A PROSPECTIVE STUDY OF CANCER RISK AMONG THE AGRICULTURAL HEALTH STUDY FARM SPOUSES ASSOCIATED WITH PERSONAL USE OF ORGANOCHLORINE INSECTICIDES

By

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ABSTRACT OF THESIS

A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides.

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BACKGROUND: Organochlorine insecticides (OCs) have historically been used worldwide to control insects, although most have now been banned in developed countries. Evidence for an association between OC exposures and cancer predominantly comes from occupational and population based-studies among men. We evaluated the association between the use of specific OCs and cancer among the female spouses of pesticide applicators in the Agricultural Health Study. **METHODS:** At enrollment (1993–1997), spouses of private applicators in the cohort provided information about their own personal use of pesticides, including

seven OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane, and toxaphene), and information on potential confounders. We used Poisson regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for cancers ($n \geq 3$ exposed cancer cases) reported to state cancer registries from enrollment through 2012 (North Carolina) and 2013 (Iowa), and the self-reported personal use OCs. **RESULTS:** Among 28,909 female spouses, 2,191 (7.58%) reported ever use of at least one OC, of whom 287 were diagnosed with cancer. Most cancers were not associated with OC use. Risk of glioma was increased among users of at least one OC ($N_{exposed}$=11, RR=3.52, 95%CI 1.72-7.21) and specifically among lindane users ($N_{exposed}$=3, RR=4.45, 95%CI 1.36-14.55). Multiple myeloma was associated with chlordane ($N_{exposed}$=6, RR=2.71, 95%CI 1.12-6.55). Based on 3 exposed cases each, there were also positive associations between pancreatic cancer and lindane, and ER-PR- breast cancer and dieldrin. No other associations with breast cancer were found. **CONCLUSIONS:** Overall, there were some associations with OC use and cancer incidence, however we were limited by the small number of exposed cancer cases. Future research should attempt to expand on these findings by assessing environmental sources of OC exposures, to fully evaluate the role of OC exposures on cancer risk in women.

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DEDICATION

To Oliver Lontok, for his unyielding faith and encouragement, particularly during times of uncertainty and self-doubt.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

OC	organochlorines
IARC	International Agency for Research on Cancer
PCP	pentachlorophenl,
DDT	dichlorodiphenyltrichloroethane
TCP	2,4,6-trichlorophenol
HCH	hexachlorocylcohexanes
HCB	hexachlorobenzene
NHL	non-Hodgkin Lymphoma
AHS	Agricultural Health Study
MM	multiple myeloma
DLBCL	diffuse large B-cell lymphoma
SEER	Surveillance Epidemiology and End Results
ER	estrogen receptor
PR	progesterone receptor
RR	relative risks
CI	confidence interval
PCB	polychlorinated biphenyl

DECLARATIONS

Ethics approval and consent to participate: Study procedures and documents were approved in 1993 by the National Cancer Institute Special Studies Institutional Review Board, Westat Institutional Review Board, and the University of Iowa Institutional Review Board-01.

Availability of data and materials: The data sets used and/or analyzed during the current study may be made available through approval by the Agricultural Health Study executive committee.

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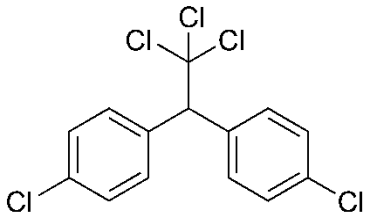
BACKGROUND

Organochlorine (OC) insecticides are a class of cyclic hydrocarbon chlorinated insecticides that have been historically used to control insects in agriculture and residential settings worldwide and that are still used for the control of vector borne illnesses in developing countries [1, 2]. Developed in the late nineteenth century, OCs came to prevalence of use during World War II (WWII) for the prevention of vector borne illnesses including, malaria, typhus, body lice, and the bubonic plaque. OC insecticides were later introduced in the United States during the 1940s and were widely used throughout the 1960s [3], comprising 72% of total U.S. insecticide use [4]. Early studies raised concern over their environmental persistence as well as potential adverse effects on wildlife and human health [5-7]. As a result, most OC insecticides (e.g., aldrin, chlordane, chlordecone, dieldrin, dichlorodiphenyltrichloroethane (DDT), endrin, heptachlor, hexachlorocylcohexanes (HCH), methoxychlor, mirex, pentachlororphenol (PCP), and toxaphene) were banned in the 1970s and 1980s [6, 8]. Lindane and endosulfan, the last remaining OC active ingredients, were banned for use in the U.S. in 2006 and 2010 respectively [9, 10].

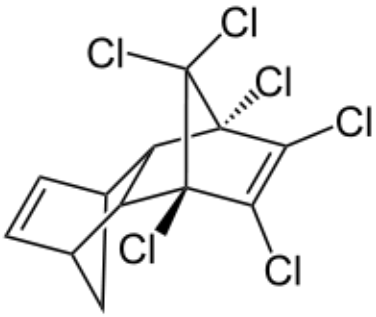
OCs exert their insecticidal toxic effects as determined by their subtype classification as either DDT-type insecticides (i.e. dichlorodiphenyldichloroethylene (DDE)) or chlorinated alicyclic insecticides (i.e. aldrin, dieldrin, chlordane, endosulfan) [11]. DDT-type OCs block sodium gate closure in peripheral nervous system axons. This leads to an increased leakage of sodium ions through the cell membrane and a

hyperexcitability of the nerve, resulting in repetitive axonal discharge after a single stimulus. Similarly, chlorinated alicyclic insecticides also cause hyperexcitablity of peripheral nerves, however they do so by blocking y-aminobutyric acid (GABA) chloride ionophore complexes thus inhibiting the flux of chlorine ions into the nerve cell.

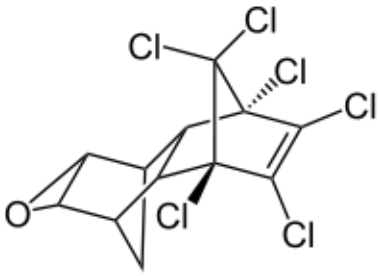
Figure 1. Structures of several historically used OCs



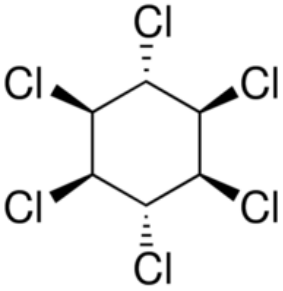
DDT



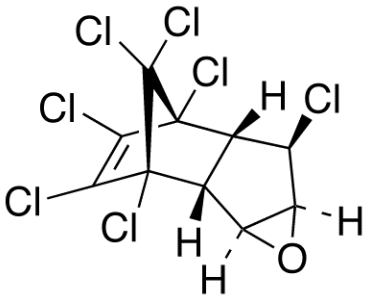
Aldrin



Dieldrin



Lindane



Heptachlor

Although OC insecticides are no longer in use in the United States, their derivatives can remain in the environment for extended durations of time and have been designated as persistent organic pollutants (POPs) [12]. Soil half-lives of DDT and its byproducts ρ,ρ'-DDE, have been reported as ranging between 2 and 20 years [13], while in an aquatic environment the half-life of DDT is reported at 150 years [14]. Sources of human OC insecticide exposures include ingestion of contaminated groundwater and food sources, past residential and occupational use, drift from treated fields and take-home pathways [15]. OC insecticides are lipid-soluble and have a propensity to biomagnify through the food chain, deposit into tissues of high fat content [6] and have been known to persist in the human body for up to 50 years [13]. Levels of OC insecticides in human tissues generally increase as a person ages due to cumulative environmental exposure [15].

Because of their persistence and bioaccumulation in humans, there is an interest in understanding the impact of OC insecticides on human health and specifically human cancer risk. Currently, the International Agency for Research on Cancer (IARC) classifies fifteen OC insecticides with respect to their human carcinogenicity. Lindane and PCP [16] have been classified as a human carcinogen (Group 1), dichlorodiphenyltrichloroethane (DDT) and DDT derivatives (including DDE) [17, 18], aldrin [16] and dieldrin [16], have been classified as probably carcinogenic to humans (Group 2A). 2,4,6-trichlorophenol (TCP) [16], chlordane [19], chlordecone [20], heptachlor [19], HCH [20], hexachlorobenzene (HCB) [19], mirex [20], and toxaphene [19] have been classified as possible human carcinogens (Group 2B). Several others, including endrin, and

methoxychlor, were not classifiable with respect to carcinogenicity (Group 3) at the time of their reviews [18, 19].

Several biological mechanisms of action have been posited to help explain the potential carcinogenic effects of OCs in humans[21-26]. A significant portion of the basic science literature has focused on OCs as endocrine disrupting compounds. It is thought that the chemical and structural similarity of OCs to endogenous human hormones, allows these chemicals to bind, either directly or indirectly, to hormone nuclear receptors including estrogen receptors (ER) and aryl hydrocarbon receptors (AhR). In doing so OCs may alter hormonal pathways by inhibiting the activation and production of key enzymes and signaling molecules responsible for the formation of steroid based hormones. These include a multitude of P450 cytochrome enzyme target genes which may be responsible for the metabolism and biotransformation of estrogenic environmental contaminants. Furthermore, changes to the expression of these cytochrome enzymes can lead to alterations in endogenous levels of hormones consequently altering and possibly compromising hormonal signaling cascades responsible for cell homeostasis. This in turn has the ability to disrupt normal cell growth and development giving opportunity for cancerous tumor growth in a number of organs including the endometrium, prostate, blood, bone marrow and most notably breast with a lesser degree in the lung, pancreas and brain. OCs may also disrupt cell homeostasis and initiate apoptosis by way of oxidative stress induction through the overproduction and accumulation of reactive oxygen species (ROS). Alteration in cellular redox homeostasis may subsequently lead to mitochondrial

dysfunction, stress to the endoplasmic reticulum and eventual DNA damage. More recently OC exposures have been postulated to also act through epigenetic mechanisms and in turn alter chromosomal stability as well as DNA methylation patterns of subsequent gene regions leading to sustained adverse multigenerational effects.

Evidence for associations between OC insecticide active ingredients and cancer has come mainly from cohort and case-control studies of occupational exposures and lymphohematopoietic cancers [27-34]. An occupational-based analysis from Sweden found a significantly increased risk for multiple myeloma among farmers exposed to DDT [33]. A population-based case-control study among white men from the U.S. Midwest reported use of lindane as having significantly increased the risk of non-Hodgkin Lymphoma (NHL) by 50% [28]. Based on questionnaire and blood plasma data, two separate case-control studies from Canada found a statistically significant increased risk for NHL with exposure to lindane and aldrin [29], as well as mirex [32] and derivatives of lindane, DDT, and chlordane [32]. OCs and lymphohematopoietic cancers have also been evaluated within the Agricultural Health Study (AHS) applicators [27, 31]. The most recent analysis from this prospective cohort study demonstrated statistically significant increased risks for NHL, with significant positive exposure-response trends for lindane and DDT [27]. In further subtype analyses, lindane was also associated with follicular lymphoma, while DDT was also associated with small cell lymphoma/chronic lymphocytic leukemia/marginal cell lymphoma. These findings were among the first to suggest links between DDT and lindane with NHL subtypes. A previous AHS study analysis also found

significantly increased relative risks for leukemia with chlordane and heptachlor use [31]. There is strong evidence that some OC insecticides, including lindane and DDT, cause immunosuppressive effects in humans, as well as oxidative stress; these biological effects are thought to possibly play a role in the development of lymphohematopoietic cancers [17, 35].

Potential associations between OCs and hormonally-mediated cancers, particularly female breast cancer, are of interest due to results of *in vitro* and animal studies that suggest OCs are endocrine disrupting compounds that act as estrogen agonists or antagonists [21, 36]. Breast cancer has been the most frequently examined cancer with OC exposure; however, the majority of findings have been inconclusive [17, 37]. In an early epidemiologic study, *Wolff et al.* found a two to four-fold increased risk of breast cancer among women with the highest serum DDE levels, with a positive trend with increasing serum DDE [38]. However, a follow-up study with greater sample size found no evidence for an association of breast cancer risk with serum DDE levels [39]. While two studies [40, 41] have suggested an association with dieldrin, other epidemiological studies of OC exposures and breast cancer risk have found null or no positive statistically significant associations [37, 42-48]. Similarly, an analysis of endometrial cancer did not observe statistically significant associations with serum DDE, HCH, HCB, oxychlordane and alachlor [49]. No studies to our knowledge thus far have investigated associations with ovarian or uterine cancers. It is possible that a lack of statistical power or specific information on exposure to OC active ingredients has prevented researchers from

determining associations between OC insecticide exposures and female-specific cancers. Nevertheless, the relationship between OCs and hormonally-mediated cancers among women remains unclear.

A few other cancer sites have been evaluated for associations with OCs. According to the IARC, the strongest evidence for associations with cancer at other sites comes from case-control studies of liver and testicular cancers [50-54]. Several nested and population-based case-control studies in China reported strong dose-related associations between hepatocellular carcinoma (HCC) and serum DDT, ρ, ρ'-DDE, and β-HCH after adjustment for potential confounders [50-52]. Another case-control analysis found statistically significant associations with testicular germ cell tumors (TGCT) and prediagnostic serum DDE and chlordane metabolites [54]. A more recent study in Norway found statistically significant associations for metastatic prostate cancer with serum oxychlordane [53]. There is also limited evidence for significant positive associations with OC exposures and cancers of the prostate [55], skin (cutaneous melanoma) [31], lung [31], rectum [31], and pancreas [56-58].

Most epidemiologic studies of OCs have included male pesticide applicators, and have had limited power for analyses among women. Female spouses of pesticide applicators are a group with potential intermediate-level OC insecticide exposures due to their personal use (i.e., mixing/applying of pesticides) [59], and indirect exposure from non-occupational exposure pathways [60] (i.e., para-occupational [61], agricultural drift, [62-64] and residential use [61]). Despite their potential higher exposure to OC insecticides

relative to the general population, only one case-control study has examined OC insecticide use and cancer risk among spouses of pesticide applicators [65]. This analysis found no association with DDT and alachlor for glioma. Moreover, the authors did not examine additional OC active ingredients or cancer sites, thus limiting this study's scope. Further research is warranted to help elucidate the impact of active ingredient-specific OC exposures on risks of female-specific cancers among this group.

This analysis examines for the first-time associations between OC insecticide exposures and cancers among the AHS farm spouses. The AHS is the largest prospective cohort of agricultural pesticide exposures in the United States and includes farm spouses (n=32,345) who are predominantly female and have been followed for cancer incidence and mortality since initial enrollment in 1993-1997 [66]. Personal use of seven OC active ingredients (i.e., aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) was collected for each AHS farm spouse using enrollment questionnaires, which covered the time period of OC use in the United States [66]. Here I examine associations between the AHS farm spouses' personal use of each of the seven OC insecticides with total and specific cancers, in order to elucidate the impact the personal use of seven OC insecticides on the risk of cancer among, a group representative of presumably higher levels of exposure than the general population.

STUDY SIGNIFICANCE AND AIM

Spouses of pesticide applicators represent a group with potential intermediate-levels of OC insecticide exposures due to their personal use of OC-containing pesticides, as well as from indirect exposures as a result of living on farms where these insecticides are applied. However, evidence for the carcinogenicity of individual OC insecticides has mainly come from studies of occupationally exposed men and lymphohematopoietic cancers [27-32]. Although breast cancer has been the most widely examined cancer in relation to OC exposures, many of these studies have been conducted among general populations of women and have been inconclusive [37, 44-46, 48]. In addition, an analysis of OC exposures and endometrial cancer did not observe a statistically significant association [49], and no studies have examined associations with uterine or ovarian cancers. This study will be able to examine associations between personal use (i.e., mixing and applying) of seven OC active ingredients (i.e., aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) with multiple specific cancers, including female-specific cancers, in the AHS farm spouses, a large population of women with intermediate to high OC exposure relative to the general population. Specifically, my aim is:

To examine the association between self-reported personal use of OC insecticides and risk of developing specific cancers among the prospective AHS cohort of farm spouses.

METHODS

Study population and follow-up

The AHS is a prospective cohort that includes licensed private pesticide applicators (mostly farmers), and the spouses of private pesticide applicators residing in Iowa and North Carolina. The AHS has been previously described in detail [66]. Pesticide applicators were recruited from 1993-1997 when obtaining a license to apply restricted-use pesticides. Private pesticide applicators who reported being married at the time of enrollment were given questionnaires to be completed by their spouses. The spouses (n=32,345) of these private pesticide applicators are the focus of this study. The Spouse Enrollment questionnaire elicited information on demographic and lifestyle factors, family and personal medical histories, farm exposures, and agricultural activities, including the application or mixing of specific pesticides. In addition, 60.5% of all spouses also completed the Female and Family Health questionnaire which focused on reproductive health histories. The study protocol was approved by all relevant institutional review boards. Study questionnaires are publicly available (https://aghealth.nih.gov/collaboration/questionnaires.html).

Cancer incidence was assessed regularly via linkage with the North Carolina and Iowa state cancer registries. Mortality incidence was assessed through regular linkage with state mortality registries and The National Death Index. Cancer sites were classified according to the *International Classification of Diseases for Oncology, 3rd revision* (World

Health Organization). For NHL, we followed the Surveillance Epidemiology and End Results (SEER) lymphoma coding scheme [67].

Exposure Assessment and Questionnaires

Spouses of private pesticide applicators reported their lifetime never/ever personal use of fifty pesticides including seven OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene). For each pesticide, they were asked 'During your lifetime, have you ever personally mixed or applied [pesticide]? (Includes pesticides used for farm use, commercial application and personal use in your home or garden)'. Participants who indicated ever use of at least one of these seven OCs were classified as having personally used 'any OC' (n=2,191) whereas those who indicated never use of any of these OCs were classified as never having personally used 'any OC'. Otherwise, participants were considered to be missing as to their 'any OC' use. In the following analysis, the term 'any OC' will be used to refer to the ever personal use of at least one of these seven OCs

Statistical Analysis

For this analysis, we excluded the 219 male spouses, women who were diagnosed with cancer prior to study enrollment (n=905), those with zero or missing person years of follow-up (n=161), and those missing information on use for all seven OCs (n=2,146), leaving 28,909 female spouses in our analytic cohort. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated for risk of cancer among ever users, compared to never users, using multivariable *Poisson* regression in SAS version 9.3 (SAS

Institute, Inc., Cary, N.C.). We evaluated all cancer sites with at least three exposed cases for associations with each of the seven individual OCs and for the use of any OC as defined previously. Person-time accrued from the date of study enrollment until date of death, cancer diagnosis, movement out of state or last study-follow-up (December 31, 2012 and December 31, 2013 for North Carolina and Iowa respectively), whichever was earliest. For the evaluation of uterine and ovarian cancers, person-time was censored at the time of hysterectomy or oophorectomy, where applicable.

All models were adjusted for age at enrollment (≤ 44 years, 45-54 years, 55-64 years, ≥ 65 years), educational attainment (high school degree or less, some college or college graduate, one or more years of graduate school), alcohol use (never, less than 1 drink per month, ≥ 1-3 per month), cigarette pack-years smoked as reported at enrollment (pack-year quartiles: Never, ≤ 6.75, 6.751-16.75, ≥ 16.751), and state of residence (Iowa or North Carolina). BMI, race, family history of cancer, and ever use of any pesticide **WHY** were also considered as potential confounders; however, these covariates did not substantially affect our results and were not included in the final models. For all cancer sites, mutually adjusting for individual non-OC and OC pesticides that were correlated at $\rho \geq 0.4$ (i.e. aldrin and dieldrin ($\rho=0.43$), aldrin and heptachlor ($\rho=0.42$)) did not appreciably change our results and these adjustments were not included in our final models. Moreover, because dieldrin is also a biological metabolite of aldrin, we performed sensitivity analyses where 'dieldrin metabolite' (i.e. those farm spouses who personally used either aldrin or

dieldrin) was modeled as the exposure. However, these analyses did not significantly alter our existing aldrin and dieldrin results, and were not included in our final analyses.

Additionally, we examined potential confounders known to be associated with specific cancer sites, such as total meat consumption (colon, rectum, stomach), sun protection (melanoma), asbestos exposure (lung), autoimmune disorders, exposure to livestock and poultry, and benzene exposure (lymphohematopoietic cancers); adjusting for these specific cancer-related covariates did not alter our results and were not included in our final models. All OC-exposed brain cancer cases were glioma subtypes, thus we report associations here for glioma only.

Breast cancers were examined overall, as well as by estrogen receptor (ER) and progesterone receptor (PR) status, where available. Female health and reproductive covariates at enrollment were also examined, with respect to breast, ovarian and uterine cancer, and included the following: menopausal status, ever use of oral contraceptives, ever use of estrogen-based hormone replacement therapy, ever use of progestin based hormone replacement therapy, age at menarche, and parity. These female reproductive covariates did not appear to significantly alter our results and thus were not included in our final models. Due to a lack of questionnaire information availability, we were unable to assess age at first live birth as a potential covariate. We conducted stratified analyses by several female health covariates, including menopausal status at enrollment (yes/no), parity (0-2 live births, > 2 live births), ever use of oral contraceptives at enrollment (yes/no), ever use of hormone replacement therapy at enrollment (yes/no) and age at first menarche ($\leq$ 12

years or below, > 12 years). Due to the small number of nulliparous women (n=294), we were unable to evaluate risks among nulliparous women.

RESULTS

From enrollment through 2012/2013, the 28,909 female spouses contributed a total of 502,895 person-years of follow-up (Mean=16.19 standard deviation +/- 3.8) (Table 1). Overall, 15,112 (52.3%) reported ever using any pesticide (data not shown), and 2,191 (7.6%) reported ever use of any of the seven OCs included in the enrollment questionnaire. The most commonly reported OCs were chlordane (4.1%), DDT (3.55%) and lindane (1.5%), with less than 1% of participants reporting ever use of aldrin, heptachlor, toxaphene and dieldrin (Table 1). Among women who reported using any OC, 718 (32.8%) reported use of more than one OC. Ever OC users tended to be older, have higher BMIs, be from Iowa, and have a higher educational level than OC non-users. They were also more likely to have reported a family history of cancer, grown up on a farm, used oral contraceptives, and have an earlier onset of menarche. Additionally, 77.5% of OC users completed the Female and Family Health Questionnaire versus 60.5% of never OC users.

Table 1. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909)[*].

	Any OC Use[1]				
	NEVER		EVER		
	N=26,718	%	N=2,191	%	p Value[±]
Age at enrollment					
≤ 44	13,153	49.23	447	20.40	<.0001
45-54	6,677	24.99	771	35.19	
55-64	4,823	18.05	731	33.36	
≥ 65	2,065	7.73	242	11.05	
Race					
White	26,164	97.93	2178	99.4	<.0001
Other	510	1.91	8	0.37	
Missing	44	0.16	5	0.23	
State of Residence					
North Carolina	8,739	32.71	632	28.85	0.0002
Iowa	17,979	67.29	1,559	71.15	
Educational Attainment					
High School or less	13,905	52.04	1102	50.3	0.0015
Some College or College Graduate	8,662	32.42	679	30.99	
1 or more years of Graduate School	3,833	14.35	378	17.25	
Missing	318	1.19	32	1.46	
Body Mass Index					
0-24.99	11,756	40.67	902	41.17	<.0001
25.00-29.99	7,448	25.76	717	32.72	
≥ 30.00	4,298	14.87	440	20.08	
Missing	3,216	11.12	132	6.02	

Table 1 Continued. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909)*.

	Any OC Use[1]				
	NEVER		EVER		
	N=26,718	%	N=2,191	%	p Value±
Alcohol					
Never	12,042	45.07	939	42.86	0.2371
less than once/month	7,099	26.57	603	27.52	
≥ 1-3 times per month	7,277	27.24	621	28.34	
Missing	300	1.12	28	1.28	
Cigarette Smoking (Pack-years)					
Never Smoker	18,820	70.44	1,493	68.14	0.0003
≤ 6.75	3,544	13.26	294	13.42	
6.751-16.75	1,752	6.56	127	5.80	
≥16.751	1,700	6.36	186	8.49	
Missing	902	3.38	91	4.15	
Family History of Cancer					
No / Missing	13,949	52.21	949	43.31	<.0001
Yes	12,769	47.79	1242	56.69	
Grew up on a farm					
No	10,913	40.85	534	24.37	<.0001
Yes	15,579	58.30	1,643	74.99	
Missing§	226	0.85	14	0.64	

Table 1 Continued. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909)[*].

	Any OC Use[1]				
	NEVER		EVER		
	N=26,718	%	N=2,191	%	p Value[±]
Menopause at Enrollment					
No	8,922	33.39	534	24.37	<.0001
Yes	6,777	25.36	1,127	51.44	
Unsure	245	0.92	22	1.00	
Missing[§]	10,774	40.32	508	23.19	
Number of Live Births					
0	235	0.88	29	1.32	<.0001
1 or 2	7,216	27.01	688	31.40	
> 2	7,526	28.17	887	40.48	
Missing[§]	11,741	43.94	587	26.79	
Oral Contraceptive Use					
Never	4,236	15.85	576	26.29	<.0001
Ever	11,722	43.87	1,106	50.48	
Missing[§]	10,760	40.27	509	23.23	
Age of first menarche					
12 years or less	7,099	26.57	788	35.97	<.0001
13 years	4,851	18.16	493	22.5	
14 years or greater	3,855	14.43	398	18.17	
Missing[§]	10,913	40.85	512	23.37	
OC Insecticides					
Overall OC (Any OC)	-	-	2,191	7.58	-
Chlordane	-	-	1,196	4.13	-
DDT	-	-	1,028	3.55	-
Lindane	-	-	430	1.47	-
Aldrin	-	-	235	0.81	-
Hepatchlor	-	-	222	0.77	-
Toxaphene	-	-	203	0.70	-
Dieldrin	-	-	105	0.36	-

[*] Excluded: n=2,146 with missing information for personal use of all OCs; n=905 female spouses

[1] Ever use of any of the seven OC insecticides

[±] Chi Square test for homogeneity

[§] From Female & Family Health Questionnaire responses

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Any OC use was significantly associated with an increased risk of glioma ($N_{exposed}$=11; RR=3.52, 95% CI 1.72 to 7.21) (Table 2). Lindane use was significantly associated with an increased risk of glioma ($N_{exposed}$=3, RR=4.45 95% CI 1.36 to 14.55) and pancreatic cancer ($N_{exposed}$=3, RR=3.70 95% CI 1.15 to 12.0). Use of any OC was also associated with non-significantly elevated risks of stomach cancer ($N_{exposed}$=5, RR=2.61, 95% CI 0.96 to 7.11), and colon cancer ($N_{exposed}$= 28, RR=1.19, 95% CI 0.80 to 1.75).

Although chlordane use ($N_{exposed}$=6, RR=2.71, 95% CI 1.12 to 6.55) was significantly associated with an increased risk for MM, any OC use ($N_{exposed}$=8, RR=2.01, 95% CI 0.91 to 4.42) and DDT use ($N_{exposed}$=4, RR=1.75, 95% CI 0.61 to 5.01) were non-significantly associated with an increased risk of MM (Table 2). There were also several suggestive associations for lymphohematopoietic malignancies. Any OC use was non-significantly associated with an increased risk for NHL overall ($N_{exposed}$=28, RR=1.23, 95% CI 0.82 to 1.83). Similarly, use of chlordane ($N_{exposed}$=17, RR=1.30, 95% CI 0.82 to 2.22), DDT ($N_{exposed}$=17, RR=1.35, 95% CI 0.81 to 2.22), and lindane ($N_{exposed}$=6, RR=1.60, 95% CI 0.71 to 3.60) were also non-significantly associated with increased risks in NHL. We had limited power for NHL subtype analyses. However, all 28 OC exposed cases were B-cell lymphomas. Among women who reported any OC use, there were eight MM cases and six diffuse large B-cell lymphoma (DLBCL); no other B-cell subtype had more than four exposed cases.

We also evaluated hormone-mediated cancers including ovarian, uterine, and breast (see Table 2). No significant associations were found for any OC use or for use of the seven

individual OCs and uterine or ovarian cancers. Similarly, we found no association between any OC use or for use of the seven individual OCs and breast cancer. In analyses of breast cancer subtype, there was a statistically significant elevated association between dieldrin use and ER-PR- breast cancer ($N_{exposed}$=3, RR=3.55, 95% CI 1.12 to 11.18).

Table 2. RR and CIs* for ever versus never use of OC insecticides, for all cancer sites. ±

		Any OC[1]			Chlordane			DDT			Lindane		
	N_{total}	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
All Cancer Sites§	3,204	287	0.96	0.85-1.08	160	0.99	0.84-1.16	158	0.98	0.83-1.15	46	0.91	0.68-1.22
SOLID TUMORS													
Bladder	103	4	0.64	0.23-1.77	1	_	_	3	0.83	0.26-2.67	1	_	_
Colon	236	28	1.19	0.80-1.75	18	1.42	0.87-2.32	16	1.17	0.70-1.95	3	0.79	0.25-2.49
Glioma	44	**11**	**3.52**	**1.72-7.21**	4	1.81	0.64-5.12	2	_	_	**3**	**4.45**	**1.36-14.55**
Kidney	71	6	0.89	0.38-2.08	3	0.85	0.26-2.72	5	1.41	0.56-3.57	0	_	_
Lung	203	15	0.70	0.41-1.20	10	0.90	0.47-1.71	10	0.84	0.44-1.59	2	_	_
Melanoma (cutaneous)	145	12	1.08	0.59-1.97	4	0.63	0.23-1.72	5	0.88	0.36-2.18	2	_	_
Pancreas	55	7	1.33	0.59-2.97	3	1.03	0.32-3.34	1	_	_	**3**	**3.70**	**1.15-12.0**
Rectum	69	8	1.27	0.60-2.70	6	1.80	0.77-4.21	6	1.79	0.76-4.22	0	_	_
Stomach	26	5	2.61	0.96-7.11	1	_	_	3	2.64	0.76-9.15	1	_	_
Thyroid	54	5	0.66	0.26-1.63	4	0.97	0.36-2.67	1	_	_	0	_	_
LYMPHOHEMATOPOIETIC MALIGNANCIES													
NHL±	233	28	1.23	0.82-1.83	17	1.35	0.82-2.22	17	1.35	0.81-2.22	6	1.60	0.71-3.60
Multiple Myeloma	42	8	2.01	0.91-4.42	**6**	**2.71**	**1.12-6.55**	4	1.75	0.61-5.01	1	_	_
DLBCL[2]	56	6	1.09	0.46-2.58	4	1.38	0.49-3.85	4	1.31	0.47-3.67	2	_	_
Follicular Lymphoma	49	4	0.86	0.3-2.43	2	0.74	0.18-3.09	2	0.78	0.19-3.24	0	_	_
CLL/SLL[3]	39	4	1.29	0.86-1.93	1	_	_	4	1.42	0.86-2.34	2	_	_
Myeloid Leukemia	34	4	1.26	0.44-3.65	3	1.82	0.55-6.09	3	1.66	0.49-5.56	0	_	_
FEMALE SPECIFIC SITES													
Breast	1,214	99	0.89	0.72-1.09	56	0.93	0.71-1.22	52	0.89	0.67-1.18	17	0.88	0.54-1.42
ER+PR+	736	64	0.94	0.73-1.23	36	0.98	0.70-1.37	33	0.93	0.65-1.33	9	0.75	0.39-1.45
ER-PR-	202	15	0.82	0.48-1.40	9	0.90	0.46-1.76	7	0.76	0.36-1.63	4	1.22	0.45-3.30
ER+PR-	125	8	0.65	0.32-1.35	5	0.78	0.32-1.92	4	0.61	0.22-1.67	2	_	_
Ovarian	106	9	0.65	0.30-1.61	7	1.05	0.40-2.89	5	0.77	0.20-2.46	2	_	_
Uterine	276	20	0.83	0.50-1.32	10	0.80	0.40-1.50	10	0.82	0.42-1.56	2	_	_

Table 2 Continued. RR and CIs* for ever versus never use of OC insecticides, for all cancer sites. ±

		Aldrin			Heptachlor			Toxaphene			Dieldrin		
	N_{total}	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
All Cancer Sites§	3,204	41	1.12	0.82-1.53	36	1.06	0.76-1.48	29	1.05	0.73-1.52	17	1.02	0.63-1.65
SOLID TUMORS													
Bladder	103	0	_	_	0	_	_	1	_	_	0	_	_
Colon	236	6	1.73	0.76-3.91	4	1.24	0.46-3.36	3	1.31	0.42-4.12	4	2.41	0.89-6.53
Glioma	44	1	_	_	2	_	_	2	_	_	0	_	_
Kidney	71	1	_	_	0	_	_	2	_	_	0	_	_
Lung	203	2	_	_	1	_	_	5	2.13	0.87-5.21	2	_	_
Melanoma (cutaneous)	145	3	2.20	0.69-7.02	3	2.40	0.75-7.64	1	_	_	1	_	_
Pancreas	55	1	_	_	1	_	_	0	_	_	0	_	_
Rectum	69	1	_	_	1	_	_	1	_	_	0	_	_
Stomach	26	1	_	_	0	_	_	0	_	_	0	_	_
Thyroid	54	1	_	_	1	_	_	0	_	_	0	_	_
LYMPHOHEMATOPOIETIC MALIGNANCIES													
NHL±	233	1	_	_	3	1.03	0.33-3.24	3	1.49	0.48-4.68	0	_	_
Multiple Myeloma	42	0	_	_	1	_	_	1	_	_	0	_	_
DLBCL[2]	56	0	_	_	1	_	_	1	_	_	0	_	_
Follicular Lymphoma	49	0	_	_	1	_	_	0	_	_	0	_	_
CLL/SLL[3]	39	1	_	_	0	_	_	1	_	_	0	_	_
Myeloid Leukemia	34	0	_	_	1	_	_	0	_	_	0	_	_
FEMALE SPECIFIC SITES													
Breast	1,214	11	0.88	0.48-1.59	11	0.93	0.51-1.68	5	0.49	0.20-1.18	6	1.06	0.48-2.38
ER+PR+	736	8	1.00	0.50-2.02	8	1.05	0.52-2.11	2	_	_	3	0.83	0.27-2.60
ER-PR-	202	2	_	_	2	_	_	1	_	_	**3**	**3.55**	**1.12-11.18**
ER+PR-	125	0	_	_	0	_	_	1	_	_	0	_	_
Ovarian	106	2	_	_	2	_	_	1	_	_	1	_	_
Uterine	276	4	1.50	0.60-4.06	3	1.12	0.40-3.51	2	_	_	1	_	_

§ Inclusive of all reported cancer sites; ± n ≥ 3 exposed cases; Significant Findings are listed in **boldface;** [1] Ever use of any of the seven OC insecticides; ± All NHL subtypes consisted of B-cell Lymphomas; [2] DLBCL: diffuse large B-cell lymphoma; § Inclusive of all reported cancer sites; [3] CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; * Adjusted for age, education, state of residence, pack-years smoked and alcohol consumption; Abbreviations: AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines; ER, estrogen receptor; PR, progesterone

We conducted stratified sensitivity analyses with respect to hormone mediated cancers (overall breast, uterine and ovarian), where we examined several female health covariates. Specifically, we examined menopausal status at enrollment (yes/no), parity (0-2 live births, > 2 live births), ever use of oral contraceptives at enrollment (yes/no), ever use of hormone replacement therapy at enrollment (yes/no) and age at first menarche (≤ 12 years or below, > 12 years). While these analyses did not demonstrate remarkable changes to our final models, they have been included for review (where n ≥2) as Tables 3-7 respectively.

In addition, we conducted sensitivity analyses, mutually adjusting for individual OC pesticides that were correlated at $\rho \geq 0.4$ (i.e. aldrin and dieldrin ($\rho=0.43$), aldrin and heptachlor ($\rho=0.42$)). While these analyses did not appreciably change the results of our final models, we have included the results of this sensitivity analyses for review, referenced as Table 8 below.

Table 3. RR and CIs* for ever use of OC insecticides, stratified by menopausal status at enrollment, compared to never use among AHS spouses for selected cancer sites. ±

	Breast						Ovarian						Uterine					
	Premenopausal			Postmenopausal			Premenopausal			Postmenopausal			Premenopausal			Postmenopausal		
	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
Any OC[1]	18	0.83	0.51-1.35	61	0.87	0.66-1.14	2	1.35	0.31-5.89	5	0.97	0.37-2.53	6	0.91	0.39-2.12	6	0.45	0.20-1.04
Chlordane	13	1.02	0.58-1.78	33	0.89	0.62-1.26	2	2.82	0.64-12.40	3	1.13	0.34-3.72	5	1.22	0.49-3.07	4	0.62	0.23-1.71
DDT	4	0.6	0.22-1.63	36	0.86	0.61-1.21	1	_	_	4	1.36	0.48-3.89	1	_	_	4	0.54	0.20-1.48
Lindane	5	0.85	0.35-2.06	9	0.98	0.51-1.90	1	_	_	0	_	_	1	_	_	1	_	_
Aldrin	2	1.17	0.29-4.74	9	1.07	0.55-2.08	0	_	_	1	_	_	2	3.09	0.68-14.1	1	_	_
Heptachlor	2	1.02	0.25-4.12	8	1.00	0.50-2.03	1	_	_	0	_	_	1	_	_	2	1.36	0.33-5.61
Toxaphene	1	_	_	3	0.43	0.14-1.35	0	_	_	1	_	_	0	_	_	0	_	_
Dieldrin	1	_	_	4	1.11	0.41-2.97	1	_	_	0	_	_	1	_	_	0	_	_

± n ≥ 2 exposed cases

[1] Ever use of any of the seven OC insecticides

* Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Table 4. RR and CIs* for ever use of OC insecticides, stratified by parity, compared to never use among AHS spouses for selected cancer sites. [±]

	Breast						Ovarian						Uterine					
	0-2 live births			> 2 live births			0-2 live births			> 2 live births			0-2 live births			> 2 live births		
	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
Any OC[1]	40	1.03	0.73-1.44	36	0.71	0.50-1.0	4	1.23	0.42-3.57	3	0.85	0.25-2.87	4	0.4	0.15-1.12	6	0.69	0.3-1.60
Chlordane	19	0.89	0.56-1.42	26	0.96	0.64-1.44	2	1.14	0.27-4.83	3	1.68	0.49-5.75	3	0.61	0.19-1.94	4	0.85	0.31-2.33
DDT	22	1.16	0.75-1.80	18	0.63	0.39-1.01	3	2.22	0.65-7.63	2	0.97	0.22-4.17	2	0.45	0.11-1.86	2	0.42	0.10-1.73
Lindane	6	0.85	0.38-1.90	6	0.84	0.37-1.89	0	_	_	1	_	_	1	_	_	1	_	_
Aldrin	4	0.92	0.34-2.49	7	1.16	0.55-2.47	0	_	_	1	_	_	0	_	_	1	_	_
Heptachlor	4	1.11	0.41-3.00	6	0.91	0.41-2.06	0	_	_	1	_	_	0	_	_	2	1.89	0.46-7.85
Toxaphene	2	0.58	0.14-2.33	2	0.38	0.09-1.53	0	_	_	0	_	_	0	_	_	0	_	_
Dieldrin	1	_	_	4	1.29	0.48-3.46	0	_	_	1	_	_	0	_	_	0	_	_

[±] $n \geq 2$ exposed cases

[1] Ever use of any of the seven OC insecticides

[*] Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Table 5. RR and CIs* for ever use of OC insecticides, stratified by ever/never lifetime oral contraceptive use, compared to never use among AHS spouses for selected cancer sites. ±

	Breast						Ovarian						Uterine					
	EVER			NEVER			EVER			NEVER			EVER			NEVER		
	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
Any OC[1]	50	0.97	0.72-1.31	29	0.67	0.45-1.00	5	1.36	0.52-3.58	1	_	_	7	0.6	0.28-1.31	5	0.57	0.23-1.43
Chlordane	33	1.12	0.78-1.60	13	0.6	0.34-1.05	4	2.04	0.71-5.89	0	_	_	5	0.77	0.31-1.90	4	0.95	0.34-2.65
DDT	18	0.72	0.45-1.16	22	0.87	0.56-1.34	3	1.7	0.50-5.80	1	_	_	1	_	_	4	0.84	0.30-2.33
Lindane	8	0.8	0.40-1.62	6	1.11	0.49-2.51	1	_	_	0	_	_	2	0.87	0.21-3.53	0	_	_
Aldrin	5	1.12	0.46-2.71	6	0.92	0.41-2.08	0	_	_	0	_	_	1	_	_	2	1.52	0.36-6.43
Heptachlor	5	1.06	0.44-2.57	5	0.86	0.35-2.09	1	_	_	0	_	_	1	_	_	2	1.54	0.36-6.52
Dieldrin	3	1.56	0.50-4.88	2	0.68	0.17-2.76	1	_	_	0	_	_	0	_	_	1	_	_
Toxaphene	3	0.6	0.19-1.86	1	0.23	0.03-1.62	0	_	_	0	_	_	0	_	_	0	_	_

± n ≥ 2 exposed cases

[1] Ever use of any of the seven OC insecticides

* Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Table 6. RR and CIs* for ever use of OC insecticides, stratified by ever/never hormone replacement therapy use, compared to never use among AHS spouses for selected cancer sites. ±

	Breast						Ovarian						Uterine					
	EVER			NEVER			EVER			NEVER			EVER			NEVER		
	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
Any OC[1]	34	0.85	0.59-1.22	27	0.93	0.61-1.39	3	1.09	0.31-3.80	1	_	_	3	0.56	0.17-1.86	3	0.37	0.11-1.2
Chlordane	20	0.87	0.55-1.38	13	0.94	0.53-1.65	2	1.27	0.29-5.59	0	_	_	1	_	_	3	0.88	0.27-2.86
DDT	16	0.65	0.39-1.09	20	1.15	0.72-7.20	2	1.26	0.28-5.60	1	_	_	1	_	_	3	0.67	0.21-2.17
Lindane	6	1.06	0.47-2.38	3	0.90	0.29-2.84	0	_	_	0	_	_	1	_	_	0	_	_
Aldrin	4	0.80	0.30-2.15	5	1.46	0.60-3.58	1	_	_	0	_	_	1	_	_	0	_	_
Heptachlor	5	1.03	0.42-2.52	3	0.93	0.29-2.93	0	_	_	0	_	_	2	4.18	0.95-18.3	0	_	_
Dieldrin	1	_	_	3	2.28	0.72-7.20	0	_	_	0	_	_	0	_	_	0	_	_
Toxaphene	3	0.78	0.25-2.44	0	_	_	0	_	_	0	_	_	0	_	_	0	_	_

± $n \geq 2$ exposed cases

[1] Ever use of any of the seven OC insecticides

* Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Table 7. RR and CIs* for ever use of OC insecticides, stratified by age at first menarche, compared to never use among AHS spouses for selected cancer sites. ±

	Breast						Ovarian						Uterine					
	≤ 12 years			> 12 years			≤ 12 years			> 12 years			≤ 12 years			> 12 years		
	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
Any OC[1]	33	0.74	0.52-1.07	46	0.92	0.68-1.26	2	0.78	0.18-3.40	5	1.24	0.47-3.24	7	0.62	0.29-1.36	5	0.6	0.24-1.50
Chlordane	21	0.86	0.55-1.34	25	0.93	0.62-1.40	1	_	_	4	1.98	0.69-5.70	6	1.04	0.45-2.41	3	0.67	0.21-2.13
DDT	15	0.65	0.39-1.10	25	0.93	0.62-1.40	2	1.57	0.35-7.0	3	1.36	0.41-4.55	3	0.46	0.06-3.35	2	0.47	0.11-1.93
Lindane	9	1.15	0.59-2.24	5	0.65	0.27-1.57	0	_	_	1	_	_	1	_	_	1	_	_
Aldrin	7	1.45	0.68-3.08	4	0.69	0.26-1.86	0	_	_	0	_	_	2	1.78	0.43-7.33	1	_	_
Heptachlor	5	1.15	0.47-2.81	5	0.84	0.35-2.03	0	_	_	1	_	_	1	_	_	2	2.13	0.51-8.90
Dieldrin	2	0.91	0.23-3.67	3	1.27	0.41-3.96	0	_	_	1	_	_	1	_	_	0	_	_
Toxaphene	1	0.25	0.03-1.77	3	0.58	0.19-1.81	0	_	_	0	_	_	0	_	_	0	_	_

± n ≥ 2 exposed cases

[1] Ever use of any of the seven OC insecticides

* Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Table 8. RR and CIs* for ever versus never use of correlated OC insecticides where ρ≥0.4, for select cancer sites. ±

		Aldrin[1]			Aldrin[2]			Heptachlor[3]			Dieldrin[3]		
	N_{total}	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
All Cancer Sites[§]	3,204	41	1.14	0.80-1.62	41	1.06	0.73-1.54	36	1.06	0.72-1.55	17	0.93	0.55-1.58
SOLID TUMORS													
Bladder	103	0	_	_	0	_	_	0	_	_	0	_	_
Colon	236	6	1.42	0.52-3.9	6	1.96	0.73-5.26	4	0.85	0.26-2.81	4	1.88	0.55-6.42
Glioma	44	1	_	_	1	_	_	2			0	_	_
Kidney	71	1	_	_	1	_	_	0	_	_	0	_	_
Lung	203	2	0.48	0.09-2.47	2	0.92	0.21-4.2	1	_	_	2	2.39	0.47-12.25
Melanoma (cutaneous)	145	3	2.52	0.68-9.29	3	1.66	0.38-7.29	3	1.82	0.41-8.0	1	_	_
Pancreas	55	1	_	_	1	_	_	1	_	_	0	_	_
Rectum	69	1	_	_	1	_	_	1	_	_	0	_	_
Stomach	26	1	_	_	1	_	_	0	_	_	0	_	_
Thyroid	54	1	_	_	1	_	_	1	_	_	0	_	_
LYMPHOHEMATOPOIETIC MALIGNANCIES													
NHL[±]	233	1	_	_	1	_	_	3	1.68	0.50-5.71	0	_	_
Myeloid Leukemia	34	0	_	_	0	_	_	1	_	_	0	_	_
FEMALE SPECIFIC SITES													
Breast	1,214	11	0.71	0.34-1.47	11	0.71	0.34-1.49	11	1.11	0.57-2.17	6	1.28	0.52-3.14
Ovarian	106	2	0.66	0.07-6.65	2	0.52	0.05-5.11	2	2.67	0.52-13.59	1	_	_
Uterine	276	4	1.84	0.63-5.34	4	1.69	0.53-5.4	3	0.86	0.23-3.29	1	_	_

[±] n ≥ 2 exposed cases

Significant Findings are listed in **boldface**

[*] Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

± All NHL subtypes consisted of B-cell Lymphomas

[1] Additionally Adjusted for Dieldrin Use

[§] Inclusive of all reported cancer sites

[2] Additionally Adjusted for Hepotachlor Use

[3] Additionally Adjusted for Aldrin Use

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines; ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

In this study, we prospectively evaluated associations between the reported personal use of individual OCs and incident cancers in a population of female farm spouses. Although the numbers of exposed cases were small, we observed statistically significant increased risks for use of individual OCs insecticides and several cancers, including any OC use and glioma, lindane use and glioma and pancreatic cancer, chlordane use and MM, and dieldrin use and ER-/PR- breast cancer.

In addition to chlordane, MM was non-significantly associated with any OC use and with DDT specifically. These associations are consistent with previous findings [27, 29, 30, 32, 33, 68]. The definition of NHL used in our study is based on the most recent lymphoma classification system, which includes MM as a subtype of NHL [67], whereas most previous studies relied on earlier classifications which considered MM separately. A previous population-based case-control study found non-significant positive associations of ever handling (mixing or applying) aldrin, DDT, or lindane with MM [69]. A pooled analysis of U.S. and Canadian case-controls studies found that DDT use was significantly associated with MM [68]; cumulative exposure to DDT, as measured by lifetime-days of use, was also significantly associated with an increasing risk trend for MM. Although not significant, in the current study, chlordane use was also positively associated with NHL and myeloid leukemia, DDT use was positively associated with NHL and myeloid leukemia, and lindane use was positively associated with NHL. In most cases, we did not have an adequate number of OC-exposed cases to examine NHL subtypes, which all

consisted of B-cell lymphomas. There is evidence that some OCs, including lindane and DDT, cause oxidative stress and immunosuppressive effects *in vitro* and it is suspected that these mechanisms may possibly play a role in the development of lymphohematopoietic cancers [17, 35, 70-72] . Specifically, an in vivo study found that when mice were fed daily doses of lindane and treated with whole body irradiation, they demonstrated a significant decrease in bone marrow progenitor cell recovery (erythrocyte precursors, granulocyte-macrophage progenitor cells, and residual progenitor cell damage) than when compared to controls. Interestingly other studies have found that OCs may act on the immune system through immunomodulation of NK cells, thereby preventing their ability to combat tumor cells in the environment [71]. It is possible that OCs may cause similar immunomodulatory disruption of NK cell activity causing the unregulated cell growth of cancerous tumor cells.

We observed no significant association with Any OC use and breast cancer overall. Although some studies have reported an increased risk of breast cancer among women exposed to OCs during critical developmental windows in early life [73-75], our findings are consistent with most other studies that also did not evaluate timing of exposure [17, 37, 38, 40-47]. Although we did not have information on timing of exposure, we conducted sensitivity analyses using year of birth as a surrogate for the potential for exposure during critical developmental periods. OCs were first registered in 1948, therefore we assumed women born before 1936 would not have any OC exposures prior to menarche. When we restricted analyses to women born after 1936, the RR for breast cancer and any OC use was 1.22 (0.94-1.59) (n=61 exposed cases) although the interaction was not significant

compared to 0.84 (0.60-1.18) (n=38 exposed cases) among women who were born prior to 1936. An early study by Wolff et al. found a two- to four-fold increased risk of breast cancer among women with the highest serum DDE levels, with a positive trend with increasing serum DDE [38]. However, a follow-up study with a larger sample size found no evidence for an association of breast cancer risk with serum DDE levels [39]. Additional studies of breast cancer and OC exposures have examined associations with mirex, HCB, and chlordane; most of these studies also reflected null or inconclusive findings [42, 45, 48, 76, 77].

We did, however, see an association between dieldrin use and ER-/PR- breast cancer based on only 3 exposed cases. Two previous studies reported positive associations with dieldrin use and breast cancer overall. The first, a Danish case-control study found a significant dose-related increased risk of breast cancer among women and increasing serum concentrations of dieldrin [41]. Additionally, a previous study of AHS farm spouses found evidence for a significant increased risk of breast cancer overall among women who never personally used dieldrin, but whose husbands did personally apply the pesticide [40]. This study was unable to assess associations between the wives' personal use of dieldrin and breast cancer due to the low number of dieldrin exposed breast cancer cases. Our current analysis includes 60 more OC exposed cases and thirteen additional years of follow-up than this previous analysis [40], and was sufficiently powered to examine breast cancer subtypes. Few epidemiologic studies have examined associations between OC exposures and breast cancer subtypes [73, 78-80], and most have not found positive associations with

ER-negative breast cancers. *In vitro* and animal studies have suggested that dieldrin, DDT, endosulfan, HCH, and toxaphene have the potential to elicit tumor promoting effects mediated through the induction of ER, androgen receptor and aromatase activities [23, 36, 81-83]. Given this body of literature and the small number of dieldrin exposed ER-PR- breast cancer cases, our positive finding warrants further investigation. Overall, we do not see strong evidence of an association between use of an individual OC and breast cancer, consistent with the existing epidemiologic literature.

Aldrin use was associated with a non-statistically significant elevated risk for uterine cancer based on four exposed cases. Only one case-control study has examined OC exposures and endometrial cancer; no statistically significant associations were observed with several OC derivatives including DDE, oxychlordane, HCH, and HCB [49]. Very few occupational studies have examined the relationship between endometrial cancer and exposure to other OC compounds, including polychlorinated biphenyls (PCBs), [84-86] and most these studies' findings were null. To our knowledge, this is the first prospective study to examine the relationship between personal use of specific OC insecticides and uterine cancer.

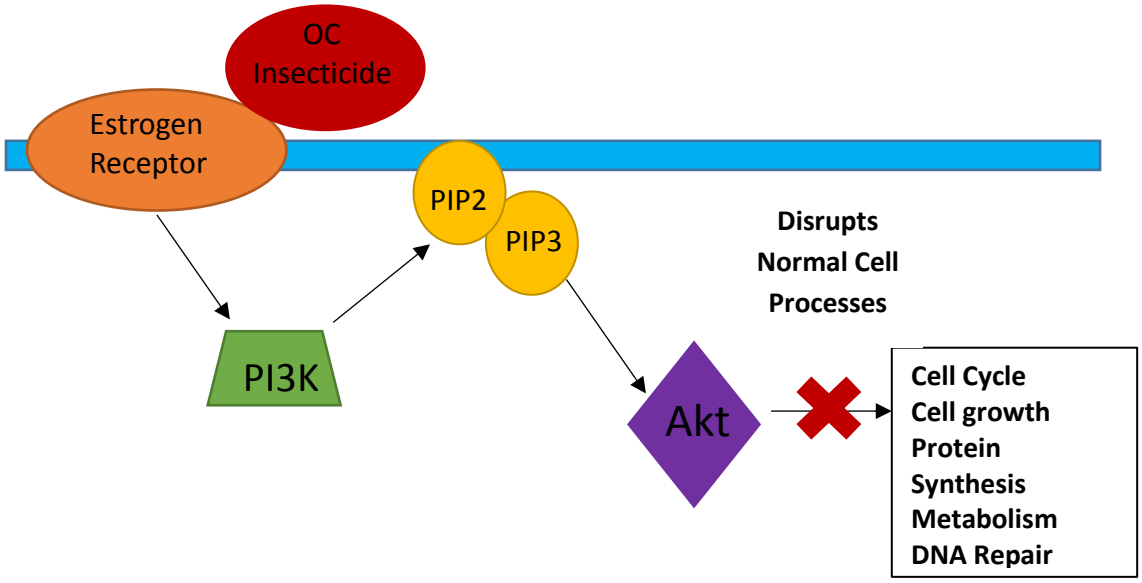
Any OC use and lindane specifically were associated with risk of glioma. While we lacked sufficient power for further subtype analyses, the OC-exposed glioma cases consisted of glioblastomas (n=7), an astrocytoma (n=1), an oligodendroma (n=1), and mixed gliomas (n=2). Previous studies of male farming populations have found some evidence for an increased risk of glioma with associated pesticide use [87-91]. However,

studies examining associations between glioma and pesticide exposures among women, in agricultural populations, have provided inconsistent results. In an earlier case-control study of central nervous system cancers among women across twenty-four U.S. states, increased risks were found for women generally exposed to herbicides, insecticides, or fungicides [92]. An analysis of occupational risk factors for glioma found significantly increased risks among women involved in occupations in agricultural services and farming, though this analysis did not examine exposures to specific pesticides [93]**.** However, a case-control analysis of women in Nebraska found no association between individually evaluated OCs (i.e. aldrin, chlordane, DDT, dieldrin, heptachlor and lindane) and brain cancer [87]. Similarly, in a case-control analysis of women in the Midwest, no association was found for gliomas and the personal application of pesticides including OCs [65]**.**

Mechanisms of action for OC-induced gliomas have not been proposed, and there appears to be little evidence among laboratory studies for OC induced glioma. However i*n vitro* studies have found evidence for the neurotoxic effects induced by the interaction of OCs with ER-mediated signaling pathways, it is possible that this may play a role [94]. In an *in vitro* study, it was found that several OCs (dieldrin, endosulfan and lindane) had endocrine-disrupting effects on cortical neurons and cerebellar granule cells (CGCs). Specifically, these chemicals inhibited estrogen receptor binding to estradiol through direct binding with the receptor's binding site. It was also found that through this interaction, dieldrin was specifically able to activate estrogen receptor mediated intracellular signaling pathways MAPK and PI3K/Akt pathways, which are critical to the neuronal cell function

and homeostasis. The ability for OCs to disrupt critical hormone mediated cell signaling pathways *in vitro*, may help to explain a biological mechanism by which uncontrolled cancerous cell growth may occur in brain tissue.

Figure 2. Schematic of example of possible pathway by which OCs may give rise to carcinogenesis



The increased risk of pancreatic cancer associated with lindane use in our study was based on only three exposed cases. Some studies have shown significant increased risks for pancreatic cancer with occupational DDT exposure [56, 57] and significantly higher levels of DDT exposure among pancreatic cancer cases versus controls [57]. However, a previous AHS study found no evidence for an increased risk of pancreatic cancer with the OCs aldrin, DDT, heptachlor or toxaphene [58]. The aforementioned study did not evaluate risk estimates among the spouses only, but examined combined risk estimates among the applicators and their spouses. Furthermore, a lack of exposed cases prohibited the

insecticide-specific evaluation of chlordane, dieldrin and lindane. To our knowledge, no other studies have evaluated OC use and pancreatic cancers among women.

Strengths of our study include the prospective longitudinal design with little loss-to-follow-up, questionnaire information on the use of specific OCs, and regular assessment of cancer incidence and mortality via linkage with state registries. The AHS also has detailed information on many possible confounders. Most previous studies of OC exposures and cancer, except for studies of DDT and breast cancer [17, 37, 38, 42, 43, 46, 95, 96] have primarily focused on occupationally-exposed men [27, 28, 30-33, 50, 54, 69, 97]. Our study examined the personal use of DDT, and other specific OCs, in a population of farm women. Few studies have evaluated personal use of specific OCs. While breast cancer has been the most widely studied cancer with respect to OCs, particularly DDT, no studies thus far have prospectively studied OCs and other hormone-mediated cancers.

Limitations of this analysis include the small number of cases exposed to specific OCs and lack of information on duration, time period, and intensity of OC use. While we had a low response rate of the female and family health questionnaire, our reported results and final models were based solely on information collected from the spousal enrollment questionnaire. Questionnaire information was collected at study enrollment (1993-1997), thus changes in individual characteristics (i.e. menopausal status, smoking) since enrollment were not captured in this analysis. In addition, most OCs examined in this analysis have been banned for use in the United States since the 1970s. Because OCs have long half-lives, and are known to persist in the environment and human body for long

periods of time [3, 6, 7], exposure to OCs through environmental exposure pathways may also contribute to lifetime cumulative exposure. This could be particularly important in farm situations where OCs may have been used in the past.

CONCLUSIONS AND FUTURE DIRECTIONS

We observed significant increased risks for some cancers associated with individual OC insecticides, including multiple myeloma, glioma, pancreatic and stomach cancer as well as ER-/PR- breast cancer. Despite the large size of the cohort, the numbers of exposed women and cancer cases were small for most cancer sites of interest. While some of our findings are consistent with previous findings, results need replication with longer follow-up time in other studies. Due to the environmental persistence of OCs, future research should attempt to expand on these findings by assessing environmental sources of OC exposures to fully evaluate the role of OC exposures on cancer risk in women.

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