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Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study

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Abstract

Objectives—Organophosphates (OP) are among the most commonly used insecticides. OPs have been linked to cancer risk in some epidemiologic studies, which have been largely conducted in predominantly male populations. We evaluated personal use of specific OPs and cancer incidence among female spouses of pesticide applicators in the prospective Agricultural Health Study cohort.

Methods—At enrollment (1993–1997) spouses provided information about ever use of specific pesticides, including ten OPs, demographic information, reproductive health history, and other potential confounders. We used Poisson regression to estimate relative risks (RRs) and 95% confidence intervals (95% CIs) for all cancers diagnosed through 2010 for North Carolina and 2011 for Iowa.

Results—Among 30,003 women, 25.9% reported OP use, and 718 OP-exposed women were diagnosed with cancer during the follow-up period. Any OP use was associated with an elevated risk of breast cancer (RR = 1.20, 95% CI: 1.01, 1.43). Malathion, the most commonly reported OP, was associated with increased risk of thyroid cancer (RR = 2.04, 95% CI: 1.14, 3.63) and decreased risk of non-Hodgkin lymphoma (RR = 0.64, 95% CI: 0.41, 0.99). Diazinon use was associated with ovarian cancer (RR = 1.87, 95% CI: 1.02, 3.43).

Conclusions—We observed increased risk with OP use for several hormonally-related cancers, including breast, thyroid, and ovary, suggesting potential for hormonally-mediated effects. This

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study represents the first comprehensive analysis of OP use and cancer risk among women, and thus a need for further evaluation.

Keywords

"Pesticides"; "Cancer"; "Women"; "Agriculture"

BACKGROUND

Organophosphates (OP) are among the most commonly sold and used insecticide active ingredients in the United States (US) in all market sectors (i.e. agriculture, home and garden, industrial, commercial, and government) and currently comprise approximately 35% of insecticides used.[1] Some OPs, such as malathion, are registered for outdoor residential use in the US,[2] while others, such as diazinon and chlorpyrifos, were once registered for residential use, but now only agricultural use is allowed.[3,4] Selected OPs are used widely in the US and abroad in public health programs for mosquito control.[5] The International Agency for Research on Cancer classifies malathion and diazinon as probably carcinogenic to humans (group 2A) and dichlorvos, parathion, and tetrachlorvinphos as possibly carcinogenic to humans (group 2B),[6] with the US Environmental Protection Agency additionally classifying parathion as a possible human carcinogen.[7]

Increased cancer risk has been associated with several OP insecticides in epidemiologic studies, including case-control studies in the US,[8] Canada, [9] and Italy,[10] nested case-control studies of structural pest control workers in Florida,[11] and farm workers in California,[12] and more recently among licensed pesticide applicators in the prospective Agricultural Health Study (AHS) cohort. AHS investigators have linked diazinon, chlorpyrifos, and terbufos use to lung cancer,[13–15] diazinon, terbufos, fonofos, and malathion use to leukemia,[14–17] and terbufos use to non-Hodgkin lymphoma (NHL) overall, as well as specific NHL subtypes.[18] Additionally, increases in aggressive prostate cancer have been observed among male applicators applying terbufos, fonofos, and malathion.[19] Many studies have focused on occupational exposure among farmers; however OP insecticides are also widely used by others occupationally engaged in pest control, as well as residentially in the general population.

Studies of OP use and cancer outcomes have largely been conducted in predominantly male populations. Consequently, little is known about the potential impact of personal OP use among women, specifically on the development of female cancers, despite the fact that OPs as a class are thought to have endocrine disrupting properties. [20–22] Moreover, many of the cancer sites to be examined, including breast, lung, ovary, uterus, and thyroid, are of major public health importance in the US because they are commonly diagnosed and important contributors to cancer deaths among women.[23] In this analysis, we plan to evaluate the association between self-reported personal use of OP insecticides among spouses of pesticide applicators and subsequent cancer risk.

METHODS

Study Population

The AHS cohort has been described elsewhere in detail.[24] Briefly, 52,394 private pesticide applicators (mainly farmers) and 4,916 commercial pesticide applicators were recruited and enrolled during 1993–1997 in Iowa and North Carolina when they obtained or renewed their licenses to apply restricted use pesticides. Private applicators who indicated at enrollment that they were married were asked to have their spouse complete a take-home enrollment questionnaire focusing on farm exposures and general health, and a second questionnaire focusing on reproductive health history. The 32,345 spouses of private applicators who responded to the enrollment questionnaire are the focus of this study.

Exposure Assessment

Use of OP insecticides and other potential confounders were assessed at enrollment using the spouse questionnaire, available at http://aghealth.nih.gov/background/questionnaires.html. Questions about pesticide use for spouses of pesticide applicators were asked as follows: 'During your lifetime, have you ever personally mixed or applied [pesticide]? (Include pesticides used for farm use, commercial application, and personal use in your home or garden).' They were prompted for specific pesticides using the active ingredient name and one or more trade names. Chemicals were grouped on the questionnaire according to functional class (insecticides, fungicides, herbicides, etc.). Spouses self-reported lifetime ever use of 50 pesticides, including ten OP insecticides (chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, trichlorfon). If any of these OPs were reported, the spouse was considered exposed to OPs as a chemical class. If they reported no exposure to any OP they were considered unexposed. Otherwise, they were considered to be missing for exposure to the chemical class grouping.

Cancer Follow-Up

Incident cancer cases were ascertained via regular linkage with Iowa and North Carolina state cancer registries. Cancer site was classified according to the International Classification of Diseases for Oncology (third revision), and lymphoma subtypes were classified according to the original Surveillance, Epidemiology, and End Results Lymphoma Subtype Recode. We analyzed first primary cancers diagnosed from the date of enrollment interview through date of death, movement out of state, or last date of study follow-up (December 31, 2011 for Iowa, December 31, 2010 for North Carolina), whichever was earliest. Our analysis included cancers with malignant behavior, as well as *in situ* bladder cancers, which were included in the analysis, as per the standard grouping for bladder cancer. The study protocol was approved by all relevant institutional review boards.

Statistical Analysis

We excluded male spouses as there were few (n = 220) and women were the focus of our evaluation. We additionally excluded women with cancer diagnoses prior to enrollment (n = 907), missing or zero person-years of follow-up (n = 110), and missing information for all ten OPs (n = 1,105), leaving 30,003 female spouses available for analysis. We excluded

persons missing information for the OP of interest for specific analyses. For analyses of ovarian and uterine cancer, women were censored at date of oophorectomy or hysterectomy, or excluded if they had an oophorectomy (n = 3,074) or hysterectomy (n = 5,208) prior to study enrollment.

Relative risks (RR) and 95% confidence intervals (CIs) were estimated using Poisson regression in SAS version 9.3 (SAS Institute, Inc., Cary, NC) for all cancer sites combined and specific sites where sample size allowed (n ≥ 10 exposed cases). For the evaluation of use of any OPs as a class, no OP use was the referent category. For individual chemical analyses, persons reporting no use of the specific OP were included in the referent category. We conducted sensitivity analyses comparing those who applied an individual OP to those who never applied any OP (referent).

We adjusted all models for age (continuous), state of residence (Iowa or North Carolina), cigarette pack-years smoked as reported at enrollment (never smoker, pack-year quartiles: ≤ 1.5, 1.51–6.625, 6.626–18, >18, missing), race (white, other, missing), alcohol use (never, less than once per month, one to three times per month, once per week or more, missing), educational attainment (high school degree or less, some college, college graduate, missing), body mass index (≤25, 25.1–30, >30, missing), and family history of cancer (yes, no, missing; specific cancer site where available). We also controlled for being the person who usually treats the home or lawn for pests, for ever use of specific pesticides most highly correlated with OP use (Spearman $\rho > 0.40$; Supplemental Table 1), and pesticides previously found to be associated with specific cancer outcomes in the AHS.[25] In analyses of cancers of the breast, ovary, and uterus, as well as all sites combined, we additionally adjusted for menopausal status at enrollment (no, before age 50, after age 50, missing), number of live births (0, 1, 2, 3, 4^+, missing), and ever use of oral contraceptives at enrollment (yes, no, missing). We additionally explored inclusion of number of live births prior to age 30, and use of hormone replacement therapy among post-menopausal women. These variables did not appreciably alter our results and thus were not included in the final models. We considered family history of cancer as a potential effect modifier, but interaction terms did not reach statistical significance in any model. We also considered adjusting for smoking using other metrics (e.g. smoking duration in years, current/former/never use), but the results were similar to adjustment for pack-years smoked.

Breast cancers were examined by estrogen receptor (ER) and progesterone receptor (PR) status. For female cancer sites (breast, ovary, and uterus), we examined the statistical interaction between OP use and menopausal status at enrollment, and additionally performed stratified analyses by menopausal status at enrollment. We conducted sensitivity analyses restricting to cases diagnosed more than five years after enrollment, and also restricted to women who reported any pesticide application. We also performed analyses in which we did not control for home and lawn use, to ensure we were not over-adjusting for OP and correlated pesticide use. Finally, we stratified results by BMI (≤25, >25) to examine whether BMI might modify associations. All tests were two-sided with $\alpha = 0.05$.

RESULTS

Median follow-up time was 15.3 years. At enrollment, 25.9% of female spouses with valid information on OP use reported ever using at least one OP insecticide (Supplementary Table 1). The most commonly used OP insecticides were malathion (19.5%) and diazinon (10.3%). Table 1 describes selected demographic, health, and behavioral characteristics of AHS spouses. Ever users of OPs were older, from Iowa, white, more highly educated, heavier users of alcohol, and more overweight than non-users. They were also more likely to have had a family history of cancer, more live births, and gone through menopause at enrollment. Ever users of OPs were also more likely to report being the one who usually treats the home and/or lawn for pests. Lawn and home pesticide users were more likely to report herbicide use (data not shown).

Table 2 summarizes the results for ever use of OPs and risk of cancers with n ≥ 10 exposed cases. Use of any OP (RR = 1.20, 95% CI: 1.01, 1.43) was significantly associated with breast cancer. Chlorpyrifos use (RR = 1.41, 95% CI: 1.00, 1.99) and terbufos use (RR = 1.52, 95% CI: 0.97, 2.36) were associated with non-significantly elevated risk of breast cancer. Chlorpyrifos was associated with a significantly increased risk of $ER^{-}PR^{-}$ breast cancer (RR = 2.26, 95% CI: 1.07, 4.75). Malathion use was associated with a significantly increased risk of thyroid cancer (RR= 2.04, 95% CI: 1.14, 3.63) and decreased risk of NHL (RR = 0.64, 95% CI: 0.41, 0.99). Diazinon use was associated with a significantly increased risk of ovarian cancer (RR = 1.87, 95% CI: 1.02, 3.43). We observed no other associations between overall or specific OP use and cancer risk for any other site.

We stratified analyses for cancers of the breast, ovary, and uterus based on self-reported menopausal status at enrollment (Table 3), with 15,144 women classified as pre-menopausal and 12,216 as post-menopausal. Among post-menopausal women, we observed significantly elevated risk of breast cancer associated with use of any OP (RR = 1.27, 95% CI: 1.00, 1.62), and non-significantly elevated breast cancer risk associated with chlorpyrifos (RR = 1.53, 95% CI: 0.96, 2.44) and terbufos (RR = 1.73, 95% CI: 0.93, 3.21). Among women who used diazinon, we observed significantly elevated risk of ovarian cancer among pre-menopausal women (RR = 3.26, 95% CI: 1.31, 8.13), but not post-menopausal women (RR = 1.18, 95% CI: 0.46, 3.03, $P_{\text{interaction}} = 0.06$). We observed significant interactions with menopausal status and malathion for ovarian cancer risk ($P_{\text{interaction}} = 0.04$), and with menopausal status and diazinon for uterine cancer risk ($P_{\text{interaction}} = 0.03$). The stratum-specific risk estimates were not statistically significant, but the relative risks were elevated among pre-menopausal women.

When analyses were restricted to cancer cases (n ≥ 10) diagnosed at least five years after study enrollment (n = 29,244), the results were mostly unchanged with a few exceptions (Table 4). The association between diazinon and ovarian cancer was no longer significant (RR = 1.88, 95% CI: 0.93, 3.78) but remained elevated (n = 10 exposed cases). We noted a statistically significant association between any OP use and multiple myeloma (RR = 3.00, 95% CI: 1.08, 8.34). Additionally, diazinon (RR = 1.24, 95% CI: 0.99, 1.56), coumaphos (RR = 1.64, 95% CI: 0.98, 2.74), and parathion (RR = 1.72, 95% CI: 0.99, 2.99) were all associated with non-significantly elevated risk of breast cancer.

When we restricted our study population to spouses who reported any pesticide application (n = 16,685) the results remained unchanged. Results were similar in sensitivity analyses in evaluation of individual OPs and using those who never use any OP as the referent group. We also evaluated the impact of controlling for home and lawn pesticide use; the results were similar with and without control. Stratification by BMI revealed that the significant results in the models were more pronounced overall among normal weight women (BMI≤25), with the exception of the association with malathion use and NHL which was stronger among women with BMI >25 (results not shown).

DISCUSSION

This is the first study, to our knowledge, to prospectively evaluate use of OPs and cancer at multiple sites among women. It also provides the first epidemiologic evaluation of many female cancers, such as ovary and uterus, with this important chemical pesticide class. We observed increased risk of several hormonally-related cancers, including thyroid, ovary, and breast.

We observed a strong association between malathion use and thyroid cancer. A previous study of male AHS private applicators found that malathion was associated with an increased prevalence of hypothyroidism;[26] however, a similar study among female AHS spouses found no association with malathion and hypothyroidism, hyperthyroidism, or other thyroid disease.[27] Although hypo- and hyperthyroidism have been hypothesized to be associated with thyroid cancer risk, the evidence has been somewhat inconsistent.[28,29] Low thyroid stimulating hormone levels are thought to be associated with future thyroid cancer risk;[30] however, laboratory studies in rats found that malathion was associated with increased thyroid stimulating hormone secretion.[31] In agricultural areas, nitrate exposure via diet and drinking water has been associated with thyroid cancer and hypothyroidism;[32] we were not able to control for nitrate intake in our analyses.

Increased risk of ovarian cancer was associated with diazinon use, with a significantly increased risk among women who were pre-menopausal, but not post-menopausal, at enrollment. We also noted a significant interaction between menopausal status and malathion use for risk of ovarian cancer, with elevated risk among pre-menopausal women. However, this may be a chance finding as there was no overall association between malathion and ovarian cancer. An excess of ovarian cancer has been reported among female pesticide applicators in the AHS,[33] but the small number of female applicators precluded evaluation by specific pesticides. Diazinon has been shown to alter DNA methylation patterns in the promoter regions of several genes associated with cancer, and has been correlated with decreased DNA excision repair *in vitro*.[34,35] Diazinon use has been associated with shortened relative telomere length in male AHS pesticide applicators.[36] Diazinon has also been shown to exhibit estrogenic properties, and to have a genotoxic effect on human mucosal cells.[37,38]

Use of any OP, terbufos, and chlorpyrifos were each associated with non-significantly increased breast cancer risk in our analyses. We also noted significantly increased risk associated with chlorpyrifos use and $ER^{-}PR^{-}$ breast cancer. An AHS study with follow-up

for breast cancers through 2000 with 309 cases saw no significantly increased risk for personal use of any OP.[39] Our analysis of the updated cohort included 1,059 accrued female breast cancer cases. A small registry-based case-control study of Hispanic farm workers in California examined use of pesticides and risk of breast cancer (n = 128 cases), finding no association with diazinon and a suggestion of an association with malathion but no exposure-response.[40] Many laboratory studies have noted associations between OPs and breast cancer *in vitro* and *in vivo*. OPs, particularly malathion and parathion, have been shown to induce malignant transformation of breast cells,[41,42] alter estrogen activity and estrogen receptor transactivity,[43,44] and upregulate genes associated with carcinogenesis, sometimes in combination with estrogen.[45]

We observed a statistically significant inverse association with NHL and malathion use. A recent AHS analysis of male applicators found null associations with malathion use and NHL risk overall.[18] Additionally, some case-control studies have shown a positive association for malathion use and NHL.[9,46,47] Adjustment for other variables shown to be associated with NHL risk in farming populations, including whether or not they grew up on a farm, self-reported history of physician diagnosed allergies, and contact with farm animals, did not alter the relationships in our study. Given these conflicting results and a lack of a plausible biological mechanism it is unclear whether our observed inverse association between malathion and NHL is real or a chance finding. In sensitivity analyses restricting our population to those diagnosed more than five years after study enrollment, we noted a positive association with use of any OP and multiple myeloma. No association was observed with any individual OP and multiple myeloma in a recent study of AHS applicators,[18] though excesses of multiple myeloma have been noted among pesticide applicators and in farming populations.[33,48] The findings in our study were based on few exposed cases; therefore, further evaluations are needed to confirm these results.

OPs' mechanism of pesticidal action involves inhibition of acetylcholinesterase activity.[49] Excess acetylcholine as a result of OP exposure may act on cervical sympathetic neuronal nicotinic receptors, and activation of these neurons can promote thyroid hormone secretion via release of norepinephrine from the interfollicular adrenergic nerve endings.[50–53] However, the potential mechanism of carcinogenesis may be unrelated to the mechanism of pesticidal action. Hypothesized OP carcinogenic mechanisms include increased cellular proliferation,[42] oxidative stress,[54–56] and immunotoxicity.[57] Given our findings with several hormonally-related cancers, it is also of note that OPs are thought to have endocrine disrupting properties. OPs may influence sex steroid hormone homeostasis, causing alterations in the levels of circulating and bioavailable sex hormones[58–61] and potentially impacting cellular proliferation and risk for hormone-related cancers.[62] We noted that the associations for hormonally-related cancers were strongest among women with BMI ≤25. While there is some evidence that exposure to endocrine disrupting chemicals may impact body size, the relationship is not clear, and there are issues surrounding timing of exposure and reverse causation that make interpretation of these studies difficult.[63] There is little information about a relationship between OP insecticide use and body size. A previous analysis in AHS examined the potential modifying effect of pesticides on the BMI-cancer association. There was a significant positive association between BMI and breast cancer in

post-menopausal women who did not use OPs, but no association with BMI among those who did; however, the test for interaction was not significant.[64]

Strengths of our study include the longitudinal design with regular linkage to population registries for cancer and mortality outcomes and little or no loss-to-follow-up, as well as information about the use of specific pesticides. Many epidemiologic studies examine OPs as a class because of a small number of exposed cases, or because exposure to individual active ingredients is not evaluated. Due to the prospective design of the AHS, there is no risk of differential reporting of pesticide use based on cancer outcome; any non-differential recall bias would bias the results toward the null. Blair et al. assessed reliability of the AHS questionnaire among pesticide applicators; the level of agreement for ever pesticide use is quite high, ranging from 70% to greater than 90%.[65] Though this work was done among applicators, we believe the spouses' responses are similarly reliable. Spouses were prompted in the survey to mark all pesticides ever applied in their lifetime. Pesticide active ingredient and common trade names were listed in the survey. Because many of these women grew up on farms (60%), it is likely they are familiar with regularly used pesticides. In focusing on spouses, we were able to examine cancer outcomes that are unique to (e.g. ovary, uterus) or most common among women (e.g. breast, thyroid).

A limitation of our analysis was sample size; only about one quarter of our sample reported OP use at enrollment. Due to a small number of cases, we were unable to evaluate very rare cancer sites and may have limited power to evaluate cancer sites with low incidence in AHS. Although information was collected on known risk factors for female cancers (e.g. menopausal status at enrollment, oral contraceptive use, parity), certain important details were either not provided (type of oral contraceptive or hormone replacement therapy) or available for only a portion of the cohort (time-varying menopausal status) and thus could not be assessed as potential confounders. Many spouses in our cohort applied more than one pesticide in their lifetime. We controlled for use of pesticides that were highly correlated with the OP of interest, as well as pesticides that had been associated with specific cancer sites in previous analyses to minimize these possible sources of confounding by use of multiple pesticides. Because we examined the use of several OP insecticides and cancer outcomes it is possible that the findings could be due to chance. We were only able to examine self-reported lifetime personal ever use, and had no information about duration or time period of use. The assumption that all exposures are equivalent may be incorrect, as patterns of OP use and chemical formulation may have changed over time. The inability to differentiate between high and low use may mask potential associations. We also only evaluated personal use of pesticides in this analysis and not exposure from other sources. Based on how pesticide information was ascertained, we were not able to distinguish between occupational OP use on the farm versus residential indoor and outdoor uses. Many women reported being the person who applies pesticides to the home and lawn, but did not report personal use of specific pesticides or pesticides overall. We controlled for being the person applying home and lawn pesticides in order to capture this use. We were concerned about potential for over-adjustment for OP use, however, insecticides applied in the home at this time were primarily pyrethroids, and insecticides used on the lawn were primarily OPs.[66] However, lawn use in our study reflected primarily herbicide and not insecticide use. Thus we feel confident we were not over-adjusting for OP use.

In the first study to prospectively examine use of OP insecticides and risk of multiple cancer sites among women, we observed associations with several cancer sites including thyroid, ovary, and, breast. Previous studies examining organophosphate insecticide use and cancer have focused primarily on men, making this a unique evaluation. The increased risks that we observed for hormonally-related cancers are consistent with the hypothesis that OPs might act as endocrine disruptors, although additional studies exploring this and other possible mechanisms are needed. Future studies should continue to consider use of individual OPs to fully understand their impact on cancer risk. Because of the ubiquitous use of OP insecticides in both agricultural and residential settings, future research should attempt to confirm these findings by assessing exposure-response trends, non-occupational environmental sources of OP exposure, and hormonal changes in women exposed to OPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What this paper adds

- Organophosphates are among the most commonly used insecticides
- Though organophosphates have been associated with increased cancer risk, there have been no prospective studies examining use of individual organophosphate insecticides and risk of multiple cancer sites in women.
- We observed increased risk with organophosphate insecticide use for several hormonally-mediated cancers, including breast, thyroid, and ovary.
- Our results suggest the potential for hormonally-mediated effects of organophosphate insecticides with respect to cancer risk among women.

Table 1

Selected characteristics of AHS spouses at enrollment with valid OP use information (n = 29,325[1]), stratified by ever use of organophosphate insecticides

	Total N = 29,325		Any OP Use: No N = 21,736		Any OP Use: Yes N = 7,589		
	N	%	N	%	N	%	*P* value[2]
Age at enrollment							
≤35	5,740	19.6	4,743	21.8	997	13.1	< 0.01
36–45	8,829	30.1	6,465	29.7	2,364	31.2	
46–55	7,493	25.6	5,172	23.8	2,321	30.6	
56+	7,263	24.8	5,356	24.6	1,907	25.1	
State							
Iowa	19,880	67.8	14,323	65.9	5,557	73.2	< 0.01
North Carolina	9,445	32.2	7,413	34.1	2,032	26.8	
Race							
White	28,757	98.1	21,208	97.6	7,549	99.5	< 0.01
Other	520	1.8	489	2.3	31	0.4	
Missing	48	0.2	39	0.2	9	0.1	
Cigarette smoking (pack-years)							
Never smoker	20,607	70.3	15,304	70.4	5,303	69.9	0.06
Q1: ≤1.5	1,894	6.5	1,361	6.3	533	7.0	
Q2: 1.51–6.625	1,973	6.7	1,456	6.7	517	6.8	
Q3: 6.626–18	2,049	7.0	1,551	7.1	498	6.6	
Q4: >18	1,802	6.1	1,311	6.0	491	6.5	
Missing	1,000	3.4	753	3.5	247	3.3	
Educational attainment							
High school or less	11,983	40.9	9,117	41.9	2,866	37.8	< 0.01
Some college	8,010	27.3	5,914	27.2	2,096	27.6	
College graduate	6,302	21.5	4,623	21.3	1,679	22.1	
Other/Missing	3,030	10.3	2,082	9.6	948	12.5	
Alcohol use							
Never	13,135	44.8	10,095	46.4	3,040	40.0	< 0.01

	Total N = 29,325		Any OP Use				
			No N = 21,736		Yes N = 7,589		
	N	%	N	%	N	%	*P* value[2]
Less than once/month	7,799	26.6	5,667	26.0	2,132	28.1	
1–3 times/month	4,579	15.6	3,321	15.3	1,258	16.6	
1 time/week or more	3,480	11.9	2,401	11.0	1,079	14.2	
Missing	332	1.1	252	1.2	80	1.1	
Body mass index							
≤25	12,853	43.8	9,514	43.8	3,339	44.0	< 0.01
25.1–30	8,285	28.3	5,936	27.3	2,349	31.0	
>30	4,795	16.4	3,491	16.1	1,304	17.2	
Missing	3,392	11.6	2,795	12.9	597	7.9	
Family history of cancer							
No	14,356	49.0	10,943	50.4	3,413	45.0	< 0.01
Yes	14,426	49.2	10,343	47.6	4,083	53.8	
Missing	543	1.9	450	2.1	93	1.2	
Menopause at enrollment							
No	14,841	50.6	11,130	51.2	3,711	48.9	< 0.01
Yes, before age 50	7,086	24.2	5,022	23.1	2,064	27.2	
Yes, after age 50	4,101	14.0	2,870	13.2	1,231	16.2	
Missing	3,297	11.2	2,714	12.5	583	7.7	
Number of live births							
0	1,554	5.3	1,149	5.3	405	5.3	< 0.01
1	2,194	7.5	1,711	7.9	483	6.4	
2	8,625	29.4	6,347	29.2	2,278	30.0	
3	6,961	23.7	4,944	22.8	2,017	26.6	
4+	5,585	19.1	3,949	18.2	1,636	21.6	
Missing	4,406	15.0	3,636	16.7	770	10.2	
Oral contraceptive use							
Never	6,838	23.3	5,049	23.2	1,789	23.6	< 0.01
Ever	19,124	65.2	13,938	64.1	5,186	68.3	
Missing	3,363	11.5	2,749	12.7	614	8.1	

	Total N = 29,325		Any OP Use: No N = 21,736		Any OP Use: Yes N = 7,589		
	N	%	N	%	N	%	*P* value[2]
Apply pesticides in home							
No	21,164	72.2	16,833	77.4	4,331	57.1	< 0.01
Yes	8,161	27.8	4,903	22.6	3,258	42.9	
Apply pesticides on lawn/garden							
No	26,158	89.2	20,417	93.9	5,741	75.7	< 0.01
Yes	3,167	10.8	1,319	6.1	1,848	24.4	

[1]Excluded n = 678 women missing information on any OP use. The overall study population included 30,003 women, as there were some women who had valid exposure information for a single OP but were missing for overall OP use.

[2]Chi-square test for homogeneity

Table 2

Relative risks (RR) and 95% confidence intervals (95% CI)[1] for ever use of organophosphate insecticides, compared to never use, for various cancers among AHS spouses

		Any OP			Malathion			Diazinon			Chlorpyrifos			Terbufos		
	N_{total}[2]	N[3]	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
All Sites[4]	2,712	718	1.08	0.97, 1.21	558	1.03	0.92, 1.15	277	1.04	0.91, 1.18	108	1.03	0.81, 1.3	88	1.26	0.94, 1.69
Brain	38	14	1.29	0.53, 3.12	11	1.57	0.65, 3.78									
Breast[4]	1,059	296	**1.20**	**1.01, 1.43**	223	1.05	0.88, 1.26	118	1.14	0.93, 1.38	50	1.41	1.00, 1.99	37	1.52	0.97, 2.36
ER+PR+	595	165	1.14	0.90, 1.44	124	1.00	0.79, 1.26	62	1.07	0.82, 1.40	28	1.37	0.86, 2.19	21	1.41	0.78, 2.55
ER−PR−	171	52	1.26	0.83, 1.92	40	1.17	0.77, 1.78	20	1.21	0.75, 1.96	11	**2.26**	**1.07, 4.75**			
Colon	204	47	0.87	0.56, 1.33	38	0.89	0.58, 1.37	19	0.98	0.59, 1.61						
Leukemia	63	19	0.83	0.40, 1.71	14	0.73	0.34, 1.54									
Lung	165	35	0.77	0.46, 1.28	30	1.00	0.60, 1.65	15	0.92	0.52, 1.64						
Melanoma	117	30	0.98	0.57, 1.67	23	0.90	0.52, 1.53									
NHL[5]	194	53	1.01	0.66, 1.53	34	**0.64**	**0.41, 0.99**	18	0.93	0.56, 1.56				10	1.54	0.59, 4.03
FL	38	13	1.24	0.51, 3.01												
MM	37	12	1.78	0.70, 4.52												
CLL/SLL/PLL/MCL	35	10	1.15	0.43, 3.09												
Ovary[4]	85	23	1.46	0.78, 2.71	16	0.89	0.48, 1.67	13	**1.87**	**1.02, 3.43**						
Pancreas	47	16	1.46	0.64, 3.32	14	1.50	0.69, 3.26									
Rectum	61	15	1.23	0.56, 2.68	12	0.92	0.43, 1.97									
Thyroid	91	24	1.27	0.70, 2.30	22	**2.04**	**1.14, 3.63**									
Uterus[4]	231	72	1.19	0.83, 1.72	58	1.28	0.90, 1.83	25	1.06	0.69, 1.64	10	0.85	0.38, 1.89			

		Dichlorvos			Phorate			Fonofos			Coumaphos			Parathion		
	N_{total}	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
All Sites[4]	2,712	81	1.08	0.86, 1.35	55	0.81	0.59, 1.10	54	0.86	0.61, 1.20	39	1.08	0.78, 1.49	34	1.18	0.83, 1.66
Breast[4]	1,059	33	1.19	0.84, 1.70	22	0.88	0.54, 1.42	17	0.65	0.36, 1.15	18	1.30	0.81, 2.08	14	1.26	0.74, 2.15
ER+PR+	595	23	1.34	0.88, 2.05	15	0.96	0.52, 1.77	10	0.59	0.28, 1.26	10	1.23	0.65, 2.30			

Bold: Significant at α=0.05

[1]Adjusted for age, race, state, pack-years smoked, family history of cancer, alcohol consumption, BMI, education, lawn/garden pesticide application, and correlated/associated pesticide use

[2]Total cases

[3]Exposed cases

[4]Additionally adjusted for menopause status at enrollment, number of live births, and oral contraceptive use

[5]NHL: Non-Hodgkin Lymphoma, FL: Follicular Lymphoma, MM: Multiple Myeloma, CLL: Chronic Lymphocytic Leukemia, SLL: Small lymphocytic lymphoma, PLL: Prolymphocytic leukemia, MCL: Mantle cell lymphoma

Table 3

Relative risks (RR) and 95% confidence intervals (95% CI)[1] for ever-use of organophosphate insecticides stratified by menopausal status at enrollment, compared to never use among AHS spouses for selected cancer sites.

	Breast							Ovary							Uterus						
		Pre-menopausal N = 381			Post-menopausal N = 603				Pre-menopausal N = 25			Post-menopausal N = 51				Pre-menopausal N = 97			Post-menopausal N = 108		
	N[2]	RR	95% CI	N	RR	95% CI	P_{int}[3]	N	RR	95% CI	N	RR	95% CI	P_{int}	N	RR	95% CI	N	RR	95% CI	P_{int}
OPs	105	1.02	0.77, 1.36	174	**1.27**	**1.00, 1.62**	0.81	9	1.92	0.67, 5.47	12	1.09	0.48, 2.51	0.24	33	1.41	0.81, 2.45	33	0.95	0.55, 1.62	0.52
Malathion	80	1.04	0.78, 1.38	132	1.03	0.81, 1.30	0.44	8	2.14	0.78, 5.93	8	0.57	0.24, 1.33	**0.04**	27	1.47	0.86, 2.49	26	0.98	0.58, 1.67	0.33
Diazinon	44	1.01	0.73, 1.40	65	1.11	0.85, 1.45	0.95	7	**3.26**	**1.31, 8.13**	5	1.18	0.46, 3.03	0.06	16	1.42	0.81, 2.50	6	0.52	0.22, 1.19	**0.03**
Chlorpyrifos	20	1.36	0.79, 2.34	27	1.53	0.96, 2.44	0.83								5	0.75	0.23, 2.42	5	1.09	0.36, 3.34	0.92
Terbufos	13	1.25	0.61, 2.54	19	1.73	0.93, 3.21	0.88														
Dichlorvos	11	1.07	0.58, 1.97	22	1.24	0.80, 1.92	0.79														
Phorate	11	1.44	0.73, 2.84	10	0.64	0.31, 1.29	0.10														
Fonofos	5	0.56	0.20, 1.56	8	0.52	0.23, 1.20	0.80														
Coumaphos	6	1.29	0.57, 2.90	12	1.36	0.77, 2.43	0.93														
Parathion	4	0.93	0.35, 2.50	9	1.46	0.75, 2.83	0.54														

Bold: Significant at α=0.05

[1] Adjusted for age, race, state, pack-years smoked, family history of cancer, alcohol consumption, BMI, education, home and garden pesticide application, correlated/associated pesticide use, number of live births, and oral contraceptive use

[2] Exposed cases

[3] *P* interaction for menopausal status at enrollment and OP use

Table 4

Relative risks (RR) and 95% confidence intervals (95% CI)[1] for ever use of organophosphate insecticides, compared to never use, for various cancers diagnosed five or more years after study enrollment among AHS spouses

		OPs			Malathion			Diazinon			Chlorpyrifos			Terbufos		
	N_{total}[2]	N[3]	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
All Sites[4]	1,953	528	1.08	0.94, 1.23	411	1.04	0.91, 1.18	209	1.08	0.93, 1.25	82	1.05	0.79, 1.38	64	1.17	0.83, 1.66
Breast[4]	740	206	1.21	0.98, 1.49	156	1.10	0.89, 1.35	88	1.24	0.99, 1.56	36	1.45	0.97, 2.18	27	1.61	0.96, 2.72
ER+PR+	431	122	1.22	0.93, 1.61	95	1.11	0.85, 1.45	46	1.10	0.81, 1.51	19	1.20	0.68, 2.11	15	1.39	0.68, 2.81
ER−PR−	115	35	1.19	0.71, 1.99	25	1.04	0.62, 1.74	16	1.48	0.86, 2.55						
Colon	143	35	0.87	0.52, 1.44	29	0.95	0.58, 1.57	15	1.06	0.60, 1.87						
Leukemia	48	15	0.92	0.41, 2.11	11	0.79	0.34, 1.85									
Lung	124	29	0.81	0.46, 1.42	26	1.11	0.63, 1.93	13	1.06	0.56, 2.00						
Melanoma	72	21	1.02	0.53, 1.97	15	0.82	0.42, 1.59									
NHL[5]	152	46	1.10	0.69, 1.74	27	**0.60**	**0.37, 0.98**	17	1.14	0.66, 1.96						
FL	30	11	1.02	0.38, 2.76												
MM	27	11	**3.00**	**1.08, 8.34**												
Ovary[4]	61	18	1.55	0.75, 3.18	15	1.28	0.64, 2.56	10	1.88	0.93, 3.78						
Pancreas	35	14	1.62	0.65, 4.08	12	1.46	0.62, 3.44									
Rectum	44	11	0.96	0.39, 2.41												
Thyroid	73	21	1.41	0.74, 2.69	19	**2.22**	**1.18, 4.17**									
Uterus[4]	170	47	1.03	0.66, 1.59	37	1.09	0.71, 1.67	15	0.81	0.47, 1.41						

		Dichlorvos			Phorate			Fonofos			Coumaphos			Parathion		
	N_{total}	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
All Sites[4]	1,953	53	0.95	0.72, 1.26	42	0.86	0.60, 1.22	42	0.90	0.61, 1.33	27	1.00	0.68, 1.47	26	1.20	0.81, 1.79
Breast[4]	740	19	1.05	0.66, 1.67	16	0.94	0.53, 1.65	12	0.66	0.33, 1.31	15	1.64	0.98, 2.74	13	1.72	0.99, 2.99
ER+PR+	431	14	1.21	0.70, 2.08	10	0.99	0.48, 2.03									

Bold: Significant at α=0.05

[1]Adjusted for age, race, state, pack-years smoked, family history of cancer, alcohol consumption, BMI, education, home and garden pesticide application, and correlated/associated pesticide use

[2]Total cases

[3] Exposed cases

[4] Additionally adjusted for menopause status at enrollment, number of live births, and oral contraceptive use

[5] NHL: Non-Hodgkin Lymphoma, FL: Follicular Lymphoma, MM: Multiple Myeloma