

SHORT COMMUNICATION

## The scope for biased recall of risk-factor exposure in case-control studies: Evidence from a cohort study of Scottish men

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### Abstract

**Aims:** Case-control studies are prone to recall bias, a participant's case-control status influencing their recall of exposure to risk factors. We aimed to demonstrate empirically the scope for this bias. **Methods:** Two thousand five hundred and fifty men without coronary heart disease at enrolment to a prospective cohort study underwent two health assessments, about 5 years apart. The association between the development of coronary heart disease in the intervening period and changes in reported stress and cigarette smoking were investigated. **Results:** Men admitted to hospital with coronary heart disease reported a greater increase in psychological stress ( $p=0.032$ ) and greater cessation of smoking (22% vs. 10%;  $p=0.007$ ) than men not admitted. Consequently, when exposure data are collected at the end rather than at the start of the follow-up period, coronary heart disease is observed to be more strongly associated with psychological stress, and more weakly associated with smoking. **Conclusions:** At the time when a case-control study is conducted, levels of exposure to risk factors will have been influenced by disease development. When participants are asked about their level of exposure for a previous time period, recall is likely to be influenced by present outcome and exposure status, especially when psychological states are being investigated.

**Key Words:** Bias (epidemiology), case-control studies, coronary disease, psychological stress, risk factors, smoking

### Background

Case-control studies are prone to recall bias, such that a participant's case-control status influences their recall of exposure to risk factors. We have previously suggested [1] that a recent case-control study has overestimated the effect of psychological stress on the occurrence of myocardial infarction, due to people being asked to recall their previous exposure to stress several days after the infarction [2]. In that situation, reports of higher stress exposure among patients may have more to do with the effect of a first heart attack on a person's mental state (myocardial infarction influencing the recall of stress) than with any pathophysiological process triggered by stress (stress causing myocardial infarction).

This report uses data from a prospective cohort study to determine empirically the scope for recall bias. Focusing on men who completed a health

questionnaire and physical examination on two occasions, we investigate how the development of coronary heart disease in the intervening 5-year period influences the reporting of psychological stress and cigarette smoking. Cigarette smoking is included as being a more established risk factor for coronary heart disease, and as being measured more objectively than psychological stress. Subsequently, we discuss how the observed associations between risk factors and coronary heart disease are affected by the time of measurement.

### Material and methods

#### Participants

The data for this analysis come from the West of Scotland Collaborative Study [3,4]. In brief, 6022

men and 1006 women were recruited from a variety of workplaces in the west of Scotland between 1970 and 1973. At enrolment, all members of the cohort were invited to complete a questionnaire and undergo a physical examination. The present analysis is based upon 2550 men aged between 35 and 64 years, without evidence of ischaemia on a six-lead electrocardiogram [3] at enrolment, who underwent a second health screening in 1977, and who provided full data on the variables used in the present analysis. Women were excluded from this analysis because they formed a minority of the cohort and few developed coronary heart disease in the study period.

#### *Exposure measurement*

Psychological stress was measured using the Reeder Stress Inventory [5] (Table I), a measure of daily stress that we have described in detail elsewhere [6]. Current cigarette smokers included men who reported having given up less than 1 year previously [3].

#### *Outcome measurement*

Completion of the Rose Angina Questionnaire [7] (Table I) at the second health screening allowed

men who reported symptoms consistent with "definite angina" to be identified. For analyses using this outcome, 122 men reporting definite angina at the first health screening were excluded. A record linkage with the Scottish Morbidity Records identified those men admitted to hospital between screening assessments, and receiving a hospital discharge diagnosis of coronary heart disease (ICD-9: 410–414).

#### *Statistical analysis*

Logistic regression analyses were used to investigate associations between exposures and outcomes. Adjustment for age at first screening assessment was achieved by including two dummy covariates distinguishing three age groups: <50, 50–54 and 55+ years. Adjustment for additional confounders was not undertaken, as the varying associations between a confounder and, for example, stress at the first assessment, stress at the second assessment and change in stress may have obscured comparisons between the different models required for this investigation. Stata statistical software, version 9, was used for all analyses (StataCorp, College Station, TX, USA).

Table I. Descriptions of the two questionnaire measures used in this study.

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#### **Reeder Stress Inventory**

Please indicate by a tick in the appropriate box in each of the following sections which description fits you best.

1. In general, I am usually tense or nervous.  
THIS DESCRIBES ME:
2. There is a great amount of nervous strain connected with my daily activities.  
THIS DESCRIBES MY SITUATION:
3. At the end of the day I am completely exhausted mentally and physically.  
THIS DESCRIBES ME:
4. My daily activities are extremely trying and stressful.  
THIS DESCRIBES MY ACTIVITIES:

Response options for each item are "Exactly", "To some extent", "Not very accurately", or "Not at all". Possible total scores range from 1 to 8, with higher scores indicating greater daily stress.

#### **Rose Angina Questionnaire**

1. Have you ever had any pain or discomfort in your chest?  
 Yes  No (if no, respondent is directed to skip the following questions)
2. Do you get this pain or discomfort when you walk uphill or hurry?  
 Yes  No
3. Do you get it when you walk at an ordinary pace on the level?  
 Yes  No
4. When you get any pain or discomfort in your chest what do you do?  
 Stop  Slow down  Continue at the same pace
5. Does it go away when you stand still?  
 Yes  No
6. How soon?  
 10 minutes or less  More than 10 minutes
7. Where do you get this pain or discomfort? Mark the place(s) with X on the diagram (diagram of the abdomen)

Definite angina is recorded when responses are YES to question 1, YES to question 2, STOP or SLOW DOWN to question 4, YES to question 5, 10 MINUTES OR LESS to question 6, and the sternum or both left chest and left arm indicated on the diagram. Question 3 distinguishes grade II (YES) and grade I (NO) angina.

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## Results

The mean age of the 2550 men was 48 years (standard deviation 6 years). The mean interval between the two health screens was 5 years (90% range: 4–6 years). At the second health screening, 141 of 2428 men (5.8%) reported symptoms of angina, and 51 of 2550 men (2.0%) had been admitted with coronary heart disease.

An association between the development of angina symptoms and higher psychological stress was apparent whether stress was reported at the onset or conclusion of follow-up (Table II). There was, however, no association between these newly reported symptoms and a greater increase in stress reported at the end of follow-up ( $p=0.64$ ). The expected greater increase in reported stress was observed in those admitted with coronary heart disease, relative to men not so admitted ( $p=0.032$ ). Consequently, very weak evidence of a protective effect of psychological stress measured at the start of follow-up becomes very weak evidence of a harmful effect of psychological stress when measured at the end of follow-up (Table II).

There was evidence of an association between the development of coronary heart disease, whether ascertained from symptoms of angina or hospital admission, and smoking status as reported at the start of the follow-up period (Table II). These associations were weaker with smoking status reported at the end of follow-up, as there was a higher rate of smoking cessation among men reporting symptoms of angina, or admitted with coronary heart disease, than among other men. However, only the latter association was supported by strong statistical evidence ( $p=0.007$ ).

## Discussion

This analysis demonstrates the potential for recall bias in case-control studies, hospital admission with coronary heart disease being followed by reports of higher psychological stress and greater smoking cessation. Consequently, there were discernable differences in the associations between coronary heart disease and these risk factors, depending upon whether risk-factor exposure was measured before or after admission. There was no evidence of angina symptoms impacting upon the reported exposure to stress or smoking, consistent with previous research suggesting that the likelihood of smoking cessation is proportional to the severity of smoking-related disease [8,9].

The experience of heart disease is known to be a source of substantial distress in itself [10], and admission for coronary heart disease is likely to be followed by reports of increased psychological stress. This [11] and the long-held popular assumption of a causal association between psychological stress and heart disease [12] are likely to influence attempts to recall preadmission levels of psychological stress. There may be a greater effect for the recall of cigarette smoking, given that a causal relationship between smoking and heart disease risk has been well known for many years and that this has led to growing social disapproval of smoking [13–15], especially for smokers requiring treatment for smoking-related illness [13,16–18].

This study adds to the sparse empirical data on the scope for recall bias in case-control studies. The development of cardiovascular disease is associated with increases in reported psychological stress and with a high rate of smoking cessation. Current

Table II. Mean (standard deviation) psychological stress and percentage of smokers at the two screening assessments by outcome (symptoms or admission), plus the change in reported exposure between assessments. For each outcome in turn, age-adjusted odds ratios (ORs) indicate the effect of higher exposure at the stated screening assessment<sup>a</sup>, or of a greater increase in stress or a greater smoking cessation rate between assessments.

	Angina symptoms at screen 2 ( $n=141/2428^b$ )					CHD admission between screen 1 and 2 ( $n=51/2550^c$ )				
	Yes	No	OR	95% CI	p	Yes	No	OR	95% CI	p
<b>Stress</b>										
Screen 1	4.04 (1.76)	3.76 (1.66)	1.12	(1.00–1.24)	0.041	3.51 (1.64)	3.82 (1.67)	0.90	(0.76–1.06)	0.20
Screen 2	4.16 (1.62)	3.85 (1.72)	1.13	(1.02–1.26)	0.016	4.04 (1.57)	3.90 (1.71)	1.06	(0.90–1.25)	0.51
Screen 2–Screen 1	0.12 (1.54)	0.12 (1.54)	1.03	(0.92–1.15)	0.64	0.53 (1.47)	0.08 (1.55)	1.21	(1.02–1.44)	0.032
<b>Smoking</b>										
Screen 1	61.7%	52.1%	1.54	(1.08–2.19)	0.016	74.5%	53.1%	2.63	(1.39–4.97)	0.003
Screen 2	49.7%	43.1%	1.33	(0.94–1.87)	0.10	52.9%	44.0%	1.44	(0.83–2.51)	0.20
Ex-smokers	12.8%	9.9%	1.39	(0.83–2.32)	0.22	21.6%	10.0%	2.55	(1.29–5.05)	0.007

CHD, coronary heart disease; CI, confidence interval. <sup>a</sup>ORs are for one unit greater stress and smoking vs. not smoking. <sup>b</sup>Excludes men with electrocardiogram ischaemia or Rose “definite angina” at screen 1. <sup>c</sup>Excludes men with electrocardiogram ischaemia at screen 1.

psychological state is likely to influence attempts to recall psychological state for previous periods. Consequently, recent case-control studies that rely upon recall of pre-disease psychological stress are likely to have overestimated the association between psychological stress and coronary heart disease [2,19,20].

The present study is limited in that it indicated the scope for recall bias with different risk factors, but did not assess men's ability to recall their exposure level for a previous time period. A cohort of women with breast cancer was found to be more likely to underestimate past alcohol consumption than a control group, although the bias was small in magnitude [21]. Furthermore, our second measure of psychological stress was taken some time after admission, and we may have observed a greater effect had we measured stress pre-discharge, as in two recent case-control studies [2,19,20].

## Conclusion

We conclude that case-control studies that have relied upon retrospective recall of risk-factor exposure may give biased estimates when that exposure is modified following the development of disease, with an overestimate of associations between disease and psychological risk factors being particularly likely. In consequence, the need for and nature of policies to address psychological risk factors for disease cannot be fully informed by data from case-control studies alone.

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## Pesticide exposure and risk of Parkinson's disease – a population-based case–control study evaluating the potential for recall bias

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**Objective** The aim of this study was to investigate whether pesticide exposure was associated with Parkinson's disease in a population-based case–control study in British Columbia, Canada.

**Methods** Patients reimbursed for anti-parkinsonian agents were identified and screened for eligibility as cases. Controls were selected from the universal health insurance database, frequency-matched to the case sample on birth year, gender, and geographic region. A total of 403 cases and 405 controls were interviewed about their job, medical and personal habits histories, and beliefs about disease risk factors. Among those reporting pesticide exposure, an occupational hygiene review selected participants exposed “beyond background” (ie, above the level expected in the general population). Unconditional logistic regression was used to estimate associations for different pesticide categories.

**Results** Of the cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background. Self-reported exposure was associated with increased risk [odds ratio (OR) 1.76, 95% confidence interval (95% CI) 1.15–2.70], however the risk estimate was reduced following the hygiene review when restricted to those considered exposed (OR, 1.51, 95% CI, 0.85–2.69). When agricultural work was added to the model, the risk for hygiene-reviewed pesticide exposure was not elevated (OR 0.83, 95% CI 0.43–1.61), but agricultural work was (OR 2.47, 95% CI 1.18–5.15). More than twice as many cases as controls thought chemicals cause Parkinson's disease.

**Discussion** This study provides little support for pesticide exposure as a cause of Parkinson's disease. The observed pattern of step-wise decreases in risk estimates might indicate differential recall by case status. The relationship to agricultural jobs suggests that farming exposures - other than pesticides - should be considered as risk factors for Parkinson's disease.

**Key terms** agricultural job; British Columbia; Canada; job history; self-report.

The etiology of Parkinson's disease is partly unknown, though 5–10% of the cases are attributed to genetic mutations (1). Parkinson's disease is thought to result from an interplay between genetic susceptibility and environmental risk factors (2). An association between pesticides and Parkinson's disease was first suspected in 1983, when the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which has a chemical structure similar to the herbicide paraquat, was observed to cause acute Parkinsonism (3). Since then, exposure to pesticides and subsequent development of Parkinson's

disease has been studied intensively (eg, 4–17) and many studies (4–8, 12–17) have confirmed associations, though some were weak and not significant, and other studies have not found an effect (9, 10).

Methods of pesticide exposure ascertainment have varied from study to study, but it would be extraordinarily difficult to include direct exposure measurement due to the rarity and late-life incidence of Parkinson's disease. Retrospective self-reporting of exposures is the most commonly used method for estimation of pesticide exposure (4–10); however, this method has the

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potential for recall bias (11). Some studies have gathered self-report of exposure prospectively (12, 13) or used more objective methods, such as job exposure matrices (14–16) or combinations of geographic information and historical data on pesticide use (17).

Here we report the results of a population-based case–control study of the relationship between pesticide exposure and Parkinson's disease. Self reports in combination with an occupational hygiene review were used to estimate exposures. We also investigated whether study participants believed that chemicals, including pesticides, cause Parkinson's disease and whether such a belief may have confounded exposure–response relationships.

## Methods

### Study population

Cases and controls were sampled from two areas of the province of British Columbia, Canada: Metro Vancouver representing an urban area (2.1 million people, population density ~735 per km<sup>2</sup>); and all of Vancouver Island, except Greater Victoria, representing a rural area (400 000 people, population density ~10 per km<sup>2</sup>). The rural area was included to increase the diversity of occupations. Persons between the ages of 40–69 years inclusive (as of 31 December 2002) who were alive and residing in the study area at the time of interview and who were able to communicate with the interviewer in English were eligible. Subjects in the age group 40–69 years were chosen because they were less likely to suffer from dementia or other illnesses that could complicate an interview and because they were in, or close to, their working years and therefore more likely to recall exposures correctly.

Potential cases were identified using the PharmaCare database of the provincial prescription payment plan, which included all those who had more than CAN\$800 in prescription costs in a given year. For inclusion, individuals had to have had at least one prescription for anti-parkinsonian drugs for at least one calendar year from 1995–2002 inclusive. The following were defined as anti-parkinsonian drugs: levodopa, bromocriptine mesylate, pergolide mesylate, levodopa/benserazide hydrochloride, levodopa/carbidopa, or seligiline hydrochloride. The populations meeting the potential case definition were identified on two occasions: in 2001 (data from 1995–1998) and 2005 (data from 1999–2002). To blind the data extractors, the extract was supplemented with a 20% “camouflage” sample of other individuals in the database.

All potential cases were verified by an initial screening phone interview about chronic diseases, anti-parkin-

sonian drugs taken, and the reason for their use. This screened out those taking the drugs for much different purposes (eg, bromocriptine for lactation cessation or levodopa for restless legs syndrome). Those taking the drugs for known or suspected Parkinson's disease had an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist with a specialty in movement disorders. The following clinical criteria for Parkinson's disease were used: (i) two of the following symptoms present on examination: Parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance; (ii) absence of specific signs of other diseases that would account for these findings. Dates of Parkinson's disease diagnosis, first symptoms, and first treatment were also recorded.

The control sample was frequency-matched to the case sample on birth year (six 5-year periods), gender, and geographic region. Controls were selected using stratified random sampling from the British Columbia (BC) Ministry of Health Services client registry, which includes all individuals covered by provincial medical insurance and represents 97.5% of the population. All potential controls were screened by phone for eligibility, including a question about whether they had any chronic diseases. Anyone who indicated Parkinson's disease were excluded.

### Subject contact procedure

This study was required to use a two-stage consent process. The BC Ministry of Health Services sent out invitation letters asking potential subjects to contact the University of BC team. If no response was received within two weeks of the mailing date, a clerk at the Ministry of Health Services phoned to ask the potential subject if their name could be released to the study team. Those who agreed were then contacted by the study coordinator who conducted the screening interview and requested study participation.

### Questionnaire information on pesticide exposure

The questionnaire was pre-tested in several steps on a sample of 40 people selected to represent the age range of the subjects. The interviewers underwent formal training about all aspects of the interview, questionnaire, and clinical examination, and were observed during mock and initial interviews to ensure consistency.

In an in-person interview, participants were asked about their job, medical, and personal habits histories. The following questions were asked for all jobs: “During this job, did you use or were you exposed to any chemicals, for example, solvents, oils, plastics, paints, metals or pesticides?” As an aid to recall, an interview guide was sent to the participants prior to the interview and

was referred to during the interview. It listed chemicals with an a priori hypothesis and included common and brand names (see the Appendix for the list of pesticides). If a participant answered “yes”, the following questions were asked: “Was this substance (i) breathed in, (ii) on skin, (iii) both, (iv) no direct contact, (v) don’t know”; and “What operations were you performing when you were exposed to this substance?” for which a list of about 90 operations was provided in the interview guide. Participants were asked about weeks exposed per year, hours exposed per week, and start and end date of the exposure in that job. At the end of the interview, participants were asked: “What do you think causes Parkinson’s disease?”

Each participant’s job history was reviewed by an occupational hygienist (blind to case status) for sensitivity (ie, to check whether potential exposures of interest commonly associated with an occupation were reported). Where exposures were missed, the participant was phoned and asked about the exposures noted by the hygienist.

### Assigning exposure to pesticides

After all interviews were completed, the self-reported exposures were again reviewed, blind to case status, this time for specificity. Using defined criteria and the information on job title, job duties, mode of exposure, operations conducted during exposure, and duration of exposure, assessments were made about whether self-reported pesticide exposures were likely to be “beyond background” or above the level expected in the general population. Of 121 persons who self-reported pesticide exposures, 53 were excluded because the reported exposure was judged to be limited. For example, sales personnel handling closed containers, construction workers occasionally handling wood treated with preservatives, and restaurant workers, security guards, administrative personnel, and care aides in locations where pesticides were occasionally applied by others were all judged to have limited exposure. In comparison, those judged to have exposures above background were mainly farmers, farm workers, forestry personnel, sawmill workers applying antisapstain fungicides, florists, and kennel and stable hands. Among those judged unlikely to be exposed beyond background, only 34% named a specific pesticide, whereas among those judged exposed, 73% did. A further 8 persons were excluded due to missing information on hours per week exposed (N=7) and whether the exposure was every week (N=1); on checking the job duties, it was likely that the information was missing because the exposure was rare in the job (eg, public health nurse applying lindane for lice).” Among those reporting exposure to pesticides, 60 were judged to be exposed beyond background.

### Categorizing pesticides

Since most previous studies have categorized pesticides according to function (insecticides, herbicides, fungicides, and wood preservatives), for comparison purposes we did the same.

We also created categories by chemical class: organochlorines and organophosphates. Finally, we grouped specific pesticides reported by the participants into two categories based on neurotoxicity (18–20): (i) pesticides with evidence of human neurotoxicity: allethrin, azinphosmethyl, diazinon, dichlorodiphenyltrichloroethane (DDT), 2,4-dichlorophenoxyacetic acid (2,4-D), dieldrin, glyphosate, lindane, malathion, 2-methyl-4-chlorophenoxyacetic acid (MCPA), nicotine, paraquat, pentachlorophenol, rotenone, tetrachlorophenol, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and (ii) pesticides with limited or no evidence of neurotoxicity: borax, brodifacoum, calcium polysulfide, captan, copper oxychloride, creosote, chromate copper arsenate, didecyl dimethyl ammonium chloride, lime sulphur, mineral oil, simazine, and sulphur. These categories were based on available evidence for neurotoxicity in case studies, animal studies, and in vitro studies (18–20).

### Statistical analysis

Unconditional logistic regression was used to estimate associations with Parkinson’s disease for different categories of pesticides: functional groups (insecticide, herbicide, fungicide, wood preservative); chemical groups (organophosphates, organochlorines); neurotoxic pesticides; and any specific pesticide reported by at least ten participants. In all analyses, persons reporting exposure to pesticides other than those relevant in the specific analysis were excluded.

Analyses were conducted for self-reported exposure and for hygiene-reviewed exposures beyond background. Analyses were performed for exposure via any job operation and for the subgroup reporting pesticide spraying operations. We also estimated risks with exposure duration and with censoring of exposures five and ten years prior to the date of diagnosis or the corresponding date for controls.

Finally, we estimated Parkinson’s disease risk among those with agricultural jobs. Two adjustment models were used: model 1 adjusted for gender, birth year (5-year age groups), and smoking (cumulative pack-years); and model 2 adjusted for the same variables as model 1 in addition to a variable indicating whether the subject believed Parkinson’s disease has a chemical cause.

Analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

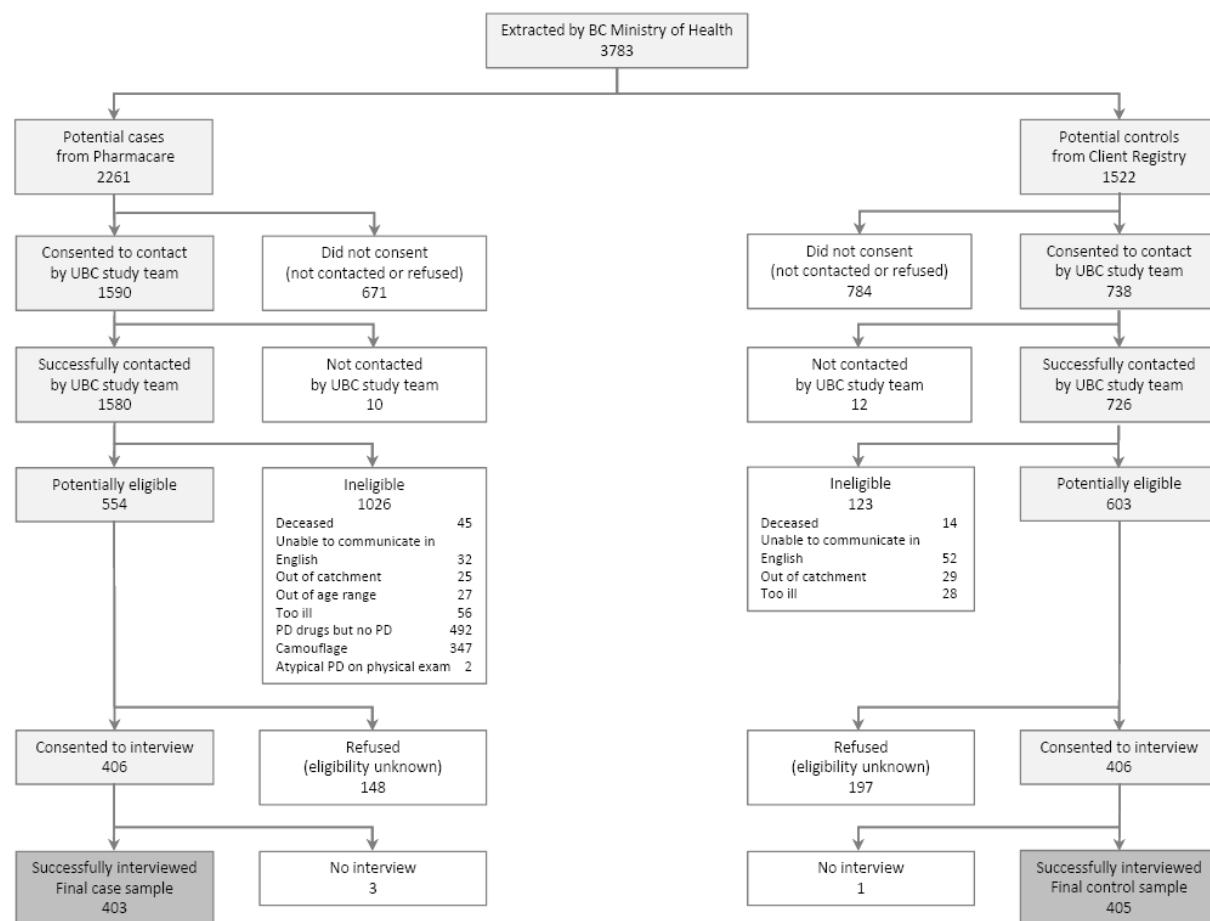
## Results

A total of 3783 potential subjects were initially sent letters from the Ministry of Health Services. Figure 1 is a participation flowchart showing the classification of potential subjects. A large proportion of potential cases did not have Parkinson's disease (most used anti-parkinsonian drugs for other indications). The multi-stage consent process resulted in uncertainty about the proportion of potential subjects who were eligible to participate. However, if we assume that the proportion of contacted subjects who were eligible ( $554/1580=0.35$  for cases and  $603/726=0.83$  for controls) was the same in the initially extracted samples, we can calculate the "potentially eligible" numbers ( $0.35 \times 2261=791$  for cases;  $0.83 \times 1522=1264$  for controls) and use these as denominators for the calculation of the participation rate. Using this method, the estimated participation rate was  $403/791$  (51%) for cases and  $405/1264$  (32%) for controls. The characteristics of the final study sample of 403 cases and 405 controls are summarized in table 1.

## Pesticide exposure

Among cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background following the hygiene review. In the control group, 47 (12%) self-reported pesticide exposure and 23 (6%) were judged to be exposed beyond background. In both the case and control groups, insecticides and herbicides were the most frequently reported types of pesticides (table 1).

Table 2, model 1 (adjusted for birth year, gender and smoking) shows the results for both self-reported and hygiene-reviewed pesticide exposure via any job operation and spraying operations. For self-reported pesticide exposure, we found a significantly increased risk of Parkinson's disease. Among those judged exposed beyond background after the hygiene review, the odds ratio (OR) was lower than among those self-reporting exposure. In the hygiene-reviewed group, exposure via spraying pesticides had a higher risk estimate than via any job operation, though neither of these risk estimates were statistically significant. The



**Figure 1.** Flow chart showing the classification of potential participants in a case control study of Parkinson's disease in British Columbia, Canada. Potential cases were those with a prescription for antiparkinsonian drugs during the study period.



**Table 1.** Characteristics of the study population: 403 patients with Parkinson's disease and 405 controls. [SD=standard deviation.]

Characteristic	Cases				Controls			
	N	%	Mean	SD	N	%	Mean	SD
Men	266	66.0	.	.	204	50.4	.	.
Women	137	34.0	.	.	201	49.6	.	.
Birth year								
1929–1938	245	60.8	.	.	175	43.2	.	.
1939–1948	131	32.5	.	.	129	31.9	.	.
1949–1958	27	6.7	.	.	101	25.0	.	.
Geographic region: Metro Vancouver	263	62.3	.	.	242	59.8	.	.
Self-reported pesticide exposure	74	18.3	.	.	47	11.6	.	.
Hygiene-reviewed pesticide exposure	37	9.2	.	.	23	5.7	.	.
Insecticides	18	4.5	.	.	13	3.2	.	.
Herbicides	17	4.2	.	.	13	3.2	.	.
Fungicides	7	1.7	.	.	6	1.5	.	.
Wood preservatives	10	2.5	.	.	5	1.2	.	.
No pesticide exposure	329	81.6	.	.	358	88.4	.	.
Ever smoker <sup>a</sup>	184	45.7	.	.	226	55.8	.	.
Named chemicals as cause of Parkinson's disease	111	27.5	.	.	43	10.6	.	.
Smoking, cumulative pack-years			11.4	20.4	.	.	15.4	22.4
Mean age at diagnosis of Parkinson's disease (years)			56.0	7.1	.	.	.	.
Mean age at the time of interview (years)			65.0	6.6	.	.	62.2	9.0

<sup>a</sup> At least 100 cigarettes in the period prior to Parkinson's disease diagnosis and a corresponding period for controls.

risk estimates for subcategories of pesticides tended to follow similar patterns: the highest risk estimates were for self-reports; the hygiene review resulted in reductions in risk estimates; and there were slightly higher risk estimates for spraying exposures. None of the OR for pesticide subcategories were statistically significant, except self-reported insecticide exposure. Risk estimates for hygiene-reviewed pesticide exposures were slightly above 1.0 in all categories of pesticides, except for organophosphates, organochlorines and DDT, however, most risk estimates had wide 95% confidence intervals (95% CI) (table 2). Censoring exposures five and ten years prior to diagnosis did not change the risk estimates markedly (data not shown) and analyses including duration of pesticide exposure showed no significant associations with Parkinson's disease (data not shown).

We also examined the relationship between agricultural work and Parkinson's disease: 36 cases and 17 controls reported an agricultural job. Of these, 20 cases and 7 controls were exposed to pesticides. Participants who reported agricultural jobs had a significantly increased risk of Parkinson's disease (OR 2.36, 95% CI 1.23–4.55, adjusted for gender, birth year and smoking). When the hygiene-reviewed pesticide exposures were added to this model, the elevated and statistically significant OR for agricultural work remained (OR 2.47, 95% CI 1.18–5.15), but the risk for pesticide exposure

was no longer elevated (OR 0.83, 95% CI 0.43–1.61). A similar pattern held for each pesticide category: when added to a model with agricultural job, the elevated risk for the job remained, but the risk estimate for the pesticide was always <1.0. There were no significant interactions between agricultural job and any of the pesticide categories.

The analyses reported above suggest that differences in exposure recall between cases and controls may have contributed to the higher risk estimates for self-reported pesticide exposures, so we examined the responses to the question about what causes Parkinson's disease. A total of 154 participants reported "chemicals" as a suspected cause of Parkinson's disease (111 cases and 43 controls). Most did not name a specific class of chemical, however 21 participants specifically mentioned "pesticides" and all of these were cases. To see whether beliefs about causes of the disease might alter the association with pesticides, we conducted an additional set of analyses with adjustment for the participants' beliefs that chemicals are a cause of Parkinson's disease (table 2, model 2). The OR for pesticides in the model 2 analyses were consistently lower than those of model 1, and none were statistically significant. In contrast, in analyses of agricultural job with adjustment for participants' beliefs that chemicals are a cause of the disease, the increased risk persisted (OR 2.28, 95% CI 1.16–4.47).

**Table 2.** Odds ratios (OR) and 95% confidence intervals (95% CI) for Parkinson's disease among persons who self-reported pesticide exposure and among those judged - by a hygiene review - to have pesticide exposure beyond background. Statistically significant OR in bold. [DDT= dichlorodiphenyltrichloroethane.]

Pesticide category	Model 1 <sup>a</sup>									Model 2 <sup>b</sup>									
	Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations			Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations			
	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	
Pesticides		<b>1.76</b>	<b>1.15–2.70</b>	1.51	0.85–2.69		1.91	0.82–4.49		1.49	0.96–2.32		1.18	0.65–2.14		1.38	0.56–3.40		
Cases	74			37			20			74			37			20			
Controls	47			23			9			47			23			9			
Insecticides		<b>1.80</b>	<b>1.03–3.15</b>	1.26	0.58–2.74		1.86	0.66–5.24		1.44	0.81–2.58		0.86	0.38–1.93		1.24	0.42–3.65		
Cases	40			18			13			40			18			13			
Controls	26			13			6			26			13			6			
Herbicides		1.82	0.97–3.40	1.33	0.60–2.97		1.60	0.53–4.87		1.59	0.84–3.00		1.16	0.51–2.60		1.49	0.47–4.71		
Cases	33			17			10			33			17			10			
Controls	19			13			6			19			14			6			
Fungicides		0.94	0.38–2.32	1.18	0.35–4.00					0.80	0.31–2.03		0.95	0.27–3.31					
Cases	11			7			3 <sup>c</sup>			11			7			3 <sup>c</sup>			
Controls	11			6			2 <sup>c</sup>			11			6			2 <sup>c</sup>			
Wood preservatives		2.20	0.90–5.34	1.56	0.51–4.77					1.80	0.70–4.62		1.34	0.42–4.28					
Cases	17			10			4 <sup>c</sup>			17			10			4 <sup>c</sup>			
Controls	9			5			0 <sup>c</sup>			9			5			0 <sup>c</sup>			
Organo-phosphates		1.57	0.53–4.64	0.74	0.20–2.78					1.47	0.49–4.45		0.72	0.19–2.68					
Cases	10			5			4 <sup>c</sup>			10			5			4 <sup>c</sup>			
Controls	6			5			3 <sup>c</sup>			6			5			3 <sup>c</sup>			
Organo-chlorines		1.23	0.53–2.85	0.62	0.19–2.00					1.05	0.44–2.52		0.38	0.11–1.31					
Cases	16			6			5 <sup>c</sup>			16			6			5 <sup>c</sup>			
Controls	10			6			4 <sup>c</sup>			10			6			4 <sup>c</sup>			
Pesticides with neurotoxic effects		1.76	0.95–3.25	1.08	0.49–2.36		1.34	0.53–3.40		1.48	0.78–0.80		0.86	0.38–1.93		1.06	0.40–2.82		
Cases	35			17			14			35			17			14			
Controls	19			13			8			19			13			8			
DDT		1.32	0.55–3.18	0.76	0.22–2.62					1.09	0.44–2.75		0.45	0.12–1.65					
Cases	15			6			5 <sup>c</sup>			15			6			5 <sup>c</sup>			
Controls	9			5			3 <sup>c</sup>			9			5			3 <sup>c</sup>			

<sup>a</sup> Model 1: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years).

<sup>b</sup> Model 2: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years), and naming chemicals as a cause of Parkinson's disease.

<sup>c</sup> Fewer than ten subjects exposed, odds ratios and confidence intervals not reported.

## Discussion

In this study, we observed significantly increased risks of Parkinson's disease with self-reported pesticide or insecticide exposures, but reductions in risk for those considered exposed based on the hygiene review, and when more specific categories of pesticides are mentioned. There were no increases in risk with censoring of exposures five and ten years prior to diagnosis, nor increasing risks with increasing duration of exposure. Only one pattern was suggestive of an association: the increases in risk for hygiene-reviewed exposures from "any job operation" to "spraying operations," though none of these OR were statistically significant. In analyses with agricultural job, pesticide exposures no longer had elevated OR. This pattern of results does not add

convincing support to the proposed association between pesticides and Parkinson's disease, and for the most part, was counter to what would be expected to support pesticides as a cause.

Two patterns suggested the potential for recall bias to explain at least a portion of the observed associations between pesticide exposure and Parkinson's disease: decreases in risk between self-reported and hygiene-reviewed exposures and decreases in risk after adjustment for participants' belief that chemicals were a cause. In our study, 27.5% of cases with Parkinson's disease reported chemicals (including pesticides) as a cause of Parkinson's disease; the corresponding percentage for controls was 10.6%. This difference indicates a greater suspicion of a chemical cause among cases than controls; the risk esti-

mates for pesticide exposures decreased when controlling for this factor, meaning that suspecting a chemical cause was also associated with reporting pesticide exposure.

Evidence of recall bias in case-control studies has generally been sparse, except with open-ended questioning of exposure or where participants suspect a disease cause (22, 23). Difficulties in recall of pesticides have been shown to differ between cases and controls in a general population sample (24). Adjusting for suspicions of hypothesized causation may be inadvisable as a routine practice, particularly if knowledge is causally related to exposure or if exposed cases become knowledgeable about the hypotheses post-diagnosis (25). The former seems unlikely in our study, although the latter is possible, so we cannot know with certainty that the effect we observed was indeed due to recall bias.

Our results raise the question of whether the prior studies may have been subject to recall bias. Previous studies that, like ours, obtained information on exposure to pesticides from interviews have this potential (4–11, 21). Nevertheless, two cohort studies using prospective self-reports of exposure, which should not be prone to recall bias, found associations between exposure to pesticides as a group and risk of Parkinson's disease (12, 13).

Non-differential misclassification of exposure to pesticides is also an important issue, which could exist in our study and thus bias our results towards the null (26). Reducing non-differential misclassification of exposure was one of the purposes of the industrial hygiene review of exposures. We expected risk estimates to be higher for hygiene-reviewed than self-reported exposures, but the opposite was the case, initiating our suspicion of recall bias.

#### Agricultural employment versus pesticide exposure: what is measured?

We observed a significantly increased risk of Parkinson's disease among those reporting an agricultural job, with a risk estimate higher than those for pesticides. The finding for agricultural jobs was little influenced by adjustment for pesticide exposure or participants' beliefs that chemicals are a cause.

This raises the question of whether there is something else about agricultural work that might be related to Parkinson's disease. A number of studies (27–29), though not all (30), have reported associations between agricultural jobs and Parkinson's disease. Most investigators have related these associations to the use of pesticides in these jobs. However, a recent Australian study investigated the extent to which farm-related jobs indicated pesticide exposure (31) and found that only 22% likely had exposure. In our study, 51% of

those in agricultural jobs were classified as "pesticide exposed". Farming jobs may share many other potential exposures, including solvents, fuels, fuel exhaust, dusts, micro-organisms, and traumatic injuries, many of which would be useful to examine in the context of Parkinson's disease. An exposure of particular interest could be endotoxin, a lipopolysaccharide component of gram-negative bacterial cell walls. Lange and coworkers (32) are among the researchers who have posited that part of the elevated risk of Parkinson's disease associated with agriculture could be explained by exposure to endotoxin, because exposure is common in the agricultural sector and there is mechanistic support from animal experiments (33).

It would be worthwhile to consider the potential for other etiological exposures to explain at least some portion of the increased risks of Parkinson's disease observed among farmers or those assessed as being exposed to pesticide due to farming jobs (12, 14–16).

#### Recent case-control studies

In other recent case-control studies, the diversity of results related to pesticide exposures and agricultural work has continued. Elbaz and colleagues (4) found increased risks with professional pesticide use, especially insecticides, though they mentioned the possibility of increased awareness among cases of the possible link between Parkinson's disease and pesticides (4). Tanner et al (8) found increased risks for self-reported use of pesticides, increasing when restricted to eight specific pesticides with high neurotoxic plausibility (very similar to our classification), but agricultural work was not found to be a risk factor. Firestone and colleagues (10) found no significant association between self-reported exposure to pesticides or agricultural work and Parkinson's disease. Regional differences in exposure patterns between study populations and methodological differences (eg, different methods of ascertaining exposure) might partly explain these inconsistent results.

Despite the large number of studies investigating the possible association between pesticide exposure and Parkinson's disease, few epidemiological studies have found associations between exposure to a specific pesticide and Parkinson's disease. In a study using geographic information systems and historic information on pesticide use, exposure to the pesticides maneb and paraquat was found to be associated with risk of Parkinson's disease (17). To pinpoint specific pesticides in an interview based case-control study, the participants' memories need to be exceptional and the number of study participants needs to be very large. To illustrate the number of subjects needed to detect a significantly increased risk of Parkinson's disease for a specific

pesticide, we calculated the sample size needed, using the pesticide with the highest proportion of controls exposed in this study [DDT (5 of 405)]. With a significance level of 5%, power of 80% and equal numbers of cases and controls, 1500 cases and controls would be needed to detect an OR of 2.0.

### Strengths and limitations

Like most case-control studies, we had in-person physical assessment of potential cases and included assessments of participants' lifestyle habits to allow control for smoking's negative association with Parkinson's disease (34). The assessment of pesticide exposure collected detailed information on the type of contact and operations performed enabling two hygiene reviews on sensitivity and specificity, respectively, both blind to case status. A list of pesticides with common names and brand names were provided to participants in advance to improve recall (see appendix) (22). Our study appears to be the only one to date that has attempted to evaluate recall bias based on participants' beliefs about the causes of Parkinson's disease.

A limitation of our study was the potential for participation bias, since those agreeing to take part in the study might differ from those refusing. Our study population was restricted to those in the age group 40–69 years, potentially limiting the generalizability of our results to older Parkinson's patients.

Further, our study was underpowered to detect 2-fold-difference associations between subcategories of pesticide exposure with a prevalence of <4% in controls. Most of our pesticide groups had sufficient power, but the number of participants who reported exposure to individual pesticides was very small, preventing analyses of most individual pesticides. The diversity of pesticide active ingredients used by this study sample reflects the diversity of farming in the province, including fruit (apple, peaches, cherries, grapes, plums, blueberries, raspberries, cranberries), market vegetable (lettuce, tomatoes, sweet peppers, cucumbers, mushrooms), grain, and flower crop farming, as well as cattle ranching and dairy farming. The resulting variety of pesticides used is another factor that lessens the likelihood that pesticides are an important cause of Parkinson's disease in this population; there is little specificity of the chemicals. In addition, few of the study subjects had exposures to the pesticides used in animal models of Parkinson's disease (35): one case and four controls reported exposure to rotenone; three cases and three controls reported exposure to paraquat; and no one reported exposure to maneb.

In summary, the results of this study do not lend support to an association between pesticide exposure and Parkinson's disease. Our results emphasize the importance of considering recall bias, via a hygiene

review to ensure specificity of exposure ascertainment, and by considering the participants' beliefs about the disease cause. The results related to agricultural work suggest that it would be valuable for future studies to explore other exposures of this occupational group that may be related to Parkinson's disease, such as bacterial endotoxin (32, 36).

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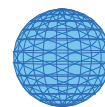
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**Appendix.** List of pesticides sent out to the participants prior to the interview.

Chemical name	Brand and common names
<b>Fungicides</b>	
Captan	Agrox D-L Plus, Orthocide
Chlorothalonil	Bravo, daconil 2787, Exotherm Termil, Termil
Copper oxychloride	Basicop, Coprantol, Fixed copper, mar-cop, neutron-Cop, Tri-Cop
Dodine	Cyprex, Equal
Formaldehyde	Formalin, Methanol
Lime sulphur or calcium polysulphide	Orthorix
Mancozeb	Dithane M-45, manzate 200
Maneb	Co-op DP, Ditane M-22, Mantox, Manzae, Mergamma, Pool NM Dual, Tersan LSRF
Metam	Pole-Fume, SMDC, Unifume Soil, Vapam, VPM, Woodfume
Metiram	Polyram
Quintozene	Brassicol, PCNB, terrachlor
Sulphur	Flortex, Giant Destroyer, Gopher Gasser, Kolodust, Kolospray, Magnetic 6, Ortho Flotox, Woodchuck Bombs
Ziram	Zerate
<b>Herbicides and plant growth regulators</b>	
2,4,5-T	Dacamine-4T, Esteron 2,4,5-T, Poison Ivy and Brush Killer, Reddox, Trinoxol, Veon, Verdon 2T, Weedone 2,4,5-T
2,4-D	2,4-D, Amkil, Aqua-Kleen, Calmix, Chlorxone, Dacamine, Desormone 7, Diachlorprop, Driamine, Estakil, Estasol, Estemine 500, Esteron, Esteron 64, Foestamine, For-ester, Formula 40-F, Herbate, Hoe-Grass, Kilmor, Rustler, Salvo, Silvaprop, Sure-Shot Forest amine, Target, Ten-Ten, Verdon, Weedar, Weedar-64, Weedaway, Weed-B-Gone, Weedex, Weedone, Weed-Rhap
Atrazine	Aatrex, Atra-Mix, Eramox 80W, gesaprim, Laddox, Marzone, Primatol A, Primextra, Vectal Atrazine
Bifenox	Modown
Chlormequat	Cycocel
Difenzoquat	Avenge
Diquat	Reglone, Reglone-A, Weedrite
Ethalfuralin	Edge
Glyphosate	Roundup, Rustler, Side-Kick, Vision
MCPA amine	Agritox, Agroxone, Bromox, Bucril, Estemine MCPA, Estakil MCPA, MCP, Mephanac, Methoxone Amine 500, No Weed, Sabre, Weedar MCPA, Weedgone MCPA
Metolachlor	Dual, Primextra
Morfamquat	Morfoxone
Norflurazon	Evitol, Zorial
Paraquat	Gramoxone, Gramoxone S, Paraquat CL, Sweep, Terraklene, Weed Rite
Simazine	Gestatop, Primatol S, Princep, Simmaprim, Simadex
Sodium chlorate	Atlacide, Atratol, Chlorax, Monobor-Chlorate, Ureabor
Sodium metaborate tetrahydrate	Borate, Ureabor
Triallate	Avadex-BW
<b>Insecticides</b>	
Allethrin	Allethrin, Synthetic Pyrethrin
Azinphos-methyl	APM, Gurhion
Cypermethrin	Ripcord
Dichlorodiphenyltrichloroethane	DDT
Diazinon	Basudin
Dieldrin	Dieldrin
Heptachlor	Heptachlor
Lindane	Agrox D-L Plus, Benolin, Co-op DP, Gamma BHC, Gammasan, Mergamma, Pool NM Dual, Thiralin, Vitaflor DP, Vitavax
Malathion	Cythion
Mineral oil	Agricultural Weedkiller #1, Dormant Oils, Petroleum Oils, Petroleum Solvents, Stoddart Solvents, Summer Oil, Superior Oil, Supreme Oil, Volck Oil, Weed Oils
Nicotine	Black Leaf 40, Nicotine, Nicotine Sulfate
Rotenone	Atox, Deritox, Derris, Noxfish Fish Toxicant, Rotenone Fish Poison
<b>Wood preservatives</b>	
3-iodo-2-propyl butyl carbamate	IPBC, NP-1, Troysan Polyphase P 100, Troysan Polyphase
Borax	Borascu, Boron, Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, Ecobrite III, F-2, Pole-Peg
Chromated copper arsenate	CCA
Creosote	Coal Tar Creosote, Pole-Peg
Didecyl dimethyl ammonium chloride	DDAC, Ecobrite III, F-2, NP-1, Timbercote II, Timbercote 2000
Pentachlorophenol	Alchem, Dowwicide, Diatox, PCP, Penta, Pole-Peg, Santobrite, Woodbrite, Woodsheath
Sodium carbonate	Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, SCB
<b>Rodenticides</b>	
Brodifacoum	Ratak, Talon
Bromadiolone	
<b>Fumigants</b>	
Methyl bromide	Brom-O-Gas, Dowfume, Dowfume MC-2, Meth-O-Gas, Sanex MB-C-2, Terr-O-Gas 67
Carbon disulfide	Dowfume, FIA 80-2, Kenfume bin fumigant, Sanifume
Hydrogen cyanide	Cyanogas, calcium cyanide, HCN



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# Self-reported chemicals exposure, beliefs about disease causation, and risk of breast cancer in the Cape Cod Breast Cancer and Environment Study: a case-control study

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## Abstract

**Background:** Household cleaning and pesticide products may contribute to breast cancer because many contain endocrine disrupting chemicals or mammary gland carcinogens. This population-based case-control study investigated whether use of household cleaners and pesticides increases breast cancer risk.

**Methods:** Participants were 787 Cape Cod, Massachusetts, women diagnosed with breast cancer between 1988 and 1995 and 721 controls. Telephone interviews asked about product use, beliefs about breast cancer etiology, and established and suspected breast cancer risk factors. To evaluate potential recall bias, we stratified product-use odds ratios by beliefs about whether chemicals and pollutants contribute to breast cancer; we compared these results with odds ratios for family history (which are less subject to recall bias) stratified by beliefs about heredity.

**Results:** Breast cancer risk increased two-fold in the highest compared with lowest quartile of self-reported combined cleaning product use (Adjusted OR = 2.1, 95% CI: 1.4, 3.3) and combined air freshener use (Adjusted OR = 1.9, 95% CI: 1.2, 3.0). Little association was observed with pesticide use. In stratified analyses, cleaning products odds ratios were more elevated among participants who believed pollutants contribute "a lot" to breast cancer and moved towards the null among the other participants. In comparison, the odds ratio for breast cancer and family history was markedly higher among women who believed that heredity contributes "a lot" (OR = 2.6, 95% CI: 1.9, 3.6) and not elevated among others (OR = 0.7, 95% CI: 0.5, 1.1).

**Conclusions:** Results of this study suggest that cleaning product use contributes to increased breast cancer risk. However, results also highlight the difficulty of distinguishing in retrospective self-report studies between valid associations and the influence of recall bias. Recall bias may influence higher odds ratios for product use among participants who believed that chemicals and pollutants contribute to breast cancer. Alternatively, the influence of experience on beliefs is another explanation, illustrated by the protective odds ratio for family history among women who do not believe heredity contributes "a lot." Because exposure to chemicals from household cleaning products is a biologically plausible cause of breast cancer and avoidable, associations reported here should be further examined prospectively.

## Background

Pesticides, household cleaners, and air fresheners are of interest in breast cancer research because many contain ingredients that are mammary gland carcinogens in animals [1] or endocrine disrupting compounds (EDCs), including compounds that affect growth of estrogen-

sensitive human breast cancer cells [2] or affect mammary gland development [3]. Mammary gland tumors have been observed in animal studies of pesticides such as dichlorvos, captafol, and sulfallate; methylene chloride (in some fabric cleaners); nitrobenzene (soaps, polishes); and perfluorinated compounds (stain-resistant, water-proof coatings) [1,4,5]. Phthalates, alkylphenols, parabens, triclosan, and polycyclic musks used as

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surfactants, solvents, preservatives, antimicrobials, and fragrances have shown weak estrogenic or anti-androgenic effects in both *in vitro* and *in vivo* tests [4-16]. Pesticides identified as EDCs include dichlorodiphenyl trichloroethane (DDT), chlordane, methoxychlor, atrazine, lindane (lice control), vinclozolin and benomyl (fungicides), and several current use insecticides such as cypermethin [6-13]. When given early in life, atrazine, nonylphenol, perfluorinated compounds, and the plastics monomer bisphenol A influence rat mammary gland development in a way that may affect tumor susceptibility [14-18]. These chemicals are widely used and many have been detected in blood and urine from a representative sample of the US population; concentrations vary over several orders of magnitude [19-26]. In household air and dust and women's urine tested in the Cape Cod Breast Cancer and Environment Study, we detected an average of 26 EDCs per home, including 27 pesticides and a variety of estrogenic phenols from household cleaners [27]. Taken together, the laboratory studies of biological activity and evidence of widespread human exposure suggest that use of products containing mammary gland carcinogens or EDCs may contribute to breast cancer in humans.

No epidemiological studies we know of have reported on the relationship between cleaning product use and breast cancer, and previous breast cancer studies of pesticides have been largely limited to organochlorine compounds [28]. Organochlorine studies have been mostly null, but interpretation is limited because proxies of exposure were measured in blood taken years after the compounds were banned in the US, often in older women and after diagnosis [29]. In a study that avoids these limitations by using archived blood collected from young women in 1959 to 1967, Cohn et al. [30] reported five-fold higher breast cancer risk among women who had the highest residues of DDT and were exposed before they were 14 years old. In addition, the Long Island Breast Cancer Study found 30% higher breast cancer risk among women who reported the highest home pesticide use [31]. Self-reported product use, such as the Long Island measures, has the potential to represent exposure over many years to a wide range of compounds; although retrospective reports may be biased by differential reporting accuracy between cases and controls [32].

To investigate the relationship between use of cleaning and pesticide products and risk of breast cancer, while considering possible recall bias, we conducted a case-control study of breast cancer and self-reported product use on Cape Cod, Massachusetts, in which we also measured beliefs about breast cancer causation, a possible source of recall bias. Cape Cod is a coastal peninsula where breast cancer incidence has been elevated. Annual

female breast cancer incidence in 2002 - 2006 was 151.0 per 100,000 (95% CI 142.6 - 159.8) [33]. The pattern of higher incidence in Cape Cod towns than elsewhere in Massachusetts dates to the initiation of the state cancer registry in 1982 [34]. In the Collaborative Breast Cancer Study, risk was elevated among Cape Cod women compared with other Massachusetts participants after controlling for breast cancer risk factors [35]. In the Cape Cod Breast Cancer and Environment Study case-control study, longer years of residence on Cape Cod was associated with higher risk after controlling for established breast cancer risk factors [36].

## Methods

### Study population

Details of the Cape Cod Study have been described previously [37]. Briefly, we conducted a case-control study of invasive breast cancer occurring on Cape Cod in 1988-1995. Cases were female permanent residents of Cape Cod for at least six months before a breast cancer diagnosis reported to the Massachusetts Cancer Registry (MCR). Controls were female permanent Cape Cod residents during the same years, had resided there at least six months, and were frequency matched to cases on decade of birth and vital status. Controls under 65 years of age were selected using random digit dialing; controls over 65 years of age were randomly selected from the Centers for Medicare and Medicaid Services (CMS).

The Cape Cod Study expands on a study of breast cancer and tetrachloroethylene (PCE) in drinking water [38]. Cases diagnosed in 1988-1993 in eight towns and their controls were interviewed in 1997-1998 in the PCE study. Cases diagnosed in 1994-1995 in those eight towns and in 1988-1995 in the remaining seven towns and their controls were interviewed in 1999-2000. Among 1,578 eligible living and deceased cases identified by MCR, 1,165 women (74%) or their proxies participated, 228 (14%) could not be located or contacted, and 185 (12%) refused to participate. Among 1,503 eligible controls, 1,016 (68%) participated.

For the present analysis, we excluded 368 cases and 287 controls who were interviewed by proxy, and 10 cases and eight controls who were missing data for one or more key analytic variables. Given that most women for whom we obtained proxy interviews were deceased, excluded women were older, and, consistent with being older, they were less educated. Within the included or excluded groups, cases and controls did not differ demographically, suggesting no selection bias. Exclusions left 787 cases and 721 controls for pesticide analyses. Cleaning product questions were asked only in 1999-2000 interviews, resulting in 413 cases and 403 controls for whom these data were available.



We obtained permission to use confidential data from MCR, CMS, and hospitals where cases were diagnosed. The Boston University Institutional Review Board and Massachusetts Department of Public Health Human Research Review Committee approved the study protocol. Participants were asked for informed consent at the outset of interviews.

### Interviews

Trained telephone interviewers administered a structured questionnaire on established and hypothesized breast cancer risk factors including family history of breast cancer, menstrual and reproductive history, height, weight, alcohol and tobacco use, physical activity, pharmaceutical hormone use, and education. Information on residential cleaning product and pesticide use was obtained. Participants in 1999-2000 interviews were asked about five categories of cleaning products, including solid and spray air fresheners, surface cleaners, oven cleaners, and mold/mildew products. All participants were asked about use of 10 categories of pesticides in and around their homes, including insecticides, lawn care, herbicides, lice control, insect repellents, and pest control on pets. The 1999-2000 interviews asked about mothballs and treatments for termites and carpenter ants. Participants were first asked if the product was ever used in their home. Participants were then asked to estimate frequency of use using predefined categories. To exclude exposures after diagnosis or index year, participants were asked to report the first and last years of use for pesticides, and use before their diagnosis or index year for cleaning products. At the end of the interview, participants were asked about their beliefs about four factors that may contribute to breast cancer: heredity, diet, chemicals and pollutants in the air or water, and a woman's reproductive or breastfeeding history. Participants were asked whether each contributes to breast cancer "a lot, a little, or not at all." "Don't know" responses were coded. Interview questions can be viewed at <http://silentspring.org/cape-cod-breast-cancer-and-environment-study-survey-instruments>.

### Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The following "core" matching variables and potential confounders were included in adjusted odds ratio analyses based on *a priori* consideration of the research design and well-established breast cancer risk factors: age at diagnosis or index year, education, family history of breast cancer in a first degree female relative, breast cancer diagnosis prior to the current diagnosis or index year, and age at first live or still birth ( $\geq 30$  years of age or nulliparous vs.  $< 30$  years of age). Pesticide analyses

were adjusted for study (PCE or Cape study). Missing values for family history for 45 (3%) participants were imputed as "no." The percent missing information on family history did not differ between cases and controls. The following potential confounders were evaluated: mammography use, medical radiation, lactation, hormone replacement therapy, oral contraceptive use, diethylstilbestrol exposure, body mass index, smoking, alcohol consumption, teen and adult physical activity, race, marital status, and religion. None of these variables changed the "core"-adjusted odds ratio estimates by  $\geq 10\%$ , so they were not included in final models.

We evaluated ever vs. never use and categorical variables reflecting frequency of use. "Never users" of each product type formed the reference group. If a participant reported ever using a product but the frequency was missing, frequency was imputed as the median for that product. To aggregate "like" exposures, three variables were constructed by summing frequency of use for two types of air fresheners, five types of cleaning products, and eight types of pesticides. Aggregated scores were divided into quartiles based on the distribution of controls. The lowest quartile constituted the reference group. Tests for trends were conducted by modeling ordinal terms for categories of product use or quartiles in the multivariate model.

Because participants' awareness of a hypothesis may bias exposure reporting [39], we evaluated differences in beliefs about disease causation between cases and controls using the chi square test. We evaluated differences in product-use odds ratios by beliefs about whether chemicals/pollutants contribute to breast cancer by 1) including an interaction term for beliefs and product use in the final model and 2) stratifying by beliefs. Beliefs were dichotomized as those who said chemicals/pollutants contribute to breast cancer "a lot" versus "a little," "not at all," or "don't know."

Weiss [40] notes that recall bias is not the only explanation for differences in odds ratios by knowledge or attitudes about a hypothesis; so to aid interpretation of product use results, we conducted a comparison analysis of differences in family history odds ratios by beliefs about whether heredity contributes "a lot" to breast cancer. This comparison is useful, because the accuracy of self-reported family history can be compared with medical records, and the relationship between family history and breast cancer is well-established independent of self-reports. As a sensitivity analysis, we also examined un-stratified and stratified family history odds ratios excluding those subjects who were missing information on family history.

All analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC). Figures were constructed in R software 2.6.1, (R Foundation for Statistical Computing,

Vienna, Austria). Statistical significance was defined by a (two-sided) *P*-value of 0.05 or lower.

## Results

Study participants were predominantly white (98%), 60-80 years of age (60%) with high school or higher education (94%); more cases (25%) than controls (19%) reported a family history of breast cancer. Characteristics of participants are shown in Table 1. Participants in this analysis of product use were demographically

**Table 1 Characteristics of Cape Cod Breast Cancer and Environment Study participants with completed pesticide use self-reports**

Characteristic	Cases (N = 787)		Controls (N = 721)	
	N	%	N	%
Age at diagnosis or index year				
< 50	128	16	149	21
50-59	115	15	129	18
60-69	277	35	226	31
70-79	221	28	184	26
≥ 80	46	6	33	5
Education				
< High school graduate	36	5	48	7
High school graduate	241	31	226	31
1-3 years college/vocational school	253	32	230	32
College graduate	144	18	122	17
Graduate work/degree	113	14	95	13
Family history of breast cancer				
Yes	196	25	135	19
No	591	75	586	81
Prior history of breast cancer				
Yes	48	6	46	6
No	739	94	675	94
Age at first live or stillbirth				
< 20	171	22	122	17
20-29	104	13	80	11
> = 30	458	58	456	63
Nulliparous	54	7	63	9
Menopause status at diagnosis or index year				
Pre-menopause	144	19	194	28
Post-menopause	615	81	505	72

Data for 27 cases and 18 controls were missing for the "Family history of breast cancer" characteristic. Data for 28 cases and 22 controls were missing for the "Menopause status at diagnosis or index year" characteristic.

similar to characteristics previously reported for all cases and controls, except for being younger and more educated, due to exclusion of proxy interviews [37].

## Products use

Breast cancer risk increased approximately two-fold in the highest compared with lowest quartile of combined cleaning product use (OR = 2.1, 95% CI: 1.4, 3.3) and combined air freshener use (OR = 1.9, 95% CI: 1.2, 3.0) (Table 2). Ever use of air freshener spray (OR = 1.2, 95% CI: 0.9, 1.8), solid air freshener (OR = 1.7, 95% CI: 1.2, 2.3) or mold/mildew control (OR = 1.7, 95% CI: 1.2, 2.3) was associated with higher risk, with evidence of positive dose response and significant  $P_{\text{trend}}$  for solid air freshener and mold/mildew control with bleach. Surface and oven cleaners were not associated with breast cancer risk.

Combined use of pesticide products was not associated with risk of breast cancer (Table 3). Odds ratios for individual pesticide types were null or slightly and nonsignificantly elevated, with the exception of insect repellent use (OR = 1.5, 95% CI: 1.0, 2.3 for most frequent insecticide use compared with never use;  $P_{\text{trend}} = 0.05$ ).

## Differences by beliefs about disease causation

Cases and controls differed significantly in beliefs about the role of heredity and of chemicals and pollutants in breast cancer (Table 4). Among controls, 66% said heredity contributes "a lot" compared with 42% of cases ( $P < 0.01$ ); 57% of controls and 60% of cases said "chemicals and pollutants in the air or water" contribute "a lot" ( $P < 0.05$ ).

In stratified analyses, odds ratios for cleaning products were consistently elevated within the group who said chemicals/pollutants contribute "a lot" to breast cancer, but associations moved towards the null in the other participants (Table 5). For example, the odds ratio for the highest quartile of combined cleaning product use was 3.2 (95% CI: 1.8, 5.9) among women who believed chemicals/pollutants contribute "a lot" compared to 1.2 (95% CI: 0.6, 2.6) among others. The interaction was not statistically significant ( $P = 0.25$ ). (However, the interaction term does not detect departures from additivity.)

Similarly, odds ratios for pesticides were higher among participants who believed that chemicals/pollutants contribute "a lot" to breast cancer. For example, the odds ratio for most frequent insect repellent use was 2.0 (95% CI: 1.1, 3.4) in this belief group compared with 0.8 (95% CI: 0.4, 1.6) among others. Pesticide odds ratios stratified by beliefs are shown in Table 6.

In addition, a similar pattern was observed in the odds ratios for family history of breast cancer stratified by

**Table 2 Adjusted odds ratios for breast cancer and reported cleaning product use, Cape Cod, Massachusetts, 1988-1995**

Product category	Cases (No.)	Controls (No.)	Adjusted OR	95% CI	<i>P</i> trend
Combined cleaning product use					
Quartile 1	91	99	1.0	Reference	
Quartile 2	100	107	1.1	0.8, 1.7	
Quartile 3	112	125	1.1	0.7, 1.7	
Quartile 4	104	70	2.1	1.4, 3.3	0.003
Combined air freshener use (sprays and solids)					
Quartile 1	74	77	1.0	Reference	
Quartile 2	113	117	1.1	0.7, 1.7	
Quartile 3	123	138	1.0	0.7, 1.6	
Quartile 4	101	71	1.9	1.2, 3.0	0.02
Air freshener spray					
Never use	90	95	1.0	Reference	
Any use	322	308	1.2	0.9, 1.8	
< Once a month	83	88	1.1	0.7, 1.7	
Monthly	47	41	1.3	0.8, 2.3	
Weekly	114	110	1.3	0.8, 1.9	
Daily	78	69	1.3	0.8, 2.1	0.15
Solid air freshener					
Never use	259	288	1.0	Reference	
Any use	153	115	1.7	1.2, 2.3	
< 2 times/year	50	41	1.4	0.9, 2.2	
2-6 times/year	77	58	1.7	1.2, 2.6	
≥ 7 times/year	26	16	2.0	1.0, 4.0	0.001
Oven cleaner					
Never use	33	33	1.0	Reference	
Any use	379	370	1.0	0.6, 1.7	
< 2 times/year	145	143	1.0	0.6, 1.8	
2-6 times/year	199	196	1.0	0.6, 1.7	
≥ 7 times/year	35	31	1.2	0.6, 2.3	0.80
Surface cleaner					
Never use	53	54	1.0	Reference	
Any use	359	348	1.1	0.7, 1.7	
< Once a month	61	60	1.0	0.6, 1.6	
Monthly	57	57	1.0	0.6, 1.8	
Weekly	186	171	1.2	0.8, 1.9	
Daily	55	60	1.2	0.7, 2.2	0.22

**Table 2 Adjusted odds ratios for breast cancer and reported cleaning product use, Cape Cod, Massachusetts, 1988-1995 (Continued)**

Mold/mildew control					
Never use	296	322	1.0	Reference	
Any use	114	81	1.7	1.2, 2.3	
Mold/mildew control with bleach					
Never use	320	334	1.0	Reference	
Any use	90	68	1.5	1.0, 2.1	
< Once a month	47	38	1.2	0.8, 2.0	
Monthly	14	11	1.5	0.7, 3.5	
≥ Weekly	29	19	2.0	1.1, 3.8	0.02

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories). "Combined cleaning product use" combines frequency of use across five product categories: air freshener spray, solid air freshener, oven cleaner, surface cleaner, and mold/mildew control with bleach.

beliefs about heredity as a cause. The odds ratio for breast cancer and family history was markedly higher among women who believed that heredity contributes "a lot" (OR = 2.6, 95% CI: 1.9, 3.6) and not elevated among others (OR = 0.7, 95% CI: 0.5, 1.1, interaction term  $P < 0.01$ ). The parallel pattern of results for both cleaning products and family history when stratified by relevant beliefs is shown in Figure 1. (For all participants, the odds ratio for family history was 1.4 (95% CI: 1.1, 1.9)). The un-stratified and stratified effect estimates for family history of breast cancer in adjusted models remain virtually unchanged after removing subjects with imputed values for family history.

## Discussion

Women with the highest combined cleaning product use had two-fold increased breast cancer risk compared to those with the lowest reported use. Use of air fresheners and products for mold and mildew control were associated with increased risk. To our knowledge, this is the first published report on cleaning product use and risk of breast cancer.

Some common ingredients of air fresheners and products for mold and mildew have been identified as EDCs or carcinogens, supporting the biological plausibility of the elevated odds ratios we observed [1,15,41-51]. EDCs such as synthetic musks and phthalates are commonly used in air fresheners [19,25-27,43,48,52-54] and antimicrobials, phthalates, and alkylphenolic surfactants are often in mold and mildew products [19,22-24,26,27,41,42,44,47,49,55]. In addition, air fresheners may contain: terpenes, which can react with background ozone to form formaldehyde, a human carcinogen [50]; benzene and styrene [51], which are animal mammary gland carcinogens [1]; and other chemicals whose mechanisms of action are not understood

[56]. Although exposure levels may be low and EDCs are typically less potent than endogenous hormones, limited knowledge of product formulations, exposure levels, and the biological activity and toxicity of chemical constituents alone and in combination make it difficult to assess risks associated with product use. Additionally, the products we assessed may be proxies for other products that we did not include, and mold/mildew products may be proxies for exposure to mycotoxins, some of which are EDCs [2,57-59].

Our results do not corroborate the findings of a Long Island, NY, case-control study [31]. The Long Island study found increased breast cancer risk associated with self-reported overall pesticide use and use of lawn and garden pesticides, but we did not. Neither study found associations for nuisance pest control (roaches, ants, etc.). While we observed increased risk with frequent use of insect repellent, the Long Island study did not. Differences between the studies may be due to differences in pesticide practices in the two regions, greater statistical power in the Long Island study, or differences in the survey instruments. Phthalates and permethrins, which are in some insect repellents, have been identified as EDCs [10,13,46,60].

Using interviews to assess product-related exposures, as we did in this study, has several advantages. It is inexpensive, noninvasive, and integrates exposures over many years and to frequently-occurring chemical mixtures. Currently available biological measures cannot achieve these important characteristics.

However, self-reported exposures are subject to multiple sources of error resulting in misclassification. Our questions were cognitively demanding in that they asked participants to report behaviors occurring months to years before. Responses failed to capture use by others, including residues from before the participant moved into the

**Table 3 Adjusted odds ratios for breast cancer and residential pesticide use, Cape Cod, Massachusetts, 1988-1995**

Product category	Cases (no.)	Controls (no.)	Adjusted OR	(95% CI)	<i>P</i> trend
Combined pesticide use					
Quartile 1	173	152	1.0	Reference	
Quartile 2	110	99	1.0	0.7, 1.5	
Quartile 3	169	143	1.1	0.8, 1.5	
Quartile 4	153	126	1.1	0.8, 1.6	0.52
Insect or bug control					
Never use	161	151	1.0	Reference	
Any use	569	514	1.1	0.9, 1.4	
Once or twice	161	155	1.0	0.7, 1.4	
3-10 times	203	188	1.1	0.8, 1.5	
> 10 times	205	171	1.2	0.8, 1.6	0.21
Termite or carpenter ant control					
Never use	293	265	1.0	Reference	
Any use	165	161	0.9	0.6, 1.2	
Once or twice	105	85	1.0	0.7, 1.5	
3-10 times	35	49	0.6	0.4, 1.0	
> 10 times	25	27	0.8	0.4, 1.4	0.11
Mosquito control					
Never use	314	312	1.0	Reference	
Any use	91	87	1.0	0.7, 1.5	
Once or twice	15	18	0.9	0.5, 1.9	
3-10 times	35	31	1.1	0.7, 1.9	
> 10 times	41	38	1.0	0.6, 1.7	0.79
Mothball control					
Never use	73	91	1.0	Reference	
Any use	340	312	1.2	0.8, 1.7	
< 5 times	92	90	1.2	0.8, 1.9	
5-10 times	62	73	0.9	0.6, 1.5	
> 10 times	186	149	1.3	0.9, 1.9	0.29
Lawn care					
Never use	316	286	1.0	Reference	
Any use	408	343	1.1	0.9, 1.3	
Once or twice	43	35	1.2	0.7, 1.9	
3-20 times	174	136	1.2	0.9, 1.6	

**Table 3 Adjusted odds ratios for breast cancer and residential pesticide use, Cape Cod, Massachusetts, 1988-1995 (Continued)**

> 20 times	191	172	1.0	0.7, 1.3	0.88
Outdoor and indoor plant care					
Never use	407	359	1.0	Reference	
Any use	334	300	1.0	0.8, 1.2	
Once or twice	33	26	1.1	0.6, 1.8	
3-20 times	158	146	1.0	0.7, 1.3	
> 20 times	143	128	1.0	0.7, 1.3	0.71
Insect repellent					
Never use	286	271	1.0	Reference	
Any use	482	428	1.2	0.9, 1.5	
Rarely	283	263	1.1	0.9, 1.5	
Sometimes	133	115	1.2	0.9, 1.7	
Often/Very often	66	50	1.5	1.0, 2.3	0.05
Lice control					
Never use	692	626	1.0	Reference	
Any use	89	83	1.2	0.8, 1.6	
Flea collar for pets					
No	257	238	1.0	Reference	
Yes	529	482	1.2	0.9, 1.5	
Flea control for pets					
Never use	465	395	1.0	Reference	
Any use	294	286	1.0	0.8, 1.2	
Once or twice	43	41	0.9	0.6, 1.5	
3-10 times	101	109	0.9	0.6, 1.2	
> 10 times	150	136	1.1	0.8, 1.4	0.95

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories), study (Cape, PCE). "Combined pesticide use" product category includes frequency data for: insect or bug control, lawn care, outdoor and indoor plant care, insect repellent, flea control on pets. Product use for termite or carpenter ant control, mosquito control, and mothball control not included because they were only assessed in study participants from the 1999-2000 interviews.

residence; exposures specific to critical periods such as adolescence; exposures outside the home; or all products that contain the chemicals of interest. Although we asked about the first and most recent years of pesticide use, we considered the quality of these data inadequate to evaluate effects of duration of use. Much of the error resulting from limitations in exposure measurement is likely nondifferential, biasing odds ratios toward the null.

Self-reports are also vulnerable to bias from differential recall between cases and controls. Women diagnosed with breast cancer may have searched their

history for explanations, priming greater recall of product use than for controls. Werler [39], among others, hypothesizes that this type of bias occurs when cases are aware of the study hypothesis, resulting in higher exposure reporting and, consequently, an elevated odds ratio. We empirically investigated this possibility by stratifying odds ratios by beliefs about breast cancer causes, and, consistent with Werler's hypothesis, we observed higher odds ratios for product use among women who believe chemicals and pollution contribute "a lot" to breast cancer than among others.

**Table 4 Beliefs about the causes of breast cancer by case status, Cape Cod, Massachusetts, 1988-1995**

How much does ... contribute to breast cancer?		Cases		Controls	
		No.	%	No.	%
Heredity	A lot	331	42	474	66 **
	A little	295	37	163	23
	Not at all	99	13	36	5
	Don't know	62	8	48	7
Diet	A lot	217	28	205	28
	A little	327	42	294	41
	Not at all	160	20	125	17
	Don't know	83	11	97	13
Chemicals and pollutants in the air or water	A lot	476	60	412	57 *
	A little	188	24	203	28
	Not at all	53	7	31	4
	Don't know	70	9	75	10
Women's reproductive or breast feeding history	A lot	67	9	70	10
	A little	262	33	261	36
	Not at all	245	31	225	31
	Don't know	213	27	165	23

Percentages may not add to 100% because of rounding. Two-sided P value calculated using chi square test; \* indicates  $P < 0.05$  and \*\* indicates  $P < 0.001$ .

However, the family history odds ratios stratified by beliefs suggest another interpretation. The much higher family history odds ratios for women who said heredity contributes “a lot” is unlikely to be primarily due to recall bias, given that self-reporting of first degree family members with breast cancer is generally accurate [61-66]. Previous research indicates that over-reporting of first degree breast cancer family history is negligible [63,65,66] and that some under-reporting by controls in comparison with cases is likely to occur (and could bias odds ratios), but this effect is unlikely to be substantial [64-66]. More likely, our results are primarily driven by cases who formed their belief that heredity does not contribute “a lot” after their own diagnosis, based on their own lack of relatives with breast cancer. Our data support this idea: 36% of cases with no family history said heredity contributes “a lot” to breast cancer compared with 61% of cases who did have a family history (Table 7). In this situation, an odds ratio for women who do not think heredity contributes “a lot” over-represents cases with no family history, lowering the effect estimate. Thus, our results support Weiss’s argument [40] that limiting estimates to a subgroup based on beliefs about disease causation may introduce error. Among the group who do not believe heredity contributes “a lot” to breast cancer, the odds ratio of 0.7 (95%

CI: 0.5, 1.1) contrasts sharply with the pooled odds ratio of 2.1 (95% CI: 2.0, 2.2) for first degree family history of breast cancer from previous studies [67]. Generally, Weiss argues, effect estimates based on one belief or knowledge subgroup lack precision and may underestimate the true effect, since they are limited to smaller numbers and not representative of the study population [40].

The divergent odds ratios in the stratified analysis for family history, which is not likely affected much by recall bias, warns us that the elevated odds ratios for cleaning products should not be too quickly dismissed as resulting from recall bias, since an alternative interpretation is that women’s beliefs about disease causation result from their experience. Women who have been intensive product users and are then diagnosed with breast cancer may form the belief that chemicals influenced their risk, or they may be sensitized to news media stories about associations between chemicals and disease and form beliefs from this experience. Social scientists have studied the phenomenon of health beliefs formed from experience in a variety of settings, including the emergence of beliefs about environmental causation among breast cancer activists [68].

Furthermore, the substantial underestimate of risk for family history among women who said heredity does

**Table 5 Adjusted odds ratios for breast cancer and cleaning product use stratified by disease causation beliefs**

Beliefs about environmental chemicals/pollutants and breast cancer										
Product category	Contributes "a lot"					Does not contribute "a lot"				
	Cases (no.)	Controls (no.)	Adj. OR	95% CI	<i>P</i> <sub>trend</sub>	Cases (no.)	Controls (no.)	Adj. OR	95% CI	<i>P</i> <sub>trend</sub>
Combined cleaning product use										
Quartile 1	39	55	1.0	Ref.		52	44	1.0	Ref.	
Quartile 2	58	69	1.4	0.8, 2.4		42	38	0.9	0.5, 1.8	
Quartile 3	71	74	1.6	0.9, 2.8		41	51	0.8	0.4, 1.4	
Quartile 4	77	47	3.2	1.8, 5.9	0.0001	27	23	1.2	0.6, 2.6	0.96
Combined air freshener use (sprays and solids)										
Quartile 1	34	43	1.0	Ref.		40	34	1.0	Ref.	
Quartile 2	67	71	1.3	0.7, 2.4		46	46	0.9	0.5, 1.7	
Quartile 3	76	86	1.3	0.7, 2.2		47	52	0.8	0.4, 1.6	
Quartile 4	69	46	2.4	1.3, 4.5	0.01	32	25	1.4	0.7, 3.0	0.53
Air freshener spray										
Never use	44	50	1.0	Ref.		46	45	1.0	Ref.	
Any use	203	196	1.3	0.8, 2.1		119	112	1.2	0.7, 2.0	
< Once a month	50	57	1.1	0.6, 2.0		33	31	1.1	0.6, 2.2	
Monthly	32	32	1.2	0.6, 2.3		15	9	1.9	0.7, 5.0	
Weekly	71	62	1.5	0.8, 2.6		43	48	1.0	0.6, 2.0	
Daily	50	45	1.4	0.8, 2.7	0.12	28	24	1.2	0.6, 2.6	0.66
Solid air freshener										
Never use	144	174	1.0	Ref.		115	114	1.0	Ref.	
Any use	102	72	1.9	1.3, 2.9		51	43	1.4	0.8, 2.3	
< 2/year	27	28	1.3	0.7, 2.3		23	13	1.9	0.9, 4.1	
2-6/year	58	32	2.6	1.6, 4.4		19	26	0.9	0.4, 1.8	
≥ 7/year	17	12	1.7	0.8, 3.9	0.0007	9	4	2.8	0.8, 10.2	0.31
Oven cleaner										
Never use	11	19	1.0	Ref.		22	14	1.0	Ref.	
Any use	236	227	1.8	0.8, 4.0		143	143	0.6	0.3, 1.2	
< 2/year	96	86	2.0	0.9, 4.6		49	57	0.4	0.1, 1.3	
2-6/year	112	121	1.5	0.6, 3.4		87	75	0.7	0.3, 1.5	
≥ 7/year	28	20	2.4	0.9, 6.5	0.58	7	11	0.4	0.1, 1.3	0.73
Surface cleaner										
Never use	29	36	1.0	Ref.		24	18	1.0	Ref.	
Any use	218	209	1.5	0.9, 2.7		141	139	0.7	0.4, 1.5	
< Once a month	23	30	0.9	0.4, 1.9		38	30	0.9	0.4, 2.0	
Monthly	39	36	1.5	0.7, 3.1		18	21	0.6	0.2, 1.4	
Weekly	120	103	1.7	1.0, 3.0		66	68	0.7	0.3, 1.5	



**Table 5 Adjusted odds ratios for breast cancer and cleaning product use stratified by disease causation beliefs (Continued)**

Daily	36	40	1.7	0.8, 3.6	0.02	19	20	0.8	0.3, 2.1	0.45
Mold/mildew control										
Never use	166	197	1.0	Ref.		130	125	1.0	Ref.	
Any use	80	49	2.1	1.4, 3.3		34	32	1.1	0.6, 2.0	
Mold/mildew control with bleach										
Never use	179	202	1.0	Ref.		141	132	1.0	Ref.	
Any use	67	44	1.8	1.2, 2.9		23	24	1.0	0.5, 2.0	
< Once a month	33	25	1.4	0.8, 2.5		14	13	1.1	0.5, 2.4	
Monthly	10	7	1.8	0.6, 5.1		4	4	1.1	0.3, 4.7	
≥ Weekly	24	12	3.2	1.4, 7.1	0.002	5	7	0.8	0.2, 2.7	0.83

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories). "Combined cleaning product use" product category combines frequency of use across five product categories: air freshener spray, solid air freshener, oven cleaner, surface cleaner, and mold/mildew control with bleach.

not contribute "a lot" cautions us against limiting product use analyses to a non-belief subgroup as a strategy for dealing with possible recall bias. In addition, the findings of elevated risk for some cleaning products and not others lends evidence that recall bias may not account for elevated risks, even if it contributes in part, since bias would be expected to similarly influence reporting for all the products.

Studies that rely on questionnaire data can sometimes assess the validity of self-reported data against another metric, such as chemical concentrations in relevant exposure media. For example, Colt et al. [69] found significant associations between self-reports of type of pest treated and concentrations of specific pesticides in house dust. We collected air, dust, and urine measurements for 120 homes and their residents, but comparison of these data with self-reports was not conducted for several reasons. The number of homes is small, the one-time environmental measurements may not correspond well with product use over years, measurements capture sources other than home product use, and our self-reports cover past residences as well as the sampled homes. Our ambiguous self-report findings point to the value of thoughtfully incorporating environmental chemical measurements into prospective cohort studies such as the National Children's Study and the Sister Study.

Overall strengths of our study are the population-based design with case identification from the MCR, extensive interviews allowing evaluation of possible confounding by established and hypothesized breast cancer risk factors, and assessment of exposures that extend years before diagnosis and encompass chemicals in use

during the past 30 years as well as the more-studied banned organochlorines. Limitations include loss of information due to deaths of women with less treatable cancers. Also, we lack a truly unexposed reference group, limiting contrast in levels of exposure. The self-reported product use exposures have potential for differential and nondifferential error. We did not have adequate numbers to separately evaluate effects in younger women, though some other studies suggest that environmental pollutants may have greater influence on premenopausal disease [28].

To our knowledge, this is the first epidemiological study to suggest an association between cleaning product use, in particular air fresheners and products for mold and mildew control, and elevated breast cancer risk. This association is biologically plausible based on ingredients of these products, such as musks, antimicrobials, and phthalates [1-27,41-49,70-73], and these reported exposures may be proxies for other un-assessed causative exposures. The modest association and possibility of recall bias make interpretation tentative. Given widespread exposure to cleaning products and scented products, follow-up study is important. Prospective designs, which avoid differential recall, can be helpful. The difficulty of obtaining human evidence on environmental chemicals and breast cancer in the short-term means we must rely more on laboratory evidence as a basis for public health policies to control exposure.

## Conclusions

Laboratory studies have found that many chemicals in home-use pesticides and household cleaning products are mammary gland carcinogens in rodents, influence

**Table 6 Adjusted odds ratios for breast cancer and residential pesticide use stratified by disease causation beliefs**

Beliefs about environmental chemicals/pollutants and breast cancer										
Product category	Contributes "a lot"					Does not contribute "a lot"				
	Cases (no.)	Controls (no.)	Adj. OR	95% CI	P <sub>trend</sub>	Cases (no.)	Controls (no.)	Adj. OR	95% CI	P <sub>trend</sub>
Combined pesticide use										
Quartile 1	91	87	1.0	Ref.		82	65	1.0	Ref.	
Quartile 2	66	47	1.5	0.9, 2.5		44	52	0.7	0.4, 1.1	
Quartile 3	104	89	1.2	0.8, 1.9		65	54	1.0	0.6, 1.7	
Quartile 4	106	75	1.5	1.0, 2.4	0.16	47	51	0.7	0.4, 1.3	0.53
Insect or bug control										
Never use	81	78	1.0	Ref.		80	73	1.0	Ref.	
Any use	367	305	1.2	0.9, 1.8		202	209	0.9	0.6, 1.3	
Once or twice	105	90	1.1	0.7, 1.8		56	65	0.8	0.5, 1.3	
3-10 times	130	117	1.1	0.8, 1.7		73	71	1.0	0.6, 1.6	
> 10 times	132	98	1.4	0.9, 2.1	0.12	73	73	0.9	0.6, 1.4	0.86
Termites/carpenter ants										
Never use	161	146	1.0	Ref.		132	119	1.0	Ref.	
Any use	112	102	1.0	0.7, 1.4		53	59	0.7	0.4, 1.1	
Once or twice	68	54	1.1	0.7, 1.7		37	31	1.0	0.5, 1.7	
3-10 times	28	30	0.9	0.5, 1.6		7	19	0.2	0.1, 0.6	
> 10 times	16	18	0.8	0.4, 1.7	0.55	9	9	0.7	0.3, 2.1	0.06
Mosquito control										
Never use	176	186	1.0	Ref.		138	126	1.0	Ref.	
Any use	65	58	1.1	0.7, 1.7		26	29	0.8	0.4, 1.4	
Once or twice	10	11	1.2	0.7, 2.2		5	7	0.7	0.2, 2.3	
3-10 times	23	22	1.1	0.6, 2.1		12	9	1.2	0.5, 3.2	
> 10 times	32	25	1.2	0.7, 2.2	0.47	9	13	0.5	0.2, 1.4	0.33
Mothball control										
Never use	40	56	1.0	Ref.		33	35	1.0	Ref.	
Any use	207	190	1.3	0.8, 2.1		133	122	1.0	0.6, 1.8	
< 5 times	50	55	1.2	0.7, 2.1		42	35	1.3	0.7, 2.7	
5-10 times	40	53	1.0	0.5, 1.8		22	20	0.9	0.4, 2.0	
> 10 times	117	82	1.6	1.0, 2.8	0.06	69	67	0.9	0.5, 1.7	0.41
Lawn care										
Never use	190	169	1.0	Ref.		126	117	1.0	Ref.	
Any use	250	196	1.1	0.8, 1.5		158	147	1.1	0.8, 1.5	
Once or twice	24	21	1.0	0.5, 2.0		19	14	1.4	0.7, 3.0	
3-20 times	115	83	1.2	0.8, 1.7		59	53	1.1	0.7, 1.8	

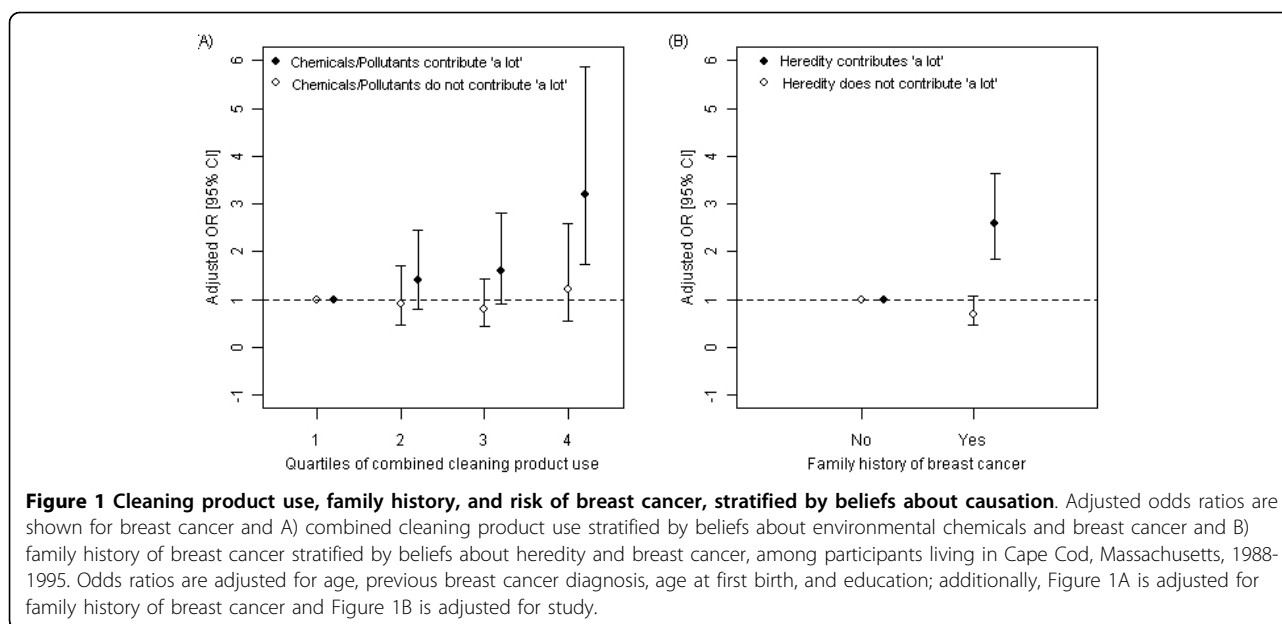
**Table 6 Adjusted odds ratios for breast cancer and residential pesticide use stratified by disease causation beliefs (Continued)**

> 20 times	111	92	1.0	0.7, 1.5	0.58	80	80	1.0	0.6, 1.5	0.98
Outdoor and indoor plant care										
Never use	235	198	1.0	Ref.		172	161	1.0	Ref.	
Any use	214	173	1.0	0.8, 1.4		120	127	0.8	0.6, 1.2	
Once or twice	18	12	1.2	0.5, 2.6		15	14	0.9	0.4, 2.0	
3-20 times	104	86	1.0	0.7, 1.5		54	60	0.8	0.5, 1.2	
> 20 times	92	75	1.0	0.7, 1.4	0.99	51	53	0.9	0.5, 1.4	0.39
Insect repellent										
Never use	153	134	1.0	Ref.		133	137	1.0	Ref.	
Any use	312	261	1.2	0.9, 1.6		170	167	1.2	0.8, 1.7	
Rarely	179	149	1.2	0.8, 1.6		104	114	1.1	0.7, 1.6	
Sometimes	85	85	1.0	0.6, 1.5		48	30	1.9	1.1, 3.4	
Often/Very often	48	27	2.0	1.1, 3.4	0.12	18	23	0.8	0.4, 1.6	0.45
Lice control										
Never use	414	344	1.0	Ref.		278	282	1.0	Ref.	
Any use	59	58	1.1	0.7, 1.7		30	25	1.4	0.8, 2.5	
Flea collar for pets										
No	132	122	1.0	Ref.		125	116	1.0	Ref.	
Yes	344	290	1.3	0.9, 1.8		185	192	1.0	0.7, 1.4	
Flea control for pets										
Never use	256	214	1.0	Ref.		209	181	1.0	Ref.	
Any use	196	177	1.1	0.8, 1.4		98	109	0.8	0.5, 1.1	
Once or twice	23	23	0.9	0.5, 1.6		20	18	1.0	0.5, 2.1	
3-10 times	63	74	0.8	0.5, 1.2		38	35	0.9	0.6, 1.6	
> 10 times	110	80	1.4	0.9, 2.0	0.27	40	56	0.6	0.4, 1.0	0.07

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories), study (Cape, PCE). "Combined pesticide use" product category includes frequency data for: insect or bug control, lawn care, outdoor and indoor plant care, insect repellent, flea control on pets. Product use for termite or carpenter ant control, mosquito control, and mothball control not included because they were only assessed in study participants from the 1999-2000 interviews.

the proliferation of estrogen-sensitive cells, or affect mammary gland development following prenatal exposure. These findings suggest effects of pesticide and cleaning product use on breast cancer risk, so we undertook a case-control study of breast cancer and self-reported product use. We found increased breast cancer risk among women reporting the highest use of cleaning products and air fresheners. We found little association with home pesticide use. The self-reported product use measures we used have the advantage of integrating

exposure over many years to chemical mixtures. However, these measures remain incomplete, likely resulting in nondifferential misclassification, and they are open to recall bias. Investigators sometimes try to avoid the influence of recall bias by limiting analyses to participants who do not subscribe to the study hypothesis, but our results show this may not be a good strategy, given that in our study it would obscure the well-established association between family history and breast cancer risk. In order to avoid possible recall bias, we



**Table 7 Beliefs about heredity as a cause of breast cancer by family history and case status**

Belief		Cases				Controls			
		Family history of breast cancer				Family history of breast cancer			
		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	
Heredity contributes "a lot" to breast cancer	Yes	120	61	211	36	83	61	391	67
	No	76	39	380	64	52	39	195	33

recommend further study of cleaning products and breast cancer using prospective self-reports and measurements in environmental and biological media.

**Abbreviations**

CI: confidence interval; CMS: Centers for Medicare and Medicaid Services; EDCs: endocrine-disrupting compounds; OR: odds ratio; MCR: Massachusetts Cancer Registry; PCE: tetrachloroethylene; Ref: reference; Adj OR: adjusted odds ratio; NY: New York; US: United States.

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**Authors' contributions**

ARZ conducted the statistical analyses and led drafting of the manuscript. AA designed and oversaw the PCE Study; contributed to the design, data collection, and epidemiological analysis of the Cape Cod Study; and

collaborated on editorial issues. RAR contributed to the design, data collection, and analysis of the Cape Cod Study, particularly with respect to the toxicologic characteristics of exposures, and collaborated in drafting the manuscript. JGB led the design, implementation, and analysis of the Cape Cod Study and collaborated in drafting the manuscript; she conceptualized the comparative analysis of product use and family history odds ratios stratified by beliefs as a strategy for understanding possible response bias. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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