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Childhood and adolescent pesticide exposure and breast cancer risk

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Abstract

Background—To date, epidemiological studies have not strongly supported an association between pesticide exposure and breast cancer. However, few previous studies had the ability to assess specific time periods of exposure. Studies that relied on adult serum levels of metabolites of organochlorine pesticides may not accurately reflect exposure during developmental periods. Further, exposure assessment often occurred after diagnosis and key tumor characteristics, such as hormone receptor status, have rarely been available to evaluate tumor-subtype specific associations. We examine the association between pesticide exposure during childhood and adolescence and breast cancer risk in the prospective Sister Study cohort (N=50,844 women) to assess this relation by tumor subtype.

Methods—During an average 5-year follow-up, 2,134 incident invasive and *in situ* breast cancer diagnoses were identified. Residential and farm exposure to pesticides were self-reported at study enrollment during standardized interviews. Multivariable hazard ratios (HR) and 95% confidence intervals for breast cancer risk were calculated with Cox proportional hazards regression.

Results—HRs were near null for the association between childhood/adolescent pesticide exposure and breast cancer risk overall or among ER+/PR+ invasive tumors. However, among women who were ages 0–18 before the ban of DDT in the U.S., exposure to fogger trucks or planes was associated with a HR=1.3 for premenopausal breast cancer (95% CI: 0.92, 1.7).

Conclusion—These findings do not support an overall association between childhood and adolescent pesticide exposure and breast cancer risk. However, modest increases in breast cancer risk were associated with acute events in a subgroup of young women.

Introduction

In 2014, 235,030 new cases of breast cancer were projected to be diagnosed in the U.S., making it the most common cancer diagnosis among women. [221] Endogenous and exogenous estrogen exposure contribute to breast cancer development; factors such as

younger age at menarche and use of postmenopausal estrogen and progestin are recognized to increase breast cancer risk.[2] Endocrine-disrupting properties have been attributed to several environmental agents used for pest control, including the organochlorine dichlorodiphenyltrichloroethane (DDT),[3–6] suggesting that exposure to pesticides could also influence breast cancer risk.

DDT use was widespread in the U.S., with use peaking in 1959, until it was banned in 1972.[7,8] Aerial crop-dusting with DDT was common on farms, and many residential communities and beaches were regularly sprayed by municipal fogger trucks.[9] Scientific reviews addressing the relationship between adult levels of dichlorodiphenyldichloroethylene (DDE), the primary metabolite of DDT, and breast cancer concluded that the weight of the evidence does not support the association between pesticides and breast cancer.[8,10–12] However, recent investigations suggest that greater focus on vulnerable periods of breast development or acute exposure events is warranted.[13]

Mammary growth is exponential during the pubertal transition and pregnancy; breast tissue may be more susceptible to environmental exposures prior to or during these developmental windows.[14,15] A nested case-control study found a 5-fold increased risk of breast cancer between the 3rd and 1st tertiles of serum p,p' DDT among women who were 14 years old when DDT came into use and those who were 20 years old during the time of peak DDT use.[7] Additionally, it has been hypothesized that potential effects of pesticides with endocrine-disrupting properties may be specific to breast tumors that express hormone receptors. In a case-control analysis of acute pesticide exposure related to fogger trucks, White et al. identified an increase in estrogen receptor (ER) positive and progesterone (PR) positive breast cancer among women who reported ever seeing a fogger truck before 1972 (OR: 1.44; 95% CI: 1.08, 1.93)[9]. These results underscore the need to consider timing of exposure and tumor subtype in order to evaluate any potential associations between pesticides and breast cancer risk.

The aim of the present study was to assess the relationship between childhood and adolescence pesticide exposure and breast cancer in the Sister Study, a prospective cohort of 50,884 U.S. and Puerto Rican women with a family history of breast cancer.

Methods

This analysis was performed using data from the Sister Study, a prospective observational cohort study designed to assess genetic and environmental risk factors for breast cancer and other conditions. During 2003–2009, 50,884 U.S. and Puerto Rican women ages 35–74 were recruited through the media, breast cancer professionals and advocates, the Internet, a network of recruitment volunteers, and a national advertising campaign in English and Spanish. Eligible participants had no prior diagnosis of breast cancer at enrollment and had a sister who had been diagnosed with breast cancer (http://sisterstudy.niehs.nih.gov/).

All participants provided written informed consent and completed a computer-assisted telephone interview that elicited detailed information on medical and family cancer history, lifestyle factors, and demographics at enrollment. Participants were asked to complete brief

annual health updates and comprehensive follow-up questionnaires every 2–3 years by mail, web, or phone to update medical and family histories, lifestyle characteristics and behaviors. Response rates were >95% for annual updates and were 94% at the 2 year follow-up questionnaire. This research was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences, NIH, and the Copernicus Group Institutional Review Board.

We excluded records from 128 women who were diagnosed with breast cancer prior to completion of study enrollment or had a missing date of diagnosis. Therefore, information from 50,756 women contributed to this analysis.

Residential pesticide exposures

All participants were asked to provide a residential history that included the residence they lived in for the longest period of time prior to age 14. Details obtained included calendar years of residence; whether the property was urban, suburban, small town or rural; if the residence was ever used as a farm or orchard; if the residence was treated regularly for pest control and if so, how frequently and by whom; and proximity ("within seeing, smelling, or hearing distance") of several land use types including orchards, golf courses, nurseries or commercial greenhouses.

Among women who reported ever living on a farm for 12 months or that their longest residence before age 14 was a farm, additional farm exposure information was collected. Living on a farm was defined as a residence where crops are grown or livestock is raised, not including small personal gardens. Women were asked to recall characteristics of the farm they lived on longest from birth to age 18. Farm characteristics included types of crops or livestock, whether pesticides were ever used on the farm, whether participants were ever present in fields on the same day as pesticides were applied, whether participants personally mixed, loaded, or applied pesticides, cleaned or help clean pesticide mixing or application equipment, or ever got an unusually high amount of pesticides on skin or clothing during these activities.

Women were also asked to report whether they were ever, "in the fog or spray of chemicals, or as a child, did you ever chase after the fogger trucks or airplanes that sprayed for mosquitos or other pests?" and, if so, whether this occurred before and/or after 1975. Study participants' ages in 1975 were calculated by subtracting their year of birth. Based on peak use of DDT in fogger trucks and planes in 1959, we performed sensitivity analyses to examine breast cancer associations specifically among women born in 1941–1958 (who would have been ages 0–18 in 1959), and women born during 1944–1949 (who would have been pubertal during peak years of DDT use).

Incident breast cancer

Women who reported an incident breast cancer diagnosis during follow-up were asked to provide additional diagnostic and treatment details, and to authorize the release of medical records. At the time of this analysis, medical records had been obtained for more than 80% of incident breast cancers. Agreement was high between self-reported and medical-record

abstracted data for estrogen receptor status (95%) and invasiveness (81%) [17]. Thus, when medical record data were not available, self-reported data were used.

Statistical analysis

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer were calculated with Cox proportional hazards regression. Statistical models used age as the time scale and person-time was accrued from age at study enrollment. Follow-up extended until breast cancer diagnosis or the date of last health follow-up. In analyses of breast cancer subtypes defined by hormone receptor status and invasiveness, competing or undefined breast cancer subtypes were censored at the date of diagnosis. For example, in analysis of ER+PR+ breast cancers, women who developed ER- or PR- breast cancers were censored from follow-up time at their date of diagnosis. Women were categorized as postmenopausal after 12 months of amenorrhea not due to pregnancy, breastfeeding, or premenopausal use of medications that induce amenorrhea. Age at menopause was defined as a woman's age at her last menstrual period. Women whose only reason for not experiencing menses was hysterectomy (without bilateral oophorectomy) were categorized as postmenopausal after age 55 with unknown age at menopause. In analyses investigating associations by menopausal status at breast cancer diagnosis, women who reported transitioning from premenopausal to postmenopausal during the follow-up period were censored at the month and year for the defined age at menopause when considering the outcome of premenopausal breast cancer. Person-time after menopausal age contributed to postmenopausal person-time at risk.

Potential confounders were determined *a priori*; final models adjusted for the following covariates: age at menarche (continuous), race (non-Hispanic White, non-Hispanic Black, Hispanic, other) and parity/breastfeeding history (nulliparous, parous/never breastfed, parous/breastfed). Age at menarche could be considered a potential mediator of the association between childhood pesticide exposure and breast cancer risk if women who were exposed to pesticides entered menarche earlier.[18] Greater duration of breastfeeding could have reduced pesticide body burdens in the years between childhood/adolescence and breast cancer diagnosis.[19] Thus, sensitivity analyses were performed to evaluate the impact of statistical adjustment for these covariates. We further evaluated the sensitivity our results in statistical models restricted to rural residents and adjusted for age at first birth. All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

Results

During 270,886 person years of follow-up (mean=5.3 years), 2,134 incident breast cancer diagnoses were reported. The majority of diagnoses were invasive breast cancers (n=1,543), followed by *in situ* (n=570) and those of unknown stage (n=21). The mean age at enrollment was 56.8 years for cases and 55.1 for non-cases, while mean age at menarche was the same (12.6 years) in both groups. Table 1 displays the distribution of person-years according to participant characteristics at enrollment. Women who developed breast cancer during follow-up were more likely to have been born in the earliest birth cohort, to have ever used postmenopausal hormones, and were slightly more likely to have a body mass index > 25 kg/m^2. The average length of time spent at the longest childhood residence was 10.8 years

before age 14 and 13.3 years before age 18. Although a minority of women (28%) lived at a single residence for their entire childhood/adolescence, the majority (76%) spent at least half their time from ages 0–14 or 0–18 at this residence (*data not shown*).

We report near null associations between residential exposure to pesticides before age 14 and breast cancer risk, both overall and specific to ER+/PR+ invasive breast cancer. We evaluated residential type, use of a residence as a farm or orchard, and proximity to facilities that often use pesticides (orchards, commercial nurseries, golf courses). Roughly 20% (N=424) of women who developed breast cancer reported their childhood residence was regularly treated with insecticides or pesticides, but few (N=44) reported personally applying pest control chemicals (Table 2).

Approximately 20% (N=409) of women who developed breast cancer reported living on a farm for 12 months before age 18. Compared to women who did not live on a farm, living on a farm with livestock, field or orchard crops, working in the fields, and pesticide use on the farm were not related to breast cancer risk. The HR for living on a cotton or tobacco farm, compared to not living on a farm, was consistent with a higher risk for total breast cancer (HR=1.3; 95% CI: 1.0, 1.6), but no association was observed for other cash crops (HR=1.0; 95% CI: 0.84, 1.3). Compared to women who lived on farms that did not use pesticides, living on a farm that did use pesticides initially appeared inversely associated with breast cancer risk (HR=0.80; 95% CI: 0.63, 1.0 for total breast cancer, HR=0.64; 95% CI: 0.46, 0.90 for ER+/PR+ invasive breast cancer). However, the direction of the association was inconsistent and near null across indicators of personal exposure to pesticides such as personally mixing, loading, applying, cleaning equipment or being present in fields when pesticides were applied to crops. The HR for breast cancer associated with an unusually high amount of pesticides on skin or clothing was suggestive of increased risk (HR=1.4; 95% CI: 0.75, 2.5 for total breast cancer; HR=1.5; 95% CI: 0.80, 3.0 for postmenopausal breast cancer); however, 12 cases reported episodes of high direct contact and the confidence intervals were imprecise (Table 3).

We observed no overall association between exposure to fogger trucks or pesticide spray from airplanes and breast cancer risk (HR=1.0; 95% CI: 0.93, 1.2) and no variation according to whether the exposure occurred before or after 1975 (Table 4). In subgroup analyses of women who were exposed to fog or spray and born 1941–1958, those who would have been ages 0–18 during years of peak DDT use in the U.S., we observed a modest increase in risk of total breast cancer (HR=1.1; 95% CI: 0.99, 1.3) that appeared to be driven by cancers diagnosed before menopause (HR=1.3; 95% CI 0.92, 1.7) (Table 4). In an analysis restricted to women born in 1944–1949 (who would have been pubertal at time of peak DDT use), point estimates were approximately the same, but with wider intervals. There were too few cases to evaluate premenopausal breast cancer specifically among women born during 1944–1949.

Sensitivity analyses considering the associations between childhood and adolescent pesticide exposure restricted to women who were of a normal body mass index at enrollment and women who never used postmenopausal hormones did not result in more pronounced estimates. Additional sensitivity analyses considering other hormone receptor tumor subtype

definitions (ER+ only, ER+ and/or PR+) did not markedly differ from results shown with ER +PR+ tumors. Similarly, analyses of rural residents only did not differ substantially compared to the results shown for all women. Finally, results were virtually unchanged after statistical adjustment for age at first birth.

Discussion

Although breast cancer risk was not related to a majority of the pesticide exposures examined in this population, there were a few subgroups in which there was a suggested increase in risk. These associations were restricted to women having episode(s) with high amounts of pesticides on their skin or clothing, those directly exposed to fog or spray, or those who would have experienced organochlorine pesticide exposure during puberty. A slight association was also found in women who reported living on a cotton or tobacco farm, compared to not living on a farm. During the 1960's and 1970's, most of the agricultural DDT used in the United States was applied to cotton, peanut, and soybean crops.[20] Atrazine, an herbicide linked to mammary tumors in rats[21], was often commonly applied to cotton crops during this time period.[20] Therefore, the suggested increase in breast cancer risk that we observed is biologically plausible.

However, the generally null results found in this paper are consistent with a majority of the previously published literature that relied on self-reported exposure pesticides for breast cancer risk.[22–24] Another recent case-control study using a self-reported measure of acute exposure to fogger trucks prior to ages 14 and 20 did not find an increased risk of breast cancer.[9] Similarly, a population-based case-control study in North Carolina with self-reported measures of pesticide exposures reported no overall association between farming during ages 9–16 years old and breast cancer[20] and growing up on a farm was not related to breast cancer risk in the study.[23] Our study adds new information to the current literature by considering both age of exposure and calendar year. The consistency of our findings with prior results lends weight to the evidence that pesticide use is not a strong risk factor for breast cancer development overall, although specific subgroups may be more vulnerable.

Few studies have evaluated pesticide exposure during adolescence, which may be a critical biologic window when breast tissue is more susceptible to carcinogens or exogenous estrogens.[14,25,26] Organochlorines can act as environmental estrogens and exposure during biologically susceptible windows may be most relevant to future breast cancer risk.[3–6] For example, a study with blood samples collected from 1959–1967 found that high levels of p,p'-DDT serum were associated with a 5-fold increase in risk of breast cancer between the 3rd and 1st tertiles of serum p,p'DDT level among premenopausal women who were born during 1931–1944.[7] Based on the age-distribution in our study, we could not attempt to replicate this finding because there were no premenopausal cancers among women born in 1931–1944. Nonetheless, our study was able to evaluate a critical time window by assessing exposures that occurred at their longest residence from ages 0–14. The average length of time that individuals lived at this residence was 10.8 years, likely reflecting exposures across childhood and adolescence.

Current serum levels of pesticides were analyzed as markers of previous exposure in multiple previous studies.[8] However, current body burden may not reflect relative exposure during vulnerable periods of breast development or acute exposures that occurred when specific pesticides were ubiquitously used. Body burdens of pesticides may vary due to differences in metabolism, body fat, and lactation [27] and residual intake from food sources. Studies with archived biological samples that were collected in the relevant time period or with adequate sample size to investigate this relationship, are rare.[7,28]

This study did not identify systematic variation in breast cancer risk when considering only ER+PR+ breast cancer. It is hypothesized that breast cancer risk factors may differ by hormone receptor status of the tumor, with recent evidence suggesting that traditional estrogen-related breast cancer risk factors are more strongly associated with hormone receptor positive tumors.[29] There have been few studies investigating the association between pesticides and breast cancer risk by hormone receptor status. One study suggested that ER+ case patients had higher DDE concentrations compared to controls[30] and a recent Environmental Protection Agency (EPA) report found that ER+ breast cancer was positively associated with proportion of agricultural land by county of residence.[31] Consistent with this, ever seeing a fogger truck at a residence prior to 1972 was associated with a higher odds of ER+PR+ tumors in the Long Island Breast Cancer Study Project (OR: 1.44; 95% CI: 1.08, 1.93).[9] However two other studies reported no difference in DDT concentration by hormone receptor status[32,33] and one report found varying associations between different organochlorine compounds and hormone receptor status.[34] Inconsistent results among hormone receptor subtypes may be due to variation across specific organochlorine compounds and lack of statistical power to investigate across multiple tumor subtypes.

Limitations of our analysis should be considered in the interpretation of our results. Multiple comparisons were performed so we cannot exclude the possibility that the few elevated effect estimates were due to chance. However, the few positive associations were related to acute exposure events and may represent a biologically plausible subgroup of exposures. We also relied on self-report of childhood and adolescent exposure to pesticides. If women were unable to accurately report pesticide exposure during this time period, this could result in exposure misclassification. For our binary exposure variables, the direction of bias produced by this nondifferential misclassification would be towards the null. For exposures with three or more exposure categories the direction of bias from nondifferential misclassification could be either toward or away from the null. However, in the highest dose category the bias is expected to be towards the null, assuming a monotonic dose-response.[35,36] Therefore, misclassification of our binary exposure variables or in the highest dose categories could result in an attenuated estimate of any true association.

Multiple studies have been carried out to assess the reproducibility of self-reported pesticide use in diverse populations.[37–42] These studies compared pesticide exposure reporting between repeat questionnaires given 1–2 years apart or, in one study[39], 21 years after the original assessment. Across studies, the kappa for pesticide-specific questions ranged from 0.5 and 0.9.[37–39] Three studies reported percent exact agreement from 70% to 94%[40–42] for general application practices, although it was slightly lower when the question asked about specific types of pesticides.[40] The authors in each study concluded that there was moderate

to high reproducibility for self-reported pesticide exposure and that the level is adequate for use in epidemiologic studies. High reliability of self-reported pesticide exposures does not exclude the possibility of repeated errors across multiple reports; however, it provides reassurance regarding the stability of recall over time.

Although we were unable to validate women's recall of pesticide exposure directly, we asked about 1,000 participants' mothers some of the same questions answered by their daughters to assess their agreement. In a preliminary analysis, we used the mother's recall of their daughter's pesticide exposure as the gold standard and assumed adult memories would be more accurate than childhood memories. Overall agreement was 94% for residence ever used as a farm or orchard, and the positive predictive value of the rarer "yes" response was 76%. The positive predictive value was greater than 90% for pesticides applied to crops on the farm. Overall agreement was 75% for longest childhood residence treated regularly with insecticides or pesticides but the PPV of a yes response was much lower (56%) (A. D'Aloisio, *personal communication*). Therefore, we are confident of the high data quality for our farm-related pesticide exposures, but cannot exclude the possibility of greater relative misclassification in residential exposures. The high level of agreement for pesticide exposures in other studies, our preliminary validation compared to mothers' reports, and the high stability of childhood residence lend confidence to our self-reported exposure measurements.

In the present study, women could have been exposed to a variety of pesticides depending on regional agricultural practices, but we did not examine individual pesticides. As previously discussed, we did not have blood measurements of organochlorine concentrations. However, blood samples at enrollment would not have been an informative exposure assessment due to lack of timing of sample collection to relevant etiologic windows and individual variations in metabolism. Finally, the women in the Sister Study cohort have a family history of breast cancer and thus have a two-fold higher risk of developing breast cancer themselves compared to women without a family history of breast cancer. However, the distribution of breast cancer risk factors in this study population was similar to that of the general population and thus suggests that results from this study may be more broadly generalizable.[44]

Despite these limitations, our study had several strengths; most notably, the self-reported pesticide exposure history was obtained prior to diagnosis, which was a unique design of our study compared to most previous studies. This is particularly relevant in case-control studies; a case-control study conducted in Cape Cod, Massachusetts found that the association between cleaning products and breast cancer risk was strongest among those who reported the belief that pollutants contributed 'a lot' to breast cancer risk.[22] Therefore, the prospective design used in our study provides assurance that it would not be susceptible to differential reporting errors. Additionally, we were able to investigate several measures of childhood and adolescent pesticide exposure with more extensive detail than any previous study to date. As noted previously, biological samples which have most often measured body burdens in later adulthood would not have appropriately addressed our study hypothesis about childhood and adolescent exposures due to concerns about degradation. Finally, it was

a strength of our analysis that we were able to consider hormone receptor subtype and menopausal status at diagnosis as distinct etiologic subgroups.

Overall, the results of this study do not support a strong association between pesticide exposure during childhood/adolescence and breast cancer risk as many of the associations were near null. Although there were a few modestly elevated breast cancer risk estimates, these were associated with acute exposure events and limited by small sample sizes. As many of the women who were exposed to organochlorine pesticides in adolescence are now coming to an age of highest risk for breast cancer, understanding the long-term impact of pesticide exposure during potentially vulnerable periods of breast development remains an important research area.

Acknowledgments

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Table 1

Distribution of Person-Years Contributed by Sister Study Participants According to Breast Cancer Diagnosis and Select Characteristics, Sister Study

	Cases (N) N=2,134	Person-Years (PY) PY=270,886	Distribution of Person Years (% PY)	
Birth cohort			Cases	Non-cases
1928–1946	778	79,389	35.9	29.1
1946–1955	809	107,160	39.1	39.6
1956–1965	491	70,715	22.4	26.2
1966–1974	56	13,622	2.6	5.1
BMI				
<18.5	19	3,114	0.8	1.2
18.5–24.9	761	103,339	36.2	38.2
25.0–29.9	685	85,650	32.6	31.6
30.0	669	78,688	30.4	29.0
Race				
Non-Hispanic White	1,850	232,444	88.5	85.7
Non-Hispanic Black	153	20,636	6.1	7.7
Hispanic	66	10,810	2.2	4.0
Other/unknown	64	6,929	3.2	2.5
Parity/breastfeeding				
Nulliparous	397	4,9752	18.5	18.4
Parous, never breastfed	547	6,6029	25.2	24.4
Parous, breastfed	1,190	154,920	56.3	57.2
Unknown	0	185	0.0	0.1
Menopausal hormone therapy				
Never	1,153	154,130	55.0	56.9
Estrogen (E) only	409	53,668	18.2	19.9
Estrogen and Progestin (E+P) only	462	51,538	21.6	19.0
E and E+P	106	10,816	5.0	4.0
Unknown	4	733	0.2	0.3

Table 2

Breast cancer risk according to residential exposure to pesticides in childhood and adolescence, Sister Study

RESIDENTIAL EXPOSURES AGES 0–14	PY	Total Breast Cancer		ER+/PR+ Invasive Breast Cancer		Premenopausal Breast Cancer		Postmenopausal Breast Cancer	
		N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]
Residence type									
Urban	59,773	483	1	209	1	95	1	384	1
Suburban	76,288	601	0.96 (0.85, 1.1)	257	0.86 (0.71, 1.0)	183	0.95 (0.73, 1.2)	414	0.96 (0.83, 1.1)
Small town	69,237	549	0.97 (0.85, 1.1)	249	0.94 (0.78, 1.1)	120	0.97 (0.73, 1.3)	426	0.99 (0.85, 1.1)
Rural	61,802	477	0.95 (0.84, 1.1)	204	0.90 (0.74, 1.1)	80	0.79 (0.58, 1.1)	393	0.88 (0.33, 2.4)
Residence used as a farm or orchard while living there									
No	228,466	1794	1	771	1	433	1	1349	1
Yes	38,103	309	1.0 (0.91, 1.2)	143	1.1 (0.93, 1.3)	42	0.90 (0.65, 1.3)	264	1.1 (0.91, 1.2)
Residence within seeing, smelling, or hearing distance of:									
An orchard	33,682	289	1.1 (0.97, 1.3)	123	1.1 (0.86, 1.3)	70	1.0 (0.80, 1.4)	215	1.1 (0.97, 1.3)
A nursery or commercial greenhouse	6,641	42	0.79 (0.58, 1.1)	23	1.05 (0.69, 1.6)	9	0.61 (0.31, 1.2)	33	0.40 (0.15, 1.1)
A golf course	12,147	96	1.0 (0.82, 1.3)	38	0.89 (0.64, 1.3)	28	0.99 (0.67, 1.5)	68	1.0 (0.80, 1.3)
None of the above	182,243	1,420	1	610	1	341	1	1071	1
Residence treated regularly with insecticides or pesticides									
No	186,722	1,501	1	673	1	323	1	1166	1
Yes	56,541	424	0.93 (0.83, 1.0)	163	0.86 (0.72, 1.0)	111	0.84 (0.67, 1.1)	310	0.99 (0.87, 1.1)
Frequency of pest control chemical application									
Residence not treated with insecticides or pesticides	186,722	1,501	1	673	1	323	1	1166	1
Weekly	3,572	24	0.87 (0.58, 1.3)	7	0.69 (0.33, 1.5)	3	Not estimated[b]	21	1.0 (0.66, 1.6)
Monthly	9,598	71	0.93 (0.73, 1.2)	32	1.1 (0.74, 1.5)	20	0.83 (0.52, 1.3)	50	1.0 (0.75, 1.3)
Every 2–3 months	10,930	85	0.96 (0.77, 1.2)	30	0.83 (0.57, 1.2)	28	1.1 (0.71, 1.6)	57	0.97 (0.74, 1.3)
At most twice per year	29,618	228	0.94 (0.82, 1.1)	90	0.86 (0.69, 1.1)	59	0.84 (0.63, 1.1)	167	1.0 (0.85, 1.2)
Personal application of pest control chemicals									

RESIDENTIAL EXPOSURES AGES 0–14	PY	Total Breast Cancer		ER-/PR+ Invasive Breast Cancer		Premenopausal Breast Cancer		Postmenopausal Breast Cancer	
		N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]
Residence not treated	186,722	1,501	1	673	1	323	1	1166	1
Residence treated, no personal application	50,293	380	0.93 (0.83, 1.0)	141	0.82 (0.68, 0.98)	100	0.85 (0.68, 1.1)	277	0.99 (0.86, 1.1)
Residence treated, personal application at least some of the time	6,110	44	0.92 (0.68, 1.2)	22	1.2 (0.81, 1.9)	11	0.78 (0.42, 1.4)	33	1.0 (0.90, 1.2)

[a] Adjusted for age, race, age at menarche, parity and breastfeeding

[b] Estimates were not determined for cells with sample size smaller than 5

Table 3

Breast cancer risk according to farm exposure to pesticides in childhood and adolescence, Sister Study

FARM EXPOSURES AGES 0–18	PY	Total Breast Cancer		ER+/PR+ Invasive Breast Cancer		Premenopausal Breast Cancer		Postmenopausal Breast Cancer	
		N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]
Ever lived on farm ≥12 months									
No	219,249	1,725	1	741	1	414	1	1300	1
Yes	51,607	409	0.99 (0.89, 1.1)	188	1.1 (0.90, 1.3)	69	1.1 (0.85, 1.4)	336	0.96 (0.85, 1.1)
Farm type:									
Livestock	49,089	394	1.0 (0.90, 1.1)	181	1.1 (0.91, 1.3)	67	1.2 (0.90, 1.5)	324	0.97 (0.86, 1.1)
Field or orchard crops	47,336	376	1.0 (0.89, 1.1)	169	1.1 (0.89, 1.3)	59	1.1 (0.83, 1.4)	313	0.98 (0.86, 1.1)
Cotton or tobacco	9,071	88	1.3 (1.0, 1.6)	34	1.3 (0.93, 1.9)	9	1.0 (0.55, 2.0)	78	1.3 (1.0, 1.6)
Other cash crops	11,093	91	1.0 (0.84, 1.3)	38	1.0 (0.72, 1.4)	10	0.91 (0.52, 1.6)	80	1.1 (0.84, 1.3)
Worked in the fields									
Yes	29,573	237	1.0 (0.88, 1.2)	102	1.0 (0.84, 1.3)	36	1.1 (0.80, 1.5)	198	1.0 (0.85, 1.2)
Farm used pesticides[b]									
Yes	27,804	209	0.95 (0.82, 1.1)	86	0.93 (0.74, 1.2)	37	0.96 (0.68, 1.4)	169	0.93 (0.79, 1.1)
Ever lived on a farm that used pesticides[c]									
No, farm did not use pesticides	11,570	110	1	58	1	15	1	95	1
Yes, farm used pesticides	27,804	209	0.80 (0.63, 1.0)	86	0.64 (0.46, 0.90)	37	0.64 (0.35, 1.2)	169	0.82 (0.63, 1.1)
Pesticide exposure:									
Personally mixed, loaded applied or helped others mix	5,403	41	0.82 (0.57, 1.2)	18	0.70 (0.41, 1.2)	6	0.51 (0.20, 1.3)	34	0.84 (0.56, 1.3)
Present in fields the same day applied to crops	8,476	65	0.82 (0.60, 1.1)	27	0.65 (0.41, 1.0)	15	0.64 (0.30, 1.4)	48	0.78 (0.54, 1.1)
Cleaned or helped clean equipment	2,274	20	0.97 (0.60, 1.6)	7	0.67 (0.30, 1.5)	4	0.74 (0.24, 2.3)	16	1.0 (0.60, 1.8)
Episode(s) with an unusually high amount on skin/clothing	949	12	1.4 (0.75, 2.5)	7	1.6 (0.71, 3.4)	1	0.55 (0.07, 4.2)	11	1.5 (0.80, 3.0)

[a] Adjusted for age, race, age at menarche, parity and breastfeeding

[b] Compared to women who never lived on a farm for ≥12 months from ages 0 to 18

[c] Compared to women who lived on a farm for ≥12 months from ages 0 to 18 that did not use pesticides

Table 4

Breast cancer risk according to fogger truck or airplane exposure, Sister Study

Exposure	PY	Total Breast Cancer		ER+/PR+ Invasive Breast Cancer		Premenopausal Breast Cancer		Postmenopausal Breast Cancer	
		N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]
Ever directly in the fog or spray of chemicals or chased after the fogger trucks or airplanes that sprayed as a child									
No	216,203	1,687	1	737	1	381	1	1291	1
Yes	53,283	434	1.0 (0.93, 1.2)	187	1.0 (0.85, 1.2)	101	1.1 (0.90, 1.4)	333	1.0 (0.89, 1.1)
Before 1975	39,238	328	1.1 (0.93, 1.2)	144	1.0 (0.86, 1.5)	67	1.2 (0.93, 1.6)	261	1.0 (0.89, 1.2)
After 1975	8,060	68	1.1 (0.85, 1.4)	29	1.0 (0.70, 1.5)	22	1.2 (0.78, 1.8)	46	0.96 (0.70, 1.3)
Both before and after 1975	5,736	38	0.85 (0.61, 1.2)	14	0.74 (0.44, 1.3)	12	0.76 (0.43, 1.4)	26	0.94 (0.63, 1.4)
Exposed to fog or spray and born between 1941–1958									
No	135,971	1,063	1	446	1	141	1	912	1
Yes	37,917	325	1.1 (0.99, 1.3)	136	1.1 (0.88, 1.3)	57	1.3 (0.92, 1.7)	268	1.0 (0.90, 1.2)

[a] Adjusted for age, race, age at menarche, parity/breastfeeding