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Original Contribution

Risk of Total and Aggressive Prostate Cancer and Pesticide Use in the Agricultural Health Study

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Because pesticides may operate through different mechanisms, the authors studied the risk of prostate cancer associated with specific pesticides in the Agricultural Health Study (1993–2007). With 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators, this is the largest study to date. Rate ratios and 95% confidence intervals were calculated by using Poisson regression to evaluate lifetime use of 48 pesticides and prostate cancer incidence. Three organophosphate insecticides were significantly associated with aggressive prostate cancer: fonofos (rate ratio (RR) for the highest quartile of exposure (Q4) vs. nonexposed = 1.63, 95% confidence interval (CI): 1.22, 2.17; $P_{trend} < 0.001$); malathion (RR for Q4 vs. nonexposed = 1.43, 95% CI: 1.08, 1.88; $P_{trend} = 0.04$); and terbufos (RR for Q4 vs. nonexposed = 1.29, 95% CI: 1.02, 1.64; $P_{trend} = 0.03$). The organochlorine insecticide aldrin was also associated with increased risk of aggressive prostate cancer (RR for Q4 vs. nonexposed = 1.49, 95% CI: 1.03, 2.18; $P_{trend} = 0.02$). This analysis has overcome several limitations of previous studies with the inclusion of a large number of cases with relevant exposure and detailed information on use of specific pesticides at 2 points in time. Furthermore, this is the first time specific pesticides are implicated as risk factors for aggressive prostate cancer.

aggressive prostate cancer; cohort study; farming; organophosphate insecticides; pesticide exposure; prostate cancer

Abbreviations: CI, 95% confidence interval; Q4, highest quartile of exposure; RR, rate ratio.

Occupational exposure to pesticides has been associated with increased prostate cancer risk in many epidemiologic studies (1–6). In the Agricultural Health Study, the largest prospective cohort study to examine this association, a significant excess of prostate cancer has been observed for both private (farmer) and commercial applicators, with standardized incidence ratios = 1.19 (95% confidence Interval (CI): 1.14, 1.25) and 1.28 (95% CI: 1.00, 1.61), respectively, compared with rates expected in the 2 study states (7). Although several groups or chemical classes have been linked to prostate cancer, including triazine herbicides (1, 8, 9), organochlorine insecticides (9–12), and organophosphate insecticides (9, 13, 14), none of the associations is conclusive, and it is unclear which specific pesticides might be driving the group findings. Alteration of hormonal signaling pathways or induction of DNA damage is each postulated as a mechanism (15–19).

Investigation of the role of pesticides in prostate cancer development is complicated because of the need to obtain information on exposure to specific individual pesticides, to track changes in pesticide use patterns over time, and, because prostate cancer is so common in older men, to consider whether pesticides are associated with clinically significant or aggressive disease. We are aware of only 2 reports that considered tumor characteristics, one that reported no association between any pesticide exposure and

Table 1. Characteristics of Incident Prostate Cancer Cases in the Agricultural Health Study, 1993–2007

Characteristic	Cohort Person-Years (Total = 638,628.4)	Total Prostate Cancer (*n* = 1,962)		Aggressive Prostate Cancer[a] (*n* = 919)		Family History of Prostate Cancer (*n* = 305)	
		No.	%	No.	%	No.	%
Age at diagnosis, years[b]							
<60	614,045.6	406	20.7	179	19.5	78	25.6
60–64	5,043.1	360	18.4	159	17.3	60	19.7
65–69	6,573.0	489	24.9	227	24.7	77	25.3
70–74	5,885.6	382	19.5	181	19.7	52	17.1
≥75	7,081.1	325	16.6	173	18.8	38	12.5
State							
Iowa	415,184.0	1,153	58.8	588	64.0	212	69.5
North Carolina	638,628.4	809	41.2	331	36.0	93	30.5
Race							
White	602,100.5	1,797	91.6	852	92.7	296	97.1
Black	21,923.0	74	3.8	42	4.6	8	2.6
Other/missing	14,604.9	91	4.6	25	2.7	1	0.3
Family history of prostate cancer							
No	532,438.5	1,399	71.3	661	72.0	N/A	
Yes	48,709.6	305	15.6	139	15.1	305	100
Missing	57,480.3	258	13.2	118	12.9	N/A	
Smoking status							
Never	331,056.9	922	47.0	442	48.1	153	50.1
Former	170,340.9	709	36.1	328	35.7	115	37.7
Current	104,753.8	198	10.1	90	9.8	28	9.2
Missing	32,476.8	133	6.8	59	6.4	9	3.0
Fruit servings							
<1/day	437,300.6	1,229	62.6	580	63.1	203	66.5
≥1/day	157,242.9	533	27.2	243	26.4	93	30.5
Missing	44,084.9	200	10.2	96	10.5	9	3.0
Leisure-time physical activity in the winter							
None	72,048.4	359	18.3	157	17.1	62	20.3
>0–2 hours/week	119,336.9	418	21.3	209	22.7	72	23.6
≥3 hours/week	79,519.3	234	11.9	107	11.6	32	10.5
Missing	367,723.9	951	48.5	446	48.5	139	45.6

Table continues

risk of localized or advanced prostate cancer (20) and another that reported a larger proportion of later stage tumors among men with "significant" exposure to pesticides compared with men with no exposure (21).

We used data from the Agricultural Health Study, a large cohort study of pesticide applicators with pesticide use data at 2 points in time, to evaluate the association between specific pesticide exposure and prostate cancer. We previously reported on pesticide use and prostate cancer risk among 566 incident cancer cases that occurred through 1999 (13). In the current study, we extend follow-up through 2007 and update analyses to include 1,962 incident cases of prostate cancer (including 919 cases of aggressive prostate cancer).

MATERIALS AND METHODS

Study population

The Agricultural Health Study is a prospective cohort study of 52,394 licensed private pesticide applicators in Iowa and North Carolina and 4,916 licensed commercial

Table 1. Continued

Characteristic	Cohort Person-Years (Total = 638,628.4)	Total Prostate Cancer (*n* = 1,962)		Aggressive Prostate Cancer[a] (*n* = 919)		Family History of Prostate Cancer (*n* = 305)	
		No.	%	No.	%	No.	%
Stage							
Localized	10,502.8	1,499	76.4	596	64.9	238	78.0
Regional	2,044.5	324	16.5	230	25.0	51	16.7
Distant	447.6	59	3.0	59	6.4	6	2.0
Unknown	517.5	80	4.1	34	3.7	10	3.3
Grade							
Well differentiated, Gleason score 2–4	381.1	88	4.5	2	0.2	14	4.6
Moderately differentiated, Gleason score 5–6	6,220.6	935	47.7	22	2.4	147	48.2
Poorly differentiated, Gleason score 7–10	6,465.5	875	44.6	875	95.2	138	45.2
Not graded	445.2	64	3.3	20	2.2	6	2.0
Gleason score							
2–6	5,813.7	840	42.8	17	1.8	141	46.2
7	4,381.1	583	29.7	583	63.4	96	31.5
8–10	1,787.7	232	11.8	232	25.2	37	12.1
Missing	1,530.0	307	15.7	87	9.5	31	10.2
Fatal prostate cancer, yes	556.8	106	5.4	106	11.5	10	3.3
Age at diagnosis, years							
<60	614,045.6	406	20.7	179	19.5	78	25.6
60–64	5,043.1	360	18.4	159	17.3	60	19.7
65–69	6,573.0	489	24.9	227	24.7	77	25.3

Abbreviations: N/A, not available; SD, standard deviation.

[a] Distant stage or poorly differentiated (after January 1, 2003, Gleason score 7–10) or Gleason score ≥7 or fatal (underlying cause: prostate cancer).

[b] Mean age at diagnosis: total prostate cancer, 66.5 (SD, 8.3) years; aggressive prostate cancer, 67.1 (SD, 8.5) years; family history of prostate cancer, 65.2 (SD, 7.9) years.

applicators from Iowa. The cohort has been described in detail by Alavanja et al. (22). Briefly, the cohort included individuals seeking licenses for restricted use pesticides from December 1993 through December 1997 (82% of the target population enrolled). All participants provided informed consent, and the protocol was approved by relevant institutional review boards. We obtained cancer incidence information by annual linkage to cancer registry files in Iowa (Surveillance, Epidemiology, and End Results Program) and North Carolina (National Program of Cancer Registries). In addition, we annually matched cohort members to state mortality registries and the National Death Index to identify vital status and to address records of the Internal Revenue Service, motor vehicle registration files, and pesticide license registries of state agricultural departments to determine residence in Iowa or North Carolina. The current analysis included all incident prostate cancers ($n = 1{,}962$) diagnosed from enrollment (1993–1997) through December 31, 2007. We censored follow-up at the time of death, movement out of state, or December 31, 2007. Among the 57,310 applicators, we excluded 2,898 participants (1,563 females, 1,071 prevalent cancers of all types, 264 with no follow-up information), leaving 54,412 individuals.

Tumor characteristics

Information on tumor characteristics was obtained from state cancer registries. Cases were characterized by stage (localized, regional, distant, or unknown extension or metastasis), histologic grade (well differentiated, moderately differentiated, and poorly differentiated), and Gleason score. Tumors that were not classified by pathologists were listed as having unknown grade. Gleason scores are currently equated with the 3 grade categories as follows: tumors with Gleason scores of 2–4 are classified as well differentiated, scores of 5–6 as moderately differentiated, and scores of 7–10 as poorly differentiated (23). For cases diagnosed prior to January 1, 2003, when the grading procedure was modified (23), we reabstracted Gleason scores

Table 2. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Organophosphate Insecticides and Risk of Total and Aggressive Prostate Cancer in the Agricultural Health Study, 1993–2007

	Total Prostate Cancer			Aggressive Prostate Cancer[a]		
	No. of Cases[b]	RR[c]	95% CI	No. of Cases[b]	RR[c]	95% CI
Chlorpyrifos						
Nonexposed	1,129	1.00	Referent	511	1.00	Referent
Q1	167	1.08	0.92, 1.28	83	1.02	0.81, 1.29
Q2	168	1.03	0.87, 1.21	83	1.10	0.87, 1.39
Q3	166	0.94	0.80, 1.11	82	1.15	0.90, 1.46
Q4	167	0.89	0.75, 1.05	82	1.01	0.80, 1.28
P_{trend}			0.11			0.84
Coumaphos						
Nonexposed	1,506	1.00	Referent	710	1.00	Referent
Q1	35	1.18	0.84, 1.65	14	0.85	0.49, 1.46
Q2	35	0.81	0.58, 1.13	14	0.64	0.38, 1.08
Q3	35	0.93	0.66, 1.30	14	0.89	0.52, 1.54
Q4	34	1.02	0.72, 1.43	14	0.90	0.53, 1.53
P_{trend}			0.97			0.59
Dichlorvos						
Nonexposed	1,515	1.00	Referent	705	1.00	Referent
Q1	43	1.07	0.79, 1.45	22	0.92	0.59, 1.44
Q2	43	1.01	0.74, 1.36	22	1.15	0.76, 1.75
Q3	43	0.85	0.63, 1.15	22	0.90	0.58, 1.39
Q4	43	0.91	0.67, 1.24	21	0.95	0.62, 1.48
P_{trend}			0.50			0.80
Diazinon[d]						
Nonexposed	727	1.00	Referent	343	1.00	Referent
Q1	66	1.30	1.01, 1.68	31	1.24	0.84, 1.85
Q2	63	1.15	0.88, 1.49	29	1.00	0.67, 1.48
Q3	66	1.04	0.81, 1.35	30	0.89	0.59, 1.34
Q4	63	0.94	0.72, 1.24	30	1.31	0.87, 1.96
P_{trend}			0.59			0.27
Fonofos						
Nonexposed	1,305	1.00	Referent	581	1.00	Referent
Q1	97	0.89	0.74, 1.17	55	0.96	0.72, 1.28
Q2	95	1.38	1.11, 1.70	50	1.20	0.89, 1.61
Q3	96	1.13	0.91, 1.39	52	1.16	0.86, 1.55
Q4	96	1.21	0.98, 1.49	52	1.63	1.22, 2.17
P_{trend}			0.03			<0.001

Table continues

and harmonized the classification scheme with current practice. For 35 cases from Iowa and 24 cases from North Carolina, Gleason score information conflicted with the reported grade category; in these instances, we used the abstracted Gleason score to assign an appropriate grade code. Gleason score was missing for 62 of 1,153 (5.4%) incident cases from Iowa and 245 of 809 (30.3%) incident cases from North Carolina. If the Gleason score was missing, the original histologic grade variable delivered from the yearly cancer registry link was used (22 well differentiated, 161 moderately differentiated, 60 poorly differentiated, and 64 not graded). For the current analysis, aggressive prostate cancer was defined as having 1 or more of the following tumor characteristics: distant stage, poorly differentiated grade, Gleason score of ≥ 7, or fatal prostate cancer (underlying cause, prostate cancer). Two alternative definitions of aggressive prostate cancer were also considered in analysis (using a Gleason score cutoff of $\geq 4+3$ or a Gleason score

Table 2. Continued

	Total Prostate Cancer			Aggressive Prostate Cancer[a]		
	No. of Cases[b]	RR[c]	95% CI	No. of Cases[b]	RR[c]	95% CI
Malathion[d]						
Nonexposed	328	1.00	Referent	140	1.00	Referent
Q1	189	1.03	0.84, 1.26	95	1.19	0.89, 1.59
Q2	187	1.13	0.94, 1.36	93	1.27	0.97, 1.67
Q3	184	1.11	0.93, 1.34	93	1.28	0.98, 1.68
Q4	186	1.08	0.90, 1.29	93	1.43	1.08, 1.88
P_{trend}			0.62			0.04
Parathion[d]						
Nonexposed	878	1.00	Referent	413	1.00	Referent
Q1	25	1.21	0.81, 1.81	12	1.96	1.10, 3.50
Q2	25	1.37	0.92, 2.05	12	1.04	0.58, 1.86
Q3	25	1.21	0.81, 1.81	12	1.51	0.82, 2.77
Q4	24	0.85	0.56, 1.28	11	0.98	0.53, 1.79
P_{trend}			0.51			0.97
Phorate[d]						
Nonexposed	675	1.00	Referent	314	1.00	Referent
Q1	76	0.96	0.76, 1.23	37	0.78	0.55, 1.12
Q2	76	1.11	0.87, 1.41	36	1.26	0.89, 1.79
Q3	77	0.88	0.69, 1.13	37	0.80	0.56, 1.14
Q4	75	1.12	0.88, 1.42	36	1.36	0.96, 1.93
P_{trend}			0.46			0.10
Terbufos						
Nonexposed	1,042	1.00	Referent	466	1.00	Referent
Q1	162	1.05	0.88, 1.24	81	1.06	0.83, 1.36
Q2	158	1.08	0.91, 1.28	80	1.06	0.83, 1.35
Q3	161	1.06	0.89, 1.25	80	1.15	0.90, 1.47
Q4	158	1.04	0.88, 1.23	80	1.29	1.02, 1.64
P_{trend}			0.63			0.03

Abbreviations: CI, confidence interval; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio.

[a] Distant stage or poorly differentiated (after January 1, 2003, Gleason score 7–10) or Gleason score ≥7 or fatal (underlying cause: prostate cancer).

[b] Numbers do not sum to total because of missing data.

[c] Adjusted for age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter.

[d] Detailed information for these chemicals was collected on the take-home questionnaire at enrollment.

of ≥8) in combination with the other factors listed above (stage, fatal disease).

Exposure assessment

Information on lifetime use of 50 pesticides was captured in 2 self-administered questionnaires (http://aghealth.org/questionnaires.html) completed during cohort enrollment (phase 1). All 57,310 applicators completed the first enrollment questionnaire, which inquired about ever/never use of the 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides. In addition, 25,291 of 57,310 (44.1%) of the applicators returned the second (take-home) enrollment questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides. We used 2 exposure metrics to assess cumulative exposure to each pesticide: 1) lifetime days of pesticide use, that is, the product of years of use of a specific pesticide and the number of days used per year; and 2) intensity-weighted lifetime days of use, that is, the product of lifetime days of use and a measure of exposure intensity. Intensity was derived from an algorithm using questionnaire data on mixing status, application method,

Table 3. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Organochlorine Insecticides and Risk of Total and Aggressive Prostate Cancer in the Agricultural Health Study, 1993–2007

	Total Prostate Cancer			Aggressive Prostate Cancer[a]		
	No. of Cases[b]	RR[c]	95% CI	No. of Cases[b]	RR[c]	95% CI
Aldrin						
Nonexposed	715	1.00	Referent	328	1.00	Referent
Q1	65	1.04	0.80, 1.35	33	0.97	0.67, 1.41
Q2	64	0.94	0.72, 1.22	33	1.09	0.75, 1.57
Q3	64	1.14	0.88, 1.48	34	1.21	0.84, 1.74
Q4	64	1.25	0.97, 1.63	31	1.49	1.03, 2.18
P_{trend}			0.07			0.02
Chlordane						
Nonexposed	740	1.00	Referent	356	1.00	Referent
Q1	59	0.79	0.61, 1.04	26	0.73	0.48, 1.10
Q2	58	1.29	0.99, 1.69	26	1.07	0.72, 1.60
Q3	58	0.96	0.73, 1.25	26	0.91	0.61, 1.37
Q4	58	1.02	0.78, 1.34	25	1.17	0.77, 1.77
P_{trend}			0.80			0.49
DDT						
Nonexposed	578	1.00	Referent	267	1.00	Referent
Q1	96	0.98	0.78, 1.22	47	1.06	0.76, 1.48
Q2	97	1.27	1.02, 1.58	46	1.17	0.85, 1.61
Q3	96	1.27	1.02, 1.58	46	1.56	1.13, 2.15
Q4	95	1.18	0.95, 1.48	46	1.30	0.94, 1.80
P_{trend}			0.14			0.10
Dieldrin						
Nonexposed	918	1.00	Referent	429	1.00	Referent
Q1	19	0.94	0.60, 1.49	8	0.83	0.41, 1.68
Q2	19	0.86	0.54, 1.36	7	2.00	0.94, 4.23
Q3	18	0.93	0.58, 1.49	8	0.68	0.33, 1.37
Q4				7	1.39	0.65, 2.94
P_{trend}			0.68			0.54

Table continues

equipment repair, and use of personal protective equipment (24). A follow-up questionnaire, which ascertained pesticide use since enrollment, was administered 5 years after enrollment (phase 2) and completed by 36,342 (63%) of the original participants. For participants who did not complete a phase 2 questionnaire (20,968 applicators, 37%), a data-driven multiple imputation procedure was used to impute use of specific pesticides in phase 2. A detailed description of the imputation process and validation is described by Heltshe et al. (25). Briefly, logistic regression and stratified sampling were used to impute use of specific pesticides in phase 2. All variables from phase 1 that had the potential to be associated with either missingness or pesticide use were considered. The variables most strongly predictive of use of any pesticide on the phase 2 questionnaire were gender, marital status, farm ownership, farm size, days/year mixing pesticides, percent time personally mixing pesticides, percent time personally applying pesticides, and application of any pesticide in the prior year. Covariates associated with nonresponse to phase 2 were age, education, state, applicator type, and years mixing chemicals. Covariates from participants with complete data from both phases were modeled and then applied to the model for participants missing phase 2 data to obtain estimates of the missing data. To assess the imputation procedure, a 20% random sample of participants was withheld for comparison. The observed and imputed prevalences of any pesticide use in the holdout data set were 85.7% and 85.3%, respectively, indicating that the logistic regression model for the multiple imputation performed well.

We combined phase 1 and phase 2 information to generate cumulative intensity-weighted and unweighted days of use. Web Table 1 (available at http://aje.oxfordjournals.org/)

Table 3. Continued

	Total Prostate Cancer			Aggressive Prostate Cancer[a]		
	No. of Cases[b]	RR[c]	95% CI	No. of Cases[b]	RR[c]	95% CI
Heptachlor						
Nonexposed	809	1.00	Referent	369	1.00	Referent
Q1	45	1.08	0.80, 1.47	24	1.29	0.83, 2.00
Q2	44	1.05	0.77, 1.44	24	1.65	1.08, 2.52
Q3	45	1.03	0.76, 1.40	24	1.17	0.77, 1.76
Q4	44	1.05	0.78, 1.44	23	0.88	0.57, 1.35
P_{trend}			0.73			0.62
Lindane						
Nonexposed	840	1.00	Referent	395	1.00	Referent
Q1	43	0.88	0.63, 1.23	19	0.81	0.50, 1.32
Q2	36	1.06	0.76, 1.49	19	0.91	0.56, 1.49
Q3	39	1.06	0.76, 1.48	19	1.45	0.91, 2.30
Q4	39	1.16	0.84, 1.60	19	1.24	0.77, 2.00
P_{trend}			0.33			0.23
Toxaphene						
Nonexposed	831	1.00	Referent	386	1.00	Referent
Q1	39	0.91	0.66, 1.26	19	1.02	0.64, 1.65
Q2	38	1.06	0.77, 1.46	19	1.32	0.83, 2.09
Q3	38	1.28	0.92, 1.78	19	1.30	0.82, 2.07
Q4	38	0.97	0.70, 1.35	19	1.14	0.71, 1.83
P_{trend}			0.95			0.48

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio.

[a] Distant stage or poorly differentiated (after January 1, 2003, Gleason score 7–10) or Gleason score ≥7 or fatal (underlying cause: prostate cancer).

[b] Numbers do not sum to total because of missing data.

[c] Adjusted for age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter.

provides the complete list of pesticides and their prevalence of use. Data were obtained from Agricultural Health Study data release versions P1REL201005.00 (for phase 1) and P2REL201007.00 (for phase 2).

Statistical analyses

We conducted analyses using unlagged exposure and 15-year lagged exposure, which excluded the most recent 15 years of exposure for both lifetime and intensity-weighted days. For each chemical, we categorized exposure into nonexposed and quartiles or tertiles of exposure on the basis of the distribution of exposed cases. This was done separately for total and aggressive prostate cancer. We used Poisson regression to calculate rate ratios and 95% confidence intervals and used the MIANALYZE procedure in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) to obtain the appropriate variance when using phase 2 imputed data in the 95% confidence interval calculation. We evaluated only pesticides with 15 or more exposed cases of prostate cancer, thereby excluding trichlorfon and ziram. Rate ratios were adjusted for statistically significant ($\alpha = 0.05$) predictors of prostate cancer in the Agricultural Health Study. We evaluated several lifestyle and demographic measures and identified the following as potential confounding variables: age at enrollment (<40, 40–49, 50–59, 60–69, ≥70); race (white, black, other, missing); state (Iowa, North Carolina); family history of prostate cancer in first-degree relatives (yes, no, missing); cigarette smoking history (never, former, current, missing); fruit servings (<1/day, ≥1/day); and leisure-time physical activity in the winter (none, >0–2 hours/week, ≥3 hours/week). We further adjusted models for other pesticides shown to be associated with prostate cancer in the current analysis. Separate analyses were conducted by disease aggressiveness, family history of prostate cancer (yes, no), state, applicator type (private, commercial), age at enrollment (<65, ≥65), and for analyses of organochlorines with additional adjustment for body mass index. Likelihood ratio tests were

Table 4. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Triazine Herbicides and Risk of Total and Aggressive Prostate Cancer in the Agricultural Health Study, 1993–2007

	Total Prostate Cancer			Aggressive Prostate Cancer[a]		
	No. of Cases[b]	RR[c]	95% CI	No. of Cases[b]	RR[c]	95% CI
Atrazine						
Nonexposed	507	1.00	Referent	228	1.00	Referent
Q1	336	0.97	0.84, 1.12	163	0.93	0.75, 1.16
Q2	335	1.05	0.91, 1.21	162	1.00	0.81, 1.24
Q3	336	0.97	0.84, 1.12	163	1.12	0.90, 1.39
Q4	335	0.98	0.85, 1.12	162	1.05	0.85, 1.30
P_{trend}			0.68			0.39
Cyanazine						
Nonexposed	1,015	1.00	Referent	462	1.00	Referent
Q1	169	0.90	0.76, 1.06	85	0.91	0.71, 1.16
Q2	169	0.99	0.83, 1.17	84	0.92	0.72, 1.17
Q3	169	0.87	0.73, 1.03	84	0.93	0.73, 1.18
Q4	168	0.94	0.79, 1.11	84	0.98	0.76, 1.25
P_{trend}			0.51			0.97

Abbreviations: CI, confidence interval; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio.
[a] Distant stage or poorly differentiated (after January 1, 2003, Gleason score 7–10) or Gleason score ≥7 or fatal (underlying cause: prostate cancer).
[b] Numbers do not sum to total because of missing data.
[c] Adjusted for age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter.

used to assess differences between strata ($P_{interaction}$). We also analyzed phase 1 data only to assess the impact of the additional information collected or imputed from phase 2. All tests were 2 sided and conducted at the $\alpha = 0.05$ level. Tests for trend used the midpoint value of each exposure category treated as grouped linear in regression models.

RESULTS

The mean age at prostate cancer diagnosis for applicators with a family history of prostate cancer was younger (65.2 years) compared with aggressive cases (67.1 years) or overall prostate cancer (66.5 years) (Table 1).

Results were comparable (not shown) for both metrics (lifetime and intensity-weighted lifetime days) for both lagged and unlagged exposures. Therefore, we present rate ratios for unlagged intensity-weighted lifetime days only. The association between cumulative exposure to selected pesticides and risk of total and aggressive prostate cancer is presented in Tables 2–4. There was no significant association between any specific pesticide and risk of total prostate cancer. Four insecticides were, however, associated with aggressive prostate cancer: fonofos (rate ratio (RR) for the highest quartile of fonofos exposure (Q4) vs. nonexposed = 1.63, 95% CI: 1.22, 2.17; $P_{trend} < 0.0001$); aldrin (RR for aldrin Q4 vs. nonexposed = 1.49, 95% CI: 1.03, 2.18; $P_{trend} = 0.02$); malathion (RR for Q4 vs. nonexposed = 1.43, 95% CI: 1.08, 1.88; $P_{trend} = 0.04$); and terbufos (RR for Q4 vs. nonexposed = 1.29, 95% CI: 1.02, 1.64; $P_{trend} = 0.03$). The observed risk for each chemical persisted when they were analyzed together (simultaneous adjustment for fonofos, malathion, terbufos, and aldrin and aggressive prostate cancer). There was no association between the use of other organochlorine insecticides, triazine herbicides, or any other pesticides not presented and prostate cancer risk. Web Table 2 provides a list of rate ratios and 95% confidence intervals for the remainder of the 48 pesticides examined that are not presented in Tables 2–4. Results from analyses of phase 1 data only yielded similar results (data not shown).

Tables 5–7 show the association between pesticide exposure and total prostate cancer stratified by family history of prostate cancer. In the Agricultural Health Study, previous analyses suggested an increased risk of prostate cancer associated with selected pesticides for those with a family history of prostate cancer (13). Here, we observed significant interactions between family history of prostate cancer and the use of fonofos ($P_{interaction} = 0.04$) and aldrin ($P_{interaction} = 0.04$). A significantly increased risk of prostate cancer was also observed for men with exposure to lindane who had a family history of cancer, while there was no increased risk among men without a family history, although this interaction was not statistically significant ($P = 0.26$). We observed no other significant interactions between pesticide exposure and family history of prostate cancer. Web Table 3 provides a list of rate ratios and 95% confidence

intervals for the remainder of the 48 pesticides examined that are not presented in Tables 5–7.

Separate analyses by state, applicator type (private, commercial), age (<65, ≥65), and organochlorine models with additional adjustment for body mass index were not statistically significant and are therefore not shown. Results for alternative definitions of aggressive prostate cancer were similar to those presented and are therefore not shown. Limited statistical power precluded detailed analysis of family history of prostate cancer with exposures to fonofos, malathion, terbufos, or aldrin among those with aggressive prostate cancer.

DISCUSSION

In this analysis, we observed significant increases in the risk of aggressive prostate cancer associated with 4 insecticides: fonofos (organophosphate), malathion (organophosphate), terbufos (organophosphate), and aldrin (organochlorine). Further, we observed significant increases in risk of total prostate cancer with increasing use of fonofos and aldrin among those with a family history of prostate cancer but no increased risk among those without a family history. These findings are consistent with some findings from an earlier follow-up of these data from the Agricultural Health Study and offer new insights about risk of aggressive prostate cancer.

An earlier report from the Agricultural Health Study that included 566 prostate cancer cases occurring from enrollment until 1999 identified only the use of the fumigant methyl bromide to be significantly associated with prostate cancer risk (aggressive prostate cancer was not evaluated). This risk does not persist with additional follow-up (26), although methyl bromide use has declined from 1993–2005 because of a US Environmental Protection Agency phase-out. Here, we found the strongest associations for aggressive prostate cancer and use of fonofos, terbufos, malathion, and aldrin. Fonofos and terbufos have previously been associated with prostate cancer in earlier follow-up analyses in the Agricultural Health Study, although these associations were observed only among men with a family history of prostate cancer (14, 27). A recent Canadian prostate cancer case-control study reported no association with fonofos (5 exposed cases) but a significant increased risk with malathion (82 exposed cases) (1). Another study from California reported no risk associated with malathion (222 exposed cases) (9). We are not aware of other epidemiologic studies that have reported on the use of terbufos and prostate cancer risk. An association between aldrin and prostate cancer was observed previously in the Agricultural Health Study (13) but not after subsequent follow-up (28). Several occupational studies have implicated organochlorine insecticide use and prostate cancer risk (11, 13, 29–31); however, risk associated with specific organochlorine insecticides was less clear. None of these studies focused specifically on aggressive prostate cancer.

Fonofos (*O*-ethyl *S*-phenyl ethylphosphonodithioate), which as of 1998 is no longer registered for use in the United States (32), and terbufos (*S-tert*-butylthiomethyl *O, O*-diethyl phosphorodithioate) are classified by the US Environmental Protection Agency as group E for carcinogenicity (evidence of noncarcinogenicity for humans) (33). Organophosphate insecticides such as fonofos and terbufos are metabolized to their highly toxic oxon intermediate. The oxon form of the compound is more toxic than the parent compound and has been associated with a number of biologic endpoints including the generation of reactive oxygen species and DNA damage (34–36). Alternatively, these pesticides might impact other important cellular functions. In the Agricultural Health Study, we observed a significant interaction between terbufos and fonofos exposure and genetic variants on chromosome 8q24 and risk of prostate cancer (37). Recent studies have suggested that 8q24 variants might be related to the nearest coding region, the *MYC* gene, and its expression (38), suggesting that these pesticides might influence prostate cancer risk by altering important cancer signaling pathways involved in cellular adhesion, proliferation, and differentiation. The US Environmental Protection Agency concluded in 2000 that there was "suggestive" evidence of carcinogenicity for malathion, while the International Agency for Research on Cancer lists malathion in group 3, or not classifiable as to its carcinogenicity to humans. Like the other organophosphate insecticides, purported mechanisms of action include direct genotoxicity (of either malathion or malaoxon) (39, 40) and potential endocrine disruption (41, 42). The International Agency for Research on Cancer lists aldrin as not classifiable as to its carcinogenicity to humans (group 3). Organochlorine insecticides are putative endocrine disruptors that accumulate and persist in adipose tissue, providing a background of continuous endocrine perturbation that may increase prostate cancer risk (43, 44). Because these compounds are stored in fat, we additionally considered body mass index as an adjustment factor in these models (not shown). Body mass index was not a confounder or effect modifier of the relation between organochlorine insecticide use and prostate cancer in our study.

Of the 9 organophosphate insecticides evaluated for risk, 4 are dithioates: fonofos, malathion, phorate, and terbufos (http://www.alanwood.net/pesticides/class_insecticides.html), and we observed significant increased risks with 3 of the 4. Interestingly, a recent study reported another dithioate insecticide, azinphos-methyl, with an increased risk of prostate cancer (1). Although these pesticides might be similar with respect to their structure, there is still little information overall about their role in the carcinogenic process. Our observation for associations between these pesticides and aggressive prostate cancer suggests they may play a role in prostate cancer progression rather than at the earlier initiation stage of transformation. Future work on the mechanisms by which dithioate insecticides might impact prostate carcinogenesis would be valuable.

An alternative explanation for the lack of association between total prostate cancer and a positive association for aggressive cancer may be screening bias. It has been suggested that pesticide applicators would have lower prostate-specific antigen screening rates than the general population on account of greater variability in the availability of health insurance or access to care in rural areas (45, 46). This would result in a bias of risk estimates toward the null for

Table 5. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Organophosphate Insecticides and Risk of Total Prostate Cancer by Family History of Prostate Cancer in the Agricultural Health Study, 1993–2007

	No Family History			Yes Family History		
	No. of Cases[a]	RR[b]	95% CI	No. of Cases[a]	RR[b]	95% CI
Chlorpyrifos						
Nonexposed	823	1.00	Referent	170	1.00	Referent
Q1	118	1.04	0.86, 1.27	32	1.20	0.81, 1.76
Q2	123	1.00	0.82, 1.21	30	1.08	0.73, 1.60
Q3	131	0.98	0.82, 1.18	24	0.77	0.50, 1.18
Q4	125	0.90	0.74, 1.09	30	0.86	0.58, 1.29
P_{trend}			0.24			0.32
$P_{interaction}$				0.81		
Coumaphos						
Nonexposed	1,187	1.00	Referent	235	1.00	Referent
Q1	26	1.09	0.73, 1.62	8	1.64	0.81, 3.33
Q2	19	0.60	0.39, 0.93	14	1.59	0.90, 2.82
Q3	25	0.84	0.57, 1.25	8	1.35	0.67, 2.75
Q4	24	0.92	0.61, 1.38	8	1.41	0.70, 2.87
P_{trend}			0.51			0.26
$P_{interaction}$				0.07		
Dichlorvos						
Nonexposed	1,185	1.00	Referent	240	1.00	Referent
Q1	31	1.02	0.71, 1.46	10	1.29	0.68, 2.44
Q2	31	1.00	0.70, 1.44	12	1.21	0.67, 2.18
Q3	36	0.93	0.67, 1.29	6	0.61	0.27, 1.37
Q4	29	0.77	0.53, 1.12	13	1.76	1.00, 3.09
P_{trend}			0.16			0.07
$P_{interaction}$				0.15		
Diazinon[c]						
Nonexposed	531	1.00	Referent	121	1.00	Referent
Q1	51	1.34	1.00, 1.79	11	1.15	0.62, 2.14
Q2	49	1.20	0.89, 1.61	9	0.93	0.46, 1.86
Q3	45	0.96	0.71, 1.31	15	1.26	0.72, 2.20
Q4	48	1.08	0.79, 1.47	8	0.88	0.42, 1.83
P_{trend}			0.78			0.82
$P_{interaction}$				0.84		
Fonofos						
Nonexposed	1,022	1.00	Referent	197	1.00	Referent
Q1	75	0.89	0.70, 1.12	18	0.91	0.55, 1.49
Q2	72	1.30	1.02, 1.65	20	1.70	1.07, 2.72
Q3	71	1.06	0.83, 1.36	18	1.22	0.74, 1.99
Q4	61	1.02	0.78, 1.32	30	2.01	1.36, 2.99
P_{trend}			0.70			0.0004
$P_{interaction}$				0.04		

Table continues

total prostate cancer and may explain the lack of association and/or smaller effect sizes observed for total prostate cancer in our study. Conversely, we would also have to consider whether the observed pesticide associations for

Table 5. Continued

	No Family History			Yes Family History		
	No. of Cases[a]	RR[b]	95% CI	No. of Cases[a]	RR[b]	95% CI
Malathion[c]						
Nonexposed	242	1.00	Referent	45	1.00	Referent
Q1	138	0.99	0.78, 1.25	44	1.37	0.87, 2.15
Q2	137	1.11	0.89, 1.37	34	1.12	0.72, 1.76
Q3	126	1.01	0.81, 1.26	35	1.23	0.79, 1.92
Q4	144	1.17	0.95, 1.44	21	0.70	0.42, 1.18
P_{trend}			0.15			0.15
$P_{interaction}$				0.15		
Parathion[c]						
Nonexposed	647	1.00	Referent	143	1.00	Referent
Q1	16	1.14	0.69, 1.87	5	1.32	0.54, 3.23
Q2	18	1.36	0.85, 2.19	5	1.54	0.63, 3.80
Q3	16	1.08	0.66, 1.79	6	1.58	0.65, 3.84
Q4	20	0.99	0.63, 1.55	3		
P_{trend}			0.98			0.88
$P_{interaction}$				0.51		
Phorate[c]						
Nonexposed	497	1.00	Referent	94	1.00	Referent
Q1	53	0.88	0.66, 1.18	21	1.39	0.85, 2.28
Q2	63	1.17	0.89, 1.54	9	0.71	0.35, 1.42
Q3	55	0.85	0.64, 1.13	18	0.99	0.59, 1.66
Q4	52	1.07	0.80, 1.43	21	1.53	0.94, 2.49
P_{trend}			0.73			0.12
$P_{interaction}$				0.15		
Terbufos						
Nonexposed	802	1.00	Referent	153	1.00	Referent
Q1	123	1.04	0.85, 1.26	34	1.34	0.90, 2.00
Q2	122	1.09	0.90, 1.32	29	1.12	0.74, 1.70
Q3	126	1.10	0.91, 1.33	29	1.09	0.73, 1.63
Q4	117	1.05	0.86, 1.27	36	1.27	0.88, 1.85
P_{trend}			0.57			0.30
$P_{interaction}$				0.72		

Abbreviations: CI, confidence interval; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio.
[a] Numbers do not sum to total because of missing data.
[b] Adjusted for age, state, race, smoking, fruit servings, and leisure-time physical activity in the winter.
[c] Detailed information for these chemicals was collected on the take-home questionnaire at enrollment.

aggressive prostate cancer reflect a true underlying risk factor that has increased the occurrence of more aggressive disease or whether this increase might be a result of decreased prostate-specific antigen screening. To explore this possibility, we calculated the prevalence of prostate-specific antigen screening in a subgroup of Agricultural Health Study men ($n = 23,265$) who provided this information from a follow-up questionnaire completed between 2005 and 2010. A large proportion of Agricultural Health Study men from Iowa (73.9%) and North Carolina (76.0%) reported having a prostate-specific antigen test within the past 5 years. This is similar to the proportion reported by the Behavioral Risk Factor Surveillance System data from Iowa (69.0%) and North Carolina (72.7%) (47). We additionally explored whether prostate-specific antigen screening might act as a confounder of the observed significant association and found no change in risk estimate with this additional adjustment. Taken together, this suggests that screening

Table 6. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Organochlorine Insecticides and Risk of Total Prostate Cancer by Family History of Prostate Cancer in the Agricultural Health Study, 1993–2007

	No Family History			Yes Family History		
	No. of Cases[a]	RR[b]	95% CI	No. of Cases[a]	RR[b]	95% CI
Aldrin[c]						
Nonexposed	538	1.00	Referent	95	1.00	Referent
Q1	50	0.99	0.74, 1.33	12	1.29	0.70, 2.40
Q2	38	0.72	0.51, 1.00	20	1.95	1.17, 3.25
Q3	45	1.06	0.78, 1.45	17	1.83	1.08, 3.09
Q4	45	1.13	0.83, 1.54	16	2.13	1.22, 3.72
P_{trend}			0.42			0.005
$P_{interaction}$				0.04		
Chlordane[c]						
Nonexposed	544	1.00	Referent	118	1.00	Referent
Q1	39	0.70	0.50, 0.96	15	1.15	0.67, 1.98
Q2	45	1.35	0.99, 1.83	11	1.33	0.71, 2.47
Q3	45	1.01	0.75, 1.38	8	0.72	0.35, 1.48
Q4	43	0.99	0.72, 1.36	9	1.12	0.57, 2.23
P_{trend}			0.88			0.91
$P_{interaction}$				0.52		
DDT[c]						
Nonexposed	421	1.00	Referent	93	1.00	Referent
Q1	73	0.96	0.74, 1.24	17	1.08	0.63, 1.85
Q2	76	1.37	1.06, 1.76	17	1.43	0.83, 2.44
Q3	70	1.25	0.97, 1.62	15	1.43	0.81, 2.51
Q4	67	1.22	0.93, 1.59	15	1.04	0.58, 1.83
P_{trend}			0.15			0.98
$P_{interaction}$				0.76		
Dieldrin[c]						
Nonexposed	675	1.00	Referent	148	1.00	Referent
T1	15	0.90	0.54, 1.51	4		
T2	13	0.73	0.42, 1.26	5	1.55	0.63, 3.82
T3	13	0.90	0.52, 1.56	5	1.54	0.62, 3.83
P_{trend}			0.56			0.29
$P_{interaction}$				0.69		
Heptachlor[c]						
Nonexposed	592	1.00	Referent	132	1.00	Referent
Q1	37	1.20	0.86, 1.69	7	0.81	0.37, 1.75
Q2	35	1.11	0.78, 1.57	7	0.83	0.39, 1.80
Q3	31	0.94	0.65, 1.36	11	1.17	0.63, 2.21
Q4	32	1.01	0.70, 1.44	8	0.91	0.44, 1.88
P_{trend}			0.93			0.91
$P_{interaction}$				0.73		

Table continues

bias is not likely an issue in the Agricultural Health Study and that pesticide exposure may truly increase aggressive prostate cancer risk.

We also observed an association between fonofos and aldrin use and risk of total prostate cancer that was modified by family history of prostate cancer. This is consistent

Table 6. Continued

	No Family History			Yes Family History		
	No. of Cases[a]	RR[b]	95% CI	No. of Cases[a]	RR[b]	95% CI
Lindane[c]						
Nonexposed	622	1.00	Referent	127	1.00	Referent
Q1	30	0.87	0.59, 1.27	11	1.02	0.52, 2.01
Q2	30	1.20	0.82, 1.75	6	0.97	0.45, 2.08
Q3	27	0.98	0.66, 1.45	10	1.48	0.77, 2.84
Q4	25	0.95	0.64, 1.42	10	2.17	1.13, 4.17
P_{trend}			0.84			0.01
$P_{interaction}$				0.26		
Toxaphene[c]						
Nonexposed	617	1.00	Referent	137	1.00	Referent
Q1	23	0.71	0.47, 1.09	10	1.18	0.62, 2.24
Q2	30	1.14	0.80, 1.64	7	1.17	0.54, 2.51
Q3	25	1.20	0.80, 1.80	7	1.36	0.63, 2.94
Q4	27	0.92	0.62, 1.36	6	1.22	0.52, 2.84
P_{trend}			0.82			0.57
$P_{interaction}$				0.96		

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio; T1, tertile 1; T2, tertile 2; T3, tertile 3.

[a] Numbers do not sum to total because of missing data.

[b] Adjusted for age, state, race, smoking, fruit servings, and leisure-time physical activity in the winter.

[c] Detailed information for these chemicals was collected on the take-home questionnaire at enrollment.

Table 7. Phase I and Phase II Data for Cumulative Lifetime Pesticide Exposure to Triazine Herbicides and Risk of Total Prostate Cancer by Family History of Prostate Cancer in the Agricultural Health Study, 1993–2007

	No Family History			Yes Family History		
	No. of Cases[a]	RR[b]	95% CI	No. of Cases[a]	RR[b]	95% CI
Atrazine						
Nonexposed	375	1.00	Referent	54	1.00	Referent
Q1	242	0.94	0.80, 1.12	53	1.07	0.72, 1.58
Q2	244	0.98	0.83, 1.16	57	1.25	0.85, 1.84
Q3	236	0.90	0.76, 1.07	67	1.26	0.87, 1.83
Q4	250	0.96	0.81, 1.13	65	1.27	0.88, 1.83
P_{trend}			0.73			0.29
$P_{interaction}$				0.64		
Cyanazine						
Nonexposed	788	1.00	Referent	150	1.00	Referent
Q1	128	0.87	0.71, 1.06	30	0.89	0.59, 1.34
Q2	129	0.98	0.81, 1.19	30	0.96	0.64, 1.46
Q3	132	0.91	0.75, 1.10	31	0.90	0.60, 1.35
Q4	125	0.90	0.74, 1.10	40	1.23	0.85, 1.77
P_{trend}			0.37			0.21
$P_{interaction}$				0.67		

Abbreviations: CI, confidence interval; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; RR, rate ratio.

[a] Numbers do not sum to total because of missing data.

[b] Adjusted for age, state, race, smoking, fruit servings, and leisure-time physical activity in the winter.

with the observed effect modification by family history for fonofos within the Agricultural Health Study (13, 14) and provides new information about potential effect modification from a family history of prostate cancer among individuals with exposure to aldrin. These observations suggest that selected insecticides may interact with genetic determinants or that nongenetic factors that track in families might account for the observed association.

Our study is able to address several limitations common in other studies of pesticide use and prostate cancer. It included a large number of prostate cancer cases with exposure to pesticides and detailed information on use of specific pesticides that was available at 2 points in time. We also provided risk estimates, for the first time, for specific pesticides and clinically significant prostate cancer. Some limitations of our study should also be acknowledged. For example, information on the Gleason score was missing for 30% of the cases in North Carolina, which most likely led to an underestimation of advanced cases from this state. If these underestimated cases were more likely to have high exposure to the observed chemicals with an association for prostate cancer, the true risk may be higher than we observed here. Furthermore, Gleason scores were not standardized by centralized pathologic review. Moreover, because detailed information on some pesticides was collected only from the take-home questionnaire, missing data on these chemicals could introduce selection bias. We believe this is unlikely however, since individuals completing the take-home questionnaire were comparable to nonrespondents (48). In addition, although information on pesticide use provided by farmers in the Agricultural Health Study is quite reliable (49, 50), exposure misclassification undoubtedly occurred. In a prospective study such as the Agricultural Health Study, such misclassification is likely to be nondifferential and would tend to bias relative risks toward the null and diminish any "real" exposure-response gradients (51). Finally, given the large number of pesticides examined, we cannot rule out the possibility that some of our findings might be due to chance.

In conclusion, we observed significant increases in the risk of aggressive prostate cancer associated with 4 insecticides: fonofos (organophosphate), malathion (organophosphate), terbufos (organophosphate), and aldrin (organochlorine). This is the first time specific pesticides have been studied as risk factors for aggressive prostate cancer. These pesticide-specific findings need to be supported by mechanistic studies where there is still limited information about how pesticides impact carcinogenesis. Future follow-up in the Agricultural Health Study to further evaluate the relation between pesticides and aggressive prostate cancer is anticipated.

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