

Breast Cancer and Pesticides in Hawaii: The Need for Further Study

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Only 30% of all breast cancer can be explained by known risk factors. Increases in breast cancer incidence rates in Hawaii over the past few decades cannot be attributed solely to improvements in screening and detection. Avoidable environmental factors may contribute to a proportion of the unexplained cases. Emerging evidence on endocrine disruption suggests that environmental chemicals may play a role in the development of breast cancer. Agricultural chemicals, including endocrine disruptors, have been used intensively in Hawaii's island ecosystem over the past 40 years leaching into groundwater, and leading to unusually widespread occupational and general population exposures. This paper discusses breast cancer patterns in Hawaii in the context of documented episodes of exposure to two endocrine-disrupting chemicals, chlordane/heptachlor and 1,2-dibromo-3-chloropropane (DBCP), at levels that sometimes exceeded federal standards by several orders of magnitude. In light of this history, detailed geographic-based studies should be undertaken in Hawaii to elucidate the potential role of environmental factors in the development of breast cancer and other diseases. — *Environ Health Perspect* 105(Suppl 3): 679–683 (1997)

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Introduction

Traditionally accepted risk factors account for less than half of all cases of breast cancer (1). Improved screening practices cannot completely account for the rise in breast cancer incidence rates over the past two decades (2). Areas where incidence rates have changed substantially over time, or where rates differ from other regions, may provide an opportunity to better

understand the etiology of the disease. Hawaii is such a region.

Breast cancer incidence rates have increased on Hawaii over the past few decades and cannot be explained by known risk factors. Research on new risk factors for breast cancer is burgeoning. Emerging evidence on endocrine disruptors suggests that environmental chemicals, such as

some pesticides, aromatic hydrocarbons, and plastics may be avoidable causes of the disease profile (3).

Hawaii is an island ecosystem with geological features and chemical use patterns that contribute to the potential for groundwater contamination. There is evidence that populations living in Hawaii have experienced unusual exposures to mixtures of probable endocrine disruptors. Over the past 40 years there has been intensive use of agricultural chemicals that have leached into island groundwater, leading to widespread occupational and general population exposures. Groundwater has remained the major source of drinking water for much of this tropical island ecosystem, which provides a supportive environment for crop-damaging pests and other agents.

This paper discusses the potential connection between these exposures to endocrine disruptors and breast cancer and other hormonally mediated disease outcomes in Hawaii. We first report unexplained and shifting patterns of breast cancer in Hawaii and discuss the links between xenoestrogens and breast cancer. Second, we discuss the vulnerability of Hawaii to chemical contamination and review documented episodes of unusually high exposures to some endocrine-disrupting pesticides that may have contributed to breast cancer in this population.

Breast Cancer Patterns and Endocrine Disruption

From 1970 to 1985 breast cancer incidence rates increased for all racial groups in Hawaii (Figure 1) (4). Differences between these groups narrowed during this period. The breast cancer incidence among Japanese women in Hawaii jumped 42% between 1970 and 1985. Rates of increase in other areas of the U.S. (Bay area, Seattle, Detroit) for the same time period did not exceed 20% (4). The rates for Caucasians and native Hawaiians are also high; in 1985 they exceeded 200 out of 100,000.

Improvements in screening and detection cannot completely explain these increases in Hawaii. National mammography screening rates for women 40 years of age and above were only 17% in 1987 and 33% in 1990, and screening was not common for the general population before 1982 (5). The screening rates are slightly higher in Hawaii, but a review of insurance claims data for the state showed that less

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Abbreviations used: DBCP, 1,2-dibromo-3-chloropropane; DD, mixture of 1,3-dichloropropene and 1,2-dichloropropane; hER, human estrogen receptor; PCBs, polychlorinated biphenyls; Telone, 1,3-dichloropropane.

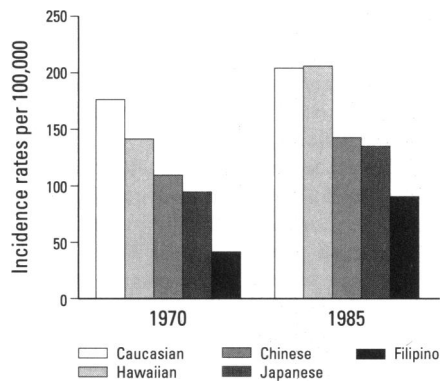


Figure 1. Breast cancer incidence rates in Hawaii. World standardized truncated rate per 100,000 year (ages 30–74). Data from IARC (4).

than half of the women over 40 years of age receive regular mammograms (6). Other explanations for breast cancer must be explored.

The known risk factors for breast cancer (age, family history of breast cancer, early menarche, late age at first birth, nulliparity, body weight over the lifetime, diet, etc.) may account for some portion of breast cancer in Hawaii, yet studies show that these factors can explain only 30 to 40% of breast cancer cases (1,7). Changes in diet and patterns of weight gain may partially contribute to the explained cases of breast cancer (8). The contribution of these traditional risk factors needs to be examined in Hawaii. Yet it is crucial that novel hormonally active environmental and occupational risk factors also be studied in Hawaii, particularly in light of the state's widespread chemical contamination over the past 40 years.

A common link among traditional risk factors is that they promote breast cancer by elevating total lifetime exposure to biologically active estrogens, principally in the form of estradiol (9). There is a growing body of evidence that suggests that environmental chemicals can disrupt the endocrine system and contribute to the development of breast cancer. The universe of compounds shown to exhibit estrogenic function is extensive. These compounds, labeled environmental estrogens, xenoestrogens, and estrogen mimickers, share the ability to disrupt the endocrine system, causing a cascade of biological effects. A number of restricted or banned pesticides used in Hawaii are estrogenic. These include DDT, DDE, kepone, heptachlor, chlordane, dieldrin, mirex, lindane, and toxaphene (10,11). Other compounds that may disrupt hormonal mechanisms include

polychlorinated biphenyls (PCBs), polyaromatic hydrocarbon combustion pollutants, and ingredients in plastics such as nonylphenol (12,13). Naturally occurring plant estrogens called bioflavonoids (e.g., coumestrol) and mycotoxins (e.g., zearalenone) may be even more estrogenic than industrial chemicals (12,14), although their ultimate biologic effect may be less toxic (15). Natural estrogens are usually metabolized and excreted rapidly, but synthetic estrogens can have long half-lives and bioaccumulate in fat (16).

Epidemiologic evidence also supports the link between exposure to organochlorines and breast cancer. Wolff et al. compared cases and controls, well matched for age and other risk factors, and found that women with the highest levels of DDE in their blood had a 4-fold risk of breast cancer (17). Another study found that women with estrogen-responsive breast cancer had nine times the risk of the disease and higher body burdens of DDE and PCBs than women with benign breast disease (18). Krieger and colleagues did not find an association with organochlorines and breast cancer in their overall study, which included Caucasians, African-Americans, and Asians. When the Asians were taken out of the analysis, however, there was evidence of excess risk of breast cancer associated with DDT in Caucasians and African Americans (19). This is consistent with the finding that Asian women in their countries of origin, and even when living in the United States, have lower rates of breast cancer, perhaps due to nutritional or genetic factors.

The above epidemiologic studies have focused on the potential etiologic role of DDT in the development of breast cancer. Although this evidence, supported by *in vitro* and *in vivo* evidence, suggests that DDT may be important, the situation is vastly more complex. While some chemicals may increase breast cancer, others such as dioxin may act as antiestrogens and reduce the risk of the disease (14). In practice, people are not exposed to one chemical at a time but complex mixtures of chemicals, and many of these may persist or bioaccumulate in fat.

Recent studies provide evidence that the synergistic activity of many common pesticides may be significant (15,20). In Arnold and McLachlan's yeast estrogen system assay (20), potencies of synthetic estrogens were measured by their ability to activate the breast cancer-galactosidase gene by binding to human estrogen receptor (hER).

Most estrogenic compounds have potencies 1/50th to 1/10,000th those of natural estrogen or of diethylstilbestrol. The potencies of these chemicals, when studied alone, suggest small effects on biological systems. However, these certain chemicals have markedly greater impact on hER activity when acting in combination. For example, a mixture of endosulfan and dieldrin was 160 to 1600 times more potent than each chemical acting alone. PCBs that were previously shown to alter sexual development in turtles also produced effects that were synergistic in this yeast system assay. Since these synthetic compounds occur as mixtures in the environment, their partnership potencies require special consideration.

Pesticide Use and Exposures in Hawaii

A number of factors contribute to extensive pesticide exposure in Hawaii. First, the year-round moderate temperatures promote a continuous life cycle for growth of nematodes, fruit flies, ants, fungi, and weeds (21). Second, since the 1940s, plantation agriculture on Hawaii has become heavily dependent on agricultural chemicals to control various pests. Third, the underlying geology is extremely vulnerable to contamination (22).

Hawaii is classified by the U.S. Environmental Protection Agency (U.S. EPA) as an area highly sensitive to groundwater contamination from agricultural pesticides. Groundwater is the primary source of fresh water for the public. On Maui, 95% of the population uses groundwater for drinking water (22). The high permeability and low organic matter content of the volcanic soil promotes the transport of pesticides into the groundwater system. High annual rainfall quickens this process. Many of the agricultural compounds used in Hawaii are highly persistent and have been detected in groundwater years after they were applied.

Despite its vulnerable ecosystem, chemically intensive agriculture has flourished and drinking water sources have been sited on agricultural lands in Hawaii. Since the 1940s, pineapples and sugar cane have been Hawaii's leading export crops. On Oahu, sugar cane cultivation accounts for 34,900 acres and pineapple, 2050 acres (21). Between 1988 and 1991, over 20 different pesticides were used by the Hawaiian sugar industry, including a number of suspect endocrine disruptors (23). During its 40 years of operation, the

Del Monte Oahu Pineapple Plantation has applied a mixture of chemicals subsequently banned for multiple health concerns, including: DBCP (1,2-dibromo-3-chloropropane—diluted with organic solvents until the early 1980s), Telone II (100% 1,3-dichloropropene, Dow Chemical, Midland, MI), ethylene dibromide, DD (a mixture of 1,3-dichloropropene and 1,2-dichloropropane), and chloropicrin (trichloronitromethane) (24). The majority of Del Monte employees and their families live on the pineapple plantation.

DBCP Exposures

DBCP is classified as a possible human carcinogen and reproductive toxicant by the Hawaii Department of Health and the U.S. EPA. Various studies link DBCP with reduced sperm counts, genetic mutations, and the ability to disrupt testicular function. Five parts per million of DBCP in the air causes specific histological alterations in the testes of male rats following repeated exposures (25). Higher exposures were even more damaging to rats, guinea pigs, rabbits, and monkeys, with severe atrophy and degeneration of the testes observed in all species. DBCP causes endocrine dysfunction, which results in increased pituitary hormone levels in men and disruption of the estrous cycle in female rats (25).

Despite controls on the use of products containing DBCP, residues remain detectable in aquifers and drinking water wells on all of the Hawaiian islands (26). Sugar and pineapple producers petitioned the U.S. EPA for an exemption on DBCP use. Before regulations were imposed in the early 1980s, mixtures of DBCP, Telone II and DD, diluted with organic solvents,

were injected into the soil to fumigate pineapple field soils (27).

The small Oahu village of Kunia is located on the pineapple plantation and is home to 65% of Del Monte's full-time employees (28). The Hawaii Department of Health twice sampled Kunia drinking water wells and confirmed above-average levels of DBCP at 0.01 ppm (29), two orders of magnitude greater than the U.S. EPA's drinking water standard for DBCP (0.0002 ppm). This contamination resulted in closure of drinking water wells in 1980. Later that same year on Maui, official state testing of the Maliko Gulch spring, located 0.2 miles from pineapple fields, showed DBCP levels at 0.6 ppb, and 0.35 ppb DBCP 0.1 miles away from another field (29).

In 1994, the Agency for Toxic Substances and Disease Registry (ATSDR) identified Kunia plantation as an indeterminate public health hazard because of widespread high levels of DBCP exposure (30). The state of Hawaii conducted a case study in 1982 to determine exposure pathways of environmental contaminants at the site (24). There is evidence that all 738 inhabitants of Kunia were exposed to DBCP through ingestion of and skin contact with contaminated water. DBCP is not known to accumulate in plants and animals; therefore, it is unlikely that people were exposed to site-related contaminants in food (31). In addition, plantation and remedial workers may have been exposed through inhalation of emissions from DBCP-contaminated soil. A significantly high rate of neoplasms, including breast cancer, was reported in Kunia compared to a community 5 miles away in the town of Poamoho, where DBCP was not found (24).

Other studies document reproductive anomalies in DBCP-exposed persons (31,32). Takahashi et al. (32) studied abnormalities in spermatogenic morphology and volume from a population on the island of Molokai. The frequency distribution of sperm count indicated a significant difference between that of the agricultural group directly exposed to DBCP and a control group not exposed. Twenty-three percent of the exposed group were oligospermic and half had low normal counts, whereas 14% of the controls were oligospermic and none had below-normal counts. High numbers of miscarriages were reported among the spouses of these agricultural workers (32). These findings of unusual hormonally related outcomes suggest that investigations need to be undertaken to determine a variety of endocrinological effects of DBCP exposure.

Heptachlor Contamination in Oahu

Chlordane and heptachlor, as well as aldrin, endrin, and dieldrin, are members of the cyclodiene pesticides. Although prohibited from sale in the United States in 1988, chlordane and heptachlor are manufactured in the United States and shipped overseas (33). Legal actions followed, and the use of chlordane/heptachlor products is still permitted for fire ant control in power transformers. The use of existing stocks continued after the ban on sale, distribution, and shipment. As recently as 1993, heptachlor was applied to pineapple fields on Oahu by Del Monte Corporation (34,35). The long half-lives, fat solubility, and bioaccumulation of these chemicals ensure that they remain biologically active for decades. Heptachlor and chlordane interfere with multiple metabolic systems and steroid function. They are immunotoxic, mutagenic, and carcinogenic, and enhance the metabolism of other xenobiotic chemicals (11).

In humans, the major metabolite of heptachlor is the oxidation product 2,3-heptachlor epoxide, which is more toxic than the parent compound heptachlor. The U.S. EPA canceled domestic use for all food crops and home use of heptachlor in August 1976. However, existing stocks of chlordane/heptachlor are legally being depleted for commercial termite control in Hawaii. The estimated usage of heptachlor ranged from 20,412 lb in 1964 to 9571 lb in 1980 (36) (Figure 2).

The U.S. Food and Drug Administration set a zero tolerance level for heptachlor in processed foods during the

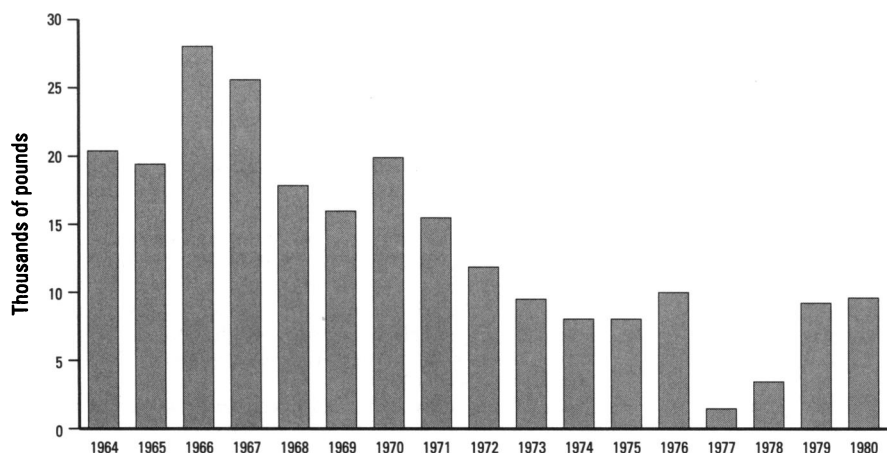


Figure 2. Estimated heptachlor usage by pineapple industry in Hawaii. Source: Cayetano (41).

1960s. At that time the available instrumentation could only detect quantities greater than 0.3 ppm (lipid basis), so an action level of 0.3 ppm was established (37). This standard was exceeded 10-fold from 1981 to 1984 in the milk and dairy products supplied by local dairies on the island of Oahu, Hawaii (38).

Heptachlor, sprayed on pineapple plants to control ants responsible for the spread of mealybugs, remained on the leaves that were chopped and fed to dairy cows on Oahu. Heptachlor-contaminated "green chop" led to contamination of the commercial milk supply on Oahu for as long as 15 months during 1981 to 1982, at levels as high as 1.2 µg/g fat basis (38).

Because of its liposolubility, heptachlor bioaccumulates in adipose tissue and is found in even higher concentrations in human milk than in cows' beef and milk. When storage fat is mobilized during lactation, so too are lipophilic contaminants (39). The pesticide levels in human milk often exceed the levels set for cow's milk by the World Health Organization. After contamination of the Hawaii milk supply, lactating women who consumed dairy products and beef from local dairies averaged 200 ppm of heptachlor in their breast milk, and in some cases levels exceeded 400 ppm. A 1979 to 1980 survey compared regions of the continental United States with Hawaii and found the levels of heptachlor epoxide in breast milk in Hawaii were 20% higher than in the southeastern states and 65% higher than in the northeastern states (36).

Newborns and nursing infants may be particularly vulnerable to exposure to heptachlor because of the infant's immature renal and hepatic function, which can delay detoxification and excretion. A

continuous intake of mother's milk could lead to clinically significant concentrations in the infant's body (40).

More than 10 years have passed since mothers and their infants were exposed to unusually high levels of heptachlor in Hawaii. A 1993 study (38) assessed levels of heptachlor epoxide in lactating women's breast milk and in the serum of adults and children on Oahu and in a comparison population on neighboring islands and on the mainland. They found elevated levels of heptachlor epoxide in both milk and serum on Oahu compared to the neighboring islands, and that the age pattern of detectable serum heptachlor in children was consistent with exposure to the contaminated milk. Oahu children who were old enough to have consumed the milk had significantly higher levels in their serum than did children on neighboring islands. Younger children from Oahu did not have detectable levels of the compound. No follow-up studies on the mothers or children who ingested the milk have been completed at this time. A lawsuit followed the milk contamination episode and the settlement money is to be used to monitor the affected children.

Conclusion

The DBCP and heptachlor contamination events resulted in high exposures in Hawaii to harmful compounds. Follow-up studies of the exposed communities are needed to assess the long-term effects of such exposures. A clear understanding of the ramifications will not be easy. For instance, environmental exposures may have contributed to the high numbers of neoplasms in the small community of Kunia but age-adjusted rates cannot readily be devised for such a small geographic region.

It will not suffice to look at these episodes in isolation. Since the intensive use of agricultural chemicals began over five decades ago, people living on Hawaii have been exposed to complex mixtures of compounds whose synergistic effects are poorly understood. Island ecosystems such as Hawaii are especially vulnerable to groundwater, food chain, and air contamination from persistent pesticides. Residential pesticide use in Hawaii for termite control is at rates of application that are 500 to 1000 times higher than rates used in agriculture. Metabolites of the pesticides may be more toxic than the parent product, may accumulate on soil surfaces from repeated applications, and may be carried inside. The emerging evidence on endocrine-disrupting chemicals and the indication that low levels of individual compounds acting in combination can be far more potent are compelling reasons to delve further into the effects of exposure in Hawaii.

There are many competing risk factors that probably play a role in breast cancer incidence rate increases. It is unlikely that exposure to chemicals could completely explain the increase, but such exposures may be preventable. Detailed analytic studies should be developed to clarify the extent to which avoidable environmental factors may account for some of the breast cancer patterns in Hawaii. These studies might include case-control studies that rely on biological measurements of contaminants in fat and serum and biomarkers of hormonal metabolism alteration. To assess the possible contribution of such exposures to breast cancer and other hormonally mediated diseases, it is critical that additional studies be undertaken.

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