Triazine Herbicide Exposure and Breast Cancer Incidence: An Ecologic Study of Kentucky Counties

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The incidence of breast cancer in the United States has steadily increased for the past three decades. Exposure to excess estrogen, in both natural and synthetic forms, has been implicated as a risk factor for the development of this disease. Considerable interest has been focused on organochlorines, such as the triazine herbicides, and their possible role in the initiation or promotion of human breast cancer. To explore this relationship, an ecologic study of Kentucky counties was designed. Exposure to triazines was estimated by use of water contamination data, corn crop production, and pesticide use data. A summary index of triazine herbicide exposure was developed to classify counties into low, medium, or high exposure levels. Data on county breast cancer rates were obtained from the state registry. A Poisson regression analysis was performed, controlling for age, race, age at first live birth, income, and level of education. Results revealed a statistically significant increase in breast cancer risk with medium and high levels of triazine exposure [odds ratio (OR) = 1.14, $p<0.0001$ and OR = 1.2, $p<0.0001$, respectively]. The results suggest a relationship between exposure to triazine herbicides and increased breast cancer risk, but conclusions concerning causality cannot be drawn, due to the limitations inherent in ecologic study design. *Key words*: breast cancer, ecologic study, organochlorines, pesticides, triazine herbicides, xenoestrogens.
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The chlorotriazine herbicides (atrazine, simazine, and cyanazine) have been widely used throughout the United States for over 35 years. They control many broadleaf weeds and some grasses. Primarily applied in corn production, these pesticides are also used on citrus, nuts, sugarcane, sorghum, and cotton. In terms of total weight used over the past 30 years, atrazine is one of the two most used pesticides in the United States (1). In Kentucky, 1 million or more pounds of atrazine are applied annually, making it the state's most heavily used pesticide (1–3).

In the early 1980s, hydrology testing detected atrazine and cyanazine in ground and surface water throughout the United States. This finding, paired with studies showing increased incidence of mammary tumors in rats exposed to chlorotriazines (4,5), prompted action by the EPA. The three chlorotriazines were classified as Group C (possible human) carcinogens. Starting in 1990, voluntary restrictions regarding the use of these pesticides were encouraged, including decreased maximum application rates and establishment of setbacks and buffer zones to avoid contamination of surface water. State testing of surface water for triazines was federally mandated in 1993 and maximum contaminant levels (MCLs) were established.

In addition to the widespread use of these compounds, two characteristics render them pervasive in the environment and of increased concern for exposure. First, they are quite mobile. Second, they are slow to metabolize. It is estimated that anywhere from 0.1 to 3% of atrazine applied to fields is lost to the aquatic environment from run-off after heavy rains (1). Measurements of atrazine in runoff water often reveal levels that are 3–5 times greater than the MCL (1). Metabolism is slow once these chemicals leach into the subsoil, due to low microbial populations and anaerobic conditions (6). The half-lives of these compounds vary considerably with soil conditions; they can persist for several months to several years. Over long periods of use, pesticide residues accumulate and concentrate in ground water. In addition, the degradates of these chemicals, especially the chloro metabolites, are considered to be as potent as the parent compounds with regard to carcinogenicity (1).

Whether the triazine herbicides cause cancer in humans is still a subject of debate. Researchers have drawn a tentative link between exposure to organochlorines and the development of human breast cancer (7). They theorize that these compounds, dubbed xenoestrogens, may initiate or promote breast cancer through several mechanisms. Some xenoestrogens may promote cancer by enhancing the production of more potent, genotoxic estrogens; others may induce genetic mutations in cells of the breast. Recent experimental and epidemiological evidence supports a role for environmental estrogens in initiating or promoting breast cancer (4,5,8–21). This proposed role merits further study for several reasons.

First, the incidence of breast cancer in the United States steadily increased from the 1940s until 1987 (22,23); this increase occurred during the peak years of organochlorine use and is not accounted for by better screening (23). Second, much of breast cancer etiology remains unexplained; established risk factors, including genetics, account for only 30% of breast cancer cases (7). Finally, total lifetime exposure to estrogen is one of the few, well-documented risk factors for the development of this cancer.

Various experimental studies have assessed the estrogenic properties of organochlorines. DDT, polychlorinated biphenyls (PCBs), chlordane, and heptachlor produce estrogenic effects such as uterine weight gain (12) and enhanced proliferation of human breast estrogen-sensitive cells (13,14). Exposure to triazine herbicides increased the incidence of mammary tumors in both male (4) and female (5) rats. Results of epidemiological studies of organochlorines and human breast cancer have been mixed. Studies concerning DDT exposure and breast cancer risk (15,16) have been too small to rule out relative risks on the order of 1.1–2.0, the magnitude of effect noted with established risk factors (24). Other studies have shown increased breast cancer risk associated with exposure to dioxin [standardized mortality ratio (SMR) = 2.15; confidence interval (CI), 0.98–4.09] (17), polycyclic aromatic hydrocarbons (18), pharmaceuticals (19), and hazardous waste [odds ratio (OR) = 8.2; χ^2 = 11.64; $p<0.0009$] (20). Similarly, a population study in Israel revealed a decrease in breast cancer rates after a decline in the use of DDT, lindane, and α-BHC pesticides (21). Recent findings by Arnold et al. have intensified discussion about xenoestrogens (25). These researchers found that combinations of otherwise mildly estrogenic compounds

were synergistic, with estrogenic properties up to 1,600 times more potent than any single chemical studied in a yeast estrogen system. But these findings were not reproducible, and the study was later withdrawn. Overall, the body of literature linking xenoestrogens and human breast cancer is inconclusive.

To further study the proposed link between breast cancer incidence and triazine herbicide exposure, an ecologic study of Kentucky counties was designed. Many ecologic studies have been done to examine the relationship between environmental exposures and cancer using townships, census tracts, or other defined geographic areas as the units of analysis (26–29). Ecologic studies are quick, inexpensive, and subject to certain conditions. Ideally, the exposure sources used should meet two criteria to ensure differences across a population. First, exposure sources should have a range of contaminant concentrations. For example, a state that is divided into a large number of counties having varying levels of pesticide use may meet this condition. Second, sources should be discrete; that is, groups should be exposed primarily through one identifiable source, such as local ground or surface water. Meeting this second condition is difficult for several reasons. Within states and counties, use of ground and/or surface water may vary or be mixed. Also, water suppliers cross county lines, making it difficult to identify discrete sources of exposure for each county. To overcome these limitations, inclusion of surrogate exposure data, such as crop production or pesticide use, has been suggested (30). By including data on crop production, it is possible to have county-specific indicators of pesticide exposure. Similarly, data on the amount of pesticide used is often available at the county level. Because they are more county specific and because they obviate the identification of a source, surrogate data such as these are complementary to water contamination data.

Methods

Study design and population. An ecologic study was designed using county-level data from the 120 counties in Kentucky. The state has a mix of urban and rural areas, with corn production being highest in the west. About 3.7 million people live in Kentucky and residents are predominantly (92%) white (31). Within the state, approximately 70% of residents use surface water; the remainder use wells or other sources for their water. Well water usage is most common in the eastern part of Kentucky (Fig. 1).

For each county, demographic data on racial composition, median family income

and level of education were retrieved from the 1990 census (31). Information on first birth rates in 1990 for women over age 30 was collected from the Kentucky Department for Health Services (Vital Statistics Division, unpublished report).

Exposure measurement. This study made use of previously collected data from several sources. All data were reported at the county level. Data on groundwater contamination with triazines were gathered from a Kentucky Geological Survey report (32). From 1990 to 1991, this group conducted a study on the quality of groundwater in counties across the state. As part of this program, 4,859 wells were tested for a variety of chemicals, including triazines; this represents 2.3% of the state's wells. Participation in the study was voluntary, and the wells tested were not randomly selected. Multiple samples were taken from each well at various times of the year. A strict sampling protocol was followed, and all samples were tested at one state-certified lab. Triazines were measured by immunoassay, and 10% of samples were verified by gas chromatography. Immunoassay is fast and inexpensive, but less reliable than gas chromatography. The sample readings were averaged to generate a single measure of exposure for each county. Concentration of triazines was reported in micrograms per liter. A total of 1,735 samples representing 79 counties was tested for triazines. Graves County was sampled most heavily with 102 measurements; 24 counties had 5 or less samples taken. Oversampling was done in counties with a history of heaviest triazine use.

Data on surface water contamination were made available through unpublished reports of the Division of Water of the Kentucky Environmental Protection Cabinet. Under federal mandate, municipal or surface water testing for triazines has been done quarterly since 1993. Water was tested directly from the faucets of nonrandomly selected homes in counties all over the state. Each home was selected to be representative

of the sites served by the distribution system. Samples were drawn in accordance with EPA protocol, and testing was performed only at labs that were state certified to perform triazine testing. Triazine levels were measured by gas chromatography. Standard quality controls were observed during sample testing. Since 1993, 3,254 triazine levels have been measured, representing 113 counties. Results were reported as positive or negative detections and not as actual values. Letcher County had the most testing, with 177 samples taken; 5 counties had less than five tests done. Sampling was not evenly distributed.

In addition to the water contamination data, we designated two surrogate measures of pesticide exposure. Information on acres of corn planted in each county for the years 1970, 1980, and 1990 was compiled from Kentucky Agricultural Statistics (33). Atrazine is most widely used for corn crop production in this state, so acres of corn planted serves as a reasonable proxy of atrazine use. Corn growth varied by county, with Henderson County planting the most over the 3 years. Correlation coefficients revealed no significant difference ($r^2 = 0.94$) in crop patterns between the years; therefore a single year of data (1970) was used in the analysis.

A final source of information on pesticide exposure came from the University of Kentucky College of Agriculture. A 1979 survey of the amount of pesticide used by applicators in each county was examined (34). Applicators in Christian County used the most pesticide (7.8% of the state total); five counties used less than 0.01% of the state total. A specific breakdown of triazine use was not available; however, herbicides generally constitute about 85% of all pesticides used in Kentucky.

Disease measurement. Kentucky has maintained a statewide cancer registry since 1991. The completeness of the registry has improved each year, based on comparison of the expected and reported number of cancer cases in each county. The expected number of
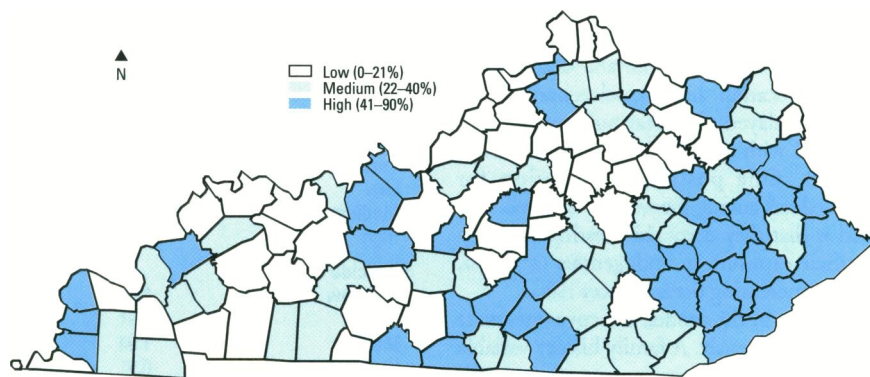

Figure 1. Percentage of homes using groundwater in Kentucky counties. Data from 1990 U.S. Census (31).

cases was calculated by applying Surveillance, Epidemiology, and End Results (SEER) program age-specific rates to the Kentucky population. In 1991, the registry received information on 92.2% of expected cases (Kentucky Cancer Registry, unpublished report). Underreporting of cases was noted consistently in the southwestern and central parts of the state for the first few years of data collection (T. Tucker, personal communication). By 1994, registry completion reached 100%. According to the latest registry report, breast cancer is the second most commonly occurring cancer in the state; from 1991 to 1994 there were about 9,900 new cases of female breast cancer in Kentucky (35,36).

Breast cancer incidence rates for each county were calculated from registry data for the period 1991–1994. Two-year age-adjusted rates for 1991–1992 and 1993–1994 were used. The breast cancer rates were reported as number of cases per 100,000 women. Reporting of cases was based on county of residence at the time of diagnosis.

Data analysis. Based on the water contaminant, corn planted, and pesticide use variables, counties were categorized by exposure status. Categorical exposure levels were defined for each variable, empirically derived from inspection of the distribution of values. Categories were then assigned corresponding numeric values from 0 to 4. Missing values in any of the four categories were reconciled by generating the average of the three known exposure variables for that county. To yield a summary index of triazine exposure for each county, the numeric values for each of the four exposure categories were summed, producing a range of scores from 3 to 16. The summary index was then divided into low, medium, and high exposure categories based on inspection of the data.

County-level predictor variables included in the models were percentage of black residents, percentage of women 25 years of age and older with at least a bachelor's degree, median family income, and delayed childbearing, measured as a rate of first births to women aged 30–44. Because breast cancer rates are higher for whites, the racial composition of counties is an important variable (22). Higher education, higher socioeconomic status, and delayed childbearing have all been associated with a higher risk of breast cancer (37,38). One possible explanation for increased risk among the wealthy and well-educated is that they delay childbearing, prolonging their exposure to endogenous estrogen, thereby increasing breast cancer risk.

For use in the model, the covariates were coded continuously. A family history variable was not included; it was not possible to estimate the percentage of women with a family history of breast cancer in each county.

A Poisson regression analysis was performed with each of the individual exposure variables and the summary index. The rationale for using the Poisson model in cancer epidemiology is well documented (39). The Poisson regression approach allows for the statistical modeling of data when there is a small number of events within strata, such as with cancer studies; it also allows for simultaneous control of covariates. Weighting of the breast cancer data was not necessary, as the rates were already standardized to the 1970 U.S. population. Separate regressions were run for the 1991–1992 and 1993–1994 breast cancer rates.

Odds ratios (OR) were calculated from the parameters generated by the models. A linear regression of the model was also done, yielding very similar results. Analysis was performed using the PC-SAS software package (40).

Results

All 120 counties of Kentucky were examined in this analysis, representing a population of approximately 1.9 million women. Table 1 shows the characteristics of the triazine exposure data. Of the groundwater samples reported, only 0.3% exceeded the triazine MCL of 3 µg/l. The percentage of surface water samples exceeding the MCL is unknown; results were reported as positive detections, not actual levels.

Table 2 is a summary of the Poisson regression results using the four individual exposure variables. Regression with the 1991–1992 breast cancer data showed that positive surface water detections of triazines, for both low and high exposed counties, were associated with a statistically significant increased incidence of breast cancer (ORs = 1.10 and 1.18, respectively). The higher the levels of contamination in surface water, the higher the incidence of breast cancer. Contamination of groundwater showed a less consistent result. Only low levels of groundwater triazines were associated with a statistically significant increased breast cancer incidence (OR = 1.17). Both acres of corn planted and pesticide use showed a protective effect at various levels.

Regression with the 1993–1994 cancer

Table 1. Characteristics of exposure data

Measurements of exposure	Mean ± SD	Counties with data (n)
Triazine levels in groundwater (µg/l)	0.11 ± 0.19	79
Triazine detections in surface water (% of positive detections)	5.56 ± 9.14	113
Corn growth by county (acres planted, in 100s, 1970)	96.84 ± 110.90	120
Pesticide use by county (% of state total, 1979)	0.85 ± 1.37	115

SD, standard deviation.

Table 2. Odds ratios (ORs)[a] for groups of counties classified according to various triazine exposure categories (2-year age-adjusted breast cancer rates)

Exposure category	1991–1992 Breast cancer rates		1993–1994 Breast cancer rates	
	OR	CI	OR	CI
Groundwater contamination				
Very low	1.00	–	1.00	–
Low	1.17	1.11–1.24	1.10	1.04–1.16
Medium	0.98	0.93–1.04	1.15	1.10–1.21
High	1.02	0.96–1.08	1.10	1.04–1.17
Surface water contamination				
None	1.00	–	1.00	–
Low	1.10	1.05–1.16	1.03	0.98–1.08
High	1.18	1.12–1.24	1.05	1.00–1.12
Acres of corn planted				
Very low	1.00	–	1.00	–
Low	0.82	0.78–0.87	0.89	0.84–0.94
Medium	0.96	0.90–1.01	1.00	0.94–1.06
High	0.87	0.82–0.93	0.94	0.88–1.00
Pesticide use				
Very low	1.00	–	1.00	–
Low	0.91	0.86–0.97	0.97	0.92–1.03
Medium	1.04	0.98–1.11	1.01	0.96–1.08
High	0.91	0.86–0.98	0.94	0.88–1.00

CI, 95% confidence interval.
[a]ORs are adjusted for race, income, education, and delayed childbearing.

Regression with the 1993–1994 cancer data showed a statistically significant increase in cancer incidence with low, medium, and high groundwater triazine levels, although there was no evidence of a dose response (ORs = 1.10, 1.15, and 1.10, respectively). An association between surface water contamination and breast cancer incidence was not noted for these years. Again, acres of corn planted and pesticide use showed a protective effect at various levels.

Overall, small but statistically significant associations between triazine exposure and breast cancer incidence are seen with the water contamination data. These results are not consistent over the 4 years of data studied. The earlier years of data indicate an association between surface water contamination and increased breast cancer risk, while the later years of data favor an association between groundwater contamination and increased breast cancer risk. Additionally, the surrogate exposure data show a protective effect against breast cancer; despite this unexpected finding, the corn planted and pesticide use variables were still included in the summary index of exposure, for reasons previously detailed.

Table 3 details the categorization of counties into low, medium, or high exposure groups based on the summary index of exposure. About half the counties fell into the lowest exposure category, while half the female population was in the medium exposure level. Mapping of the summary index was performed using geographic information system (GIS) software to reveal patterns of exposure in the state. Figure 2 shows the geographic distribution of the summary index categorization. Populations in western Kentucky appear to have the potential for highest exposure. Comparison of Figure 1

and Figure 2 reveals an interesting pattern. Groundwater usage is highest in the eastern part of the state, but the risk for triazine exposure is low in that area. Although eastern counties rely heavily on wells as a water source, they do not grow corn or use triazine pesticides so their groundwater is far less contaminated.

Table 4 shows the results of the Poisson regression using the summary index of exposure. A small, but statistically significant, increased risk of breast cancer is noted with medium or high exposure to triazines; this association is strongest for the most recent years of breast cancer data (ORs = 1.14 and 1.20, respectively). The results of the Poisson regression are confirmed by the linear regression summarized in Table 5. The relative risk of breast cancer is increased for counties falling into the medium or high exposure categories. A stronger association is again seen for the 1993–1994 data (RRs = 1.15 and 1.22, respectively).

Discussion

The results suggest a modest association between triazine herbicide exposure and an increased incidence of female breast cancer. This association is most apparent with the water contamination data and most consistent with the summary index. The 1991–1992 surface water data, the 1993–1994 groundwater data, and the 1993–1994 summary index show the strongest associations in the analysis. Despite these associations, the limitations inherent in an ecologic study preclude any statement of causal inference.

The finding of a protective effect against breast cancer with higher levels of corn planting and pesticide use is puzzling (Table 2). One explanation may be that farmers who plant larger amounts of corn and use higher amounts of pesticide are more skilled at the application process, leading to decreased pesticide run-off and
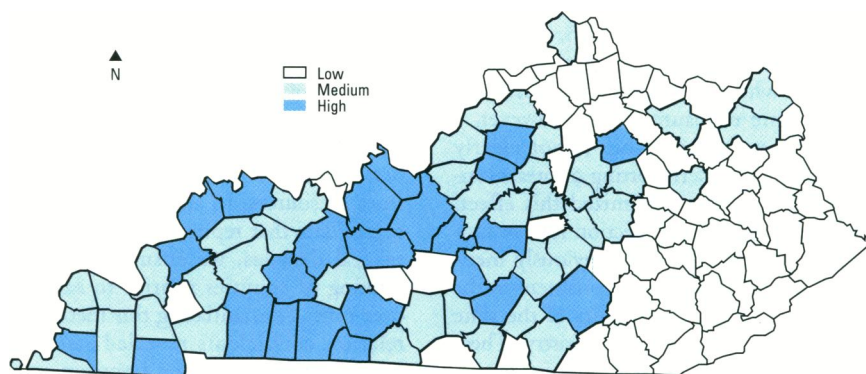

Figure 2. Pattern of triazine exposure in Kentucky counties as categorized by summary index scores.

Table 3. Assignment of counties to summary index categories of exposure

Exposure category	Summary index score	Number of counties	Population (total females)
Low	3	9	141,902
	4	11	80,995
	5	11	126,382
	6	8	58,050
	7	15	189,357
Total low		54	596,686
Medium	8	10	183,867
	9	13	464,789
	10	9	178,404
	11	10	144,941
Total medium		42	972,001
High	12	9	79,189
	13	3	75,861
	14	7	110,331
	15	2	20,879
	16	3	45,281
Total high		24	331,541

Table 4. Odds ratios (ORs)[a] for groups of counties classified according to the summary index of triazine exposure (2-year age-adjusted breast cancer rates)

Exposure category	1991–1992 Breast cancer rates			1993–1994 Breast cancer rates		
	OR	p	CI	OR	p	CI
Low	1.00	–	–	1.00	–	–
Medium	1.09	<0.0004	1.04–1.14	1.14	<0.0001	1.08–1.19
High	1.07	<0.0203	1.01–1.14	1.20	<0.0001	1.13–1.28

CI, 95% confidence interval.
[a]ORs are adjusted for race, income, education, and delayed childbearing.

Table 5. Relative risk[a] for groups of counties classified according to the summary index of triazine exposure (2-year age-adjusted breast cancer rates)

Model	Exposure	Intercept	Estimate	Relative risk	SE
1991–1992	Low	–	–	1.00	–
Breast cancer rates	Medium	74.92	8.14	1.11	7.08
	High	74.92	6.68	1.09	9.00
1993–1994	Low	–	–	1.00	–
Breast cancer rates	Medium	77.80	11.88	1.15	5.49
	High	77.80	17.36	1.22	6.98

SE, standard error.
[a]Results are adjusted for race, income, education, and delayed childbearing.

less water contamination. By including the data on corn growth and pesticide use in the summary index, the association between triazine herbicide exposure and breast cancer may have been diluted. Water contamination data better characterize the relevant exposure pathway (ingestion), but when water data are incomplete, surrogate measures of exposure help to fill in the gaps. Although the surrogate data are less direct measures of exposure, they are more county-specific and more complete. For these reasons, use of the summary index served to enhance our overall analysis.

The inconsistent association seen with the two measures of water contamination (Table 2) may be due to the limitations previously noted for these data. Groundwater data were not available for all counties, and surface water data, although available for the majority of counties, were measured only as positive or negative detections, not actual triazine levels. Despite these limitations, a pattern of elevated odds ratios is noted for both surface and groundwater contamination.

In examining Tables 4 and 5, one might expect a dose–response relationship to be apparent when comparing medium and high triazine exposure levels. However, a dose–response relationship is not clearly demonstrated; underreporting of breast cancer cases may have minimized this effect. The first year of data collection for the cancer registry was 1991. As previously mentioned, underreporting was consistent in the southwestern and central parts of the state for the first few years of the registry. These areas are the ones of primary concern for triazine exposure, as illustrated in Figure 2.

The performance of two of the covariates validated this ecological approach. Black race showed a small protective effect against breast cancer, as expected. Higher education was associated with higher incidence of breast cancer. The other two covariates did not show the expected effects. Income level showed no association with disease occurrence. Finally, delayed childbearing was not predictive of breast cancer incidence.

There are several advantages to performing an ecologic study of pesticide exposure. First, regional data on crop growth are readily available and can serve as relative estimates of pesticide application (30). Second, by examining community water contamination instead of individual exposure, unneeded variability is eliminated, yielding group level averages that more precisely approximate the population's exposure. Finally, group level exposure assessments may eliminate the recall bias, which is likely to occur in case–control studies inquiring about water use.

Because they reflect group rather than individual characteristics, ecologic studies must be interpreted cautiously. Bias may result if factors operating at the individual level, such as family history of cancer, are not accounted for in the aggregate exposure assessment. In addition, multicollinearity can yield bias in ecologic studies, as predictor variables may have a high degree of correlation at the group level. For these reasons, ecologic studies are often best used to generate hypotheses, rather than test them. In this study, attempts to minimize the effect of these biases were made by using narrow exposure data, small units of analysis, weighting of units of analysis by a standardized population, and regression to estimate effect (41–43).

A limitation of this study is the possible misclassification of counties as to exposure level. Counties were given their relative exposure ranking by equally weighting all four exposure variables. Because the water testing data had limitations, such as untested counties, nonrandom sample collection, and suboptimal accuracy, the summary index was deemed the most comprehensive indicator of triazine exposure. By combining the water data with more complete, county-specific indicators, we hoped to better describe potential triazine exposure from all sources. In addition, by using surrogate data that represents triazine use over several decades, we ensure the accurate ranking of counties relative to each other over time. Substantiating this method, correlation coefficients revealed statistically significant associations between surface water positive detections and corn growth ($r^2 = 0.36$), between surface water positive detections and pesticide use ($r^2 = 0.16$), and between corn growth and pesticide use ($r^2 = 0.49$). Since the preliminary analysis showed a protective effect for both surrogate variables, inclusion of this data could only serve to favor the null hypothesis.

Misclassification of counties with missing data could affect results. It should be noted that most missing values occurred as a result of lack of water testing in counties where small amounts of pesticides were used. Most counties with missing data fell into the lowest exposure group after final categorization. Therefore, if the pesticide exposure in these groups were actually higher, misclassification would favor the null hypothesis.

Misclassification of individuals as to county of exposure is a possible limitation of this study. Cancer rates were based on county of residence at time of diagnosis, without information as to length of time at current residence. Because the latency period for cancer can be long, an assessment of migration into and out of counties would have been useful, but was beyond the scope of this study.

It is possible that the results presented could be due to another unmeasured exposure. Other water contaminants, such as trihalomethanes, could be acting as confounders. These chemicals are known carcinogenic by-products of water chlorination; but, rat and human studies have linked trihalomethanes with gastrointestinal and genitourinary cancers only (44,45).

Total breast cancers were analyzed in this study, without regard to disease stage. An analysis of stage-specific incidence was beyond the scope of this study, but could be an important distinction to explore. By combining all stages together in this ecologic study, we may have obscured an effect.

The results suggest a relationship between female breast cancer incidence and triazine herbicide exposure, although this ecologic study cannot lead to a causal inference. The possibility of a causal relationship is supported by several criteria. First, the strength of association between the exposure and outcome is in the range of 1.1–2.0, a level that has been demonstrated for other established breast cancer risk factors (24). Second, there has been considerable attention devoted to the biologic mechanism by which these pesticides could increase breast cancer risk. The xenoestrogen hypothesis suggests these chemicals are capable of altering estrogen metabolism in the body, leading to the production of more potent, genotoxic metabolites (7). Third, consistency with other investigations is apparent after reviewing the body of literature that associates organochlorine exposure with increased breast cancer risk (17–21). Fourth, by using surrogate data that are representative of several decades of triazine exposure, a plausible time sequence from exposure to development of disease can be inferred. Finally, the finding of a stronger association for the most complete years of breast cancer data further supports the possibility of a causal relationship.

More study will be necessary to determine if the observed associations do reflect an underlying causal relationship. A logical next step would be a population-based case–control study. This type of study would allow for the analysis of multiple risk factors as well as stage-specific incidence. Further study of environmental risks may help us to understand more about the etiology of breast cancer. Identification of a modifiable risk factor for this disease is of critical importance; the currently confirmed risk factors, which relate to reproductive and/or lifestyle behaviors, are not easily amenable to change.

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