Cancer Risk and Residential Proximity to Cranberry Cultivation in Massachusetts

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ABSTRACT

Objectives. This study evaluated the relationship between cancer risk and residential proximity to cranberry cultivation. [1]

Methods. A population-based case–control study was conducted. [2-3] Cases, diagnosed during 1983 through 1986 among residents of the Upper Cape Cod area of Massachusetts, involved incident cancers of the lung (n = 252), breast (n = 265), colon–rectum (n = 326), bladder (n = 63), kidney (n = 35), pancreas (n = 37), and brain (n = 37), along with leukemia (n = 35). Control subjects were randomly selected from among telephone subscribers (n = 184), Medicare beneficiaries (n = 464), and deceased individuals (n = 723). [3-5]

Results. No meaningful increases in risk were seen for any of the cancer sites except for the brain. [6] When latency was considered, subjects who had ever lived within 2600 ft (780 m) of a cranberry bog had a twofold increased risk of brain cancer overall (95% confidence interval [CI] = 0.8, 4.9) and a 6.7-fold increased risk of astrocytoma (95% CI = 1.6, 27.8). [7-9]

Conclusions. Residential proximity to cranberry bog cultivation was not associated with seven of the eight cancers investigated; however, an association was observed with brain cancer, particularly astrocytoma. Larger, more detailed studies are necessary to elucidate this relationship. (*Am J Public Health.* 1996;86: 1289–1296) [10]

Introduction

Since the inception of the Massachusetts Cancer Registry in 1982, statistically significant increases in the standardized incidence ratios for cancers of the lung, breast, colon–rectum, and blood-forming organs and statistically unstable excesses of cancers of the kidney, bladder, and pancreas have been observed in the Upper Cape Cod area relative to statewide averages.[1] The elevated rates cannot explained by differences in age, gender, or reporting practices.[1] [12-13]

During this period, many environmental hazards affecting the Upper Cape area also have come to public attention, including groundwater and air contamination from a variety of sources such as the Massachusetts Military Reservation (currently a Superfund National Priority List site), perchloroethylene in water distribution system pipes,[2] and possible exposure to herbicides and pesticides among residents who live near cranberry cultivation. [14]

Residential proximity to cranberry bog cultivation has warranted concern because, unlike most of Massachusetts, the Upper Cape region has had substantial acreage devoted to cranberry cultivation since the late 1800s.[3–5] Numerous herbicides, insecticides, and fungicides have been approved for use on the bogs for varying periods of time since the 1930s. These chemicals include kerosene, dichlorobenil, DDT, dieldrin, aldrin, 2,4,5-trichlorophenoxyacetic acid, heptachlor, chlordane, pyrethrum, malathion, parathion, cryolite, lead arsenate, carbaryl, diazinon, azinphos-methyl, and aminotriazole (I. Demoranville, Director, Cranberry Experiment Station, East Wareham, Mass, personal communication, March 1989).[4–7]

From the 1930s through the mid-1950s, these chemicals were applied primarily through ground-based methods, including truck and power nozzle spraying, power dusting, and hand spraying (I. Demoranville, personal communication, March 1989).[5] From the mid 1950s through the 1970s, aerial methods were used more often (both fixed-wing aircraft and helicopters). In the 1980s, chemicals were applied primarily through sprinkler systems in the bogs. [15]

We undertook a population-based case–control study to evaluate the relationship between nine types of cancer (lung, breast, colorectal, bladder, kidney, pancreas, brain, and liver cancer, along with leukemia) and several sources of environmental contamination in the region.[2,8,9] The current report focuses on the risk of cancer among Upper Cape residents who lived near cranberry cultivation. On the basis of studies of occupational and nonoccupational exposure to agricultural chemicals similar to those applied to the bogs,[10–19] we hypothesized that positive associations were likely for cancers of the kidney, colon–rectum, brain, and hematopoietic system. [16]

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Note. The views expressed here are the authors' and do not necessarily represent those of the Massachusetts Department of Environmental Protection or the Massachusetts Department of Public Health.

1. The study was conducted to determine if there is evidence of an association between the **exposure** (living near a cranberry farm) and the **outcome** (the likelihood of developing cancer).

2. The type of study is identified; it is a **case-control** study. A **case-control** study is an efficient way to study rare diseases and diseases that take a long time to develop, such as cancers. **Case-control** studies begin with known cases, and then select non-cases, known as **controls**, from the same source population, for the purpose of comparing the exposures of the cases and controls.

3. **Population-based** means that the cases and controls were selected from an area defined by its geography. This study includes residents of several towns on Cape Cod.

4. **Incident** cases are newly diagnosed/reported cases, as opposed to all people who currently have cancer but were diagnosed in the past.

5. "n" is the number of people in the study with each diagnosis. They are referred to as research "subjects."

6. For cancer in parts of the body other than the brain, small increases in risk may have been observed, but the study's authors believed that the reason for increased risk was random, and not the effect of exposure.

7. Cancer does not develop immediately after exposure to an environmental hazard; it takes time to develop (often 10-20 years). The fact that such period of time exists between **exposure** and **outcome** is called disease **latency**. The authors took this into consideration in their analysis.

8. In this study, the people who lived within 2600 feet of a cranberry farm, or bog, were twice as likely to develop brain cancer compared to people who lived further away. A **confidence interval** presents a range of values (low to high), between which we expect the true value of the measure of interest to be, to a certain level of confidence (very often a 95%, meaning that the researcher would be 95% confident the true value would fall in the calculated interval). The 95% **confidence interval** was quite narrow in this case, suggesting the estimate of risk was fairly accurate.

9. Astrocytoma is a particular kind of brain cancer. When astrocytoma was considered separately from other brain cancers, the increased risk was even larger (see Table 5).

10. In parentheses is shown the standard format to refer to (cite) this study: (Journal title abbreviation. Year; volume: page start – page end). Researchers with access to only the abstract can use this standard citation to look up the full article.

11. "**Statistical significance**" is a term used for results that have been statistically tested and found to be meaningful according to statistical standards. In this example, when compared with the entire State of Massachusetts, the measure of incidence ratios for certain cancers in areas of Cape Cod are so much higher that the authors figured the cancers in these areas may not be simply the result of bad luck. In other words, the difference in cancer rates was not likely to be the result of chance alone and very likely the result of environmental exposures. These statistically significant measurements were the basis for further study.

12. Statistically unstable results are results that do not fall at or below the level of significance (in most cases, .05). This indicates that chance may be responsible for the excesses, though it does not tell you for certain that chance *is* the cause of the result. Unstable results often occur when there are small sample sizes. In the case of small samples, each additional person's outcome could swing the total result in one direction or the other because each additional outcome would be a large fraction of the small group of cases.

13. Differences in age, gender, and reporting practices are three factors which might have caused the observed differences in cancer incidence between the Upper Cape Cod area and statewide averages. On Cape Cod, for example, many people who live there have retired, and the general population is older than the general US population. However, the authors took this fact into consideration and ruled out these differences as possible explanations for the high cancer.

14. The **Superfund site** (a hazardous waste site on the National Priorities List for evaluation and possible cleanup) and the other environmental hazards were mentioned in an attempt by the authors to describe exposures they thought might affect the health of residents on the Cape, particularly cancers. For example, perchloroethylene is a solvent that is considered a probable human carcinogen (there is evidence that it causes cancer in humans, though it is not conclusive) by several international health organizations.

15. This entire section of the article summarizes historic exposures that might have contributed to the cancers. Thorough consideration of methods used for applying pesticides revealed that nearly all involved the chemicals traveling through the air, which means that they probably traveled to areas beyond the intended target area.

16. Epidemiologic studies, particularly **case-control** studies, are expensive and time consuming. Here the authors are justifying their investment in a case-control study by acknowledging the results of similar studies done in the past that have found associations. Based on this existing data, the authors hypothesized that people who lived near cranberry bogs (and as a result, were exposed to pesticides that drifted from the bogs) would likely have elevated cancers of the kidney, colon, brain and hematopoietic system (organs and tissues involved in the production of blood, e.g., bone marrow, spleen, etc.).

TABLE 1—Selection and Enrollment of Cancer Case Patients and Control Subjects, Upper Cape Cod, Mass, 1983 through 1986

	Selected, No.	Excluded, No.			Interviewed, No.
		Never Found or Contacted	Not Eligible	Physician or Subject Refusal	
Case subjects, by cancer site					
Lung	326	46	8	20	252
Breast	334	33	6	30	265
Colorectal	420	51	3	40	326
Bladder	79	7	0	9	63
Kidney	42	6	0	1	35
Pancreas	43	3	1	2	37
Brain	42	1	1	3	37
Leukemia	44	4	2	3	35
Control subjects, by selection method					
Health Care Financing Administration	611	21	53	73	464
Deceased	918	97	27	71	723
Random-digit dialing	2236	456	1531[a]	65	184

[a]Includes 129 individuals who refused to answer the eligibility screening questions.

Methods

Selection and Enrollment of Study Population

The cases involved incident cancers of the lung (n = 326), breast (n = 334), colon–rectum (n = 420), bladder (n = 79), kidney (n = 42), pancreas (n = 43), brain (n = 42), and liver (n = 6), as well as leukemia (n = 44), diagnosed from 1983 through 1986 among permanent residents of the five Upper Cape towns (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich) and reported to the Massachusetts Cancer Registry. Liver cancer is omitted from this report since there were too few cases for meaningful evaluation. [17-18]

Cancer incidence rates from the Massachusetts registry are comparable to those of the nearby Connecticut registry and the American Cancer Society, indicating good ascertainment for the cancers and geographic area under study.[20] The [19] rates for all sites except brain and liver were elevated at the start of the study among men and/or women in at least one of the Upper Cape towns. Brain and liver cancer were not initially included for study but were added during the first year because of their possible environmental etiology.[21] [20]

The control subjects came from the same population that gave rise to the cases: permanent residents of the Upper Cape towns during 1983 through 1986. Since many case patients were elderly or deceased at the time the study began, three sources were used to identify comparable controls efficiently. [21]

A random sample of living control subjects less than 65 years of age who resided in the Upper Cape towns during the case ascertainment period was selected via random-digit dialing. According to the 1980 census, more than 95% of Massachusetts housing units had telephone service.[22] A total of 2236 residential households were identified (Table 1). Of these, 249 households with an eligible respondent were identified, and 184 of these respondents were interviewed (74%). [22]

Living control subjects 65 years of age and older were identified through lists of the elderly provided by the Health Care Financing Administration (HCFA). These lists are estimated to include 95% of individuals 65 years of age and older in the United States.[23] Six hundred eleven HCFA control subjects were randomly selected from the Upper Cape population by means of an age- and gender-stratified sampling scheme. Vital status and residence were determined, and all deceased individuals and non–Upper Cape residents were excluded. [23]

Control subjects who had died from 1983 through 1989 were randomly selected from a listing of all Upper Cape resident deaths, furnished by the Massachusetts Department of Vital Statistics and Research, that included all individuals regardless of cause of death. A sampling scheme stratified on age, gender, and year of death produced 918 deceased control subjects. The deceased control subjects' residences during the case ascertainment period were determined, and nonresidents were excluded. [24]

Follow-Up and Interviews

Current addresses and telephone numbers of subjects or their next of kin were determined through Massachusetts Cancer Registry, HCFA, and physician records; voter registration lists; driver's license and vital statistics records; and telephone directories. Permission to interview the living case patients was obtained from physicians, in accordance with Massachusetts Cancer Registry guidelines.

Structured interviews were carried out by trained personnel to obtain information on demographic characteristics, smoking, alcohol consumption, medical conditions, reproductive events, occupations since the age of 18 years, and a residential history from 1943 through 1986. These calendar years were defined as the study period since they encompassed the relevant etiologic period for the inception and development of the cancers under study. [25]

Seventy-nine percent of the case patients, 74% of identified eligible random-digit dial control subjects, 76% of the HCFA control subjects, and 79% of next of kin for deceased control subjects were interviewed (Table 1). Response rates were fairly similar across cancer sites (77% to 88%; see Table 1). Eighty-six percent of the interviews were conducted by telephone; the remainder were conducted in person. Interviews were conducted with next of kin or household members when subjects were very ill or deceased. [26]

Interviewed and noninterviewed case and control subjects were similar demographically. Of the noninterviewed case patients, 39.0% were male, 96.5% were White, 80.3% were 60 years of age and older, and 44.0% were alive at the time of the interview. By comparison, 41.2% of the noninterviewed HCFA and deceased control subjects were male, 94.7% were White, and 89.5% were 60 years of age and older; 43.5% were alive at the time of the interview. No data were available on noninterviewed random-digit dialing control subjects. [27]

Pathologic records of the cancer cases confirmed that they were nonmetastatic in origin. Among the brain cancer cases, there were astrocytomas (n = 9),

17. Only permanent residents were included; the Cape has many seasonal residents who live in other places during most of the year, when they would likely not live near cranberry bogs.

18. The low number of cases of liver cancer would likely result in **statistically unstable** results, so it was omitted from this report.

19. Since cancer incidence rates from the Massachusetts Cancer Registry overall are not much different than rates from other, independent information sources (one source reporting in geographically-near Connecticut and another source reporting incidence rates nationwide), the authors were confident that the cancer cases reported by Massachusetts Cancer Registry were accurate and that they were able to count all of the cases that actually existed in the area.

20. **Etiology** means the cause of a disease. Though the measures for brain and liver cancer did not appear higher than would be expected on the Upper Cape, those two sites of cancer were included in the study because there is strong evidence to suggest that these diseases are often caused or triggered by environmental exposures. All of the other sites of cancer were analyzed because they appeared high among men and/or women in at least one of the Upper Cape towns.

21. Ensuring that the controls are similar enough to the cases (in age, gender, race, income), so that their unique exposures may be compared, is a big task in case-control studies. The reason for such care in selecting controls is to avoid **bias**, specifically, **selection bias**. **Selection bias** refers to systematic differences in the way participants are selected, which causes compared groups to have different characteristics. Three methods of choosing control subjects are described in the following paragraphs.

22. At the time of this research, a high proportion of Massachusetts households still had land-lines, or home telephone service. Random-digit dialing was an effective method for recruiting control subjects that are similar to the cases. Now, with cell phones, recruitment by this method would be much more difficult.

23. Factors other than the exposure of interest that affect the study **outcome** are known as **confounders.** Confounders confuse the relationship between the exposure of interest and disease. Age and gender are common **confounders.** For example, cancer is more common in older people, so if controls were all older people, it could seem like there is more cancer in the control group and elevations in cancer rates in the cases might appear “normal” when they are actually not. To help prevent confounding, controls from the Health Care Financing Administration (HCFA) lists were **stratified**. In other words, they were separated by age groups and gender and selected so that the proportion of people in each age and gender group was the same as that of the cases. For example, if 53% of the cases were in the 50-59 age group, 53% of the total controls would be in that age group as well. The “n” (number of subjects) does not have to be the same as the cases, as long as the proportions in each age group/gender are the same for the cases and controls.

24. This data source is an example of registry data that is, in theory at least, also available to community groups.

25. Gathering as much information as possible on risks of disease related to lifestyle, genetics, jobs, diet, the environment, medications, etc. is an essential task in characterizing exposures, since it is the differences in exposures that will be compared between the cases and controls. Careful training of interviewers is also critical so that **interviewer bias** is not introduced. For example, prior to the interview, questionnaires are written and carefully followed by interviewers so that all the interviews are almost identical, and cases and controls receive equal treatment.

26. Having similar response rates across subjects adds weight to the internal **validity** of the study. Internal **validity** is maintained by keeping the compared groups as similar as possible in every way, including the proportion of people who were contacted and that were actually interviewed. In this study, both groups seemed to have responded to request for an interview equally.

27. If all participants had not been similar demographically between case and control groups, **bias** could have occurred because the differences (e.g. in age or race) may have been the reason for whether or not the cases became diseased. In other words, the researcher would no longer know what is responsible for the disease.