SCIENCE AND SOCIETY

The Long Island Breast Cancer Study Project

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Abstract | In the early 1990s, breast cancer advocates petitioned the United States Congress to investigate the high rates of breast cancer on Long Island in the state of New York. The resulting law led to the Long Island Breast Cancer Study Project (LIBCSP) — more than ten research projects designed to study the possible causes of this increased incidence of cancer. This project reported that there was no evidence that environmental exposures were responsible. Controversial from its start, the LIBCSP has had an important role in efforts to understand the reasons for the high rates of breast cancer in some regions of the United States.

In the United States, there are several regions in which there is an unusually high incidence of breast cancer, such as Marin County near San Francisco, California, and much of the Northeast. Chemical and physical environmental factors in these areas have been proposed as a cause for this increased incidence, resulting in many epidemiological investigations — including several studies carried out in the northeastern states. One of the most detailed analyses was carried out on the Long Island population, and the results of this project have given valuable lessons about possible aetiologies of breast cancer, as well as some insights into the other 'breast cancer clusters'.

Long Island lies to the east of New York City in the state of New York. A set of research studies comprising the Long Island Breast Cancer Study Project (LIBCSP) has included case–control studies of the relationship between breast cancer and environmental factors, development of a geographical information system (GIS), and other research that has yielded a wealth of information about what factors are or are not associated with the risk of developing breast cancer on Long Island.

The LIBCSP is not the only significant effort to investigate the reasons underlying the high rates of breast cancer in specific geographical regions. However, the congressional genesis of the LIBCSP, the role of the advocates in the research enterprise, the level of controversy engendered by the research, and the research findings themselves make the study unique. The findings from the study are important because geographical variation in cancer incidence and mortality remains a public health as well as personal concern for many people. The LIBCSP has also revealed many of the challenges of examining geographical patterns of cancer. What was the genesis of this project, how was it executed, and what did the outcomes tell us about the environmental factors involved in the development of cancer?

The genesis of the LIBCSP

Maps describing mortality patterns across the United States[1] (FIG. 1) provide clear evidence that death rates for patients with breast cancer are higher in the northeastern United States, including parts of Long Island, than in the United States as a whole. As a result of these observations, in 1992 the United States Congress passed a law requiring the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS), both part of the federal National Institutes of Health, to fund a study on factors that might contribute to the high rates of breast cancer mortality in the northeastern and mid-Atlantic states. Six proposed studies were funded and became collectively known as the New England/Mid-Atlantic (NE/MA) Breast Cancer Study.

Meanwhile, these mortality patterns also generated interest, concern and activity on Long Island — one of the NE/MA studies was conducted there. In the early 1980s, the New York State Department of Health (NYSDOH) published statistics on breast cancer, and it was found that Nassau County on Long Island had one of the highest incidence rates of breast cancer in the state[2]. Statistics on the incidence of cancer from 1988–1992 (REF. 3) showed that 137.8 per 100,000 females in Nassau County and 133.0 per 100,000 females in the adjacent Suffolk County developed breast cancer annually, whereas for New York State as a whole the rates were lower (121.8 per 100,000; FIG. 2). The publication of these statistics created concern among the residents of Long Island, especially among survivors of breast cancer. In 1990, the NYSDOH issued a series of reports that suggested that this pattern was probably because of known, primarily socio-demographic and reproductive risk factors[4–7], and this conclusion was repeated in a report by the federal Centers for Disease Control and Prevention (CDC) in 1992 (REF. 2).

Much of the Long Island area had formerly been farmland, and pesticides had been used extensively both in agricultural and residential settings[8], which generated concern that these agents might be involved in the high incidence of breast cancer. So, owing to their disappointment in the initial findings from the NYSDOH and the CDC and their concern about toxic substances, groups of breast cancer survivors and others organized themselves to address the issue[9,10]. They demonstrated for action at the Nassau County Courthouse, and lobbied their congressmen to legislate an investigation that focused on potential environmental contributions to this pattern of disease. With the persistence of these congressmen, a law was passed by Congress in 1993 mandating the NCI and the NIEHS to conduct a case–control study "to assess biological markers of environmental and other potential risk factors contributing to the incidence of breast cancer in … the Counties of Nassau and Suffolk, in the state of New York" and in two other counties. This included specifying the development of "… a geographic system to evaluate the current and past exposure of individuals"[11].

Environmental exposures

In response to the congressional mandate, the NCI identified and encouraged a number of studies, which, collectively, formed the LIBCSP. The mandated GIS, also called the GIS for Breast Cancer Studies on Long Island (Long Island GIS), has been completed and is available to researchers (BOX 1). GISs can be especially useful for capturing and mapping information about the locations of multiple environmental exposures in relation to patterns of disease. However, there are limitations of GISs, including the difficulty in identifying data for periods of time in the past that might be relevant to diseases of long latency such as breast cancer, accounting for people at different levels of disease risk who are migrating in and out of the geographical area, and other methodological issues. Although there has been limited interest in and use of the Long Island GIS for studies on Long Island specifically, the custom spatial

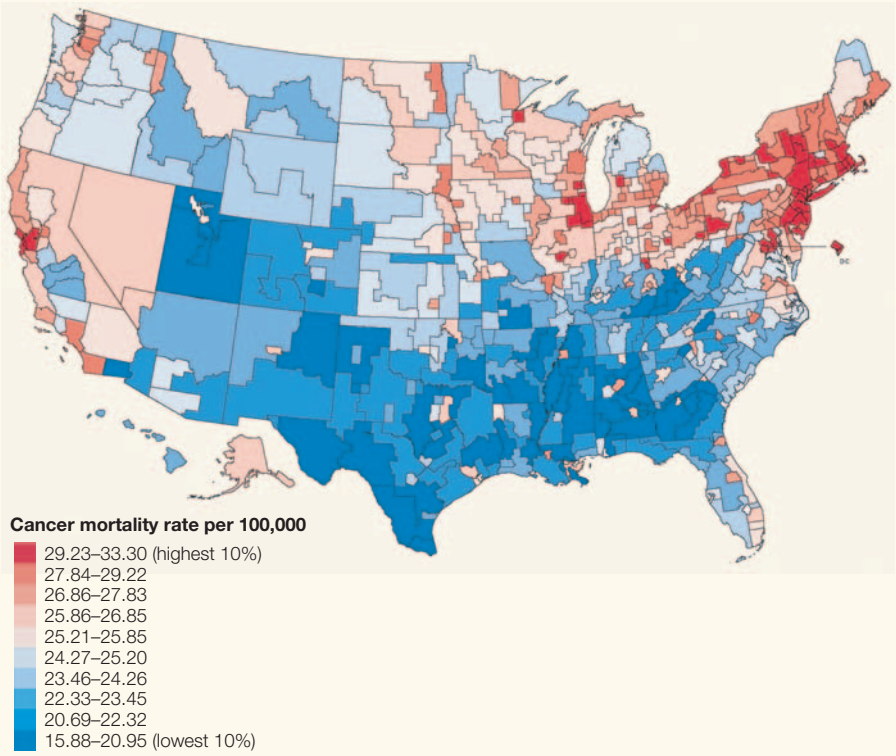

Figure 1 | **Map of mortality from breast cancer among white women in the United States for 1970–1994, by state economic area.** Areas of high incidence are shown in red, and areas of low incidence are shown in blue. The map shows that populations in the northeastern United States, as well as the Great Lakes area and regions of California, had exceptionally high rates of breast cancer mortality during the period 1970–1994. Figure reproduced from REF. 1.

and statistical tools developed for the LIBCSP by the federal contractor, Titan Corporation, are available for free download and are being extensively used by many investigators for GIS studies.

The other important LIBCSP studies involve populations of women on Long Island and nearby areas, and the most important findings of these studies so far, are described below. Many of the studies were case–control studies (BOX 2). In these studies, information about possible breast cancer risk factors was usually obtained using a standardized questionnaire that was given to the study participants by trained interviewers. The environmental risk factors that were investigated in these studies are described in BOX 3. A description of these studies and the most important findings regarding physical and chemical exposures are summarized here, and additional information is available in supplementary information S1 (table).

The Breast Cancer and the Environment on Long Island Study. The Breast Cancer and the Environment on Long Island Study (BCELIS) is the largest case–control study of the LIBCSP[12]. As the study is population-based, both the newly diagnosed cases and the control subjects were generally representative of the geographical areas where the study took place[12]. This investigation was led by Marilie Gammon, now of the University of North Carolina. Eligible case subjects were all females who had been newly diagnosed with breast cancer in Suffolk and Nassau counties on Long Island in 1996 and 1997, and who were identified through the New York Cancer Registry. Population-based controls were identified. Overall, 1,508 women who had been newly diagnosed with breast cancer and 1,556 control subjects were studied.

The investigators hypothesized that exposure to organochlorines and polycyclic aromatic hydrocarbons (PAHs) increase the risk of breast cancer among women on Long Island. They focused on organochlorines because laboratory animals that were exposed to the chemical agents were found to have increased risks of mammary cancer[13] and because the chemicals have both oestrogenic and anti-oestrogenic effects[14]. The investigators found no increased risk of breast cancer associated with blood concentrations of individual organochlorines, including the pesticides 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) and its metabolite 1,1-dichloro-2,2-bis (4-chlorophenyl)ethylene (DDE), chlordane and dieldrin among others. Also, no associations were found between breast cancer risk and blood concentrations of the four most common members of a class of organo-chlorines, the polychlorinated biphenyls (PCBs), that were previously used in some industrial processes.

However, a 50% increase in cancer risk was noted for women in the highest quartile of levels of exposure to PAHs. PAHs can cause mammary cancers in animal models[15] through their ability to bind DNA[16] and form PAH adducts. Adducts that were measured in mononuclear cells only reflected exposures up to 3 years before the time of collection of the blood in this case–control study, which might not have reflected long-term exposures that would be more aetiologically relevant to breast cancer carcinogenesis.

The New York State Cohort Study of Diet and Cancer. The New York State Cohort Study of Diet and Cancer, conducted with separate funding, included male and female long-term residents of the state in 1980. The investigators identified individuals in the cohort who developed cancer over the next 12 years. Erin O'Leary and her colleagues identified the 3,097 female cohort members who were residents of Nassau and Suffolk counties in 1980 (REF. 8). In this regional cohort, 105 individuals who developed *in situ* and invasive breast cancer were identified and each matched with 2 control subjects drawn from the same cohort. Pesticide-exposure estimates were based on records of previous agricultural land use near the homes of the study participants, physical distance of the residences of the study participants from hazardous waste sites containing pesticides, and pesticide concentrations in drinking water. The key finding was an almost threefold increased breast cancer risk that was observed for residents living within 1 mile of hazardous waste sites containing organochlorines.

Hospital-based studies. Two hospital-based case–control studies were conducted. One of these studies involved cases that were identified at two large Long Island hospitals[17]. The investigators enrolled women who were undergoing breast biopsies or breast surgery between 1994 and 1996. Organochlorine concentrations were determined in the women's breast adipose tissue, obtained during the biopsies/surgeries. Total pesticide, DDE, total PCBs, and individual PCB chemical variant

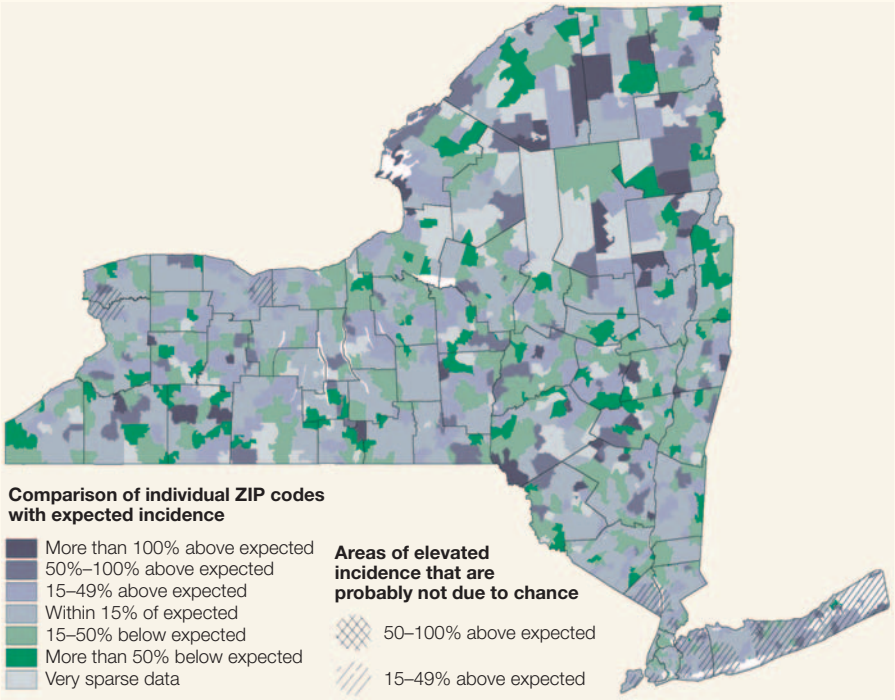

Figure 2 | **Map of breast cancer incidence in New York, 1993–1997, by ZIP code.** The hatch marks on the map indicate areas where the incidence of breast cancer is statistically higher than New York State as a whole. Long Island, which lies in the lower right corner of the state, has breast cancer rates that are 10–14% higher than for New York State during the time period 1993–1997. Figure reproduced from REF. 68.

concentrations were not found to be increased in the samples taken from 232 women with breast cancer, compared with samples from the 323 who did not have breast cancer.

In this study, the investigators also examined whether organochlorines increase the risk of breast cancer recurrence. The researchers assessed concentrations of PCBs in the breast adipose tissues of women who had been diagnosed with breast cancer and assessed the risk of recurrence of cancer after an average of 3.6 years of follow-up[18]. The risks of recurrence after diagnosis were four times higher for those with high concentrations of a specific PCB variant. Other organochlorines and self-reported exposure to termiticides were not associated with recurrence in this study.

A second study was conducted in Connecticut and was based on 304 breast cancer cases and 186 controls from 1994–1997 (REF. 19). These individuals were patients at a single hospital who had breast surgery or biopsies, and were subsequently classified either as having or not having cancer, or were from Tolland County, Connecticut[20], a county with high breast cancer incidence rates. In this study there was no evidence of an increased breast cancer risk associated with adipose concentrations of a number of organochlorines in the women's breast adipose tissue. In the Tolland County component, serum concentrations of PCBs and DDE were not higher in cases than in controls[20].

In summary, the LIBCSP investigators observed no association between breast cancer risk and levels in breast adipose tissue of DDT[19] and DDE[17,19], total pesticides[17], total PCBs and various variants or configurations of PCBs[17,21], hexachlorobenzene[22], the fungicide β-benzene hexachloride[23], or oxychlordane and *trans*-nonachlor[24]. Also, following analysis of the blood samples, there were no associations between the risk of developing cancer and concentrations of DDT[25]; DDE[21,25]; chlordane, dieldin, and the four most common PCB variants[25]; and total PCBs[20] and various PCB variants[20,25]. The only exception was a threefold increased risk of breast cancer among residents living within 1 mile of hazardous waste sites that contained organochlorines[8] and increased risks of breast cancer recurrence in patients who had been exposed to β-benzene hexachloride (also known as β-hexachlorocyclohexane).

In the congressionally mandated NE/MA studies, some positive findings for some chemicals were observed from individual studies. However, when the data were pooled in a combined analysis, there was no association made between cancer risk and concentrations of DDE or PCBs in blood[26].

Electromagnetic fields and breast cancer. The Electromagnetic Fields and Breast Cancer on Long Island Study[27,28], led by M. Cristina Leske, drew its participants from the BCELIS. The investigators included only women from the latter study who had been at their current residence for 15 years or more. The residence restriction was needed because the investigator's hypotheses concerned past exposures to electromagnetic fields, which could only practically be evaluated by taking measurements on the current home and extrapolating back in time[27,28]. Breast cancer risk was not associated with the levels of 24-hour electromagnetic-field exposure in the women's bedrooms or the rooms that they spent the most time in, or the measurements of ground current in those rooms[27,28]. Furthermore, in this study, neither measurements that were based on types of outdoor overhead wiring near the home[27,28] nor reported electric blanket use showed any association with breast cancer risk[29].

Summary of the findings from Long Island. In short, the reports arising from the LIBCSP have not identified any environmental factors that could be responsible for the high incidence of breast cancer in the area. The

Box 1 | **Long Island Geographical Information System — a research resource**

Geographical information systems (GISs) are powerful computer systems that can be used to store, manipulate, analyse and display the spatial (geographical location) relationships between dissimilar data types. The Long Island Geographical Information System (Long Island GIS) research resource was initiated for use in examining environmental factors that the Long Island population were exposed to and exploring relationships between these exposures and breast cancer incidence. The Long Island GIS warehouse has more than 80 datasets that cover geospatial data on Long Island. These include demographical data, health data, data on breast cancer incidence (by ZIP code) relative to the rates of cancer incidence in New York State, and environmental data for Long Island. Researchers can go to the Long Island GIS to apply to use the Long Island GIS warehouse database, as well as the suite of GIS tools, or to download free custom software extensions developed for the Long Island Breast Cancer Study Project, but also available for other GIS applications.

exceptions among the many negative findings are a report of a modest increase in the risk of breast cancer from PAH exposure in the largest of these studies[16], a risk with proximity to organochlorine-containing hazardous waste sites in one smaller study, and a possible risk of breast cancer recurrence in women who have been exposed to β-hexachlorocyclohexane[18].

The LIBCSP case–control studies have many strengths. By undertaking case–control studies the investigators were able to address specific high-priority environmental exposures. They were able to rule out other breast cancer risk factors, such as age and reproductive history, when examining these specific environmental factors. This is because the investigators were able to measure these factors and, statistically or using other methods, remove their effect in estimating the relationship between organochlorines and breast cancer. Although a few of the studies are small with limited statistical power, the BCELIS included more than 1,500 cases. In addition to its large size, the BCELIS had the advantage of using population-based methods of identifying study participants, which means that the study population was representative of the geographical area from which the participants were drawn — namely Suffolk and Nassau counties on Long Island.

An additional strength was that several of the studies evaluated organochlorine concentrations in adipose tissue[17,19,21–24], which is where PCBs are stored in the body[30], and also showed that the concentrations of these chemicals were similar in the blood and adipose tissue[31]. This helped to interpret findings from earlier studies that made measurements on blood — a much easier biological specimen to obtain than fat tissue — and to justify using blood measurements in future studies. In the largest of the case–control studies, information about environmental exposures was obtained from both the physical environment in which the study participants lived as well as from the measurements made on their blood and urine, which can provide information about the biological dose of the environmental agents that the women received.

However, there are also limitations to case–control studies. By definition, they involve identifying people who already have the disease that is being studied and comparing them to control subjects (people without the disease), assessing their histories of exposure to factors that might be involved in the development of the disease. This can be a problem for studies of environmental exposures and cancer risk because cancer takes a long time to develop, and the relevant environmental exposures that potentially caused the cancer might have occurred in the past. This can make it difficult to obtain accurate information about environmental factors because records that document environmental exposures might not be available, and study subjects might not recall or might not have been aware of the exposures when they occurred.

Box 2 | **Epidemiology terms**

Case–control study
A study in which people with a particular disease are compared with people who do not have the disease with respect to exposures that have occurred in the past. In this article, 'cases' are women with breast cancer and 'controls' are women who do not have breast cancer. In these studies, the women with breast cancer were compared with women who did not have breast cancer with respect to past reproductive factors, environmental exposures and other factors.

Cohort study
A study in which a group of people without the disease of interest is categorized as 'exposed' or 'not exposed' to certain environmental factors. These people are followed over time and disease incidence is tracked.

Odds ratio
The odds of exposure among the cases divided by the odds of exposure among the controls.

Relative risk
The risk of disease for those who have been exposed to a potential risk factor divided by the risk of disease among the non-exposed.

Population-based cases and controls
The cases and of controls in a case–control study are considered to be 'population-based' if they are identified in such a way as to be representative of the geographical area from which they are derived.

Population-based cases. In the United States, 'population-based cases' are usually all cases of a particular type of cancer in a geographical area over a defined time period that are systematically identified from a cancer registry.

Population-based controls. There are usually no lists available in the United States that contain names and contact information from which to obtain a random sample of people to serve as controls. A common alternative is to obtain eligible control subjects under the ages of 65 using random digit dialling — a technique that involves random dialling and telephone screening to find eligible controls. To find controls who are 65 years of age and older, lists of nearly all people who are of these ages can be obtained from Medicare lists provided by the federal Centers for Medicare and Medicaid Services. Because nearly all Americans have telephone service, and the Medicare lists provide nearly complete coverage of people in the United States who are 65 years and older, these two processes are generally considered to yield controls that are representative of the geographical area from which the cases are derived.

Towards a better understanding

Implicit in the wording of the legislation mandating the LIBCSP was that environmental factors were to be studied as potentially significant causes of breast cancer on Long Island. However, although the BCELIS had an initial focus on environmental risk factors, the investigators have pursued many additional lines of investigation in this population. These include an evaluation of whether organochlorine exposures influence prognosis after breast cancer. The LIBCSP has provided the opportunity to examine other factors that could increase breast cancer risk (as discussed below and in BOX 4), as well as initiating development of the Long Island GIS (BOX 1) — a resource that can be used for other studies of geographical and spatial factors in disease.

Gene–environment interactions. Although no significant environmental risk factors were found in the BCELIS, it will be important to follow up the finding of an increased cancer risk among women who had higher concentrations of PAH adducts. It is also possible that environmental factors could have a role only in genetically susceptible women. Gammon *et al.* are aggressively pursuing studies of gene–environment interactions. Interestingly, reductions in the risks associated with particular genotypes were only evident in (or more often among) women who consume large amounts of fruits and vegetables (TABLE 1; BOX 4).

Box 3 | **Environmental factors studied by the LIBCSP**

Organochlorines

Organochlorines are a class of chemicals that includes the pesticides 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), its metabolites (1,1-dichloro-2,2-bis(4-chlorophenyl)ethylene (DDE) and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDD)), chlordane, dieldrin, *trans*-nonachlor, hexachlorobenzene and β-hexachlorocyclohexane, as well as polychlorinated biphenyls (PCBs). PCBs have previously been used in transformers, capacitors and other electrical equipment.

Evidence for an association between exposure to these chemicals and cancer risk in humans is unclear. Organochlorines can have oestrogenic effects[14]. These chemicals cause cancer *in vitro* and *in vivo*[13]. These chemicals are also components of pesticides, which were often used on Long Island.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are products of combustion that are found in cigarette smoke, burned fossil fuels, and grilled and smoked food[69].

Before 1993, PAHs were known to be carcinogens that caused mammary tumours in animal models[13], so they have been proposed to cause breast cancer in human populations[70].

Electromagnetic fields

Electromagnetic fields are the regions of space near electrical currents, magnets, broadcasting antennas, and so on — regions in which electrical and magnetic forces are present.

The effects of exposure to electromagnetic fields and its relationship to breast cancer were studied in the Long Island population because of reports that these fields increased melatonin production. Melatonin increases oestrogen production, and higher levels of oestrogen production have been associated with an increased risk of developing breast cancer[71].

Negative results — success or failure?

Some members of the advocacy community and the media have been disappointed in the findings of the LIBCSP. They are unhappy with the length of time that it took to complete the case–control studies and the Long Island GIS[32,33]. They are also disappointed that certain chemicals of interest to them were not studied[97] and that specific environmental factors have not been identified that are responsible for the increased breast cancer incidence on Long Island[32,34,35].

However, there are few established environmental causes of cancer in the general population — for example, radon[36], environmental tobacco smoke[37], arsenic in drinking water[38], and solar and ultraviolet radiation[39]. Additionally, cancer clusters are very difficult to assess — studies of these generally find no environmental cause[40].

In the view of some, findings of no association (findings not supporting a hypothesis) indicate failure of the research. However, findings of no association that are obtained through rigorous research are important. The LIBCSP studies were able to fairly conclusively rule out several suspected environmental agents. If the evidence shows that there are no credible associations between the studied putative causative factors and the disease, then research resources can be directed toward other potential carcinogens. At least one prominent scientist has suggested, based on the evidence to date on environmental factors and breast cancer risk, that research resources be focused elsewhere[41].

Negative studies that have been well executed, as the LIBCSP studies have, can reassure people that exposures that they have experienced have probably not caused their cancer. They also reduce anxiety among women without cancer who are living in these geographical areas and are concerned about their own risk. However, some members of the advocacy community on Long Island continue to think that environmental factors are responsible for the increased cancer rates there[34,42,43].

Other breast cancer clusters

Women on Long Island are not the only people who are concerned about locally high rates of breast cancer incidence. Two other areas of concern are Marin County, outside San Francisco, California, and the area of Cape Cod in Massachusetts. In these areas, residents are concerned about high rates of breast cancer and whether environmental factors could be involved. Research projects that have been carried out in these locations have also provided insights into geographical variations in breast cancer incidence and mortality.

Cancer rates in a geographical area depend on many factors. One factor is the accuracy in measuring incidence. For example, the breast cancer rate in Marin County was thought to be increasing during the 1990s at a rate of 6.7% per year for women aged 45–64 (REF. 44). However, as the authors of that report suspected, some of the apparent increase over time was accounted for by the rates being calculated, by necessity, based on population size projections from the earlier 1990 Census of the population[45,46]. The migration of women into the county during the 1990s was not captured in these population projections, leading to inflated breast cancer incidence rates during that time period[45]. However, corrected incidence rates in Marin County during the 1990s, based on the now available 2000 Census, are still 7% higher than the rest of the San Francisco Bay area and 18% higher than the United States as a whole[45]. Other factors that can affect cancer rates in geographical areas include the age distribution of the population (as most cancer rates increase with age), the distribution of other known risk factors in the population, local environmental risk factors, and other factors that are unknown or not measurable.

Marin County in California, and Nassau and Suffolk counties in New York are among the wealthiest counties in the United States[47]. Women who have a higher socio-economic status will probably have reproductive factors that increase breast cancer risk, including later age at first birth and fewer pregnancies[48]. Two studies in California that included Marin County or the entire San Francisco Bay area, in which Marin County is located, indicate that socio-economic status might account for some, if not all, of the

Box 4 | **Other breast cancer risk factors identified by the BCELIS**

- Increased consumption of aspirin is associated with a lower risk of developing hormone-receptor-positive breast cancer[72].
- Increased consumption of fruits and vegetables lowers the risk of developing breast cancer[73].
- In a small case–control study, certain oestrogen metabolites detected in urine samples were associated with an increased breast cancer risk[74].
- Weight gain after the age of 20 years is associated with an increased breast cancer risk, especially after the age of 50 (REF. 75).
- There was an increased breast cancer risk in a subgroup of non-smoking women who lived with a spouse for more than 27 years[76].

Table 1 | **Genes examined in the Breast Cancer and the Environment on Long Island Study**

Gene (function of gene product)	Comparison of genotypes or amino-acid differences	Effect on breast cancer risk*	Interacting factors that also affect breast cancer risk	Reference
CAT (catalase enzyme)	262CC (high activity of gene product) versus 262TC and 262TT	–	262CC is associated with a reduced risk among those who consume large amounts of fruits and vegetables but do not take supplemental vitamins§	77
MTHFR (folate-reducing enzyme)	677TT (reduced activity of gene product) versus 677CC	+	677TT is associated with an increased risk among those who have the lowest intake of folate‡ and those who do not take supplemental vitamins‡	78
MTHFR (folate-reducing enzyme)	1298CC or 1298AC versus 1298CC	–	1298CC§ and AC§ are both associated with a reduced risk among those who do not take supplemental vitamins	78
XRCC1 (DNA repair protein)	399Gln/Gln or Gln/Arg versus Arg/Arg	ND	One or two alleles of 399Gln are associated with an increased risk, but only for never smokers with detectable DNA adducts‡	79
XRCC1 (DNA repair protein)	194Trp/Trp and Trp/Arg versus Arg/Arg	ND	One or two alleles of 194Trp are associated with a reduced risk, but only in individuals who consume large amounts of fruits and vegetables‡ and who consume and take supplemental anti-oxidants§	79
MGMT (repairs nitrosamine-related DNA adducts)	84TT or 84CT versus 84CC	ND	One or two alleles of 84T are associated with an increased risk, but only among heavy smokers‡	80
MGMT (repairs nitrosamine-related DNA adducts)	143GG or 143GA versus143AA	ND	One or two alleles of 143G are associated with a reduced risk in individuals who consume large amounts of fruits and vegetables‡, dietary α-carotene‡, or β-carotene plus β-carotene supplements§	80
MGMT (repairs nitrosamine-related DNA adducts)	178GG or 178GA versus 178AA	ND	No data available	80
ERCC2 (DNA repair protein that is mutated in patients with xeroderma pigmentosum)	751CC(Gln/Gln)or 751AC (Lys/Gln) versus 751AA(Lys/Lys)	+	751CC(Gln/Gln) is associated with an increased risk in current smokers§ and for those who have high levels of polycyclic aromatic hydrocarbon (PAH)–DNA adducts§	81
XRCC1 (DNA repair protein)	194C/T and 399G/A, CA or CG versus TG	ND	No data available	82
MPO (haem protein that is synthesized during myeloid differentiation)	463AA and 463AG versus 463GG	–	463AA§ and 463AG§ are both associated with a reduced risk in individuals who consume large amounts of fruits and vegetables	83

*Increased risk of breast cancer indicated by '+'; decreased risk of breast cancer indicated by '–'; ND, no difference. Indicated differences are either statistically significant (indicated by ‡) or marginally significant (indicated by §). *ERCC2*, excision repair cross-complementing rodent repair deficiency complementation group 2; *MGMT*, 0^6-methylguanine DNA methyl-transferase; *MPO*, myeloperoxidase; *MTHFR*, 5,10-methylenetetrahydrofolate reductase; *XRCC1*, X-ray repair complementing defective repair in Chinese hamster cells 1.

regional variation of breast cancer rates in California[49,50]. Findings from a case–control study in Marin County, which included 285 cases and 286 controls, indicate that breast cancer occurrence in these areas is associated with high levels of alcohol consumption (2 or more drinks per day)[51]. Additionally, there has been an increase over time in the incidence of oestrogen- and progesterone-positive tumours among women, which could potentially be explained by the high level of alcohol intake[51] or the use of hormone-replacement therapy[52]. Cases and controls were similar in their distributions of age at first residence, and years of residence in Marin County[51].

The Cape Cod area of Massachusetts is another area where environmental factors and breast cancer risk have been studied and where pesticide use was widespread[53]. Relative to the rest of Massachusetts, the breast cancer incidence rates were 20% higher on Cape Cod during the period 1982–1994 (REF. 54). To evaluate the reasons for this excess, the state of Massachusetts mandated research[55] that resulted in a population-based case–control study involving 1,121 breast cancer cases and 992 controls ascertained from 1988–1995. Cases were more likely to have lived on Cape Cod for 5 or more years than controls, with women who had been living there for 25–30 years — since 1948, the year that use of DDT began in that area — being those with the greatest odds ratio for developing cancer[53].

The investigator team also used a GIS approach on Cape Cod by geocoding (pinpointing the geographical location of) the cases and controls, and incorporating into the analysis extensive data on pesticide exposures, models of wind dispersion, and other factors. This analysis yielded no evidence of an effect of pesticides on breast cancer risk[56], although a subsequent report noted a clustering of breast cancer cases near a military reservation, which have been caused by groundwater-related exposures[57]. In this study population, a small increase in breast cancer risk with an estimate of exposure to tetrachloroethylene in drinking water flowing into the home in one analysis[96] was not confirmed in another analysis that incorporated indicators of personal drinking and bathing behaviours[58]. Factors that were not linked to breast cancer in this population included physical activity[59], electromagnetic field exposure[60] or workplace exposures to

33 substances that had oestrogenic activity[61], including many of those studied in the Long Island case–control study[25].

Future directions

The LIBCSP has been important not only because of its findings, but also because it set an example for the role that patient advocates and the United States Congress can have in shaping research, based on the public's deep concern about regional differences in cancer incidence and mortality. The cancer advocacy community had a key role in determining the research agenda and conduct — an important reality of this type of research. The project also highlighted the challenges that studies of the environment and cancer typically face.

Although some of the LIBCSP studies have ended, others will continue to yield additional scientific findings. Future research will probably improve the understanding of gene–environment interactions in the aetiology of breast cancer, and result in better measurements of environmental exposures.The Long Island GIS has also provided a research resource and a set of tools that can both be used in other studies involving geospatial patterns of health and disease.

There are several key messages that can be derived from the LIBCSP. One is that extensive research on the Long Island population has not identified any significant environmental risk factors for breast cancer. This is even though the geometric mean concentrations of at least two of the agents studied, DDE and dieldrin, were higher among women on Long Island compared with the rest of the United States[62]. Findings for the Long Island population are consistent with those from studies in two other geographical areas, which reported no correlation between breast cancer incidence and environmental factors, as well as the findings from the NE/MA Breast Cancer Study[26].

Studies of other populations with a high incidence of breast cancer have used different approaches to those of the LIBCSP to assess the role of environmental factors, but all have reached similar conclusions. The Long Island case–control studies focused on measurements in biospecimens from the cases and the controls, as well as objective measures of electromagnetic fields. In the Marin County and Cape Cod studies, the length of residence in a particular area was used as an indicator of potential exposure to local environmental agents, along with GIS analyses that employed historical documents to identify geographical areas that had been exposed to pesticides. The lack of evidence for an association between environmental factors and breast cancer risk in these studies is consistent with studies of other populations[63–65].

The LIBCSP was in the forefront of the current trend to include cancer survivors and advocates as an integral part of research teams. These people served on the advisory committee of the Long Island GIS, provided input on the large case–control study and served on the advisory committee of the project as a whole. The community was frequently updated on the status of the research throughout the course of the various studies. This is not to say that the scientist–advocate partnerships that were forged during the LIBCSP were always smooth. However, the research benefited from the relationship, and it is now commonplace to include patient advocates in many different capacities throughout epidemiological research studies[66].

Investigating the reasons for the high rates of cancer in limited geographical areas is a serious challenge for many reasons. Cancer is sufficiently rare that small numbers and chance findings are a significant problem. Measuring environmental exposures that occured in the past is very difficult. Some measurements, such as the assessment of organochlorines in adipose tissue or blood, provide accurate indicators of past exposures, but biomarkers for other chemical exposures are not available. Routine cancer surveillance systems can be used to predict incidence, mortality and survival rates of patients based on various characteristics of people and places. However, it would be difficult to develop a surveillance system to collect data on all the risk factors that are associated with each cancer type to determine the extent to which the distribution of known risk factors can account for differences in breast cancer rates. GISs and the addition of new features to surveillance systems, such as the inclusion of socio-economic data, are helping to address some of these issues.

The LIBCSP has provided some evidence of the effects of genetic predisposition on breast cancer risk, although primarily among women who consume large amounts of fruits and vegetables (TABLE 1). Studies of gene–environment interactions present many challenges because of the need for large sample sizes and because of inconsistencies in genetic analysis. So, the data from the BCELIS need to be carefully compared with those from other studies before we can draw conclusions about the role of gene–environment interactions in breast cancer aetiology.

The studies in California[49,50] indicate that differences in the socioeconomic factors of areas at higher and lower risk of breast cancer might account for a significant amount of the differences in breast cancer incidence rates across the state. This provides some indirect evidence that in California, region-specific environmental factors probably do not play an important role in explaining higher rates in some geographical areas. These socioeconomic characteristics could reflect non-environmental risk factors for breast cancer, such as reproductive history (for example, late age at first birth), or behavioural factors, such as the level of alcohol consumption. However, what breast cancer-related characteristics are captured by socioeconomic status variables is not clear.

A 1995 study found that the high breast cancer mortality rates in the Northeast and other important regions of the United States relative to the South could be partially accounted for by regional breast cancer risk and breast cancer progression factors[98]. In both the Long Island and Marin County populations, certain known risk factors were associated with increased breast cancer risk, including low parity, late age at first birth and little or no breast feeding. On Long Island, a family history of breast cancer[12] and, in Marin County, drinking alcohol were both associated with breast cancer risk[51]. When the BCELIS is fully analysed, it might be feasible to assess the contribution to the incidence of breast cancer on Long Island from the specific breast cancer risk factors identified.

However, even if most of the regional variation in nationwide breast cancer incidence can be explained by known risk factors, most cases are not associated with any known factors[41]. Breast cancer aetiology is complex, and no single scientific approach can be used to fully understand the factors that cause this cancer. There are inherent strengths and weaknesses in study designs and approaches for evaluating regional differences in cancer incidence and mortality.

One innovative approach that is being used to better understand the role of environmental factors and breast cancer risk is being undertaken by the Breast Cancer and the Environment Research Centers. This approach comprises four NIEHS- and NCI-funded studies that are focused on the determinants of puberty in young girls, as well as in animal models, and the effect of environmental factors on this process. These studies represent a different direction from the study of environmental factors and breast cancer because they focus on a developmental window that is

thought to be important in breast cancer development.

This initiative resulted, in part, from a 'brainstorming' session in 2002 that brought together scientists from various disciplines, patient advocates and breast cancer specialists, who jointly identified research gaps and promising future areas of research[67]. At this session, the director of the NIEHS remarked on the role of the breast cancer advocacy community in the research from conception through to implementation of the studies. Future studies will focus on the role of factors that influence the onset of puberty in breast cancer risk, and, again, patient advocates will work closely with members of the NIEHS and NCI to coordinate the studies. In this manner, the LIBCSP has already provided some answers to important questions about breast cancer aetiology, and has served as a good example for future cancer epidemiology studies.

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1. Devesa, S. S. *et al. Atlas of Cancer Mortality in the United States. NIH Publication Number 99–4564* (National Institutes of Health, Bethesda, Maryland, 2005).
2. Reynolds, T. Congress may order breast cancer study on Long Island. *J. Natl Cancer Inst.* **85**, 520–522 (1993).
3. New York State Department of Health. Cancer Trends by County, 1976–2002 (New York State, Albany, 2005). http://www.health.state.ny.us/nysdoh/cancer/nyscr/vol3.htm
4. New York State Department of Health Bureau of Cancer Epidemiology. *Long Island Breast Cancer Study Report #1. Overview and Descriptive Variables: Breast Cancer Screening Practices* (New York State Health Department, Albany, 1990).
5. New York State Department of Health Bureau of Cancer Epidemiology. *Long Island Breast Cancer Study Report #4. Termiticide Use and Breast Cancer Risk* (New York State Health Department, Albany, 1992).
6. New York State Department of Health Bureau of Cancer Epidemiology. *Long Island Breast Cancer Study Report #3. The Relationship of Lifestyle Factors to Breast Cancer Risk* (New York State Health Department, Albany, 1990).
7. New York State Department of Health Bureau of Cancer Epidemiology and Division of Environmental Epidemiology and Occupational Health. *Long Island Breast Cancer Study Report #2. Risk Factors, Regional Distribution, Pathology Appraisal, Evaluation of Selection Bias, and Water Sources and Landfills* (New York State Health Department, Albany, 1990).
8. O'Leary, E. S., Vena, J. E., Freudenheim, J. L. & Brasure, J. Pesticide exposure and risk of breast cancer: a nested case-control study of residentially stable women living on Long Island. *Environ. Res.* **94**, 134–144 (2004).
9. Goldstein, M. Come and be counted: the story behind the Long Island breast cancer study. *Mamm.* 42–43, 46, 49, 72–73 (1999).
10. Marks, P. U. S. to finance project to study breast cancer on Long Island. *New York Times* B1–B6 (25 Nov 1993).
11. US Congress. *National Institutes of Health Revitalization Act of 1993. Study of Elevated Breast Cancer Rates in Long Island, Public Law 103–43, June 10, 1993, Section 1911. Potential Environmental and Other Risks Contributing to Incidence of Breast Cancer* (US Government Printing Office, 1993). http://epi.grants.cancer.gov/LIBCSP/PublicLaw.html
12. Gammon, M. D. *et al.* The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res. Treat.* **74**, 235–254 (2002).
13. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Supplement Number 7. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*. 322 (International Agency for Research on Cancer, Lyon, France, 1987).
14. Wolff, M. S. & Toniolo, P. G. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. *Environ. Health Perspect.* **103** (Suppl.), 141–145 (1995).
15. Ambrosone, C. B. *et al.* Etiology of breast and gynecological cancers (eds Aldaz, C. M., Gould, M. N., McLachlan, J. C. & Slaga, T. J.) 93–99 (Wiley-Liss, 1997).
16. Gammon, M. D. *et al.* Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. *Cancer Epidemiol. Biomarkers Prev.* **11**, 677–685 (2002).
17. Stellman, S. D. *et al.* Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York. *Cancer Epidemiol. Biomarkers Prev.* **9**, 1241–1249 (2000).
18. Muscat, J. E. *et al.* Adipose concentrations of organochlorine compounds and breast cancer recurrence in Long Island, New York. *Cancer Epidemiol. Biomarkers Prev.* **12**, 1474–1478 (2003).
19. Zheng, T. *et al.* DDE and DDT in breast adipose tissue and risk of female breast cancer. *Am. J. Epidemiol.* **150**, 453–458 (1999).
20. Zheng, T. *et al.* Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2′-bis(p-chlorophenyl)ethylene. *Cancer Epidemiol. Biomarkers Prev.* **9**, 167–174 (2000).
21. Zheng, T. *et al.* Breast cancer risk associated with congeners of polychlorinated biphenyls. *Am. J. Epidemiol.* **152**, 50–58 (2000).
22. Zheng, T. *et al.* Environmental exposure to hexachlorobenzene (HCB) and risk of female breast cancer in Connecticut. *Cancer Epidemiol. Biomarkers Prev.* **8**, 407–411 (1999).
23. Zheng, T. *et al.* β-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. *Cancer* **85**, 2212–2218 (1999).
24. Zheng, T. *et al.* Oxychlordane and trans-nonachlor in breast adipose tissue and risk of female breast cancer. *J. Epidemiol. Biostat.* **5**, 153–160 (2000).
25. Gammon, M. D. *et al.* Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol. Biomarkers Prev.* **11**, 686–697 (2002).
26. Laden, F. *et al.* 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene and polychlorinated biphenyls and breast cancer: combined analysis of five U. S. studies. *J. Natl Cancer Inst.* **93**, 768–776 (2001).
27. Schoenfeld, E. R. *et al.* Magnetic field exposure assessment: a comparison of various methods. *Bioelectromagnetics* **20**, 487–496 (1999).
28. Schoenfeld, E. R. *et al.* Electromagnetic fields and breast cancer on Long Island: a case-control study. *Am. J. Epidemiol.* **158**, 47–58 (2003).
29. Kabat, G. C. *et al.* Electric blanket use and breast cancer on Long Island. *Epidemiology* **14**, 514–520 (2003).
30. Jaga, K. & Dharmani, C. Global surveillance of DDT and DDE levels in human tissues. *Int. J. Occup. Med. Environ. Health* **16**, 7–20 (2003).
31. Stellman, S. D. *et al.* Relative abundance of organochlorine pesticides and polychlorinated biphenyls in adipose tissue and serum of women in Long Island, New York. *Cancer Epidemiol. Biomarkers Prev.* **7**, 489–496 (1998).
32. Rather, J. Breast cancer groups question new study. *New York Times* (3 Dec 2000).
33. Fagin, D. Still searching: a computer mapping system was supposed to help unearth information about breast cancer and the environment. *Newsday* (30 Jul 2002).
34. Toy, V. What next? *New York Times* (11 Aug 2002).
35. Fagin, D. Breast cancer causes still elusive. Study: no clear link between pollution, breast cancer on Long Island. *Newsday* (6 Aug 2002).
36. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 43: Man-made Mineral Fibers and Radon.* (International Agency for Research on Cancer, Lyon, France, 1988).
37. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 83: Tobacco smoke and involuntary smoking.* (International Agency for Research on Cancer, Lyon, France, 2002).
38. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 84: Some Drinking-water Disinfectants and Contaminants, Including Arsenic* (International Agency for Research on Cancer, Lyon, France, 2004).
39. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 55: Solar and Ultra-violet Radiation* (International Agency for Research on Cancer, Lyon, France, 1992).
40. Thun, M. J. & Sinks, T. Understanding cancer clusters. *CA Cancer J. Clin.* **54**, 273–280 (2004).
41. Whittemore, A. S. Breast cancer in Marin County. *Breast Cancer Res.* **5**, 232–234 (2003).
42. Kolata, G. What causes cancer: can science find the missing link? *New York Times* (8 Nov 2002).
43. Twombly, R. After Long Island study, advocates look for a stronger voice. *J. Natl Cancer Inst.* **94**, 1349 (2002).
44. Clarke, C. A. *et al.* Breast cancer incidence and mortality trends in an affluent population: Marin County, California, USA, 1990–1999. *Breast Cancer Res.* **4**, R13 (2002).
45. Ward, E., Jemal, A. & Thun, M. Regarding 'increase in breast cancer incidence in middle-aged women during the 1990s'. *Ann. Epidemiol.* **15**, 424–425 (2005).
46. Clarke, C. A., Prehn, A. W., Keegan, T. H., Glaser, S. L. & West, D. W. Response to letter by ward *et al. Ann. Epidemiol.* **15**, 426–427 (2005).
47. Bureau of Economic Analysis, US Department of Commerce. *Regional Economic Accounts*. http://www.bea.gov/bea/regional/data.htm (2005).
48. Kelsey, J. L. & Bernstein, L. Epidemiology and prevention of breast cancer. *Annu. Rev. Public Health* **17**, 47–67 (1996).
49. Reynolds, P. *et al.* Regional variations in breast cancer among California teachers. *Epidemiology* **15**, 746–754 (2004).
50. Reynolds, P. *et al.* Regional variations in breast cancer incidence among California women, 1988–1997. *Cancer Causes Control* **16**, 139–150 (2005).
51. Wrensch, M. *et al.* Risk factors for breast cancer in a population with high incidence rates. *Breast Cancer Res.* **5**, R88–R102 (2003).
52. Hwang, E. S. *et al.* Risk factors for estrogen receptor-positive breast cancer. *Arch. Surg.* **140**, 58–62 (2005).
53. McKelvey, R. A., Wright, J. P. & Honegger, J. L. A comparison of crop and non-crop plants as sensitive indicator species for regulatory testing. *Pest. Manag. Sci.* **58**, 1161–1174 (2002).
54. Cape Cod Breast Cancer and Environment Atlas. http://library.silentspring.org/atlas/breastcancer/sir.asp (2005).
55. General Court of the Commonwealth of Massachusetts. *An Act Making Appropriations for the Fiscal Year 2001 for the Maintenance of the Departments, Boards, Commissions, Institutions and Certain Activities of the Commonwealth, for Interest, Sinking Fund and Serial Bond Requirements and for Certain Permanent Improvements.* Acts and Resolves of Massachusetts, Section 2, 4570–1500. Boston, Massachusetts. http://www.mass.gov/legis/laws/seslaw00/sl000159.htm (2005).
56. Brody, J. G. *et al.* Breast cancer risk and historical exposure to pesticides from wide-area applications assessed with GIS. *Environ. Health Perspect.* **112**, 889–897 (2004).
57. Vieira, V., Webster, T., Weinberg, J., Aschengrau, A. & Ozonoff, D. Spatial analysis of lung, colorectal, and breast cancer on Cape Cod: an application of generalized additive models to case-control data. *Environ. Health* **4**, 11 (2005).
58. Vieira, V., Aschengrau, A. & Ozonoff, D. Impact of tetrachloroethylene-contaminated drinking water on the risk of breast cancer: using a dose model to assess exposure in a case-control study. *Environ. Health* **4**, 3 (2005).
59. Coogan, P. F. & Aschengrau, A. Occupational physical activity and breast cancer risk in the upper Cape Cod cancer incidence study. *Am. J. Ind. Med.* **36**, 279–285 (1999).
60. Coogan, P. F. & Aschengrau, A. Exposure to power frequency magnetic fields and risk of breast cancer in the Upper Cape Cod Cancer Incidence Study. *Arch. Environ. Health* **53**, 359–367 (1998).
61. Aschengrau, A., Coogan, P. F., Quinn, M. & Cashins, L. J. Occupational exposure to estrogenic chemicals and the occurrence of breast cancer: an exploratory analysis. *Am. J. Ind. Med.* **34**, 6–14 (1998).
62. National Center for Environmental Health, Centers for Disease Control and Prevention. *Third National Report on Human Exposure to Environmental Chemicals* 307–344 (National Center for Environmental Health, Centers for Disease Control and Prevention, 2005).

63. Calle, E. E., Frumkin, H., Henley, S. J., Savitz, D. A. & Thun, M. J. Organochlorines and breast cancer risk. *CA Cancer J. Clin.* **52**, 301–309 (2002).
64. Feychting, M., Ahlbom, A. & Kheifets, L. EMF and health. *Annu. Rev. Public Health* **26**, 165–189 (2005).
65. Negri, E., Bosetti, C., Fattore, E. & La Vecchia, C. Environmental exposure to polychlorinated biphenyls (PCBs) and breast cancer: a systematic review of the epidemiological evidence. *Eur. J. Cancer Prev.* **12**, 509–516 (2003).
66. Collyar, D. How have patient advocates in the United States benefited cancer research? *Nature Rev. Cancer* **5**, 73–78 (2005).
67. Claudio, L. Breast cancer takes center stage. *Environ. Health Perspect.* **112**, A92–A94, A95 (2004).
68. New York State Department of Health. *Breast cancer in New York State by ZIP Code, 1993–1997*. http://www.health.state.ny.us (2005).
69. Menzie, C. A., Potocki, B. B. & Santodonato, J. Exposure to Carcinogenic PAHs in the Environment. *Environmental Science & Technology* **26**, 1278–1284 (1992).
70. Morris, J. J. & Seifter, E. The role of aromatic hydrocarbons in the genesis of breast cancer. *Med. Hypotheses* **38**, 177–184 (1992).
71. Stevens, R. G. Electric power use and breast cancer: a hypothesis. *Am. J. Epidemiol.* **125**, 556–561 (1987).
72. Terry, M. B. *et al.* Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA* **291**, 2433–2440 (2004).
73. Gaudet, M. M. *et al.* Fruits, vegetables, and micronutrients in relation to breast cancer modified by menopause and hormone receptor status. *Cancer Epidemiol. Biomarkers Prev.* **13**, 1485–1494 (2004).
74. Kabat, G. C. *et al.* Urinary estrogen metabolites and breast cancer: a case-control study. *Cancer Epidemiol. Biomarkers Prev.* **6**, 505–509 (1997).
75. Eng, S. M. *et al.* Body size changes in relation to postmenopausal breast cancer among women on Long Island, New York. *Am. J. Epidemiol.* **162**, 229–237 (2005).
76. Gammon, M. D. *et al.* Environmental tobacco smoke and breast cancer incidence. *Environ. Res.* **96**, 176–185 (2004).
77. Ahn, J. *et al.* Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use. *Am. J. Epidemiol.* 28 Sept 2005 (doi:10.1093/aje/kwi306).
78. Chen, J. *et al.* One-carbon metabolism, MTHFR polymorphisms, and risk of breast cancer. *Cancer Res.* **65**, 1606–1614 (2005).
79. Shen, J. *et al.* Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **14**, 336–342 (2005).
80. Shen, J. *et al.* MGMT genotype modulates the associations between cigarette smoking, dietary antioxidants and breast cancer risk. *Carcinogenesis* 13 Jul 2005 (doi:10.1093/carcin/bgi179).
81. Terry, M. B. *et al.* Polymorphism in the DNA repair gene *XPD*, polycyclic aromatic hydrocarbon–DNA adducts, cigarette smoking, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **13**, 2053–2058 (2004).
82. Santella, R. M. *et al.* DNA adducts, DNA repair genotype/phenotype and cancer risk. *Mutat. Res.* 14 Jul 2005 (doi:10.1016/j.mrfmmm.2005.06.001).
83. Ahn, J. *et al.* Myeloperoxidase genotype, fruit and vegetable consumption, and breast cancer risk. *Cancer Res.* **64**, 7634–7639 (2004).
84. O'Leary, E. S. *et al.* Wire coding in the EMF and Breast Cancer on Long Island Study: relationship to magnetic fields. *J. Expo. Anal. Environ. Epidemiol.* **13**, 283–293 (2003).
85. Wolff, M. S., Camann, D., Gammon, M. & Stellman, S. D. Proposed PCB congener groupings for epidemiological studies. *Environ. Health Perspect.* **105**, 13–14 (1997).
86. Lisitsyn, N. A. *et al.* Comparative genomic analysis of tumors: detection of DNA losses and amplification. *Proc. Natl Acad. Sci. USA* **92**, 151–155 (1995).
87. Jacquez, G. M. & Greiling, D. A. Local clustering in breast, lung and colorectal cancer in Long Island, New York. *Int. J. Health Geogr.* **2**, 3 (2003).
88. Jacquez, G. M. & Greiling, D. A. Geographic boundaries in breast, lung and colorectal cancers in relation to exposure to air toxics in Long Island, New York. *Int. J. Health Geogr.* **2**, 4 (2003).
89. Gammon, M. D. *et al.* Treatment for breast cancer and blood levels of chlorinated hydrocarbons. *Cancer Epidemiol. Biomarkers Prev.* **5**, 467–471 (1996).
90. Gammon, M. D. *et al.* Temporal variation in chlorinated hydrocarbons in healthy women. *Cancer Epidemiol. Biomarkers Prev.* **6**, 327–332 (1997).
91. Shantakumar, S. *et al.* Residential environmental exposures and other characteristics associated with detectable PAH–DNA adducts in peripheral mononuclear cells in a population-based sample of adult females. *J. Expo. Anal. Environ. Epidemiol.* 27 Apr 2005 (doi:10.10.38/sj.jea.7500426).
92. Yao, Y. *et al.* Scatter factor protein levels in human breast cancers: clinicopathological and biological correlations. *Am. J. Pathol.* **149**, 1707–1717 (1996).
93. Lane, D. S., Messina, C. R. & Grimson, R. An educational approach to improving physician breast cancer screening practices and counseling skills. *Patient. Educ. Couns.* **43**, 287–299 (2001).
94. Teitelbaum, S. L. Questionnaire assessment of nonoccupational pesticide exposure in epidemiologic studies of cancer. *J. Expo. Anal. Environ. Epidemiol.* **12**, 373–380 (2002).
95. Wolff, M. S. *et al.* Improving organochlorine biomarker models for cancer research. *Cancer Epidemiol. Biomarkers Prev.* **14**, 2224–2236 (2005).
96. Aschengrau, A., Rogers, S. & Ozonoff, D. Perchloroethylene-contaminated drinking water and the risk of breast cancer: additional results from Cape Cod, Massachusetts, USA. *Environ. Health Perspect*. **111**, 167–173 (2003).
97. Fagin, D. 'No closed doors'. Activists to push studies on toxins, breast cancer link. *Newday* (7 Aug 2002).
98. Sturgeon, S. R. *et al*. Geographic variation in mortality from breast cancer among white women in the United States. *J. Natl Cancer Inst.* **87**, 1846–1853 (1995).

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Competing interests statement

The author declares no competing financial interests.

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Cancer and the environment: what you need to know, what you can do: http://www.cancer.gov/cancerinfo/wyntk/overview/page16

National Cancer Institute factsheet on cancer clusters: http://cis.nci.nih.gov/fact/3_58.htm

National Center of Environmental Health cancer clusters factpage: http://www.cdc.gov/nceh/clusters/

Geographical patterns of cancer mortality in the United States: http://www3.cancer.gov/atlasplus/

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SUPPLEMENTARY INFORMATION

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