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Atrazine in public water supplies and risk of ovarian cancer among postmenopausal women in the Iowa Women's Health Study

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Abstract

Background—Few studies have evaluated environmental chemical exposures in relation to ovarian cancer. We previously found an increased risk of ovarian cancer among postmenopausal women in Iowa associated with higher nitrate levels in public water supplies (PWS). However, elevated nitrate levels may reflect the presence of other agricultural chemicals, such as atrazine, one of the most commonly detected pesticides in Iowa PWS.

Methods—We evaluated the association between atrazine in drinking water and incident ovarian cancer (N=145, 1986–2010) among 13 041 postmenopausal women in the Iowa Women's Health Study who used their PWS for 11 years as reported in 1989. Average levels of atrazine (1986–1987), nitrate-nitrogen (NO₃-N, 1955–1988) and estimated levels of total trihalomethanes (TTHM, 1955–1988) from PWS monitoring data were linked to the participants' cities of residence. We computed HRs and 95% CIs by categories of the average atrazine level (not detected, or >0.37 parts per billion=median) using Cox proportional hazards regression adjusting for ovarian cancer risk factors.

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Results—Atrazine was detected in water samples from 69 cities where 4155 women (32%) lived and levels were moderately correlated with NO₃-N ($p=0.35$) and TTHM ($p=0.24$). Atrazine levels were not associated with ovarian cancer risk with or without adjusting for NO₃-N and TTHM levels (p -trend=0.50 and 0.81, respectively). Further, there was no evidence for effect modification of the atrazine association by NO₃-N or TTHM levels.

Conclusions—In our study with low atrazine detection rates, we found no association between atrazine in PWS and postmenopausal ovarian cancer risk.

INTRODUCTION

Ovarian cancer is the most fatal cancer of the female reproductive system,¹ yet its aetiology is not well understood. Most known risk factors are related to duration or levels of endogenous oestrogen such as nulliparity and late menopause, but very few modifiable risk factors have been identified.¹² One possible modifiable risk factor which has not been studied extensively in relation to ovarian cancer is environmental exposure to endocrine disrupting compounds (EDC). EDC are exogenous agents that interfere or disrupt the normal synthesis, secretion, transportation, binding and metabolism of natural hormones. Although evidence from human studies is limited, animal studies have suggested that environmental EDC may contribute to the incidence of hormone-related cancers.³

We previously developed metrics of exposure to nitrate and other water contaminants in public water supplies (PWS) in the Iowa Women's Health Study (IWHS), a prospective cohort study of postmenopausal women in Iowa, where more than 90% of the land is used for agriculture.⁴ Among about 13 000 women, we found that the risk of ovarian cancer was more than double in women who drank PWS water in the highest quartile of average nitrate levels compared with the risk in the lowest quartile.⁵ Nitrate is a precursor of *N*-nitroso compounds (NOC), which are formed endogenously in humans.⁶ Most NOC are animal carcinogens and cause tumours in many organs, including the ovary.⁶⁷ Nitrate has also been suggested to function as an EDC.⁸ However, nitrate in drinking water sources in agricultural areas is derived mostly from crop fertiliser use and animal feeding operations; therefore, nitrate may be an indicator of contamination by other agricultural EDC, such as atrazine.

Atrazine is a triazine herbicide and is one of the most heavily used pesticides in the USA.⁹ It is extensively used to control germinating weeds on agricultural crops, especially corn. The highest use of atrazine is in the Midwest corn belt that includes Iowa.⁹ PWS in the Midwest using surface water and shallow ground water are vulnerable to atrazine contamination due to agricultural run-off.⁹¹⁰ Indeed, atrazine is the most commonly detected pesticide in water sources in the Midwest corn belt region.⁹¹¹

Atrazine was categorised as 'not classifiable as to its carcinogenicity to humans' by the International Agency for Research on Cancer (IARC) in 1999 due to inadequate evidence from epidemiological studies. IARC concluded that there was sufficient evidence from animal studies that atrazine induces an early onset of mammary gland adenocarcinomas through hormonally mediated mechanisms; however, this mechanism is not relevant to humans.¹² Although previous studies have been limited, atrazine has been hypothesised as an occupational risk factor for ovarian cancer. In a case-control study in Italy, where triazine

herbicides were heavily used in corn cultivation, female agricultural workers who were exposed to triazine herbicides were at threefold risk of ovarian cancer compared with unexposed workers.¹³ Studies among spouses of pesticide applicators in Iowa and North Carolina showed that women who ever mixed or applied atrazine and other pesticides that had probable hormonal activity experienced disruption of their menstrual cycles¹⁴ or delayed menopause.¹⁵

Environmental atrazine exposure from PWS is likely to be considerably lower than occupational exposure levels because atrazine levels in US PWS are regulated with a maximum contaminant level (MCL) of 3 parts per billion (ppb). However, atrazine is known to have endocrine disrupting effects at very low levels. There have been few studies of health outcomes in relation to atrazine exposure via drinking water. One study found that exposures to moderately elevated levels of atrazine in PWS (but at levels below the MCL) were associated with intrauterine growth retardation,¹⁶ but another study found no association with low birth weight, preterm delivery or small-for-gestational age.¹⁷ A cross-sectional study of premenopausal women in the Midwest USA drinking PWS with atrazine at levels below the MCL found that higher atrazine levels were associated with increased menstrual cycle irregularity, longer follicular phase and decreased reproductive hormone levels.¹⁸ To the best of our knowledge, atrazine levels in PWS have been evaluated in relation to the risk of ovarian cancer in only one ecological study, which did not find an association between county-based or district-based atrazine level and risk of ovarian cancer.¹⁹

Evaluating atrazine in drinking water in relation to ovarian cancer risk is challenging because drinking water sources have not been assessed in most large cohorts and few large cohorts are located in agricultural areas. In this study, we were able to link atrazine data from the Iowa historical PWS monitoring database to the IWHS, a large prospective cohort study with information on drinking water sources in 1989, to evaluate whether atrazine levels in PWS were associated with postmenopausal ovarian cancer accounting for nitrate and total trihalomethanes (TTHM).

MATERIALS AND METHODS

Study population

In 1986, a self-administered questionnaire on demographic, anthropometric, medical and dietary factors was mailed to women aged 55–69 years who were randomly selected from Iowa driving licence records, and was completed by 41 836 women (42% response rate).²⁰ In the second follow-up questionnaire in 1989, 36 127 women (89% response rate) provided information on their main drinking water source (PWS, private well water, bottled water) and duration of use (<1, 1–5, 6–10, 11–20, >20 years). Of these, 27 409 women (78%) reported using a PWS. Eighty-two per cent used the PWS for 11 years and 70% for >20 years. Our analyses included the same subcohort as our previous analysis of nitrate levels in PWS and ovarian cancer among 13 051 women in the IWHS who met the baseline inclusion criteria (eg, no history of cancer, postmenopausal, no history of bilateral oophorectomy), who used a PWS that derived >75% of its water from the same source, who used a PWS for which nitrate and TTHM data were available, and who had used the PWS for 11 years.⁵ The cohort has been followed via annual linkage with the State Health Registry of Iowa's

cancer registry, which is a part of the Surveillance, Epidemiology and End Results programme of the National Cancer Institute for cancer incidence and mortality. Diagnosis date, type, stage and morphology were obtained for each incident cancer. Vital status is also ascertained through the State Health Registry, and deaths that occur outside Iowa are supplemented by the National Death Index. The IWHS was approved by the Institutional Review Boards of the University of Minnesota and the University of Iowa.

Atrazine exposure assessment

We estimated average atrazine levels in PWS serving the women's 1989 residence using an Iowa historical water supply monitoring database that included measurements of atrazine from finished water samples collected from 1986 to 1987.²¹ These atrazine measurements were conducted as part of the first comprehensive survey of pesticides in Iowa PWS and before the regulation of atrazine became effective in accordance with the Phase II Rule of the Safe Drinking Water Act in 1992.¹⁰ All atrazine measurements were conducted by the University of Iowa Hygienic Laboratory using Environmental Protection Agency (EPA) Method 507.^{22,23}

We excluded 10 women who lived in 2 cities (Melcher and Ocheyedan) where atrazine data were not available in 1986–1987, resulting in the analytic cohort of 13 041 women who lived in 471 cities. A majority of these 471 cities (421 cities, 85%) had only one atrazine measurement in 1986–1987; there were 566 atrazine measurements in total. Of these measurements, 84 (15%; 69 cities) were above the limit of detection (LOD). For undetectable test results, we imputed half the LOD (0.1 or 0.2 ppb). For the 50 cities with multiple atrazine measurements, we computed the average of all atrazine measurements including imputed values.

We also estimated levels of nitrate-nitrogen ($\text{NO}_3\text{-N}$) and TTHM—the sum of four trihalomethanes (chloroform, bromoform, bromodichloromethane and dibromochloromethane)—using historical monitoring data (1955–1988) for Iowa PWS,²¹ as described previously.⁵ Direct measurements of TTHM were sparse before the 1980s when their regulation was implemented. Most data of TTHM before the 1980s were estimates based on an expert assessment using measurements and information on water source, treatment practices and other factors.²⁴ On the basis of complete water source histories from female controls of comparable age in a population-based case-control study in Iowa in 1986–1989,²⁵ we estimated the median duration of water use within the reported categories of 11–20 years and >20 years as 16 and 40 years, respectively. We computed 16-year and 40-year averages of $\text{NO}_3\text{-N}$ and TTHM levels for each city, and assigned one average to each woman depending on the city of her residence and the duration of her water source use.

The levels of atrazine in drinking water sources, especially surface water sources receiving an agricultural run-off, have a seasonal pattern.¹⁷ In the USA, the highest levels are generally found 6 weeks to 2 months after atrazine application to crops in spring. During the rest of the year, levels are typically lower or undetectable.^{18,19} In our study cities, average atrazine levels in finished water samples of Iowa PWS from surface water sources were indeed higher in late spring to summer (1.32 ppb) than the levels in fall to early spring (0.49 ppb). In finished water samples of Iowa PWS from groundwater sources, average atrazine

levels were similar in late spring to summer (0.22 ppb) and in fall to early spring (0.19 ppb). Therefore, in addition to a yearly average, we computed peak season average atrazine levels for 203 cities for which at least one atrazine measurement was available from April to July in 1986–1987. Of the 228 measurements in this peak season in 1986–1987, 18.4% were above the LOD while the overall detection rate was 14.8%.

Statistical analysis

Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the date of ovarian cancer diagnosis, death, emigration from Iowa (<0.5% annual emigration rate), the midpoint between the date of last contact and the date the participant was located outside Iowa, or 31 December 2010, whichever came first. For deaths that occurred outside Iowa, we censored participants at the midpoint between the date of last contact and death.

We created three categories of average atrazine levels. The reference group included women with atrazine levels below the LOD or with an average level ≤ 0.10 ppb. About 85% (n=7548) of the 8886 women in the reference group lived in cities where all atrazine measurements in 1986–1987 were below the LOD; the rest (15%, n=1338) lived in 24 cities with two to four atrazine measurements that were a combination of low concentrations and non-detections. The other two categories were >0.37 ppb, the median average level in the cities with at least one atrazine detection. Of the 1984 women in the highest atrazine category (>0.37 ppb), 1154 lived in two cities including Des Moines (N=1114) and Urbandale (N=40), where two of three measurements available in each city in 1986–1987 were non-detections.

We computed HRs and 95% CIs using Cox proportional hazards regression models adjusting for an a priori set of risk or protective factors for ovarian cancer, including age, body mass index (computed on the basis of self-reported height and weight at baseline), familial history of ovarian cancer, number of live births (0, 1–2, 3–4, ≥ 5), history of unilateral oophorectomy, age at menarche ($\leq$ or >12 years), age at menopause (<45 , 45–49, 50–54, ≥ 55 years), age at first live birth (<20 , 20–24, 25–29, ≥ 30 years, nulliparous), oral contraceptive use (never, ever), and oestrogen use (never, ever). The measure person-years of follow-up was used as the underlying time metric. We tested for linear trends using the median values of the atrazine categories as an ordinal variable. We also adjusted the atrazine models for NO₃-N and TTHM levels. Since levels of NO₃-N and TTHM were highly skewed towards higher values, we used logarithmically transformed values as covariates. We further stratified the risk associations of atrazine levels by low and high levels of NO₃-N and TTHM using their medians as cut points.

Owing to the seasonality of atrazine levels, we performed sensitivity analyses restricting to the 8341 women who lived in 203 cities with at least one atrazine measurement in April to July when atrazine levels in PWS are generally the highest. We also evaluated whether women who reported drinking PWS water from nine water utilities (Centerville, Chariton, Creston, Lamoni, Leon, Montezuma, Osceola, Rathburn and Winterset) that have participated in the Atrazine Monitoring Program (AMP) were at higher risk of ovarian cancer compared with women who lived in other cities. Starting in 2003, community water

systems, primarily in the Midwest, were selected on the basis of a history of atrazine use in the area and a screen of EPA's monitoring data.²⁶ Any community water system with a total combined triazine (atrazine and other structurally related members of the chlorinated triazine class of pesticides, including simazine, propazine and their three chlorinated degradates) exceeding the trigger values of 2.6 ppb for finished water or 12.5 ppb for raw water over a 90-day rolling average was required to monitor its water weekly during the peak atrazine use season and biweekly during the rest of the year. A total of 300 women in our study lived in 40 cities which were served by the nine water utilities monitored by the AMP; all used surface water sources. All statistical analyses were performed using SAS V.9.3 (Cary, North Carolina), and p values <0.05 (two-sided) were considered statistically significant.

RESULTS

The mean age of study participants was 61.7 years at enrolment. Over the average follow-up of 19.7 years, we identified 145 incident ovarian cancers from 1986 to 2010. Of the 471 cities, 69 cities where 4155 (32%) study participants lived had at least one detectable atrazine measurement. Average atrazine levels in 1986–1987 exceeded the MCL in four cities (Oxford Junction, Oxford, Osceola and Sioux Rapids), covering only 0.4% of the women in our study. Mean atrazine levels in PWS ranged from 0.08 to 14 ppb and the median (IQR) was 0.1 (0.08–0.17) ppb. Of our study participants, 72% used PWS served from groundwater sources, 18% used PWS from surface water sources and 10% used PWS from mixed water sources. The mean atrazine level was higher in surface water (0.59 ppb) than in groundwater (0.15 ppb). Baseline demographic, reproductive/gynaecological and lifestyle factors are compared by categories of atrazine levels in table 1. Women who used PWS with higher average atrazine levels were more likely to be current/former smokers, have a larger number of live births, have used oestrogen, have higher education, have had early menarche, and live in cities with a larger population compared with women who drank PWS water with no atrazine detections ($p<0.05$).

In categorical models (table 2), there was no evidence of a dose–response association. There was a non-significant elevated risk of ovarian cancer in the middle level of atrazine (0.1–0.37 ppm) compared with the reference group (HR=1.48, CI 0.99 to 1.23). The relative risk for women with the highest atrazine level (>0.37 ppm) was not elevated (HR=1.05, 95% CI 0.65 to 1.69). When additionally adjusted for levels of NO₃-N, TTHM or both, however, the elevated relative risk in the middle atrazine level was no longer observed (HR=1.10, 95% CI 0.69 to 1.75). Atrazine levels were moderately correlated with NO₃-N (Spearman $\rho=0.35$) and TTHM ($\rho=0.24$) levels. About 66% of women in the highest category of atrazine were in the second highest quartile of NO₃-N, while about 65% of women in the middle level category of atrazine were in the highest quartile of NO₃-N. This may explain why the positive association with the middle level of atrazine levels of 0.1–0.37 ppm did not remain after adjustment for NO₃-N levels. Additional adjustment for residential area (farm, non-farm rural, city) did not change the observed risk associations.

In the IWHS, higher NO₃-N levels in PWS were previously associated with a higher risk of ovarian cancer, whereas TTHM levels were not associated with ovarian cancer.⁵ Stratified analyses showed that there was no evidence of effect modification of the atrazine association

by NO₃-N or TTHM levels (table 3). These results did not change considerably when restricting the analyses to the women with atrazine data from a peak season (data not shown). The risk of ovarian cancer for women who used PWS water from the nine water utilities that participated in the AMP was not different from that of women who used PWS water from other water utilities (HR=1.08, 95% CI 0.50 to 2.31).

DISCUSSION

In our study of postmenopausal women in Iowa, atrazine levels in PWS were not associated with ovarian cancer risk after adjusting for nitrate and TTHM levels. Occupational and environmental exposures to atrazine have been most frequently investigated in relation to prostate and breast cancers and non-Hodgkin's lymphoma.²⁷ Only a few analytical or ecological studies have investigated ovarian cancer, with inconsistent results.²⁷ Occupational exposure to atrazine was shown as a risk factor for ovarian cancer in a case-control study in agricultural areas of Italy.¹³ Compared with controls, ovarian cancer cases had 2.7 times higher atrazine exposure based on self-reported use of triazine herbicides and history of work in corn cultivation. However, another case-control study in central California reported that probable occupational exposure to triazine herbicides, assessed using a crop-specific job-exposure matrix, was not associated with ovarian cancer.²⁸

The rationale for the current study was driven by our previous finding of an increased risk of ovarian cancer among women who drank PWS water with elevated nitrate levels in Iowa.⁵ Nitrate is categorised as a probable carcinogen in humans because it is a precursor of endogenous NOC, but it has also been suspected as an EDC.⁸ Nitrate in Iowa PWS comes mostly from agricultural use of nitrogen fertilisers; therefore, nitrate levels in PWS may be an indicator of other agricultural contaminants. However, adjustment of the previously observed association with nitrate levels in PWS (HR_{Q4 vs Q1}=2.03, 95% CI 1.22 to 3.38) for atrazine levels did not change the risk estimate (HR_{Q4 vs Q1}=2.21, 95% CI 1.30 to 3.76, p-trend=0.002) (see online supplementary table S1).

Lack of information about drinking water source and limited atrazine measurement data in large prospective studies are the major challenges to evaluating atrazine exposure via drinking water in relation to ovarian cancer risk. Until now, environmental exposure to atrazine levels in PWS have been assessed in relation to ovarian cancer in only one epidemiological study in Kentucky, and this ecological study did not find an association between atrazine levels and ovarian cancer risk.¹⁹ To estimate exposure to atrazine in PWS, the average level of all the atrazine measurements obtained from the Kentucky Division of Water was computed for each water utility. Then the atrazine exposure for counties or Area Development Districts (ADD; public bodies under Kentucky law) was estimated by averaging all the water utility-based averages across all the water utilities in each county or ADD. Limitations due to the ecological study design and lack of study participants who were exposed to atrazine exceeding the MCL in PWS make interpretation of a lack of association difficult.

Atrazine has been reported as one of the most commonly detected pesticides in PWS in the US Midwest.⁹ However, in spite of the high historical use of atrazine in Iowa, there were

very few detections in the first comprehensive survey of PWS in 1986–1987 in our study. In our atrazine estimates in 1986–1987, only 54 (0.4%) of the 13 041 women in our study were exposed to average atrazine levels exceeding the MCL (3 ppb). A narrow distribution of relatively low atrazine levels in PWS may partly explain a lack of association between atrazine levels in PWS and ovarian cancer risk in our study. It should be noted that many pesticides and other EDC are found as complex mixtures in drinking water sources, and the removal of EDC differs by treatment methods and is not complete by current standard water treatment processes.²⁹³⁰ For example, other hormonally active pesticides, such as organophosphates,³¹³² may also be present in waters in or near agricultural areas. Current evidence is limited on mixture effects of multiple EDCs on cancer, and there is no consensus on how mixtures of contaminants in PWS water should be assessed. Future studies should evaluate mixture effects of EDC present in PWS on the risk of ovarian and other hormone-related cancers.

Our atrazine estimation was based on the first comprehensive measurement data for atrazine in Iowa PWS from 1986 to 1987. Therefore, our atrazine estimates did not reflect atrazine measurements retrospectively due to lack of monitoring data from earlier years. Triazine herbicides have been used in the USA since the 1940s, and atrazine levels in PWS were not regulated until 1992. It is unlikely that drastic changes in atrazine levels in PWS occurred before regular monitoring started. The average atrazine level in 1992–1998 (0.09 ppb) was indeed significantly lower than the average level in 1986–1987 (0.51 ppb) ($p < 0.0001$) in our study, showing that atrazine levels in PWS decreased after the regular atrazine monitoring started. Yet cities with average atrazine levels exceeding half the MCL (1.5 ppb) in 1986–1987 had relatively high atrazine levels in 1992–1998 compared with other cities in our study (see online supplementary table S2). We were challenged by a high rate of left-censoring (non-detections); our non-detection rate (~85%) in all available atrazine data from the Iowa PWS monitoring database (1986–1987) is similar to previously reported rates in community drinking water quality monitoring data in eight Midwest states (range 76–99%).³³ Although women who lived in cities where all test results were non-detections were included in the reference group of our risk analyses, about 10% of our study participants who lived in cities with multiple atrazine measurements including both detections and non-detections in 1986–1987 were included in the highest category of the average atrazine levels because of one or two high atrazine measurement(s). Misclassification of exposure to atrazine in drinking water due to the limited and varied availability of measurements among cities may have biased our results towards the null.

To the best of our knowledge, our study is the first to assess an association between atrazine in PWS and ovarian cancer risk in a prospective cohort study. We also assessed risk associations adjusting for and stratifying by $\text{NO}_3\text{-N}$ and TTHM levels. Owing to the cohort study design, we were able to adjust the risk associations for potential confounders including demographic factors and established risk factors for ovarian cancer. Another strength of our study is the long follow-up period that enabled us to identify almost 150 incident ovarian cancer cases, accounting for latency in ovarian cancer development. The residential stability of our study population enabled us to estimate women's long-term exposure to atrazine in drinking water. We are aware of some limitations of our study. We were unable to adjust for occupational atrazine exposure; however, most of our study participants reported that they

were not employed in occupations likely to have occupational atrazine exposure, such as farmers. Information on the amount of daily water consumption and the water source at work was not collected. Different atrazine levels have been reported in surface and groundwater.²⁶ Since a majority (72%) of our study participants drank PWS water from groundwater sources, we were underpowered to evaluate risk associations stratified by surface and groundwater sources. The lack of water quality data for women using private wells is another limitation. Data on water contaminant levels in private wells have been very sparse, and thus we were not able to include women who used private wells as their main drinking water source. In the 1988–1989 state-wide survey, atrazine was detected in about 5% of the sampled private wells in Iowa.¹¹ Finally, EDC may have non-monotonic effects on endocrine systems. Thus, effects may be greater at very low levels, perhaps at levels that are not quantifiable with current technology.³⁴

In summary, in our study of postmenopausal women who were exposed to atrazine mostly below the MCL in Iowa PWS, elevated atrazine levels in PWS were not associated with increased risk of ovarian cancer, independently or in combination with nitrate or TTHM levels. Our findings indicate that a large proportion of people in Iowa are exposed to atrazine in drinking water at very low levels and that these levels are unlikely to be associated with ovarian cancer risk. Challenges in the assessment of atrazine exposure from PWS need to be addressed in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

- ▶ Atrazine is a hypothesised risk factor for hormone-related cancers and is a common contaminant of water supplies in agricultural areas, yet few studies have evaluated exposure to atrazine in drinking water supplies in relation to cancer risk.
- ▶ We did not find an association between atrazine levels in public water supplies and ovarian cancer risk among postmenopausal women in Iowa after adjusting for levels of nitrate and water disinfection by-products.
- ▶ Limitations of our study include the low detection rates for atrazine, the lack of information on water consumption and the lack of water quality data for women using private wells.

Table 1

Selected demographic, reproductive, and lifestyle factors and atrazine levels in public water supplies (1986–1987) among 13 041 women in the Iowa Women's Health Study

	All	Atrazine levels (ppb)			p Value
		0.1	>0.1-0.37	>0.37	
Age (mean±SD)	61.7 (4.2)	61.7 (4.2)	61.8 (4.1)	61.5 (4.1)	0.06
Body mass index (mean±SD)	26.7 (5.0)	26.7 (4.9)	26.9 (5.1)	26.6 (5.1)	0.07
Education, high school (%)	84.4	83.7	85.2	86.6	0.002
Smoking, ever (%)	38.5	36.8	41.7	42.6	<0.0001
Physical activity, low (%)	47.1	46.6	49.7	46.8	0.03
Age at menarche, 12 years (%)	42.8	41.8	43.5	46.0	0.002
Oral contraceptive use, ever (%)	20.1	20.5	18.3	20.0	0.06
Age at first live births, 30 years (%)	7.4	7.2	7.3	8.4	0.25
Number of live births, 3 (%)	57.1	58.8	54.7	52.2	<0.0001
Age at menopause, 50 years (%)	52.6	53.0	50.9	52.6	0.20
Oestrogen use, ever (%)	33.2	32.8	32.4	35.6	0.04
Residential area (%)					
Farm	2.8	3.5	1.2	1.4	<0.0001
Rural (non-farm)	2.1	2.0	2.4	2.0	
City (<1000 population)	9.5	12.4	2.7	3.8	
City (1000 to <2500 population)	13.5	17.0	4.6	7.7	
City (2500 to 10 000 population)	20.7	24.1	12.3	15.0	
City (10 000 population)	51.4	41.0	76.8	70.1	

ppb, parts per billion.

Table 2

Average atrazine level in public water supplies (1986–1987) and ovarian cancer risk among 13 041 women in the Iowa Women's Health Study

	n	Case, n	Median	Multivariable[*] HR (95% CI)	Plus NO₃-N[†] HR (95% CI)	Plus TTHM[†] HR (95% CI)	Plus NO₃-N and TTHM[†] HR (95% CI)
0.1 ppb	8886	90	0.1	1.00	1.00	1.00	1.00
>0.1–0.37 ppb	2171	33	0.15	1.48 (0.99 to 2.23)	1.21 (0.78 to 1.90)	1.34 (0.87 to 2.05)	1.10 (0.69 to 1.75)
>0.37 ppb	1984	22	0.46	1.05 (0.65 to 1.69)	0.97 (0.60 to 1.57)	0.91 (0.55 to 1.52)	0.85 (0.51 to 1.42)
p-trend				0.77	0.89	0.69	0.50

NO₃-N, nitrate-nitrogen; ppb, parts per billion; TTHM, total trihalomethanes.

^{*} Adjusted for age, familial history of ovarian cancer, number of live birth, history of ovarian removal, age at menarche, age at menopause, age at first live birth, oral contraceptive use, oestrogen use, and body mass index.

[†] Log-transformed values.

Table 3

Average atrazine levels in public water supplies (1986–1987) and ovarian cancer risk stratified by low and high NO₃-N and TTHM levels *

	<u>NO₃-N 1.08 mg/L</u>		<u>NO₃-N>1.08 mg/L</u>	
	Case, n	HR (95% CI) [†]	Case, n	HR (95% CI) [†]
0.1 ppb	46	1.00	44	1.00
>0.1–0.37 ppb	17	1.21 (0.66 to 2.21)	16	1.48 (0.80 to 2.73)
>0.37 ppb	10	0.70 (0.33 to 1.52)	12	1.17 (0.21 to 1.55)
p-trend		0.36		0.69

	<u>TTHM 4.59 µg/L</u>		<u>TTHM>4.59 µg/L</u>	
	Case, n	HR (95% CI) [†]	Case, n	HR (95% CI) [†]
0.1 ppb	55	1.00	35	1.00
>0.1–0.37 ppb	3	0.82 (0.25 to 2.69)	30	0.98 (0.56 to 1.70)
>0.37 ppb	2	1.00 (0.24 to 4.18)	20	0.76 (0.43 to 1.34)
p-trend		0.94		0.32

NO₃-N, nitrate-nitrogen; ppb, parts per billion; TTHM, total trihalomethanes.

* High or low levels with cut points at medians.

[†] Adjusted for age, familial history of ovarian cancer, number of live births, history of ovarian removal, age at menarche, age at menopause, age at first live birth, oral contraceptive use, oestrogen use, body mass index, and NO₃-N or TTHM level (log-transformed).