Pesticides are of interest in etiologic studies of breast cancer because many mimic estrogen, a known breast cancer risk factor, or cause mammary tumors in animals, and some cause mammary tumors in animals (Andersen et al. 2002; Bennett and Davis 2002; Brody and Rudel 2003; Davis et al. 1993; Wolff et al. 1996). Previous investigations include a small number of occupational and ecologic studies, with both positive and null findings (Abdalla et al. 2003; Band et al. 2000; Dolapakis et al. 2001; Fleming et al. 1999a, 1999b; Hopenhayn-Rich et al. 2002; Janssens et al. 2001; Kettles et al. 1997; Kogevinas et al. 1993; Manz et al. 1991), and a larger number of population-based studies of serum and adipose measurements of dichlorodiphenyltrichloroethane (DDT), its metabolite dichlorodiphenyldichloroethene (DDE), and a few other persistent organochlorines [reviewed by Brody and Rudel (2003)]. Many of the serum studies failed to find an association with breast cancer (Gammon et al. 2002; Laden et al. 2001; Snedeker 2001); however, a few have shown positive associations (Charlier et al. 2003; Cohn et al. 2002; Hoyer et al. 1998, 2000, 2002).

This available epidemiologic evidence is inadequate to resolve the question of whether pesticides contribute to breast cancer. Ecologic studies have well-known limitations (Rothman and Greenland 1998), and the occupational literature is problematic because it is sparse and vulnerable to confounding by demographic and lifestyle factors, such as physical exercise [discussed by Brody and Rudel (2003)]. Serum studies are limited by their a) use of a single measurement to represent lifetime exposure or exposure during a relevant stage of development, b) use of serum DDE measures to reflect exposure to the more estrogenic parent DDT (this relationship is affected by individual differences in metabolism and excretion and relative intake of the DDT vs. DDE in foods), and c) focus on a small number of pesticides compared with the hundreds currently or historically in use.

Because pesticide exposure is widespread in the general population (Centers for Disease Control and Prevention 2003; Rudel et al. 2003), and breast cancer is the most common cancer in women and the leading cause of cancer death in women 35–54 years of age [National Center for Health Statistics 1997; Surveillance Epidemiology and End Results (SEER) 2004], it remains important to determine whether pesticide exposure contributes to breast cancer risk. Additional studies are needed to assess a wider range of compounds using measurements that capture exposures over different periods in the life course.

Geographic information systems (GIS) are a promising tool for exposure assessment that meets this need, because they can efficiently integrate a) records of locations where pesticides were used; b) models of how these compounds travel in the environment via aerial drift at the time of application or in surface water, groundwater, and soil; and c) locations of individuals at the times and places of likely exposure (Brody et al. 2002; Stellman et al. 2003b; Ward et al. 2000). This approach has several strengths compared with other exposure assessment techniques, such as self-report, which is prone to error and recall bias, and biologic or environmental sampling, which is expensive, limited in the number of agents that can be measured, and typically limited to single and recent samples available for testing.

GIS-based exposure assessment has been used in a small number of epidemiologic studies of pesticides to date. Using the California database of registered pesticide applications, Bell et al. (2001) found an association between risk of fetal death due to congenital anomalies and large-scale pesticide use near the mother’s residence. Using remote sensing to identify areas of crop cultivation, Xiang et al. (2000) found an association between low birth weight and proximity of the mother’s residence to crops. Stellman et al. (2003a) report perhaps the most detailed reconstruction of pesticide exposure using GIS in a study of U.S. troops and Vietnamese civilians exposed to Agent Orange and herbicides in Vietnam.

**Pesticide use and breast cancer on Cape Cod, Massachusetts.** Cape Cod is a sandy peninsula on the Massachusetts coast. The year-round population of 227,000 (U.S. Census Bureau 2000) is roughly doubled by vacationers in the summer (Cape Cod Commission 1998). The population has grown rapidly since the 1980s, with an influx of retirees and, to a lesser extent, Boston commuters (Cape Cod Commission 2003).
The possible role of pesticides in breast cancer etiology is of particular interest on Cape Cod because of a history of elevated breast cancer incidence and distinctive pesticide use. Three different data sources analyzed in the Cape Cod Breast Cancer and Environment Study (Cape Cod Study) provide evidence of elevated risk that is not explained by mammography or established breast cancer risk factors. Massachusetts Cancer Registry (MCR) data showed age-adjusted breast cancer incidence was approximately 20% higher on Cape Cod compared with the rest of the state from 1982, when MCR began, through 1994 (Silent Spring Institute 2000). The Collaborative Breast Cancer Study showed 21% higher risk for Cape Cod women 50–74 years of age compared with other Massachusetts women after controlling for a comprehensive list of established and suggested risk factors, including family history, reproductive history, use of pharmaceutical hormones and alcohol, and aspects of diet (Silent Spring Institute 1997). The Cape Cod Study showed higher breast cancer risk associated with longer years of residence on Cape Cod after controlling for established risk factors (McKevy et al. 2004).

Mortality has not been elevated on Cape Cod. Although this suggests the logical possibility that increased incidence could be due to a higher rate of diagnoses through greater mammography use rather than to a higher underlying rate of disease, existing evidence does not support this explanation. A Massachusetts state survey in the mid-1990s showed that 88% of Cape Cod women had ever had a mammogram compared with 89% in the rest of Massachusetts, and Cape Cod women were about 6% less likely to report a mammogram within the last year (Massachusetts Department of Public Health 1997). The proportion of cases diagnosed at earlier stages (an indicator of mammography use) was lower on Cape Cod than in the rest of the state in years when incidence was most elevated (Silent Spring Institute 1998).

Previous research also has shown that pesticides were applied widely on Cape Cod to support tourism, cranberry cultivation, and other agriculture (Brody et al. 2002). Forests were repeatedly sprayed for gypsy moths and other tree pests, and wetlands were sprayed for mosquito control. Other wide-area uses include golf course and rights-of-way management. Persistent organochlorine chemicals were used from the late 1940s to the mid-1970s, and less persistent compounds, including carbaryl, malathion, and carbamates, have been applied in more recent years (Brody et al. 2002). Table 1 lists pesticides applied by type of use. Maps of pesticide use areas and residential land use are accessible in the study’s on-line atlas (Silent Spring Institute 2000). Testing of air and dust samples from 120 Cape Cod homes identified 27 pesticides (Rudel et al. 2003). A comparison of dust samples from Cape Cod; Detroit, Michigan; Iowa; Long Island, New York; Los Angeles, California; Seattle, Washington; and Yuma County, Arizona, indicates that household levels of DDT, carbaryl, chlordane, methoxychlor, propoxur, and pentachlorophenol were higher on Cape Cod, whereas levels of diazinon and permethrin were lower (Rudel et al. 2003).

The present study. We investigated breast cancer risk associated with residential proximity to wide-area pesticide use on Cape Cod in a case–control study of 1,165 women diagnosed with breast cancer in 1988–1995 and 1,016 controls. Exposure was assessed by historical reconstruction and GIS-based modeling of pesticide applications for tree pests, cranberry bogs, other agriculture, and mosquito control. This approach adds to previous studies by including a wide range of persistent organochlorine pesticides and less persistent current-use compounds, assessing exposures yearly based on historical pesticide application data and residential history dating back to 1948, evaluating risk in a region with a history of unexplained higher incidence, and demonstrating the use of newly developed GIS exposure assessment methods that can be applied in other studies.

Materials and Methods

Study population. Women who were permanent residents of Cape Cod for at least 6 months at the time of an invasive breast cancer diagnosis in 1988–1995 and whose diagnosis was reported to the MCR were eligible cases. MCR verifies diagnoses by medical and pathologic record review and reports nearly complete ascertainment for breast cancer (Massachusetts Department of Public Health 1995).

Controls were selected from women who were permanent residents of Cape Cod for at least 6 months in 1988–1995. They were frequency matched to cases on date of birth in decades and vital status. Living controls identified 27 pesticides (Rudel et al. 2003). A comparison of dust samples from Cape Cod; Detroit, Michigan; Iowa; Long Island, New York; Los Angeles, California; Seattle, Washington; and Yuma County, Arizona, indicates that household levels of DDT, carbaryl, chlordane, methoxychlor, propoxur, and pentachlorophenol were higher on Cape Cod, whereas levels of diazinon and permethrin were lower (Rudel et al. 2003).

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Table 1. Pesticides applied on Cape Cod, Massachusetts, for tree pests, cranberry cultivation, and mosquito control, 1948–1995.

| Use                  | Pesticides                                                                 |
|----------------------|-----------------------------------------------------------------------------|
| Tree pests           | DDT, daconil, dieldrin, gordona, malathion, methoxychlor, Sevin, Sevin-4-oil, Sevin XLR, Sevin XLR Plus |
| Cranberry cultivation| 2,4-D, 2,4,5-T, 2,4,5-TP, acephate, aldrin, aminiochlorazol, azinphos-methyl, carbaryl, chlordane, chlorothalonil, chlorpropham, chlorpyrifos, cupric hydroxide, dalapon, DDT, diazinon, dichlobenil, dieldrin, diquat, ethephon, ferbam, fluor neurop-butyl, glyphosate, heptachlor, kerosene/fuel oil as agent, malathion, mancozeb, methoxychlor, napropamide, naptalam, nufilmur, p-dichlorobenzene, parathion, phthalan, piperonyl butoxide, propargite, pyrethrum soap/dust, rotenone, ryania, seltiophyllum, simazine, Stoddard solvent, thiram, triclopyr, zineb, ziram |
| Mosquito control     | Atabate (temephos), DDT, methoxychlor |

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid.

Table 2. Selection and participation of breast cancer cases and controls.

| Study characteristics | Cases No. (%) | Medicare No. (%) | Deceased No. (%) | Random-digit-dial No. (%) |
|-----------------------|--------------|------------------|-----------------|------------------------|
| Full study            |              |                  |                 |                        |
| Selected and eligible | 1,578        | 806              | 355             | 342                    |
| Excluded              |              |                  |                 |                        |
| Never located or contacted | 228 (14) | 71 (9)           | 56 (16)         |                         |
| Refused               | 185 (12)     | 239 (30)         | 51 (14)         | 70 (20)                |
| Interviewed           | 1,165 (74)   | 496 (62)         | 248 (70)        | 272 (80)               |
| Interviewed in PCE study | Selected and eligible | 704 | 348 | 175 | 167 |
| Excluded              |              |                  |                 |                        |
| Never located or contacted | 74 (11) | 16 (5)           | 20 (11)         |                         |
| Refused in PCE study  | 53 (8)       | 77 (22)          | 19 (11)         | 33 (20)                |
| Unable to contact for sharing | 28 (4) | 13 (4)           | 14 (8)          | NA*                    |
| Refused to share      | 22 (3)       | 27 (8)           | 21 (1)          | NA*                    |
| Excluded              |              |                  |                 |                        |
| Interviewed in Cape Cod Study | Selected and eligible | 876 | 453 | 178 | 175 |
| Interviewed           |              |                  |                 |                        |
| Selected and eligible | 128 (15)     | 39 (9)           | 20 (11)         |                         |
| Excluded              | 110 (13)     | 133 (29)         | 30 (17)         | 37 (21)                |
| Interviewed           | 638 (73)     | 281 (62)         | 128 (72)        | 138 (79)               |

— The random digit dialing procedure did not allow us to determine the number of eligible women whose telephone numbers were randomly selected but who were not reached by interviewers.

*MCX allowed sharing of information regarding PCE study subjects who were identified by random-digit dialing without an additional consent procedure, because we had no identifying information to recontact these subjects.
< 65 years of age were selected using random digit dialing. Living controls ≥ 65 years of age were selected randomly from lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS; Baltimore, MD). Deceased controls were selected randomly from Massachusetts Registry of Vital Records and Statistics (Boston, MA) death certificates for residents in the appropriate age categories who died after January 1988.

For cases and controls not identified by random digit dialing, addresses were obtained from MCR, CMS, the National Death Index (NDI; Hyattsville, MD), town books, telephone books, Internet directories, telephone directory assistance, and the Massachusetts Registry of Motor Vehicles (Boston, MA). Next of kin were identified from death certificates and obituaries as proxies for deceased participants and traced using similar methods. Cases, controls, and proxies for whom addresses were obtained were sent a letter about the study before telephone contact. Informed consent was obtained at the outset of telephone interviews.

Cases diagnosed in 1988–1993 in eight towns and their controls were interviewed in 1997–1998 in a study of breast cancer and tetrachloroethylene (PCE) in drinking water (Aschengrau et al. 2003). Cases diagnosed in 1994–1995 in those towns and in 1988–1995 in the remaining seven towns and their controls were interviewed in 1999–2000. Permissions to use confidential data were obtained from the Massachusetts Department of Public Health Human Research Review Committee. MCR, CMS, NDI, the Boston University Institutional Review Board, and review boards at hospitals where cases were diagnosed. In accordance with MCR policies, Boston University recontacted participants in the PCE study to obtain their informed consent to use data in the present study.

Among 1,578 eligible cases, 1,165 (74%) participated, 228 (14%) were never located or contacted, and 185 (12%) refused to participate. Among 1,503 eligible controls, 1,016 (68%) participated. Data on selection and participation of study participants are shown in Table 2. Participants and nonparticipants were similar in age, race, and town of residence. Among PCE study participants, 9% of cases and 14% of controls could not be located or refused permission to use their data. Aschengrau compared PCE study participants who were included versus not included in the present study and found the groups similar for vital status at interview, age at diagnosis or referent year, family history of breast cancer, age at first live or stillbirth, and race (data not shown). PCE study participants included in the present study had somewhat lower occurrence of a prior breast cancer than those not included (5 vs. 10%; p = 0.09) and were more educated (10% of included and 20% of not included participants had less than high school education; p = 0.01).

After interviewing, controls were assigned reference years according to the distribution of diagnosis years among the cases. If a control had moved to Cape Cod after the randomly assigned reference year, she was considered ineligible and excluded from analyses (n = 71). Exposures after diagnosis (for cases) or referent year (for controls) were excluded as not etiologically relevant.

Interviews. Trained interviewers asked about women’s Cape Cod addresses and years of residence from birth or 1948 (whichever was later) to the interview date. We chose 1948 as the beginning of the exposure period because it was the first year of spraying with DDT on Cape Cod (Brody et al. 2002). Interviews included established and hypothesized risk factors for breast cancer: family history of breast cancer (in a mother, sister, or daughter), menstrual and reproductive history, height and weight, alcohol and tobacco use, physical activity, pharmaceutical hormone use, and education. Interviews assessed home pesticide use, which will be reported separately and is considered here as a possible confounder.

GIS assessment of exposure from wide-area pesticide application. Exposure was assessed using historical records and GIS (Brody et al. 2002). Records include locations and other data (e.g., dates, specific agents, application rates) for tree pest control, mosquito control on wetlands, cranberry cultivation, other agriculture (typically truck farms growing vegetables), golf courses, and right-of-way maintenance. Locations of spraying for tree pest control were obtained from towns, state, and federal agencies. Locations for the other uses were obtained from aerial photographs taken in 1951, 1971, 1984, and 1990 (MacConnell 1975; MacConnell et al. 1984; Massachusetts Executive Office of Environmental Affairs 2001).

Geocoding of residential addresses. Women’s residential addresses on Cape Cod were incorporated into the GIS by “geocoding” each address to a latitude and longitude. We mapped addresses wherever possible to the center of a visible residential rooftop using town parcel maps and the state base map for Massachusetts, which is 0.5 m resolution Color Ortho Imagery (Massachusetts Executive Office of Environmental Affairs 1995). Mapping to a rooftop has the advantage of more accurately defining residential positions in larger parcels, which are common on Cape Cod.

Addresses that could not initially be geocoded were researched using county deeds, telephone books, town books, and vital statistics records and then geocoded. If the house could not be identified on the orthophotos, the address was geocoded, if possible, to the center of a cluster of rooftops in the parcel or the center of the parcel if no rooftops were visible. Addresses identified by a cross street or landmark rather than a numerical address were geocoded using the following rules in descending order: to the nearest rooftop, to the center of the nearest parcel, or to the middle of the street if the street was less than a mile long. Addresses that could not be located with this level of accuracy were not geocoded.

Among 3,794 addresses reported, 83% were geocoded to exact addresses. Of these, 90% were matched to a rooftop and 10% to the center of the parcel. The accuracy of geocoding is better for more recent than earlier addresses, because street numbers became more common (Table 3). “Move in” and “move out” years were linked to each address to allow for analysis of exposures during intervening years.

Exposure calculations. Relative exposure intensities were calculated for the six wide-area pesticide uses, based on modeling of drift and deposition. The modeling and development of exposure measures is fully described by Brody et al. (2002) and summarized here. Relative exposure intensity is a proxy for exposures via all routes and is designed to be proportional to actual exposures in order to rank exposures correctly.

We attempted to aggregate “like” exposures and differentiate “unlike” exposures. Exposure variables are shown in Table 4. We calculated exposures separately by the purpose of use, because these categories correspond to typically different sets of chemicals and frequency and method of application. For example, tree pest spraying was typically a single active ingredient applied once or twice a year, whereas cranberry bogs were typically treated many times a season with multiple active ingredient mixtures. We separately aggregated

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Table 3. Geocoding accuracy for participant addresses by decade.9

| Address match status | No. (%) |
|----------------------|---------|
| ≤ 1990               |         |
| Rooftop, parcel      | 85 (37) |
| Cross street, landmark, street | 108 (47) |
| Not geocoded         | 38 (16) |
| 1961–1970            |         |
| Rooftop, parcel      | 135 (50) |
| Intersection, landmark, street | 103 (38) |
| Not geocoded         | 31 (12) |
| 1971–1980            |         |
| Rooftop, parcel      | 322 (62) |
| Intersection, landmark, street | 141 (27) |
| Not geocoded         | 59 (11) |
| 1981–1990            |         |
| Rooftop, parcel      | 1,255 (90) |
| Intersection, landmark, street | 109 (6) |
| Not geocoded         | 27 (2) |
| 1991–2000            |         |
| Rooftop, parcel      | 1,396 (97) |
| Intersection, landmark, street | 31 (2) |
| Not geocoded         | 8 (1)   |

9 Each participant’s address is classified by the most recent year she lived there.
exposures corresponding to persistent organochlorine chemicals and less persistent compounds because these classes differ in their environmental fate and toxicologic properties. For many tree pest applications, records identify the specific pesticide, and the spray event was appropriately categorized regardless of date. If the active ingredient was not known, we grouped pesticides applied in 1948–1974 as persistent organochlorines, and in 1975 and later as less persistent (Brody et al. 2002). We estimated exposures to residues from persistent pesticides during the years after they were applied. For cranberry bogs and other agriculture, we estimated exposure with and without taking into account whether homes were protected from pesticide drift (i.e., were unexposed or less exposed) by a tree buffer of at least 10 m between the pesticide use area and the residence.

We used different algorithms to calculate exposures from predominantly aerial- and ground-based applications (Brody et al. 2002). For aerial applications, which were used for tree pests and cranberry bogs, we used local climate data, the Spray Drift Task Force AgDRIFT model (Teske et al. 1997), and the U.S. Environmental Protection Agency (EPA) Industrial Source Complex Short-Term (ISCT3) air model (Kumar et al. 1999; U.S. EPA 1995) to develop the following algorithm:

\[ RE = bX^{c\ln A}d, \]

where \( RE \) = relative exposure; \( X \) = distance from edge of sprayed area; \( A \) = size of sprayed area; and \( b, c, d \) = direction-dependent constants derived to account for northeast, southeast, northwest, and southwest wind directions. These constants differ between the cranberry bog and tree pest models because aircraft height, which affects drift distance, is higher above trees than above bogs. We used wind direction data for early morning hours in spring when pesticides were applied, and the wind pattern is similar for July through August. We tested the sensitivity of the algorithm to assumptions about the droplet size distribution, and model output differed by a factor of \( \leq 2 \). For uses that were typically ground based (mosquito control and agriculture other than cranberries; Sakolski G, personal communication), we calculated relative exposure intensity as the inverse distance squared from a residence to the edge of the pesticide use area. Exposures from golf courses and rights-of-way were not calculated, because few women were exposed from these sources.

Relative exposure intensity was calculated for each type of pesticide use for each residence in each year the woman lived at that address. A woman’s exposures were then summed for each type of use across all of her Cape Cod addresses during the exposure assessment years (1948 to diagnosis/reference year). These scores (\( \Sigma \) relative exposure intensity at an address multiplied by years at that address) are the exposure estimate used in odds ratio (OR) analyses.

We did not calculate exposures for residues from tree pest spraying, because these exposures are dominated by two Cape-wide spray events in the late 1940s and mid-1950s. Because all Cape Cod addresses were exposed, relative exposure does not vary geographically and simply represents the number of years a woman lived on Cape Cod, which has been analyzed separately (McKelvey et al. 2004).

We imputed exposure at addresses that were geocoded to the middle of a street. We identified residential parcels on the street from the land use map for the closest year, calculated relative exposure intensity for residential parcels, and assigned the mean. Weinberg et al. (1996) describes a similar method in a radon study.

Data analysis. We used unconditional logistic regression to calculate crude and adjusted ORs and 95% confidence intervals (CIs) for each source of pesticide exposure and breast cancer. Statistical tests for trend were conducted to assess a dose–response relationship. The reference group for each exposure consisted of women classified as unexposed for that variable. The following matching variables and potential confounders were controlled in all adjusted OR analyses based on a priori consideration of the research design, well-established breast cancer risk factors, and the completeness of data: age as a continuous term, birth decade (six categories), PCE versus Cape Cod Study, vital status, year of diagnosis/reference year, prior breast cancer, age at first diagnosis, and reference year. These scores (\( \Sigma \) relative exposure intensity at an address multiplied by years at that address) are the exposure estimate used in odds ratio (OR) analyses.

### Table 4. Wide-area pesticide exposure variables, by chemical class, for which ORs were calculated.

| Source | Persistent organochlorines at the time of application: 1948–1974 | Residues of persistent organochlorines in years after they were applied: 1949–1995 | Less persistent compounds at the time of application: 1975–1995 |
|--------|-------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------|
| Aerial application | | | |
| Tree pests | Yes | — | — |
| All cranberry bogs | Yes | Yes | Yes |
| Cranberry bogs not buffered by trees | Yes | Yes | Yes |
| Ground application | | | |
| Other agriculture | Yes | Yes | Yes |
| Mosquito control in wetlands | Yes | Yes | Yes |
| Other agriculture not buffered by trees | Yes | Yes | Yes |

*Not calculated because Cape-wide spraying results in lack of geographic variation in relative exposure intensity within the Cape. *Models assuming 5-year latency and 5-year tumor promotion periods were also analyzed. *Not calculated because biologic pest control was adopted during this period.

### Table 5. Associations between established risk factors and breast cancer.

| Risk factor | Cases (n = 1,165) | Controls (n = 1,016) | Adjusted OR (95% CI)* |
|-------------|------------------|---------------------|-----------------------|
| Family history of breast cancer | | | |
| No | 795 (68) | 789 (76) | 1.0 (referent) |
| Yes | 293 (25) | 192 (19) | 1.4 (1.2–1.8) |
| Unknown | 77 (7) | 55 (5) | |
| Prior breast cancer | | | |
| No | 1,074 (92) | 919 (90) | 1.0 (referent) |
| Yes | 80 (7) | 89 (8) | 0.7 (0.5–0.9) |
| Unknown | 11 (1) | 8 (1) | |
| Education | | | |
| < High school graduate | 76 (6) | 90 (9) | 1.0 (referent) |
| High school graduate | 380 (33) | 332 (33) | 1.5 (1.0–2.0) |
| 1–3 years college/vocational school | 355 (30) | 308 (30) | 1.5 (1.0–2.1) |
| College graduate | 199 (17) | 166 (16) | 1.5 (1.1–2.3) |
| Graduate work/degree | 144 (12) | 119 (12) | 1.5 (1.0–2.3) |
| Unknown | 11 (1) | 8 (1) | |
| Age at first live or stillbirth | | | |
| < 20 | 80 (7) | 83 (8) | 1.0 (referent) |
| 20–29 | 648 (56) | 634 (62) | |
| ≥ 30 | 175 (15) | 121 (12) | 1.5 (1.2–1.8)* |
| Nulliparous | 246 (21) | 189 (17) | |
| Unknown | 18 (2) | 9 (1) | |

*Adjusted ORs calculated from a model include age as a continuous term, decade of birth (six categories), PCE study versus Cape Cod Study, vital status, year of diagnosis/reference year, education (five categories), family history of breast cancer, previous diagnosis of breast cancer, age at first birth (≥ 30 years of age or nulliparous vs. < 30 years of age). Women with missing values for education or age at first birth were excluded (n = 36); missing values for family history or previous diagnosis of breast cancer were assumed to be negative. *First-degree female relative diagnosed with breast cancer. For cases, prior breast cancer is a diagnosis before the diagnosis that resulted in selection for this study; for controls, prior breast cancer is a diagnosis before the diagnosis. Statistical tests for trend were conducted to assess a dose–response relationship. The reference group for each exposure consisted of women classified as unexposed for that variable. The following matching variables and potential confounders were controlled in all adjusted OR analyses based on a priori consideration of the research design, well-established breast cancer risk factors, and the completeness of data: age as a continuous term, birth decade (six categories), PCE versus Cape Cod Study, vital status, year of diagnosis/reference year, prior breast cancer, age at first diagnosis, and reference year. These scores (\( \Sigma \) relative exposure intensity at an address multiplied by years at that address) are the exposure estimate used in odds ratio (OR) analyses.
were at least five exposed cases and five exposed controls. We estimated ORs ignoring latency and assuming a 5-year latency period and a 5-year promotion period. In the latency analysis, we consider only exposures > 5 years before diagnosis/referee year. In the promotion analysis, we consider only exposures ≤ 5 years before diagnosis/referee year. The latency and promotion analyses are limited to less persistent pesticides, because use of the persistent pesticides ended > 5 years before the earliest breast cancer diagnosis.

Results

Characteristics of cases and controls. Study participants were predominantly white (98%), 60–80 years of age with a high school or higher education; 72% of cases and 76% of controls were living at the time of interview. As expected, more cases (25%) than controls (19%) reported a family history of breast cancer. Most (59%) were born in Massachusetts, including 6% of cases and 7% of controls born on Cape Cod. Characteristics of cases and controls and ORs for potential confounders included in adjusted models are shown in Table 5.

Years of Cape Cod residence at geocoded addresses. We assessed missing exposure data by examining the number and percentage of years during the relevant exposure period that women lived a) on Cape Cod, b) at addresses where wide-area pesticide exposure could be assessed (including addresses with imputed exposures), and c) at addresses geocoded to a rooftop or parcel (excluding addresses with imputed exposures). Results are shown in Table 6. On average, the women lived on Cape Cod for 17 (controls) to 18 (cases) years of the exposure period, representing 40% (controls) to 42% (cases) of the exposure period. More than 95% of the exposure years when women lived on Cape Cod were geocoded to a rooftop or parcel. Ten percent of participants lived at least 90% of exposure years on the Cape; about half lived at geocoded addresses for 15 continuous years before diagnosis or reference year.

Breast cancer risk. Associations between wide-area pesticide application and breast cancer were inconsistent across different exposure sources and statistically unstable. Results did not change much after adjustment for possible confounders, so only adjusted ORs are presented. Results are shown in Table 7.

Considering ORs for pesticide exposure during the persistent pesticide years (1948–1974), breast cancer risk is somewhat increased with exposure from some sources but not others. For exposure from living near cranberry bogs, adjusted ORs show increasing risk for increasing exposure across the three exposure levels for relative intensity ≥ 0.001 (ORs = 1.2, 1.4, and 1.8); however, risk estimates are statistically unstable. For exposure from tree pest spraying, adjusted ORs are slightly elevated and unstable (ORs = 1.3 and 1.2). No consistent pattern is observed for proximity to mosquito

Table 6. Number and percentage of possible exposure years when women lived on Cape Cod and at an address geocoded to a rooftop or parcel (n = 1,139 cases, 1,008 controls).

|                          | No. of exposure years | Mean ± SD | Minimum | 25th | 50th | 75th | 90th | Maximum |
|--------------------------|-----------------------|-----------|---------|------|------|------|------|---------|
| Possible exposure yearsa | Cases                 | 43 ± 3    | 28      | 41   | 43   | 45   | 47   | 47      |
|                          | Controls              | 43 ± 3    | 27      | 41   | 43   | 45   | 47   | 47      |
| Exposure years when women lived on Cape Cod | Cases | 18 ± 12 | 0.50 | 0.50 | 16 | 25 | 40 | 47 |
|                          | Controls              | 17 ± 12   | 0.50   | 0.50 | 15  | 24  | 39  | 47      |
| Years for which relative exposure was assessedb | Cases | 18 ± 12 | 0.50 | 0.50 | 16 | 25 | 40 | 47 |
|                          | Controls              | 17 ± 12   | 0.50   | 0.50 | 14  | 23  | 39  | 47      |
| Exposure years at an address geocoded to a rooftop or parcel | Cases | 17 ± 12 | 0.00 | 0.00 | 8.0 | 24 | 38 | 47 |
|                          | Controls              | 16 ± 12   | 0.00   | 0.00 | 6.0 | 22  | 36  | 47      |

*Years from the beginning of exposure assessment period in 1948 (or the woman’s birth year if later) to diagnosis/reference year; the maximum value of 48 years occurs for a woman born in 1947 or earlier and diagnosed in 1995. *Includes addresses where the exposure was imputed because the address could not be geocoded to a rooftop or parcel. *Percentage is calculated for an individual woman based on her own “possible exposure years.”
control or agricultural land other than bogs; adjusted ORs are mostly less than one and unstable.

No consistent association is seen between breast cancer and residues from persistent pesticides. These adjusted ORs are generally below one and statistically unstable.

Table 7. Associations between exposure to wide-area pesticide application on Cape Cod, Massachusetts, and breast cancer.

| Exposure source | Σ RE intensities across years | Cases | Controls | Adjusted OR (95% CI) | p-Trend |
|-----------------|-------------------------------|-------|----------|----------------------|---------|
| Persistent pesticides at application | | | | | |
| Aerial application | | | | | |
| Cranberry bogs | Not exposed | 1,027 | 908 | 1.0 (referent) | 0.69 |
| < 0.001 | 15 | 24 | 0.8 (0.4–1.6) |
| 0.001 to < 0.01 | 36 | 31 | 1.2 (0.7–2.1) |
| 0.01 to < 0.1 | 41 | 29 | 1.4 (0.7–2.5) |
| ≥ 0.1 | 20 | 14 | 1.8 (0.7–4.5) |
| Tree pests | Not exposed | 949 | 866 | 1.0 (referent) | 0.91 |
| < 18 | 83 | 57 | 1.3 (0.8–2.0) |
| ≥ 18 | 107 | 83 | 1.2 (0.7–1.8) |
| Ground application | | | | | |
| Other agriculture | Not exposed | 1,030 | 908 | 1.0 (referent) | 0.50 |
| < 0.001 | 72 | 56 | 0.9 (0.6–1.4) |
| 0.001 to < 0.01 | 19 | 19 | 0.6 (0.3–1.4) |
| 0.01 to < 0.1 | 8 | 12 | 0.5 (0.2–1.4) |
| ≥ 0.1 | 10 | 11 | 0.3 (0.2–2.3) |
| Wetlands | Not exposed | 1,077 | 945 | 1.0 (referent) | 0.83 |
| < 0.01 | 30 | 36 | 0.8 (0.4–1.6) |
| 0.01 to < 0.1 | 23 | 14 | 1.6 (0.7–3.7) |
| ≥ 0.1 | 9 | 14 | 0.4 (0.2–1.5) |

Residues from persistent pesticides

| Exposure source | Σ RE intensities across years | Cases | Controls | Adjusted OR (95% CI) | p-Trend |
|-----------------|-------------------------------|-------|----------|----------------------|---------|
| Aerial application | | | | | |
| Cranberry bogs | Not exposed | 822 | 700 | 1.0 (referent) | 0.26 |
| < 0.01 | 33 | 42 | 0.7 (0.4–1.2) |
| 0.01 to < 0.1 | 59 | 71 | 0.8 (0.5–1.2) |
| 0.1 to < 1 | 132 | 112 | 1.1 (0.7–1.6) |
| 1 to < 10 | 71 | 54 | 0.9 (0.5–1.7) |
| 10 to < 100 | 17 | 21 | 0.4 (0.1–1.2) |
| ≥ 100 | 5 | 6 | 0.2 (0.2–2.5) |
| Ground application | | | | | |
| Other agriculture | Not exposed | 640 | 567 | 1.0 (referent) | 0.55 |
| < 0.01 | 67 | 67 | 0.9 (0.6–1.3) |
| 0.01 to < 0.01 | 187 | 152 | 1.0 (0.7–1.3) |
| 0.01 to < 0.1 | 138 | 99 | 1.1 (0.8–1.5) |
| 0.1 to < 1 | 45 | 42 | 1.0 (0.6–1.7) |
| 1 to < 10 | 8 | 17 | 0.5 (0.2–1.2) |
| 10 to < 100 | 23 | 26 | 0.7 (0.4–1.4) |
| ≥ 100 | 31 | 36 | 0.8 (0.4–1.3) |
| Wetlands | Not exposed | 1,012 | 881 | 1.0 (referent) | 0.43 |
| < 0.1 | 47 | 47 | 1.1 (0.7–1.9) |
| 0.1 to < 1 | 48 | 54 | 0.7 (0.5–1.2) |
| 1 to < 10 | 14 | 9 | 1.1 (0.4–3.0) |
| 10 to < 100 | 10 | 8 | 1.7 (0.6–5.5) |
| ≥ 100 | 8 | 7 | 1.8 (0.5–6.8) |

Less persistent pesticides

| Exposure source | Σ RE intensities across years | Cases | Controls | Adjusted OR (95% CI) | p-Trend |
|-----------------|-------------------------------|-------|----------|----------------------|---------|
| Aerial application | | | | | |
| Cranberry bogs | Not exposed | 929 | 802 | 1.0 (referent) | 0.24 |
| < 0.001 | 36 | 41 | 1.1 (0.6–2.0) |
| 0.001 to < 0.01 | 58 | 68 | 0.8 (0.5–1.3) |
| 0.01 to < 0.1 | 62 | 64 | 1.1 (0.6–1.8) |
| ≥ 0.1 | 33 | 31 | 1.2 (0.6–2.8) |
| Tree pests | Not exposed | 1,107 | 987 | 1.0 (referent) | 0.26 |
| < 1 | 20 | 11 | 1.7 (0.8–3.7) |
| ≥ 1 | 12 | 8 | 1.6 (0.6–4.0) |
| Ground application | | | | | |
| Other agriculture | Not exposed | 921 | 844 | 1.0 (referent) | 0.63 |
| < 0.001 | 191 | 140 | 1.5 (1.1–1.9) |
| 0.001 to < 0.01 | 22 | 14 | 1.8 (0.9–3.7) |
| ≥ 0.01 | 5 | 8 | 0.9 (0.3–3.0) |

*RE is defined by equation 1. Adjusted for age as a continuous term, birth decade (six categories), PCE study versus Cape Cod Study, vital status, year of diagnosis/reference year, age at reference year, previous breast cancer diagnosis, age at first birth (≥ 30 years of age or nulliparous vs. < 30 years of age), family history of breast cancer, education (five categories), exposure-relevant years on Cape Cod, and other exposures listed in this table.
Discussion

Results of this population-based case-control study do not show an overall pattern of association between residential exposure to wide-area pesticide application on Cape Cod since 1948 and breast cancer diagnosed there in 1988–1995. We did not find consistent dose–response trends or consistency within categories of exposure, including the chemical type (persistent, residue from persistent, or less persistent), method of application (aerial or ground), and type of use (e.g., cranberry cultivation, tree pest control). These findings are consistent with results of many recent studies of certain organochlorine pesticides and breast cancer (Gammon et al. 2002, Laden et al. 2001; Snedeker 2001), although associations have been reported in some others (Charlier et al. 2003; Cohn et al. 2002; Aschengrau et al. 1996). The present study adds to this literature by using novel GIS-based methods that assess exposures to mixtures of many chemicals from multiple types of use over many years. Other strengths of the study include the relatively large number of participants and the extensive interview data that allow for control of confounding.

Although there was lack of consistency overall, we observed some suggestive associations. These are reviewed below, followed by discussion of the strengths and weaknesses of the GIS exposure assessment.

Persistent pesticides. We observed somewhat increased risk associated with persistent pesticides applied aerially (i.e., for cranberry bogs and tree pests), and risk increased with increasing exposure across the top three of four exposure categories for cranberry bogs (adjusted ORs = 0.8, 1.2, 1.4, and 1.8), although not for tree pests (adjusted ORs = 1.3 and 1.2). As expected, risk was higher for women in residences with no tree buffer to protect them from pesticide drift. However, no increased risk was seen for exposure to persistent pesticides from ground application (i.e., for other agriculture and mosquito control in wetlands).

The differing results for aerial and ground-based persistent pesticides could be because cranberry bog and tree pest applications used chemicals similar to each other and different from the ground-based preparations, because application practices resulted in higher exposures, or because of chance. The increased risk associated with living near a cranberry bog at the time of persistent pesticide application was greater than was observed in a previous study that reported a 20–30% increased breast cancer risk for women diagnosed in 1983–1986 and living within 2,600 ft of a cranberry bog in the five towns of Upper Cape Cod, with no latency (adjusted OR = 1.2; 95% CI, 0.8–1.6) and with 15 years latency (adjusted OR = 1.3; 95% CI, 0.9–2.0; Aschengrau et al. 1996). Results may be different because the earlier study did not distinguish between exposures to persistent and less persistent pesticides.

Residual exposure from persistent pesticides. We found no pattern of association between breast cancer and residual exposures from persistent pesticides. Residual exposures are not well modeled in this study, however, because we did not account for rates of decay or transformation of the originally applied compounds to compounds with different toxicologic characteristics.

Less persistent current-use pesticides. For exposures to less persistent current-use pesticides, we found some evidence of increased risk associated with exposure from spraying for tree pests and agriculture other than cranberry bogs, although we saw no increased risk for the small number of women (n = 13) with the highest exposure from agriculture. Although results provide only weak evidence of an association and may be attributed to chance, they warrant follow-up because the current-use pesticides result in ongoing and common exposures and have not been studied much by others. In one study that did include current-use pesticides, Duell et al. (2000) reported elevated risk among women who reported being in fields during or shortly after application (OR = 1.8; 95% CI, 1.1–2.8) and for those who said they did not use protective clothing while applying the chemicals (OR = 2.0; 95% CI, 1.0–4.3). The lack of an association in the present study for current-use pesticides applied on cranberry bogs may be due to the adoption of chemigation (application via irrigation systems) during this time period, which most likely reduces the extent of exposure.

Strengths and weaknesses of GIS exposure assessment. The GIS-based exposure assessment represents a new approach with a different set of strengths and weaknesses than the predominant method for studying pesticides and breast cancer, which has relied on one-time serum measures of persistent organochlorines, notably DDT/DDE, chlordane, and dieldrin. Serum measures have the advantage of reflecting individual-level biologic processes and all sources of exposure, including wide-area, home-use, occupational, and dietary sources. However, serum measurements are limited to a small number of persistent compounds and leave many plausibly relevant exposures unstudied because of cost and intrusiveness, lack of chemical analytical methods for some compounds, and the rapid diminution of current-use pesticides from the body. Individual differences in metabolism and excretion result in measures that may not represent original exposure levels, particularly when the assessment is many years after exposure.

In contrast, the GIS measures in this study assess exposures to real-world mixtures of many chemicals. Both current-use and banned pesticides were included, and exposures were

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Table 8. Associations between exposure to wide-area application of less persistent pesticides on Cape Cod, Massachusetts, and breast cancer, with 5-year latency and 5-year tumor promotion assumptions.

| Exposure source | Σ RE intensities across years | Cases | Controls (95% CI) | p-Trend |
|----------------|-----------------------------|-------|------------------|--------|
| **Assuming 5-year latency period** | | | | |
| Cranberry bogs | Not exposed | 975 | 859 | 1.0 (referent) | 0.40 |
| | < 0.001 | 26 | 31 | 0.8 (0.5–1.4) |
| | 0.001 to < 0.01 | 53 | 47 | 1.0 (0.7–1.5) |
| | 0.01 to < 0.1 | 66 | 51 | 1.2 (0.8–1.7) |
| | ≥ 0.1 | 19 | 18 | 0.9 (0.5–1.6) |
| Tree pests | Not exposed | 1,117 | 989 | 1.0 (referent) | 0.54 |
| | > 0 | 22 | 17 | 1.2 (0.6–2.2) |
| Other agriculture | Not exposed | 971 | 880 | 1.0 (referent) | 0.41 |
| | < 0.001 | 150 | 110 | 1.3 (1.0–1.7) |
| | ≥ 0.001 | 18 | 16 | 1.2 (0.6–2.4) |
| **Assuming 5-year tumor promotion period** | | | | |
| Cranberry bogs | Not exposed | 963 | 825 | 1.0 (referent) | 0.46 |
| | < 0.001 | 34 | 43 | 0.7 (0.4–1.1) |
| | 0.001 to < 0.01 | 69 | 70 | 0.9 (0.6–1.3) |
| | 0.01 to < 0.1 | 59 | 52 | 1.0 (0.7–1.5) |
| | ≥ 0.1 | 14 | 16 | 0.8 (0.4–1.6) |
| Tree pests | Not exposed | 1,127 | 1,001 | 1.0 (referent) | 0.54 |
| | > 0 | 12 | 5 | 2.6 (0.9–7.7) |
| Other agriculture | Not exposed | 944 | 852 | 1.0 (referent) | 0.90 |
| | < 0.001 | 181 | 127 | 1.4 (1.1–1.8) |
| | ≥ 0.001 | 14 | 17 | 0.8 (0.4–1.6) |

RE is defined by equation 1. *Adjusted for age as a continuous term, birth decade (six categories), PCE study versus Cape Cod Study, vital status, year of diagnosis/reference year, age at reference year, previous breast cancer diagnosis, age at first birth (≥ 30 years of age or nulliparous vs. < 30 years of age), family history of breast cancer, education (five categories), exposure-relevant years on Cape Cod, and other exposures listed in this table.
assessed for multiple sources, including applications for tree pests, cranberry bogs, other agriculture, and mosquito control in wetlands. Golf course and right-of-way maintenance was assessed, and we found few women affected by residential exposure.

Although the assessment of mixtures has the advantage of reflecting real exposures, it has the drawback of combining chemicals with different toxicologic properties, perhaps obscuring effects. This limitation may be mitigated by separating exposures that correspond to time periods when particular chemicals dominated (e.g., the organochlorine years 1948–1974) and to types of use (e.g., cranberry cultivation) characterized by relatively consistent use of certain agents.

**Limitations in the application of GIS in this study.** Some of the theoretical strengths of GIS exposure assessment were not fully realized because of limitations in the data. The most significant limitations derive from missing information a) in the underlying GIS database describing pesticide use on the Cape, b) about exposures during years when women lived off Cape Cod, and c) about address locations before universal use of street numbers. Assumptions in environmental models that link environmental data with exposure to individuals and health effects models that link individual exposure to breast cancer are another source of error. For example, our analysis models breast cancer risk as a function of cumulative exposure, but exposure during a particular life stage may be important. These sources of error may lead to exposure misclassification and mispecification of causal relationships.

As described by Brody et al. (2002), the pesticide use database comes from aerial photography and from written records of tree pest spraying, often including maps used by the pilots. We can be confident that the events mapped in the GIS occurred. However, other, unmapped pesticide use is also known to have occurred, so exposure is generally underestimated. The most serious gaps are likely to be town and private spraying for tree pests and mosquitoes. There is an opportunity in future research to evaluate completeness by testing sediment core samples from wetlands. Because sediments are laid down in successive years and remain undisturbed, these samples would provide information about the temporal as well as spatial history of pesticide deposition. Concordance between core samples and GIS exposure measures would support inferences about exposure.

Information about exposures is further limited by the restriction of the GIS to addresses on Cape Cod. We are somewhat reassured about the impact of missing off-Cape exposure data by the finding that adjustment for the number of years women lived on Cape Cod has little impact on the pesticide risk estimates, indicating that the number of years off-Cape is not confounded with pesticide exposure estimates even though women with longer years of residence on the Cape are at higher risk of breast cancer (McKelvey et al. 2004).

We expect greater error in exposure estimates for addresses that were not geocoded to a rooftop or parcel, and lack of street numbers in earlier years means that this type of error is most common during the years of persistent pesticide use. We conducted analyses with and without imputed exposures, and results were similar.

Participants also were exposed to pesticides from sources other than wide-area application on or near their homes, including diet, home use, and occupation. Few women in the study worked in occupations with likely pesticide exposure (5% of cases and 13% of controls). Home pesticide use was common, with 90% of women reporting “frequent” use of at least one type of home pesticide. However, we saw no evidence that home use confounds the relationship between breast cancer and wide-area pesticide exposure, and we had no a priori expectation of confounding. In addition, exposure misclassification results from missing information about other personal behaviors, for example, time spent outside, housekeeping practices, and activities like gardening or golf.

A variety of elements in the environmental models could also lead to exposure misclassification. Although others have validated the aerial drift model, and we tested its sensitivity to changes in certain input parameters, such as spray droplet size and selection of climate data, the model was not tested on Cape Cod. We expect that uncertainties due to application of the drift model to Cape Cod are small compared with uncertainties due to incomplete ascertainment of spray events. Others have demonstrated that a tree buffer reduces exposure, but our assumption that a 10-m tree buffer reduces exposure to zero is imprecise.

Despite these limitations, this GIS method represents the application of advanced computing capability to a long-standing public health approach: examining geographic patterns of disease using proximity as an indicator of exposure. The premise that proximity to pesticide application areas results in residential exposure has been demonstrated in a variety of settings (Fenske et al. 2002; Lu et al. 2000; Simcox et al. 1999). The environmental models we used, borrowing from models developed and validated for regulatory purposes, take advantage of GIS capability to incorporate more complex algorithms than simple distance.

These GIS methods have the potential to address questions about exposures with long latency to disease and during critical periods in the life cycle, because exposure is estimated for every year. For example, in a breast cancer study, we would like to analyze only exposures that occurred before a first pregnancy, when the breast is believed to be more vulnerable. However, in this study, the number of women in subgroups restricted by latency or critical exposure period assumptions was too small to have confidence in these analyses. Failure to take the timing of exposure into account may misclassify causal relationships and produce misleading null results. Similarly, the number of women was too small to pursue the possibility that exposure results in higher risk only for participants with a family history of disease, as was found in a study of pesticides and prostate cancer (Alavanja et al. 2003).

A related limitation is the effect of studying women who lived on Cape Cod in recent years while excluding those who lived there in earlier years and moved away. Out-migration of girls born and raised on the Cape means that information about exposures during early years when more persistent, and perhaps more toxic, compounds were in use and exposures earlier in the life cycle is lost. The GIS contains specific records of selected spray events, including the date, location, chemical, volume, and application method. These records could be used to assess exposures during gestation or childhood, which are hypothesized to affect future breast cancer risk. Women exposed during gestation were ≤ 47 years of age during the diagnosis years in this study and are now ≤ 55, so such a study is somewhat premature.

Furthermore, by studying only women on Cape Cod, we may reduce variability in exposures, because wide-area spraying was extensive, and in outcome, because breast cancer risk is known to be elevated on the Cape. Limited variability could result in failure to detect a real relationship in a study restricted to this region.

**Future use of GIS in health studies.** The environmental data developed here may be used in studies of other health effects on Cape Cod, and the GIS methods are applicable to other settings. They will be most effective when the population remains relatively stable within the geographic extent of the GIS. GIS methods may become more useful as geographically based environmental and health effects databases, such as the California pesticide reporting system and the proposed national health and environment tracking infrastructure, become available (California Environmental Protection Agency 1995; Wakefield 2000). Modernization of cancer registries to incorporate residential history data would improve GIS exposure assessment (Hurley et al. 2003).

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