disease, again including cancers.[23] It is unclear why tonnes per square kilometre of manure applied in 1991 was found to be positively associated with colon cancer. There is little evidence to support the hypothesis that excess nitrate exposure contributes to colon cancer incidence.

The regression results for stomach cancer contradict findings from other researchers which found positive associations or correlations with drinking water nitrate levels.[24,25] Neither of these earlier studies accounted for potential synergistic actions or complex feedback loops which one would expect to find in agroecosystems. For instance, the earlier research on nitrates did not examine atrazine levels, which in this study were found to be positively correlated with nitrate levels (Pearson's correlation coefficient $r = 0.3336$, $P = 0.0354$), and equally or more strongly associated with stomach cancer than nitrate levels in the final models. Nitrate may have been a confounding variable for unmeasured exposure to atrazine. Weisenburger[26,27] has suggested that nitrate and atrazine may actually act in concert to form nitroso-atrazine compounds which may be more carcinogenic than either chemical in isolation. Nitroso-atrazine was not among the chemicals analysed in the ODWSP or OFGQS to test this hypothesis.

Obtaining similar direction and strength of association between drinking water nitrate and atrazine exposure and stomach cancer incidence in both the male and female population of Ontario, determined within highly statistically significant ($P = 0.0001$) models, strengthens the argument that the associations are not occurring simply by chance alone. However, this research does not provide conclusive evidence of causality at the ecodistrict scale because data on drinking water contaminants were not available prior to the period of cancer incidence, and therefore temporality could not be specifically established. Total triazine (the family of herbicides to which atrazine belongs) application for the province of Ontario declined from 1983[28] to 1988[29] by 37% and from 1988[29] to 1993[30] by another 31%. Therefore, atrazine levels in drinking water during the 1987–1991 period were likely to be lower than in years before that, and thus, the concern for temporality and an appropriate lag phase is reduced. Perhaps future studies may address this deficiency, along with other conditions of causality such as consistency and coherence.

Other variables in the stomach cancer models were again not surprising. Socioeconomic variables such as low income and lower education levels are known indirect risk factors of health and disease, including cancers.[23] Similarly, many industrial chemicals are also known to be risk factors of various cancers[31,32] and therefore their self-reported exposure could be expected to be positively associated with stomach cancer. Fertilizer expenditures per square kilometre were also found to be positively associated with stomach cancer incidence, a variable which may be modifying the effect of the nitrate contamination level of drinking water on stomach cancer.

It should be noted that so-called 'ecologic studies', the type of analysis conducted in this research, have a number of weaknesses, including ecologic fallacy and multiple collinearity.[1] However, as explained by Schwartz,[33] ecological studies may give more valid and reliable results in situations where there is widespread exposure (i.e. individual level studies may be misleading because they leave out the interactions of social and ecological variables at the population level). Individual level studies that corroborate ecological studies may help to clarify why ecodistrict level outcomes are found, but they do not necessarily discredit those ecological associations if opposing results are found. For example, atrazine itself may or may not have specific consequences for individuals involved, but the use of atrazine may occur in a context which includes both direct biological consequences and various feedback loops which result in other, equally real but perhaps context specific, consequences.

In conclusion, it would appear that at the level of the ecodistrict, atrazine contamination levels in drinking water were positively associated with stomach cancer incidence and negatively associated with colon cancer incidence in Ontario during 1987–1991. The aggregate level associations were found despite the fact that all of the atrazine exposure levels, ranging from

50 ng/l to 649 ng/l, were below current Ontario maximum acceptable concentration (MAC) limits of 60 000 ng/l, the exposure limit that has previously been considered to be safe. Acceptable levels in some other countries are lower, including the US (3000 ng/l) and Europe (100 ng/l).

If these results are confirmed by other studies, serious questions arise regarding maximum allowable limits for atrazine, as well as possibilities of complex trade-offs among disease outcomes, and interactions of biophysical and social mechanisms which might explain them. Although the negative associations appear to have no direct biological explanations, such counter-intuitive outcomes may occur in complex systems where social and biological variables interact.

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