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DDT exposure in early childhood and female breast cancer: Evidence from an ecological study in Taiwan

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ABSTRACT

Researchers still lack consensus on the association between exposure to DDT and the risk of breast cancer. One reason could be that the measurements of DDT obtained during or near the time of diagnosis may not reflect exposure during the etiologically relevant time period in a woman's life. This study undertook an ecological analysis to investigate whether exposure to DDT among cohort born between 1951 and 1959 (i.e. age 0–5 years) and who reached the age 50–54 years during 2001–2013 had an increased risk of breast cancer in adulthood. To do this, we used the number of DDT sprays in each township during the anti-malaria campaign in Taiwan in the 1950s as a proxy for direct DDT exposure. The DDT sprays were then linked to the township female breast cancer incidence rate in the 2000s when the birth cohorts had reached age 50–54 years. Insurance claims data were used to identify breast cancer cases during 1996–2013. Zero-Inflated Poisson regression was performed to estimate the effect of DDT sprays on the breast cancer incidence rate. The analysis was based on a total of 9 birth cohorts (1951–1959) in 349 townships who had lived at least up to age 50. On average, one DDT spray experienced during age 0–5 years was associated with an increase of 8 more female breast cancer cases per 100,000 during age 50–54. The effect appears to increase with the number of sprays. Our finding suggests that DDT exposure in early childhood could raise the risk of breast cancer in adulthood.

1. Introduction

Breast cancer has become the most common cancer and ranks the fourth cause of cancer death among women in Taiwan since 2003. The incidence and mortality rates of breast cancer in Taiwan have increased by 32. 5% and 2.5% from 2003 to 2008, respectively (Chang et al., 2012). Lifelong exposure to endogenous or exogenous oestrogens may contribute to the development of breast cancer. Reproductive factors such as early age at menarche and early or an absence of childbearing have been shown to increase exposure to endogenous oestrogens, while factors such as the use of oral contraceptive pills and hormone replacement therapy are associated with an increased exposure to exogenous oestrogens (Travis and Key, 2003). Given that breast cancer is a hormone dependent cancer, the question arises whether the growing incidence of breast cancer may be due other factors such as to exposure to pesticides, including the organochlorine dichlorodiphenyltrichloroethane (DDT), which have hormone disrupting properties (Macon and Fenton, 2013).

DDT and its major metabolite, dichlorodiphenyldichloroethylene (DDE), have been extensively studied in relation to female breast cancer because of their long biological half-lives, and estrogenic and lipophilic properties. However, the evidence of this association is not conclusive. For instance, a number of studies have found an increased risk of breast cancer associated with exposure to DDT and DDE (Arrebola et al., 2015; Charlier et al., 2004), while the results of a more recent body of literature, including three meta-analyses (Ingber et al., 2013; Lopez-Cervantes et al., 2004; Park et al., 2014), have largely been null. The lack of an association maybe because the DDT measurements were obtained at the time of breast cancer diagnosis or near the time of diagnosis, which might not properly reflect exposures during the etiologically relevant periods in a woman's lifetime such as the breast development. Indeed, two case-control studies that examine exposure in utero and during teenage years found that the DDT exposure at these early life stages was associated with a higher breast cancer risk (Cohn

Abbreviations: DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene

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et al., 2015; Cohn et al., 2007). In-utero exposure was found to increase the odds of breast cancer 4-fold when comparing the highest and lowest quartiles of exposure (Cohn et al., 2015) and a fivefold increase in the risk of breast cancer among women exposed to DDT prior to age 14 years (Cohn et al., 2007). It has been hypothesized that exposure to chemicals including DDT during early life may alter breast development and hence increases women susceptibility to breast cancer (Osborne et al., 2015).

Another possible explanation for the lack of association seen between DDT and breast cancer risk is that DDE concentrations as measured in biological media collected since the late 1980s are lower than those observed during the 1960s or 1970s. DDE concentrations were approximately eight times lower in 1997 than 1963 (Bachelet et al., 2010). Hence, measuring DDT or DDE in blood or adipose tissue during adulthood or at the time of breast cancer diagnosis may not reflect lifetime cumulative exposure. Furthermore, most studies measuring DDT or DDE concentrations in serum or adipose tissues lack a history of exposure pathways and thus it is not clear whether the concentration comes from direct exposure to technical DDT or from consuming the residues of its metabolites deposited in the food chain. Moreover, in vivo and in vitro studies of the estrogenic potency of DDT and its metabolites have shown that the most estrogenic component of technical DDT is *o,p′*-DDT, whereas another congener *p,p′*-DDT shows much weaker estrogenic response and its metabolite, *p,p′*-DDE, displays very little or even nil potency. Therefore, knowing the history of direct exposure to DDT is critical in identifying the effect of DDT exposure on breast cancer (Gellert et al., 1972; Welch et al., 1969).

We undertook an ecological analysis to investigate whether exposure to DDT in early childhood, i.e. age 0–5 years, increases the risk of breast cancer in adulthood. We utilized a large-scale ecological study in Taiwan in the 1950s. In the early 1950s, malaria was prevalent among the 8 million people on the island. It was estimated that the island had 1.2 million malaria cases in 1952 (Department of Health et al., 2005). A four-year anti-malaria campaign plan was drafted in 1951 (Department of Health et al., 2005). Based on epidemiological data available at the time, the Taiwanese government stratified the island into hyperendemic area (foothills of the central mountains), mesoendemic area, hypoendemic area, and non-malarious area (large cities and high mountains). At the core of the campaign was the use of DDT residual spray to kill *Anopheles* mosquitoes. In particular, DDT was sprayed on the indoor surfaces of every single house in each of the endemic areas once a year. The dosage was 2 g per square meter of technical grade DDT.

The DDT spraying campaign first began in the hyperendemic area in 1953 and then expanded to mesoendemic and hypoendemic areas in 1954. In 1956, spraying was applied to the whole of Taiwan except for a few non-malarious cities. In 1957, the last year of the campaign, DDT was applied only in the original hyperendemic area and the aboriginal areas where the indigenous people live.

Because the beginning year of DDT spraying differed across areas, the total number of sprays during 1952–1957 also varied across areas. Fig. 1 shows the DDT sprays distribution with the darkest area indicating townships with the most sprays and the white area indicating no DDT sprays during 1952–1957. The large white area in the middle coincides with the Central Mountain Range with very few inhabitants and thus no sprays.

The original plan of DDT spraying was based on the malaria distribution before 1952 and malaria declined rapidly soon after the campaign started. As shown in Fig. 2, malaria prevalence rate reduced from about 15,000 cases per 100,000 people in 1952 to < 5000 cases in 1953 and only 1143 cases in 1954. On the contrary, the share of townships receiving DDT sprays kept increasing to almost 93% in 1956 before it dropped to 38% in 1957 (authors' own calculation). Eventually, malaria was eradicated in Taiwan in the early 1960s; the World Health Organization declared Taiwan as malaria-free in 1965.

The aim of the current study was to investigate the incidence of breast cancer among Taiwanese females who as children (≤5 years) had varying degrees of exposure to DDT spraying during 1952–1957.

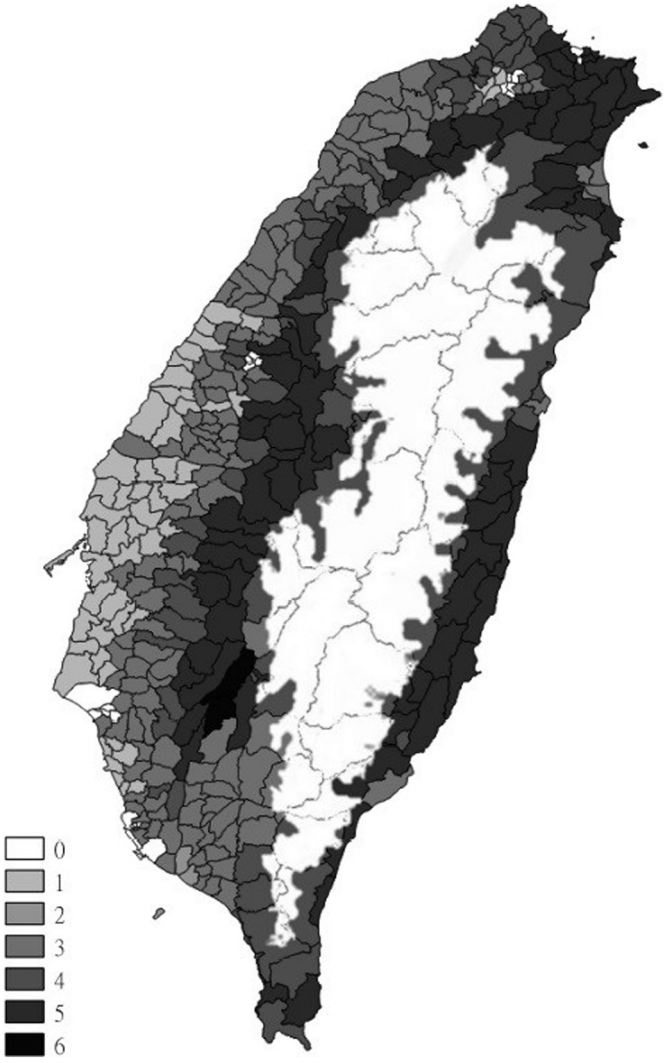

Fig. 1. DDT sprays during 1952–1957
Notes: the numbers indicate the total DDT sprays during 1952–1957.
Source: authors' own calculation based on data collected from various *Taiwan Province Gazettes* during 1952–1957.

2. Data and methods

The campaign directly exposed the cohort born in 1952–1957 to technical DDT with variation in the intensity of exposure across townships. In our ecological analysis, we used the exact number of DDT sprays in each township in the 1950s as a proxy for direct DDT exposure in early childhood. We then linked the DDT sprays in the 1950s to the township female breast cancer incidence rate in the 2000s when the cohort had reached age 50–54 years.

We examined the cohorts born in 1951–1959, who reached age 50–54 during 2001–2013. These cohorts were chosen for three reasons. First, they covered exposure before, during and after the anti-malaria campaign years. Cohorts born before and after the malaria campaign period are likely to have been exposed to DDT in utero, through breastfeeding and the environment due to its long half-life. Second, due to a massive influx of immigrants from Mainland China in 1949 and 1950, it was difficult to ascertain the DDT exposure for the 1949/1950 cohort. Third, our cancer incidence data were only up to 2013, implying the youngest cohort that we could observe up to age 54 is the 1959 cohort.

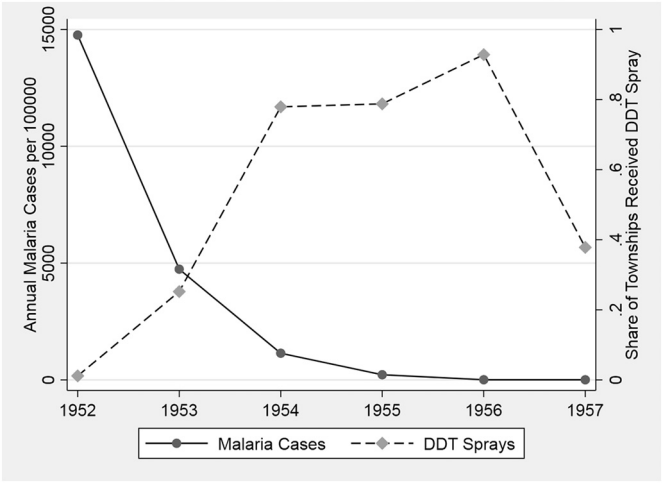

Fig. 2. Malaria prevalence and proportion of townships that received DDT sprays in Taiwan, 1952–1957

Notes: malaria prevalence rate is the number of annual malaria cases divided by population times 100,000.

Sources: data on malaria cases are obtained from *Malaria Eradication in Taiwan* by Department of Health, Executive Yuan, R. O. C.; population data are obtained from Department of Household Registration, M.O.I., Taiwan; information about DDT sprays is collected from various *Taiwan Province Gazettes* during 1952–1957.

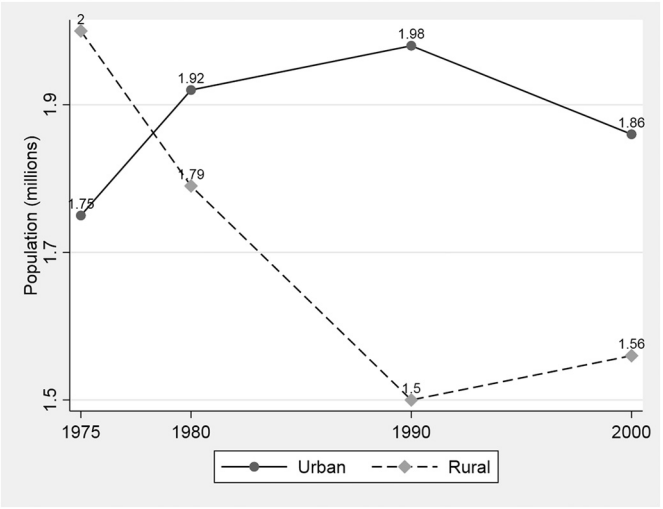

Fig. 3. Population size of birth cohort by urban and rural area, 1951–1960, Taiwan

Notes: population sizes of birth cohort 1951–1960 in urban and rural area are defined by the population of age 15–24 in 1975, 20–29 in 1980, 30–39 in 1990 and 40–49 in 2000.

Sources: Population and Housing Census 1975, 1980, 1990 and 2000, Directorate-General of Budget, Accounting and Statistics, Executive Yuan, R.O.C. (Taiwan).

The township female cancer incidence rate is defined as follows.

$$B_{cj}^{50-54} = \frac{\sum_{a=50}^{a=54} N_{cj}^{a}}{\sum_{a=50}^{a=54} P_{cj}^{a}} \times 100\,000, \tag{1}$$

where B_{cj}^{50-54} denotes female breast cancer incidence rate during age 50–54 for birth cohort c in township j; N_{cj}^{a} is the number of new cases of female breast cancer at age a for birth cohort c in township j; P_{cj}^{a} is the number of women at age a for birth cohort c in township j.

2.1. Cancer data

Female breast cancer cases were identified from the insurance claims of the National Health Insurance program, which is a universal and compulsory public insurance program covering essentially the entire population and most of the medical care providers since 1995 (Cheng, 2003). We obtained a data set that contained all cancer-related insurance claims during 1996–2013. Population data were acquired from the Department of Household Registration of the Ministry of Interior.

One limitation of the insurance claims data is that we only know the township where an individual signed up for the insurance and it is possible that this differed from her place of residence at 0–5 years as a result of internal migration. Nevertheless, due to economic development and urbanization in Taiwan in the last 50 years, the migration pattern has been generally been from rural area to urban area. Fig. 3 uses various waves of population census to show the population size of birth cohorts 1951–1960 decomposed by rural (dashed line) and urban (solid line) area from 1975 to 2000. It is clear that the urban population was growing while the rural population was declining. Given that there is no clear evidence that fertility and mortality rate over this period moved in opposite directions in the rural and urban area, the changes in the rural and urban population support the rural-to-urban migration pattern. In the following statistical analysis, we assume there was no internal migration, and that the DDT sprays at age 0–5 are a proxy for direct exposure.

2.2. DDT exposure data

DDT sprays data were collected from various Taiwan Province Gazettes published by the Taiwan provincial government during 1952–1957. Taiwan Province Gazettes each year announced the plan to be implemented in the following year, including the townships to be sprayed and related budget and staff. We thus used the Gazette information to calculate the number of DDT sprays in each township as a proxy for DDT exposure during age 0–5 for each birth cohort. Throughout the remaining of this article, one DDT spray is equivalent to one DDT exposure and they are used interchangeably.

2.3. Statistical analysis

To account for the nature of cancer incidence which takes on non-negative integers with a large presence of zeros, we performed Zero-Inflated Poisson (ZIP) regression that is suitable to this type of outcome variable (Lambert, 1992). In addition, there may be unknown confounders that are specific to township or birth cohort that could have had influenced breast cancer but not available in our data. For instance, urban and rural townships may differ in both exposure and risk of cancer. To control for these unobserved confounders, we add a full set of township and birth cohort dummy variables in the regressions. For statistical inference, we use robust standard errors clustered at township to account for possible correlation within a township.

As aforementioned, DDT sprays in the early stage of the anti-malaria campaign were more correlated with the malaria distribution. While malaria is not known to play a role in the breast cancer risk, we undertook a sensitivity analyses in which the 1951 and 1952 cohorts who were most likely to be influenced by malaria, were excluded from the analyses.

3. Results

Fig. 4 shows the average DDT exposures up to age 5 by cohort and region. Overall, the early childhood exposure varied across birth cohorts. The 1951–1954 cohorts were subject to the most exposures. The later cohorts were exposed less and less until the 1958 and 1959 cohorts

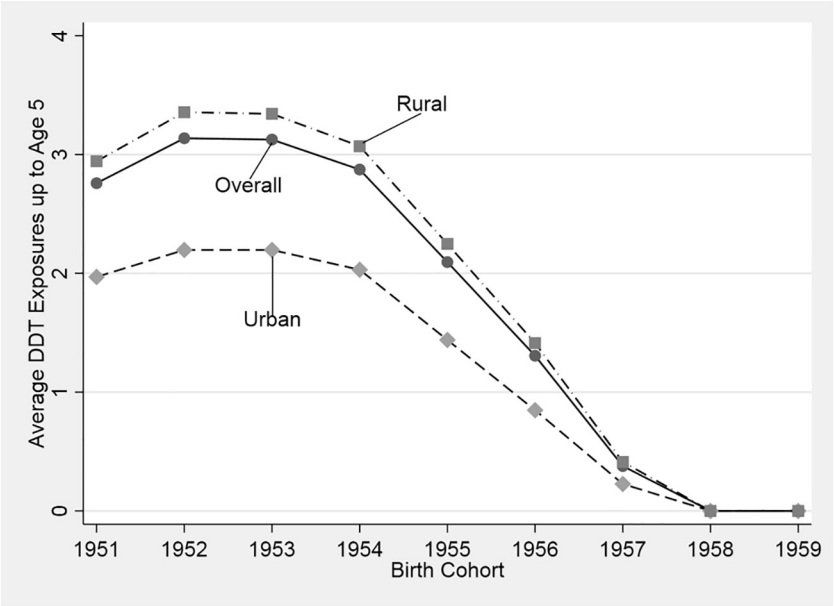

Fig. 4. Average DDT exposures up to Age 5 by cohort and region, Taiwan
Notes: exposure is calculated based on the DDT sprays during 1952–1957 at township level and the assumption that individuals lived in the same township during age 0–5.
Sources: authors' own calculations based on data collected from various *Taiwan Province Gazettes* during 1952–1957.

who received no direct exposure.

Fig. 5 illustrates our calculation of the average township female breast cancer incidence rate at age 50–54 for each cohort and by region in the 2000s. Overall, the incidence rate increased from about 130 cases per 100,000 people for the 1951 cohort to about 160 cases per 100,000 people for the 1959 cohort. The incidence rate in the urban region was much higher than the rural region. The urban region also had a larger increase across cohorts.

To corroborate our calculation of township incidence rate using the insurance claims data, Fig. 6 plots the population-based female breast cancer incidence rate by age published by the *Taiwan Cancer Registry*, which is organized and funded by the Department of Health in Taiwan. Hospitals that have 50 beds and more and provide outpatient and hospitalized cancer care are recruited to participate in reporting all newly diagnosed malignant neoplasms to the registry. As shown, the incidence rate for age 50–54 is about 124 cases per 100,000 in 2001–2005 (solid line) and 164 cases 2006–2010 (dashed line). Since the cohorts 1951–1959 reached age 50–54 during 2001–2013, our calculated incidence rate should lie somewhere in between, which falls into the ballpark.

Table 1 reports the summary statistics of our sample. The sample consists of 3141 observations, each of which represents a particular birth cohort in a particular township. There are a total of 9 birth cohorts (1951–1959) and 349 townships. Among them, 2547 observations are from rural area and 594 observations from an urban area. The overall average township female breast cancer incidence rate is 143 cases per 100,000 people. It is 294 cases per 100,000 for the urban area and 108 per 100,000 for the rural area. Median incidence rates are reported in parentheses. The overall DDT exposure during age 0–5 was on average 1.74 sprays. By region, the rural area had an average of 1.87 sprays, while urban area had only 1.21 sprays. About 66% of observations had at least one exposure. Yet, nearly 55% of the urban observations had no exposure at all, while there was only 29% in the rural area that had no exposure.

The main regression results are reported in Table 2. We use two different specifications. The first specification (columns (1) and (2))

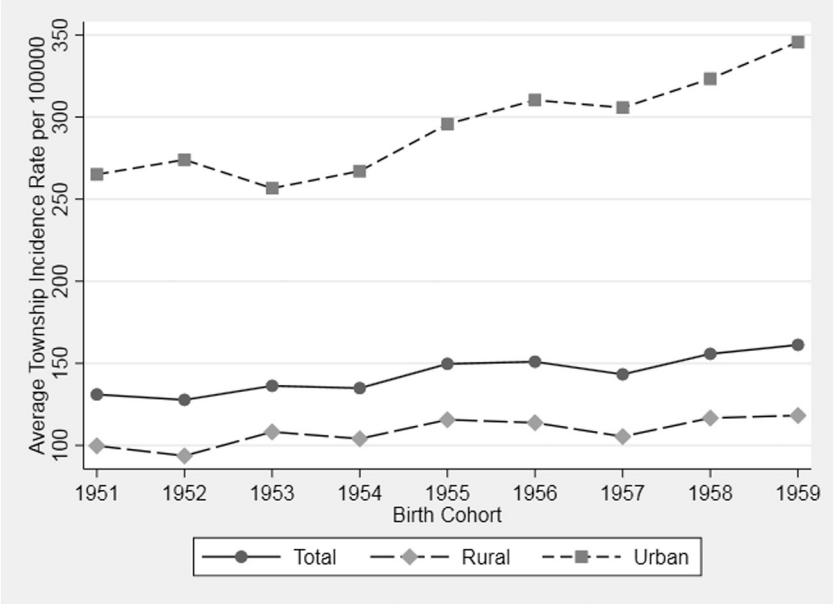

Fig. 5. Average township female breast cancer incidence rate at Age 50–54 by Cohort and Region, Taiwan
Notes: urban region includes administrative division of *Shi* 市 and *Chu* 區; rural area includes administrative division of *Zheng* 鎮 and *Xiang* 鄉.
Sources: Authors' own calculations.

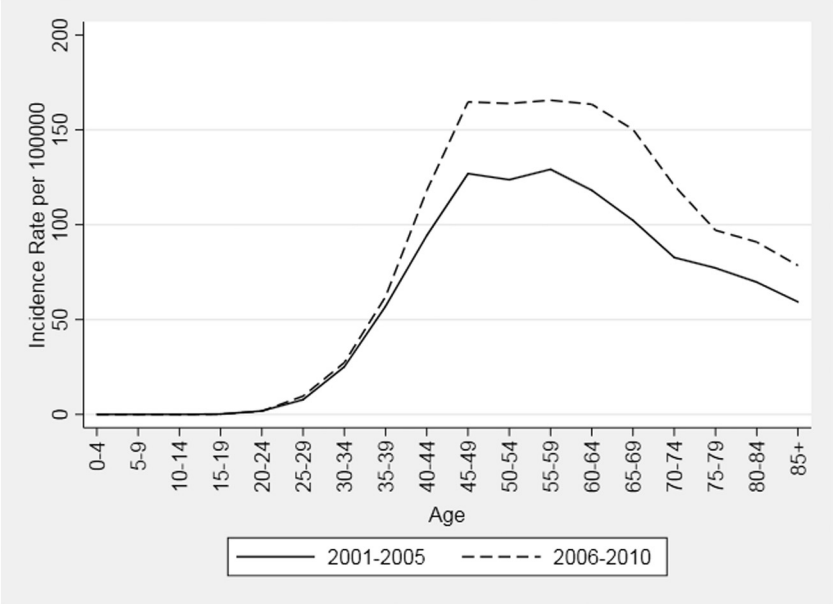

Fig. 6. Population-based female breast cancer incidence rate by age, Taiwan. Source: Taiwan Cancer Registry.

Table 1
Summary of township female breast cancer incidence rate and DDT exposures during Age 0–5 among birth cohorts 1951–1959 in Taiwan.

	Overall (1)	Urban (2)	Rural (3)
Township female breast cancer incidence rate per 100,000 during Age 50–54 (median)	143 (111)	294 (221)	108 (84)
DDT Exposures during age 0–5			
0	33.6%	54.4%	28.7%
1	18.5%	10.6%	20.3%
2	9.1%	6.6%	9.7%
3	22. 7%	19.4%	23.4%
4	11.2%	6.1%	12.4%
5	4.8%	3.03%	5.3%
6	0.1%	0%	0.1%
Average exposures during age 0–5	1.74	1.21	1.87
Observations	3141	594	2547

Notes: each observation represents one township-cohort cell. There are 349 townships and nine birth cohorts (1951–1959). DDT exposure during age 0–5 for a particular cohort in a particular township is defined as the total number of DDT sprays in that township during the first six years following birth. Column (1) uses the whole sample, while column (2) and (3) uses only the urban and rural townships.

uses the number of total DDT sprays during age 0–5 as the main exposure measure. To allow for non-linearity in the DDT effect, we used five dummy variables to indicate different number of sprays as the regressors with no spray as the reference group (columns (3) and (4)). We grouped 5 and 6 sprays in the same dummy variable because there were only 2 township-cohort observations with 6 sprays. Since Poisson model is a non-linear model, we present the original coefficients in columns (1) and (3) and provide the corresponding average marginal effects in columns (2) and (4).

The result in column (2) suggests that one DDT spray experienced during age 0–5 is associated with an increase of 8 more female breast cancer cases per 100,000 during age 50–54. This is about 5% of the average incidence rate. The results in column (4) suggest a substantial nonlinearity in the DDT effect. The effect appears to be increasing along with the number of sprays. For example, the effects for the cohorts that experienced 3 sprays or more are five to six times larger than those with only 1 spray.

Table 2
Zero-inflated Poisson Regressions of Township Female Breast Cancer Incidence Rate during Age 50–54 on Total DDT Exposures during Age 0–5.

Exposures	Coefficient (1)	Average marginal effect (2)	Coefficient (3)	Average marginal effect (4)
Total sprays	0.05 (0.02, 0.07)	7.71 (3.40, 12.02)		
			No Spray (reference)	
1 spray			0.03 (−0.06, 0.12)	5.09 (−9.10, 19.23)
2 sprays			0.08 (−0.01, 0.18)	13.84 (−1.69, 29.38)
3 sprays			0.16 (0.07, 0.25)	26.23 (11.17, 41.29)
4 sprays			0.21 (0.09, 0.33)	34.38 (14.17, 54.60)
5/6 sprays			0.16 (−0.00, 0.32)	25.90 (−0.09, 51.89)
Observations	3141	3141	3141	3141

Notes: dependent variable is female breast cancer incidence rate per 100,000 during age 50–54 at the township-cohort level. The birth cohorts include 1951–1959. DDT exposure is measured by the total DDT sprays that each birth cohort in a certain township received during age 0–5. Column (1) and (3) report the estimated coefficients, while column (2) and (4) report the average marginal effects. All regressions additionally control for a full set of birth cohort dummies and township dummies. The 95% confidence intervals based on robust standard errors clustered at township are in parentheses.

When we re-estimated the regressions by excluding the 1951 and 1952 cohorts, who are most likely to be influenced by malaria, the sample drops to a total of 2443 observations. The re-estimation results reported in Table 3 suggest that the DDT effects remain similar even if we drop the early cohorts.

4. Discussion

Prior epidemiologic studies on the association between DDT exposure and breast cancer have shown mixed findings. It has been suggested that exposure to DDT at the ages of the critical developmental window may impact on the risk of breast cancer (Cohn et al., 2015; Cohn et al., 2007).The large-scale anti-malaria campaign in Taiwan in

Table 3
Zero-inflated Poisson Regressions of Township Female Breast Cancer Incidence Rate during Age 50–54 on Total DDT Exposures during Age 0–5: Excludes Birth Cohort of 1951 and 1952.

Exposures	Coefficient (1)	Average marginal effect (2)	Coefficient (3)	Average marginal effect (4)
Total sprays	0.05 (0.02, 0.08)	7.81 (3.13, 12.48)		
			No Spray (reference)	
1 spray			0.04 (−0.05, 0.13)	6.31 (−8.59, 21.21)
2 sprays			0.10 (0.00, 0.19)	15.68 (0.10, 31.25)
3 sprays			0.16 (0.06, 0.25)	25.57 (10.00, 41.13)
4 sprays			0.23 (0.08, 0.37)	37.40 (13.87, 60.92)
5/6 sprays			0.14 (−0.06, 0.34)	23.27 (−9.61, 56.14)
Observations	2443	2443	2443	2443

Notes: dependent variable is female breast cancer incidence rate per 100,000 during age 50–54 at the township-cohort level. The birth cohorts include 1953–1959. DDT exposure is measured by the total DDT sprays that each birth cohort in a certain township received during age 0–5. Column (1) and (3) report the estimated coefficients, while column (2) and (4) report the average marginal effects. All regressions additionally control for a full set of birth cohort dummies and township dummies. The 95% confidence intervals based on robust standard errors clustered at township are in parentheses.

the 1950s allowed us to investigate exposure that might have occurred in utero and early childhood by studying, the cohorts who we know were exposed to technical DDT sprays at some of the critical ages of development. Our population-based results show a positive association between areas with greater DDT exposure during early life and female breast cancer in adulthood.

The positive association found in this paper is consistent with two previous studies, which showed that exposure to DDT during critical periods are associated with significant increase risk of breast cancer (Cohn et al., 2015; Cohn et al., 2007). These two studies measured exposure to DDT using biological samples. However, studies that relied on self-reported exposure during adolescence/childhood found non-significant increased risk. For instance a recent case-control study found that seeing a fogger truck at a residence they lived prior to ages 14, as proxy measure for acute DDT exposure, was not associated with an increased risk of breast cancer. However, the study found imprecise positive associations for women who reported seeing a fogger truck at their residence when they were 15–20 years of age (OR = 1.86; 95% CI: 0.98, 3.52) (White et al., 2013). Similarly, another study found that women who were exposed to DDT fogger trucks or planes when they were aged between 0 and 18 had a non-significant increased risk of breast cancer (HR = 1.1, 95% CI: 0.99–1.3), which appeared too driven by cancer diagnosed before menopause (HR = 1.3; 95% CI 0.92, 1.7) (Niehoff et al., 2016).

This study did not investigate the association between DDT and breast cancer risk by hormone receptor status due to lack of data. It is known that breast cancer risk factors differ according estrogen receptor (ER) and progesterone receptor (PR) status, with recent evidence indicating that traditional estrogen-related risk factors are more strongly associated with hormone receptor positive breast cancer (Colditz et al., 2004). For instance a study found that women with ER+/PR+ breast cancers had increased odds of ever seeing a fogger truck at residence they lived at when ≤20 years of age (OR = 1.50; 95% CI: 0.97, 2.32) and when ≤14 years of age (OR = 1.15; 95% CI: 0.99, 1.33) compared to all other subtypes (White et al., 2013). On the other hand, another study did not identify systematic variation between exposures to fogger trucks or airplane sprays during childhood/adolescent and types of breast cancer tumours (Niehoff et al., 2016).

Other studies have investigated exposure to other pesticides during younger age and the risk of breast cancer. For instance, a case control study in Australia found an increased breast cancer risk among women who ever noticed pesticide spray drift from agricultural areas, with stronger association among women who first noticed the drift at the age of 20 or younger (OR = 1.61; 95% CI 1.19, 2.16) (El-Zaemey et al., 2013). Another population based case control study conducted in North Carolina found an elevated increase risk of breast cancer among women who personally applied pesticides to crops during thelarche (OR = 1.2; 95% CI 0.7–2.2) (Duell et al., 2000).Hence, these findings are consistent with the assumption that the timing of environmental exposures are critical component in breast cancer risk.

Our study is consistent with the study in Taiwan that investigated the temporal changes in mortality rates of breast cancer during the 1971–2010 period. The study found that 1951 birth cohort had the greatest mortality risk from breast cancer, overlapping with the large amount of DDT that was used to prevent deaths from malaria (Ho et al., 2015).

In addition to the direct exposure to DDT, our birth cohort might have been exposed to DDT and its metabolites through placental transfer during gestation, breastfeeding or the environment due their persistence, which may explain the continuous increased risk of breast cancer beyond 1957. Studies have shown that DDT released before the ban of use are still present in various environmental and biological media. For instance, two studies have detected high ratio DDE/DDT in recent human breastmilk in Taiwan, (Chao et al., 2006; Chen et al., 2018; Tsai, 2010), implying that our birth cohort could have been exposed to DDT if they were breastfeed. DDT has the ability to cross the placenta and several studies have detected their presence in the umbilical cords and found their concentration was similar to those in maternal blood (Herrero-Mercado et al., 2011; Waliszewski et al., 2001). Hence, our birth cohort could have also been exposed to DDT or it metabolites in utero, which has been shown to be associated with increased breast cancer risks (Cohn et al., 2015).

The major limitations of our data are that we do not have individual exposure data and we lack information on residence during age 0–5 years, which is likely to be different from the place where we observed their cancer outcome fifty years later. Given that the rural area was more heavily exposed to DDT sprays than the urban area and, as shown in Fig. 3, people tended to move from rural to urban area, we suspect that our estimates based on the assumption of no migration are most likely to be biased downward. In particular, rural women may have moved to urban areas to improve access to treatment and management of their illness or to search for better economic opportunities. It is also noteworthy in Fig. 5 that the incidence rate has risen significantly from 2001–2005 to 2006–2010. The rise may in part have been related to the free biennial mammography program started in 2004, which was initially aimed at women aged 50–69 and then expanded to further include those aged 45–49 in 2009. However, there is no mammography screening rate data at the township level that would allow us to investigate the variation across townships.

Unlike prior studies, we do not have data on the DDT/DDE concentration in serum or adipose tissues nor other individual measures of exposure. However, there is an indication of a possible dose-response relationship based upon the average number of DDT applications. Regardless as we only have an ecological measure of exposure and we need to be cautious in drawing conclusions about individual risk on the basis of these data. Other known risk factors for breast cancer, such as age at first pregnancy, length of breastfeeding oral contraceptive, hormone replacement therapy and BMI are factors that may vary by region and thus confound the observed relationship.

Furthermore, due to data limitation, this study only investigated the association between exposure to DDT and breast cancer diagnosed at age 50–54. A full estimate of the DDT effect would ideally also look into older ages. Future research is needed to assess the full impact of DDT

when more data become available.

Another concern is the role of malaria in determining breast cancer. Although there is no evidence that malaria is a risk factor for breast cancer, we removed from the regressions the earliest cohorts whose DDT sprays are most likely to be correlated with their exposure to malaria. Very similar findings were observed when these cohorts were excluded.

Today, DDT is still used in some countries for malaria vector control. While DDT might be useful in controlling malaria, evidence of its adverse effect on human health is needed to balance between risk and benefits of DDT (Rogan and Chen, 2005). Our finding suggests that DDT exposure in early childhood could raise the risk of breast cancer in adulthood.

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Conflict of interest

The authors declare they have no actual or potential competing financial interests.

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